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SUPPLEMENT ARTICLE

Abstract

1. Time-Trends and Predictors of Oral Disease Modifying Drug Treatment for Multiple Sclerosis

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Background: The approval of new oral disease modifying drugs (DMD) – fingolimod, dimethyl fumarate (DMF), and teriflunamide– for relapsing forms of multiple sclerosis (MS) have expanded treatment options. However, data describing the use of these agents in routine clinical practice are limited.

Objectives: To describe time-trends and identify predictors of oral DMD treatment initiation and switching among privately insured MS patients.

Methods: Using insurance claims from a large commercial insurer, we identified a cohort of MS patients between 2009 and 2014. DMD initiation was identified among patients not using any DMDs for ≥ 6 months and DMD switching was identified among patients using an injectable DMD at the time of their index MS visit. Time trends in initiation and switching of oral DMDs were estimated as proportions of total DMD initiations and switches among new and prevalent DMD users, respectively. To evaluate predictors, oral DMD initiators and switchers were matched on calendar time (± 90 days) to injectable DMDs initiators and switchers to a second injectable DMD, respectively. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for predictors measured up to the sampling date.

Results: Our cohort included 7,576 DMD initiations and 1,342 DMD switches, of which oral DMDs accounted for 6% and 39%, respectively. Oral DMD initiation and switching steadily increased from 5% to 16% and 35% to 84%, respectively, between 2011 and 2014. DMF was the most widely used oral agent accounting for roughly 60% of the total oral DMD use. A history of infections predicted oral DMD initiation (OR 1.55, 95% CI 1.08-2.22) and switch (OR 1.56, 95% CI 0.99-2.24). A neurologist visit significantly predicted oral DMD initiation (OR 1.47, 95% CI 1.09-1.99), but not switching.

Conclusions: Oral DMDs have been widely adopted in routine clinical practice as alternatives to injectable DMDs. Only select claims-based factors predicted use of oral DMDs, implying that their use may be driven in part by patient preferences. Rapidly increasing use of oral DMDs highlights the need for future research examining their comparative effectiveness and safety.

2. Drug Utilization Patterns in Relapsing-Remitting Multiple Sclerosis: A Population-Based Cohort Study

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Background: Over the past five years several new drugs have become available for relapsing-remitting multiple sclerosis (MS) patients. Until recently, conducting conclusive drug utilization (DU) studies in therapeutic areas involving both outpatient and inpatient drugs has been difficult, but the regional healthcare data warehouse of Stockholm County (VAL) may facilitate such studies.

Objectives: The objective was to describe DU patterns in MS over the past five years using VAL.

Methods: This was a population-based cohort study of all treatment-naïve MS patients in Stockholm County who started on MS drugs from 1 January, 2011, until 31 December, 2015. MS drugs available during the period were interferon-β-1a and -1b, peginterferon-β-1a, glatiramer acetate, natalizumab, alemtuzumab, fingolimod, teriflunomide, dimethyl fumarate (DF), and rituximab used off-label. All data were derived from VAL. Patients were followed from starting on the first MS drug until the earliest of: emigration, death or latest data collection date. The choice of the first-, second- and subsequent-line drug, switching and discontinuation rates were the outcomes. Descriptive statistics were used to summarize the data.

Results: The study population comprised 697 patients (mean follow-up 2.8 years). Before the introduction of DF in May 2014, interferon-β-1a (Avonex) was the most commonly used first-line drug (58%). Of patients initiating therapy from May 2014 to December 2015 (n = 201), 57% started on DF. Overall, throughout the study period, 37% continued on the first MS drug, 14% discontinued and did not restart, and 49% switched (37% one-time and 12% multiple-time switchers). Of those who switched, 29% switched to DF, 21% to rituximab, 21% to natalizumab, and 12% to fingolimod. The most commonly used subsequent-line drugs were rituximab (57%) and natalizumab (23%).

Conclusions: DU patterns in MS have changed considerably over the past five years. The use of interferon-β-1a declined and a rapid DF uptake was due to first-line use and switching from other treatment options. A substantial off-label use of rituximab in MS patients warrants further studies of its effectiveness and safety in this population.

3. Psoriasis Patients New to Specialist Care in Sweden 2007-2009: A Two-Year Follow-Up of Treatment Allocation

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Background: Treatment allocation to patients with psoriasis is a process that has not been thoroughly elucidated in large populations.

Objectives: To examine which factors predict choice of conventional (non-biologic systemic) or biologic treatment.

Methods: A cohort study on patients with a main diagnosis of psoriasis in the National Swedish Patient Register between 2007 and 2009, without such diagnosis since 2001.

Treatment before and after the first diagnosis was assessed by cross-linkage with the National Prescribed Drug Register.

In order to analyze patients naïve to systemic treatments used in psoriasis, patients with such treatment before the first diagnosis of psoriasis were not included.

Two Cox' proportional hazards models were fitted for the remaining 24,411 patients, giving Hazard Ratios (HR) with 95% confidence intervals (CI) for the two outcomes i) start of conventional systemic treatment, and ii) start of biologic treatment.

Adjustments were made for sex, age, residency in metropolitan area, level of education, presence of psoriatic arthritis, and quantity of topical treatment dispensed on prescription during the year prior to follow-up.

Results: Systemic treatment was initiated in 2,582 (10.6%) and biologic in 197 (0.8%) patients during up to two-years of follow-up.

Residency in a metropolitan area was associated with start of biologic treatment: HR 1.9 (CI 1.4-2.5), whilst start of conventional treatment was not: HR 1.0 (CI 0.9-1.1).

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University education was associated with the two treatments similarly: biologic treatment HR 1.6 (CI 1.0-2.4); conventional: HR 0.8 (CI 0.7-0.9).

Quantity of dispensed topical treatment was positively associated with both treatments: the HR's increased with increasing quantity.

Female sex was negatively associated with start of both biologic and conventional treatment, albeit non-statistically so for the former: HR 0.8 (CI 0.6-1.1) and HR 0.8 (CI 0.7-0.9), respectively.

Conclusions: In the choice of treatment for psoriasis - a choice between inexpensive conventional and costly but efficient biological treatment - non-medical factors play an important role. Equal access for all to the best treatment is not at hand.

4. Cardiovascular Medication Utilization by Educational Level Among Heart Failure Patients: A Population-Based Cohort Study in the Lazio Region, Italy

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Background: Medications play a key role in the treatment of heart failure (HF), reducing mortality and hospitalizations. Angiotensin-converting enzymes inhibitors (ACEIs), Angiotensin-Receptor Blockers (ARBs) and beta-blockers have been shown to decrease the risk of death and rehospitalisation and should be considered in every patient. Low socio-economic position (SEP) is associated with increased HF morbidity and mortality but the relationship between SEP and HF medication adherence remains uncertain.

Objectives: To investigate differences in utilization to evidence-based therapy with ACEIs/ARB and beta-blockers by educational level in a population-based cohort of patients with HF.

Methods: Using regional Health Information Systems we identified patients (≥35 yrs) newly discharged with HF between 01/01/2010 and 12/31/2013. We estimated the proportion of patients receiving at least two prescriptions of ACEIs/ARBs and at least one prescription of beta-blockers during the year after discharge by educational level. Multivariate logistic regression analysis was used to identify factors associated to HF medication use.

Results: The study population included 30,886 patients, 51% were female, and 59% aged ≥75 years; 8% did not have formal education while 3% attained a post-secondary degree. Overall, 48% filled at least two prescriptions of ACEIs/ARBs and at least one prescription of beta-blockers in the year after discharge (38% and 54% among uneducated and with the highest educational level, respectively). Patients without formal education were less likely to have prescriptions for ACEIs/ARB and beta-blockers compared with those with a post-secondary degree (OR: 0.81; 95% CI 0.69-0.95). Additionally, females and older patients (≥65 years) had a lower probability to receive HF evidence-based therapy.

Conclusions: Preliminary findings from this study suggest inequity in access to evidence-based therapy with ACEIs/ARB and beta-blockers among HF patients, based on education, gender, and age. Adherence to appropriate HF medication therapy and determinants of adherence will be investigated.

5. Influenza Vaccination Uptake Among Adult Asthma Patients in the United States

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Background: The Advisory Committee on Immunization Practices (ACIP) classified asthma patients as a high-risk population of developing severe influenza-related complications. Little is known about how adults with asthma or health care providers recently comply with influenza vaccination recommended by the ACIP.

Objectives: The objectives of this study were to assess influenza vaccination uptake, to examine racial and ethnic disparities and to identify influential factors on influenza vaccination status among adults with asthma in the United States.

Methods: Data from the 2011-2013 Behavioral Risk Factor Surveillance System were analyzed to estimate national prevalence of self-reported influenza vaccination uptake among patients aged 18-64. Multivariate logistic regression was used to calculate odds ratios for flu vaccination, adjusted for demographics, social-economic status (e.g., level of education) and various health related characteristics (e.g., perceived health).

Results: 44,680 asthma patients were included (representing 24,625,862 individuals). Between 2011 and 2013, unadjusted influenza vaccination rate was 41.41% among adults with asthma. The proportion of asthma patients receiving a flu shot increased slightly from 2011 (41.55%) to 2013 (42.33%). Logistic regression analyses showed that White Americans were 26.6% more likely to receive a flu shot (odds ratio (OR) = 1.26; 95% CI = 1.12-1.43) versus African American. Compared to Hispanics, White Americans had 18.2% (OR = 1.18; 95% CI = 1.01-1.38) higher odds for being vaccinated. Individuals with any type of health insurance (OR = 1.63; 95% CI = 1.44-1.86) and with a primary health care provider (OR = 1.89; 95% CI = 1.66-2.15) had an increased likelihood of vaccination.

Conclusions: Although there was a trend toward increases in influenza vaccination in patients with asthma, the rates were far below from recent Healthy People targets of 90%. This study found significant racial disparities in influenza vaccination uptake in adults with asthma. In addition to race, having any type of health insurance and the availability of a PCP significantly increased the likelihood of receiving influenza vaccination.

6. The Impact of a Blood Glucose Test Strip Quantity Limit Policy on Clinical Outcomes

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Background: In August 2013, the Ontario Public Drug Program in Canada introduced a policy limiting the number of blood glucose test strips (BGTS) reimbursed annually based on an individual's diabetes therapy, aligned with Canadian Diabetes Association guidance. The policy led to a 22% reduction in utilization and related costs in the year after its implementation, resulting in a one-year savings of $23.9 million. The clinical impact of this policy is unknown.

Objectives: To evaluate the impact of the BGTS quantity limit policy on diabetes-related clinical outcomes.

Methods: We conducted a population based cross-sectional time series analysis between April 1, 2008 and March 31, 2015 among public drug plan beneficiaries aged 19 and older who were dispensed BGTS. We measured rates of emergency department (ED) visits for hyperglycemia and hypoglycemia, mean HbA1c values and rates of physician visits quarterly, stratified by age (19-64, 65+). A sensitivity analysis was performed among high users of BGTS who exceeded the quantity limits in the year prior to the policy, since we anticipate this group is most likely to be impacted by restricted BGTS access. We used interventional autoregressive integrated moving average (ARIMA) models with a ramp function to assess the impact of the policy on outcomes.

Results: Rates of ED visits for hyperglycemia and hypoglycemia decreased among patients aged 19-64 (by 40.0% and 15.6%, respectively) and aged 65+ (by 55.2% and 37.2%, respectively) over the study period, however these rates were not influenced by the BGTS quantity limit policy ($p>0.05$ for each outcome). Mean HbA1c values ranged on average between 7.0 and 7.5 over the study period, and were also not influenced by the policy ($p>0.05$ for all comparisons). Rates for all remaining outcomes were stable over the study period ($p>0.05$ for all outcomes). Our findings were consistent in our sensitivity analysis of high users of BGTS ($p>0.05$ for all comparisons).

Conclusions: Our findings suggest no adverse outcomes for patients following the implementation of a BGTS quantity limit policy. Further monitoring of outcomes over a longer follow-up period is warranted to confirm the long-term impact of the policy.

7. Risk Minimization Evaluation in a Distributed Data Network – An IMEDS Evaluation Pilot Assessment of the 2010 Class Label Change for Proton Pump Inhibitors

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Background: Evaluation of risk minimization (RM) actions is an emerging area of regulatory science.

Objectives: We used publicly-available Sentinel analytic tools for a RM evaluation of the 2010 class-wide proton-pump inhibitors (PPIs) label change that warned of a potential increase risk of bone fracture, recommended using PPIs for the lowest dose and shortest duration, and to manage bone status for those at risk for osteoporosis (OP).

Methods: The cohort consisted of adults aged >=18 yr prescribed PPIs; incident (no PPI claim in >=183d) and prevalent users were evaluated separately. Patients with fracture risk factors were excluded.

Users of the 8 PPIs noted in the label change were defined using National Drug Codes in outpatient pharmacy claims. Outcomes evaluated PRE (1Jan07-31May10) and POST (1Jun10-30Apr15) label change were: number of PPI users overall; mean duration of PPI use; proportions of PPI use: ≥1 yr; at low/high doses; with incident fractures; and OP screening or interventions.

Nine Sentinel data partners participated. Feasibility data informed use of more complex analyses. Consistent with typical FDA use of these tools, analyses did not include direct comparisons or statistical testing, but include rates and proportions stratified by age, sex, and year.

Results: There were 1,488,869 and 2,224,420 incident PPI users in the PRE and POST periods, respectively. The proportion of use ≥1 yr decreased across periods (7.8% vs. 7.0%), as did days supplied/user from 130.4 to 113.7 d among all users, and from 830.8 to 645.4 d among users ≥1 yr. OP screening and interventions did not appear to increase (data not shown), but the proportion of patients with fractures decreased (4.4% vs. 3.1%). Results were similar for prevalent users.

Conclusions: This analysis demonstrated the ability to use Sentinel tools to assess the effectiveness of RM actions. Limitations include lack of confounding control, simple descriptive analysis techniques, and several outcomes were defined only by diagnosis or medication code. The results show the potential value of a large distributed data network in assessing RM effectiveness.

8. The Impact Of Risk Minimisation Measures On The Incidence And Prevalence Of Use Of Strontium Ranelate At The Population Level: Preliminary Results Of A Multi-National Cohort Study Including 5 European Countries

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Background: Concerns on strontium ranelate (SR) cardiovascular safety have recently led to risk minimisations measures (RMM), imposed by the EMA in April 2014.

Objectives: To determine the prevalence and incidence of SR use before and after the imposition of new RMM at the European population-based level.

Methods: Setting and Design: Population-level, electronic medical records-based, multi-database, multinational (Denmark, Italy, Netherlands, Spain, UK), cohort study.

-Follow-up: from (latest of) start of study period or 1 year of valid data, until (earliest of) moving out, death or date of last data extraction.

-Study periods: Reference (January 2004 -may 2013), Transitional (june 2013-march 2014) and Assessment (from april 2014 onwards).

-Exposure: RMMs as imposed by EMA in April/2014.

-Outcomes: Use (prescription/dispensation) of SR.

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-Statistical analysis: Incidence (IR) and average monthly prevalence rates of SR use in each study period were computed, overall and stratified by age, gender, and country.

Results: Over 114.8 million person-years (py) of data were included. 73,157 SR users were identified (89.6% women). The overall IR of SR use in the reference period was 7.19/10,000 py [95%CI 7.19 to 7.19]), subsequently decreased by almost 75% in the transition (IR 1.82 [1.82 to 1.82]), and further (by >95%) in the assessment period (IR 0.34 [0.34 to 0.34]). Similarly, prevalence rates decreased from 63.68/10,000 py [95%CI 63.42 to 63.94] to 51.01 [49.14 to 52.88]) in the transition, and then by almost 80% in the assessment period: 13.34 [12.93 to 13.76]. Similar trends were observed after stratification by country, age, and gender (data not shown).

Conclusions: The newly imposed RMM measures have had a substantial impact on the use of SR in 5 European countries, with overall reductions of >95% in incidence and almost 80% in prevalence in the community. Further data and statistical testing for significance are needed to characterise the sustained effect of these RMM measures in the coming years.

9. Evaluating Patient Knowledge of Risks and Safe Use of Xarelto (Rivaroxaban)

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Background: \Rivaroxaban is an oral direct Factor Xa inhibitor approved in Europe in 2011 for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation and treatment of deep vein thrombosis (DVT), and for prevention of recurrent DVT and pulmonary embolism following an acute DVT in adults. As part of a safety risk management plan revision, a prescriber guide and patient alert card (PAC) were distributed in Europe to provide education on key safety information.

Objectives: To measure whether patients received and used the PAC and evaluate their knowledge of the key safety messages.

Methods: This study was conducted in the United Kingdom, Germany, France, and Spain. Patients were identified through a diverse sample of medical sites. Physicians invited patients who had taken rivaroxaban in the last 3 months to complete questionnaires on their knowledge of key safety information for rivaroxaban.

Results: A total of 427 patients (90% of the total invited) were included in the analysis. Approximately half of patients (47%) reported having received the PAC. Among those patients, 81% reported reading the card, with 85% keeping the card with them some (14%) or all (71%) of the time. Most patients reported they show it to every doctor or dentist they visit. Eighty percent were aware of the most important risk (i.e., anticoagulants can cause bleeding). Knowledge was generally high > 85% correct) for questions about the indication for treatment, when to consult with their doctor, and when to inform other physicians they are taking rivaroxaban. A lower percentage of patients (60%) correctly reported that rivaroxaban should be taken with food. Fewer than half of patients (43%) knew that they should not miss a dose of rivaroxaban in order for it to be effective in preventing thromboembolic events. Knowledge about the signs or symptoms of bleeding varied by symptom, with the highest correct response proportion (61%) for unusual bruising and the lowest (18%) for pain.

Conclusions: The observed patterns of knowledge are as expected with highest levels of patient knowledge on the most important risks and safe-use conditions.

10. An Association Between Beliefs About Medicines and Drug Non-Adherence in Patients with Chronic Diseases in China

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Background: Non-adherence to medications is a global problem in chronic disease management. Patient's beliefs about medicines measured by the Beliefs about Medicines Questionnaire (BMQ) have been associated with medicine non-adherence in numerous studies conducted outside of China.

Objectives: To investigate what is the current medicine belief and whether medicine belief is associated with medication adherence in patients with chronic diseases in China.

Methods: A cross-sectional study was conducted in two large urban hospitals in Hefei and Tianjin, China. Patients were hospital inpatients and outpatients recruited between January 2014 and September 2014 (313 stroke patients, 315 diabetic patients and 339 rheumatoid arthritis (RA) patients). They completed a questionnaire consisting of demographic and information, the Beliefs about Medicines Questionnaire (BMQ) including subscales measuring beliefs about medication used for patients' conditions (stroke/diabetes/RA) and beliefs about medicines in general, the perceived sensitivity to medicines scale (PSM) and the medication adherence report scale (MARS). Medication adherence was measured by MARS. Non-adherence was defined as $<80\%$ adherence. The association between non-adherence and beliefs about medicines was assessed using a logistic regression model.

Results: 311 patients were non-adherent to their drug treatment [159 (51.0%) in the stroke group, 60 (26.7%) in the diabetes mellitus group and 62 (19.8%) in the RA group, $p<0.01$]. After adjusting for baseline characteristics, patients who had higher concerns about their medicines, believed that they were personally sensitive to the effects of medications, and had a weaker belief in the benefits of pharmaceutical medicine were typically more non-adherent (BMQ-Concern ORs, 1.35, 95%CI 1.07-1.71 and PSM OR 1.44, 95%CI 1.16-1.80).

Conclusions: The BMQ is a useful tool to identify non-adherent patients with stroke, diabetes mellitus and RA. In future, adherence intervention studies could use the BMQ to screen for patients who are at risk of non-adherence.

11. Improving Medicines Management at Patients Hospital Discharge

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Background: Continuum of medicine management and clinical handover is a major risk in the Australian health system.

Objectives: Examine how medicines information is communicated from hospital to community, how it can be improved? Explore the implementation and sustainability of a new handover tool.

Methods: Intervention: Medicines Information Transfer Fax (MITF) provided by hospital pharmacists (HP) at discharge to community health practitioners.

Mixed method using explanatory sequential design conducted over 7-year period in 4 Tertiary Teaching Hospitals. Quantitative data (4 audits; accuracy and timeliness of Hospital Discharge Summary (HDS) ($n=76$), comparing severity of errors in medicines handover in HDS and MITF ($n=80$), selection of high risk patients by HP ($n=79$), and 2 surveys ($n=78$)) were analysed using Chi-square (CS). Qualitative data (workshop of 19 pharmacists, and survey of 47 Medical Practitioners and 31 Community Pharmacists) analysed thematically and interpretively.

Results: Quantitative results confirmed medicines information within the HDS was sub-optimum although improving over the study period. Accuracy within the HDS improved 11% (8/74) in 2009 to 77% (58/75) in 2014 ($CS=14.3$, $p=0.00015$). Timeliness of HDS improved; 45.9% (28/61) in 2009 to 60% (47/78) in 2014 ($CS=17.1$, $p=0.00036$). MITF accuracy improved: 93% (71/76) in 2009 to 98% (81/83) in 2014 ($CS=18.5$, $p=0.00017$). Timeliness showed a decrease from 100% (80/80) in 2009 to 93% (71/76) in 2014 ($CS=18.5$, $p=0.000017$). HP correctly identified high risk patients to receive MITF; 100% (79)

met high risk criterion indicating appropriate prioritization. Of community medical staff and pharmacists 42/47 (89%) and 25/31(80%) found the MITF useful. The workshop specified MITF as a valuable service and a standardized tool is beneficial. Limitations included staffing, time, and frustration with electronic systems. Community medical staff expressed a need for MITF to be independent of the HDS due to unacceptable time delays with the HDS.

Conclusions: A tool which included concise, informative, timely, accurate and trusted medicines information was developed. Success of the program was clear by end user satisfaction and sustainability.

12. Everyone Isn't Average: Quantifying Heterogeneity in Crohn's Disease Patients' Benefit-Risk Tradeoff Preferences

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Background: Health-technology assessment (HTA) models employ utility weights to quantitatively assess the benefit-risk balance of therapies but do not routinely account for heterogeneity in patients' preferences for different health states or therapy risks.

Objectives: To assess heterogeneity in patients' stated preferences for health states and medication-related risks relevant to Crohn's disease (CD).

Methods: An online stated-preference survey was administered to CD patients comparing two medical therapies for moderately active CD. Each treatment option was characterized by differing levels of: time with active disease symptoms, severity of symptoms, duration of therapy with steroids, and risks of serious infection, cancer, and need for surgery. Latent-class choice models identified groups of patients with similar treatment-outcome preferences.

Results: Among 811 respondents, latent -class analysis demonstrated three distinct groups whose choices were strongly influenced by: 1) duration of active symptoms (61%), 2) duration of steroid use (25%), or 3) avoidance of risks of cancer, infection or surgery (14%) when choosing a therapy. Class membership was significantly correlated with disease history, current symptoms and having a family member with cancer. The more risk-tolerant participants who prioritized reducing time with active symptoms were more often under age 44 ($p<0.001$) and were more likely to be men ($p<0.001$).

Conclusions: Substantial heterogeneity exists among CD patients' preferences for medication efficacy and potential harms. Avoiding the ecological fallacy of assuming all patients have mean-value preferences could result in significant differences in the conclusions of HTA models evaluating benefits and risks of alternative therapeutic options.

13. Clinical Outcomes Of Concomitant Use Of Warfarin And Selective Serotonin Reuptake Inhibitors

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Background: Patients treated with warfarin are often co-prescribed selective serotonin re-uptake inhibitors (SSRIs) for co-existing depression. The SSRIs, fluoxetine and fluvoxamine, are potent CYP2C9 inhibitors that may increase warfarin plasma concentrations and subsequently, lead to increased risk of bleeding or decreased risk of thrombosis.

Objectives: To examine whether treatment with warfarin and a SSRI that is a potent CYP2C9 inhibitor has higher rates of bleeding or lower rates of thrombosis.

Methods: We identified warfarin initiators who had a subsequent SSRI prescription in 5 US claims databases. Patients were followed from the date of SSRI use for as long as they were exposed to both warfarin and their index SSRI groups up to 180 days. Stratified Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for hospitalized bleeding events, thrombosis events, and mortality comparing patients treated with SSRIs that are potent CYP2C9 inhibitors (fluoxetine, fluvoxamine) to those treated with SSRIs that are

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non-potent CYP2C9 inhibitors after variable-ratio propensity score matching.

Results: The eligible cohort comprised 52,129 patients, with a total of 822 bleeding events, 1,169 thrombosis events, and 766 deaths. 8,011 (15%) used SSRIs that are potent CYP2C9 inhibitors. HRs comparing patients treated with SSRIs that are potent CYP2C9 inhibitors to those treated with SSRIs that are non-potent CYP2C9 inhibitors were 1.14 (95% CI, 0.94-1.38) for bleeding events, 1.03 (95% CI, 0.87-1.21) for thrombosis events, and 0.90 (95% CI, 0.72-1.14) for mortality. Results were consistent across individual component outcomes, different warfarin stabilization periods, and subgroup analyses.

Conclusions: Patients concomitantly treated with warfarin and SSRIs that are potent CYP2C9 inhibitors had comparable rates of bleeding events, thrombosis events, and mortality as patients treated with warfarin and SSRIs that are non-potent CYP2C9 inhibitors. SSRI inhibition of CYP2C9 does not appear to affect the safety or effectiveness of warfarin treatment in clinical practice.

14. Propranolol Use and Survival from Breast Cancer: A Pooled Analysis of 133,251 Breast Cancer Patients from the European Cancer Pharmacoepidemiology Network

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Background: Preclinical studies have demonstrated that propranolol inhibits several pathways involved in breast cancer progression and metastasis.

Objectives: We investigated whether breast cancer patients who used propranolol, or other non-selective beta-blockers, had reduced breast cancer-specific or all-cause mortality in eight European cohorts.

Methods: Incident breast cancer patients were identified from eight cancer registries and compiled through the European Cancer Pharmacoepidemiology Network. Propranolol and non-selective beta-blocker use was ascertained for each patient. Breast cancer-specific and all-cause mortality were available for five and eight cohorts, respectively. Cox regression models were used to calculate hazard ratios (HR) and 95% confidence intervals (CIs) for cancer-specific and all-cause mortality by propranolol and non-selective beta-blocker use. HRs were pooled across cohorts using meta-analysis techniques. Dose-response analyses by number of prescriptions were also performed. Analyses were repeated investigating propranolol before cancer diagnosis.

Results: The combined study population included 133,251 breast cancer patients. Overall, there was no association between propranolol use after diagnosis of breast cancer and breast cancer-specific or all-cause mortality (fully adjusted HR = 0.94, 95% CI, 0.77, 1.16 and HR = 1.09, 95% CI, 0.93, 1.28, respectively). There was little evidence of a dose-response relationship. There was also no association between propranolol use before breast cancer diagnosis and breast cancer-specific or all-cause mortality (fully adjusted HR = 1.03, 95% CI, 0.86, 1.22 and HR = 1.02 95% CI, 0.94, 1.10, respectively). Similar null associations were observed for non-selective beta-blockers.

Conclusions: In this large pooled analysis of breast cancer patients, use of propranolol or non-selective beta-blockers was not associated with improved survival.

15. Statins and Reduced Risk of Liver Cancer: Evidence for Confounding

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Background: Several studies have reported a strong negative association between statin use and risk of liver cancer. While statins have anti-carcinogenic properties, this inverse association may suffer from confounding by indication (high cholesterol) or contraindication (liver disease).

Objectives: To examine the association between statins and liver cancer risk, after accounting for potential confounding by laboratory measures of cholesterol and liver enzymes (to our knowledge, not done previously).

Methods: We conducted a case-control study within Kaiser Permanente Northern California (KPNC), an integrated health care system. The study was restricted to adults with pharmacy benefits and no history of cancer. The cancer registry was used to identify diagnoses of primary liver cancer. Each case of liver cancer (n = 2,877) was matched to up to 50 controls (n = 142,850) on age, sex, and length of health plan membership. Pharmacy records were used to identify statin prescriptions. Data on cholesterol and liver enzymes, as well as other covariates, were obtained from electronic health records. We used conditional logistic regression to calculate adjusted odds ratios (ORs) for the association between statins and liver cancer risk. We then used restriction and adjustment to examine whether the association was confounded by levels of cholesterol or liver enzymes.

Results: Before restricting on and adjusting for cholesterol and liver enzymes, there was a strong inverse association between statins and liver cancer risk; the adjusted OR for 18+ statin prescriptions vs. 0 prescriptions was 0.41 (95% CI 0.35-0.49), similar to previous findings. The OR for 18+ prescriptions rose to 0.87 (95% CI 0.55-1.39) after restricting to individuals with a first elevated cholesterol level not preceded by statin use. After restricting to those with a liver function test within 1 year of the elevated cholesterol and adjusting for enzyme levels, the negative association with statins disappeared for prescription categories 3-7, 8-17, and 18+, with OR = 1.21 (95% CI 0.53-2.75) for 18+ prescriptions.

Conclusions: Our findings cast doubt on the causality of the frequently observed inverse association between statins and liver cancer.

16. Acute Liver Injuries and Antiarrhythmic Drugs: A Case-Referent Study from the PGRx Surveillance System on Medicine Use

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Background: Spontaneous reports of acute liver injury (ALI) in patients using dronedarone triggered an alert by the EMA in 2011.

Objectives: To assess the risk of ALI with class III antiarrhythmic drugs controlling for other potential ALI-inducing drugs.

Methods: All consecutive cases of ALI aged ≥50 years were identified in hepato-gastroenterology centres across Germany (September 2010-February 2014). ALI was defined as a new increase ≥3 times the upper limit of normal (ULN) for at least one of the transaminases or ≥2 times the ULN if alkaline phosphatase ≥2 times the ULN, with (definite case) or without (biochemical case) suggestive signs and symptoms assessed by a panel gastroenterologist blind to drug exposure. Each case was matched for gender, age and date of recruitment to a set of community controls without liver disorder recruited by general practitioners. Drug exposure was assessed up to two years prior to the index date (ALI onset for cases, recruitment date for controls) using telephone standardised interviews to patients validated against physicians' prescriptions. Conditional logistic regressions were controlled for co-medication and for a ALI risk score that included body mass index, smoking, alcohol consumption and diabetes.

Results: 252 cases (136 definite and 116 biochemical) were matched to 1,081 controls, of which 59.1% were females with a mean age of 63.9 years. A high risk score for ALI (fourth quartile) was observed in 32.5% and 22.3% of cases and controls, respectively. Any exposure to class III antiarrhythmic drugs was 4.0% in cases and 1.5% in controls for an adjusted Odds ratio (OR) of 3.61 (95% confidence interval (CI): 1.56 – 8.35). Associations with exposure to dronedarone and amiodarone were respectively 3.13 (95% CI: 0.66 – 14.78) and 5.90 (1.74 – 20.00). Restriction to definite ALI cases did not change these results.

Conclusions: Class III antiarrhythmic drugs were associated to ALI and results were robust to case definitions. This study could not rule out a bias by indication which would not, in itself, explain the results. Continued vigilance must be enforced with the use of this class of drugs.

17. Association of Idiopathic Inflammatory Myositis with Statin Exposure: A Population Based Case Control Study

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Background: Statins are widely prescribed for cardiovascular risk reduction. The muscular adverse effects associated with statin use, including myalgia and rhabdomyolysis are well recognised. Idiopathic inflammatory myositis is a rare, severe, debilitating condition, most commonly presenting with painless proximal limb girdle weakness. It requires aggressive immunosuppressive therapy and may result in permanent disability and even death. The relationship between statin use and idiopathic inflammatory myositis is less certain.

Objectives: To examine the association between histologically confirmed idiopathic inflammatory myositis and prior exposure to statins.

Methods: A retrospective case control study was conducted between 1990 and 2014 of all histologically confirmed cases of inflammatory myositis in adults aged 40 years and older from the South Australian Myositis Database. Data on exposure to statins were obtained from medical records and compared to population-based controls matched 3:1 on age (within two years) and gender from the North West Adelaide Health Study. The prevalence and odds ratio (95% CI) for statin exposure were calculated.

Results: A total of 221 cases and 662 controls were included in the study. Polymyositis (n = 87, 39.4%), was the most common type identified, followed by inclusion body myositis (n = 66, 29.9%), dermatomyositis (n = 26, 11.8%), necrotising myositis (n = 24, 10.9%) and non-specific chronic inflammatory myositis (n = 18, 8.1%). A total of 30.8% of cases were exposed to statins, compared to 21.6% controls. Exposure to statins was associated with an OR 1.6 (95% CI 1.15-2.27, $p<0.001$) and stratification of the analysis by time of exposure the OR increased to 2.11 (95% CI 1.33-3.35, $p = 0.0015$).

Conclusions: Patients with histologically confirmed inflammatory myositis had an increased likelihood of prior statin exposure compared with general population. This warrants further investigation in view of the increasing population exposure to statins and the severity of the disease outcome.

18. Confounding of the Association Between Statins and Parkinson Disease: Review and Meta-Analysis

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Background: Both statins and higher serum cholesterol have been reported to reduce the risk of Parkinson disease (PD). Accounting for baseline cholesterol levels is therefore necessary to avoid confounding by indication in observational studies of the association between statins and PD; however, it is not routinely done.

Objectives: To conduct a systematic review and stratified meta-analysis of epidemiologic studies to assess the impact of cholesterol adjustment on the association between statins and PD.

Methods: We systematically searched the Medline (through June 2015) for studies that reported

quantitative estimates of the association between statins and incident PD. Random-effects meta-analysis was used to assess the effect of statins on PD separately among studies that adjusted for either cholesterol or hyperlipidemia and studies that did not. Studies with possible bias due to reverse causation, immortal time bias, and outlying results were excluded in sensitivity analyses.

Results: Ten eligible studies were identified. Among the six studies that did not adjust for cholesterol, a protective effect of statins was observed (relative risk [RR], 0.75; 95% confidence interval [CI] 0.60-0.92). Excluding studies with possible bias due to reverse causation and stratifying on study design did not affect the results. No protective effect was observed among the four studies that adjusted for either cholesterol or hyperlipidemia (RR, 0.91; 95% CI, 0.68-1.22). The effect estimate increased to 1.04 (95% CI, 0.68-1.59) when a study with immortal time bias was excluded. Significant heterogeneity in results was observed in both groups ($I2 = 92\%$ and 75%, for cholesterol-unadjusted and adjusted group, respectively). Begg's funnel plot and Egger's test (p-value for bias = 0.01) suggested possible publication bias; however, the number of studies was small and other factors, such as true heterogeneity and poor methodological design of individual studies, could be responsible for the asymmetry.

Conclusions: The apparent protective effect of statins on risk of PD is at least partially, if not fully, explained by confounding by statin indication.

19. Ondansetron Use Among Pregnancies Identified In The Sentinel Distributed Database

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Background: Ondansetron is a selective 5HT-3 receptor antagonist approved for prevention of nausea and vomiting (NV) associated with chemotherapy, radiotherapy, and post-operatively. Ondansetron is not approved for NV in pregnancy (NVP), yet it is commonly prescribed. Recent reports of possible ondansetron-associated congenital malformations prompted a review of ondansetron use for NVP.

Objectives: To assess ondansetron use in pregnancy in the context of other antiemetics among a large insured U.S. population of women delivering live births.

Methods: We assessed ondansetron and other antiemetic use among pregnant women delivering live births from 2001-2014 using administrative healthcare data contributed by 15 data partners to the Sentinel Distributed Database. This retrospective pregnancy cohort consists of a primarily commercially insured U.S. population. Pregnancies ending in live birth were identified using a previously validated algorithm. All forms of ondansetron and two other common antiemetics, promethazine and metoclopramide, were identified using National Drug Codes. We calculated the prevalence of anti-emetic use by trimester and calendar year.

Results: In a population of over 2.1 million pregnancies, the prevalence of ondansetron, promethazine, or metoclopramide use anytime in pregnancy was 14.5%, 10.8%, and 4.1%, respectively. Ondansetron use increased from $<1\%$ of pregnancies in 2001 to 22.1% of pregnancies in 2014, with much of the increase attributable to oral ondansetron beginning in 2006. Promethazine use increased modestly between 2001 (13.8%) and 2006 (16.0%) but decreased annually after 2006 to 8.5% in 2014. A similar trend was observed for metoclopramide, with the highest use in 2006 (6.0%) and decreasing annually to 3.4% in 2014. For all antiemetics, use was highest in the first trimester and decreased in the second and third trimesters.

Conclusions: Recent data suggest nearly one-quarter of insured U.S. pregnant women received ondansetron sometime during their pregnancy. This off-label use continues despite reports of possible adverse fetal outcomes and the availability of an FDA-approved product for management of NVP.

20. Use Of Antibiotics During Pregnancy And The Risk Of Spontaneous Abortion

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Background: Although antibiotics are widely used during pregnancy, evidence regarding their fetal safety remains limited.

Objectives: To assess the association between the use of antibiotics classes and types and the risk of spontaneous abortion (SA) taking into account indication of use.

Methods: We conducted a nested case-control study within the Quebec Pregnancy Cohort (1998-2009). Planned abortions and pregnancies exposed to fetotoxic drugs were excluded. SA was defined as having a diagnosis or procedure related to SA before the 20th week of pregnancy. Index date was defined as the gestational age of the SA. Ten controls per case were randomly selected and matched on index date and calendar year of pregnancy. Use of antibiotics was defined by filled prescriptions between the 1st day of gestation until index date and was compared to i) non-exposure, and to ii) exposure to penicillin/cephalosporins.We also studied each specific type of antibiotics separately using the same comparator groups. Conditional generalized estimation equation (GEE) regressions were used to estimate crude and adjusted odds ratios (OR), and 95% confidence intervals (95%CI), taking into account the indications and other potential confounders.

Results: Adjusting for potential confounders, use of azithromycin (aOR 1.65, 95%CI 1.34-2.02, 110 exposed cases) and clarithromycin (aOR 2.35, 95%CI 1.90-2.91, 111 exposed cases) were associated with an increased risk of SA. Use of tetracyclines and quinolones had similar impact on the risk of SA suggesting a class effect (aOR 2.59, 95%CI 1.97-3.41, 67 tetracycline exposed cases; aOR 2.72, 95%CI 2.27-3.27, 160 quinolone exposed cases). Sulphonamide (aOR 2.01, 95%CI 1.36-2.97; 30 exposed cases), and metronidazole (aOR 1.70, 95%CI 1.27-2.26; 53 exposed cases) were also increasing the risk of SA. Similar results were found when using penicillin/cephalosporins as comparator group.

Conclusions: Macrolides excluding erythromycin as well as quinolones, tetracyclines, sulfonamides and metronidazole use during early pregnancy were associated with an increased risk of SA even after taking into account maternal infections.

21. Pregnancy Outcomes in Women with Chronic Hypertension Initiated on Labetalol versus Methyldopa

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Background: Labetalol and methyldopa are first-line antihypertensive medications for the treatment of chronic hypertension in pregnancy. There are few comparative data regarding the effect of these medications on pregnancy outcomes to guide clinicians in the choice of agent.

Objectives: To compare hypertension-related pregnancy outcomes in women with chronic hypertension initiated on labetalol versus methyldopa.

Methods: We used a cohort of completed pregnancies linked to liveborn infants of women with chronic hypertension enrolled in Medicaid from 2000 to 2010 who were not using antihypertensive medications prior to pregnancy. We identified women who initiated treatment with either labetalol or methyldopa from the last menstrual period to week 20 of pregnancy. Pregnancy outcomes assessed included preterm delivery, preeclampsia, placental abruption, maternal end-organ injury, small for gestational age (SGA), and neonatal ICU admission. Propensity score stratification was used to control for potential confounders including maternal demographics, co-morbid conditions, timing of antihypertensive initiation, and proxies for the severity of hypertension.

Results: 742 women initiated labetalol and 1497 methyldopa; the median duration of treatment prior to the start of follow-up (week 20) was similar in both groups (42 vs. 40 days). In those who initiated labetalol versus those who initiated methyldopa, the proportion with preterm delivery was 30.9% vs. 25.5%, preeclampsia was 27.8% vs. 24.0%, placental

abruption was 1.9% vs. 1.9%, maternal end-organ injury was 5.5% vs. 3.2%, SGA was 44.3% vs. 36.3%, and neonatal ICU admission was 13.5% vs. 10.0%.

The adjusted RR (95% CI) for preterm delivery was 1.08 (0.94 to 1.23), for preeclampsia 1.08 (0.94 to 1.25), for placental abruption 0.87 (0.47 to 1.63), for maternal end-organ injury 1.68 (1.12 to 2.51), for SGA 1.17 (1.06 to 1.30), and for neonatal ICU 1.12 (0.89 to 1.40).

Conclusions: The risks of maternal end-organ injury and SGA were significantly elevated in women who initiated labetalol compared to methyldopa, suggesting that methyldopa may be the preferred antihypertensive for the treatment of chronic hypertension in pregnancy.

22. Risk Comparison for Prenatal Use of Different Analgesics and Selected Birth Defects

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Background: Previous research suggests that the use of opioid analgesics during early pregnancy increases the risk for certain birth defects, while the use of acetaminophen is not associated with an increase in risk.

Objectives: To compare use of analgesic medications to each other with respect to risk for selected birth defects.

Methods: We used data from the National Birth Defects Prevention Study (1997-2011), a population-based, multi-site case-control study. Exposure was based on self-reported maternal analgesic use from 1 month before to 3 months after conception (periconceptional period), excluding maternal reported pre-gestational diabetes, heroin or recreational opioid use, and exposure to known teratogens. We compared use of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or opioids to use of acetaminophen alone. To examine associations with 15 selected birth defects, adjusted odds ratios (aORs) were estimated using logistic regression controlling for maternal age, race/ethnicity, obesity, parity; periconceptional alcohol, smoking, antibiotic use; and study location.

Results: Among 40,040 mothers, 81% reported use of analgesic medications at any time in pregnancy, with 56% reporting use in the periconceptional period. Of the 16,450 case and 5,944 control mothers reporting periconceptional analgesic use, 48% of case (54% of control) mothers reported using acetaminophen as the only analgesic, 48% (42%) NSAIDs, 2% (2%) opioids, and 2% (1%) NSAIDs and opioids. NSAIDs were significantly ($p<0.05$) associated with 3 of 8 heart defects (range of aORs: 1.3-1.4) and 7 of 7 non-heart defects (aORs: 1.2-1.6); opioids were associated with 3 of 8 heart defects (aORs: 1.7-2.2); NSAIDs and opioids were associated with 2 of 8 heart defects (aORs: 2.5-2.7) and 3 of 7 non-heart defects (aORs: 2.0-2.7) evaluated.

Conclusions: Compared to periconceptional use of acetaminophen, use of NSAIDs and/or opioids appears to pose a greater risk of selected birth defects. Additional studies comparing the relative fetal safety of individual analgesics within these classes are needed.

23. High Exposure to Phthalates from Medications and Male Genital Malformations

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Background: Manufacturers may use various phthalates as inactive ingredients in orally administered pharmaceutical preparations. Some of these phthalates, such as dibutyl phthalate (DBP) cause male genital malformations in laboratory animals.

Objectives: To evaluate the association between prenatal exposure to specific phthalate containing

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medications, bisacodyl and mesalamine, and the risk of cryptorchidism and hypospadias in humans.

Methods: We used data collected between 1998 and 2015 as part of a multicenter case-control surveillance program of birth defects in North America, the Slone Epidemiology Center Birth Defects Study. Mothers were interviewed within six months of delivery about demographic, reproductive, medical and behavioral factors, and details of all medications used. We compared data on first trimester exposure to any oral bisacodyl or mesalamine products (with and without DBP) for 2,505 infants with male genital malformations (cases) with data on 11,113 infants without major malformations (controls). We estimated odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression.

Results: Among 10 cases exposed to bisacodyl, 4 were exposed to a DBP-containing product; among 12 cases exposed to mesalamine, 3 were exposed to a DBP-containing product. Use of any bisacodyl product was not associated with an increased risk of male genital malformations (OR = 0.9; 95% CI 0.5-1.8). However, bisacodyl containing DBP was associated with an increased risk (OR = 2.2; 95%CI 0.7-7.4) while DBP-free products were not (OR = 0.5; 0.1-1.6). Use of any oral mesalamine product during the first trimester was associated with an increased risk of male genital malformations (2.4; 1.2-4.9). In contrast to bisacodyl, the risk was elevated for products with (1.7; 0.4-6.3) and without (3.1; 1.3-7.2) DBP.

Conclusions: Given the wide confidence intervals due to the low prevalence of exposure to DBP-containing products, and the potential confounding by indication suggested by the association with mesalamine without DBP, the potential effect of DBP-containing pharmaceuticals on the risk of male-genital malformations warrants further study.

24. Language Development in 3 Year Old Children After Prenatal Exposure to Opioids

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Background: Limited information is available regarding the effect of prenatal exposure to opioids on long-term neurocognitive function in children. In Norway opioids have been reported to be the CNS acting drugs most frequently prescribed to pregnant women. The prevalence of use in Norway is about 3% of all pregnant women.

Objectives: The primary aim of the present study was to assess the effect of opioid exposure during pregnancy on language development in 3 year old children.

Methods: The Norwegian Mother and Child Cohort Study (MoBa) is a large prospective population-based pregnancy cohort consisting of 90 700 women and 108 000 children, constituting 40.6% of all invited pregnant women during the recruitment period (Norway: 1999-2008). A total of 45 211 women with 51 679 singleton pregnancies were included in this study.

MoBa participants reported medication use during pregnancy at week 17/18 and 30, and 6 months after birth, covering three periods in pregnancy (week 0-13, week 13-29 and week 29 to birth).

Language competence at three years of age was evaluated by a validated language grammar rating scale. The mother classified her child's language competence in one of six different categories; ranging from not yet talking to talking in long, completed sentences.

The data were analyzed by ordinal logistic regression.

Results: The women reported use of opioids in 892 pregnancies (1.7%). Of these, opioid use during one period only was reported in 720 pregnancies (1.4%), whereas drug use in at least two periods was reported in 172 (0.3%). Codeine was the dominating substance reported (89.6%), mostly in combination with paracetamol.

Opioid use did not seem to increase the risk of reduced language competence neither in unadjusted analyses, nor when adjusting for the confounding factors maternal work situation, paternal education, maternal BMI, parity, maternal smoking, and maternal SSRI and paracetamol use during pregnancy, and reported pain; adjusted OR = 1.04 (0.89-1.22).

Conclusions: In this large prospective study no significant association between prenatal use of opioids and language development at 3 years of age was found.

25. Serious Opioid Toxicity in Children with Non-Cancer Pain: A Retrospective Cohort Study

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Background: The use of opioids for non-cancer pain in children is increasing. However, little is known about opioid toxicity in this population.

Objectives: We set out to estimate the incidence of opioid toxicity and its relationship to dose and type of opioid in healthy children with non-cancer pain.

Methods: We studied a Tennessee Medicaid cohort of 424,382 children who filled 1,133,089 prescriptions for opioid analgesics, primarily for minor conditions. Children with serious diseases were excluded. The primary study endpoint was serious opioid toxicity, defined as an emergency department visit, hospitalization, or death attributed to opioid analgesic use. Medical records were reviewed to adjudicate the outcomes and Poisson regression models used to estimate toxicity as a function of dose and specific opioid.

Results: There were 365 confirmed cases of opioid toxicity with an incidence rate of 19.5/1,000,000 patient-days and 74.5% of the cases were related to therapeutic use of opioids. Neuropsychiatric, gastrointestinal, central nervous system and dermatologic symptoms accounted for most cases. Children filling prescriptions for tramadol (incident rate ratio (IRR) = 3.06, 95% confidence interval (CI) 2.02-4.64) or oxycodone (IRR = 1.88, 95% CI 1.19-2.95) had a higher risk of toxicity compared to children filling prescriptions for codeine. The risk increased with increasing doses of opioid. Children taking morphine-equivalent doses in the highest tertile had an 84% higher risk of toxicity than those in the lowest tertile (IRR = 1.84, 95% CI = 1.35-2.50).

Conclusions: In a cohort of children without an underlying serious disease who received opioid analgesics primarily for minor, self-limited conditions, the incidence of opioid toxicity was 19.5/1,000,000 patient-days. Higher doses and the use of tramadol and oxycodone increased the risk of toxicity.

26. Long-Acting Oxycodone Co-Prescribing Among US Nursing Home Residents

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Background: Co-prescribing of extended-release (ER) oxycodone with central nervous system (CNS) drugs can present serious risks for elderly patients.

Objectives: To quantify CNS drug and oxycodone ER co-prescribing in elderly nursing home residents and the association of individual and facility traits with this co-prescribing.

Methods: This was a cross-sectional study sourced from Linked Minimum Data Set (MDS) assessments; Online Survey, Certification and Reporting (OSCAR) records; and Medicare Part D claims. Among a cross-section of all long-stay U.S. nursing home residents (≥65 years old) in 2008 with an MDS assessment and Medicare Part D enrollment, we identified initiators of oxycodone ER, excluding those with severe cognitive impairment, cancer or hospice care. From Medicare Part D claims, we identified dispensings of products from the antidepressant, antipsychotic, anti-anxiety, mood stabilizer, and muscle relaxant classes within 30 days after oxycodone ER initiation. We obtained resident and facility characteristics from MDS and OSCAR records. We estimated associations of patient and facility attributes and CNS drug co-prescribing (≥3 CNS classes) at oxycodone ER initiation using multilevel mixed effects logistic regression analyses.

Results: Among 4,317 residents initiating oxycodone ER, 1,640 (38.0%) were co-prescribed drugs in ≥2 CNS classes and 431 (10.0%) in ≥3 classes. In adjusted analyses, residents with moderate-severe cognitive impairment (compared to no cognitive impairment, Odds Ratio (OR) = 1.70, 95% CI = 1.22-2.35) or extensive mood disturbances (compared to least mood disturbance, OR = 3.70, 95% CI = 1.63-8.39) were more likely to have co-prescribing in ≥3 CNS classes.

Conclusions: Many nursing home residents initiating oxycodone ER were co-prescribed multiple CNS drugs. Prescribing practice changes may be necessary to prevent adverse effects, particularly among

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residents with cognitive impairment or mood disturbances.

27. Doctor/Pharmacy Shopping Measures for Opioid Analgesics and Diagnosed Abuse and Addiction in a US Administrative Database

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Background: Doctor/pharmacy shopping refers to the practice of seeking prescriptions from multiple sources without their coordination or knowledge. Doctor/pharmacy shopping may be a valuable measure of diversion or abuse of prescription medicines in healthcare databases.

Objectives: This study examines the relation between doctor and pharmacy shopping patterns in claims data and physician diagnoses of opioid abuse or dependence/addiction.

Methods: This cross-sectional study used the HealthCore Integrated Research Database, a US administrative claims database, to identify patients with at least 2 opioid dispensings. Patients were grouped into one of four doctor/pharmacy shopping categories based on their opioid dispensing patterns over an 18-month period: no shopping (≤2 prescribers and ≤2 pharmacies), minimal shopping (2 prescribers and >2 pharmacies or 3-4 prescribers and 2 pharmacies), moderate shopping (3-4 prescribers and >2 pharmacies or >4 prescribers and 2 pharmacies) and severe shopping >4 prescribers and >2 pharmacies). For a random sample of patients, behaviors suggestive of misuse, diversion, abuse and/or addiction will be identified based on review of medical records.

Results: Of 312,472 opioid patients, 77.9% had pharmacy claims patterns indicating no shopping, 11.2% minimal shopping, 7.5% moderate shopping and 3.3% severe shopping. Compared with opioid users with no shopping behavior, severe shoppers were younger (mean age 47 versus 54), more often female (58.7% versus 55.0%), and more likely to have a claims-identified death (2.3% versus 1.4%). Claims-based addiction or abuse diagnoses were recorded for 2.1% of patients in the no shopping, 4.6% of patients in the minimal shopping, 8.1% of patients in the moderate shopping, and 16.2% of patients in the severe shopping categories.

Conclusions: In this commercially-insured population, a substantial group of opioid users had varying degrees of doctor/pharmacy shopping behavior. We confirmed an association between doctor/pharmacy shopping and diagnoses of opioid abuse or dependence/addiction.

28. The Role of Socioeconomic Status in Regional Variation of Opioid Utilisation in the Greater London Area

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Background: Studies in other countries suggest a relationship between socioeconomic status and increased opioid utilisation but this has not been explored in the United Kingdom (U.K).

Objectives: This study aimed to explore the association between socioeconomic status and opioid utilisation in U.K primary care in the London area.

Methods: This cross-sectional study used practice-level dispensing data (October 2014 to September 2015) from the U.K Health and Social Care Information Centre. The Index of Multiple Deprivation (IMD), number, gender and age distribution of registrants for each practice were extracted from the U.K government website. General practices (GPs) in London which prescribed opioid analgesics and were able to be assigned an IMD were included. All opioid analgesics listed in the British National Formulary and assigned a defined daily dose (DDD) were included. IMD was categorized into deciles where 1 is the most deprived areas. Monthly opioid consumption in each practice was calculated by total DDD/1000 registrants. Descriptive analysis was used to report monthly DDD/1000 registrants and socioeconomic status. Multivariate regression was used to assess the association of socioeconomic status with monthly DDD/1000

registrants and adjusted the proportion of female and age over 65 years.

Results: Overall, 765 to 778 practices per month were identified in study period, and 56% of practices located in the 3 most deprived decile ranks. The median of monthly DDD/1000 registrants was 475.6 (interquartile range: 327.3, 640.6). Practices categorised in the first IMD decile (10.1%) significantly prescribed 56 more DDD/1000 registrants (95% confidence interval [CI]: 34.6, 77.5; $p<0.001$) per month compared with other practices. The monthly DDD/1000 registrants increased 8.2 (95%CI: 5.9, 10.6; $P<0.001$) for every increase in IMD score after adjusting age and gender.

Conclusions: The aggregated population data in London area demonstrated a significant association between socioeconomic status and opioid consumption. Further longitudinal study and individual patient data analysis are needed to explore the impact of the change of socioeconomic status on opioid utilisation.

29. Opioid Tolerance Prior to Initiation of High-Dose Oxycodone in Commercially-Insured Adults in the US, 2010-2014

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Background: Increasing rates of opioid overdose highlight the importance of responsible opioid prescribing. According to product labelling, high-dose oxycodone should only be prescribed to patients who have demonstrated prior opioid tolerance (OT).

Objectives: To estimate the proportion of patients receiving high-dose oxycodone who did not meet OT recommendations.

Methods: Using Truven's MarketScan Commercial Claims data (2010-2014), we identified new users of high-dose oxycodone (tablet >40 mg, or daily dose ≥80 mg). Incident use was defined using a 182-day baseline period without claims for high-dose oxycodone. OT was defined as having ≥7 days of 30 mg oxycodone equivalents immediately prior to the index high-dose prescription. We estimated the proportion of high-dose initiators who did not meet OT recommendations overall and by selected patient characteristics.

Results: We identified 61,529 high-dose oxycodone initiators with mean age of 51 years; 52% were male. While the MarketScan population was relatively constant from 2010-2014, the number of individuals with new use of high-dose oxycodone decreased from a high of 14,969 in 2011 to 9,393 in 2014. Among this cohort, 35.5% (95%CI: 35.2, 35.9) did not meet OT recommendations. Lack of OT was most common among new users age 18-24 yrs (55%, 95%CI: 52, 58) and ≥85 yrs (50%, 95% CI: 46, 55) and varied by baseline pain indication. Lack of OT was greatest among those with diagnosis codes for acute pain (49%, 95%CI: 47, 50) or no diagnosis coded for pain (44%, 95%CI: 43, 45) within the past 182 days.

Conclusions: While use of high-dose oxycodone appears to be decreasing in recent years, 36% of adults initiating treatment did not meet OT recommendations, increasing to ≥50% in some subgroups. Sensitivity of these results to varying the definition of high-dose prescriptions as well as OT will be examined. Our analysis is limited by relying solely on reimbursed dispensed prescriptions. Our findings nevertheless highlight the importance of prescriber training in opioid titration, especially for younger adults and the elderly who may be at increased risk of accidental overdose.

30. The Preventable Risk of Fentanyl Prescribing

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Background: Transdermal fentanyl patches are a convenient opioid delivery system. Several deaths have resulted in safety warnings, indicating that fentanyl patches should only be used in patients that have had adequate prior exposure to opioids. This study assessed the safety of fentanyl patch use by examining past opioid exposure in new users of fentanyl patches.

Objectives: The objective was to assess the potential influence of the various warnings and safety bulletins related to safe fentanyl prescribing and to determine the current level of risk imposed on the Manitoba population.

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Methods: A longitudinal utilization analysis was conducted in Manitoba, Canada of fentanyl users between April 1, 2001, and March 31, 2013, using Drug Program Information Network Database. All opioid use was converted to oral morphine equivalents and the average daily dose in the 7-30 day period prior to fentanyl patch use was determined. The main outcome measure was the safety of fentanyl prescriptions. Prescriptions were considered unsafe if patients did not achieve the monograph recommended prior opioid exposure. Chi-square statistics were used to compare the safe starts for sex, age group and the first versus last years of the study period.

Results: Of the 11,063 persons initiating fentanyl patches during the study period, 74.1% were patients with inadequate previous opioid exposure. Women ($\chi2=46.8$, $P<0.0001$) and those over 65 years ($\chi2=272.6$, $P<0.0001$) were significantly more likely to have inadequate opioid exposure. The percentage of patients with inadequate prior opioid use significantly improved from 87.4% in 2001 to 50.0% in 2012 ($\chi2=234.9$, $p<0.0001$).

Conclusions: The safety of fentanyl patch prescribing improved over the period in review, but still half of all fentanyl prescriptions were written for patients with inadequate opioid tolerance. Some aspects of opioid stewardship and risk reduction are challenging; review of previous opioid exposure may be a simple but important way to improve the safe use of fentanyl patches.

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31. Effects of Expanding the Look-Back Period to All Available Data in the Assessment of Covariates

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Background: A fixed baseline period has been a common covariate assessment approach in pharmacoepidemiological studies from claims but may lead to high levels of covariate misclassification. Simulation studies have suggested expanding the look-back approach to all available data (AAD) for binary indicators of diagnoses, procedures, and medications, but there have been few real data analyses using this approach.

Objectives: To explore the impact on treatment effect estimates and covariate prevalence of expanding the look-back period within five validated studies in the Aetion system, a rapid cycle analytics platform.

Methods: We reran the five studies and assessed covariates using 1) a fixed window approach (usually 180 days before treatment initiation), 2) AAD prior to treatment intiation, and 3) AAD with a categorize by recency (CBR) approach, where the most recent occurrence of a covariate was labeled as recent (occurring within the fixed window) or past (before the start of the fixed window). For each covariate assessment approach, we adjusted for covariates via propensity score matching.

Results: In the study comparing the risk of acute coronary syndrome in high versus low intensity statin users, there was a little change in the estimated hazard ratio (HR) from the fixed window approach (1.11, 95% CI [0.98, 1.25]) to the AAD (1.21, 95%CI[1.07, 1.37]) and CBR approaches (1.19, 95%CI[1.05, 1.35]). Similarly, in the study comparing the risk of gastrointestinal bleed in celecoxib versus ns-NSAID users, the HRs changed only slightly across covariate assessment approaches, including the fixed window (0.83, 95%CI[0.65, 1.07]), AAD (0.89, 95%CI [0.69, 1.15]), and CBR approaches (0.86, 95%CI [0.67, 1.10]). Results for the other 3 studies were similar. All studies had at least one covariate that that had an increase in prevalence of 15% or higher from the fixed window to the AAD approach.

Conclusions: Expanding the baseline period to AAD improved covariate sensitivity by capturing data that would otherwise be considered missing, yet did not meaningfully change the overall treatment effect estimates compared to the fixed window approach.

32. Classifying Patient Histories in Medicare Claims: Fixed vs. All-Available Lookbacks

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Background: Claims studies typically apply fixed periods of continuous enrollment in which medical history is characterized. Simulations indicate that, under some circumstances, examining all available data may be superior.

Objectives: Compare the bias and efficiency of effect estimates produced using fixed vs. all-available lookbacks in a real-world setting.

Methods: Using 2007-2013 Medicare data, we identified beneficiaries with outpatient visits in 2011-2012 and evaluated statin initiation within 14 days. We included those age ≥68 with established cardiovascular risk and no statin claims within 180 days before the index visit. We required 1 or 3 years of continuous enrollment for fixed lookbacks and 180 days for the all-available (AA) approach. We identified prevalent cancer (exclusion criterion) and measured covariates during the 1 or 3 year baseline period for fixed lookbacks and using all available claims history for AA. We compared time to incident cancer other than non-melanoma skin cancer during 180 days of follow-up between initiators and non-initiators (a known null association). We estimated crude and inverse probability of treatment weighted (IPTW) hazard ratios (HR).

Results: The AA cohort had n = 2,743,154 which was reduced by 15% and 27% with 1-yr and 3-yr fixed lookbacks, respectively. Prevalent cancer exclusions further reduced the 1-yr, 3-yr and AA cohorts by 14.8%, 23.5%, and 24.0%, respectively. Within the 1-yr and 3-yr cohorts, 19.7% and 6.1% had identifiable cancer history in AA data. The crude HR (SE(lnHR)) for 1-yr, 3-yr, and AA was 0.84 (0.037), 0.86 (0.048), and 0.88 (0.039), respectively. The IPTW HR (SE(lnHR)) for 1-yr, 3-yr, and AA was 0.85 (0.042), 0.87 (0.053), and 0.90 (0.043), respectively. Compared to the expected null effect, the MSE of the crude estimate for 1-yr, 3-yr, and AA was 0.028, 0.022, and 0.016, respectively. The MSE of the IPTW estimate for 1-yr, 3-yr, and AA was 0.025, 0.019, and 0.013, respectively.

Conclusions: Nearly 20% of individuals selected with a 1-yr lookback had identifiable cancer history when all-available claims were considered. The AA approach was least biased and nearly as precise as the 1-yr look-back with the best MSE overall.

33. Recency of Comorbid Diseases and One-Year Mortality: A Registry-Based Cohort Study in Denmark

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Background: To assess prognostic comparability of contrasted groups, pharmacoepidemiologists often use Charlson Comorbidity Index (CCI) calculated using automated databases, such as the Danish National Registry of Patients (DNRP). Longer lookback periods identify more patients but also capture distant diagnoses that might be irrelevant for prognosis. The prognostic importance of the recency of diagnosis may vary by disease type.

Objectives: To evaluate how the recency of the most proximally recorded diagnosis, for each of the major CCI-diseases, affects the one year mortality among MI-patients.

Methods: We included patients with first-time myocardial infarction (MI) in Denmark, in 2009-2011, and identified registrations of comorbid diseases looking back up to 32 years based on the DNPR. We classified the patients according to each disease's recency relative to the index-MI diagnosis {0-<1, 1-<5, 5-<10 or 10-32} years. We used logistic regression to estimate odds ratios (ORs) for 1-year mortality associated with each CCI-disease/recency compared with no diagnosis, controlling for age, sex and other comorbidities. Data on deaths were linked from the Danish Civil Registration System.

Results: Among the 21,371 MI patients, 50% had at least one hospital-recorded comorbidity during the 32-year lookback period. The overall 1-year mortality was 22%. The greatest prognostic disparity between recent and distant diagnoses was seen for cancer (ORs were 3.9 (95% confidence interval [CI]: 3.2-

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4.8) for 0-1 year recency; and 1.1 (0.9-1.3) for 10-32 year recency. For stroke, the prognostic significance did not vary by recency of diagnosis OR = 1.5 (1.2-1.8) for 0-1 year recency; and OR = 1.4 (1.2-1.7) for 10-32 year recency.

Conclusions: Magnitude of the association between recency of diagnosis and mortality depends on the disease.

34. Avoiding Pitfalls When Combining Multiple Imputation and Propensity Scores

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Background: Observational studies are useful for studying comparative effectiveness or safety of pharmaceuticals; however they are prone to bias due to confounding and missing data. Propensity scores are commonly used to deal with the first problem and Multiple Imputation (MI) for the latter. Unfortunately, it is not known how best to proceed when both techniques are required. There are two methods of combining MI with propensity scores in the current literature.

Objectives: This research investigates whether the two methods of combination lead to differences in the accuracy or precision of treatment effect estimates.

Methods: Both methods start by imputing each missing value multiple times. Propensity scores are then estimated in each of the resulting datasets. In Method 1 the propensity scores are averaged and the average propensity score is used for a single subsequent analysis. Alternatively, Method 2 uses the propensity scores individually to obtain multiple estimates of the exposure effect which are combined to produce an overall estimate. These methods were compared by conducting an extensive series of Monte Carlo simulations, where the confounders differ in number, strength and direction of association with treatment exposure.

Results: Consistently across simulations, Method 2 produced unbiased results with appropriate confidence intervals. Method 1 not only underestimated the standard error (SE) of the estimate (as might be expected) but also produced biased estimates. For example, when three confounders were simulated with 25% missing data in each, the average bias in Method 1 was 0.126, compared to 0.051 in Method 2. At 35% missing data the bias increased to 0.203 in Method 1 and 0.052 in Method 2. The empirical (and estimated) SE's for Method 1 were 0.124 (0.101) and 0.134 (0.099) at 25% and 35% missing data respectively. For Method 2 the corresponding SE's, at 25% and 35% missing data, were 0.118 (0.121) and 0.125 (0.130).

Conclusions: Researchers are encouraged to implement Method 2 when conducting a propensity score analysis with incomplete data. This research is particularly relevant in medical research, where missing data are unavoidable and propensity scores are on the rise.

35. Generalizing Randomized Clinical Trials: Challenges Due to Missing Data on the Target Population

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Background: Statins are indicated in patients with normal LDL-C but elevated hsCRP values based on the results of the JUPITER trial (NCT00239681). Due to the observed heterogeneity of benefit in JUPITER, the expected benefit of statins in a representative real-world population meeting JUPITER LDL-C and hsCRP criteria is unknown. Standard methods of generalizing trial estimates to target populations do not allow for missing data on any effect modifiers.

Objectives: To generalize the results of the JUPITER trial to the Clinical Practice Research Datalink (CPRD) population.

Methods: The JUPITER trial estimated the effect of rosuvastatin on the risk of cardiovascular disease (CVD) in people with LDL-C <130 mg/dL and

hsCRP ≥2 mg/L. To identify the target population, we first used multiple imputation (MI) for all relevant baseline characteristics among CPRD patients (2001-2014) under the assumption of missing at random. We then selected all trial-eligible CPRD patients and standardized the trial participants to this target population by predicting the probability to be in the target and reweighting the trial population. We also standardized the trial participants to the target population with complete data.

Results: Comparing the trial participants (n = 17,802) with the imputed (n = 361,834) and complete (n = 2,794) target populations, we observed differences in effect modifiers including age (median: 66 vs 64 vs 63 years), hsCRP (4.1 vs 4.8 vs 5.0 mg/L), and BMI (28.3 vs 26.7 vs 28.4 kg/m2). All characteristics of the trial population approached those observed in the target populations after weighting. The treatment effect was HR = 0.56 (95% CI: 0.46-0.69) in the trial and changed to 0.61 (0.43-0.85) and 0.67 (0.46-0.98) after standardizing to the imputed and the complete target populations, respectively.

Conclusions: The estimated effect of rosuvastatin on CVD events after standardizing to trial-eligible patients within CPRD moved slightly toward the null. Only a small fraction of the target population had complete data on all effect modifiers. Data on effect modifiers were not missing at random, limiting the value of both MI and complete data approaches in this setting.

36. Confounding by Healthcare System Characteristics in Comparative Effectiveness Research

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Background: Clinically significant variation in healthcare practice and outcomes has been documented at nearly all levels of the healthcare system. Comparative effectiveness research (CER) occurs within this complex healthcare delivery structure, but the role of the healthcare system in CER is not well understood.

Objectives: To explore the potential for confounding from healthcare system characteristics in 2 example studies.

Methods: We identified cohorts of commercially insured patients initiating 1) a high-intensity versus low-intensity statin and 2) a new oral anticoagulant (NOAC) versus warfarin. Statin patients were followed for hospitalization for acute coronary events. Anticoagulant patients were followed for stroke and for clinical bleeding events. We measured covariates from claims during the year up to and including the index date describing patient health status and the healthcare environment. We estimated hazard ratio (HR) treatment effects after matching on a propensity score that included patient characteristics only or patient and healthcare characteristics.

Results: Healthcare characteristics were important determinants of treatment choice in the anticoagulant cohort, but were less important in the statin cohort. The healthcare characteristics most associated with receiving a NOAC versus warfarin were a visit with both a cardiologist and a primary care physician in the year prior to index (odds ratio = 2.24 [95% CI 2.11-2.37]), average prescription out of pocket cost prior to index (1.20 [1.18-1.22] per $10 increase), and receiving the index prescription from a hospital (0.24 [0.23-0.26]). Adjusting for healthcare characteristics led to a small improvement in confounding adjustment in the comparison of anticoagulants (HR = 0.69 [0.62-0.78] vs 0.66 [0.60-0.72] for bleeds and 0.80 [0.74-0.87] versus 0.77 [0.72-0.82] for stroke), but no change in the comparison of high versus low-intensity statins.

Conclusions: In these examples, adjusting for healthcare characteristics had little impact on confounding; however, investigators should consider the information available on the healthcare system and evaluate the potential for confounding in their data.

37. Trends In Incidence, Prevalence And Prescribing In Type 2 Diabetes Mellitus

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Background: Type 2 diabetes mellitus (T2DM) is a growing public health burden and its management is

becoming increasingly challenging and costly. Understanding trends in the disease is important for future health services planning.

Objectives: To investigate trends in incident and prevalent diagnoses of Type 2 Diabetes Mellitus (T2DM) and its pharmacological treatment between 2000-2013.

Methods: We used The Health Improvement Network (THIN) primary care database to investigate the incidence and prevalence of T2DM between 2000-2013. The association with age, sex and social deprivation on these measures were also examined as well as the changes in prescribing patterns of anti-diabetic therapy between 2000-2013.

Results: From a total of 8,838,031 individuals aged 0-99 years examined, 406,344 individuals had a diagnosis of T2DM of which 203,639 were newly diagnosed between 2000-2013. The incidence of T2DM rose from 3.69 per 1000 person-years at risk (PYAR) (95% CI 3.58-3.81) in 2000 to 3.99 per 1000 PYAR (95% CI 3.90-4.08) in 2013 among men; and from 3.06 per 1000 PYAR (95% CI 2.95-3.17) to 3.73 per 1000 PYAR (95% CI 3.65-3.82) among women. Prevalence of T2DM more than doubled from 2.39% (95% CI 2.37-2.41) in 2000 to 5.32% (95% CI 5.30-5.34) in 2013. Being male, older and from a more socially deprived area was strongly associated with having T2DM, ($p<0.001$). Prescribing changed over time. In 2013, metformin prescribing peaked among those prescribed treatment; 83.6% (95% CI 83.4-83.8) while sulphonylureas prescribing reached a low; 41.4% (95% CI 41.1-41.7). Both remained, however, the most commonly used pharmacological treatments as first line agents and add-on therapy. Thiazolidinediones and incretin based therapies (gliptins and GLP-1 analogues) were also prescribed as alternate add-on therapy options, although rarely used first-line.

Conclusions: Both incidence and prevalence of diabetes have increased between 2000-2013. Prevalent cases of T2DM more than doubled between 2000-2013. Metformin prescribing has increased and is the most commonly prescribed treatment, while sulphonylureas has declined. Changes in prescribing patterns observed may reflect emerging clinical guidance and novel treatments.

38. Estimated Life Expectancy and Cause-Specific Mortality in White, South Asian and Black Patients with Type 2 Diabetes

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Background: Little is known about ethnic variations in cause-specific mortality rates or the effect of diabetes on life expectancy across ethnic groups.

Objectives: To examine differences in cause-specific mortality and life expectancy in patients with and without type 2 diabetes (T2D), and observe ethnic patterns.

Methods: Using the Clinical Practice Research Datalink, we identified 176,796 patients with T2D between 1998 and 2015, and 629,031 age, sex and practice-matched controls without diabetes. Deaths were obtained through linkage with the Office for National Statistics and ethnicity from Hospital Episode Statistics (HES). Life expectancy was estimated from Chiang II abridged life tables. Adjusted cause-specific hazard ratios and cumulative incidence functions were obtained from a competing risk flexible parametric model.

Results: The presence of T2D in White, South Asian and Black individuals was associated with an estimated life expectancy, at age 20, of 55.2y, 60.2y and 59.5y, respectively for men and 58.2y, 64.9y and 64.2y for women; reductions of between 0.4-6.3y compared to those without diabetes. Paradoxically, above the age of 55, South Asian men and women and Black men with T2D had 1-2 years extended life expectancy compared to those without diabetes. The main causes of death in T2D were cardiovascular disease (CVD), malignancy, and respiratory disease. The estimated probability of death from CVD within 15 years (study window end) for Whites, South Asians and Blacks with T2D was 21.6%, 13.3% and 13.3%,

respectively for men and 20.8%, 13.3% and 13.3%, respectively for women. The probability of death from cancer within 15 years for Whites, South Asians and Blacks with T2D was 14.9%, 6.6% and 13.3%, respectively for men and 11.6%, 5.0% and 9.1%, respectively for women.

Conclusions: T2D has a more detrimental impact on mortality in Whites when compared to South Asians and Blacks. This is partly explained by the lower risk of death from cancer and CVD in these minority ethnic groups. The apparent extended life expectancy associated with diagnosed diabetes in South Asians and Blacks requires further investigation.

39. Preferential Prescribing of Linagliptin to Patients with Renal or Cardiac Disorders in Japan

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Background: Preferential prescribing to patients with certain characteristics can influence assessments of effectiveness or tolerability. Linagliptin (LINA), a dipeptidyl peptidase-4 inhibitor (DPP-4i) approved for the treatment of type 2 diabetes mellitus (T2DM), has labeling that does not require dose adjustment or monitoring in patients with renal or hepatic impairment.

Objectives: To assess the extent of channeling of LINA in Japan, especially in patients with renal, hepatic or cardiac disease.

Methods: Baseline characteristics of patients with T2DM starting LINA or any other non-insulin glucose lowering drugs (GLDs) were assessed using data from an ongoing LINA post-marketing surveillance study (enrollment: 2012-2014). Patients with T2DM never treated with LINA and T2DM patients starting any other non-insulin GLDs were included. Patients' baseline characteristics were assessed at the time of treatment initiation.

Results: A total of 3923 patients with T2DM were included; 53% started LINA. Interim results showed that age, sex, BMI, and HbA1c of LINA initiators were similar to patients treated with other DPP-4i but differed from other non-insulin GLD initiators. For example, compared to patients initiating biguanides, LINA initiators were older (mean 58.9 vs 66.5 yrs.), less obese (19.3% vs 9.2%), and had a lower mean baseline HbA1c (7.9% vs 7.5%). The mean eGFR (per mL/min/1.73 m2) in LINA users (70.8) was lower than the initiators of other DPP-4i (75.2), sulfonylureas (83.2), biguanides (83.1), with only thiazolidinediones (70.9) and alpha glucosidase inhibitors (71.8) having similar mean eGFR. Patients starting LINA tended to have higher prevalences of baseline cardiac disorders (11.9 vs. 8.4%), vascular disorders (55.1 vs. 51.6%), and renal disorders (9.3 vs. 6%) compared to the initiators of other non-insulin GLDs; the prevalence of hepatic disorders was slightly lower (7 vs. 8.8%).

Conclusions: Patients in Japan initiating LINA had a higher burden of comorbidities, including renal, vascular and cardiac disorders. Similar results have been reported from the U.S. This preferential prescribing needs to be accounted for in comparative effectiveness or safety studies of LINA.

40. Augmentation Patterns Amongst Metformin Initiators with Type 2 Diabetes Mellitus (T2DM)

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Background: Metformin (MET) is the preferred initial agent for T2DM. When patients fail to achieve glycemic targets on MET monotherapy, an increasingly wide array of options are available to be added-on as a second agent. Although certain patient or disease characteristics may favor the use of a specific drug for this augmentation, clinicians often face a decision for which limited comparative data exists.

Objectives: To characterize augmentation patterns among patients on MET monotherapy over a 10-year period.

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Methods: Within a large US health insurance database (Optum Clinformatics), we identified T2DM naïve initiators of MET monotherapy during July 2004-December 2013. These patients were followed for treatment augmentation with 2nd generation sulfonylureas (SUs), glitazones (TZD), GLP-1 receptor agonists (GLP1-RAs), DPP-4 inhibitors (DPP-4i), SGLT-2 inhibitors (SGLT-2i), or insulin. Augmenters were required to be continuously using MET up to the time of augmentation and to have ≥2 MET prescriptions in the 180 days prior and 1 MET prescription in the 90 days after. Mean baseline hemoglobin A1C (HbA1C) before augmentation was explored in a subgroup of patients with available lab results.

Results: We identified 339,347 MET naïve initiators; among these patients, 38,849 augmented with a second agent (mean time to augmentation = 0.8 years). Overall, patients were most likely to add a 2nd gen SUs (47.2%), followed by DPP-4i (21.2%), TZD (19.8%), GLP-1 RAs (7.1%), insulin (6.6%) and SGLT-2i (0.2%). The proportion of patients augmenting to DPP-4i (18% in 2007, 31% in 2013), and insulin (4% in 2004, 9% in 2013) increased over time, whereas the use of TZDs (45% in 2004, 3% in 2013) decreased; the use of GLP-1RAs and SUs remained fairly stable over time. Mean pre-augmentation HbA1C (available in approximately 20% of augmenters) ranged from 7.9% (GLP-1 RAs) to 9.5% (insulin), and the overall mean of 8.7% remained stable over the study period.

Conclusions: Almost half of the patients on MET monotherapy augmented with SUs. Augmentation patterns for TZD and DPP-4i changed substantially, while the HbA1C level leading to augmentation did not.

41. Trends Of Use Of Non-Insulin Antidiabetic Drugs Between 2006-2013 In France

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Background: Treatments for type II diabetes have greatly changed during the last decade. New drugs were marketed (dipeptidylpeptidase-4 inhibitors [DPP-4i], glucagon-like peptide-1 analogues [GLP-1a]) while others have been withdrawn (glitazones).

Objectives: To describe trends in incident use of non-insulin antidiabetic drugs (NIADs) between 2006-2013 in France.

Methods: Cross-sectional studies repeated on an annual basis from 2006 to 2013 were performed on NIAD new users identified from a representative sample of the French national healthcare insurance system. NIADs of interest were: metformin, sulfonylureas, α-glucosidase inhibitors, glitazones, DPP-4i, glinides, GLP-1a. NIAD new users were defined as patients with no delivery of any NIAD (first-line new users) or no delivery of a NIAD of the same class (other-line new users) in the 12-months period before the date of first identified reimbursement for a given year. Incidences and associated 95% confidence interval were performed per 1,000 persons.

Results: During the study period, 18,762 patients were identified as first-line new users; they mainly started with metformin (72%) or sulfonylureas (21%). The incidence of metformin use increased from 2.3 (2.2-2.4) to 3.4 (3.2-3.6) per 1,000 persons between 2006-2013. Over the same period, incidence of sulfonylureas use declined from 1.4 (1.3-1.5) to 0.6 (0.5-0.7) per 1,000 persons.

A total of 24.953 patients were identified as other-line new users; they were mainly initiated with DPP-4i (36%), sulfonylureas (22%), or metformin (20%). The incidence of DPP-4i use increased up to 4.5 (4.3-4.7) per 1,000 persons in 2010, then declined to 1.9 (1.8-2.0) per 1,000 persons in 2013. The incidence of sulfonylureas increased from 1.1 (1.0-1.2) to 1.6 (1.5-1.7) per 1,000 persons between 2006-2013; that of metformin decreased from 1.2 (1.1-1.3) to 0.9 (0.8-1.0) per 1,000 persons.

Conclusions: Metformin and sulfonylureas are the most prescribed NIADs in first-line. The use of DPP-4i as alternative or add-on therapy has declined since 2010. Since then, prescribers seem to shift back towards older and well-known therapies, which safety appears better assessed with longer experience of use.

42. Antidepressants and the Risk of Type 2 Diabetes Mellitus Among Publicly-Insured U.S. Youth

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Background: Antidepressants (ATDs) are one of the most commonly prescribed psychotropic medications in U.S. youth. In adults, there is emerging evidence on the risk of type 2 diabetes associated with ATD use. Yet, no previous study has examined ATD treatment-emergent risk of type 2 diabetes in youth.

Objectives: To assess the association between ATD use and the risk of incident type 2 diabetes in publicly-insured U.S. youth, according to ATD subclass and cumulative duration.

Methods: This retrospective cohort study of youth (5-20 years) initiating ATD treatment [selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and other antidepressants] anytime from 2005 to 2009 was conducted using Medicaid claims data from 4 states. Type 2 diabetes was ascertained using a validated algorithm (positive predictive value = 83.9%). To assess the risk of type 2 diabetes according to 1) current vs. former use and 2) cumulative duration of each ATD subclass, discrete time failure models were employed, adjusting for disease risk score estimated using >150 time-variant and time-invariant covariates. Also, to compare the risk among initiators of SSRIs to the initiators of TCAs and other ATDs, a propensity score-weighted model was used.

Results: In this cohort of 113,377 youth initiating ATD treatment (mean follow-up = 22.5 months), 61.6% were SSRI initiators. Compared to former users, there was increased risk of type 2 diabetes for current users of SSRIs [Relative Risk (RR) = 1.80, 95% Confidence Interval (CI) = 1.26-2.55] and TCAs (RR = 2.46, 95% CI = 1.19-5.11). By contrast, current users of other ATDs, compared to former users, did not have an increased risk (RR = 1.07, 95% CI = 0.68-1.66). The risk of type 2 diabetes increased with cumulative SSRI exposure, having a RR of 2.0 (95% CI = 1.1-3.8) for >180 days of exposure compared to those with <60 days of exposure. The risk of type 2 diabetes did not differ between the initiators of SSRIs and TCAs, but was lower among other ATD initiators.

Conclusions: In Medicaid-insured youth, SSRIs, the most commonly used ATD subclass, were associated with an increased risk of type 2 diabetes which intensified with increasing cumulative duration of use.

43. Predictors of Induction Chemoimmunotherapy Among Older US Adults with Follicular Lymphoma

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Background: Induction treatment for follicular lymphoma (FL) includes rituximab with anthracycline chemotherapy (AC), with non-anthracycline chemotherapy (NAC), or alone (monotherapy). Treatment decisions should balance safety and effectiveness. AC is highly effective but more toxic than other FL treatments. To avoid toxicity, guidelines recommend that patients with congestive heart failure (CHF) initiate NAC and that elderly or frail patients initiate monotherapy. Information is needed on predictors of FL treatment decisions and how decisions align with guidelines.

Objectives: To identify real-world treatment patterns and predictors of initial chemoimmunotherapy in older FL patients.

Methods: Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, we identified patients aged >66 diagnosed with stage I-IV FL from 2007-09 who had continuous Medicare Parts A/B enrollment and no managed care coverage 12 months pre- and post-diagnosis. Patients were classified as receiving initial AC, NAC, or monotherapy if they had >2 cycles within 12 months post-diagnosis. Potential predictors included age at diagnosis, sex, race, census tract poverty, comorbidities, predicted functional dependence, FL stage, FL symptoms, and extranodal disease. Multinomial logistic regression identified predictors of receipt with AC as a reference.

Results: Among 360 older FL patients receiving chemoimmunotherapy, 36% received AC, 33% received NAC, and 30% received monotherapy. Patients living in high-poverty areas were more likely to receive NAC over AC (OR = 2.4, 95%CI:1.1,5.1). Patients aged ≥75 were more likely to receive monotherapy over AC (OR = 2.3, 95%CI:1.3,4.1).

Functional dependence, comorbidity score, and CHF did not predict receipt of less toxic treatments.

Conclusions: The proportion of FL patients receiving initial AC, NAC, or monotherapy was similar. In concordance with guidelines, patients aged ≥75 were more likely to receive monotherapy. Although CHF and functional dependence increase patient vulnerability to toxicity, they did not predict treatment receipt. Findings can inform guidelines and the design of real-world comparative effectiveness or safety studies on FL treatments.

44. Validation of Claims-Based Definitions of Incident Colorectal Cancer (CRC) in a North Carolina (NC) Medicare Population

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Background: Cancer studies performed in administrative data require algorithms to identify cases, because pathology information is not available. Setoguchi et al. developed a suite of 4 commonly used claims-based definitions to identify incident CRC (cbCRC) —using diagnosis and treatment codes—in a low-income, Pennsylvania, 1997-2000, 65+ population receiving drug benefits. The performance of these definitions in a contemporary, socio-economically diverse, fee-for-service Medicare population is unknown.

Objectives: Evaluate the performance of cbCRC definitions in a contemporary NC population.

Methods: We identified NC Medicare beneficiaries age 65+ who were continuously enrolled in parts A/B for 36+ months between 7/1/2006-12/31/2009. A subset of these beneficiaries developed CRC, identified by linking their administrative claims data to the NC Cancer Registry. Beneficiaries not appearing in the registry with CRC were non-cases. We calculated sensitivity (Se), specificity (Sp), and positive predictive value (PPV) with 95% confidence intervals (CI) for 4 cbCRC definitions (def) including: def 1 which requires both diagnostic and procedure codes (surgery, chemotherapy, radiotherapy); defs 2 and 4 are based only on diagnoses codes (2+ within 60d and single code respectively); and def 3 is defined either as def 1 or 2.

Results: Among 117,347 Medicare enrollees, 1895 had an incident, registry-confirmed CRC (1496 colon, 399 rectal) diagnosis during the period of continuous Medicare coverage. Def 1 obtained Se = 87.9% (95% CI: 86.3-89.3); Sp = 99.4% (95%CI: 99.4-99.5); PPV = 71.0% (95%CI: 69.1-72.8). Def 4 obtained Se = 94.7% (95%CI: 93.6-95.7); Sp = 97.8% (95%CI: 97.7-97.9); PPV = 41.6% (95%CI: 40.1, 43.1). Performance for both def 2 and def 3 were between those listed for def 1 and def 4.

Conclusions: Compared to the population in which it was originally developed, when evaluated in a recent and more economically diverse population, the Setoguchi et al. cbCRC definitions had better sensitivity but worse specificity. This may result in more biased relative effect estimates than expected. Further work is needed to improve cbCRC algorithms in contemporary populations.

45. Clinical Outcomes of Stage II and III Breast Cancer Patients in Denmark

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Background: Between 3% and 6% of breast cancer patients present with bone metastases within five years of diagnosis. However, breast cancer recurrence (BCR) and metastases may be underreported in population-based health registries.

Objectives: To develop and validate algorithms predicting any BCR, bone and visceral metastases in Danish medical registries, and to examine the incidence rate (IR) of these outcomes in stage II/III breast cancer patients.

Methods: We identified a cohort of women in Denmark diagnosed 1999-2011 with incident regional (Summary Stage, available through 2003) or TNM stage II/III breast cancer (2004+). We ascertained

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information on tumor size and lymph node status (to derive stage), hormone receptor status, cancer treatment, comorbidities, and HER-2 status. Follow-up began 180 days after diagnosis and continued to BCR, metastases (any, bone or visceral metastases), death, or 31/12/2012. We validated algorithms identifying the study outcomes in 128 patients diagnosed 2004-2011 randomly sampled from two Danish regions. We computed positive predictive values (PPV) of BCR, bone and visceral metastases using medical records as a gold standard thus comparing the algorithm-identified outcomes with those recorded in the medical records. We estimated the cumulative incidence and IR per 10,000 person years (p-y) of BCR and bone and visceral metastases.

Results: Among 23,478 patients, 7,073 had regional stage and 16,405 had stage II/III breast cancer. The PPV for BCR was 69.8% (95%CI = 55.1, 81.9) with high sensitivity [88.2% (95%CI = 74.4, 95.9)]. The PPVs for bone and visceral metastases were 92.3% (95%CI = 69.3-99.2) and 71.4% (95%CI = 50.3-87.1), but had low sensitivity at 50.0% (95%CI = 31.0, 69.0) and 48.4% (95%CI = 31.6, 65.5). The 5-year cumulative incidence of BCR was 17.6%, with a 5-year IR of BCR of 540 (95%CI = 524, 557). The 5-year cumulative incidence and IR for metastases to the viscera were 3.2% and 144 (95%CI = 136, 152), and bone was 1.1% and 60 (95%CI = 55, 65) respectively.

Conclusions: The sensitivity of Danish registry data for bone and visceral metastases was low, so the IRs of these outcomes may be underestimated.

46. Post-Diagnostic Statin Use and Breast Cancer Survival: A Nationwide Cohort Study in Scotland

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Background: Preclinical evidence suggests that statins could delay breast cancer progression. Results from epidemiological studies however have been inconsistent and are limited by small sample sizes and certain time-related biases. Moreover, few studies have investigated the impact of statins on breast cancer-specific mortality.

Objectives: This study aimed to investigate whether breast cancer patients who were exposed to statins had reduced cancer-specific mortality. Secondary analyses investigated all-cause mortality.

Methods: We conducted a retrospective cohort study of 15,140 newly diagnosed breast cancer patients diagnosed from 2009 to 2012 within the Scottish Cancer Registry. Dispensed medication usage was obtained from linkages to the Scottish Prescribing Information System and breast cancer-specific deaths were identified from the National Records of Scotland Death Records. Using time-dependent Cox regression models, hazard ratios (HR) and 95% CIs were calculated for the association between post-diagnostic exposure to statins (including simvastatin) and breast cancer-specific mortality. Adjustments were made for a range of potential confounders including cancer stage, grade, cancer treatments received, comorbidities, deprivation and use of aspirin.

Results: A total of 1,190 breast cancer-specific deaths occurred up to January 2015. Overall, after controlling for potential confounders, there was no evidence of an association between statin use and cancer-specific death (adjusted HR 0.94, 95% CI 0.78, 1.13). No significant dose-response relationship was observed by increasing number of prescriptions and findings were similar in analysis of all-cause mortality. Breast cancer-specific mortality rates were also comparable for simvastatin users compared to non-users.

Conclusions: Overall, we found little evidence of a protective association between statin use after diagnosis and cancer-specific mortality in a nation-wide cohort of breast cancer patients diagnosed in Scotland. These findings will help inform the decision whether to conduct randomised controlled trials of statins as an adjunct treatment in breast cancer.

47. Low-Dose Aspirin and Survival Benefit in Gastrointestinal Malignancies

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Background: Many studies suggested a relationship between aspirin use and cancer; a reduced incidence and reduced mortality are described. The survival benefit for the use of aspirin after diagnosis has been mainly studied in colorectal cancer patients. The underlying mechanism for the beneficial effect of aspirin on cancer outcome remains part of debate.

Objectives: The aim of this study was to provide epidemiological evidence on the potential beneficial effects of low dose aspirin after diagnosis of cancer that arises from the gastrointestinal tract.

Methods: A retrospective cohort study was conducted in all patients with cancer of the gastrointestinal tract diagnosed between 1998 and 2011 in the southern region of the Netherlands. The population-based Eindhoven Cancer Registry was linked to drug dispensing data from the PHARMO Database Network. Patients using aspirin before diagnosis were excluded from the analysis. The association between aspirin use after diagnosis and overall survival was analysed using Cox regression models with time-varying exposure.

Results: In total, 13715 patients were diagnosed with a gastrointestinal malignancy. In this cohort, 1008 patients were solely postdiagnosis users (7%) and 8278 (60%) were nonusers. The largest groups were colon (3977; 43%), rectal (2358; 25%) and oesophageal (946; 10%) cancer patients. Median survival time for all patients was 48 months. Adjusted for possible confounders, the hazard ratio for patients using aspirin vs not using aspirin was 0.52 (95% CI 0.44-0.63). Stratified according to cancer type, patients with oesophageal, hepatobilliary, and colorectal cancer showed a significant association between the use of aspirin and improved survival.

Conclusions: Our observation that aspirin use is associated with improved overall survival in various cancer types with different biology makes the hypothesis of a nonspecific mode of action more plausible. The Aspirin trial started in 2015 in the Netherlands. This phase III multicentre, placebo-controlled, randomised trial studies the effects of adjuvant aspirin treatment on survival and recurrence in patients with stage II and III colon cancer.

48. Initiation and Adherence with Bone-Targeting Agents in US Men with Bone Metastases from Prostate Cancer

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Background: Bone metastases (BM) are common in advanced prostate cancer (PCa) and can lead to serious skeletal-related events (SREs) (eg, pathological fracture). Two bone-targeting agents (BTAs) are approved in the US for SRE prevention in men with BM from PCa – denosumab and zoledronic acid.

Objectives: To provide a current description of BTA use in men with BM from PCa.

Methods: Using structured and unstructured data (processed via technology-enabled abstraction) from a large, longitudinal electronic health record database of patients receiving care at oncology practices across the US (Flatiron Health), we identified adult PCa pts with a confirmed diagnosis of BM in 2012/2013 and no evidence of BTA use in the 6 months (mos) prior to diagnosis. Patients were followed through 04/30/2015. We estimated the cumulative incidence of BTA initiation after BM diagnosis, treating death as a competing event. Among BTA users, we used multivariable repeated measures generalized linear models to examine demographic/clinical factors associated with non-adherence (defined as absence of treatment in a 30-day interval to closely reflect the labels).

Results: Of 897 men in the cohort, mean age at BM was 71 years, 22% also had non-bone metastases, and 8% experienced a prior SRE. During 1150 person-mos of follow-up, 706 pts initiated a BTA and 77 pts died prior to initiation. The cumulative incidence of BTA initiation after BM diagnosis was 24% (95% confidence interval [CI] 21-26%) at 30 days, 76% (95% CI 68-84%) at 180 days, and 89% (95% CI 74-100%) at 1 year. Adherence at 6, 12, and 24 mos after initiation was 86% (95% CI 83-88%), 73% (95% CI 70-76%), and 32% (95% CI 28-35%), respectively. We observed an increased risk of non-adherence in

men who initiated treatment shortly after a diagnosis of BM (treatment initiated <3 mos vs. ≥3 mos after BM diagnosis).

Conclusions: This study of real-world treatment patterns in a population of PCa pts with BM treated in oncology clinics in the US found that most men initiated a BTA >30 days after BM diagnosis. Adherence to BTAs decreased over time, with a substantial decline after 12 mos.

49. Birth Cohort Effects on Overall and Subtype-Specific Antibiotic Use Among Infants Born in Denmark 2004-2012

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Background: Widespread antibiotic use leads to bacterial resistance at the population level. Antibiotic use in early life may also be associated with adverse effects on immune function. Data are limited for cohort effects on antibiotic use.

Objectives: To estimate birth year cohort effects on overall and substance-specific antibiotic use during the first year of life (henceforth, infancy).

Methods: This nationwide cohort study included all live singleton births from 2004-2012, identified in the Danish Medical Birth Registry. We linked data from the National Database of Reimbursed Prescriptions for all filled antibiotic prescriptions (ATC codes J01). We estimated three measures of antibiotic use, and censored at death, emigration, or 31 Dec 2012: (1) risk of at least one antibiotic fill during infancy, using Kaplan-Meier cumulative incidence; (2) rate of antibiotic fills, allowing for multiple fills per infant; and (3) antibiotic burden, equal to the number of total days on prescribed antibiotic treatment during infancy. All 99% confidence limits were within 0.6% of the estimate and are thus not presented. We compared overall and substance-specific use by birth-year cohort.

Results: Among 561,737 infants, the overall risk of at least one antibiotic fill was 41.5%, the overall rate was 0.8 fills per infant per year, and the overall burden was 2.6 daily doses per infant per year. Overall risk decreased across birth-year cohorts from 42.6% in 2006 to 36.9% in 2011. Overall rate and burden, however, did not change over time. The most common antibiotics were amoxicillin and penicillin V. Amoxicillin's share of the overall rate and burden increased from 2004-2012 (rate: 50% to 57%; burden: 56% to 65%), whereas penicillin V's share decreased (rate: 36% to 33%; burden: 27% to 23%).

Conclusions: The proportion of infants born in Denmark receiving antibiotics decreased from 2004-2012. Over time, infants who received antibiotics received an increasing number of prescriptions. Amoxicillin, a broad-spectrum antibiotic, became increasingly prominent over time. These findings have implications for antibiotic safety and effectiveness studies that span multiple birth cohorts.

50. Development and Validation of an Algorithm for Identifying Pediatric Patients with Type 2 Diabetes in Claims Data

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Background: The number of children with type 2 diabetes mellitus (T2DM) is increasing. Administrative claims databases can provide an efficient and cost-effective data source for the study of childhood T2DM, if these patients can be accurately identified.

Objectives: To develop and validate an algorithm to identify newly diagnosed children with T2DM.

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Methods: Data from the US Department of Defense health system from October 2007 to September 2013 were used to identify patients aged 10-18 years with incident diabetes. Algorithms were developed based on clinical insight, the literature, and quantitative approaches, with DM type ascertained via a 200-patient chart review, and evaluated by sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Candidate algorithms were validated by a second chart review in an independent set of 200 patients. Population-weighted measures (accounting for over-sampling of T2DM patients) were calculated and confidence intervals (CI) estimated from 10,000 bootstrapped samples.

Results: Among the 400 patients, mean age was 14.2 ± 2.5 years (14.9 ± 2.2 for T2DM), and 50% were female (57% for T2DM). The best performing algorithm consisted of 4 steps, each applied to the remaining patients who did not meet a previous condition:

1 Oral antihyperglycemics other than metformin or (metformin but not insulin) = T2DM
2 <2 T2DM ICD9 diagnosis codes (Dx), or (insulin and T2DM to T1DM Dx ratio < 0.8) or insulin pump or continuous glucose monitor = Non-T2DM
3 T2DM to T1DM Dx ratio >= 0.8 or (long acting insulin and no short/rapid acting insulin) = T2DM
4 Non-T2DM

It correctly classified 88 of 91 T2DM patients (97%) and 97 of 109 (89%) non-T2DM, with weighted sensitivity of 90% (95% CI 82-100), weighted specificity of 95% (92-97), PPV 87% (81-93) and NPV 96% (93-100).

A simpler algorithm based on combining 3 conditions of dx and drug use correctly classified 84% of T2DM and 91% non-T2DM.

Conclusions: Our results suggest that a claims algorithm can identify pediatric T2DM patients with good accuracy. External validation in other data sources is needed.

51. Suicide Trends and Risk Factors in Youth Aged 10-19 Years, Texas, USA

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Background: Youth suicide is a second leading manner of death in the U.S. Prior research focused on those aged 10-24 years obscuring rates and risk factors in the true "youth" population.

Objectives: To examine suicide rates and identify potential risk factors in those aged 10-19 years in a racially and ethnically diverse population.

Methods: WISQARS™ (Web-based Injury Statistics Query and Reporting System) was used to obtain fatal self-injury rates and mechanisms using ICD-10 codes X60-X84, Y87.0, and U03 among 10 to 19 year olds from 2004 to 2014. Joinpoint regression assessed rate trends and a significance level of 0.05. The Harris County Institute of Forensic Sciences database was the source of additional details regarding 312 deaths in Texas classified as suicide in this age group that were autopsied during 2004-2014.

Results: The suicide rate in Texas among those aged 10-19 years increased from 2004 at an annual percentage change (APC) of 1.9% rising to 5.65 per 100,000 in 2014, exceeding the U.S. rate in those aged 10-19 years (5.41 per 100,000). In Texas, the annual rates among white youth were higher than Black and Hispanic youth and increased significantly (APC = 2.1%, since 2004). Significant suicide rate increases were noted for firearms (APC = 3.4%, since 2007) and suffocation/hanging (APC = 2.8%, since 2004). The decedent case sample characteristics were: male, 80.4%; White race, 49.7%; Black, 14.1%, Asian, 2.6%; Hispanic ethnicity, 33.6%; and median age of 17 years. The distribution of method of suicide was firearm, 50.3%; hanging/suffocation, 38.1%; poisoning, 6.1%; and other, 5.5%. Prescription drugs accounted for 5.1% of suicides with 50.0% of those having multiple prescription drugs listed as a cause. Significant differences between the sexes noted hanging/suffocation was more common among females, whereas suicide by firearms more common among males. No differences were found between the sexes regarding poisonings or other mechanisms of suicide. No seasonal patterns were identified.

Conclusions: This analysis provides insight into suicide risk of a true youth population, ethnically and racially diverse, not examined in previous research.

52. ADHD Treatment and Diagnosis – Importance of Relative Age in Grade in Norway

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Background: Studies from several countries have reported that the youngest children in a grade are at higher risk of being diagnosed with ADHD or to receive ADHD drugs than their older-for-grade peers. The school start age cut-off follows the calendar year in Norway, i.e. the youngest-for-grade children are born in December.

Objectives: To investigate whether birth month is associated with the risk of receiving ADHD drugs (primary endpoint) or an ADHD diagnosis (secondary endpoint) in primary or specialist healthcare in Norway.

Methods: The study population included all children born in Norway during 2000-2008 (31 December 2014, N = 507,292). Information was retrieved from three nationwide databases: the Norwegian Prescription Database (dispensed ADHD drugs), the Norwegian Patient Register (ADHD diagnoses in specialist healthcare), and reimbursement data (ADHD diagnoses in primary healthcare). Children were followed from birth and until the first endpoint, death, emigration or end of the study period using Kaplan-Meier (KM) estimators by birth month and separately for boys and girls. Cox proportional hazard analyses were subsequently performed separately for boys and girls with number of days since birth as the time metric, birth month as exposure, and adjusting for calendar year of birth and parental education.

Results: 11,003 children (2.17%) had received ADHD drugs. By the end of follow-up, 2.54% of boys born in January, 3.08% of boys born in June, and 3.93% of boys born in December had received ADHD drugs. Corresponding proportions for girls were 0.81%, 1.02%, and 1.68%. The adjusted hazard ratio was 1.57 (95% CI: 1.41-1.75) for boys born in December (ref.: boys born in January), and 2.11 (1.75-2.55) for girls born in December (ref.: girls born in January). The same pattern of higher risk for children born later in the year compared to children born early in the year was also observed for ADHD diagnoses.

Conclusions: Children born later in the year are at higher risk of receiving ADHD drugs and of receiving an ADHD diagnosis than children born early in the year.

53. Safety of Stimulants in Children with Epilepsy: A Retrospective Cohort Study

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Background: Epilepsy is the most common neurological disorder in children in the US (~1.0%). Over 60% of children with epilepsy meet the diagnostic criteria for attention deficit/hyperactivity disorder (ADHD). Stimulants, the first-line therapy for ADHD, may lower seizure threshold and worsen seizure control, but their safety hasn't been addressed in large cohort studies.

Objectives: To evaluate the safety of stimulants in terms of seizure control in children with epilepsy.

Methods: This is a retrospective cohort study based on Medicaid Analytic eXtract database from 27 US states (1999-2010). Children aged 3-18 enrolled in fee-for-service plans with ≥2 outpatient claims of epilepsy (ICD9-CM: 345.xx) were included. We measured drug exposure via National Drug Codes and days' supply. We followed stimulant new users (defined as first prescription after 6-month continuous enrollment during which there was no seizure-related hospitalization/ED visit) for up to one year or until end of exposure, their 19th birthday, Dec 31 2010 or the study endpoint, whichever occurred first. We used frequency matching based on the interval between the second outpatient claim of epilepsy and stimulant initiation to assign index dates for non-users. The study endpoint was the first seizure-related hospitalization/ED visit (ICD9-CM: 345.xx, 780.39). We calculated the hazard ratios of stimulant use versus no use using Cox proportional hazard model to adjust for

demographic factors and baseline psychiatric comorbidities and anticonvulsant use.

Results: We identified 18,196 stimulant users and 55,099 non-users in this study. Current use of stimulants did not increase seizure-related hospitalizations (HR 0.98, 95%CI 0.83, 1.16) or ED visits (HR 0.88, 95%CI 0.81, 0.95). Children with cerebral palsy (HR 1.12, 95%CI 0.96, 1.30), nervous system anomalies (HR 1.11, 95%CI 0.89, 1.38) or intellectual disability (HR 1.12, 95%CI 0.97, 1.30) had higher risks of ED visits than children without, but the adjusted hazard ratios were not significantly increased.

Conclusions: This study provides reassuring evidence that effect of worsening seizure control of stimulants in children with epilepsy, as used in current practice, may be minimal.

54. Comparative Effectiveness Of NSAID Treatment Versus No Treatment For PDA In Preterm Infants

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Background: Given a paucity of randomized controlled trials on the topic, we applied physician preference-associated practice variation to evaluate mortality and bronchopulmonary dysplasia (BPD) following non-steroidal anti-inflammatory drug (NSAID) treatment to close patent ductus arteriosus (PDA).

Objectives: To determine whether NSAID treatment for PDA affects mortality or moderate/severe BPD at 36-weeks postmenstrual age.

Methods: We included ≤28-weeks gestation infants admitted to NICUs on their birth date as recorded in the 2006-2013 Pediatric Health Information System. Indomethacin or ibuprofen initiated on postnatal days 2-28 was considered to be PDA treatment. We first calculated a traditional generalized estimating equation (GEE) estimate of NSAID treatment on mortality/BPD. We then calculated the percent of NSAID-treated infants at each individual infant's institution within the period 6 months prior to 6 months after that infant's birth. This percent of treated infants was used as an instrument to reduce bias and more accurately determine the effect of NSAID treatment on a primary composite outcome of mortality or BPD.

Results: The cohort included 11,419 infants in 24 hospitals. GEE models controlling only for gestation, gender, and race showed an increase in the mortality/BPD composite outcome (odds ratio [OR] 1.29; [95% CI: 1.11-1.49]) and increased BPD (OR 1.50; [1.32, 1.72]) following NSAID treatment, but showed decreased mortality (OR 0.56; [0.46, 0.66]). The instrument, the % of infants at each infant's hospital receiving NSAID treatment within a year of that unique infant's birth, was a strong predictor of NSAID treatment ($p<0.001$, $F=900$) and not significantly associated with gestation, race, or gender. Instrumental variable analysis demonstrated no significant risk difference between NSAID treatment and mortality/BPD (-0.03 [95% CI:-0.10, 0.04]), mortality (-0.02 [-0.07, 0.03]), or BPD in survivors (-0.02 [-0.10, 0.06]).

Conclusions: Among similar ≤28-week gestation preterm infants admitted to the NICU on their birthdate, we found no significant increase in mortality or BPD at 36-weeks during periods of decreased center-specific usage of NSAIDs to treat PDA.

55. Potential Impact of Proposed Limits on Clinical Data Collected from Primary Care for a National Research Database

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Background: A program for extracting primary care data from all English GP practices has been proposed which could replace separate data collections for existing primary care databases. The program proposes several restrictions on the extracted data. Collection of historic data would be limited to recently recorded high priority disease areas, namely those which GPs are incentivised to record, and no data would be collected for defined sensitive conditions

such as miscarriage, STIs including hepatitis, and abuse.

Objectives: Conduct a systematic review to assess the effect of data restrictions on research using primary care data.

Methods: Studies using data from an existing primary care database (the Clinical Practice Research Datalink) were included if they had been cited in the development of national clinical guidelines or were published in one of five highest impact factor medical journals in the relevant research fields. Recently published studies (01/2007-07/2015) were double reviewed using a structured questionnaire to identify the potential impact of data limits on overall feasibility and risk of major bias. We assessed whether studies could be replicated with only 6 years of data, without data on sensitive conditions and with historical data available for high priority disease areas only.

Results: From 136 identified studies, 57 were included. With only 6 years of data - 41 (72%) studies could not be feasibly replicated or replicated without major bias. With historical data only for high priority disease areas - 22 (39%) studies could not be replicated, and without data on sensitive conditions - 6 (10%) studies could not be replicated. Overall, 26 (46%) studies could not be feasibly replicated without major bias using primary care data from the proposed program.

Conclusions: The restrictions proposed by a national program to extract data from English primary care would, if adopted, prevent up to half of recently published high impact studies. Researchers need to engage with national data programs to ensure the full value of the resource is realised. Incomplete collection of historic and prospective data would limit research for public health benefit.

56. The Impact of State Chemotherapy Parity Laws on Use and Spending for Oral Chemotherapy

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Background: Oral cancer medications are increasingly important in treating cancer but are costly for patients and insurers. By mid-2015, 39 states and Washington, D.C. had passed laws to ensure privately-insured patients pay no more for oral chemotherapy than intravenous chemotherapy.

Objectives: To estimate the effect of oral chemotherapy parity laws on patient out-of-pocket and drug and non-drug health plan spending.

Methods: We used administrative claims from 2008-2012 for three nationwide insurers aggregated by Health Care Cost Institute. We compared oral chemotherapy (OC) use and out-of-pocket spending for oral chemotherapy pre- and post-parity in states with and without legislation among individuals in fully-insured vs. self-funded plans using a difference-in-difference-in-differences approach. We included adults (18-64) with cancer diagnoses for which OC is available and who used any oral or infused chemotherapy from 2008-2012.

Results: We studied 29,944 individuals, representing 172,239 chemotherapy-months. OC use increased as a proportion of all chemotherapy use from 16.6% to 22.0% from 2008-2012. There were no differences in use by parity or plan funding type (aDDD risk ratio:0.93, 95%CI:0.75-1.15;$p=0.50$). For patients in plans subject to parity, out-of-pocket spending decreased by \$26.55 ($p<0.001$) at the median and \$222.20 at the 90th percentile ($p<0.001$), but benefits for high spenders were inconsistent. There were no parity-associated increases in chemotherapy-related or total spending by health plans.

Conclusions: Chemotherapy parity laws are associated with reductions in out-of-pocket spending for many patients without corresponding increases in plan spending; however, savings were inconsistent, including among the highest spenders. Cancer parity laws alone may be insufficient to ensure patients are protected from high out-of-pocket costs. Federal initiatives to expand parity to all privately insured patients,

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including those in self-funded plans may be warranted given the overall benefits observed for patients and the lack of impact on health plan spending. However, more should be done to understand why out-of-pocket spending remained high for some patients.

57. Disclosure of Industry Payments to Prescribers: Industry Payments Might Be a Factor Impacting Generic Drug Prescribing

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Background: One way to combat rising prescription drug costs is to encourage use of generic prescription drugs. Generic drug use is largely impacted by certain key groups such as prescribers and manufacturers. However, the influence of interactions between these key groups on generic drug use remains unclear. The Centers for Medicare and Medicaid Services' (CMS) Open Payments data include payments or other transfers of value between applicable manufacturers/group purchasing organizations and physicians, which provides a unique opportunity to study factors that influence generic prescribing.

Objectives: To examine the impact of industry payments on prescribers' practice of generic prescribing.

Methods: Using the National Provider Identifier as a cross-walk, we linked the 2013 CMS Open Payments data with Medicare Provider Utilization and Payment data (n = 1,049,381 unique prescribers) to examine the association between annual industry payments and Medicare Part D prescribers' annual proportion of generic prescription claims, controlling for state generic substitution laws and prescribers' characteristics. Multivariable logistic regression model was used to identify factors associated with the likelihood of generic prescribing at $P < 0.0001$.

Results: One third of Part D prescribers (33%) received industry payments in 2013. The mean annual proportion of generic claims was higher among prescribers receiving payments (60%) than those without payments (53%). Prescribers with annual payments > \$250 were less likely to prescribe generic drugs than those with less or no payment. Prescribers who served >100 Medicare Part D beneficiaries per year were less likely to prescribe generics than those who served less. Prescribers who prescribed >200 Part D claims annually were more likely to prescribe generics. State generic substitution laws as well as prescribers' sex, geographic region, and specialty were also associated with generic prescribing.

Conclusions: The amount of industry payments may influence prescribers' practice of generic prescribing. How this affects patient care and total medical costs warrants further study.

58. What has Been Achieved Five Years After Approval of New Drugs with the Requirement to Set up Patient Registries? A Follow-Up Study

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Background: Regulators are exploring ways how to bring drugs earlier to patients. This means that at time of approval the knowledge of the benefits and risks of new medicines will not be complete. Because uncertainties remain, regulatory authorities often require post-authorisation studies as part of the approval process. These include setting up patient registries, in addition or as a substitute for further clinical trials. Evidence whether it is realistic to expect that this kind of early approval (with real world registry data being provided post-approval) works is lacking.

Objectives: We investigated whether registry studies agreed on for authorised drugs were performed as agreed at the time of approval.

Methods: Around five years after approval the status (ongoing, completed, not started) was evaluated of 73 registries that were proposed and agreed upon at the time of approval of 43 (37%) out of 116 new drugs approved by the Committee for Medicinal Products for Human Use in Europe from 2007 up to 2010. Ten were imposed as a condition to be fulfilled post-approval. The proportion of patients recruited of the total number of patients planned to-be-enrolled was retrieved. The data were verified in the latest study

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reports (data lock point 1 Nov 2015) submitted to the Medicines Evaluation Board in the Netherlands.

Results: At the data lock point 62 registries were ongoing, four registries had finalised and seven registries were not started. In the ongoing registries, 29 had predefined the number of patients to-be-enrolled, 40% (SD 49%) of the patients were recruited 5.4 (SD 1.2) years after approval. For the 10 registries imposed as a condition, seven had predefined the number of patients to-be-enrolled, with 77% (SD 77%) recruited, however four registries had not started as the drug had been withdrawn.

Conclusions: More than 80% of the registries were initiated within five years of approval of the new drugs, but enrolment is poor for non-imposed registries. Only, if registries are imposed as a condition to be fulfilled post-approval they may realistically be expected to increase the knowledge on benefits and risks after marketing approval.

59. Between Risk Management and Pharmacoepidemiology: Where Do Post-Authorisation Safety Studies Stand Today?

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Background: The European Pharmacovigilance legislation implemented in July 2012 set forth a firm legal foundation for Post-Authorisation Safety Studies (PASS) under the Pharmacovigilance Risk Assessment Committee (PRAC) oversight. A PASS is defined as a study aiming to assess safety concerns, patterns of drug utilisation relevant to product's safety profile and effectiveness of risk minimisation measures (eRMM) set in the Risk Management Plan (RMP).

Objectives: The aim of this review is to describe the PASS landscape over the first three years of the new Legislation.

Methods: A systematic approach was used to compile all public data on the cohort of the 189 PASS protocols submitted from July 2012 to July 2015 identified from the PRAC meeting minutes. Regulatory details from the European Medicines Agency (EMA) webpages and methodological variables from the European Network of Pharmacovigilance and Pharmacoepidemiology (ENCePP) electronic register (EU-PAS) were analysed. Protocol documents were available for 57 PASS.

Results: Around one third (n = 58) of the 189 PASS were imposed to the Marketing Authorisation (categories 1- 2) whereas 89% of the remaining 131 were category 3 studies in the RMP. Slightly more PASS involved primary data collection (58%), mostly with a longitudinal design (75%). Most drug utilisation studies used secondary data sources where eRMM were largely evaluated using cross-sectional designs ($p<0.05$). Along with safety endpoints, 35% of the 57 sample embedded effectiveness outcomes. Most PASS analyses were descriptive, and only 65% included a comparison group.

Conclusions: This is the first exhaustive review of three years PASS protocols submissions since July 2012. Although some PASS were more likely designed according to their main safety objective, our results show that PASS are generally single exposure straight forward observational studies. ENCePP toolkits offer to PASS stakeholders strong scientific and methodological pharmacoepidemiologic principles to improve the quality of PASS. It will be important to assess the impact of this pharmacovigilance activity on effective risk management and its alignment with the products' benefit-risk strategy.

60. The Availability of Pharmacies and Pharmacy Services in the United States: 2007-2015

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Background: Pharmacies are an increasingly important component of health care delivery in the U.S. Despite this, information on the availability of pharmacies and their services is limited.

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Objectives: We sought: (1) to examine trends in the availability of community pharmacies and pharmacy services in the U.S. overall and by pharmacy type (e.g. chain, independent) between 2007 and 2015; and (2) to determine whether and how these trends vary by community demographics.

Methods: Retrospective observational study using national data on the number, location and type of pharmacies and pharmacy services from the National Council for Prescription Drug Programs. We mapped these data and linked them to the 2010 U.S. Census and 2009-2013 American Community Survey data to derive information on community demographics, such as racial/ethnic composition, poverty level, and urbanicity, at the ZIP-code level.

Results: The total number of community pharmacies increased by 6.6% from 63,279 to 67,469 during the period 2007 to 2015. Retail chain and independent pharmacies persistently accounted for 40% and 35% of all pharmacies, respectively. In urban, predominately minority and low-income communities, however, there were persistently fewer pharmacies, and independent pharmacies were the most prevalent pharmacy type. In 2015, three-quarters of pharmacies were handicap-accessible, 27% offered home-delivery services, 18% had a drive-thru, 12% were staffed with bilingual personnel, and 5% operated for 24 hours. The availability of these access-related services, however, varied by community and pharmacy type. Chain pharmacies located in urban, predominately black communities were the least likely to offer a 24 hour service. All of these differences were statistically significant ($p<0.001$).

Conclusions: Despite the growth of community pharmacies in the U.S over the last eight years, the provision of access-related pharmacy services has not changed. There are persistently fewer pharmacies, particularly chains, located in predominately minority and low-income communities. Residents of black communities are disproportionately more likely to encounter barriers in accessing 24-hour pharmacies.

61. Longitudinal Asthma Management Profiles: Visualisation of Patient Histories Using Multiple Data Sources

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Background: Electronic medical records (EMR) offer valuable information for research and clinical management. Barriers to a more common use include the limited data on medication use and health outcomes, the challenge of linking multiple sources, and the lack of methods to reconstitute patients' complete medical trajectories. The ASTRO-LAB cohort study, assessing the safety of long-acting β-agonists (LABA) in asthma, collected data both from patients and healthcare databases, thus allowing a more comprehensive exploration over time of medication use patterns and patient-reported outcomes.

Objectives: To develop longitudinal patient profiles of asthma management by integrating prescription, dispensation and patient-reported data.

Methods: Asthma patients aged 6-40, with a stable therapy pattern (≥6 months out of 12) of either LABA without inhaled corticosteroids (ICs), ICs without LABAs, LABAs and ICs in separate canisters (LABAs + ICs), or LABA/ICs fixed-dose combinations were included in France and the United Kingdom. Patients were followed via 4-monthly computer-assisted telephone interviews and monthly text messages: they reported their drug use and severe asthma exacerbations (SAEx). Patient-reported data were linked with EMR and claims data. Longitudinal data visualization plots of medication management during follow-up were developed for each patient.

Results: At inclusion, 1,051 patients (48% women, mean age = 22), 2.9% were prescribed LABA without ICs, 29.8% ICs without LABA, 10.0% LABA + ICs and 57.4% LABA/ICs fixed-dose combinations. Among those with ≥12 months of follow-up, 36% had ≥ a SAEx. Longitudinal plots allowed to assess patient's regularity of drug exposure, to understand the chronology between prescriptions and dispensations and possible links between drug exposure and

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SAEx. Several profiles will be presented to illustrate possible research and clinical applications.

Conclusions: Combining data from different sources allows a comprehensive overview of asthma drug management over time. Further improvements of data visualization and applications in clinical practice and research are worth exploring, and would facilitate EMR valorisation.

62. Determinants of Antihypertensive Adherence Trajectories Among Older US Adults in the First Year After Initiation

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Background: Antihypertensives are indicated to reduce the risk of cardiovascular events among older adults but many older adults are not adherent. Previous methods of quantifying adherence fail to account for varying patterns of use over time.

Objectives: To identify patterns of antihypertensive adherence using group based trajectory models (GBTM), and to identify whether individual factors can predict adherence patterns.

Methods: We identified older adults initiating antihypertensive therapy between 2008-2011 using a 20% random sample of Medicare beneficiaries with simultaneous parts A, B, and D coverage. We developed monthly adherence indicators using prescription fill dates and days supply data in the 12 months following initiation. Adherence was defined as having at least 80% of days covered. Logistic regression models were used to identify trajectory groups using ProcTraj. Bayesian Information Criterion (BIC) and trajectory group size were used to select the optimal model for defining trajectory groups. We compared the distribution of covariates across trajectory groups using multinomial logistic regression models using the most adherent group as the referent.

Results: Between 2008 and 2011, 286913 Medicare beneficiaries initiated antihypertensive therapy (mean age:75). The majority of new users were women (60%) and white (84%). Six distinct patterns of adherence were identified ranging from perfect adherence (mean p[adherence] = 0.98, proportion of sample 40.6%) to rapid stopping (mean p[adherence] = 0.09, 15.6%). The strongest predictors of belonging to the most adherent trajectory group were mono vs combo antihypertensive initiation (aOR = 2.15 (95% CI: 2.11-2.02)), race (white vs non-white, 0.58 (0.57-0.59), history of myocardial infarction (1.85 (1.78-1.95)), opioid use (0.82 (0.80-0.83)), and history of hospital admissions (0.73 (0.58-0.91)) (C-statistic: 0.63).

Conclusions: GBTMs are effective for identifying patterns of antihypertensive adherence among older adults. Certain patient characteristics appear to be determinants of patterns of antihypertensive use. We hypothesize that gaps in Medicare coverage may contribute to the varying patterns of use.

63. Impact of Statin-Related Media Coverage on the Use of Statins: An Interrupted Time Series Analysis Using UK Primary Care Data

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Background: There are concerns that media coverage questioning the risk-benefit balance for statins could affect their use, with implications for public health.

Objectives: We aimed to quantify how a period of intense UK media coverage affected initiation and cessation of statin therapy.

Methods: Using prospectively collected electronic data from UK primary care, the proportion of patients initiating and stopping statins for primary and secondary cardiovascular disease prevention was calculated each month from January 2011-March 2015. Interrupted time series analyses were used to investigate changes in statin use after a pre-defined time period in which there was intense media coverage of statins (October 2013-March 2014). The number of

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cardiovascular events that may have resulted from such changes was calculated by combining the estimated number of people affected with established statin efficacy estimates.

Results: There was no evidence that the period of high media coverage was associated with changes in statin initiation among patients with a high recorded risk score (primary prevention) or a recent cardiovascular event (secondary prevention) (OR = 1.00, 95% CI: 0.8-1.16 and 0.98, 0.87-1.11 respectively). There was strong evidence that patients were more likely to stop statin therapy for both primary and secondary prevention after the high media coverage period (OR = 1·12, 1·05-1·18 and 1·12, 1·04-1·21 respectively). In post-hoc analyses, the increased cessation rates were no longer observed after 6 months. Assuming causality, we estimated that the media coverage resulted in 218,971 patients across the UK stopping statin therapy, and would account for at least 2173 excess cardiovascular disease events over 10 years.

Conclusions: Media controversy over the risks-benefit balance of statins was followed by a transient rise in the proportion of people stopping statins. This research highlights the potential for widely covered health stories in the lay media to impact upon healthcare-related behaviour.

64. Changes in Statin Adherence in Response to a Myocardial Infarction: The Impact of a Stressful Life Event on Medication Taking Behavior

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Background: Statin adherence is important for secondary prevention of myocardial infarction (MI). No studies have evaluated adherence changes in response to an MI, a stressful life event.

Methods: To measure changes in statin adherence after MI and identify predictors of this behavior change.

Methods: Medicare claims were used to identify a retrospective cohort of all fee-for-service beneficiaries with an MI from 2008-2010. Subjects must have 1) ICD-9 discharge diagnosis of 410.x1, 2) ≥66 years old at time of index MI, 3) 1-year continuous enrollment pre-MI, 4) survived hospitalization and discharged home, 5) continuous enrollment through study end, and 6) prescription claim for statin in 12 months pre-MI. Patients were followed until date of death or 6 months post-discharge. In pre- and post-MI periods, adherence was measured using proportion of days covered (PDC) and categorized as <20%, 20 to <50%, 50 to <80%, and ≥80%. The primary outcome of interest was change in PDC group from pre-MI to post-MI and was categorized as an increase (pre-MI < post-MI PDC), no change, or a decrease. Exposures included pre-MI PDC as a continuous variable, age, race, gender, and dual eligibility for Medicaid. Multinomial logistic regression with adjusted odds ratios and 99% confidence intervals [OR (CI)] was used to identify predictors of adherence change compared to no change.

Results: The final cohort consisted of 158,771 patients. Overall, 89,177 (56.2%) had no change in adherence while 30,090 (19.0%) improved and 39,504 (24.9%) decreased. Compared to 65-74 year olds, subjects who were 85+ were less likely to have improved adherence [0.72 (0.68,0.77)] and more likely to decrease [1.50 (1.44,1.56)]. Compared to whites, blacks were more likely to decrease [1.18 (1.11,1.24)] and Hispanics were more likely to increase [1.37 (1.22,1.54)]. Patients with dual eligibility were more likely to decrease [1.19 (1.15,1.23)].

Conclusions: Patients' medication adherence responds to an MI differently based on differences in age, race, and socioeconomic status. Different strategies are needed to address how patients differentially respond to a stressful life event.

65. Comparative Adherence of Overactive Bladder Agents Among Older Patients

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Background: Anticholinergic drugs are commonly used to treat overactive bladder (OAB) but differ in

their side effect profiles, which may lead to differential adherence to therapy.

Objectives: To compare patient adherence to OAB therapy among older patients newly prescribed one of six available anticholinergic products in Ontario, Canada.

Methods: We conducted a population-based cohort study among residents of Ontario, aged 66 years and older who newly initiated an OAB medication between April 1, 2012 and March 31, 2014 and who refilled their prescription at least once (to ensure they became active medication users). New users were defined as having no prescription for an OAB medication in the past year. Adherence to therapy was defined as a refill for the original drug within a period equal to 150% of the previous prescription's duration. Individuals who switched therapy were defined as those who were prescribed a new anticholinergic that was not the original drug within the period of continuous use. We followed individuals forward until drug discontinuation (defined as date of last prescription plus the day supply), death, end of study period (March 31, 2015), or 2 years maximum follow-up.

Results: We identified 23,211 new users of OAB medications who met our eligibility criteria. A majority of users (83.5%, N = 19,399) were dispensed only one type of OAB medication throughout their period of use. Among all new users, 57.9% (N = 13,439) were still on therapy at 6 months and 39.9% (N = 9,276) were still on therapy at 1 year. The median time to discontinuation differed significantly by the OAB drug initiated ($p<0.0001$). In particular, approximately 25% (N = 1,011) of new oxybutynin users discontinued use or switched to a different OAB agent within 6 months after initiation compared to a range of 7%-12% among those who initiated other OAB medications (including solifenacin, fesoterodine, trospium, darifenacin and tolterodine). The median time to discontinuation was lowest for oxybutynin users (112 days) and highest among solifenacin users (248 days).

Conclusions: We found that adherence to OAB therapy among older patients differed considerably by drug initiated.

66. Self-Reported Adherence to Different Classes of Antiretroviral Medication as a Predictor of HIV Viral Suppression

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Background: It is well known that poor adherence to antiretroviral medication leads to poor outcomes among people living with HIV (PLWH). It is less clear whether thresholds for adequate adherence differ for newer compared with older drug classes, and what level of medication adherence qualifies as "adherent", in the context of self reported adherence, in a clinical setting.

Objectives: To compare HIV viral load achieved in PLWH at various thresholds of self-reported medication adherence for regimens containing Integrase Inhibitors (IIs), Protease Inhibitors (PIs), and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs).

Methods: Among PLWH on antiretroviral therapy at 5 US sites in the CFAR Network of Integrated Clinical Systems (CNICS), self-reported adherence to all medications was measured at the most recent clinic visit by a 30-day visual analogue scale (VAS) and examined in relation to HIV viral load. Goodness of model fit for the association between various adherence thresholds and HIV viral loads less than 400 copies/ml was estimated using Akaike information criterion (AIC) with logistic regression models. We adjusted for age, sex, calendar year, and time on antiretroviral medication. Non-linearity was assessed using generalized additive models (GAMs).

Results: There were 835 users of IIs (18% female), 1317 users of PI (15% female), and 1802 users of NNRTI-containing (12% female) regimens. Higher self-reported adherence was associated with increased viral load suppression ($P<0.01$) for all classes of antiretroviral medication. All medication classes showed extremely high levels of viral suppression in the highest adherence participants (VAS 95%+). Best

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fitting regression models suggested that a threshold for the VAS to demark adherent versus non-adherent is at 85% for IIs, at 80% for PIs, and at 75% for NNRTIs. These empirical cut-points matched with observed inflection points in GAM plots of adherence versus viral suppression.

Conclusions: Different classes of antiretroviral medications demonstrated effective viral suppression at varying levels of self-reported adherence, although all regimens were similarly effective at very high adherence levels.

67. Instrumental Variable Analysis Using Pooled Data in Pharmacoepidemiology: A Simulation Study

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Background: Instrumental variable (IV) analysis has been used to control for unmeasured confounding in pharmacoepidemiology using pooled healthcare databases. However, the performance of the IV analysis is not well known in such cases.

Objectives: We aimed to assess the performance of the IV analysis using pooled data on patient level in realistic pharmacoepidemiologic settings.

Methods: We simulated three separate datasets in several scenarios with varying incidence of the outcome (5 to 20%), probability of exposure (15 to 30%), probability of IV (20 to 40%), sample sizes (10000, 20000 and 30000), and strength of confounders. In each scenario, the number of replications was 1000 times. The true exposure effect (risk difference, RD) of 0.05 for all datasets was considered. The IV was a time-invariant and satisfied its basic assumptions. Two-stage IV models were applied to estimate the exposures effects on the outcome. Analyses were conducted separately on each dataset and on the pooled data. For pooled data, the exposure effects were estimated with and without adjustment of the heterogeneity between patients. 95% confidence intervals (CI) were estimated using 2.5 and 97.5 percentiles of the 1000 estimates.

Results: The exposure effects based on per dataset were similar with the true value (RD = 0.05), RD = 0.05 [95% CI: 0.01-0.09], RD = 0.05 [0.01-0.09], RD = 0.05 [-0.01-0.12]. However, the pooled effect estimate without adjustment of the heterogeneity between patients was shifted away from the true value, RD = 0.12 [0.10-0.15]. When the adjustment of the heterogeneity between patients was taking into account, the effect estimate was similar with the true value, RD = 0.05 [0.02-0.07]. For pooled data, the exposure effects were more precise and stable as compared to the analysis of per dataset.

Conclusions: The exposure effects from the IV analysis using pooled data can be valid when the estimates are reported from IV models with adjustment of the heterogeneity between patients. Nevertheless, in empirical studies, the exposure, outcome, and confounder definitions should be harmonized across the databases and estimates should be interpreted cautiously as IV generally violates its assumptions.

68. A Reference-Likelihood Alternative to Inverse Probability of Treatment Weighting

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Background: Inverse probability of treatment weighting (IPTW) is a useful method to adjust statistical models for confounding. However, IPTW requires exposed and unexposed patients at every level of the measured confounders, and IPT weights must be stabilized.

Objectives: To introduce a method of reference likelihood weighing (RLW) and compare its performance with IPTW and conventional logistic regression.

Methods: For a dichotomous exposure, treatment assignment of each patient is assumed to behave according to a Bernouilli likelihood. A log-likelihood for a treatment assignment probability of 0.5 is therefore -0.693, which can be then subtracted from the observed probability of treatment, the antilog of which, inversed, is the reference likelihood weight. A simulated example of a single dichotomous confounder in 1000 patients is used to show how RLW will yield the same adjusted cumulative incidence ratio (CIR) as IPTW when there are exposed and unexposed patients at every level of the confounder. In situations involving multiple confounders, including an absolute

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contraindication, RLW weights can be obtained by solving a system of 4 equations in 4 unknowns. Another simulated population of 1000 patients is used to compare the point estimates and precision of odds ratios from RL weighting, IPT weighting, and conventional logistic regression.

Results: In the example of 1000 patients and a single dichotomous confounder, the crude CIR was 0.53. The IPTW-adjusted and RLW-adjusted CIRs were both 0.60. The variance of the logCIR from the RL-adjusted and IPT-adjusted analyses were 1084.19 and 1417.90, respectively, when the reference likelihood was -0.693. The variance of the logCIR could be increased or decreased by using different reference likelihoods. In logistic regressions of 1000 patients with multiple confounders, RL-weighting usually yielded logCIRs closer to those from conventional logistic regression than were those from IPTW regressions, which sometimes resulted in quasi-complete separation of data points.

Conclusions: In the simulations attempted, RLW was robust to challenges of the positivity assumption, and it yielded estimates closer to conventional logistic regression than did IPTW.

69. Variation in Propensity-Adjusted Marginal Estimates of Treatment Effect

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Background: It has been shown that matching, stratification, and weighting on the propensity score (PS) can lead to widely varying treatment effect estimates due to different targeted estimands across methods. However, there has been little research on variation in effect estimates when targeting a common estimand.

Objectives: To explore the variation across PS adjustment approaches in estimated marginal hazard ratios (HRs) among the treated in a study of bleed risk in initiators of new oral anticoagulants (NOACs) versus warfarin.

Methods: We estimated 6 PS models, including a standard PS model with pre-specified covariates and a high-dimensional PS (hdPS), each estimated using ordinary, Bayesian, and boosted logistic regression. Using each of these PSs, we implemented 6 methods for estimating the marginal HR: 1) 1-to-1 matching, 2) full matching, 3) standardized mortality ratio (SMR) weights, 4) matching weights, 5) decile stratification, and 6) fine stratification (40 strata). In the full matching and stratification approaches, weights were developed from the matched sets or strata in order to estimate the marginal HR among the treated. Each approach was implemented without trimming, after trimming the nonoverlap, and after asymmetrical trimming at the 2.5th and 97.5th percentiles. Finally, we estimated a linear mixed effects model for the log-HRs to estimate the standard deviation (SD) due to each analytic component.

Results: HR estimates varied across the 108 approaches from 0.86 (0.71, 1.04) to 1.10 (0.93, 1.31). The most important source of variation was the PS (hdPS versus standard, SD = 0.051). The second most important component was the PS model estimation method (SD = 0.040). The least important analytic components were the level of trimming (SD = 0.015) and the HR estimation method (SD = 0.010).

Conclusions: Although the targeted estimand depended on the HR estimation method and the level of trimming, these were not the most important components determining treatement effect. The PS model estimation method can have nearly as large of an effect on the HR as the covariates included in the PS. Variation will be explored in other examples to characterize differences across studies.

70. The Impact of Study Design and Analysis on "Measurable" and "Un-Measurable" Patient Characteristics in Observational Studies of Glucose-Lowering Drugs in Type 2 Diabetes Mellitus (T2DM)

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Background: Administrative databases can provide information on comparative effectiveness and safety of T2DM medications, but often do not contain data on important clinical characteristics such as diabetes duration, body mass index (BMI), and hemoglobin A1c (HbA1c) that are routinely captured in electronic medical records (EMR).

Objectives: To assess potential residual confounding associated with unmeasured characteristics in administrative datasets, through an internal validation study.

Methods: Within a large US health insurance database, we identified T2DM patients initiating linagliptin or a comparator diabetes agent between May 2011-December 2012. We focused on 3 comparator drugs used at a similar stage of diabetes progression as linagliptin, i.e. other DPP-4 inhibitors (DPP-4s), pioglitazone (PIO) or 2nd generation sulfonylureas (SUs). For each comparison, 1:1 propensity score (PS) matching was used to balance >100 baseline claims-based characteristics, including proxies of diabetes duration or severity. For a subset of patients, we obtained additional data from EMR. We calculated standardized differences (SD) to assess the balance of claims- and EMR-based covariates after PS matching.

Results: We identified 3 PS-matched populations comparing linagliptin initiators vs. other DPP-4s (N=11,378), PIO (N=7,926), and SUs (N=6,820). In each of those, a subset (ranging between 4.3-4.5%) was linked to EMR. Claims-based characteristics, e.g. demographics, comorbidities, and medication use, were balanced within each population with SD>0.1. Within the linked subsets, though EMR-based characteristics were not used to estimate PS, mean diabetes duration was balanced across comparison groups (SD>0.1), with some moderate imbalances (SD>0.1) for BMI and HbA1c (ranging between 0.3-2.2 m2/kg and 0.2-0.6%, respectively), likely not large enough to be clinically meaningful.

Conclusions: Choosing appropriate comparison groups, using a new user design and matching cohorts using PS enriched by proxies of diabetes progression can mitigate confounding associated with unmeasured characteristics.

71. Calendar Time as an Instrumental Variable in Assessing the Risk of Heart Failure with Antihyperglycemic Drugs

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Background: In recent years 2nd line treatment of patients with type 2 diabetes with dipeptidyl peptidase-4 inhibitors (DPP) increased with a corresponding decrease in thiazolidinediones (TZD). This crossover over a short period of time may provide an opportunity to use calendar time as an instrumental variable (IV).

Objectives: Using hospitalization for heart failure (HF) as a positive control outcome we explored the use of calendar time as an IV and compared this approach to an active comparator new-user study comparing DPP versus TZD.

Methods: Using Medicare claims from 2008-2013, we identified initiators of DPP or TZD (100%) after a 6 month washout. We examined IV strength and estimated risk differences (RD) for HF using unadjusted Kaplan-Meier curves. Under the active comparator approach, we estimated propensity scores for DPP vs TZD and used weighted Kaplan Meier curves to get RD for HF.

Results: Calendar time greatly affected initiation of DPP and TZD with the two curves crossing between June and August 2010. The calendar time IV compared patients treated from September 2010 to December 2013 (N=20283; 70% DPP) with those treated from January 2008 to May 2010 (N=22696; 34% DPP), i.e., 39% compliance. The active-comparator approach compared 26198 DPP and 18842 TZD initiators. Covariate balance across levels of IV was slightly better than across treatments (average standardized mean difference 3.6% vs 4.3%). The 1 and 2 year local average treatment effect of RD of HF per 100 patients in the "compliers" (95% CI) were -0.7 (-1.0, -0.2) and -1.0 (-1.5, -0.2). Corresponding propensity score weighted results were -0.2 (-0.4, 0.0) and -0.3 (-0.6, 0.2).

Conclusions: Both the treatment cohorts and the IV study design indicate lesser risk of HF among DPP vs TZD initiators. The magnitude of the estimated effects could be different as the analyses are based on different populations and assumptions. The use

calendar time as an IV in settings where real-world market dynamics lead to profound changes in preferred treatments is worth consideration as previously suggested in other settings (Mack et al 2015). Additional analyses including adjusted IV analyses will be presented.

72. Propensity Score Trimming to Identify the Target Population for Comparative Effectiveness Research

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Background: Focus on a target population by trimming observations in the tails of the propensity score (PS) can improve treatment equipoise as well as the precision of treatment differences estimated by inverse probability of treatment weighting (IPTW), and reduced bias in simulation studies of realistic settings. Several alternative approaches are available, but their relationships and relative performance in real data settings are not well characterized.

Objectives: We compared trimming at absolute PS levels of .1 and .9 (Crump et al 2007), asymmetric 5th and 95th percentile trimming (Stürmer et al 2010), and trimming at preference scores of .3 and .7 (Walker et al 2013), in terms of percentages of trimmed subjects, relationships with PS C-statistics, and performance in a real data setting.

Methods: We generated PSs from alternative beta distributions with treatment prevalence .25 and .5 and C-statistics ranging from .61 to .94, and also compared estimated risk differences in alternative target populations in a real dataset, i.e. comparison of the 1-year risk of myocardial infarction, stroke or death between Medicare beneficiaries initiating rosuvastatin versus atorvastatin (N = 69,142).

Results: In all simulated settings, the target population was largest with trimming at absolute PS levels; with C-statistics above .7, asymmetric trimming yielded a larger target population than preference score trimming which trimmed more than half the population when $C > .8$, while smaller percentages were trimmed, but more with asymmetric trimming when $C < .65$. In the statin comparison, estimates of the risk difference based on each of the three targeted populations were smaller, and had smaller standard errrors, than the estimate in the entire population obtained by IPTW. Consideration of trimmed subjects in both PS tails showed less covariate balance and marked treatment effect heterogeneity.

Conclusions: Targeting primary analyses to subjects with greater treatment equipoise can improve estimation in comparative effectiveness settings. If covariate imbalance in the tails of the PS is a particular concern, asymmetric or preference score trimming may be preferred to absolute PS trimming.

73. Catch the Wave: Diffusion of Methodological Innovation in Pharmacoepidemiology

Suzanne M. Cadarette[1], Robert W. Platt[2], Joann K. Ban[1], Giulia P. Consiglio[1], Mina Tadrous[1,3] and Malcolm K. Maclure[4]

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Background: The uptake of methodologic innovation is often slow and many novel methods are not widely adopted.

Objectives: The main objective of the symposium is to introduce the Diffusion of Innovations model; and through comparative case study analysis, demonstrate how innovation attributes, communication channels and the social system work to impact the diffusion of methodologic innovation. The symposium is of broad interest to those keen to understand how to improve the uptake of methodological innovation.

By the end of the symposium, audience members should be able to: 1) describe the Diffusion of Innovations model; 2) consider the value of: comparative case study analysis, co-authorship network analysis, proportional Venn diagrams, and assignment of institutional credit; 3) discuss the diffusion of confounder summary scores, indirect comparison meta-analytic approaches, and self-controlled study designs in the field of pharmacoepidemiology; 4) use twitter to comment on or push pharmacoepidemiology (#RxEpi) innovation; and 5) plan or reflect upon how to improve the uptake of methodological innovations.

Description: Dr. Platt will set the symposium stage by reviewing the lack of uptake of novel statistical

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methods in the medical literature. Next, Dr. Tadrous will briefly summarize the use of the disease risk score (DRS) in epidemiology. Dr. Cadarette will then introduce the Diffusion of Innovations model, and use co-authorship network analysis to illustrate the comparative diffusion of DRS, and the high-dimensional propensity score (hdPS) in the field of pharmacoepidemiology. Following, Ms. Ban (indirect comparison meta-analytic applications) and Ms. Consiglio (self-controlled study designs) will cover the diffusion of other innovations in pharmacoepidemiology more broadly. Dr. Maclure will then introduce concepts of quality improvement to help optimize the application of pharmacoepidemiologic methods. The symposium will conclude with a twitter tutorial led by Dr. Tadrous, and an open panel discussion led by questions from the audience.

@CadaretteSM @RobertWPlatt @Mina__T @joannkban @GiuliaConsiglio @MalcolmMaclure #RxEpi #caseXover.

74. Patient Engagement in Observational Pharmacoepidemiology Research: Where Are We, Where Do We Need to Be, and What Are the Steps for Getting There?

Nicholas Heath[1,2], Wendy Camelo Castillo[3], Tabassum Majid[3], Emre Yucel[4], Kimberly Yang[5], Irene Petersen[6,7], Nancy Santanello[8], Susan DosReis[3] and Suzanne West[9]

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Background: Multiple guidance, initiatives, and workshops have addressed the importance of patient engagement/involvement and input in drug and biologics research and development, but there has been little discussion of how to include the patient voice in pharmacoepidemiology studies. In 2015 the ISPE Patient Engagement Work Group was formed in order to evaluate the current state of patient engagement/involvement as research partners in pharmacoepidemiology and pharmacovigilance research.

Objectives: To provide the ISPE membership with a status update on how the patient voice is incorporated within pharmacoepidemiology research conducted today and to present initial findings on patient perspectives on involvement in drug safety and benefit-risk research.

Description: In this symposium we will discuss the results of the work by the ISPE Patient Engagement Work Group, specifically the development of a literature review and results from focus groups conducted in 2016 in the United States and the United Kingdom. Discussion of the literature review will present our methods and key findings on current approaches to patient engagement/ involvement as partners in benefit-risk and drug safety studies. Using focus groups, chronic disease patients will provide their perspectives on drug safety and benefit-risk research, focusing on: a) how to best engage patients on the development of research questions, b) which exposures and safety and effectiveness outcomes to study, c) barriers to building partnerships, and d) understanding patient concerns about data privacy.

The symposium will be structured in four parts.Introduction to patient engagement/involvement in pharmacoepidemiologic research (Heath, 15 min)Key findings from the literature review (Castillo, Yucel, 25 min)Summary from US and UK focus groups (Majid, 20 min)Discussion on how to use what we have learned to promote patient engagement in pharmacoepidemiology (West, dos Reis, Santanello, Petersen, 30 min).

75. Impact of Pharmacovigilance: From PRAC Strategy to Demonstrable Better Health Protection

Peter Arlett[1], Marieke De Bruin[2], Robert Reynolds[3], Gerald Dal Pan[4], Saad Shakir[5], Almath Spooner[6], Xavier Kurz[7] and June M. Raine[8]

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Background: Ensuring that pharmacovigilance processes and risk minimisation measures are demonstrably effective and efficient is essential in delivering for

public health promotion and protection. In January 2016 the EMA Pharmacovigilance Risk Assessment Committee (PRAC) adopted a strategy on measuring the impact of pharmacovigilance measures. The symposium will explore the methodological challenges and set the scene for a dedicated workshop I November 2016 on impact methods where places will be reserved for ISPE members.

Objectives: Outline the approach to measuring impact of pharmacovigilance measures endorsed by the PRAC; explore the work by different partners and stakeholders that is already ongoing; identify the most appropriate methods and gaps for measuring process impact and effectiveness of risk minimisation; taking into account the need for independent input propose ways to collaborate between stakeholders and internationally, and set the scene for the dedicated impact workshop in November 2016.

Description: The session will be chaired by Dr June M Raine, Chair of the PRAC. Dr Xavier Kurz, Head of Monitoring and Incident Management at EMA will outline the approach to measuring impact of pharmacovigilance measures in the PRAC strategy, Dr Marieke De Bruin, Chair of the PRAC Special Interest Group on Impact will identify methods and gaps on process impact measurement and Professor Saad Sakir, Head of the Drug Safety Research Unit will identify methods and gaps on measuring the effectiveness of risk minimisation. The session will then move to an extended panel discussion, including interaction with the audience, which will be co-led by Dr June M Raine and Dr Gerald Dal Pan (FDA) and will include the speakers together with Dr Robert Reynolds (Pfizer), Dr Almath Spooner (HPRA and PRAC Vice Chair) and Dr Peter Arlett (EMA). The panel will further explore the benefits of a structure impact measuring approach, of the methodological challenges, and ways to collaborate between stakeholders and internationally. The Chair will conclude and make clear how the discussion will feed into and support the two-day workshop on impact to be held in November 2016.

76. Big Data, Big Picture - Data Visualization of Health

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Background: Current pharmacoepidemiology practice is grounded in protocol-based assessments for specific hypotheses that yield linear generation and static presentation of summary statistics about the effects of medical products. Data visualization techniques that marry interactive analysis with graphical representation offer new opportunities to yield insights, and will become increasingly important to our community as the scale of observational health data grow.

Objectives: Researchers involved in the analysis or interpretation of database studies should benefit, and will learn to:

1) Understand what data visualization is; 2) See why it is more important now with more Big Data & complex data becoming available; 3) Have an awareness of different types of visualizations & what make them effective (or not).

Description: This symposium will open a discussion about the evolution of data visualization and how it can be applied to pharmacoepidemiology. The symposium will provide four cross-disciplinary perspectives and offer practitioners a forum to debate how these techniques can become part of the epidemiologist toolkit.

Alison Bourke will introduce the topic of data visualization and highlight why it is important now to pharmacoepidemiology.

Dr. Ryan will explore how the hypothesis-testing paradigm can be augmented by interactive data exploration mediated through data visualizations of prespecified marginal statistics. He will highlight examples where visualization at the cohort and population-level can facilitate knowledge discovery and evidence dissemination within a protocol-based assessment.

Dr. Elhadad will discuss how informatics approaches to information synthesis and design can provide visual representations of narrative not accessible through static statistical analysis alone. She will demonstrate how patient-level summarization of electronic health records can support epidemiologic research at the point of care.

Dr. Perer will discuss the role visual analytics can play in the real-world evidence process, including statistical workflows in variable selection and model interpretation. He will illustrate how predictive modeling in observational data can be enabled through data visualization.

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77. Drug Utilisation In Older Populations: The Irish View On Knowing Right From Wrong

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Background: High medication use, complex comorbidities and aged related physiological and functional changes put older populations at a high risk of medication-associated harm. In addition, changes in treatment goals from active life prolongation to symptom management towards the end of life contribute further to the complexity of pharmacoepidemiology and drug utilization studies among older populations. Quality and safety of medication use is an important aspect of drug utilization studies in older individuals. The need for a treatment and the consideration of under and over treatment has long been considered in assessments of appropriateness, however such assessment has trended to focus solely on the need for treatments in the context of the presence or absence of relevant conditions, and has not tended to take age into consideration.

Objectives: The aim of this workshop is to understand the challenges of conducting medication quality and safety drug utilization studies in older populations and to work on strategies for development of such studies.

Description: In this workshop, we involve leading experts Professors Paul Gallagher, and Stephen Byrne from the University of Cork, Ireland who have developed and implemented the STOPP START criteria for identification of potentially inappropriate medications in the elderly. They will present their views on the challenges of assessing quality and safety of medication use among older populations. Following these presentations, participants will work in small groups of 5-10 through case based scenarios to better understand the challenges and complexity of conducting drug utilization studies around medication quality and safety among older populations. The groups will be facilitated by the panelists and at the end of the workshop groups will feedback and discuss their views.

Program: Introduction and welcome –Dr A Fourrier-Reglat

Identifying potentially inappropriate medications among older persons-Dr P Gallagher

Changing the use if potentially inappropriate medications in practice-Dr S Byrne

Group work case studies: challenges on drug utilization research among older populations

Feedback from groups and concluding remarks- Dr L Pont.

78. Does Randomization Work? Selection Bias in Pragmatic Randomized Clinical Trials and Unblinded Observational Studies: A CER SIG Endorsed Symposium

Cynthia J. Girman[1,2], Kourtney J. Davis[2,3], Liam Smeeth[4,5], Sarah Garner[6], Mary E. Ritchey[7], Corrine De Vries[8] and Andrew W. Roddam[3]

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Background: Randomized controlled trials (RCTs) blinded to treatment are the basis for most regulatory product approvals and considered the gold standard for research evidence, but may not reflect effectiveness in routine clinical practice. Pragmatic randomized clinical trials (pRCTs) have gained popularity by presumably balancing groups through randomization yet collecting data in routine care on more diverse patient populations. pRCTs are useful for certain research questions but can still result in treatment imbalances due to selection biases in enrollment. Regardless whether randomization is at the site (cluster) or patient level, physicians may decide on enrollment based on patient characteristics and the unblinded product profile, particularly if the physician or patient prefers

one product. Even with baseline comparability, pRCTs may suffer when changes post-randomization (i.e. usual care) alter the intent of randomization – the real-world' nature of these studies provides little control over long-term treatment changes. Hence, analytic methods may be needed to account for non-comparability despite randomization, so why go to the expense of randomizing?

Objectives: To review a) how selection bias at enrollment and changes over time during pRCTs might result in non-comparability similar to observational studies, b) when pRCTs or observational studies may better address research questions, c) how to improve pRCTs, and d) future directions in payer and regulatory worlds for when pRCTs vs observational study designs are preferred.

Description: Introduction (10 min, Dr. C. Girman) will be followed by case examples (5 min each, Drs. L. Smeeth, K. Davis, M. Ritchey, A. Roddam). The panel will constructively discuss issues (30 min) and ask provocatively whether observational studies suffice over pRCTs if non-comparability may result despite randomization. Suggestions for improvement will be presented along with future directions in payer (Dr. S. Garner) and regulatory (Dr. C. De Vries) realms for study design interchangeability and preferences. Moderated Q&A (30 min) with audience polling will wrap the session.

79. Exploring Innovative Methods to Conduct Validation Using United States Medicare Administrative Claims Data

Elizabeth Andrews[1], Til Stürmer[2], Leah J. McGrath[1], Michele Jonsson Funk[2], Jennifer L. Lund[2], Catherine B. Johannes[3], Alicia W. Gilsenan[1] and Christopher Powers[4]

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Background: Since the introduction of prescription drug coverage in 2006, United States Medicare data are increasingly used in pharmacoepidemiology research. The data capture a large proportion of those aged 65 years and older, often allow follow-up until death, and can be linked to other data sources. Using supplemental data sources can increase validity and should be considered when designing pharmacoepidemiology studies to evaluate and mitigate bias due to measurement error in exposures, outcomes, and covariates.

Objectives: This symposium aims to 1) provide an overview of Medicare data available for research; 2) illustrate novel methods of using supplemental data sources to increase validity of exposure, confounder, and outcome definitions; 3) provide examples of current validation studies for Medicare data; and 4) discuss remaining gaps and the feasibility of future linkages to other data sources.

Description: The symposium will focus on sharing best practices for validation studies using Medicare data. The co-chairs of the session, Til Stürmer and Elizabeth Andrews, will provide an introduction to the challenges of identifying exposures, confounders, and outcomes using claims data in an older population. Five speakers will present examples using different methods to validate Medicare data, highlighting best practices for implementing each method and operational challenges:Introduction (5')Overview of Medicare data available for research: Powers (15') Exposure validation: Using linked interview data to assess prevalent drug use prior to claims-based drug initiation: Jonsson Funk (12')Covariate validation: Using cohort data to validate claims-based measures of physical function in older adults: Lund (12')Outcome validation:Chart abstraction to obtain clinical information: Johannes (12')Linkage with state cancer registries: Gilsenan (12')Interactive discussion with the audience about conducting validation using Medicare data, including CMS perspectives on data linkage (20').

80. Polypharmacy and Adherence to TNF-alpha Inhibitors: Variation by Specific Concurrent Medications

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Background: Polypharmacy is the concurrent use of multiple medications and is hypothesized to impact overall medication adherence. However, it is defined differently across multiple observational studies.

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These typically include categories based on the overall number of drugs prescribed and frequency of refills. Less is known about how specific types of medication use in polypharmacy impact adherence.

Objectives: Our objective was to determine possible differences by specific polypharmacy medications on adherence to TNF-alpha inhibitors (TNFI) among patients with rheumatoid arthritis.

Methods: We conducted a retrospective cohort study of patients aged 18+ years using the Truven Health MarketScan Database between 2009 and 2013. Patients were required to newly initiate TNFI therapy for rheumatoid arthritis. Pharmacy dispensing data were used to calculate 12-month medication possession ratios (MPR) and determine adherence (MPR $\geq$0.80) for up to three years after starting therapy. Time-varying concurrent medication use per each 12-month period was defined as never, infrequent $<$2 dispensings), or frequent ($\geq$3 dispensings). Multivariable generalized estimating equation models were used to calculate odds ratios (OR) and 95% confidence intervals (CI) for associations between use of specific medications and repeated adherence measures over time.

Results: Among 39,302 new TNFI initiators, most were middle-aged (35-54, 49%) or older adults (55+, 39%). Overall, 46% of patients were adherent to TNFIs in their first year of therapy. Statin users were more adherent whereas users of antibiotics, opioid analgesics, and anxiolytics were less adherent. In multivariable models, frequent use of statins (OR = 1.37, 95% CI 1.30-1.44) and NSAIDs (OR = 1.38, 95% CI 1.31–1.45) was associated with TNFI adherence; whereas frequent opioid analgesic use (OR = 0.72 95% CI 0.67–0.78) was associated with non-adherence.

Conclusions: We found that use of specific medications has varying effects on TNFI adherence. Studies of polypharmacy and medication adherence should take into account types of concurrent medication used. Reasons for lower adherence among users of opioid analgesics warrant further investigation.

81. Predicting Adherence to Chronic Disease Medications in Patients with Long-Term Initial Medication Fills

Julie C. Lauffenburger[1], Jessica M. Franklin[1], Alexis A. Krumme[1], William H. Shrank[2], Troyen A. Brennan[2], Olga S. Matlin[2], Claire M. Spettell[3], Gregory Brill[1] and Niteesh K. Choudhry[1]

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Background: Efforts to improve adherence to essential medications have included providing patients with more medication so that they need to request refills less frequently. Despite much growth in patients initiating long-term prescriptions, the ability to predict adherence in these patients has been poor. Short-term refill adherence has previously been shown to highly predict future adherence.

Objectives: To extend methods involving short-term filling behavior and develop novel variables to predict adherence among patients receiving longer initial prescriptions.

Methods: We used claims from a large national insurer to identify patients initiating 90-day supply medications for diabetes, hypertension and hyperlipidemia between 2011 and 2013. Adherence was measured in the subsequent 12 months using the proportion of days covered (PDC) with PDC$\geq$0.80 considered to be full adherence. In total, 163 baseline demographic, clinical, and medication use characteristics and novel indicators of behaviors in the first 1 to 4 months after initiation were used to predict adherence using logistic regression models. We used 10-fold cross-validation to measure predictive accuracy by discrimination (C-statistic) measures.

Results: Of 37,692 patients including 17,436 statin, 16,467 antihypertensive, and 6,260 antidiabetic initiators, prediction using only baseline variables was relatively poor (cross-validated C-statistic: 0.653). Including short-term indicators, such as visiting the same provider or pharmacy, improved predictive ability (C: 0.706). A model including only an indicator of filling within the first 120 days had similar predictive ability (C: 0.698). The best performing model that included all baseline, short-term indicators and filling had strong predictive ability (C: 0.811). Predictive ability was similar across all three chronic disease conditions.

Conclusions: The use of a combination of short-term filling behaviors after treatment initiation and novel

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variables accurately predicted future adherence in patients initiating longer prescriptions. Efforts to predict adherence for potential intervention may benefit from examining short-term health behaviors.

82. Association Between Trajectories of Diabetes Medication Adherence and Hospitalization Risk in a Large Medicaid Program

Wei-Hsuan Lo-Ciganic[1], Julie M. Donohue[2], Bobby L. Jones[2], Joshua M. Thorpe[2,4], Subashan Perera[2,4], Zachary A. Marcum[3] and Walid F. Gella[2,4]

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Background: Numerous interventions are available to boost medication adherence, but the targeting of these interventions often relies on static measures of poor adherence. Group-based trajectory models, which identify distinct prescription filling behaviors over time, may be more useful for targeting interventions, although the association between adherence trajectories and clinical outcomes is unknown.

Objectives: To examine the association between longitudinal adherence trajectories for oral hypoglycemics and subsequent hospitalizations among diabetes patients.

Methods: A retrospective cohort study of 14,481 Pennsylvania Medicaid enrollees (aged 18-64) initiating oral hypoglycemics between 2007-2009. We used group-based trajectory models to identify oral hypoglycemic trajectories based on proportion of days covered (PDC) in the 12 months following oral hypoglycemic initiation. Multivariate Cox proportional hazard models were used to examine the association between trajectories and time to first diabetes-related hospitalization visit in the following year.

Results: The mean annual PDC was 0.59 (SD 0.27). The 7-group trajectories were identified and distinguished by the adherence level before and after the midpoint of the year: perfect-to-perfect (35.0% of the cohort), high-to-moderate (12.3%), moderate-to-high (13.4%), moderate-to-low (8.6%), moderate-to-poor (9.2%), poor-to-low (9.6%), and low-to-poor (11.9%). Except for high-to-moderate adherers, all trajectories had greater risk of diabetes-related hospitalizations compared to perfect-to-perfect adherers (moderate-to-high: HR = 1.30, 95%CI 1.10-1.53; moderate-to-low: HR = 1.45, 95%CI 1.19-1.76; moderate-to-poor: HR = 1.42, 95%CI 1.16-1.74; poor-to-low: HR = 1.68, 95%CI: 1.40-2.02; low-to-poor: HR = 1.33, 95%CI 1.10-1.62).

Conclusions: Oral hypoglycemic use trajectories were highly variable in this large Medicaid cohort, demonstrating the dynamic nature of medication adherence. Most of the suboptimal adherence trajectories were associated with a modest risk of diabetes-related hospitalizations compared to those persistently refilling oral hypoglycemics during the first-year treatment.

83. Association Between Patient-Centered Medical Homes and Adherence to Chronic Medications

Julie C. Lauffenburger[1], William H. Shrank[2], Asaf Bitton[3], Alexis A. Krumme[1], Olga S. Matlin[2], Edmund J. Pezalla[4], Claire M. Spettell[4], Gregory Brill[1] and Niteesh K. Choudhry[1]

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Background: Despite the widespread adoption of patient-centered medical homes (PCMH) into primary care practice, the evidence supporting their impact on healthcare outcomes has primarily been from geographically-localized and well-integrated health systems.

Objectives: Due to the strong ties between adherence to chronic disease medications and healthcare quality and spending, we sought to assess the association between adherence and PCMHs in a nationally-representative patient and provider population.

Methods: In this retrospective cohort study, we identified whether patients sought care from a National Committee for Quality Assurance (NCQA)-recognized PCMH, the most widely-used way to recognize PCMHs. We linked the full NCQA practice roster with insurer administrative claims data. The outcome of interest was medication adherence for one of three

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therapeutic conditions during the 12 months after medication initiation. Baseline characteristics, including demographic, clinical, health utilization, and medication use, were measured in the 180 days prior to initiation. Propensity scores were calculated to construct matched non-PCMH controls. We used generalized estimating equations to examine the association between PCMH transformation and adherence in the 12 months after treatment initiation among patients cared for by providers practicing in recognized PCMHs and propensity score-matched controls.

Results: Of 313,765 patients meeting study criteria, 20,825 (5.7%) received care in PCMHs. Mean adherence was 64% in the PCMH group compared with 59% among the controls. Medication adherence was significantly higher in PCMHs (Odds Ratio (OR): 1.22, 95%CI: 1.17-1.27), and the association with PCMH recognition increased significantly over the study period (interaction p-value =0.044). The association between PCMHs and better adherence did not differ significantly by disease state (Diabetes: OR 1.28, 95%CI: 1.16-1.42; Hypertension: OR 1.25, 95%CI: 1.17-1.33; Hyperlipidemia: OR 1.18, 95%CI: 1.12-1.26).

Conclusions: Receiving care in a NCQA-recognized PCMH is associated with better adherence among individuals initiating medications for common high-cost chronic diseases.

84. Influence of Antidepressant Treatment on Use of and Adherence to COPD Maintenance Medications

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Background: Depression is one of the most prevalent and undertreated comorbidities among patients with chronic obstructive pulmonary disease (COPD). Inadequately treated depression may impede optimal COPD management. Although studies have examined the association between treated depression and COPD medication use and adherence, none has empirically established causality.

Objectives: To estimate the causal influence of antidepressant treatment on use of and adherence to COPD maintenance medications.

Methods: Utilizing 2006-2012 Medicare billing data, a retrospective longitudinal cohort study was conducted among 25,458 beneficiaries with newly diagnosed COPD and new onset major depression. The COPD-depression cohort was identified in 2006-2011 and then followed 1-7 years from index date until death or study end (12/31/2012). The index date was defined as the date of first depression episode. Antidepressant use (treatment exposure) was assessed quarterly and categorized as use and non-use. Two outcomes--COPD maintenance inhaler use and adherence measured by proportion of days covered (PDC) --were also assessed quarterly and dichotomized (use vs. non-use; PDC of $\geq$0.8 vs. $<$0.8). Generalized linear regression models incorporating Marginal Structural Modeling stabilized weights were used to estimate the effects of previous antidepressant exposure on subsequent COPD use and adherence outcomes.

Results: The COPD-depression cohort was predominantly female and white, with two-thirds aged 65 years or older. Over half were low-income subsidy recipients. At any given 3-month interval of follow-up, nearly half (48%) used $\geq$1 COPD maintenance inhaler. Among users, 61% had a PDC of $\geq$0.8. After MSM weighting for time-invariant and time-varying confounders, we observed that compared to patients who had no antidepressant treatment for their depression comorbidity, those with antidepressant use were more likely to use (relative risk [RR] = 1.32, 95% CI = 1.30-1.34) and adhere (RR = 1.07, 95% = 1.01-1.11) to their COPD respiratory maintenance inhalers.

Conclusions: In a Medicare COPD-depression cohort, treated depression increased use of and adherence to necessary maintenance medications for COPD.

85. Impact of Treatment Satisfaction and Adverse Drug Events on Antihypertensive Medication Adherence in Ambulatory Patients in Ethiopia

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Background: Improving adherence to antihypertensive medication remains a major healthcare challenge. This may especially be the case in resource limited countries, where low priority is given to hypertension prevention and management.

Objectives: To explore the impact of treatment satisfaction and self-claimed adverse drug events (ADEs) on antihypertensive medication adherence in Ethiopian ambulatory patients.

Methods: A cross-sectional study was conducted in 6 public hospitals in Ethiopia. Ambulatory hypertensive patients included were aged ≥18 years and using antihypertensive medication. Adherence was defined as a score of ≥7 on the 8-point Morisky Medication Adherence Scale (MMAS). Multivariable logistic regression was used to identify determinants for good adherence. Determinants included were socio-demographics, disease characteristics, medication, and Treatment Satisfaction Questionnaire for Medication [TSQM] v. 1.4. TSQM has 4 domains with each a score of 0 to 100 (max) to indicate level of satisfaction.

Results: We enrolled 966 patients, of which 96% completed MMAS. The mean age was 57(SD 14) years and 63% were females. Overall, 41% of patients were adherent. Mean (SD) TSQM score was 64(18) for effectiveness, 88(26) for ADEs, 64(14) for convenience, and 51(14) for global satisfaction. 198 patients reported 371 ADEs mainly gastric problems (6%), headache (5%), cough (5%), fatigue/weakness (4%), and leg swelling (3%). Negatively associated determinants for good adherence were alcohol use Adjusted Odds Ratio [95% CI]; 0.68 [0.51;0.92], cardiac disease 0.46 [0.23;0.92], >10 year on antihypertensive medication 0.53 [0.30;0.94], and experiencing ADEs 0.27 [0.10;0.73]. The factor affecting adherence positively was medication convenience 1.05 [1.03;1.06].

Conclusions: Most study participants were poorly adherent. As may be expected, having experienced an ADE is an important factor for non adherence, and should also in resource limited settings be addressed in patient consultation. In addition, convenient therapies led to better adherence, while patients using alcohol, who are treated longer and with HF deserve specific attention.

86. Impact of High Deductible Health Plans on Adherence to Essential Medications for Patients with Chronic Conditions

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Background: High deductible health plans (HDHPs) are increasingly used as a strategy for controlling health care costs but higher levels of patient cost-sharing may lead patients to reduce their use of essential therapies. Patients with common conditions may be particularly vulnerable to high out-of-pocket costs incurred as a result of high deductibles.

Objectives: To determine if patients taking evidence-based medications for hypertension, high cholesterol, or diabetes who switch to a HDHP experience lower rates of subsequent medication adherence compared to patients who do not switch to a HDHP.

Methods: We used medical and pharmacy claims from Aetna to identify patients using a medication to treat hypertension, high cholesterol, or diabetes who were enrolled in a non-HDHP and who subsequently switched to a HDHP. We compared medication

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adherence among these individuals to contemporaneously enrolled patients in a non-HDHP who did not switch. HDHP cohort members were propensity score-matched to controls. Medication adherence was calculated as the proportion of days covered in each month after cohort entry. We used a linear interrupted time-series model with generalized estimating equations to evaluate the impact of HDHP enrollment on changes in adherence.

Results: We identified 15,972 individuals who switched to a HDHP plan. We matched 96% of all HDHP cohort members to controls (n = 15,390 in each cohort) with good balance of covariates after matching. Switching to a HDHP was associated with an immediate decrease in adherence of 4.7 percentage points (95% CI -5.7 to -3.7%, $p < 0.0001$) compared to controls who did not switch. Prior to switching, adherence rates were declining at 0.88 percentage points per month. After switching, rates declined by 0.27 percentage points per month in the HDHP cohort (change in slope after switch compared to controls, 0.19, 95% CI 0.07 to 0.31, $p = 0.0016$).

Conclusions: Switching to a HDHP was associated with a significant and immediate decrease in adherence to evidence-based medications. The magnitude of the observed reduction in adherence has been associated with clinically meaningful increases in untoward medical outcomes.

87. An Example of Exposure Heterogeneity When Pooling Epidemiologic Studies for Meta-Analysis of Antiretroviral Medication Adherence

Mary-Ellen Mackesy-Amiti[1], Lauren Strand[2], Robin Nance[2], Redonna Chandler[3], William Cunningham[4,17], Elise Riley[5], Shruti Mehta[6], Frederick Altice[7,16], Wendee Wechsberg[8], Chinazo Cunningham[9], Charles Cleland[10], Lisa Metsch[11], Daniel Feaster[11,12], Carlos del Rio[13,18], Curt Beckwith[14], Ann Kurth[10], Irene Kuo[15], Bridget Kruszka[2] and Sandra Springer[16]

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Background: When estimating associations with rare exposures, combining multiple studies may be key to improving power. The Seek, Test, Treat, Retain (STTR) HIV consortium is comprised of more than 22 observational and intervention studies in the United States (US) and abroad, including studies targeting persons involved in the criminal justice system. We investigated harmonized substance use patterns, and potential relations with antiretroviral drug adherence (ARVDA) in a subset of 9 studies.

Objectives: To estimate cross-sectional associations between substance use and ARVDA using harmonized data.

Methods: Estimates were obtained from a random-effects individual patient data meta-analysis. Substance use categories (user/non-user) were defined as: binge alcohol, cannabis, cocaine, opioids, stimulants, and other. ARVDA was assessed with the visual analogue scale (VAS) for all studies.

Results: There were 980 participants in 9 US-based studies. Two studies were further excluded because they contributed zero participants in the cross-tab of adherence and non-user status. Over the remaining 7 studies, there were only 166 non-users among 857 participants. Substance use clustered differentially by study. For single-substance use, the study with the most opioid-only users provided 1 stimulant-only user and no participants who were binge-drinkers only. The study with the most cocaine-only users, had no opioid or stimulant-only users. The most common categories of multiple substance use had similar issues. In

individual patient data meta-analysis, multiple substances users were significantly less likely to achieve adherence (VAS > 95%) relative to single substance users (OR: 0.65; 95%CI: 0.42-1.00) and to non-users (OR: 0.60, 95%CI: 0.34-0.96).

Conclusions: The composition of substances differed greatly by study, which precluded estimating associations by class. Estimates for single and multiple substance use were possible. Exposure heterogeneity in harmonized cross-sectional data may lead to an inability to separate true exposure and study effects, especially for substance use, which can be quite diverse across sub-populations.

88. Monitoring All Drugs for a Specific Outcome in the Sentinel System

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Background: In post-market drug safety surveillance, one important approach is to evaluate all exposures for potential association to specific designated medical events.

Objectives: Perform data-mining using tree-based scan statistics to evaluate all exposures to determine if any were associated with an increased frequency of a pre-specified medical event.

Methods: We identified all cases of new onset angioedema using a validated ICD9 algorithm in patients aged >= 18 years enrolled in three health insurers from 2000-2014. We classified all drug exposures up to 63 days before the date of diagnosis using the hierarchical Medi-Span Therapeutic Classification System, which covers over 300,000 National Drug Codes. We scanned all drug exposures and groups of drug exposures using variable intervals between exposure and outcome to identify statistically significant associations. A self-controlled design was used to control for fixed confounders. Tree-based scan statistics control for multiple testing. Statistically significant elevated frequencies generate "alerts" for triage and evaluation using other pharmacoepidemiologic methods.

Results: We identified 45,580 incident angioedema events and 110,785 incident drug exposures in the 63 days before these events. Fifteen of the incident drug exposures that generated statistically significant alerts (N = 28) were therapies used to treat allergic reactions (ie, suspected time-varying confounding). Upon removing these therapies and then re-performing the analysis with 89,536 exposures, we detected known positive associations (eg, lisinopril) or suspected positive associations (eg, antibiotics). We detected one likely false positive association, triazolam, and one potential new finding of interest, clopidogrel. There were few unique alerts (N = 13) considering the large number of incident drug exposures evaluated.

Conclusions: Signal identification has traditionally been driven by spontaneous reports that lack population data to provide context. Data-mining using tree-based scan statistics can generate a complementary stream of new information on high-priority safety outcomes without being overwhelmed by false positive alerts.

89. Pilot Test of the Sentinel Modular Program for Propensity-Score Matched Cohort Analyses: Application to Glyburide, Glipizide, and Severe Hypoglycemia

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Background: Sentinel is a program sponsored by the US Food and Drug Administration to monitor the safety of medical products.

Objectives: To evaluate the ability of the semi-automated, customizable Sentinel Propensity Score Matching (PSM) Tool to reproduce the increased risk of severe hypoglycemia seen in users of glyburide vs. glipizide in an expedited fashion.

Methods: We conducted a retrospective cohort assessment including data from 2008-2014 in 13 Sentinel Data Partners. A pre-tested and customizable analytic program was run at each individual site to identify new users of each drug, measure pre-exposure potential confounders, fit a propensity score (PS) model, match glyburide and glipizide initiators on the PS, and follow patients for the outcome of severe hypoglycemia. Analyses were conducted with Cox proportional hazards models with 1:1 matching on predefined PS or high-dimensional propensity scores (hdPS) to adjust for confounding. De-identified summary results from each Data Partner were returned and aggregated at the Sentinel Operations Center.

Results: We identified a total of 198,550 and 379,507 new users of glyburide and glipizide, respectively. In the unmatched cohorts, the incidence rate of emergency department visits and hospital admissions for severe hypoglycemia was 18.8 per 1,000 person-years (95% confidence interval, 17.9, 19.7) for glyburide users and 22.2 (21.6, 22.7) for glipizide users, while the hazard ratio (HR) stratified by site was 1.11 (1.05, 1.18) for glyburide vs. glipizide. In cohorts matched by PS based on predefined variables, the HR was 1.36 (1.24, 1.49). The hdPS program ran to completion at 5 of 13 Data Partners. The HR for cohorts matched on hdPS was 1.49 (1.31, 1.70). In cohorts matched on PS including both predefined variables and empirically selected variables via the hdPS algorithm, the HR was 1.51 (1.32, 1.71).

Conclusions: These findings are consistent with the literature, and demonstrate the ability of the Sentinel PSM Tool to reproduce this known association in an expedited fashion.

90. Quality of Diabetes Recording: How Does Coding Impact Incidence Estimates?

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Background: Conflicting evidence exists regarding trends in UK diabetes incidence since 2004, when the Quality and Outcomes Framework (QOF) was introduced. The accuracy of GP coding of diabetes, and the resulting impact on incidence estimates, is unknown.

Objectives: To assess coding practices and the associated impact on estimates of diabetes incidence.

Methods: Primary care data from the Clinical Practice Research Datalink was used to examine diabetes coding from 1995-2014. Read codes indicative of diabetes (e.g. 9N1Q.00 Seen in diabetic clinic), and a subset representing diabetes diagnosis (e.g. C10F.00 Type 2 diabetes mellitus), were identified. Incidence rates were calculated using broad and restricted codelists. Practices with ≥10% of patients with incident diabetes inaccurately coded from 2004-2014 were identified using a published algorithm and subsequently excluded. A linear regression model was used to determine the difference in incidence between practices with good and poor quality of diabetes recording, with non-linear terms for year and adjusting for repeated measures by practice.

Results: Diabetes incidence rates and coding accuracy varied between the 684 practices included in the study. Using the codes indicative of a diabetes diagnosis, the incidence of type II diabetes increased sharply between 1995 and 2004 and then stabilised. This contrasted with an increase in incidence until 2012 using the broader codelist. The number of patients miscoded, misclassified or misdiagnosed per 100,000 halved from 60 in 1994 to 30 in 2014. 15% of practices were identified as having poor quality of recording. When these practices were excluded from the analysis, incidence rates were significantly lower ($p < 0.01$).

Conclusions: This study demonstrates that GPs use of ambiguous, vague or inaccurate codes for diabetes,

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and the use of these codes in analyses, has a significant impact on incidence estimates. The quality of recording of diabetes should be assessed when evaluating diabetes incidence rates using GP data.

91. Evaluation of Free-Text Comments to Validate Common Cancer Diagnoses in the UK CPRD

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Background: Some primary care databases include physicians' free-text comments, which reflect physicians' thinking without constraint to coded entries. Free text may be used in database studies to help validate outcomes. Starting in April 2016, free text will not be available for research in CPRD owing to transparency and governance concerns.

Objectives: Evaluate the relative contribution of free-text comments in the validation of incident cases of prostate, breast, lung, and bladder cancer.

Methods: For Read code-identified potential cancer cases in CPRD, we created two sets of electronic medical record profiles (prescriptions, diagnoses, procedures, laboratory tests, referrals, clinical information), one with and one without free text. One physician reviewed profiles of patients with free text and determined cancer type (e.g., breast) and status: confirmed or not confirmed (diagnosed before cohort entry, not incident cancer, unclear). Another physician independently reviewed profiles without free text. Prior to reviews, reviewers underwent training to decrease interrater variability.

Results: We identified 168 potential cases, of which 143 (85%) were confirmed in the review with free text and were considered the gold standard for calculations. The positive predictive value of case confirmation in the review without free text was 0.93 (128 of 137; 95% confidence interval [CI], 0.88-0.97), negative predictive value was 0.52 (16 of 31; 95% CI, 0.34-0.69), sensitivity was 0.90 (128 of 143; 95% CI, 0.84-0.94) and specificity was 0.64 (16 of 25; 95% CI, 0.44-0.81). Results were similar for individual cancer types. Cancer type matched in 142 of 143 confirmed cases.

Conclusions: Free text did not add information on cancer type. The review without free text classified most cases correctly. However, about half (15 of 31) of cases not confirmed in the review without free text were actually cases, and one third (9 of 25) of cases not confirmed by free text were falsely considered confirmed. Although some discrepancies may be due to interrater variability, misclassification of case status (confirmed vs. not) would likely increase without availability of free text.

92. Abstract Withdrawn

93. An Algorithm to Identify Duplicate Patients When Pooling Aggregate Data from Two Primary Care Databases in the United Kingdom

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Background: The Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN) are two similarly structured, de-identified electronic medical record databases in the United Kingdom. To increase the number of patients available, both data sources can be pooled. However, some practices provide data to both databases, and duplicate

patients should be identified and steps taken to avoid double-counting patients and study outcomes.

Objectives: To describe a patient-level algorithm to de-duplicate patients in CPRD and THIN using a cohort of prucalopride users.

Methods: Adult users of prucalopride were identified in CPRD and THIN, April 2010 through May 2014, in England, Wales, and Northern Ireland. Patients were considered duplicated if they had the same value for year of birth, sex, region, month and year of at least one prucalopride prescription, and either the same registration date or family ID. For potentially duplicated patients with a discrepancy in the number of prescriptions, all drugs prescribed during the study period were manually reviewed. A practice was considered duplicated in CPRD and THIN if at least one patient was found to be duplicated. Duplicate practices were retained in CPRD if the practice participated in linkage with the national death register at the Office for National Statistics (ONS) and Hospital Episode Statistics (HES), otherwise the practice was retained in THIN.

Results: There were 994 users of prucalopride in CPRD and 808 in THIN. The de-duplication algorithm identified 424 duplicate patients. Manual review of an additional 95 potentially duplicate patients with discrepant prescriptions identified 86 additional duplicate patients. There were 214 duplicate practices. Pooling the databases increased the number of available prucalopride users by 30% had only CPRD been used and by 60% had only THIN been used.

Conclusions: Pooling of data from similar databases is a convenient way to increase study size. Using patient-level demographic and pharmacy data can identify duplicate patients and practices, allowing reliable de-duplication in CPRD and THIN without compromising patient or practice confidentiality.

94. Methods to Estimate Days' Supply within Pharmacy Data of the Health Improvement Network (THIN)

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Background: The extent to which days' supply is missing in electronic medical records is unknown. Methods to estimate days' supply are essential for determination of exposure time in pharmacoepidemiologic studies.

Objectives: Within a cohort of adult patients with type 2 diabetes, we sought to: 1) quantify the percentage of oral anti-diabetic (OAD) prescriptions missing days' supply, 2) compare the accuracy of 3 methods for predicting days' supply, and 3) compare the incidence rates (IR) of acute myocardial infarction (AMI) across these methods.

Methods: We conducted a cohort study among patients initiating an OAD within The Health Improvement Network (THIN) from 2009-2013. We calculated days' supply of OAD as the number of tablets/prescription divided by the number of tablets/day. We first determined the prevalence of OAD prescriptions missing days' supply. We then evaluated 3 methods to estimate missing days' supply: 1) impute 30 days' supply, 2) impute mode number of tablets/day by drug strength and number of tablets/prescription, and 3) impute number of tablets/day by drug strength, number of tablets/prescription, and several patient characteristics via a machine learning algorithm. We quantified the accuracy of each method in a random sample of prescriptions for which the true days' supply was known. We then assessed the IRs of AMI in the cohort using each method for predicting missing days' supply.

Results: Days' supply was missing for 32% of 6.4 M prescriptions (impacting at least one prescription for 57% of patients). For methods 1-3, the percentage of predictions within 10 days of the true days' supply was 64%, 99%, and 99% for sitagliptin (prescribed 1 tablet/day), and 59%, 76%, and 90%, for glyburide (prescribed 1-3 tablets/day), as examples. The percent difference in IRs of AMI across methods ranged from 0-13%, with IRs from methods 2 and 3 being most similar.

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Conclusions: Days' supply was missing for a large percentage of OAD prescriptions in THIN. Imputing the number of tablets/day by drug strength and number of tablets/prescription is easy to implement, very accurate for some OADs, and results in IRs comparable to those based on machine learning.

95. Evaluating the Utility of the CPRD GOLD-HTI Linkage: Anticoagulant Prescribing at the GP Practice Compared to Hospital Dispensed Medication at Discharge Date

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Background: There is a lack of information on hospital medications in UK electronic healthcare data. CPRD and IMS Health have been collaborating to make linked data combining hospital pharmacy prescribing records with longitudinal primary care data available for public health research.

Objectives: This study aims to demonstrate the utility of the linkage between CPRD primary care data (GOLD) and the HTI (Hospital Treatment Insights) which links hospital dispensing information with events in hospital. Anticoagulants (novel oral anticoagulants (NOACs) heparin and warfarin) have been chosen as an example medication that may be initiated in hospital and continued by the GP.

Methods: Patients were limited to those eligible for the linkage between HTI and GOLD, with at least one of the study anticoagulants dispensed. ICD-10 codes associated with the anticoagulant dispensing were examined for specific treatment indications (Atrial Fibrillation, Venous Thromboembolism (VTE) and Stroke). GOLD therapy records were examined for further anticoagulant treatment following discharge.

Results: From a population of 328,930 patients in the HTI database that have been individually linked to GOLD, 19,421 had at least one record for rivaroxaban, apixaban, heparin or warfarin dispensed in hospital. Atrial Fibrillation was the most commonly recorded indication (18%); followed by VTE (5%) and Stroke (2%). 59.4% of patients had further anticoagulation prescribing at the GP; 2.4% within 30 days of discharge.

Conclusions: In this study we were able to show that further anticoagulation was continued in primary care in over half of hospitalisations discharged with these medications. Individual linkage between hospital dispensing information and existing primary care data offers the opportunity to fill the gaps in longitudinal data and follow the care pathway for patients starting treatment in secondary care in the UK.

96. Estimated Effects of Treatment Changes on Hemoglobin A1c in a Cohort with Incident Type 1 Diabetes

Richard S. Swain[1,2], Janet T. Holbrook[1], Dana Y. Teltsch[2], Christina L. Cristaldi[3], Jodi B. Segal[1] and G. Caleb Alexander[1]

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Background: The risk of complications from type 1 diabetes mellitus (T1DM) is minimized by tight glycemic control. Initiation of continuous subcutaneous insulin infusion (CSII), known as an insulin pump, and continuous glucose monitoring (CGM) has been shown to improve glycemic control in clinical trials. However, little data exist on the effectiveness of these treatments in real-world settings.

Objectives: To estimate the effectiveness of initiating CSII and/or a CGM on hemoglobin A1c (HbA1c) in a cohort of patients with incident T1DM.

Methods: This study was performed using data from the US Department of Defense Military Health Systems database between October 2007 and September 2013. A validated claims algorithm with high accuracy was used to identify new-onset T1DM patients age $\leq$ 18. Study follow-up began one year after T1DM onset to create a cohort with established (post-honeymoon) T1DM. A multivariate mixed effects model estimated the effects of switching insulin delivery from multiple daily injections to CSII and/or augmenting treatment with CGM on the first HbA1c measured after treatment change.

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Results: The cohort included 1,318 patients with incident T1DM (48% female; mean age 13.6 years at presentation). During follow-up, 174 patients initiated CSII and 159 patients initiated CGM, including 24 instances where initiation of CSII and CGM occurred simultaneously. The mean HbA1c during follow-up was 9.1% (median: 8.7%). Glycemic control did not improve following treatment change among patients already exhibiting tight control (HbA1c of 6%). However, patients with an initial HbA1c of 9% showed an average absolute reduction of 0.55% (95% CI, 0.37–0.73%) after initiation of CSII and a reduction of 0.30% (0.11–0.49%) after initiation of CGM. On average, patients with a HbA1c of 12% experienced reductions of 1.13% (0.80–1.46%) and 0.51% (0.14–0.87%) from initiation of CSII and CGM, respectively. Improvements in glycemic control from initiation of both CSII and CGM were additive.

Conclusions: Many patients experienced clinically meaningful reductions in HbA1c after initiation of CSII and/or CGM. Improvements were greater among patients with higher initial HbA1c measurements.

97. Cement Leakage and New Vertebral Fractures after Kyphoplasty and Vertebroplasty: A Meta-Analysis

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Background: Kyphoplasty (KP) and vertebroplasty (VP) reduce pain and improve quality of life for patients with osteoporotic vertebral compression fractures (VCF). The benefit of these two procedures is undermined due to concerns with subsequent spinal fractures and cement leakage.

Objectives: We undertook a meta-analysis to compare these adverse events (AEs) between KP and VP in the current clinical practice.

Methods: Articles comparing cement leakage and new spinal fractures between KP and VP in 2011-2015 were systematically searched in PubMed and Embase. The search was restricted to randomized controlled trials and cohort studies. Summary estimates of relative risk (RR) and risk difference (RD) and respective 95% confidence intervals (CI) were estimated with random effects meta-analysis. Study heterogeneity was assessed by Cochran's Q test and I-squared statistic.

Results: We identified six studies that reported 698 leaks in 1417 treatment levels and seven studies that reported 233 fractures in 1072 patients. The range of the number of patients is 77 to 271; mean age 67 - 76 years; women 67% - 77%; vertebral levels T5 to L5 except one study with T1 to L5. The endpoints were summarized at 12-16 months post-procedure. The pooled estimate for cement leakage was non-significantly reduced for patients who underwent KP in comparison with VP (RR = 0.98, CI 0.75 to 1.28, Cochran's Q test with $p = 0.0006$, $I^2 = 77\%$; RD = -0.017, CI -0.12 to 0.09, Cochran's Q, $p < 0.0001$, $I^2 = 82\%$). The pooled estimate for new spinal fracture was also non-significantly reduced for patients who underwent KP (RR = 0.96, CI 0.77 to 1.19, Cochran's Q test with, $p = 0.7$; RD = -0.02, CI -0.02 to 0.06, Cochran's Q test with $p < 0.6$).

Conclusions: Unlike the reported higher rate of new fractures associated with KP and higher rate of cement leakage associated with VP in earlier studies, we observed a comparable risk of subsequent spine fractures and cement leakage between KP and VP at 12-16 months. A noticeable dispersion of reported leakage rates suggests a possibly non-random variation. Further research is warranted to rule out potential confounding effects and to evaluate effect modification among subgroups of patients.

98. Assessing Real-World Use and Outcomes of Newly Marketed Bioprosthetic Aortic Valves Using Japanese Nationwide Cardiovascular Surgical Registry

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Background: Because high-risk medical devices are sometimes approved in Japan without evidence from clinical trials on Japanese patients, means of assessing

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their performance in the real world setting after market entry is needed.

Objectives: To evaluate the usefulness of a nationwide cardiovascular surgical registry for the assessment of use and clinical outcomes of newly marketed bioprosthetic aortic valves.

Methods: In this retrospective cohort study, we identified all patients in the Japan Adult Cardiovascular Surgery Database who had undergone aortic valve replacement with bioprosthetic valves during 2012–2014, during which time two newly-approved surgical bioprosthetic valves had entered the market. We assessed the utilization of these valves and compared baseline patient characteristics by valve type. We developed a mortality prediction model from surgical risk factors among patients receiving other bioprosthetic valves, and used it to evaluate the changes in predicted mortality in the new valve patients. We also assessed the overall standardized mortality ratio (SMR) in the two groups.

Results: We identified 32,221 eligible patients. After their introduction, the valves newly marketed in 2012Q2 (Device A) and in 2013Q1 (Device B) quickly replaced more than 25% of all bioprosthetic valves implanted in Japan (Device A 10.5% vs. Device B 15.3% vs. others 74.1% in 2014). The new valves were used in slightly older patients (median age: device A 78.9 years vs. device B 77.3 vs. others 76.3, p-value < 0.001), and patients receiving Device B were more likely to be classified as NYHA III/IV (device A 14.1%, device B 18.6%, others 15.6%; p-value < 0.001). Median predicted mortality remained stable over time for both device A (2.5% in 2012Q2 and 2.4% in 2014Q4) and device B (2.5% in 2013Q1 and 2.6% in 2014Q4). During the study period, the overall SMR was 0.92 (0.78–1.07) for Device A recipients and 1.27 (1.06–1.49) for Device B.

Conclusions: A nationwide surgical registry can provide valuable information on the use and clinical outcomes of new valve products entering the market without evidence from prior clinical trials in Japan.

99. Comparison of New Vertebral Fractures After Kyphoplasty and Vertebroplasty Usinig Medicare Data

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Background: Vertebroplasty (VP) and kyphoplasty (KP) are procedures aimed at reducing pain and stabilizing spinal fractures for patients with vertebral compression fractures. New fractures at adjacent vertebrae after VP or KP is one of the major safety concerns, but data comparing these two procedures are scarce and often controversial with large variations due to small sample size.

Objectives: The purpose of this study is to compare new claims of vertebral fractures (VF) between VP and KP in the entire Medicare population in the US from 2007 to 2012.

Methods: A retrospective cohort study was conducted using medical claims in all Medicare beneficiaries from 01/01/2006 to 07/31/2012. New claims of VF after VP and KP from January 2007 were comparted among KP, VP and non-surgery groups over 4 years of follow-up with logistic regression and Cox regression.

Results: A total of 1,757,409 beneficiaries in non-surgery group, 98,082 in VP group, and 205,535 in KP group were identified. With a mean age of 78, around 70% beneficiaries were women, and over 90% were White. While unitization of KP and VP was slightly decreased from 2007 to 2011, the proportion of beneficiaries with claims of KP was relatively increased in comparison with VP. The risk ratio (RR) of new claims of VF in VP and KP group compared with non-surgery group was 1.31 (95% CI 1.29-1.33) at 1 year and increased to 2.43-2.47 for patients with longer than 1-year of follow-up. Compared with KP, the RR of new claims of VF in VP group was 0.95 (95% CI 0.93-0.97) at year 1 and decreased to 0.77-0.72 for patients with longer than 1-year follow-up. The hazard ratio of new claims of VF in VP group was 0.86 (95% CI 0.856-0.872) compared with KP group.

Conclusions: In contrast to the perception that kyphoplasty is the preferred procedure with less adverse events, the results of this study suggest that patients who receive vertebroplasty may have a lower risk of new VF compared with kyphoplasty. This advantage of vertebroplasty appears to be more significant after the first year post-procedures.

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100. Treatment Patterns in a Cohort of Patients with Incident Type 1 Diabetes

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Background: Patients with type 1 diabetes mellitus (T1DM) require regular insulin treatment and regular monitoring of blood glucose. Insulin can be delivered by multiple daily injections or by continuous subcutaneous insulin infusion (CSII), known as an insulin pump. Glucose monitoring can be performed by finger stick measurements, called self-monitoring of blood glucose (SMBG), and may be augmented by a continuous glucose monitor (CGM) device.

Objectives: To describe patient characteristics and treatment patterns at T1DM presentation and during follow-up.

Methods: This study was performed using data from the US Department of Defense Military Health Systems database between October 2007 and September 2013. A validated claims algorithm with high accuracy was used to identify new-onset T1DM patients age ≤ 18. Treatment patterns over time were examined using Kaplan-Meier analyses and Cox proportional hazards models estimated predictors for initiation of CSII and CGM.

Results: The cohort consisted of 1,953 patients with incident T1DM (45.2% female; mean age 12.4 years at presentation). The majority (96.3%) used conventional therapy (injections and SMBG) at T1DM presentation. Over half (57.1%) of patients initiated CSII and about a third (32.6%) initiated CGM during follow-up. Most (81%) patients who initiated CGM did so concurrently or after initiating CSII. Previous use of CGM (HR = 2.5; [95% CI, 1.7–3.3]), younger age (HR = 0.94; [0.92–0.96]), female sex (HR = 1.3; [1.1–1.5]), and higher military sponsor rank ($p < 0.0001$) were associated with initiation of CSII in multivariate analysis. Previous use of CSII (HR = 22.8; [18.1–28.6]) and calendar year of diabetes presentation (HR = 10.2; [6.4–16.1] for 2012 vs 2008) were associated with CGM initiation.

Conclusions: Overall, about half the patients in our cohort initiated CSII, and about half of CSII users initiated CGM. Calendar year of diagnosis was associated with initiation of CGM but not CSII, suggesting that CGM was becoming a more common treatment while CSII initiation patterns were stable during the study period.

101. Risk Factors for Persistent and New Chronic Opioid Use in Patients Undergoing Total Hip Arthroplasty

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Background: Use of opioids for pain management in total hip arthroplasty (THA) patients, both before and after surgery, is common, putting THA patients at risk of opioid abuse.

Objectives: To identify risk factors for persistent or new chronic opioid use post-THA.

Methods: A retrospective cohort study of 9525 patients who underwent THA between 01/01/2001 and 12/31/2012 was conducted. Using the Australian Department of Veterans' Affairs administrative data, opioid use pre- and post-THA and patient characteristics were identified. Chronic opioid use was defined as 90 days of continuous use or 120 days of non-continuous use. Chronic use patterns were characterized according to: age, gender, surgical indication, comorbidities, other analgesic medication, and history of opioid utilization. Logistic regression models were employed.

Results: Post-THA, 3.2%(n = 302) of patients remained chronic users while 2.0% (n = 190) became new chronic users. Risk factors for persistent chronic use were younger age (OR = 0.63, 95% CI 0.49-0.82/10 year increment), back pain (OR = 1.89, 95%CI 1.16-3.07), diabetes (OR = 2.89, 95%CI 1.08-7.73), hypnotics use pre-THA (OR = 2.38, 95%CI 1.45-3.90), and higher levels of opioid exposure pre-THA (OR = 2.17, 95%CI 1.92-2.46/30 day increment). Risk factors for becoming a chronic opioid user after THA

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were female gender (OR = 1.40, 95%CI 1.00-1.96), back pain (OR = 3.90, 95%CI 2.85-5.33), depression (OR = 1.70, 95%CI 1.20-2.41), gastric acid disease (OR = 1.62, 95%CI 1.16-2.25), migraine (OR = 5.11, 95%CI 1.08-24.18), liver disease (OR = 4.33, 95%CI 1.08-17.35), weight loss (OR = 2.60, 95%CI 1.06-6.39), use of hypnotics (OR = 1.56, 95%CI 1.13-2.16) and anti-neuropathic pain medications (OR = 3.11, 95%CI 2.05-4.72) pre-THA.

Conclusions: We identified groups at risk of chronic opioid use, as well as potentially modifiable factors, including level of opioid exposure pre-surgery and hypnotic use. These indicators of chronic opioid use can be used to target specific patient groups for suitable pain management interventions.

102. A Comparative Analysis of Secondary Surgeries of Six Total Cervical Disc Arthroplasty Devices to Cervical Arthrodesis at 5-Years

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Background: Spinal cervical degenerative disc diseases (DDD) are a major cause of morbidity and impairment for the general population effecting roughly 2,000,000 amount of people each year in the US, with approximately 80,000 requiring surgery. Several treatment options exist ranging from conservative management to surgical, consisting of: discectomy, decompression, cervical total disc replacement (C-TDR) to anterior cervical discectomy and fusion (ACDF). There are seven different C-TDR systems indicated cervical disc repairs available in the US yet how they perform long term compared to their most common alternative, ACDF, remains unknown.

Objectives: Provide an overall comparison of all US commercially available C-TDR devices to ACDF for up to 5 years post-operatively, using long-term follow-up data from FDA-mandated post-market studies.

Methods: Long term follow-up data from all 7 US-approved total C-TDR devices was used. All 7 RCTs were reviewed to ensure similarity in design features as far as baseline patient demographics, control procedural characteristics. Then data from the originally randomized groups from each individual study was abstracted systematically from the most recent follow-up reports submitted between 2014-2015 to the FDA as part of the manufacturers post market requirement. The data was then pooled for an overall weighted comparison for a variety of secondary surgical outcomes up to 60 months post-op using a random and fixed effect model.

Results: In total a pooled total sample size of 500 patients were reviewed, with The overall pooled risk at 60-months was 0.08 [0.05,0.13] (C-TDR as reference) for revisions, 0.043 [0.32,0.60] for removal, 0.13 [0.07,0.22] Supplemental Fixation, and 1.53 [0.57,4.06] for reoperation.

Conclusions: Pooled long-term follow-up data from the 7 US-approved randomized clinical trials evaluating C-TDR demonstrate significantly non-inferior (or reduced) rates of both early and long-term secondary surgery up to 5 years post-operatively. C-TDR reached significantly different rates of revision as early as 6 months postoperatively, compared to the ACDF control group.

103. Hospital Variation And Patient Characteristics Associated With Vena Cava Filter Use For Venous Thromboembolism

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Background: Vena cava filters (VCFs) have increased in use over the last decade despite lack of consensus regarding their use. It has been suggested that use may be associated with upcoding to increase hospital reimbursement.

Objectives: To evaluate the hospital level variation in VCF utilization and to assess patient factors associated with VCF use for deep vein thrombosis (DVT) and pulmonary embolism (PE).

Methods: Inpatient discharge data from all acute care hospitals with DVT/PE in Kentucky were used. Hierarchical logistic regression models were used to evaluate the relationships of study variables with VCF use controlling for clustering of patients at each institution.

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A linear model was also used to predict hospital utilization while controlling for patient case-mix and institutional characteristics.

Results: During the study period, 84,357 discharges for DVT/PE were observed and 10.2% of these received a VCF. This included 12,313 cases of PE + DVT, 19,197 cases of PE only, and 52,847 cases of DVT only. VCF use among these groups was 21.0%, 5.8%, and 7.6%, respectively. In adjusted analyses, VCF use was associated with increasing age, indicating that those over age 65 were twice as likely to receive a filter compared to the reference (21-25 year-old) group. Significant comorbidities associated with VCF use included cancer, liver disease, cerebrovascular disease, atrial fibrillation, anemia, and concurrent bleeding. Lower extremity, proximal DVTs, and patients receiving thrombolytic therapy or embolectomy, those having surgery, and those who were unstable or had trauma, were also more likely to receive a filter. Among cancer types, brain and colorectal cancer were significantly associated with VCF use. Hospital random effects were not significant. For the linear model, an R-squared of 0.96 was observed showing that most of the variation between institutions was explained by the model.

Conclusions: Several patient factors associated with high comorbidity and severity were associated with VCF use. After controlling for these factors, there did not appear to be any differences between institutions.

104. Use of Contraindicated Drugs in Pediatric Outpatients in the Nordic Countries

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Background: Only a few pharmacoepidemiological register studies have included nationwide data from several countries. Children are an underrepresented patient group in every type of trials and studies. In addition, real-life data on use of contraindicated drugs is scarce.

Objectives: The aim of this study was to survey utilization of contraindicated drugs in children and adolescents in Finland, Sweden, Norway and Denmark in 2008-2013.

Methods: Finnish summaries of product characteristics (SPCs) that mention any type of pediatric patients in the contraindications chapter were searched, and the results were then reviewed in Swedish, Norwegian and Danish SPCs. After this, users of contraindicated drugs were identified in national administrative prescription databases in the four Nordic countries. The searches were based on anatomical therapeutic chemical classification codes (ATCs).

Results: Of 49 contraindicated drugs found, the greatest single numbers of users were seen for etoricoxib in Finland (N = 2661; 29/10 000 <16-y.), oxymetazoline in Norway (N = 2160; 177/10 000 <2-y.), betamethasone in Denmark (N = 1617; 283/10 000 <1-y.), zopiclone in Denmark (N = 1586; 13/10 000 <18-y.), and diclofenac in Sweden (N = 1212; 8/10 000 <14-y.). Many of the ATCs identified represented over-the-counter drugs of which the purchases were not shown in the prescription data.

Conclusions: The age limits in the contraindication texts in the SPCs could vary between the Nordic countries. Combined with adequate local knowledge the Nordic nationwide prescription registers can, however, serve as exceptional data sources for multinational pharmacoepidemiological studies. Our aim is to further survey use of different type of off-label use in children.

105. Recent U.S. Drug Utilization For Pediatric Inflammatory Bowel Disease, 2009-2015

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Background: Although 10%-20% of IBD is diagnosed in childhood, the development of drugs for this population lags behind adult IBD drug development and few studies have examined the use of these agents in the pediatric IBD population (pIBD).

Objectives: To describe recent US drug utilization patterns for pIBD, using a sequential cross-sectional study design nested in health insurance claims data.

Methods: The data source was Truven Health Analytics MarketScan®, containing medical service and prescription drug claims from commercial, Medicaid (11 states) and Medicare supplemental insurance plans for over 80 million US patients. pIBD cases were identified using previously-established methods for claims data, required to have pharmacy benefits, and grouped into mutually exclusive categories of ulcerative colitis (UC) and Crohn's disease (CD) for the study period (2009-2015Q3). The first ICD-9 claim was assigned as an index date. The main outcome, drug utilization (% with ≥1 dispensing), for anti-TNFs, aminosalicylates (ASAs), corticosteroids (CSs), and immunosuppressants was described among cross-sections of children (0-18) with 6, 12, 24, and 36 months of post-index date follow-up time by IBD type (8 cohorts in total). Statistical hypothesis testing was not performed in this descriptive study.

Results: Patient N varied by cohort membership; the largest cohorts (6-month) had 13,802 CD and 7,629 UC patients, while the smallest (36-month) had 4,610 CD and 2,474 UC patients. ASAs were the most commonly-used group by 6 months among both CD (40.4%) and UC (50.6%) patients, followed by CSs (33.1% CD, 30.9% UC). Use of anti-TNFs was 6.3% in CD and 2.3% in UC. By age strata, six month use was always lowest among children <5 compared to 5+ for all drug groups. In the 36-month cohorts for CD and UC, >56% of patients aged 0-18 had used ASAs or CSs over the 3-year period, while 17.1% / 7.5% of the CD / UC patients, respectively, had used anti-TNFs.

Conclusions: In the context of a changing treatment landscape, the present study provides a recent snapshot of real-world drug utilization among children with IBD at various time points during the disease course.

106. Psychiatric Diagnoses and Medication Patterns in a Medicaid-Insured Birth Cohort

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Background: Over the last three decades, the increase in psychotropic medication use among children and adolescents has been prominent. Most studies have assessed psychotropic medication use in cross-sectional studies at annual intervals. However, little is known about the patterns of psychiatric service use in young children from longitudinally designed studies.

Objectives: The main objectives of this study were: 1) To estimate the cumulative incidence of the first clinician-reported psychiatric diagnosis and first psychotropic medication use from birth through age 5; 2) To compare the cumulative incidence of psychiatric diagnoses and medication use to annual prevalence derived from cross-sectional data.

Methods: A longitudinal cohort of children born in 2007 and continuously enrolled through 2012 was created (N = 15,380) representing 39.4% of the Medicaid births in 2007. We assessed psychiatric diagnoses and psychotropic medication use cumulatively and annually from birth to age five.

Results: At birth, the cohort was 51.1% male and largely nonwhite (67.0%). Cross-sectionally, the annual percent of any psychiatric diagnosis ranged from 0.91% in 2007 (age 0-1 year) to 4.80% (age 5-6 years) in 2012. By contrast, the cumulative incidence for a psychiatric condition reached 20.66% of children in the total cohort by age 5. The annual percent of any psychotropic medication use ranged from 0.11% in 2007 (age 0-1 year) to 3.56% (age 5-6 years) in 2012. By age 5, the cumulative incidence for any psychotropic medication use was only slightly elevated (4.64%) compared with the annual percent prevalence at age 5-6 years.

Conclusions: In this large birth cohort of Medicaid-insured preschoolers, the longitudinal patterns for psychiatric diagnoses and psychotropic medication use were distinctly different. By 5-6 years of age, the cumulative incidence for psychiatric diagnoses was substantially greater than for psychotropic medication use.

107. Poor Guideline Adherence In The Initiation Of Antidepressant Treatment In Children And Adolescents In The Netherlands: Choice Of Antidepressant And Dose

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Background: The Dutch guideline for the treatment of depression in young people recommends initiating antidepressant treatment with fluoxetine, as the evidence for its efficacy is strongest and the risk of suicidality may be lower than with other antidepressants. Furthermore, low starting doses are recommended.

Objectives: We aimed to determine whether antidepressant prescriptions are in accord with guidelines.

Methods: A cohort of young people aged between 6 and 17 at the time of antidepressant initiation was selected from IABD, a Dutch pharmacy prescription database. The percentage of prescriptions for each antidepressant was determined. Starting and maintenance doses were determined and compared with recommendations for citalopram, fluoxetine, fluvoxamine, and sertraline.

Results: During the study period, 2942 patients initiated treatment with an antidepressant. The proportion of young people prescribed fluoxetine increased from 10.1% in 1994 – 2003 to 19.7% in 2010 – 2014. However, the most commonly prescribed antidepressants were paroxetine in 1994 – 2003 and citalopram in 2004 – 2014. The median starting and maintenance doses were ≤0.5 DDD/day for tricyclic antidepressants and 0.5 – 1 DDD/day for SSRIs and other antidepressants. Starting doses were guideline-concordant 58% of the time for children, 31% for preteens, and 16% for teens. Sixty percent of teens were prescribed an adult starting dose.

Conclusions: Guideline adherence was poor. Physicians preferred citalopram over fluoxetine, in contrast to the recommendations. Furthermore, although children were prescribed a low starting dose relatively frequently, teens were often prescribed an adult starting dose. These results suggest that dedicated effort may be necessary to improve guideline adherence.

108. The Association Between Fluoroquinolone and Musculoskeletal Adverse Events in Pediatrics

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Background: Fluoroquinolones (FQ) are very important antibiotics, they have a broad spectrum of activity and good pharmacokinetic profile which makes them useful in treating numerous infectious diseases. Although general consensus is that FQ may be acceptable for pediatric use under special circumstances, clinicians are still concerned about their risk for reversible arthropathy or tendinopathy in children.

Objectives: The objective of this study was to evaluate FQ-associated short-term musculoskeletal adverse events in comparison with matched controls by using National Health Insurance Research Database (NHIRD) in Taiwan.

Methods: We conducted a population based retrospective cohort with a nested case control study to evaluate short-term musculoskeletal risks of FQ compared with other antibiotics. With cases who had musculoskeletal events in admission datasets during 2008 to 2013, the first admission date was the index date. Matched controls (1:10) with age, gender and calendar year, who have never had musculoskeletal events in admission datasets during the study period. Exposure status was defined as current users (within 30 days), recent users (30-365 days) and non-users >365 days). We estimated the odds ratio (OR) and 95% confidence interval (CI) for current and non-users on musculoskeletal events by using a conditional logistic regression model to adjust potential confounding factors. All analysis will be performed with SAS for Windows, version 9.3.

Results: The major diagnoses of FQ prescriptions was respiratory tract infection and ofloxacin was the most frequency use fluoroquinolones, followed by ciprofloxacin. Total 1,183 cases and 8,093 matched controls enrolled in this study, mean age is 15 years and 61% are male. We found that use of fluoroquinolones increased the risk of admission with musculoskeletal events (current user OR 10.3 (95% CI 6.8-15.5), recent user OR 2.75 (95% CI 2.2-3.3)) compared with non-users.

Conclusions: The NHI claims database becomes a particularly appropriate resource for the in-depth

studies of drug related problems, especially in pediatrics. Several sensitivity analyses to confirm our findings in the future.

109. First Time Signal Detection of Global Paediatric Data – Putting Theory into Practice

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Background: Drugs and adverse reactions reported for children have a different pattern than for adults. There is limited published evidence on how open-ended detection of previously unrecognized adverse drug reactions (ADRs) in paediatric data works in practice.

Objectives: To explore the feasibility of detecting new possible ADRs in paediatric individual case safety reports (ICSRs).

Methods: ICSRs on ages 0-17 years were retrieved from VigiBase® in September 2014. Reports for vaccines or in-utero exposure and suspected duplicate reports were excluded. A table with drug-ADR-age group triplets was generated using four age groups: 0-27 days (A); 28 days to 23 months (B); 2-11 years (C); and 12-17 years (D). vigiRank™, a new strength-of-evidence measure, was applied to prioritize the triplets. The table was restricted to drug-ADRs represented by at least one report received after 2011, ≥ 2 countries, and ≤ 30 reports for the paediatric age groups combined. Drug-ADRs previously checked were excluded. During the week-long manual screening additional table restrictions were applied, alone or in combination: serious events, drugs reported recently for the first time in age group, negative disproportionality measure for age-independent dataset, and automatic exclusion of labelled ADRs. Assessors classified the triplets as being labelled/non-signal/to be kept under review (KUR)/potential signal. The potential signals were clinically evaluated in-depth to determine whether a signal should be communicated.

Results: A total of 472 triplets (per age group A=13; B=37; C=217; D=205) were manually assessed. The proportion (%) of labelled ADRs/non-signals/KURs/potential signals per age group were: A: 31/69/0/0; B: 35/65/0/0; C: 61/30/0.5/8; D: 70/24/0.5/5. Combining serious events with new drugs and combining non-labelled reactions with the negative reference disproportionality measure contributed with the greatest rate of potential signals. The in-depth clinical evaluation resulted in eight signals.

Conclusions: Clinically relevant signals can be detected by using paediatric age subgroups in global ICSRs. It is noteworthy that no signals were identified in the two youngest age groups.

110. The Impact of Birth Season on Time to First Antibiotic Use Among Infants Born in Denmark 2004-2012

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Background: Antibiotic use in early life may be associated with adverse effects on immune function that depend in part on age at first use. Data are limited on determinants of age at first antibiotic use.

Objectives: To estimate how birth season impacts age at first antibiotic use.

Methods: This nationwide cohort study included all live singleton births from 2004-2012, identified in the Danish Medical Birth Registry. We assigned birth season as winter (Dec-Feb), spring (Mar-May), summer (Jun-Aug), and autumn (Sep-Nov). We linked data from the National Database of Reimbursed Prescriptions for all filled antibiotic prescriptions (ATC codes J01) during the first year of life. Using age (in months) as the time scale and first antibiotic fill as the event, we estimated Kaplan-Meier cumulative incidence (risk) and hazard functions, censoring at death, emigration, or on 31 Dec 2012. All 99% confidence

limits for risks were within 0.3% and are thus not presented. We compared results across birth-season cohorts.

Results: Among 561,737 children, risk of first antibiotic use increased from 2.2% (3 months of age) to 9.3% (6 months) to 41.5% (12 months). Hazard increased with age through 12 months (up to 3.1 per 1,000 infants per day), and peaked in winter. As a result of these two influences on hazard, risk profiles through the first year varied by birth-season cohort. Spring births had the lowest risk through 6 months of age (6.7%) and the highest through 12 months (46.8%), whereas autumn births had the highest risk through 6 months (12.5%) and the lowest through 12 months (36.8%). Through 9 months, summer births had the highest risk (28.5%), spring and autumn births had lower risk (23.1%), and winter births had the lowest risk (18.4%).

Conclusions: Hazard of first antibiotic use increased with age and peaked in winter; as a result, autumn births had the highest 6-month risk, summer births had the highest 9-month risk, and spring births had the highest risk of use during the first year. Because infants' age at first antibiotic use may modify their response, these findings about birth-season cohort effects on time to first use may inform safety and effectiveness studies of antibiotics.

111. Prevalence and Risk Factors for Opioid Misuse in Youth: Results from a National Study in the US

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Background: Adolescents in the US have a higher prevalence of prescription opioid misuse than some other age groups in the general population. Further research is needed on the factors associated with opioid misuse in youth.

Objectives: To determine prevalence and examine risk factors for opioid misuse in a national study of youth aged 10-18 in the US.

Methods: The National Monitoring of Adolescent Prescription Stimulants Study (N-MAPSS) was conducted in four waves from 2008 to 2011. Participants 10 to 18 years of age were recruited from entertainment venues in urban, rural and suburban areas of 10 US cities. Participants completed a survey including questions on the use of opioids (e.g. Oxycontin® and Vicodin®), source of opioids and route of administration. Misuse was defined as a non-labeled route of administration or use that was not prescribed. Additionally, information on age, gender, alcohol, cannabis and tobacco use was also collected. Summary descriptive and chi square statistics were calculated using SAS 9.4.

Results: Of the 10,963 youth who provided information about past 30 day opioid use, 10,445 had not used opioids (95.3%). Overall, prevalence of opioid misuse was 2.7% (n = 300) and opioid use with no misuse was 2.0% (n = 218). While more females than males reported not using opioids (52.4% vs 47.6%) or opioid use without misuse (60.1% vs 39.9%), more males than females (59.0% vs 41.0%) misused opioids ($p<0.0001$). Older teens (16 to 18 years) had misused opioids (72.3%) more than younger teens (14-15 years; 25.3% and 10-13 years; 2.3%; $p<0.0001$). Current tobacco use and past 30 day cannabis and alcohol use were positively correlated with misuse (55.7%, 74.3% and 81.7%, respectively). All correlations were significant ($p<0.0001$).

Conclusions: Youth who misused opioids, compared to youth who did not, were more likely to be male and to report current tobacco use, and recent cannabis and alcohol use. Interventions are needed for this important group, especially older teens.

112. Urosepsis and Urinary and Genital Infections Among Diabetes Patients and Matched Controls

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Background: Type 2 Diabetes (T2DM) is associated with increased risk of infection.

Objectives: To compare the documented history of urosepsis, genital infections (GI) and urinary tract

infections (UTI) among T2DM (pts) with matched non-T2DM pts.

Methods: We identified T2DM pts from electronic medical records (EMRs) of Kaiser Permanente Northwest during a 7-year window (2006-2012). The cohort study included 39,301 people with T2DM and 39,301 non-T2DM pts matched on age, sex, index year, and availability of a serum creatinine measurement in the index year (to account for health and propensity to use services). The T2DM group included pts with prevalent T2DM and newly diagnosed (incident) pts. Those with a diabetes recognition date prior to 2006 were assigned an index date of 1 January 2006. For cases identified on or after that date, the actual diagnosis date was the index date. Non-T2DM pts were assigned the same index date as their matched T2DM pts. History of urosepsis, UTI, and GI were identified from all available EMR data (look-back 1 January 2000 through the index date). We compared the outcomes of interest in total and separately for prevalent and incident T2DM.

Results: Incident T2DM pts (41% of total, n = 16,234) had a mean age of 58.3; 48% women. Mean age of prevalent T2DM pts (59%, n = 23,067) was 61.6; 48% women; mean diabetes duration at index date was 5.8 years. Overall, T2DM pts were more likely to have a history of urosepsis (29% vs. 26%, $p<.001$), UTI (31% vs. 28%%, $p<.001$) or GI (41% vs. 37%%, $p<.001$). T2DM incident pts compared with non-T2DM pts were more likely to have a history of urosepsis (28% vs. 26%, $p<.001$), UTI (30% vs. 28%, $p<.001$) and GI (40% vs. 39%, $p=.039$). However, these differences were substantially larger when comparing prevalent T2DM with non-T2DM pts (urosepsis, 30% vs. 25%; UTI, 32% vs. 27%; GI, 42% vs. 36%; $p<.001$ for all).

Conclusions: Compared with nondiabetic patients, history of urosepsis, UTI and GI was already more common among T2DM pts at diabetes diagnosis. The larger differences seen among prevalent T2DM patients vs. non-T2DM suggest that diabetes increases the risk of genitourinary infections.

113. Gastrointestinal Cancer Incidence in Type 2 Diabetes Mellitus; Results from a Large Retrospective Population-Based Cohort Study in the UK

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Background: Type 2 diabetes mellitus (T2DM) has been suggested as a risk factor for liver, pancreatic, and colorectal cancer. T2DM patients show higher incidences of these cancers compared to the non-diabetic (non-DM) population. Current evidence, however, is inconsistent with respect to the incidences of other gastrointestinal (GI) malignancies.

Objectives: To determine incidence rates (IRs) of all GI cancers in patients with and without T2DM.

Methods: A retrospective cohort study was conducted using the UK Clinical Practice Research Datalink (CPRD) during 1988-2012. A T2DM cohort of antidiabetic drug users was matched to a non-DM reference cohort, by age, sex, and practice. Crude incidence rates (IRs) per 100,000 person-years (10^5 py) and 95% confidence intervals (CI) were calculated, stratified by age, sex, and calendar period. IRs were compared using the normal theory test.

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Results: 333,438 T2DM subjects and 333,438 non-DM subjects were analyzed, with a total duration of follow-up of >3.6 million py and 10,977 observed GI cancer cases. Overall, IRs of any GI cancer (IR 330 vs. 276 per 10^5 py), liver cancer (IR 26 vs. 8.9 per 10^5 py), pancreatic cancer (IR 65 vs. 31 per 10^5 py), and colon cancer (IR 119 vs. 109 per 10^5 py) were significantly higher in the T2DM cohort compared to the non-DM cohort, whereas the IR of esophageal cancer was significantly lower (IR 41 vs. 47 per 10^5 py, $p<0.05$). After stratification by sex, the higher IR of colon cancer only remained statistically significant in men, and the lower IR of esophageal cancer only remained statistically significant in women. No differences in IRs between the T2DM and non-DM cohort were found for gastric, biliary, and rectal cancer.

Conclusions: Higher IRs for liver, pancreatic, and colon cancer were found in T2DM patients versus non-DM controls. Furthermore, we found no differences in IRs for gastric, biliary, and rectal cancer. The results of this study underline the importance of clinical awareness for liver, pancreatic and colon cancer in the T2DM population. In addition, the lower observed IRs of esophageal cancer in T2DM patients warrants further investigation.

114. Association Between Insulin Treatment and Breast Cancer Characteristics

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Background: It is hypothesized that there is a link between insulin (analogues) and (breast) cancer. However, epidemiological studies regarding breast cancer (BC) among patients using insulin (analogues) are inconsistent.

Objectives: To investigate whether treatment with insulin (analogues) before BC diagnosis is associated with the development of specific BC characteristics.

Methods: For this case-control study, females with invasive BC (stage I-IV) diagnosed between 1998 and 2011 were selected from the Eindhoven area of the linked Netherlands Cancer Registry-PHARMO Database Network cohort. Females using insulin (analogues) were compared twice: once to females using oral antidiabetics (OAD) prior to their primary BC diagnosis (unmatched) and once to females with no antidiabetic (AD) treatment prior to diagnosis (matched (1:4)). Patient and tumour characteristics (TNM stage, morphology, grade, hormone receptor status and clinical subtype) were determined at the date of the first primary BC diagnosis. Multivariate (conditional) logistic regression analyses were used to investigate the association between AD treatment and different BC characteristics.

Results: A total of 149 females using insulin (analogues) were compared to 289 females using OAD and to 596 females with no AD treatment. Females using insulin (analogues) were more likely to have BC clinical subtype luminal B than BC clinical subtype luminal A compared to females using OAD (OR (95%CI): 3.0 (1.3-7.3)). This association was also observed compared to females with no AD treatment, but was statistically not significant (OR (95% CI): 2.2 (0.5-9.1)). Females using insulin (analogues) were more likely to have a poorly differentiated tumour (grade 3) than a well differentiated tumour (grade 1) compared to females using OAD (OR (95% CI): 2.2 (1.0-4.7)). This association was also observed when comparing to females with no use of AD treatment (OR (95%CI): 4.7 (1.5-15.2)). No statistical significant association was found for the other BC characteristics.

Conclusions: The results of this study indicate that females using insulin (analogues) are at increased risk of developing more aggressive breast tumours than females using oral or no AD treatment.

115. A Population Based Study of Metformin and the Association with Survival in Pancreatic Cancer Patients

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Background: Previous studies have suggested an association between the use of metformin and an improved overall survival in patients diagnosed with pancreatic cancer. Both epidemiological and preclinical data claim a beneficial effect of metformin on pancreatic cancer, however some of these studies have been subject to several important methodological limitations.

Objectives: The aim of this study was to assess the association between overall survival and the use of metformin in patients with pancreatic cancer. The difference in overall survival between metformin users and nonusers was assessed, and additionally between metformin users and sulfonylurea derivatives users.

Methods: A retrospective observational cohort study was conducted using data of patients diagnosed with pancreatic cancer from the Netherlands Comprehensive Cancer Organization (1998-2011). Data were linked to the PHARMO Database Network containing drug-dispensing records from community pharmacies. Patients were classified as metformin user or sulfonylurea derivatives user from the moment of first dispensing until the end of follow up. Univariable and multivariable parametric survival models were used. Metformin use and sulfonylurea derivatives use were included as time varying covariates.

Results: In total 907 patients were analysed. Overall, 77 users of metformin, 43 users of sulfonylurea derivatives, and 787 nonusers were identified. The adjusted rate ratio for overall survival for metformin users vs nonusers was 0.86 (95% CI 0.66-1.11; P = 0.25). The difference in overall survival between metformin users and sulfonylurea derivatives users showed an adjusted rate ratio of 0.90 (95%CI 0.59-1.40; P = 0.67).

Conclusions: In this study there was no association found between overall survival and pancreatic cancer patients using metformin, despite several previous epidemiological studies describing a survival benefit. This was in concordance with two recently published randomized controlled trials. Future research should focus on the development or repurposing of other drugs for pancreatic cancer and the use of adjuvant metformin in other cancer types.

116. Prevalence of Type 1 and Type 2 Diabetes Among U.S. Pediatric Population in the MarketScan Multi-State Medicaid Database, 2002-2013

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Background: The prevalence of type 1 (T1DM) and type 2 diabetes (T2DM) among U.S general pediatric population have been reported. However, there is limited information on the prevalence of diabetes among children on social welfare and covered by Medicaid.

Objectives: To estimate the prevalence of T1DM and T2DM among U.S. Medicaid pediatric population aged <18 years from 2002 to 2013 by age, sex and ethnicity.

Methods: Patients aged <18 years old from 2002 to 2013 were identified from the MarketScan Multi-State Medicaid Database. Diabetes was defined as having 1) one claim for an outpatient or inpatient diabetes diagnosis and two or more prescriptions for any anti-diabetes medications or 2) records of two or more claims for an outpatient or inpatient diabetes diagnosis that were at least 30 days apart. Patients with one or more claim (s) for secondary diabetes, diabetes insipidus, or gestational diabetes mellitus before or on the earliest date of the recorded claim for diabetes were excluded. Annual prevalence of diabetes (overall, T1DM, and T2DM) and 95% confidence intervals were calculated. Age-, sex- and race- stratified prevalence were also assessed.

Results: A total of 49,647 patients aged <18 years at first claim of diabetes in the Medicaid between 2002 and 2013 were included in the analysis. Overall, the annual prevalence of diabetes increased from 1.98/1,000 in 2002 to 4.39/1,000 in 2013: 1.29 to 2.07/1,000 for T1DM and 0.69 to 2.31/1,000 for T2DM. Prevalence of both T1DM and T2DM increased with age. While prevalence of T1DM was similar between boys and girls and was most prevalent in non-Hispanic White, prevalence of T2DM was higher in girls than boys and was most prevalent in Blacks.

Conclusions: To our knowledge, this is the first study that examined T1DM and T2DM prevalence stratified by age, sex and ethnicity among pediatric population covered by Medicaid. The annual prevalence of T1DM and T2DM patients enrolled in the U.S.

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Medicaid pediatric population increased from 2002 to 2013, with age, sex and ethnic disparities seen in diabetes prevalence, overall and by diabetes type.

117. Renal Function Measurements in Diabetes Patients; A Population Based Study in the Netherlands

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Background: Adverse drug effects due to medication errors are a major source of potentially avoidable hospitalizations. Since 2006 various guidelines advise to yearly monitor renal function in patients with diabetes mellitus (DM). Awareness of the renal function is pivotal to improve medication safety in patients with impaired renal function. Creatinine is used to monitor renal function, where a low value indicates a better renal function.

Objectives: To determine the availability of renal function measurements for the overall population and especially for DM patients over time in the Netherlands.

Methods: A descriptive cross-sectional study was performed using data from the PHARMO Database Network, a population-based network in the Netherlands combining data from different healthcare settings such as out-patient pharmacies and clinical laboratories. Per year, creatinine measurements were identified for patients in the overall population and for a sub cohort of DM patients in the period 1999-2014.

Results: From 165,967 patients in 1999 to 858,147 in 2014 were included in the overall population (mean age was 52 years, 45% was male and the mean number of creatinine tests per patient per year was around 0.8, similar distribution over time). In 1999 35% of the population did have a creatinine measurement, in 2006 29% and in 2014 32%. The mean (±SD) creatinine value decreased from 92.7 (±29.9) in 1999 to 81.6 (±28.0) in 2014. For DM, 3,842 patients were included in 1999 and 28,900 in 2014 (mean age was 68 years and 51% was male, similar distribution over time). In 1999 70% of the DM patients did have a creatinine measurement, in 2006 76% and in 2014 75%. In 1999 the mean (±SD) number of creatinine tests per patient per year was 1.9 (±5.4) and in 2014 this was 2.4 (±6.3). The mean (±SD) creatinine value decreased from 94.6 (±30.2) in 1999 to 88.2 (±31.4) in 2014.

Conclusions: In the overall population, no change in monitoring of renal function was observed. In DM patients, there was an increase in the number of creatinine measurements and the mean value of these measurements decreased over time. Monitoring creatinine in DM patients is crucial to prevent complications.

118. Prevalence of Combinations of Diabetes Complications Across NHANES and NHWS

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Background: Diabetes-related complications and comorbidities affect health outcomes to varying degrees.

Objectives: This study quantified prevalent complications and their combinations across two national patient surveys, to better understand the potential impact of diabetes in the US.

Methods: Data were analyzed from the 2013 National Health and Wellness Survey (NHWS), a cross-sectional, self-reported online survey of 75,000 adults, and from 2009-2014 National Health and Nutrition Examination Survey (NHANES), a nationally representative interview and clinical assessment of approximately 5,000 persons each year. Measures included demographics and patient-reported diagnosis with comorbidities, including the following diabetes-related complications: retinopathy and cardiovascular (CVD) conditions (hypertension, high cholesterol, atherosclerosis, stroke, heart attack, and angina). Descriptive analyses included means, standard deviations,

percentages, and frequencies, weighted to the general population based on US Census Bureau numbers.

Results: Among 8,361 diabetic adults (24.2 M weighted; 10.4%) in NHWS, and based on prevalence and conceptual relevance, groups included: non-comorbid controls (18.4%); mild CVD only (65.1%); CVD (inclusive of mild CVD; 10.8%); retinopathy (inclusive of mild CVD; 4.4%); and CVD/retinopathy combined (1.3%). Among 2,184 adults (20.6 M weighted; 8.9%) with diabetes in NHANES, corresponding groups included: controls (10.5%); mild CVD (56.6%); CVD (15.4%); retinopathy (12.6%); and CVD/retinopathy (4.9%). In both surveys, 18-64 year-old patients had the fewest comorbidities, 65-74 year-old females had fewer combinations than same-age males, and CVD increased with age.

Conclusions: Diabetes-related complications exhibited similar prevalence patterns across NHANES and NHWS, with more severe combinations among the elderly. Lower rates of CVD, retinopathy, and combinations were seen in NHWS (16.6%) than NHANES (32.9%). Differentiating the prevalence of complications can improve targeted, effective management of multimorbidity, recognizing unmet needs among patients with more impactful conditions.

119. Estimating the Prevalence and Incidence of Type 2 Diabetes Mellitus Using Population Level Pharmacy Claims Data

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Background: Pharmacy claims data present an alternative measure of the burden of type 2 Diabetes mellitus (T2DM) to complement existing estimates derived from cohort and cross-sectional studies.

Objectives: To use a national pharmacy claims database to estimate the prevalence and incidence of T2DM.

Methods: We used data from the Health Service Executive-Primary Care Reimbursement Service database in Ireland to conduct this cross sectional study. Prevalent cases of T2DM were individuals using an oral hypoglycaemic agent, irrespective of insulin use, in 2012. Incident cases were individuals using an oral hypoglycaemic agent in 2012 who had not used one in the past. We used denominator data from the Central Statistics Office. Estimates were calculated for the entire population, and stratified by age and sex.

Results: In 2012, there were 114,957 prevalent cases of T2DM giving a population prevalence of 2.51% (95% CI 2.49 – 2.52). When restricted to the adult population (≥15 yrs) this was 3.16% (95% CI 3.15-3.18). The highest prevalence was in those aged 55-64 years (6.50%), 65-70 years (10.75%) and 70+ years (12.1%). 21,574 people developed T2DM in 2012 giving an overall incidence of 0.48% (95% CI 0.48 – 0.49). In the adult population this was 0.60% (95% CI 0.60-0.61). Incidence rose with age to a maximum of 2.08% (95% CI 2.02-2.15) in people aged 65-69 years and fell to 1.86% (95% CI 1.81 – 1.90) in those aged 70+ years. Men had both a higher prevalence and incidence of T2DM than women.

Conclusions: Pharmacy claims data provide an opportunity to measure objectively defined T2DM at the population level using up to date data. Comparisons with existing cross-sectional and cohort study data are required because undiagnosed and lifestyle treated diabetes are unidentifiable in pharmacy data.

120. Incidence of Diabetes in Two National Surveys – What's Driving the Trend?

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Background: Over the past two decades the prevalence of diabetes reached epidemic level in the United States, but recently prevalence stabilized at approximately 22 million adults. It is one of the most costly chronic conditions to treat considering both direct medical care costs along with indirect costs from disability, productivity loss and premature death.

Objectives: To determine the trend in incidence from 2005 through 2014 among adult diabetics and whether variations exist by age, gender, or race.

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Methods: This analysis was based on the National Health Interview Survey (NHIS) and the National Health and Wellness Survey (NHWS). Both surveys are cross-sectional, self-reported surveys of similar sample size (75,000 – 100,000 with year over year variations), but NHIS is a household survey while NHWS is on-line. The diabetic population was based on self-reported doctor diagnosis and incidence was calculated by subtracting the diabetic patients age at diagnosis from their current age. Diabetic patients with <1 year since diagnosis along with a proportion of the diabetic patients 1 year since diagnosis constituted the incident diabetic population. A regression analysis was used to determine trends over time.

Results: Both the NHIS and NHWS exhibited similar incidence patterns over time and within subgroups. Age-adjusted incidence in males declined in both surveys (0.8%-0.7% NHIS, 1.3%-0.6% NHWS) while the trend in females wasn't as consistent. Differences in incidence were also noted across age cohorts. In NHIS incidence declined in the 18-64 year olds from a high in 2009 of 0.9% to 0.6% in 2014, while in NHWS a steady decline occurred in 2005 to 2014 of 1.1%-0.6%. Age-adjusted incidence in whites declined from a high of 0.8% in 2008 to 0.6% by 2014 while in NHWS incidence was 1.2% in 2005 and declined to 0.6% by 2013.

Conclusions: After many years of an increasing trend in diabetes recent data illustrate a reversal of this trend. This change in incidence is driven by younger age cohorts, males, and whites. The impact of a reversing trend in diabetes should result in a reduction in healthcare costs along with improving patient lives.

121. An Algorithm To Identify And Classify Individuals With Type 1 And Type 2 Diabetes Mellitus In A Primary Care Database

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Background: Epidemiological research into diabetes mellitus (DM) often requires a reproducible method for identifying and distinguishing individuals with type 1 and type 2 DM.

Objectives: To develop an algorithm to identify individuals with type 1 and type 2 DM using The Health Improvement Network (THIN) primary care database.

Methods: We developed an algorithm to identify individuals with DM based on diagnostic records, treatment and additional health data such as HbA1c test results. To identify an individual with DM, we required that individuals had at least two separate records indicative of DM; one of which was required to be a diagnostic record. We then developed an additional algorithm to distinguish these individuals as type 1 and type 2 DM, while excluding those who had diagnostic records of gestational diabetes or other rarer DM subtypes. A combination of DM diagnostic code type, DM medication type prescribed, age of DM diagnosis and timing of diagnosis relative to practice registration were used in this classification process. Following classification, we internally validated the classification algorithm by examining a random sample of 500 full electronic healthcare records in THIN manually for individuals with DM.

Results: Out of 8,838,031 individuals aged 0-99 years between 2000-2013, we identified 36,134 individuals with Type 1 DM and 406,344 with type 2 DM. 35,369 (97.9%) individuals with type 1 DM and 404,488 (99.5%) individuals with type 2 DM were classified with major certainty. 765 (2.1%) of all individuals with type 1 DM and 1,856 (0.5%) of all individuals with type 2 DM had an ambiguous record of diabetes type and hence were difficult to classify. In our internal validation, manual assignment of DM type based on clinical assessment of the entire record and algorithmic assignment led to equivalent classification in all instances.

Conclusions: The vast majority of individuals with type 1 and type 2 DM can be readily identified from UK primary care electronic health records. This approach to identify and classify patients with DM can also be adapted to other health care settings.

122. Trends in Incidence and Prevalence of Type 2 Diabetes in the United Kingdom (2004 - 2014) Using the Clinical Practice Research Datalink (CPRD)

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Background: Type 2 diabetes mellitus (T2DM) accounts for 90% of all cases of diabetes and is associated with increased morbidity and premature mortality. In the UK, there are currently 4 million patients diagnosed with diabetes, but limited data are available on the epidemiological changes associated with incidence and prevalence trends in the past decade. The Quality and Outcomes Framework (QOF) voluntary incentive scheme was introduced in 2004 to reward UK general practices providing high-quality care based on defined indicators.

Objectives: To describe the annual incidence and prevalence rates of T2DM in the UK between 2004 (QOF launch) and 2014 and to examine the effects of age, gender, socio-economic status and geographic region on the observed trends.

Methods: Using the primary care database (CPRD), overall annual incidence and prevalence rates of T2DM were calculated per 10,000 person-years (PYR) at risk. Variation in rates by 10-years age bands, gender, UK country and neighbourhood socio-economic quintiles were also examined.

Results: Over the study period, 170,405 new cases and a total of 344,331 T2DM patients were identified. Overall, mean incidence of T2DM per 10.000 PYR [95% confidence intervals] was 50.8 [47.26; 54.28] in men, and 36.1 [33.44; 38.77] in women; and mean prevalence per 10.000 PYR was 535.7 [478.94; 592.37] in men and 377.1 [338.69; 415.60] in women. In 2004, incidence of T2DM was 44.8 per 10.000 PYR and remained steady afterwards before decreasing to 36.9 per 10.000 PYR in 2014. Annual prevalence rates nearly doubled from 320.6 to 526.4 per 10.000 PYR between 2004 and 2014 (from 3.2% to 5.3%, respectively). Higher incidence and prevalence rates were recorded in individuals who were aged ≥65 years, male, and resident in the most deprived locations.

Conclusions: Our findings show the rapid increase in T2DM prevalence over the last decade. Age, gender, geographic region and level of deprivation affect the epidemiology of T2DM in the UK. The fairly stable incidence rates but growing prevalence rates suggest that patients may now be living longer with T2DM; an important area to investigate in future research.

123. Population Trends in the Ten-Year Incidence and Prevalence of Diabetic Retinopathy in the UK: A Cohort Study in the Clinical Practice Research Datalink 2004-2014

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Background: Diabetic retinopathy (DR) is the most common form of eye disease amongst individuals with diabetes. Though DR is one of the leading causes of blindness in the UK, population-wide measures of incidence and prevalence remain unknown.

Objectives: to examine trends in the incidence and prevalence of diabetic retinopathy according to age, sex, ethnicity, deprivation, time, and region.

Methods: A prospective cohort study utilizing 7.7 million patients, including 338,390 patients with type 2 diabetes and 30,657 patients with type 1 diabetes, from the Clinical Practice Research Datalink during the period 2004-2014 was conducted. Main outcome measures included the age standardised prevalence and incidence of DR. Cox proportional hazards regression was used to estimate relative risk of DR between population subgroups.

Results: The prevalence of DR was 48.4% in the population with T1DM and 28.3% in the population with T2DM. Amongst patients with T2DM, age-standardised prevalence of DR decreased over time, while incidence increased over time. Age-adjusted risk of incident DR was lower for females compared to males (HR 0.92, CI95 0.91-0.93, $p<0.001$), higher for South Asian (HR 1.07, CI95 1.03-1.11, $p=0.001$) and Mixed ethnic groups (HR 1.15 CI95 1.00-1.33, $p=0.047$) relative to White, and raised in the least affluent group compared to the most affluent (HR 1.08, CI9 1.06-1.11, $p<0.001$). Amongst patients with T1DM, age-standardised prevalence of DR remained stable over time, with incidence increasing over time,. Age-adjusted risk of incident DR was raised for

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females compared to males (HR 1.05, CI95 1.01-1.11, p = 0.03). Amongst Black patients with T2DM, the risk of DR was increased by 40% for those in the most deprived group relative to the least deprived group (HR 1.39, CI95% 1.00-1.92, p = 0.047).

Conclusions: This is the largest study to date of the burden of diabetic retinopathy in the UK. Increasing incidence of DR over time, likely reflects improved ascertainment. Evidence that deprivation and ethnicity are both associated with a higher risk of DR, highlights a significant health inequality to be addressed.

124. Intensification of Basal Insulin Treatment Among Patients with Type 2 Diabetes Mellitus in the Netherlands

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Background: In keeping with local guidelines, patients with type 2 diabetes mellitus (T2DM) who do not achieve glycaemic control initiate basal insulin treatment. This treatment is intensified should goals still not be achieved. To date there is limited information regarding the state of insulin treatment of T2DM in a real world population.

Objectives: To characterise T2DM patients in the Netherlands initiating basal insulin and those intensifying treatment.

Methods: Antidiabetic dispensing records were obtained from the PHARMO Database Network. New users, i.e. first-time dispensing, of basal insulin only were selected during 2007-2012. Treatment intensification was defined as either an add-on of GLP-1, bolus insulin or DPP-4i or a switch to premixed insulin. Demographics and HbA1c before basal insulin start (pre-insulin), at intensification and after intensification were assessed as well as time to intensification.

Results: A total of 15,986 T2DM patients initiated basal insulin only (median age at start basal insulin: 65 years, 52% male, 87%, 75% and 51% had a pre-insulin HbA1c >53, >58 and >64 mmol/mol, respectively). Overall, 4,945 patients (31%) intensified treatment during a median follow-up of 14 months (median age at start basal insulin: 63 years, 50% male, 88%, 78% and 54% had an HbA1c at intensification >53, >58 and >64 mmol/mol, respectively). Intensification mostly was an add-on of bolus insulin (58%) or a switch to premixed insulin (39%). Median (IQR) time to intensification was 8 (2-15) months. Among patients with an HbA1c >53, >58 and >64 mmol/mol at intensification, median time to intensification was 12 months. After intensification, 32%, 52% and 73% of the patients attained an HbA1c of ≤53, ≤58 and ≤64 mmol/mol, respectively, with median reduction of 6 mmol/mol HbA1c.

Conclusions: About one third of T2DM patients initiating basal insulin intensified treatment later on, leading to an HbA1c ≤53, ≤58 and ≤64 mmol/mol in 32%, 52% and 73%, respectively. Further research might provide more information on the underlying reasons for intensifying versus not intensifying, such as patient characteristics, co-medication and occurrence of hypoglycaemic events.

125. Validation and Incidence of Pneumonia in Patients with Diabetes in BIFAP Database

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Background: Validity and completeness of the recorded diagnosis is key for data source selection in pharmacoepidemiology.

Objectives: To identify Community-Acquired Pneumonia (CAP) through validation of pneumonia records in the Spanish primary care database BIFAP, allowing

for an accurate automatic strategy proposal for CAP detection. Incidence is also presented.

Methods: From a cohort of 76009 patients aged ≥18 with treated type 2 diabetes (T2DM) during 2002-2013 selected from BIFAP population, 2966 patients with a recorded pneumonia were identified automatically (2040 diagnosis and 926 pneumonia comments) after 1st antidiabetic drug.

Validation included a manual review of clinical profile of 2966 pneumonia + -3 months of the record. Patients were classified as probable CAP when confirmed in recorded test result (X-ray or lab), referral/discharge letters, or by CAP localization; as non-cases when referring to other illness/etiology, past CAP or exclusion criteria; and possible CAP when key information lacked to confirm/deny CAP, or doubtful diagnosis/date.

Confirmation rate and incidence rate (IR)/100,000 person-years were estimated.

Results: We classified 1803 (60.9%) patients as probable CAP (83.8% diagnosis and 16.1% comments), 574 (19.4%) possible CAP (441 without extra information, 133 with doubtful diagnosis/date) and 589 (19.8%) non-cases (393 other illness, 93 other etiology, 78 past CAP, 25 exclusion).

Confirmation as probable CAP was 74.2% for diagnosis and 31.4% for comments, and 90.5% and 42.9% when including also possible CAP without key information.

The IR of CAP in T2DM was 604 probable CAP per 100,000py, and 752 when including probable and possible cases without key information to confirm/deny CAP.

Conclusions: When interested in high confirmation, computer strategy to detect CAP in BIFAP should retrieve only pneumonia recorded in diagnosis: most of them confirm CAP in recorded test result, referral letters, or CAP localization. Pneumonia comments has low confirmation rate, however, they detected 16% of CAP cases, which is relevant when interested in sensitivity. Incidence of CAP in T2DM is higher than the published for general population.

126. A Validation Study of Algorithms to Identify *Clostridium difficile* Infection Using a Japanese Hospital-Based Administrative Database

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Background: *Clostridium difficile* infection (CDI) is a leading cause of antibiotic-associated diarrhea and treated with oral/injectable metronidazole (MNZ) and oral vancomycin (VMC) in Japan. Prior to conduct an epidemiology study for CDI using a hospital-based administrative database, we investigated extent of validity of diagnosis algorithms.

Objectives: To identify algorithm(s) providing well-balanced Positive Predictive Value (PPV), Negative Predictive Value (NPV), sensitivity and specificity using results from *Clostridium difficile* toxin detection tests (rapid test) as gold standard.

Methods: This was a retrospective database study of all patients identified in seven acute care hospitals with either positive or negative rapid tests between April 2008 and June 2015. Three algorithms were defined based on patient records for the same month as the rapid test: 1) having International Classification of Diseases 10th revision (ICD-10) for "Enterocolitis due to *Clostridium difficile*" (A04.7), which is the only specific diagnosis code for CDI, 2) having prescription record for MNZ or VMC, 3) both 1 and 2.

Results: 185 test-positive and 1,096 test-negative patients were identified. 85% of test positive patients were ≥ 65 years old. Algorithm 1 provided PPV of 71% (95% CIs: 62-80) but sensitivity was only 44% (37-52). Algorithm 2 provided sensitivity of 77% (70-82) but PPV was limited to 61% (55-68). Algorithms 3 raised sensitivity to 82% (75-90) but decreased PPV to 60% (54-66). NPV and specificity were consistently above 90%.

Conclusions: In this study setting, less than half of test-positive patients had a specific diagnosis code for CDI (A04.7). MNZ and VMC were also prescribed to test-negative patients. As a limitation, anaerobic culture results were not available and rapid test negative patients might have been culture positive. Consequently, these algorithms showed limited validity in defining CDI and are not suitable to quantify incidence or prevalence reliably in database studies.

127. Disease and Treatment Epidemiology of Initial Clostridium Difficile Infection (CDI) in a National Cohort

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Background: CDI is a major public health threat with high mortality and recurrence. However, the epidemiology of initial CDI (iCDI) is not well described in Veterans.

Objectives: To describe clinical characteristics, treatment patterns, and outcomes among Veterans with iCDI between 2010 and 2014.

Methods: This national, retrospective cohort study included patients with a positive stool sample for C. diff toxin(s) or an ICD9 code for CDI (008.45) and at least 2 days of CDI therapy (PO or IV metronidazole [MTZ], PO or PR vancomycin [VAN|, or fidaxomicin [FID]), with no CDI in the last year. Descriptive statistics were used to summarize the data.

Results: iCDI was identified in 54,354 patients (32,804 [60.4%] identified by a positive laboratory test, 6,345 [11.7%] identified by ICD9 code, and 15,205 [28.0%] with both). The percent of enrollees with iCDI increased by 37% from 2011 to 2014. The mean age of patients was 66.6 ± 14.1 years, 93.7% (N = 50,913) were male, and 74.2% (N = 40,330) were white. Commonly observed comorbid conditions that are considered risk factors for recurrent CDI included COPD (8.1%, N = 4,378), CKD (9.0%, N = 4,892), diabetes (9.6%, N = 5,207), and malignancies (9.0%, N = 4,911). Most iCDI was diagnosed in the outpatient setting (65.9%, N = 35,820). Utilization of MTZ monotherapy was high (81.1%, N = 44,099), as compared with combination therapy of MTZ + VAN (10.6%, N = 5,778) or VAN monotherapy (8.1%, N = 4,383). FID was used in <1% of iCDI. The 30-day all-cause mortality was 10% (N = 5,432).

Conclusions: CDI continues to be a concern among Veterans with iCDI. Most Veterans were treated outpatient with MTZ. We found that 30-day mortality was relatively common.

128. Impact of Macrolides Use on Hepatotoxicity in 4 European Countries

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Background: Idiosyncratic drug-induced liver injury (DILI) is a relevant cause of acute liver injury accounting for 13% of all acute liver failure cases in the USA and for 10-20% of fulminant and subfulminant cases of hepatitis in Europe.

Objectives: To estimate the public health impact of macrolides on hepatotoxicity.

Methods: Meta-analysis: a systematic review (SR) and several observational studies were conducted examining the association of macrolides and hepatotoxicity. We included 10 publications from the SR (2 randomized clinical trials and 8 non-randomized studies) and 9 PROTECT observational studies. A random-effects generic inverse variance model was used to obtain a summary risk estimate for macrolides: Relative risk (RR) = 3.91 (95% Confidence Interval [CI] 2.66-5.74), I2 = 72%, $p < 0.0001$). Prevalence of exposure: One-year period prevalence rates (PPRs) for macrolides were obtained from electronic medical records databases in Germany, Netherlands, Spain and United Kingdom. PPRs were expressed as number of users with at least one prescription dispensed/1,000 people registered in the databases at mid-2008. PAF calculation: We used the Greenland's approach. PAF = Exposure prevalence odds (Oo)*(Adjusted relative risk (RRa)-1)/ [(RRa-1) + 1/Oo], (STATA v13.1).

Results: The macrolides effect measure was RR = 3.91, 95% CI 2.66-5.74, I2 = 72%, $p < 0.0001$. The PPRs and PAF depicted by database were the following: United Kingdom (CPRD), PPR = 48.2, PAF = and 95%CI 12.3% (95% CI:6.6-17.6%); United Kingdom (THIN), PPR = 56.3, PAF = 14.0% (95% CI:7.6-20.1%); Spain (BIFAP) PPR = 62.1, PAF = 15.3% (95% CI: 8.4-21.7%); Netherlands (Mondriaan NPCRD), PPR = 21.7, PAF = 5.9% (95% CI: 3.0-8.8%); Netherlands (Mondriaan AHC), PPR = 116.2, PAF = 25.3% (95% CI: 14.9-34.4%);

Germany (Bavarian Statutory Health Insurance database) PPR = 62.6, PAF = 15.4% (95% CI: 8.4-21.9%).

Conclusions: The impact of macrolides use on liver injury ranged between 6 and 25%. Discrepant PAF results might be primarily related to differences in PPRs. This is the first study to calculate the attributable fraction of macrolides use on DILI. The standardization of the calculation of the prevalence of exposure to macrolides has enhanced the cross-country comparison of PAF.

129. Prevalence of Risk Factors for Vancomycin-Associated Nephrotoxicity in a National Cohort

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Background: Vancomycin (VAN) is one of the most widely used antibiotics. Several patient-related risk factors for VAN-associated nephrotoxicity have been identified, including advanced age, renal function, and obesity. Despite the increased risk of nephrotoxicity among VAN-treated patients with these risk factors, VAN continues to be used in these patients.

Objectives: To describe the prevalence of risk factors for VAN-associated nephrotoxicity in a national cohort of VAN-treated patients.

Methods: We conducted a retrospective cohort study of Veterans (2010-2014) treated with >2 days of intravenous VAN in the hospital setting. We assessed the prevalence of previously established risk factors for VAN-associated nephrotoxicity, including age (≥65), baseline serum creatinine (SCr), chronic kidney disease (CKD), obesity, intensive care unit (ICU) stay, diabetes (DM), hypertension (HTN), congestive heart failure (CHF), cancer, and concomitant aminoglycoside (AMG) or piperacillin-tazobactam (P/T) use during the VAN-related admission. Obesity was defined as a BMI >30 kg/m2. Current comorbid conditions and concomitant antibiotic exposures were determined using ICD-9 codes and pharmacy barcode medication administration data, respectively. We used descriptive statistics to summarize the data.

Results: In our 4 year study period, we identified 40,781 admissions where patients were treated with VAN for >2 days. Patients were mostly white (74%, n = 29,998) and male (97%, n = 39,422). Mean age was 67+/-12 years; 55% (n = 22,593) were ≥65. Baseline SCr was high >1.3) in 37% (n = 15,265) of patients. There were 7,422 (18%) patients treated in the ICU. The overall prevalence of CKD was 20% (n = 8,214), obesity was 38% (n = 15,073), DM was 40% (n = 16,240), HTN was 58% (n = 23,468), CHF was 20% (n = 8,295), and cancer was 19% (n = 7,578). The prevalence of concomitant P/T use was 61% (n = 24,933) and AMG use was 3% (n = 1,115) during the admission.

Conclusions: This study demonstrates a high prevalence of several risk factors for nephrotoxicity in a national cohort of Veterans treated with VAN. Future studies should identify which risk factors have the greatest impact on VAN-associated nephrotoxicity among Veterans.

130. Predictors of Mortality among Unvaccinated Veterans with Serious Streptococcus Pneumoniae Infections

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Background: Serious S. pneumoniae infections are a major cause of mortality worldwide. However, factors influencing mortality have not been fully elucidated.

Objectives: The purpose of this study was to identify predictors of mortality among unvaccinated Veterans with pneumococcal disease.

Methods: This was a case-control study of older Veterans (≥50 years) with positive S. pneumoniae cultures (blood, cerebrospinal fluid, respiratory) during

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admissions to Veterans Affairs medical centers between 2002 and 2011. Patients with a pneumococcal vaccine within 5 years of culture were excluded. Using multivariable logistic regression, we identified independent predictors of all-cause 30-day mortality (significant at $p<0.05$). Potential predictors included patient demographics, as well as comorbidities during admission and medical history within the year prior to culture, identified by diagnosis codes.

Results: Among 9,730 serious pneumococcal infections, 18% died within 30 days of culture (1,764 cases, 7,966 controls). Cases were significantly older (71 vs 67 years), and more likely to have a history of pneumococcal infections (39% vs 28%) and comorbidities. Pneumonia (62%), bacteremia (26%), and bacteremic pneumonia (11%) were the most common infections. Predictors of mortality present during the pneumococcal admission included invasive pneumococcal disease (odds ratio [OR] 2.10, confidence interval [CI] 1.85-2.39), intensive care (OR 2.26, CI 1.99-2.57), dialysis (OR 3.35, CI 2.37-4.72), endocarditis (OR 2.74, CI 1.28-5.90), neutropenia (OR 2.67, CI 1.32-5.42), non-metastatic (OR 2.34, CI 1.91-2.87) or metastatic malignancy (OR 2.54, CI 1.89-3.41), and moderate or severe liver disease (OR 2.47, CI 1.53-3.99). History of MRSA infections (OR 1.59, CI 1.12-2.25) and metastatic malignancy (OR 1.53, CI 1.19-1.97) in the year prior to admission, and corticosteroid use within 30 days of admission (OR 1.30, CI 1.13-1.50) were also predictors.

Conclusions: Organ or immune system dysfunction-related conditions were the most common predictors of 30-day mortality among unvaccinated Veterans. Increased vaccination efforts among patients with these conditions may improve survival.

131. Partner Bereavement and Risk of Herpes Zoster: Results from Two Population-Based Case-Control Studies in Denmark and United Kingdom

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Background: Immune function is critical for preventing herpes zoster (HZ). Although severe stress has been linked to immune dysregulation, data on its impact on risk of HZ are conflicting.

Objectives: To examine whether one of the most stressful negative life events, partner bereavement, is associated with an increased risk of HZ.

Methods: We used electronic health data to conduct two parallel case-control studies in Denmark and the UK. We identified all patients with a record of HZ in general practice or hospital between 1997 and 2013 in Denmark (n = 295,833) and between 2004 and 2013 in the UK (n = 579,532). In Denmark, we used prescriptions for systemic acyclovir, valacyclovir or famciclovir as proxies for HZ treated in general practice, due to lack of data on diagnoses made in this setting. Using risk-set sampling, we matched up to ten controls to each case by age, sex, and in the UK, general practice. The date of the first diagnosis/prescription was considered the index date for cases and their controls. We used conditional logistic regression to compute odds ratios (ORs) with 95% confidence intervals for bereavement among cases with HZ compared with matched controls. We performed analyses for any bereavement prior to index date and for bereavement in periods defined by time intervals between date of death and index date.

Results: We observed no association between any history of partner bereavement and HZ in either Denmark (OR 1.00, 0.99–1.01) nor in the UK (OR 1.03, 1.00–1.06). In the UK, ORs were 0.81 (0.48–1.37), 0.67 (0.35–1.27), 1.16 (0.86–1.60), 1.06 (0.89–1.25), 1.04 (0.96–1.13), 1.03 (0.98–1.09), and 1.03 (1.00–1.06) within 0–7 days, 8–14 days, 15–30 days, 1–3 months, 3 months–1 year, 1–3 years, and 3 years after partner death, respectively. Corresponding estimates were 0.73 (0.54–0.99), 0.76 (0.55–1.05), 0.98 (0.81–1.18), 1.03 (0.94–1.14), 1.03 (0.94–1.14), 1.02 (0.99–1.05), 1.00 (0.98–1.01) in the Danish data.

Conclusions: We found no evidence of an increased risk of HZ following partner bereavement. The potential decrease within 14 days following partner death is likely to be explained by delayed health contact.

132. The Future of Herpes Zoster: Increasing Incidence?

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Background: Herpes zoster (HZ) is an illness caused by reactivation of latent varicella zoster (VZ) virus typically occurring later in life causing rash with moderate to severe pain. Lifetime prevalence is 20-30%. It has been hypothesized that childhood varicella zoster vaccination could lead to increasing rates of HZ due to decreased adult exposure to wild-type varicella virus.

Objectives: To examine trends in the incidence of HZ before and after the introduction of the varicella zoster vaccine.

Methods: A retrospective population-based study using administrative data was conducted on persons 20 years of age and older, in the province of Manitoba (Canada) between April 1st 1997 and March 31st 2014. The databases contain virtually all contacts between residents and the universal health care system. Diagnoses of HZ were determined using ICD-9 and -10 codes in medical and hospital records. Age-adjusted incidence rates for HZ were calculated by fiscal year. As a sharp increase in HZ rates was noted in 2009/10, a segmented regression was performed to determine its significance.

Results: Two linear trends in age-adjusted incidence of HZ with a significant breakpoint in 2009/10 ($F(3,13) = 59.63$ $p < 0.0001$) were observed. Prior to 2009/10, incidence of HZ remained constant ($p = 0.96$ $R2 = 0.0002$) at 4.70 cases/1000 PY (95% CI: 4.65, 4.75). In 2009/10, incidence began to increase at a rate of 0.29 cases/1000 PY/year (95% CI: 0.20, 0.37)($p = 0.0149$ $R2 = 0.99$), and reached 5.70 cases/1000 PY in 2013/14 (21% increase from 1997).

Conclusions: A 21% increase in HZ incidence was observed in Manitoba. Increase began in 2009/10, 5 years after the introduction of VZ vaccine in the recommended childhood schedule. These results echo results in other jurisdictions where an increase in HZ incidence followed the introduction of the varicella vaccination and support the hypothesis that adult exposure to wild VZ help maintain immune suppression of latent varicella infection.

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133. Quantification Of Risk Factors For Postherpetic Neuralgia In Herpes Zoster Patients: A Cohort Study

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Background: Postherpetic neuralgia is a disabling neuropathic pain that commonly follows herpes zoster. A vaccine is now available which can prevent zoster. Risk factors for postherpetic neuralgia are poorly understood.

Objectives: We aimed to investigate risk factors for postherpetic neuralgia.

Methods: Using primary care data from the Clinical Practice Research Datalink, we fitted multivariable logistic regression models to investigate potential risk factors for postherpetic neuralgia (defined as pain ≥90 days after zoster, based on diagnostic and/or prescription codes), including demographic characteristics, co-morbidities, and characteristics of the acute zoster episode. We also assessed whether their effects were modified by antiviral use.

Results: Of 119,413 zoster patients, 6,956 (5.8%) developed postherpetic neuralgia. Postherpetic neuralgia risk rose steeply with age, most sharply between 50-79 years (adjusted odds ratio for a 10-year increase, 1.70, 99% confidence interval 1.62-1.77). Postherpetic neuralgia risk was higher in women (6.3% vs 5.1% in men: OR = 1.17, 1.08-1.26); and those with severely immunosuppressive conditions, including leukaemia (14.4%: 2.23, 1.16-4.30) and lymphoma (12.1%: 2.61, 1.63-4.19); autoimmune conditions, including rheumatoid arthritis (9.1%: 1.17, 0.96-1.43); and other comorbidities including asthma and diabetes. Current

and ex-smokers, as well as underweight and obese individuals were at increased risk of postherpetic neuralgia. Antiviral use was not associated with postherpetic neuralgia (OR = 1.04, 0.97-1.12). However the increased risk associated with severe immunosuppression appeared less pronounced in patients given antivirals.

Conclusions: Postherpetic neuralgia risk was increased for a number of patient characteristics and comorbidities, notably with age and among those with severe immunosuppression. As zoster vaccination is contraindicated for patients with severe immunosuppression, strategies to prevent zoster in these patients, which could include the new sub-unit zoster vaccine, are an increasing priority.

134. Exploring The Treatment Pathways Of Breast Cancer Survivors In Primary Care In England

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Background: Early diagnosis and advances in treatment have improved the survival of breast cancer women and increased demand for primary care services. To facilitate the development of such services, research into breast cancer treatment pathways and the pharmaceutical care needs of survivors is required.

Objectives: To explore the characteristics of breast cancer survivors and the utilisation of endocrine therapy in primary care in England.

Methods: This retrospective cohort study uses data from the Clinical Practice Research Database linked to the Hospital Episode Statistics database from November 2005 to 2015. Newly diagnosed female breast cancer survivors with a follow-up period of 2-10 years were included and followed up from the date of discharge following initial breast cancer treatment until either leaving the GP surgery; death; or the end of the study. Endocrine therapy received, duration of endocrine treatment and common comorbidities were measured. Descriptive statistics were used to summarise the patients' characteristics and utilisation of endocrine therapy.

Results: Of the 15,039 included breast cancer survivors, 86% were of white ethnicity. The mean age at discharge was 62 ± 13.3 (range 18 to 108) years, and the mean follow up duration was 5.5 ± 2.3 years. Most patients (52%) have over 5 years follow up duration, and 30% and 17% patients had 3-5 years and <3 years follow up, respectively. The most commonly recorded comorbidities were hypertension (33%), depression (19%) and osteoporosis (17%). Of the 12,404 (82%) patients who received endocrine therapy, 9092 (78%) received monotherapy. This consisted of tamoxifen (43%), anastrozole (37%) letrozole (19%) and fulvestrant <1%). The mean duration of each endocrine treatment varied from 1.3 ± 1.3 (tamoxifen) to 2.8 ± 1.9 years (anastrozole).

Conclusions: More than half of breast cancer patients survived more than 5 years, and the majority received endocrine monotherapy with the mean duration of less than 3 years. To identify patients' pharmaceutical care needs, further research will explore the association between multiple comorbidities, non-adherence, side effects, drug-drug interactions during long-term endocrine therapy.

135. Validity of Cutaneous Squamous Cell Carcinoma Diagnosis in the Health Improvement Network

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Background: Despite the substantial public health burden of both types of non-melanoma skin cancer (NMSC), basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC), little is known about the epidemiology. A major barrier for the epidemiological study of NMSC stems from poor registration practices across the majority of countries.

Objectives: The objective of our study was to determine the validity of cSCC diagnoses in The Health Improvement Network (THIN) Database compared to the gold standard of direct query of the general practitioner (GPs).

Methods: We performed a cross-sectional study to determine the positive predictive value (PPV) of diagnosis codes for cSCC in THIN, an electronic medical records database from the United Kingdom. A mail-in questionnaire was sent to the GPs of 100 randomly selected patients with at least one diagnostic code for SCC (B338.00, B33z.00, B33z.11, BB29.00, BB29.12, BB29.13, BB2A.00, BB2A.13 and BB2L.00) recorded in THIN with the time period of July 1st-December 31st 2012. Respondents were asked to answer the following: (1) confirm of date diagnosis; (2) location of lesion; (3) who made the initial diagnosis; (4) was the patient referred to a specialty clinic for care; (5) diagnosis confirmed by skin biopsy; (6) how was the specific lesion treated; (7) reason for erroneous coding of cSCC; and (8) location of lesion if SCC code was not a cSCC. The PPV(95%CI) of the cSCC code for GP-confirmed diagnoses was calculated.

Results: The PPV for a single code to identify cSCC in THIN was 76.5% (95% CI, 65.8-85.3%). The codes for SCC NOS (BB2A.00) and SCC of the skin (B338.00) yielded PPVs of 85.0% (95% CI, 70.2-94.3%) and 83.3% (95% CI, 65.3-94.4%), respectively. The codes B33z.00 (malignant neoplasm of skin NOS) and BB2L.00 (Bowen's disease) had low PPVs, 33.3% (95% CI, 84.0-90.6%) and 16.7% (95% CI, 0.4-64.1%), respectively.

Conclusions: Diagnosis codes for SCC NOS and SCC of the skin in THIN had sufficiently high PPVs for epidemiological studies of cSCC. Additional studies on the epidemiology of NMSC and its risk factors are needed and there is potential for THIN to be useful in helping us overcome this significant knowledge gap.

136. Prevalence Of Bone Metastases In Patients With Prostate Cancer: A Meta-Analysis

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Background: Bone metastases worsen prognosis in prostate cancer, but to date, no study has quantified their global prevalence.

Objectives: To systematically assess reports of the prevalence of bone metastases in prostate cancer patients and derive summary estimates from these data.

Methods: We searched MEDLINE and EMBASE using words relating to bone metastasis, prostate cancer and prevalence to identify relevant articles in English, published between January 1999 and December 2013. We included publications for clinical trials and observational studies that reported on the presence of bone metastases at study entry and/or their development during follow-up. Random-effect meta-analyses of logit prevalences were then conducted to estimate the mean prevalence and explore statistical heterogeneity.

Results: Of the 7,375 unique studies screened, 65 articles reporting on 171,011 patients met the pre-defined inclusion criteria. Included studies evaluated either newly-diagnosed (n = 11,618) or metastatic prostate cancer (mPC) patients. The studies of newly-diagnosed patients were much more heterogeneous with regards to prevalence of bone metastases (mean 17.6%; 95% CI 14.2% to 21.6%; I2 = 95.1%). Mean prevalence in newly-diagnosed patients ranged from 10.6% to 25.5%, it was higher in Korea, Iran, China, and Turkey (25.5%) than in the US (10.6%), and increased by prostate-specific antigen [PSA] level (0-10 ng/mL: 1.6%; PSA >100 ng/mL: 51.6%). In mPC studies, the prevalence of bone metastases was 90.0% (95% CI 88.0% to 91.7%; I2 = 62.7%). There were insufficient data to assess the likelihood of developing bone metastases after any given treatment.

Conclusions: The prevalence of bone metastases in prostate cancer varies widely by country but it was reported as at least 10%. Estimating the incidence during the follow-up was not feasible with the data available now. To quantify the manifestation of bone metastases, the predictive factors for developing bone metastases, and to understand the additional challenges in managing up to 90% of patients with advanced disease requires further research, particularly in non-metastatic patients.

137. Incidence of Second Primary Malignancies In Patients With Primary Myelofibrosis

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Background: Cancer survivors are at increased risk of new malignancies and information on the underlying disease is necessary to contextualize them. Primary myelofibrosis (PMF) and polycythemia vera (PV) share many clinical and biological features. Several authors have shown that patients with PV are at increased risk of subsequent malignancies, but there is scarce information for patients with PMF frequently exposed to carcinogenetic cytoreductive therapies.

Objectives: To analyze the frequency and types of second primary malignancies (SPM) in patients with PMF.

Methods: Retrospective cohort design based on the SEER registries (US). Patients with a PMF diagnosis in 2001-2012 reported as the first ever primary malignancy (except non-melanoma skin cancer which is not reportable to SEER) were included. Follow-up was until the first subsequent malignancy (i.e., SPM), death, end of SEER database follow-up or lost to follow-up, whichever occurred first. Time at risk of SPM started 2 months after PMF diagnosis. Because of changes in SEER reporting rules, myeloproliferative neoplasms, acute myeloid leukemia and myelodysplastic syndromes were not considered SPM. SPM incidence rate (IR) and cumulative incidence (CI, 1-event free Kaplan-Meier probability) five years after diagnosis were calculated. To evaluate SPM frequency, standardized incidence ratios (SIR) to the US population were calculated.

Results: Sixty two out of 1173 PMF patients developed a SPM after a median of 1.8 years at risk (range: 0.04-9.1). The most frequent SPM were of respiratory system (27.4%), male genital system (19.4%), digestive system (17.7%) and lymphomas (12.9%). The IR was 1.67 (95% CI: 1.30-2.14) per 100 patient-years and the CI 7.62% (95% CI: 5.74-10.08). An increased risk of respiratory system malignancies (SIR: 1.86, 95% CI: 1.08-2.98) was observed, although not for overall solid cancers (SIR: 0.91, 95% CI: 0.67-1.21). The risk of lymphoma was also increased (SIR: 2.88, 95% CI: 1.24-5.67).

Conclusions: Patients with PMF are at an increased risk of SPM from the respiratory system and lymphomas. Further study is warranted to investigate the incidence of SPM in relation to previous PMF therapies and increasing survival.

138. Validation of an Algorithm to Estimate Global Cancer Incidence from Health Administrative Databases in France

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Background: Monitoring cancer incidence is essential to assess drug exposure effects. In France, while cancer registries represent the gold-standard system, they cover only 15% of the population. Cancer data from the health administrative databases could allow for a national coverage and quick availability but are less accurate. Their uses in pharmacoepidemiological studies require a well-defined algorithm.

Objectives: To develop an appropriate algorithm to estimate cancer incidence using administrative databases and to examine its accuracy with regard to the one estimated by registries.

Methods: We identified a cohort of 573888 subjects present the 1st January 2012 in the EGB (1/97th representative sample of the French healthcare insurance system). It contains informations about patient's long-term diseases (LTD), treatments and hospitalizations, including discharge diagnoses and medical procedures. After exclusion of all prevalent cancer, we applied five algorithm definitions to estimate the incident rate of cancer between 2012 and 2013. These algorithms jointly used cancer related codes from LTD, discharge diagnosis, medical/surgical procedures as well as other complications of cancer treatments codes. Finally, we calculated the standardized incidence ratios (SIR) of the observed number of cancer in the EGB to the expected number in the registries by indirect age and sex standardization. The analyses were conducted separately for both sexes and compared graphically with registries data.

Results: The algorithm defined by the only presence of an LTD cancer declaration underestimate cancer incidence in men and women. The only use of hospitalized data with a principal cancer diagnosis of cancer

was more exhaustive, especially among women with an SIR of 1.00 [95% CI; 0.97-1.04]. For men, the best algorithm was defined by (i) a LTD cancer declaration; or (ii) a principal cancer diagnosis; or (iii) a related cancer diagnosis with another cancer related medical/surgical procedure or cancer complication code with an SIR of 1.00 [95% CI; 0.96-1.03].

Conclusions: Health administrative databases may be used for an appropriate estimation of global cancer incidence in France.

139. Cervical Cancer Screening and Subsequent Excisional Procedures in Women Below 25 Years in France Between 2007 and 2013. A Nationwide Study on the French Healthcare Databases

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Background: Most high grade cervical intraepithelial lesions spontaneously regress in young women and screening may expose them to overtreatment and potential pregnancy-related morbidity. French guidelines therefore recommend initiating screening by Papanicolaou (Pap) test from the age of 25 years. Little is known about French screening below 25 years; most data is extrapolated from survey series.

Objectives: To describe the rates of cervical cancer screening and cervical surgical procedures in women aged below 25 in France.

Methods: Data were obtained from the general scheme of the French National Health Insurance databases (86% of population living in France) and extrapolated to the entire French population. Pap tests rates were calculated among women aged 15-24 between 2007 and 2013. Cervical excisional procedures were assessed during the 15-month period following a Pap test in women aged 20-24 at year 2007 and 2012. The target population for screening (women aged 25-65) according to national guidelines was considered as the reference group.

Results: Among the nearly six millions of women aged 15-65 with at least one Pap test each year, 10.5% (N = 596 278) in 2007 and 7.2% (N = 373 400) in 2013 were younger than 25 years of age. In 2013, 85.2% of the later belonged to the 20-24 age group with a screening rate of 16.2%. During the study period, the annual screening coverage decreased in all age groups: -57.1% in women aged 15-19 and -29.5% in the age group of 20-24, as well as in the target population (-8.7%). Management of detected lesions in screened women aged 20-24 became less conservative with an increase in conizations (+16.5%) as well as other excisional treatment (+74.5%). Nevertheless, due to overall decrease in screening coverage, the absolute number of women aged 20-24 who had a conization decreased from 1 974 to 1 766 between 2007 and 2012.

Conclusions: Higher adherence to French guidelines is needed to decrease cervical cancer screening among women aged under 25 and to reduce the burden of surgical treatments potentially associated with obstetrical adverse outcomes such as preterm delivery.

140. Incidence of Myeloid Neoplasms in Patients with Primary Myelofibrosis

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Background: Transformation to AML is the leading cause of death in patients with primary myelofibrosis (PMF). There has been a debate whether the evolution to AML/MDS is inherent of this group of disorders or associated with the use of cytoreductive drugs. Information specific to the frequency of myeloid neoplasms (MN) in patients with PMF is necessary for contextualization.

Objectives: To analyze the frequency and types of MN in patients with PMF.

Methods: Retrospective cohort design based on the SEER registries (US). Patients with a PMF diagnosis in 2010-2012 reported as the first ever primary malignancy (except non-melanoma skin cancer which is not reportable to SEER) were included. Patients with secondary myelofibrosis were not considered. Only patients diagnosed in 2010 or after were included because of changes in SEER reporting rules of

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hematologic malignancies. Follow-up was until the first MN, a non-myeloid neoplasms, death, end of SEER database follow-up or lost to follow-up, whichever occurred first. Time at risk of MN started 2 months after PMF diagnosis. MN incidence rate (IR) and cumulative incidence (CI, 1-event free Kaplan-Meier probability) 1 and 2 years after diagnosis were calculated. To evaluate the frequency of MN, age-, sex-, race- and year of diagnosis-standardized incidence ratios (SIR) to the US population were calculated.

Results: The number of PMF patients was 279. 13 patients developed a MN after a median of 0.83 years at risk (range: 0.04-2.25). The observed MN were: AML and related neoplasms (n = 9, 69.2%), acute leukemias of ambiguous lineage (n = 2, 15.4%) and MDS/MPN (n = 2, 15.4%). The IR was 3.9 (95% CI: 2.3-6.8) per 100 patient-years and the CI at 1 and 2 years were 3.8% (95% CI: 1.9-7.6) and 7.0% (95% CI: 3.6-13.4), respectively. The risk of MN was increased overall (SIR: 64.3, 95% CI: 34.3-110.0) and also for all MN groups.

Conclusions: Patients with PMF are at an increased risk of MN. Further study is warranted to investigate the risk of MN in relation to previous PMF therapies. The interpretation of MN frequency should consider baseline risk of patients with PMF.

141. Incidence of Cardiovascular Disease Among Early Stage Breast Cancer Patients in Denmark

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Background: The increasing number of breast cancer survivors necessitates better understanding of the clinical course of the disease and survivorship.

Objectives: To examine the incidence of cardiovascular disease (CVD) among early-stage breast cancer patients.

Methods: Using Danish medical registries we identified a cohort of women with incident regional (Summary Stage, available through 2003) or TNM stage II/III (2004+) breast cancer diagnosed 1999-2011. We ascertained information on tumor size, lymph node status, stage, hormone receptor status, cancer treatment, comorbidity (excluding patients with prior CVD), and HER-2 status. We collected information on CVD—myocardial infarction (MI), venous thromboembolism (VTE), stroke, and heart failure (HF)—from the Danish National Patient Registry. Follow-up began 180 days after diagnosis and extended to the first of CVD, mortality, or 31/12/2012. We computed the overall cumulative incidence and incidence rate (IR per 10,000 person years (p-y)) and associated 95% confidence interval (CI) of CVD. We used Fine and Gray proportional hazards regression models to compute the sub-distribution hazard ratio of CVD, and associated 95%CI, accounting for death as a competing risk.

Results: Among 22,399 patients, 6,838 had regional stage (1999-2003), and 15,561 had stage II/III breast cancer (2004-2011). Median follow-up was 3.8 years. The 5-year risks of MI, stroke, VTE and HF were low at 0.73%, 1.43%, 0.35%, and 0.03%, respectively. Corresponding 5-year incidence rates (per 10,000 p-y) of each outcome were MI: 19.65 (16.76, 22.90), stroke: 24.58 (21.33, 28.19); VTE: 9.45 (7.48, 11.78); and HF: 0.59 (0.19, 1.39). Compared with patients aged 50-59 years, younger patients were less likely, while older patients were more likely to develop CVD. Increasing extent of comorbid disease correlated with increased risk of CVD.

Conclusions: CVD occurs in about 1% of early stage breast cancer patients in Denmark during the first five years after diagnosis. Older age and increasing comorbidity were associated with an increased risk of CVD.

142. Characteristics And Outcome Of Newly Diagnosed Immune Thrombocytopenia In Adults: Results From The PGRx Information System

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Background: The rela-life management and predictors of outcomes in adults with immune thrombocytopenia (ITP) are poorly known.

Objectives: The objectives of the study were (1) to describe the clinical features of adult patients presenting with an ITP and (2) to explore the predictors of chronicity.

Methods: Data were drawn from the PGRx Information System, a set of observational, prospective disease registries, designed to identify risk factors of specific diseases, medications, to describe the real-world course and management of specific diseases. The PGRx-ITP registry was set-up in France nationwide and involved 21 physicians from haematology centres. During a 28-month period, all consecutive adults ≥18 years old diagnosed with an incident ITP were included. Data were collected at baseline and 12 months: clinical, biological signs of ITP and medication, from which the outcome was derived (chronicity / recovery). Predictors of chronicity at baseline were explored using univariate logistic regression models providing the Odds Ratio (OR) and their 95% Confidence Intervals (95%CI).

Results: 153 patients were included: 94 (61%) patients were female, mean age was 48 years (SD = 18.8), and 128 (84%) presented with bleeding symptoms at diagnosis. The median platelet count was 10 × 109/L. An initial treatment was required in nearly 90% of patients. After 12 months, only 36% of patients were cured without receiving any disease-modifying treatment. The baseline predictors of chronicity at 12 months were a lower platelet count (OR, 1.0; 95%CI, 1.0-1.2) and mucocutaneous bleeding (OR, 0.3; 95%CI, 0.1-1.0).

Conclusions: ITP is a serious disease in adults with a chronic evolution in a majority of patients that is in contrast with children. Low platelet count and severity of bleeding at the diagnosis were associated with a lower risk of chronicity.

143. Infection and Anti-Infective Treatment Preceding a Diagnosis of Primary Persisting Immune Thrombocytopenia

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Background: Patients with chronic immune thrombocytopenia (ITP), even those unexposed to immunomodulation treatments, have increased risk of infection after ITP diagnosis. Recently, we found that chronic ITP was associated with an increased risk of infections and anti-infective treatments occurring before diagnosis of ITP. However, this risk among patients within other ITP subgroups is not known.

Objectives: To investigate the risk of infections and anti-infective treatments before newly diagnosed and persisting ITP.

Methods: We identified 1,945 adults (≥18 years old) with a diagnosis of primary non-chronic ITP during 2006-2013, using the Swedish Patient Register (NPR) and ICD-10 codes D69.3 and D69.4. Data on infections not already listed as cause of secondary ITP was also retrieved from NPR. Data on treatments for infections were retrieved from the Prescribed Drug Regis-ter. The Standardized Incidence Ratios (SIR; the ratio of the observed to the expected number of infections and anti-infective treatments), and 95% confidence intervals (CI), were estimated as a measure of relative risk of infections diagnosed within five years before ITP and anti-infective treatment for the year preceding ITP diagnosis. The expected numbers were calculated using the rates from the general population, divided into strata of sex, age, and year of diagnosis.

Results: Patients with non-chronic ITP had increased risks of infections requiring inpatient or outpatient care (SIR = 7.79, 95% CI 7.00-8.64) and being exposed to anti-infective treatments (SIR = 1.36, 95% CI 1.27-1.46) before ITP diagnosis. Higher magnitude SIRs were found for upper respiratory infections, otitis media, candidiasis and viral infections; and for anti-infective drugs more marked risks were observed for sulphonamides, amoxicillin, macrolides and antivirals.

Conclusions: Pattern of infections and anti-infective treatments before newly diagnosed and persisting ITP diagnosis is similar to that in chronic ITP. The findings suggest that for all subtypes of immune thrombocytopenia infection is not only related to the immunomodulation treatment but also to the disease itself.

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144. Comorbidities in the Young and Aging Populations with Haemophilia A

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Background: Haemophilia A (HA), a rare hereditary condition, impacts ~1/5000 male births globally. Treatment advances in recent decades have improved life expectancy for affected individuals, now approaching normality. Thus, an aging population of people with HA (PWHA) is emerging, but with little published research on their comorbidity profile.

Objectives: We evaluated comorbidity rates from real world data sources to show key comorbidities in PWHA by age strata.

Methods: Analyses used 3 data sources, and their concordance was evaluated. Clinical Practice Research Database (CPRD) provides a comprehensive record from a nationwide representative sample of UK general practitioners. MarketScan provides insurance claims data for ~46 million US patients. Patients from CPRD and MarketScan were included if they had a HA diagnosis on/before 1 Jan 2014 (index date), with ≥12 mo of medical history. An age- and gender-matched sample of the general population was derived in the CPRD. Diagnoses for ≤5 years preceding were evaluated. A cross-sectional physician survey, CHESS, collected data for EU patients with severe HA.

Results: The population included MarketScan 1903, CPRD 310, CHESS 996; mean age was 39 y (CPRD and MarketScan) and 36 y (CHESS). In adults, hepatitis C, pain, arthropathy, chronic pulmonary disease (including asthma), diabetes, cancer and anxiety/depression appeared to be reported more often in PWHA than the general population, though prevalence was inconsistent across data sources. Prevalence of diabetes, pain, depression/anxiety increased with age, while HIV and hepatitis C prevalence was highest in 30-40 y group (likely due to childhood exposure to contaminated blood products). Arthropathy was reported in MarketScan in PWHA aged 3-5 y (8%) and 6-11 y (27%), but not CPRD, maybe due to lack of reporting in primary care.

Conclusions: PWHA, across age groups, suffer considerable comorbidities. Management of PWHA should consider the likely higher prevalence of diseases such as diabetes, mental health issues, pain, arthropathy and asthma. Use of different types of data source provides a comprehensive overview that may enhance the recognition of comorbidities.

145. Epidemiologic and Clinical Characteristics of Thalassemia (THAL) Intermedia (TI) in the US

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Background: TI is increasingly prevalent in the US due to changing immigration patterns. It is underdiagnosed, leading to inadequate or delayed management.

Objectives: To review the epidemiology and clinical characteristics of TI in patients (pts) in the US.

Methods: Medical records of pts with a TI diagnosis (≤8 mean packed red blood cell transfusions (tx) per year (yr) over a ≥3-yr period) and ≥12 months of follow-up from 1/1997- 4/2014 at 4 US hematology centers were reviewed for demographic and clinical characteristics by TI subtype.

Results: Of 138 pts reviewed, 84 had α-thal, 39 had β-thal, and 15 had E/β-thal. 74% of α-thal pts had deletional (del) Hb H, and 26% had non-del (ndel) Hb H. Median age was 2.3 yr (1.64 del; 6.1 ndel) in the α-thal group, 9.2 yr in the β-thal group, and 2.2 yr in the E/β-thal group. Most α-thal (77%) and E/β-thal (87%) pts were Asian, and β-thal pts were White (46%) or African-American (AA; 36%). 21%, 10%, and 20% of α, β, and E/β-thal pts were foreign-born, and 5%, 3% and 7% were transfused outside of the US.

Top 5 comorbidities were splenomegaly, extramedullary hematopoiesis, growth retardation, hepatomegaly, and infections needing hospitalization/IV antibiotics. 22% of pts had ≥1 tx, while 7% of pts had

≥8 txs in any 1 yr. β-thal pts had a higher mean number of txs per pt per yr (PPPY) (α: 0.4 (0.0 del; 1.5 ndel), β: 0.9, E/β: 0.2) and higher mean serum ferritin (SFN; ng/mL) (204.3; 511.7; 362.4), and more often had iron chelation therapy (ICT) (11%; 28%; 7%). 22% of pts had ≥1 liver iron test, of whom 78% (25/32) had abnormal results. Median (range) LIC based on R2/SQUID was 10.8 (2.5-18.2) mg/g dw, with corresponding within-12-month SFN of 494 (127-1770) ng/mL.

Conclusions: TI in the US affects a diverse population. Prevalence in AAs was higher than previously documented. 18% and 4% of pts were born and transfused outside of the US, potentially leading to additional tx-related morbidity. Consistent with extant data, SFN in TI often underestimated actual LIC; more pts may be potentially eligible for ICT than observed. Morbidities in this study underscore the need for better/earlier diagnosis, and nationwide surveillance to optimize TI care.

146. Risk Score for Major Hemorrhage Among Chronic Lymphocytic Leukemia Patients in the US Veterans Administration Healthcare System

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Background: Chronic lymphocytic leukemia (CLL) patients are at risk for major hemorrhage (MH). A composite risk score (RS) for MH in CLL patients can assist clinicians to identify patients at high risk for MH.

Objectives: To develop a composite RS based on risk factors for MH in the CLL patient population.

Methods: ICD-9 codes were used to identify patients with CLL (1999–2013) from Veterans Affairs (VA) electronic medical records. Those with <6 months of VA care before CLL diagnosis were excluded to capture a newly diagnosed patient cohort. Follow-up was from first CLL diagnosis until death, 12/31/2013, or first MH onset, whichever occurred first. MH was defined as having bleeding in a critical area or having bleeding that was treated with blood transfusion within 7 days. Potential risk factors included demographics and medical history in the 6 months before CLL diagnostic. A score for each significant ($P<0.05$) or known (age) risk factor was assigned based on the hazard ratio from Cox proportional hazards regression and then summed to create a composite RS.

Results: Of 24,581 veterans with newly diagnosed CLL, 24,166 (98.3%) were male; median age at diagnosis was 72.0 years; 2,013 (8.2%) had MH after CLL diagnosis with a median time of 2.6 years between diagnosis and MH event. Risk factors included history of MH (score = 4), anemia (3), male (2), African American (2), hypertension (2), stroke (2), atrial fibrillation (2), CAD (1), and age >75 years (1). Patients had a median RS of 3 (range: 0-17). RS was categorized into 2 strata: RS <5 [n = 21,849 (88.9%)] and ≥5 [2,727 (11.1%)]. There were 1,627 (7.5%) and 389 (14.3%) MH cases among patients with RS <5 and ≥5, respectively. In patients with RS ≥5, cumulative risk of MH by years 1, 2, and 3 was 6.3%, 8.8%, and 10.4%, respectively, compared to 1.7%, 2.8%, and 3.8% in patients with RS <5, with corresponding risk differences of 4.6%, 6.0%, and 6.5%.

Conclusions: A composite risk score for MH was developed in a cohort of US veterans with newly diagnosed CLL. Utility of this risk score needs to be validated in other CLL patient populations.

147. Diabetes and New-Onset Atrial Fibrillation in a Hypertensive Population

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Background: The association of diabetes with new-onset atrial fibrillation remains controversial. Hypertension may partly explain the risk association ascribed to diabetes.

Objectives: We studied the role and characteristics of diabetes over new-onset atrial fibrillation in hypertensive patients with no ischemic vascular disease.

Methods: Records of 262,892 persons from the Information System for the Development of Research in Primary Care in Catalonia (Spain) were examined from July 2006 to December 2011. Included participants were ≥55 years old and hypertensive with no ischemic heart disease, stroke, or peripheral artery disease. We used Cox proportional hazards regression to model incidences in the diabetic compared to non-diabetic subgroups of our population, and among diabetic patients, diabetes duration and pharmacological treatment, haemoglobin A1C, and body mass index.

Results: New-onset atrial fibrillation incidence in diabetic patients was 13.3 per 1000 person-years (mean follow-up: 4.3 years). In nondiabetic patients, it was 10.4 per 1000 person-years (mean follow-up: 4.1 years). Diabetes hazard ratio (HR) for new-onset atrial fibrillation was 1.11 (95% confidence interval (CI): 1.06–1.16). Diabetic patients also diagnosed with obesity had an HR of 1.41 (95% CI: 1.22–1.64).

Conclusions: Diabetes was modestly associated with new-onset atrial fibrillation in hypertensive patients with no ischemic vascular disease. Among diabetic patients, only obesity reached significance in its association with this arrhythmia.

148. Risk of Hypertension (HTN) and Malignant Hypertension (mHTN) in Patients Treated for Multiple Myeloma (MM)

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Background: HTN is commonly reported in patients (Pts) with MM and may be associated with older age, disease-related complications, or sequelae of MM treatments.

Objectives: To evaluate incidence rates (IR) of HTN and mHTN in treated MM Pts in the United States and the risk of mHTN development in MM Pts with pre-existing HTN.

Methods: Newly-treated adult MM Pts were identified from Truven MarketScan claims database from 1/1/05 to 3/31/14 using ICD-9 codes to identify disease state, HTN, mHTN, and comorbidities. Inclusion criteria were new diagnosis of MM with start of MM treatment, ≥12 months continuous enrollment (CE) prior to diagnosis, prescription drug coverage, and ≥30 days of CE following initial diagnosis. Non-MM Pts were matched on age (within +/- 5 yrs), gender, and distribution of index dates to MM Pts. Risk of HTN and mHTN based on existing HTN and other cardiovascular (CV) comorbidities were evaluated over time.

Results: Study included 7895 MM Pts (38% with HTN history) and 23685 non-MM patients (24% HTN history). The IR of HTN in MM and non-MM Pts was 260 and 178 per 1000 person-years (PYRs), respectively. The IR of mHTN in Pts with and without HTN history were 10.25 and 3.29 per 1000 PYRs, respectively for MM patients; 4.25 and 1.88 per 1000 PYRs, respectively for non-MM Pts. Risk of HTN (HR: 1.30; 95% CI: 1.22, 1.37) increased 30% in MM vs. non-MM Pts. MM Pts with (HR: 1.90; 95% CI: 1.26, 2.87) or without (HR: 1.54; 95% CI: 1.04, 2.28) HTN history had a higher risk of mHTN events during the observation period vs. non-MM Pts. In MM Pts with HTN history, the risk of mHTN was significantly increased with the following comorbid conditions: cardiomyopathy (HR: 2.79; 95% CI: 1.20, 6.48), renal failure (HR: 2.13; 95% CI: 1.36, 3.34), and diabetes mellitus (HR: 1.59; 95% CI: 1.05, 2.39).

Conclusions: This study confirms that incidence of HTN and mHTN is higher in newly-treated MM Pts vs non-MM Pts. Existing HTN is a risk factor for MM Pts developing mHTN. Management of CV risk factors and comorbidities in MM Pts is important based on the increased risk of HTN and mHTN among these Pts.

149. Pharmacological Treatments Preceding Diagnosis of Idiopathic Intracranial Hypertension

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Background: Idiopathic intracranial hypertension (IIH) is a neurological disorder with symptoms related to high intracranial pressure where the cause behind disease onset is not completely known. Common clinical presentation is headache in combination with visual disturbances due to papilledema. IIH mainly affects overweight women of childbearing age. Although there is no strong evidence, exposure to some medications such as tetracyclines, lithium, corticosteroid and contraceptives is thought to be a possible risk factor for IIH. An IIH diagnosis is not always accurate and epidemiology of the disease, such as the true incidence and patient characteristics, is incompletely described.

Objectives: To identify pharmacological treatments preceding correct diagnosis of IIH by review of medical records.

Methods: Patients with IIH diagnoses in Stockholm county between 2006 and 2013 were identified through the Patient Register using ICD 10 code G93.2 (n = 210). Medical records were available for 207 patients and information on clinical characteristics and treatments during one year preceding diagnosis were collected. Each of the diagnoses was determined as IIH or non-IIH based on the modified Dandy diagnostic criteria for IIH. (PMID:12455560).

Results: In total, 112 (54%) patients fulfilled all the criteria for IIH and 23 (11%) were regarded as probable IIH. Among them 83 patients (77 definite IIH and 6 probable IIH) were diagnosed for the first time during the study period which represents a yearly incidence of 0.65 per 100,000 population. Medical record review showed that 79 individuals with a correct IIH diagnosis were taking medication prior to their diagnosis: 15 out of the 135 IIH patients (11%) were exposed to oral contraceptives, 8 (6%) to corticosteroids, 1 (1%) to lithium, 12 (9%) to tetracycline, 6 (4%) to penicillin and 12 (9%) were exposed to other antibiotics.

Conclusions: A substantial proportion of IIH diagnoses in Stockholm are incorrect. Incidence of IIH seems to be lower in Sweden compared with some other European countries which could be due to lower prevalence of obesity in Sweden. Exposure to corticosteroids before diagnosis of IIH is common among patients with IIH.

150. Risk of Thrombotic and Hemorrhagic Event Associated with Oral Anticoagulants: A Retrospective Analysis in a Local Health Authority in Northern Italy

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Background: Oral anticoagulants modify blood clotting capacity and are widely used for long-term prevention or treatment of thrombosis. The traditional drugs are vitamin K antagonists, while the new agents target either factor Xa or thrombin.

Objectives: To determine the safety of new oral anticoagulant (NAO) compared with traditional ones (TAO) in terms of thrombotic and hemorrhagic events.

Methods: Data were retrieved from administrative databases; they included the register of residents in the province of Cremona, dispensed drugs, hospitalizations and outpatient care. A retrospective drug utilization study was conducted, enrolling subjects ≥ 40 years old with at least one prescription of drugs with ATC codes B01AA, B01AE or B01AF during the period January 1st, 2013 – September 30th, 2015. Thrombotic and hemorrhagic events of interest were defined based on ICD-9-CM codes and all hospitalizations occurring during use of anticoagulants were identified. The risk of thrombotic or hemorrhagic events stratified by type of anticoagulant was estimated by calculating crude and adjusted incidence rates (multivariate logistic models included gender, age, residence and naïve use).

Results: Incidence rate of thrombotic events was 18.82 per 1000 patient-year [95% CI: 15.77–22.29] for TAO versus 6.55 [95% CI: 2.64–13.50] for NAO, with a resulting Incidence Rate Ratio (IRR) of 2.87 [95% CI: 1.36-7.28]. Incidence rate of hemorrhagic events was 24.86 per 1000 patient-year [95% CI: 21.33-28.80] for TAO versus 14.04 [95% CI: 7.86-23.17] for NAO, with an IRR of 1.77 [CI: 1.04-3.23]. After adjustment for potential confounders, the IRR of thrombotic events was 1.64 [95% CI: 0.95-

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2.83], while for hemorrhagic events increased to 3.37 [95% IC: 1.55-7.32]. In addition to older age, thrombotic risk was positively associated with naïve use [IRR 1.52, CI: 1.09-2.14], while risk of hemorrhages was higher in males [IRR 1.79, CI: 1.26-2.54].

Conclusions: The use of NAO results in a reduction of hospitalizations for thrombotic and hemorrhagic events; further analyses on the impact of anticoagulant treatment on access to emergency care are underway.

151. Treatment Practices for Acute Ischemic Stroke (AIS) in Quebec (Canada)

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Background: Acute Ischemic Stroke (AIS) is an important cause of death worldwide and is a main cause of disability. According to Canadian Guidelines (2008), secondary prevention of stroke recurrence should include the monitoring of risk factors, such as high blood pressure and atherosclerosis, as well as the prescription of antiplatelet therapy or anticoagulants. AIS treatment in the clinical practice setting remains poorly examined to date.

Objectives: i) To describe treatments dispensed following hospital discharge for AIS in Quebec (Canada), overall and according to patient subpopulations; ii) To assess adequacy of treatments relative to the Canadian Guidelines.

Methods: A retrospective cohort study was conducted using the RAMQ claims databases (prescriptions and medical services). A random sample of adult drug plan members discharged for an incident AIS between 1st January 2011 and 31st December 2012 were included. Incident AIS was assessed through absence of AIS diagnostic code in the medical services database during the year prior to the considered AIS. Treatments dispensed during the 10 days following hospital discharge were evaluated. Patient characteristics and risk factors were assessed through diagnostic codes and drug dispensings.

Results: Cohort included 6609 incident AIS patients (84.8% age 65+, male: female ratio = 1: 1), of whom 3278 (49.6%) received a treatment during the 10 days following discharge. Most patients received antiplatelets (acetyl salicylic acid ASA, clopidogrel, ASA-dipyridamole or ASA-Clopidogrel) combined with an antihypertensive and/or a statin (n = 1853; 56.5 %). Antiplatelet therapy alone was taken by 411 patients (12.5%). Statins alone/combined were prescribed to 2098 (64%) patients, with 842 (40.1%) initiating treatment after AIS while 1256 (59.9%) continuing previous use. Among the 2793 patients treated with ASA or clopidogrel combined/alone virtually all patients (99% and 100%, respectively) received the recommended dose.

Conclusions: AIS treatments are aligned with Canadian guidelines. Patterns of treatments according to socio-demographic characteristics and risk factors for AIS will be presented.

152. Stroke Risk in Individuals with versus without Atrial Fibrillation at Varying CHA_2DS_2-VASc Score Levels: Implications for Anti-Coagulant Treatment

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Background: CHA_2DS_2-VASc scores are widely used to determine the indication for anti-coagulant therapy (ACT) in patients with atrial fibrillation (AF) to reduce stroke risk. The risk of stroke in individuals without AF has never been compared with that of AF patients who, according to the CHA_2DS_2-VASc score, would be offered ACT.

Objectives: To compare the stroke risk of non-AF individuals at different levels of CHA_2DS_2-VASc score with that of AF patients fulfilling minimum CHA_2DS_2-VASc criteria for ACT.

Methods: In this nationwide population-based cohort study, we used individually-linked data from Danish medical registries to identify patients who were diagnosed with AF between 1980 and 1990 (i.e., pre-

ACT era) and 1995 and 2005 (i.e., post-ACT era). The non-AF general population cohort was then identified from the Danish Civil Registration System, matched (10:1) on sex and birth year. Individuals were followed until stroke diagnosis, death, emigration, or 10 years of follow-up, whichever came first. Comparing stroke risk among patients without AF to those with AF, we computed hazard ratios (HRs) based on Cox proportional-hazards regression, across CHA_2DS_2-VASc scores.

Results: For the pre-ACT era cohort, the overall HR of stroke among patients without AF was 1.02 (95% Confidence Interval [CI]: 0.82-1.26) for females and 2.23 (95% CI: 1.83-2.72) for males with CHA_2DS_2-VASc scores between 4 and 6 when comparing them to the AF cohort with a CHA_2DS_2-VASc score of 2 (females) or 1 (males). When non-AF individuals presented with CHA_2DS_2-VASc scores between 7 and 9, the HRs were 2.12 (95% CI: 1.29-3.48) for females and 1.83 (95% CI: 0.83-4.05) for males. For the post-ACT era cohort, the risk of AF was elevated in both males and females, given a CHA_2DS_2-VASc score over 4.

Conclusions: In Denmark, risk of stroke was elevated in non-AF affected individuals, with a high CHA2DS2-VASc score in comparison to ACT eligible AF patients fulfilling minimum CHA_2DS_2-VASc criteria, in both pre- and post-ACT eras. It may therefore be important to consider broadening the use of ACT to include high-risk patients without AF.

153. Incidence and Risk Factors for Atrial Fibrillation in Patients with Newly Diagnosed Heart Failure in UK General Practice

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Background: Heart failure (HF) and atrial fibrillation (AF) frequently co-exist and the relationship between the two conditions is complex with each pre-disposing to the other. To date, few studies have evaluated the risk of AF in a cohort of incident HF patients.

Objectives: To establish the incidence and identify risk factors, including co-morbidities and medications, for first ever episodes of AF among patients with newly diagnosed HF.

Methods: A cohort study with nested case–control analysis in UK general practice was performed. Patients with a first diagnosis of HF aged 20–89 years, without AF or cancer, from 2000–2005 (N = 14,457) were identified from The Health Improvement Network database and followed for a mean of 2.67 years to ascertain first ever cases of AF. We manually reviewed a sample of AF cases' electronic medical records, including free-text comments, to validate diagnosis. Controls (N = 3,000) were frequency matched to cases by age and sex. Adjusted odds ratios (ORs) with 95% CIs for potential associated risk factors were estimated using unconditional logistic regression.

Results: After validation, 1,489 patients (10.3%) of the cohort were classified as incident AF cases, resulting in an overall incidence rate (95% CI) of 27.3 cases per 1000 person-years (25.9–28.7). A three-fold increased risk of AF was seen in the first six months after HF diagnosis (OR 3.62, 95% CI: 2.97–4.42) compared with the risk after five years. Other risk factors were excessive alcohol consumption (OR 2.91, 95% CI: 1.60–5.30), valvular heart disease (OR 1.98, 95% CI: 1.63–2.40) and asthma (OR 1.23, 95% CI: 1.05–1.43). Reduced risks of AF were found with use of beta-blockers (OR 0.78, 95% CI: 0.67–0.91) and statins (OR 0.65, 95% CI: 0.56–0.76).

Conclusions: The absolute risk of first ever AF is high in patients with a first diagnosis of HF, particularly in the first six months after diagnosis. This temporal relationship, together with identified risk factors for AF, warrants consideration in the medical care of patients with AF.

154. One-Year Survival After Acute Myocardial Infarction (AMI): The Effect of Care Pathway in Italy

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Background: The relationship between guide-lines adherence and outcomes in patients with AMI has been widely investigated considering the phases

(emergency, acute, post-acute) of the Care Pathway (CP) separately.

Objectives: To evaluate the effect of the AMI CP on 1-year survival.

Methods: We conducted a cohort study selecting AMI patients from health information systems during 2011-13. Patients' clinical history was defined by retrieving previous hospitalizations and drugs prescriptions. For each subject the probability to arrive in hospital and the conditional probabilities to survive to 30 days from admission and to 365 days post discharge were estimated through multivariate logistic models. The 1-year survival probability was calculated as the product of the three probabilities.

Different scenarios of CP quality were defined in terms of emergency timeliness (time between residence and the nearest hospital), hospital performance in treatment of acute phase (number/timeliness of PTCA on STEMI) and drug therapy in post-acute phase (number of drugs among: antiplatelet, β-blockers, ACE inhibitors/ARBs, statins). The 1-year survival Probability Ratio (PR) and its Bootstrap Confidence Intervals (BCI) between who effected the best CP (timeliness < 20', hospitalization in high performance hospital, complete drug therapy) and who effected the worst (timeliness ≥ 20', hospitalization in low performance hospital, suboptimal drug therapy) were calculated for a mean-severity patient and varying sex and age.

Results: We identified 29392 AMI. The out-of-hospital mortality was 27.9%. Among the people arrived in hospital, 41.4% had a hospitalization for STEMI with 11.3% of mortality in acute phase and 5.6% in post-acute phase. For a patient of mean-severity the PR was 1.39 (BCI 1.26-1.60). The ratio didn't change by sex, while it moved from 1.13 (BCI 1.09-1.20) for age < 65 years to 2.39 (BCI 1.86-3.26) for age > 85 years.

Conclusions: The 1-year survival probability post AMI depends strongly on CP. Improving the performance in the different phases, taking into account the relationship among these, can lead to considerable saving of lives, in particular for older subjects.

155. Epidemiology of Pulmonary Arterial Hypertension in a Large US Commercially Insured Pediatric Population, 2010-2013

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Background: Pulmonary arterial hypertension (PAH) is associated with important morbidity and mortality. Research on epidemiology and characteristics of PAH in a pediatric general population is limited.

Objectives: To estimate the annual incidence rates and prevalence of PAH in a US-based general population of patients less than 18 years in 2010-2013, and to describe these PAH patients with respect to characteristics, co morbidities, treatments, and diagnostic procedures used.

Methods: Using the US MarketScan claims database we identified 695 pediatric patients with treated PAH in 2010-2013 (including 219 incident cases). We estimated annual incidence rates and prevalence overall, by age and type of PAH (idiopathic and non-idiopathic) using Byar's method. We also described characteristics, co morbidities, treatment patterns, and diagnostic procedures for these patients.

Results: The annual incidence rates of PAH per 1,000,000 person-years in the pediatric population ranged from 4.84 to 8.14 in 2010-2013; 0.47 to 0.88 for idiopathic PAH, and 4.34 to 7.32 for non-idiopathic PAH. The annual prevalence of PAH in pediatric patients ranged from 25.71 to 32.62 per 1,000,000 children; 4.42 to 6.03 for idiopathic PAH, and 21.29 to 26.96 for non-idiopathic PAH in 2010-2013. Incidence rates and prevalence were highest in children aged less than 2 years. Around 36% of cases were born prematurely. Most PAH cases (75%) had some type of congenital heart defect, and 13% had Down's syndrome. Monotherapy was the most common treatment option (83%), followed by dual therapy 13%, and only 4% concomitantly received three or more drugs. PDE-5 inhibitors were the most commonly used treatments. Around 93% had at least one echocardiogram or right heart catheterization.

Conclusions: PAH is very rare in children and especially rare in the absence of mitigating factors such as premature birth or congenital heart defects. The annual incidence rates and prevalence of PAH in the US

commercially insured pediatric population were similar to the estimates reported in European countries.

156. Doubling of Serum Creatinine and the Risk of Cardiovascular Outcomes in Patients with Chronic Kidney Disease and with Diabetes Mellitus Type 2: A Cohort Study

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Background: Doubling of serum creatinine is often used as a surrogate marker for worsening kidney function in nephrology trials. Most people with chronic kidney disease die of other causes before reaching end-stage renal disease.

Objectives: We were interested in the association between doubling of serum creatinine and the risk of a first-time diagnosis of angina pectoris, congestive heart failure, myocardial infarction, stroke or transient ischemic attack in patients with chronic kidney disease and with diagnosed type 2 diabetes mellitus.

Methods: We identified adult patients registered in the 'Clinical Practice Research Datalink' with incident chronic kidney disease defined by at least two estimated glomerular filtration rate values <90 ml/min per 1.73 m2 and type 2 diabetes mellitus. We did a cohort study with a cox-proportional hazard analysis with doubling of serum creatinine as time-dependent variable to assess the cardiovascular risk.

Results: We identified in total 27'811 patients, 693 developed angina pectoris, 1069 congestive heart failure, 508 myocardial infarction, 970 stroke, and 578 transient ischemic attacks. Patients whose serum creatinine doubled during follow-up had increased risks of congestive heart failure (HR 2.98, 95% CI 2.27-3.89), myocardial infarction (HR 2.53, 95% CI 1.62-3.96), and stroke (HR 1.93, 95% CI 1.38-2.69), as compared to patients whose serum creatinine did not double. The relative risks of angina pectoris (HR 1.18, 95% CI 0.66-2.10) or a transient ischemic attack (HR 1.32, 95% CI 0.78-2.22) were similar in both groups.

Conclusions: Diabetic patients with a doubling of serum creatinine were at an increased risk of congestive heart failure, myocardial infarction or stroke, compared to diabetic patients whose serum creatinine did not double during follow-up.

157. Use of Antidepressants Before and After Start of Treatment for Psoriasis. A Nation-Wide Cohort Crossover Study

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Background: Psoriasis is associated with an increased risk of depression, particularly among those with a severe disease.

Objectives: To study differences in use of antidepressants before and after initiation of biological, non-biologic systemic and topical treatment.

Methods: A cohort cross-over study of psoriatic patients, who between July 2007 and December 2011 started a first (since July 2005) regimen with i) biologics, ii) non-biologic systemics, or iii) topicals (calcipotriol).

Rate Differences per 100 person-years of observation (RD, [95% confidence interval]) of subjects filling prescriptions of antidepressants, yearly, two years before treatment start and three years thereafter were calculated (in an intent-to treat analysis), comparing starters of biologics and non-biologic systemics; and non-biologic systemics and topicals, respectively.

Results: A total of 3,618 patients started a biologic regimen, with a total of 10,785 years of follow-up (FU); 15,855 started non-biologic systemic (43,399 years of FU); and 54,678 started topical treatment (154,338 years of FU).

In all three treatment groups, the rate of users of antidepressants increased most before and during the first year after start of psoriatic treatment, e.g. biologics: from 15.1 per 100 before to 16.7 one year after. The rates slightly increased during years 2 and 3.

Those treated with biologics and non-biologic systemics showed no differences in the rate of patients prescribed antidepressants (highest RD 0.61/100 [-0.79 to 2.01] two years prior to start of treatment). Comparing non-biologic systemics to topicals, lower rates of antidepressant use were seen among those treated with topicals, throughout the observation

period: RD per 100 person-years from 2.42 (1.76-3.08) two years before start to 2.85 (2.08-3.61) in the third year after.

Conclusions: No difference in the use of anti-depressants could be observed between those treated with biologicals compared to those with non-biologic systemics. However, those with a less severe psoriasis, only treated topically, showed consistently less use of anti-depressants.

158. Association Between Atopic Diseases and Attention-Deficit/Hyperactivity Disorder: Systematic Review and Meta-Analyses

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Background: A review by Schmitt and colleagues showed an association between eczema and attention-deficit/hyperactivity disorder (ADHD). Though such an association was not observed for asthma and allergic rhinitis more recent studies indicated also an association with these atopic diseases.

Objectives: We aimed to systematically review the available evidence on the association between atopic diseases and ADHD in children and adolescents and to estimate the strength of the association in a meta-analysis.

Methods: We performed a systematic review of observational cross-sectional and longitudinal studies with a time-component that assessed the association between atopic disorders and ADHD, including asthma, atopic eczema, and allergic rhinitis in children and adolescents. For longitudinal studies, we estimated a weighted Mantel-Haenszel odds ratio of these associations using a meta-analysis of crude data.

Results: The majority of cross-sectional and longitudinal studies reported a statistically significant positive association between one or more atopic diseases and ADHD. The meta-analysis among longitudinal studies revealed an overall weighted odds ratio for asthma of 1.34 (95% confidence interval [CI] 1.24-1.44), 1.32 (95% CI 1.20-1.45) for atopic eczema, and 1.52 (95% CI 1.43-1.63) for allergic rhinitis. Heterogeneity of study data was low (I2: 0%, $p = .46$ and $p = .64$, respectively) for both studies examining asthma and eczema, but substantial for rhinitis studies (I2: 82%, $p = .004$).

Conclusions: Our systematic review provides firm evidence that ADHD is associated with atopic diseases with an average of 30% to 50% higher odds of developing ADHD compared with persons without these diseases.

159. High Prevalence of Hypovitaminosis D in Patients with Chronic Low Back Pain: Evidence from Systematic Review and Meta-Analysis

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Background: In major proportion of patients with LBP, the anatomical pathology cannot be pinpointed through physical examination and diagnostic tests, and thus the condition is classified as nonspecific low back pain. Evidence about vitamin D deficiency in patients with chronic low back pain (CLBP) was conflicting and heterogeneous.

Objectives: To conduct a systematic review and a meta-analysis to assess the prevalence of Hypovitaminosis D in CLBP, and to assess the factors responsible for heterogeneity.

Methods: A systematic research on all published articles until August 2015 was conducted in PubMed and EMBASE. All observational studies that had measured serum vitamin D levels in CLBP patients were included in the systematic review. According to the level of 25-OHD, vitamin D deficiency was defined as a 25-OHD level of ≤ 20 ng/mL and vitamin D insufficiency as 21 to 29 ng/mL, and normal level as above 30 ng/mL. Pooled prevalence percentage (PPP) estimates and 95% confidence intervals (CIs) were calculated using the random-effects model. Subgroup analyses and sensitivity analysis were also carried out.

Results: Overall prevalence of vitamin D deficiency in CLBP patients was found to be 69.2% (95% CI,

58.8%-79.5%). Subgroup analyses based on study design, study quality, and study location did not explain between-study heterogeneity; however, type of biomarker assessed [25-hydroxyvitamin D3 vs 25-hydroxyvitamin D (D2 D3)] could account for some degree of heterogeneity.

Conclusions: This study indicates a strong association between vitamin D deficiency and CLBP and justifies serum 25-OHD assessment in patients with CLBP. Vitamin D supplementation may be used as an adjuvant treatment for patients with CLBP. However, randomized clinical trials are required to confirm our findings.

160. Correlates of Osteoporotic Fractures Among Type 2 Diabetic Patients

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Background: Little is known about the association between type 2 diabetes (T2DM) and fragility fractures.

Objectives: To identify diabetes-specific predictors of an osteoporotic fracture.

Methods: This study utilized the computerized database of a large insurer and provider of healthcare services in Israel. The first phase included a cross sectional analysis to assess the current prevalence of fracture history among OP patients with and without T2DM. Subsequently, a sub-cohort of osteoporotic T2DM patients with no fracture at OP diagnosis (index date), was retrospectively analyzed to identify correlates of incident fractures among diabetic OP patients, using time to event (Cox's-proportional hazard) analysis.

Results: A total of 97,454 OP patients were identified of whom 18% were diabetic. The prevalence of major osteoporotic fractures (hip, spine, Colle's or humerous) was significantly higher among T2DM (42%) compared to DM-free patients (31%) across all fracture sub-types (age and sex standardized ratio = 1.19, $P < 0.001$), and particularly increased in hip fractures (8.8% vs. 5.8%). Diabetic OP patients were more likely to be older (mean current age 74.3y vs. 69.1y) and males (20.8% vs. 14.4%, $p < 0.001$) as compared with DM-free ones. Screening rates for bone mineral density were similar in both groups (79.3% vs. 79.9%), and median most recent t-scores were significantly ($P < 0.001$) higher in both total-hip (-1.3 vs. -1.6) and vertebrae (-1.4 vs. -1.8) yet relatively similar in femur neck (-1.8 vs. -1.9, $p < 0.001$) for T2DM patients vs. DM-free.

In a multivariable model among T2DM patients with osteoporosis, fracture risk was significantly associated with neuropathy (HR = 1.22, 95% CI: 1.05-1.42), history of hypoglycemic events (HR = 1.21, 1.07-1.37), cardiovascular disease (HR = 1.25, 1.14-1.38), chronic kidney disease, and prolonged intake of thiazolidinedione (12+ months vs. <12 months: HR = 1.34, 1.04-1.73).

Conclusions: This large population-based study quantifies the unique risk factors for fracture among diabetic patients, and confirms that patients with T2DM are at increased risk for major osteoporotic fractures and that the presence of micro and macro vascular disease appears to further increase the risk.

161. Osteonecrosis Of The Jaw And Cancer Survival: A Danish Population-Based Cohort Study

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Background: Osteonecrosis of the jaw (ONJ) is a severe adverse effect associated with bone-targeted agents (BTAs) in cancer patients. The impact of ONJ on the prognosis of cancers is poorly understood.

Objectives: To examine survival among cancer patients with a clinically-confirmed diagnosis of ONJ, and in cancer patients using BTAs.

Methods: Using individually-linked data from Danish nationwide registries and research databases, we identified a cohort of 150 cancer patients (52% breast cancer) with clinically-confirmed ONJ between 2009 and 2014. Two comparison cohorts without ONJ were

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constructed. The first comparison cohort was drawn from the source population of cancer patients. The additional requirement for drawing a second comparison cohort was a record of hospital-administered treatment with bisphosphonate or denosumab before the index date. Both comparison cohorts were matched on year of birth, cancer site, metastatic stage at diagnosis and year of cancer diagnosis at the date of ONJ diagnosis (index date). Follow-up started on the index date and continued until emigration, death or September 9, 2015. Survival was estimated using the Kaplan-Meier method. We used Cox regression to estimate mortality rate ratios and 95% confidence intervals (CIs), adjusting for sex, comorbidity and presence of distant metastases at index date.

Results: The one and five-year survival of the cancer patients diagnosed with ONJ were 68% (95% CI: 60% to 75%) and 19% (95% CI: 4.7% to 41%), respectively. Compared with cancer patients without ONJ (N = 1,374), their adjusted mortality rate ratio was 3.0 (95% CI: 2.2 to 4.1). Compared with cancer patients without ONJ and with hospital-based BTA use history (N = 854), the adjusted mortality rate ratio was 1.4 (95% CI: 1.0 to 1.9).

Conclusions: ONJ is a predictor of poor survival in cancer patients. The association was attenuated in those with known history of BTA use.

162. Comorbid Diseases Preceding Diagnosis of Progressive Multifocal Leukencephalopathy

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Background: Progressive multifocal leukencephalopathy (PML) is a rare, often fatal viral disease characterized by progressive damage of the white matter of the brain. It is associated with the John Cunningham (JC) polyomavirus, which is carried by a majority of people and is usually harmless except among those with an impaired immune system, such as patients exposed to immunosuppressant medications. A PML diagnosis is not always accurate and epidemiology of the disease, such as the true incidence and patient characteristics, is incompletely described.

Objectives: To identify diseases preceding diagnosis of definitive, probable and possible PML, after excluding incorrect PML diagnoses by medical record review.

Methods: Patients with PML diagnoses in Sweden between 1988 and 2013 were identified through the Patient Register using ICD 9 code 046D and ICD 10 code A81.2 (n = 281). The register also provided data on comorbidity. Medical records were reviewed and information on clinical characteristics was collected. Each of the diagnoses was determined as definite PML, possible PML, probable PML or non-PML based on the consensus statement for the AAN neuroinfectious disease section published in 2013 (PMID 23568998).

Results: In total 251 (89%) medical records were available and examined, and 84 (33%) of the diagnoses were confirmed. The most common comorbidity preceding PML diagnosis were solid tumor malignancies, haematological malignancies, HIV infection, multiple sclerosis, rheumatoid arthritis and organ transplant. Of the 23 people identified as having HIV, 15 (65%) had definite, 3 (13%) had possible PML diagnosis and 5 (22%) have an incorrect PML diagnosis. Of the 50 patients with a solid tumor malignancy, 17 (34%) had definite, 6 (12%) possible PML and 27 (54%) was diagnosed incorrectly. Of the 49 patients with haematological malignancies, 26 (53%) had definite, 2 (4%) had probable, 10 (20%) possible PML and 11 (22%) was diagnosed incorrectly.

Conclusions: A substantial proportion of PML diagnoses recorded in Sweden are incorrect, particularly among those with malignancies. Assessing comorbidity history could be an important part of the diagnostic processes for PML.

163. Comorbid Diseases Preceding Diagnosis of Idiopathic Intracranial Hypertension

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Background: Idiopathic intracranial hypertension (IIH) is a neurological disorder with symptoms related to high intracranial pressure where the underlying causes are not fully known. The common clinical presentation is headache in combination with visual disturbances due to papilledema. IIH mainly affects overweight women of childbearing age. Although incompletely understood, it is thought that hormonal disturbances and exposure to medications such as tetracyclines might be associated with an increased risk of IIH. An IIH diagnosis is not always accurate and patient characteristics are incompletely described.

Objectives: To identify comorbid diseases preceding correct diagnosis of IIH by review of medical records.

Methods: Patients with IIH in Stockholm county between 2006 and 2013 were identified through the Patient Register using ICD 10 code G93.2 (n = 210). Medical records were available for 207 individuals and information on clinical characteristics and treatments one year preceding diagnosis was collected. Each of the diagnoses was determined as IIH or non-IIH based on the modified Dandy diagnostic criteria for IIH.[1]

1. Friedman DI and Jacobson DM. Diagnostic criteria for idiopathic intracranial hypertension. *Neurology*. 2002; 59: 1492-5.

Results: In total, 112 (54%) patients fulfilled all the criteria for IIH and 23 (11%) were regarded as probable IIH. Female to male ratio was 6.1:1. Over 90 % of patients with definite or probable IIH with available data (103) were overweight. 28 (21%) of the patients had received a diagnosis of an infection (respiratory infections 10 (7%) and gastrointestinal infections 4 (3%)) prior to their IIH diagnosis, and 34 (25%) had a diagnosis of a hormonal disorder including diabetes 9 (7%) and thyroid disorders 10 (7%), or related to sex hormone changes 16 (12%). Over 20% of men but none of the women with IIH had been diagnosed with obstructive sleep apnea prior to their IIH diagnosis.

Conclusions: Prior to a correct IIH diagnosis, a large proportion of patients are exposed to infections, hormonal disorders and obstructive sleep apnea amongst men. This information can be useful in aiding an accurate diagnosis of IIH.

164. Psoriasis and Suicide

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Background: Despite concerns about depression, anxiety, or suicidal ideation in psoriasis, there are limited data on the rates of suicide or all-cause mortality in patients with psoriasis.

Objectives: Despite concerns about depression, anxiety, or suicidal ideation in psoriasis, there are limited data on the rates of suicide or all-cause mortality in patients with psoriasis.

Methods: Design: Retrospective observational cohort study (2006-2012)

Setting: A large administrative claims database of commercially insured patients

Participants: 60,695 patients with a psoriasis claims-based diagnosis and equal number of controls, frequency-matched by age, sex, and year-of-cohort-entry.

Eligibility Criteria: Complete medical and pharmacy benefit coverage, at least 18 years of age, and continuously enrolled for at least 12 months at cohort entry.

Exposure: Psoriasis, defined as at least one claim (ICD-9 code of 696.1) associated with an inpatient or outpatient physician visit. The severe psoriasis sub-cohort additionally required evidence of systemic treatment.

Outcomes: Suicide rates using an expanded definition (E-SR) of self-harm resulting in death (ignoring determination of intent); using a restricted definition (R-SR) of suicide indicating death by intention; and all-cause mortality.

Results: We identified 60,695 patients with psoriasis; 6,235 of these were treated with methotrexate or biologics. Suicides rates per 100,000 person-years (PYS) among all psoriasis patients were 33.33 (95% CI, 26.31-41.66) for E-SR and 15.59 (95% CI, 10.92-21.58) for R-SR. All-cause mortality rates were 389.63 (95% CI, 364.58-415.93). Adjusted hazard ratios (HRs) compared to the general population comparator group (GPC) were E-SR: 1.87 (95% CI, 1.28, 2.74), R-SR: 1.38 (0.83, 2.28), and all-cause mortality: 1.08 (95% CI, 0.98-1.19).

Conclusions: In this large study, psoriasis was associated with an increased risk of self-harm resulting in death. Among those with severe psoriasis, there was

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an association with an increased risk of all-cause mortality. Providers should be aware that psoriasis may carry an increased risk of suicide.

165. Cluster Headache Diagnosis and Treatment in the Clinical Practice Research Datalink (CPRD)

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Background: Cluster headache (CH) is an uncommon primary headache disorder characterized by attacks of severe unilateral orbital, supraorbital, or temporal pain lasting 15 to 180 minutes and is often associated with ipsilateral autonomic symptoms and/or restlessness or agitation. Attacks occur daily or near-daily during cluster periods or bouts, which may last for weeks, months, or longer. Available data suggest that a lack of familiarity with the diagnosis and standard of care for CH contribute to substantial delays in the diagnosis and effective treatment of CH.

Objectives: We hypothesized that the treatment patterns associated with the diagnosis of CH could serve as an indirect indicator of the standard of care for patients with CH.

Methods: We examined the primary care diagnostic and treatment records from the UK CPRD database from 1999 to 2013. Those with a CH diagnosis recorded at ≥1 visit were in Cohort 1, and the subset with ≥2 visits with a record of CH were in Cohort 2. We examined the population characteristics, abortive and preventive CH treatments, and analgesics prescribed to these patients at any point following their first CH record.

Results: Over 3.5 million individuals of any age had eligibility in the CPRD in 2013. Cohort 1 consisted of 12,258 patients, of whom 47.7% were male. In Cohort 1, 15.4% received abortive and 36.5% received preventive treatments. Of the 2746 patients in Cohort 2, 62.7% were male. Of those in Cohort 2, 39.2% received abortive and 62.2% received preventive treatments. Prescribing of abortive medication recognized for CH (sumatriptan injection; oxygen) was low overall and was lower in Cohort 1 versus Cohort 2 (6.7% vs. 20.5% sumatriptan injection; 2.6% vs. 9.1% oxygen). Prescribing preventive treatments with recognized efficacy for CH was also lower for Cohort 1 versus Cohort 2 for verapamil (10.8% vs. 31.3%) and corticosteroids (18.3% vs. 30.8%).

Conclusions: Based on a lower than expected proportion of males in either cohort and the under-utilization of recognized CH treatments, these real-world clinical data raise significant concerns about the awareness of the diagnosis and treatment of CH.

166. Difference in the Rate of Multiple Sclerosis-Related Hospitalizations in Portugal Between 2008 and 2013

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Background: Multiple sclerosis (MS) is the most common acquired neurological disorder in young adults. Recent studies have suggested that MS patient hospitalisation rates have been declining over the last decades. Portugal is considered a region of medium MS prevalence, but epidemiological data from the country for MS are limited.

Objectives: We sought to investigate the difference in the rate of MS-related hospitalizations in Portugal between 2008 and 2013.

Methods: Data on MS-related hospitalizations in 2008 and 2013 were obtained from the Portuguese National Hospital Discharge Registry. This database includes all hospitalizations in all public hospitals; MS-related hospitalizations were identified through an MS diagnostic code reported as the primary reason for admission. MS prevalence was obtained from the Atlas of MS. The total number of hospitalizations, as well as the estimates of the Portuguese population, were obtained from Portuguese official statistics. The incidence of hospitalizations was calculated by dividing the number of hospitalizations in each year by the number of patients at risk in the same year. The Wald method was used to calculate the 95% confidence intervals (95% CI) for the rates.

Results: The rate of MS-related hospitalizations decreased by 44%, from 15.9/100 person-years (95% CI: 14.9-16.9) in 2008 to 8.9/100 person-years (95% CI: 8.2-9.6) in 2013. Over the same period, the rate

of all hospitalizations in Portugal decreased from 11.7 per 100 person-years (95% CI: 11.7-11.7) to 11.2 per 100 person-years (95% CI: 11.1-11.2). The mean (standard deviation) age of the MS patients hospitalized was 39.1 (11.9) and 40.5 (12.3); 66.8% and 71.5% were female and the median (interquartile range) length of stay was 3 (1-6) and 4 (1-6) days, respectively in 2008 and 2013.

Conclusions: The reported decrease in MS-related hospitalizations between 2008 and 2013are in accordance with what has been observed in other countries and coincides with the release of new therapies for MS in Portugal. Our findings provide further epidemiological data on MS in Portugal and health care resource use in these patients.

167. Comparing the Incident Rates of Multiple Outcomes in Multiple Sclerosis Population by Marketscan and Clinformatics Data Mart

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Background: It is estimated that 400,000 people in the United States (US) and about 2.5 million people worldwide have Multiple Scoliosis (MS). Every week in US, 200 new cases are diagnosed. Meanwhile, the incidence of many disease conditions that develop in MS patients is unknown.

Objectives: In this study, using US claim database Marketscan and Clinformatics Data Mart, the incident rates of multiple conditions were estimated in an MS cohort population. The outcomes measured included depression, diabetes, sepsis, pneumonia, non-infectious colitis and convulsions.

Methods: MS population was identified from Commercial data by ICD9-CM codes, in Marketscan from 1/1/2009 to 6/30/2014; in Clinformatics from 4/1/2008 to 12/31/2013. The first MS diagnosis date in database was defined as the index date. The patients were at least 18 years old and had a second diagnosis of MS on a date at least 30 days after the index date. The outcomes were defined by any ICD-9 CM diagnosis codes in the inpatient records. The incidence rates were measured overall or by age group and gender for each cohort, while any cases with an outcome diagnosis code within 183 days prior to index date were excluded. Age and gender standardized incident ratios (SIRs) were calculated using Clinformatics results as standard.

Results: There were 72,429 patients in Marketscan and 10,833 patients in Clinformatics before excluding baseline cases from each cohort. The mean age in years was 46.6 (±10.5) in Marketscan vs. 43.9 (±12.5) in Clinformatics; there were 23.3% vs. 24.7% of male for MarketScan and Clinformatics, respectively. Comparing MarketScan results to Clinformatics, ratios of overall incident rate ranged from 1.37 to 2.13 across different outcomes. Based on age and gender SIRs, pneumonia indicated the highest result: 2.20 (95% CI: 2.08 to 2.32), and depression was the lowest at 1.35 (96% CI: 1.29 to 1.42).

Conclusions: These two databases include different groups of MS patients. The population in MarketScan is larger and older than patients in Clinformatics. Across all six outcomes, SIRs vary and range from1.35 to 2.20 using Clinformatics results as standard.

168. Multiple Sclerosis and VTE

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Background: Multiple sclerosis (MS), an immune-mediated disease is associated with muscle weakness and reduced activity. Venous thromboembolism (VTE) is associated with immobility; however, studies of VTE and MS are scarce.

Objectives: To examine the association of MS and VTE.

Methods: DESIGN: Secondary analysis in a retrospective cohort study

SETTING: Optum Research Database, containing eligibility, pharmacy, and medical claims data from a large U.S. health insurer

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PATIENTS: Patients with 2 or more claims for the diagnosis of MS (ICD-9 code 340) between 01JAN2003 and 31DEC2007 (n = 21,952), enrolled at least 6 months prior to entry were further stratified by treated vs untreated status, defined by drug codes indicating the dispensing or administration of therapies used for the treatment of MS: interferon beta-1a, interferon beta-1b, glatiramer acetate or natalizumab. A comparison cohort from the same time-period (n = 70,748) with no claims for MS or MS drugs during baseline or follow-up were age-gender-frequency-matched 4:1 to the treated MS sub-cohort.

OUTCOME MEASURES: Diagnoses of deep vein thrombosis (DVT), pulmonary embolism (PE) and VTE were defined by in hospital or emergency room ICD-9 diagnosis codes and claims for anticoagulant treatment starting within 2 weeks of the first claim and continuing for at least 15 days. If there were only outpatient claims, we required claims for an associated procedure with 15 days.

STATISTICAL ANALYSIS: Analyses compared period prevalence rates (PR) of outcomes per 1000 person-years of enrollment in each MS cohort (i.e., treated and untreated) to the age- and gender-matched general population cohort. These are presented as prevalence rate ratios (PRRs) with 95 percent confidence intervals.

Results: PRRs for outcomes were significantly elevated compared to the general population cohort for both treated and untreated MS patients. PRRs for VTE, comparing treated and untreated MS patients to the general population were 2.6 (95% CI: 2.1-3.1) and 2.3 (95% CI: 1.6-3.4), respectively. Results for PE and DVT were similar.

Conclusions: Our results expand the knowledge of the relationship between MS and VTE and reveal a strong signal that MS patients need careful management of VTE risk factors.

169. Epidemiology of Treatment Resistant Depression in Taiwan: Estimates and Limitations

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Background: Treatment resistant depression (TRD) is often defined by non-response to 2 antidepressant (AD) regimens in a single episode of major depressive disorder (MDD). Epidemiologic data on TRD in Asia-Pacific countries are limited.

Objectives: Describe the epidemiology of TRD in the population of Taiwan including incidence, prevalence, and the AD medications and health services used.

Methods: Cohort study of approximately 1 million subjects randomly sampled from Taiwan's National Health Insurance Research database. Incident MDD cases aged >= 18 had a clean period of 120 days with no diagnosis of depression and no dispensing of an AD medication followed by a depression diagnosis and an AD medication dispensing within <= 30 days in 2005. Cases were followed through 2013 or until 120 days passed with no depression diagnosis and no AD medication dispensing. TRD was defined by 2 AD regimens that were each followed by different AD regimens.

Results: Among 2,756 subjects with MDD, TRD developed in 567 (20.1%, 95% CI: 19.1, 22.1); i.e., 8.1 (95% CI: 7.4, 8.7) incident TRD cases /10,000 population in 2005; a median of 449 days from onset of MDD to onset of TRD. On seeing these results, several psychiatrists practicing in Taiwan, indicated that if an AD medication was not effective, they would switch in <= 3 months. Thus, > 6 months from onset of MDD to onset of TRD, i.e., to starting the third AD medication, suggested changing prophylactic treatment rather than changing treatment during a non-responsive MDD episode. With a limit of 6 months from onset of MDD to TRD, 2.3%, (95% CI: 1.8, 3.0) of the MDD subjects developed TRD; i.e., 0.9 (95% CI: 0.7, 1.6) incident cases/10,000 population in 2005.

Conclusions: The estimate without a limitation on time from MDD to TRD is consistent with estimates from US database studies that also didn't impose such a limitation. If a time limit is imposed to reflect clinical strategies for changing ineffective AD medications, the estimated incidence of TRD drops markedly, indicating a need for better ways to identify the ends of MDD episodes in database studies of the epidemiology of TRD.

170. Characterizing the Epidemiology of Myasthenia Gravis and Neuromyelitis Optica Using the Clinical Practice Research Datalink

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Background: Myasthenia gravis (MG) and neuromyelitis optica (NMO) are rare autoimmune disorders. Accurate estimates of the epidemiology of these conditions are required to determine the burden of disease.

Objectives: The aim of this study was to determine the prevalence and incidence of MG and NMO in a UK population.

Methods: This was a descriptive study. Data was sourced from the Clinical Practice Research Datalink (CPRD); a database derived from UK general practice. Analysis was limited to practices participating in the CPRD linkage scheme to allow access to secondary care data. Cases of MG and NMO were identified by Read and ICD-10 codes. In addition identified cases of MG were defined as 'probable' based on therapy and treatment rules. Period prevalence was calculated for 2013. Annual incidence was estimated based on average annual incidence observed between 2000 and 2013. 95% confidence intervals were calculated for all estimates.

Results: 2,460 patients with a diagnosis of MG were identified. 1,052 patients were registered with a CPRD practice during 2013; a period prevalence of 40.1 (95% CI 37.8–42.6) per 100,000 patients. Incidence of MG was 2.2 (2.0-2.3) per 100,000 patient years (kpy). 1,612 (65.5%) cases were defined as probable MG of which 799 cases were registered during 2013; a period prevalence of 30.5 (95% CI 28.4–32.7) per 100,000 patients. Incidence of probable MG was 1.6 (95% CI 1.5-1.8) per 100,000 kpy. 213 patients with a diagnosis of NMO were identified and 95 were registered during 2013; a period prevalence of 3.6 (95% CI 2.9–4.4) per 100,000 patients. Incidence of NMO was 0.21 (95% CI 1.73-2.64) per 100,000 kpy.

Conclusions: This study estimated the prevalence of MG as between 30.5 and 40.1 per 100,000 and NMO as 3.6 per 100,000. These estimates are a higher than those previously estimated. Limitations of observational data sources need to be considered when interpreting these results. Use of multiple data sources and confirmation of recorded diagnoses using other criteria may be important in accurately estimating epidemiological parameters.

171. Irritable Bowel Syndrome, Depression and Antidepressant Dispensing: A Study of Administrative Claims

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Background: Irritable Bowel syndrome (IBS) is a common idiopathic disorder subtyped by dominant complaint of chronic diarrhea, constipation, or both (IBS-D/C/A). Antidepressants (AD) are 'off-label' treatments for IBS. Prescribing ADs in the context of IBS is complex. AD subclasses such as Tricyclics (TCA) and SSRI/SNRIs cause constipation or diarrhea 'de novo'. AD use in the context of IBS with and without depression has yet to be described.

Objectives: Describe AD dispensing to IBS patients by AD subclass and by the presence or absence of incident depression.

Methods: We identified adult patients (18+) with an ICD-9 code for IBS from 1/1/2002 through 12/31/2013 from the PharMetrics Legacy Health Plans Claims Data, a large U.S. administrative claims database. The IBS cohort included patients with one year of continuous health plan enrollment prior to their index IBS diagnosis. Incident depression was defined as depression occurring after the index IBS diagnosis, with no depression diagnoses in the year prior. AD dispensing by subclass (SSRI, SNRI, combination or TCA) was tabulated after index IBS diagnosis and compared between patients with and without a subsequent depression diagnosis.

Results: 89,994 patients with an index IBS diagnosis were included. The overall incidence of depression was 11.36%. The AD subclasses differed significantly by depression status in IBS patients (Chi-Square ($p<.0001$). The odds of depression onset was 1.8 times (CI: 1.6-2.0) higher for those dispensed TCAs as compared to those on multiple ADs. The odds of depression onset was also twice (2.04, CI: 1.9-2.2) as high in those on no AD treatment compared to those on combination.

Conclusions: There's an association between ADs and incident depression in IBS patients with possible

preventative effects against developing depression which is a common comorbidity in this population.

172. Blood Pressure and Risk of Dementia in a Cohort of 2.6 Million People Over Two Decades

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Background: Dementia and high blood pressure are huge public health issues and it has been proposed that hypertension in middle age may lead to dementia in old age.

Objectives: To investigate the association between systolic blood pressure (SBP) and risk of dementia.

Methods: A cohort derived from the United Kingdom Clinical Practice Research Datalink included people aged 40 years or older with a first SBP recording between 1992 and 2009. People with a prior record of dementia were excluded. Incidence rates and risk ratios for dementia were calculated for each SBP category using Poisson regression, adjusted for age at diagnosis and sex.

Results: In our cohort of 2,665,880 people in UK general practices (median baseline age 54 years, median follow-up 8.2 years) dementia occurred in 68,827 people, a rate of 3.0 per 1,000 person years. Compared to people with SBP of 95-124 mmHg, those with SBP <95 mmHg had an increased risk of dementia (risk ratio 1.52, 95% CI 1.35-1.71), while those with SBP 125-144 mmHg had a lower risk of dementia (risk ratio 0.85, 95% CI 0.83-0.87), as did those with SBP >145 mmHg (risk ratio 0.72, 95% CI 0.71-0.74). However, much of this association appears due to reverse causality for when analysis is restricted to dementia occurring >10 years after the recording of SBP, we found that compared to people with SBP of 95-124 mmHg, rates were similar in those with SBP <95 mmHg (risk ratio 1.09, 95% CI 0.79-1.51), SBP 125-144 mmHg (risk ratio 0.98, 95% CI 0.93-1.02) and >144 mmHg (risk ratio 0.96, 95% CI 0.92-1.00). When further restricted to 10 years after measurement and age <55 years, there was a weak association of increased BP with dementia: risk ratio 1.11, 95% CI 0.97-1.27, p = 0.12 for SBP 125-144 mmHg; risk ratio 1.15, 95% CI 1.00-1.33, p = 0.048 for SBP >144 mmHg. These patterns persisted after adjustment for potential baseline confounders (antihypertensives, cardiovascular disease, chronic obstructive pulmonary disease and smoking).

Conclusions: There is little evidence for the hypothesis that hypertension in middle age increases the risk of dementia in old age, and if true is much weaker than previously suggested.

173. Body Mass Index and Risk of Parkinson's Disease in a Cohort of Two Million People Over Two Decades

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Background: The association of body mass index (BMI) and Parkinson's disease is unclear. A few epidemiological studies suggest that overweight/obesity may be a modest risk factor, while others show no such association.

Objectives: To investigate the association between BMI and risk of Parkinson's disease.

Methods: A cohort derived from the United Kingdom Clinical Practice Research Datalink (CPRD) included people aged 40 years or older with a first BMI recording between 1992 and 2009 and followed for a median 9.3 years identifying all new cases of Parkinson's disease. People with a prior record of dementia and/or Parkinson's disease were excluded. Incidence rates were calculated for each BMI category using Poisson regression.

Results: In our cohort of 1,952,587 people in UK general practices with mean baseline age 56 years, Parkinson's disease (PD) occurred in 11,616 people, a rate of 0.55 per 1,000 person-years. Compared to normal weight people, those underweight (BMI < 20 kg/m2) had a 15% excess risk of PD (95% CI 7%-24%) while the overweight (BMI 25-29.9 kg/m2) and the obese (BMI > 30 kg/m2) had 12% (95% CI 9%-18%) and 17% (95% CI 2%-21%) lower risk,

respectively. These patterns persisted throughout two decades of follow-up and after adjustment for potential confounders. There was also an inverse association of smoking with PD.

Conclusions: Being underweight in middle and old age carries an increased risk of Parkinson's disease over two decades, while the risk appears lower in overweight and obese people. These findings are broadly similar to those for risk of dementia and suggest that a common mechanism may operate; the reasons require further investigation.

174. Demographics and Comorbidities in Parkinsons Disease

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Background: Parkinsons Disease (PD) occurrence increases with age and is more common in men than women. Assessment of differences between populations and methodologies that give rise to these findings is needed. The objective of this study was to assess demographics, comorbidities, and medication usage among PD patients.

Objectives: This study aimed to assess demographics, comorbid diagnoses, and medication usage among PD patients and odds ratios (OR) for comparison to non-PD patients within US commercial/ Medicare and Medicaid databases.

Methods: PD patients were selected between 2009 and 2013. PD patients were identified as those with ≥2 medical claims for PD (ICD-9 Code: 332.0, 332.1 and 333.0). Two non-PD patients were matched to every PD case based on birth year, gender, time in the database, and pharmacy benefit eligibility. Comorbid diagnoses were grouped using the Clinical Classification System.

Results: There were 141,482 PD cases in commercial/ Medicare and 22,531 PD cases in Medicaid. More cases in commercial/ Medicare were majority male (58.0%) than in Medicaid (39.8%). About 73% of cases in each database were aged 65 years or more. More cases in the commercial/ Medicare had pharmacy benefits (69%) than in Medicaid (10%). Comorbidities found among at least 70% of cases in both databases included Other Nervous System Disorders, Hypertension, Diseases of the Heart, and Other Connective Tissue Disease. Compared to matched controls, PD patients were more likely to experience: Other Nervous System Disorders (OR: 5.9–8.1), Delirium Dementia and Amnestic and Other Cognitive Disorders (OR: 7.4), Schizophrenia and Other Psychotic Disorders (OR: 4.3-4.8), and Mood Disorders (OR: 3.8-4.8. The most frequent medication categories were Movement Disorders (including levodopa)(75.7–84.4%), Anti-infectives (72.7-76.8%), Analgesic Narcotics (54.1-67.5%).

Conclusions: There are noteworthy demographic differences between the patients in the US commercial/ Medicare database compared to those in a Medicaid database. Despite these differences, this analysis demonstrates that other nervous system disorders and hypertension are the most frequent comorbid diagnoses in PD cases, and medications for Movement Disorders are common.

175. Increasing Mental Health Diagnosing and Treatment Among U.S. Medicaid Youth, 2001-2010

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Background: In the United States, several studies have suggested an increase in attribution of childhood behavioral difficulties to diagnosable mental disorder, although survey data do not indicate an increase in mental health symptoms.

Objectives: To address this question, we examined trends in diagnosing of specific mental disorders among low-income American children, enrolled in the Medicaid program.

Methods: Data were used from the Medicaid Analytic Extracts for 2001-2010 for 20 states.

Results: Diagnosing increased for all common mental health disorders, with increases particularly marked for disorders marked by challenging behaviors. The diagnosis rate increased by 83% for ADHD, 75% for oppositional defiant disorder, 27% for conduct disorder, 100% for bipolar disorder, and 250% for autism spectrum disorders. Rates also increased by 160% for anxiety disorders and 29% for depressive disorders. In contrast, there was a decline in the proportion diagnosed with developmental disability diagnoses such as intellectual disability (17% decline) and cerebral palsy

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(20%). The proportion with multiple mental health disorders increased. Most diagnosed youth received treatment with medication and/or psychotherapy (95% for ADHD, 84% for conduct disorder, 87% for emotional disturbance, 89% for ODD, 97% for bipolar disorder, and 69% for autism spectrum disorder). For example, for ADHD, both the proportion receiving medication and the proportion receiving psychotherapy increased, and the proportion receiving neither treatment declined from 15% to 8%.

Conclusions: During the decade of the 2000s, there was a sharp increase in diagnosing of mental health conditions associated with challenging behaviors and/or difficulties in school adjustment among youth enrolled in Medicaid. These developments likely reflect a combination of forces including changes in educational policies as well as societal trends to increasingly pathologize challenging behavior of children.

176. Benzodiazepine Use and Risk of Developing Alzheimer's Disease - A Case-Control Study Based on Swiss Claims Data

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Background: A possible association between benzodiazepine use and Alzheimer's disease (AD) has been hypothesized in previous studies. We explored the relation between benzodiazepine exposure and the risk of developing AD in the Swiss ambulatory setting.

Objectives: To estimate the relative risk of developing AD in relation to previous benzodiazepine use.

Methods: We conducted a matched case-control study using claims data from the Helsana group, a large Swiss health insurance provider, to explore benzodiazepine use in cases with AD in 2013 or 2014 and in controls. We identified cases via recorded incident use of acetylcholinesterase inhibitors or N-methyl-D-aspartate receptor antagonist memantine, based on recorded anatomic therapeutic chemical classification codes for these drugs. For each case, we identified at random one control patient with no prescriptions for one of the above mentioned AD-specific drugs but matched on age, sex, index date and canton. Every patient was required to be constantly insured in the Helsana Group from 2008 on. The date of the first prescription for an AD-specific drug was referred to as the 'diagnosis date'. Because of the assumption that first-time prescription of a benzodiazepine close to the diagnosis date may be due to symptomatic treatment of prodromal symptoms of early dementia, we shifted the index date to 2 years before the diagnosis date. We conducted conditional logistic regression analyses to calculate relative risk estimates as odds ratios (ORs) of developing AD with 95% confidence intervals (CIs), adjusted for use of antidepressants.

Results: The adjusted OR (AOR) (95% CI) of developing AD for those who started benzodiazepines in the year before diagnosis was 1.36 (0.94-1.96). After accounting for benzodiazepine use initiated during the prodromal phase by shifting the index date, use of benzodiazepines was not associated with an increased risk of developing AD 0.84 (0.72-0.97). Long-term benzodiazepine use yielded an AOR of 0.82 (0.58-1.17).

Conclusions: Benzodiazepine use was not associated with an altered risk of AD after taking into consideration a prodromal phase of 2 years.

177. Association Between Prescription Opioid Use and Insomnia Among Community Members in Northeast Florida

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Background: Approximately 20% of the American population suffers from sleep disorders, and approximately 5% of adults will take an opioid in any given week. Additional research is needed to investigate the relationship between insomnia and opioid use.

Objectives: The current analysis aims to determine whether opioid use has an association with insomnia in a Northeast Florida community setting.

Methods: A survey study design method was used. We interviewed community members as part of a community outreach program, HealthStreet in Northeast Florida. Community Health Workers assessed baseline health information, including use of opioids (i.e., Vicodin®, Oxycodone, Codeine, Demerol®, Morphine, Percocet®, Darvon®, Hydrocodone). Insomnia was determined based on self-report: "Have you ever been told you had, or have you ever had a problem with insomnia? (yes/no)." Summary descriptive statistics were calculated and logistic regression modeling was used to determine adjusted odds ratios (ORs) with 95% confidence intervals for insomnia, controlling for other variables.

Results: Among 7,177 community members recruited into the sample between 2011-2015 (median age: 44 (IQR: 29, 55)), 43% male; 63% black), 1706 (24%) reported insomnia, and 3484 (48.5%) reported use of opioids. Insomnia was associated with opioid use (66% vs 34%), even after controlling for age, sex, race, and history of depression (adjusted OR, 1.76; 95% CI, 1.56-2.00).

Conclusions: Opioid use was significantly associated with self-reported insomnia, and the implications are significant as insomnia continues to be a large public health concern.

178. Utilization of Psychotropic Drugs in Spouses of Dementia Individuals: A Population-Based Study

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Background: Spouses of dementia patients face tremendous physical, emotional and financial stress. Studies suggested increased prevalence of depressive symptoms amongst dementia caregivers, but little is known about psychotropic drug utilization in this population.

Objectives: This study aimed to evaluate the utilization of psychotropic medications amongst spouses of dementia individuals in the community setting.

Methods: In this population-based, matched cohort study using the Manitoba administrative databases between April 2000 and March 2015, spouses of dementia individuals were identified using household unique registration numbers in the provincial health insurance database. Each dementia spouse was then matched to three comparison spouses based on age, sex and geographic region. Use of psychotropic drugs was evaluated based on corresponding ATC codes for antidepressants, mood stabilizers, benzodiazepines and related sedatives. Prevalent use of psychotropic medications was calculated as defined-daily dose (DDD) per person years, and intensity of use was estimated as DDD per user per year.

Results: Over a median follow-up period of 3.4 years (IQR 1.3 to 6.7 years), we observed 10,038 users of psychotropic drugs among 13,463 spouses of dementia individuals, and 22,992 users among 42,264 comparison spouses. DDD rate was 142.6 (95% CI 142.5 – 142.6) per person-year and 84.5 (95% CI 84.4 – 84.5) per person-year for dementia spouses and non-dementia spouses, respectively. DDD rates were significantly higher for dementia spouses for all classes of psychotropic drugs. Intensity of use over time amongst psychotropic users was not significantly different between the dementia and non-dementia spouses.

Conclusions: Use of psychotropic drugs is more prevalent in spouses of dementia individuals compared to non-dementia spouses. However, there is no difference in intensity of use amongst users of the two groups.

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179. The Incidence of Ventilator-Associated Pneumonia in Mainland China: A Systematic Review and Meta-Analysis

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Background: Ventilator-associated pneumonia (VAP) is one of the most frequent results of unsafe patient care worldwide, particularly in developing countries. However, data to date is far from sufficient to describe the epidemiology of VAP in mainland China.

Objectives: This systematic review aimed to estimate the nationwide incidence of VAP, with a special focus on its distribution among various settings and populations.

Methods: Medline, Embase, and three Chinese databases were searched to find studies with publication dates from 2010–2014. Prospective studies that reported the incidences of VAP in mainland China were included. VAP was defined as pneumonia that arises more than 48 hours after the initiation of mechanical ventilation. The methodological quality was assessed using a modified Leboeuf-Yde and Lauritsen tool. Meta-analyses were conducted to pool the arcsine- or log-transformed incidences of VAP, followed by subgroup meta-analyses by methodological quality, predefined setting characteristics, and attributes of populations.

Results: In 146 studies with overall moderate quality, the pooled cumulative incidence of VAP in mainland China was 23.3% (95% CI, 19.5–27.4%) and decreased from 2006–2013 ($p<0.001$). Meanwhile, the pooled incidence densities were 24.80 (95% CI, 21.97–27.98) episodes and 23.16 (95% CI, 20.42–26.26) patients per 1000 ventilator-days. The cumulative VAP incidence differed across provinces ($p<0.001$). In addition, VAP occurred frequently in surgical intensive care units (29.4%; 95% CI, 20.3–39.5%), the elderly (30.8%; 95% CI, 15.2–49.1%), the comatose (55.9%; 95% CI, 42.5–69.0%), and in tracheotomy patients (55.6%; 95% CI, 38.2–72.4%), re-intubated patients (54.6%; 95% CI, 43.9–65.2%), and patients mechanical ventilated for more than two weeks (79.4%; 95% CI, 49.7–97.7%).

Conclusions: In mainland China, the incidence of VAP remained high despite an overall declining trend. Our findings highlighted some modifiable risk factors that could serve as targets for improved management and prevention of VAP across the country.

180. Validation of Claims Approach to Identify Asthma and COPD Overlap Syndrome Patients in the US

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Background: Asthma and COPD overlap syndrome (ACOS) patient identification is challenging. Currently, there is no validated claims-based ACOS patient selection algorithm available.

Objectives: To assess the validity of a claims-based algorithm to identify high likelihood ACOS patients using patient medical records as the criterion.

Methods: Patients were identified from the US HealthCore Integrated Research Database (HIRD) between Jan. 1, 2006 and Oct. 31, 2014. A claims-based algorithm to identify high likelihood ACOS patients was based on the following inclusion criteria: age ≥40 years, ≥2 ICD-9 diagnoses for asthma (493.xx), ≥2 diagnoses for COPD (491.xx, 492.xx, and 496.xx), ≥2 ICD-9 procedure, Current Procedural Terminology (CPT), or Healthcare Common Procedure Coding System codes for COPD-related procedures, ≥3 prescription fills for asthma/COPD medication, and ≥2 CPT codes for spirometry test. Patients with cancer (140.xx – 209.3x, 230.xx – 234.xx) were excluded. Based on the chart review, at least 2 features (positive history of allergic rhinitis, chronic sinusitis, eczema, positive skin test, asthma history before 40 years, or family history of asthma) were needed to confirm the asthma component; a post-bronchodilator FEV1/FVC ratio of < 70% confirmed the COPD component. ACOS was confirmed when both asthma and COPD criteria were met.

Results: A total of 20,459 high likelihood ACOS patients were identified. 5,000 were randomly sampled for chart abstraction. Of those, 3,038 could not be obtained. Among the 1,962 obtained charts, 1,181 were unusable with no spirometry results. Thus, 781 charts were reviewed. Among those, 391 (50.1%) were confirmed as ACOS. Non-confirmed patients included 206 (26.4%) asthma only (showing no evidence for COPD), 106 (13.6%) COPD only (showing no

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evidence for asthma), and 78 (10.0%) showing no evidence for either asthma or COPD.

Conclusions: A patient chart review was able to corroborate only 50% of the patients identified by the claims-based algorithm as ACOS. Improvement in patient identification methods will require longitudinal studies using a battery of claims data and electronic records, patient charts, and patient and physician surveys.

181. Chronic Oral Corticosteroid Use in Adults with Persistent Asthma

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Background: Chronic oral corticosteroid (OCS) use in persistent asthma is an indicator of severe asthma.

Objectives: We studied factors associated with chronic OCS dispensing in a large managed care organization (MCO).

Methods: Using administrative pharmacy and healthcare utilization data, we identified 9,546 patients aged 18-64 years with persistent asthma. We calculated cumulative average daily dosage of OCS dispensed in a year per patient and examined distribution of baseline demographics, clinical characteristics, and comorbidities by various daily dosages of OCS. We established ≥2.5 mg/day/year as the cutoff to define chronic OCS use. Associations of factors in baseline year (2010) with chronic OCS use in follow-up year (2011) were investigated by multivariable Poisson regression with robust error variance.

Results: 782 (8.2%) patients at baseline were classified as chronic OCS users. Chronic OCS users were more likely to be older, female, from an ethnic minority, have had longer MCO membership and more comorbidities (including obesity, gastroesophageal reflux, pneumonia, rhinitis, sinusitis, nasal polyps, and eczema). They also had more asthma specialist care, received greater GINA step-care, greater dosages of inhaled corticosteroids, used asthma controllers and omalizumab more often, and had more asthma exacerbations, emergency room visits and hospitalizations but were less likely to be current smokers compared with those who received no or <2.5 mg/day OCS. In multivariable analyses, factors at baseline significantly associated with ≥2.5 mg/day/year of OCS in follow-up year included (a) demographics: older, being female, blacks vs. whites, and whites vs. others/unknown ethnicity; (b) disease features: asthma exacerbations, high GINA step-care, excessive short-acting beta-agonist dispensing, theophylline use, asthma specialist care, and nasal polyposis; and (c) chronic OCS use.

Conclusions: Adults with persistent asthma who were chronic OCS users were different from non-chronic OCS users for many characteristics, with greater asthma burden and more comorbidities. Current chronic OCS use was the strongest risk factor for chronic OCS use in the future.

182. Use of β-Blockers and Risk of Asthma Exacerbations

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Background: β-blockers are contra-indicated in asthma because of potential bronchoconstriction. There is emerging evidence that β-blockers might be safe in asthma patients with cardiovascular comorbidity.

Objectives: To study the association between use of β-blockers and the risk of moderate to severe asthma exacerbations.

Methods: We conducted 2 observational case-control (cc) studies nested in a cohort of asthmatics within the Dutch Integrated Primary Care Information (IPCI) medical record database. Study period was from 2008-2013. Cases were asthma patients >18 years old) with a first severe asthma exacerbation requiring hospitalisation/ED visit (first cc-set). In the second cc-set, cases were asthma patients with an exacerbation requiring systemic corticosteroids or hospitalisation/ED visit. To each case, all eligible

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asthmatic controls were matched on age, gender, GP practice and index date. Exposure to β-blockers was categorized by type of β-blocker (cardioselective vs. non-cardioselective) and categorized into no use, current or past use. Effect of duration and dose of β-blocker was investigated. Data were analyzed using conditional logistic regression analysis.

Results: In the first cc-set, 1,454 patients (mean age 49 yrs, 70% females), requiring hospitalization or ED visit due to an asthma attack were matched to 11,199 controls. Current use of β-blockers was not associated with an increased risk of asthma exacerbations (ORadj 0.8, 95% CI 0.6-1.0). No association was observed by type of β-blocker (non-cardioselective vs. cardioselective) and no dose effect relationship was observed. In the second cc-set, 10,934 cases with an asthma exacerbation consisting of either hospitalization, ED visit or use of systemic corticosteroids were matched to 74,415 controls (mean age 54 yrs, 67% females). Also in this second cc-set, there was no association between current use of β-blockers and risk of moderate to severe asthma exacerbations (ORadj 0.9, 95% CI 0.8-1.0).

Conclusions: Our study did not show an increased risk of moderate to severe exacerbations in asthma patients treated with β-blockers. These observational findings might be influenced by confounding by contra-indication, and should thus be interpreted with caution.

183. Stability of the Frequent Exacerbator - A Danish Nationwide Register-Based Study

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Background: The existence of a stable frequent exacerbator phenotype constitutes the basis of most treatment guidelines in chronic obstructive pulmonary disease (COPD).

Objectives: To investigate the stability of the frequent exacerbator over a 10-year follow-up period in a population-based setting.

Methods: We conducted a nationwide register-based epidemiological study with a 10-year follow-up period of patients with COPD and at least one medically treated exacerbation in 2003. Exacerbations were defined as short-term treatment with oral corticosteroids or hospitalization due to COPD. First, we categorized the population as frequent, infrequent and non-exacerbators each subsequent year during the 10-years of follow-up and quantified the flow between categories. Second, we calculated the proportion of frequent and severe exacerbators at baseline that remained in the same category throughout a 3- and 5-year follow-up period.

Results: Among all 1.5 million Danish citizens who were 55 years or older, we identified 19,752 patients with COPD and an exacerbation in 2003. Thirty percent were frequent exacerbators and 50% were hospitalized due to COPD. Overall, a large proportion of exacerbators in 2003 were non-exacerbators in the following years (60% in 2004 increasing to 68% in 2012). Approximately half of those categorized as frequent exacerbators in one year switched category and were either infrequent or non-exacerbators in the subsequent year. This pattern was stable throughout follow-up. A minority of frequent exacerbators in 2003 stayed in this category throughout a 3- and 5-year follow-up period (11% and 6%, respectively), while a substantial proportion (43%) did not have further years as frequent exacerbators except from the index year. Among those hospitalized due to COPD in 2003, 47% and 42% did not experience an exacerbation requiring hospitalization throughout the 3- and 5-years of follow-up, respectively.

Conclusions: The concept of a stable frequent exacerbator phenotype appears inapplicable in the general population. This finding underlines the need for regular assessment of patients with COPD.

184. Multimorbidity Clusters Differ by Exacerbation Frequency in Chronic Obstructive Pulmonary Disease

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Background: Multimorbidity contributes to disease severity in patients with chronic obstructive pulmonary disease (COPD). The coexistence of identified morbidities in the pathophysiology of COPD remains to be better clarified.

Objectives: To identify multimorbidity clusters among COPD patients and explore if they differ by exacerbation frequency.

Methods: Data were obtained from the Swedish healthcare consumption database VEGA, from 2006-2012. The population included 43 629 patients (53,5% women, mean age 67 years) who were at least 35 years old at the index year 2006, and had at least one recorded healthcare visit registered with an ICD-10 (International Statistical Classification of Diseases and Related Health Problems - Tenth Revision) code J43, J44 (COPD). Comorbidities were defined by ICD-10 codes. Multimorbidity clusters were identified by principal component analysis.

Results: Essential hypertension was the most commonly reported comorbidity and was diagnosed in 54% of the patients. Other common comorbidities were pneumonia (28%), asthma (27%), and heart failure (27%). Five multimorbidity clusters were identified: (1) Ischemic heart disease, (2) Metabolic syndrome, (3) Osteoporosis, (4) Psychological, and (5) Less comorbidity. The frequency of exacerbation differed with respect to multimorbidity cluster. Overall, patients in the Ischemic heart disease cluster had a higher frequency of annual exacerbations, whereas patients in the Less comorbidity cluster had a lower frequency of exacerbations.

Conclusions: Multimorbidity is common in patients with COPD, and different multimorbidity clusters may be identified. The frequency of exacerbations was found to differ between the clusters.

185. Review Of The Epidemiology Of Chronic Obstructive Pulmonary Disease In The Asia-Pacific Region

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Background: Chronic obstructive pulmonary disease (COPD) is a progressive condition, associated with high morbidity and mortality worldwide. The burden of COPD in Asia is likely to continue to increase due to rapid industrialization and high smoking prevalence.

Objectives: To perform a review of COPD epidemiology in the Asia-Pacific region, with a focus on prevalence, risk factors, diagnosis, treatment, economic burden and outcomes.

Methods: English language articles published from January 2000 to April 2015 were identified via PubMed.

Results: Forty-seven single and multi-country observational studies were identified as relevant. Although there was wide geographic variation, the overall prevalence of COPD in the Asia-Pacific region ranged from 6 - 7%. Common risk factors included tobacco smoking, air pollution, noxious irritants from workplaces and biomass exposure. A multi-national, population-based survey (n = 1,841) reported that 41% of subjects with symptomatic COPD were not accurately diagnosed. Under-utilization of spirometry could be a possible reason since studies showed that more than 50% of general practitioners did not use spirometry as the first diagnostic tool for COPD. Evidence from multiple countries also revealed a lack of prescriber

adherence to published COPD management guidelines, resulting in over-prescription of oral medications including corticosteroids and underutilization of inhaled bronchodilators for appropriate disease control. Only 25% of Asian COPD patients reported use of inhalers. Studies generally agreed that the severity of COPD correlates to healthcare costs, with hospitalization owing to exacerbations being a major cost contributor. Almost half of COPD patients experienced exacerbations within a year, with 19% reporting being hospitalized.

Conclusions: COPD burden in the Asia-Pacific region has risen to surpass the West. Increasing smoking prevalence, under-diagnosis and suboptimal management lead to high rates of exacerbations and hospitalization, which in turn strain healthcare systems. Studies have highlighted the need for education to increase COPD awareness in both Asian physicians and patients.

186. Incidence and Prevalence Time Trends of Idiopathic Pulmonary Fibrosis (IPF) in the United States (US) Over a 14-Year Period - A Claims Database Study

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Background: The epidemiology and recent time trends in incidence and prevalence of IPF in the US general population are insufficiently described. Further exploration of this disease to characterize the evolving healthcare burden is warranted.

Objectives: To examine time trends in the prevalence and incidence of IPF in the US using a claims database.

Methods: Using the MarketScan Commercial and Medicare Supplemental databases, we further developed previously described diagnostic algorithms to identify cases of IPF relying on ICD-9 codes alone ("broad" definition) or ICD-9 codes in combination with procedure codes for lung biopsy and/or computed tomography of the thorax ("narrow" definition). Exclusion criteria included age <18 years, any interstitial lung disease diagnosis (except post-inflammatory pulmonary fibrosis) after last IPF diagnosis, and at least one diagnosis claim for rheumatoid arthritis at any time. Patient counts, incidence, and prevalence (cumulative and annual) rates with 95% confidence intervals (CI) overall and by age, gender, and case definition were calculated by year from 2000 to 2013.

Results: A total of 33,987 patients met "narrow" definition, with the majority aged 50 years or older (90.6%) and 53% male between 2000 and 2013. Increasing trends for prevalence and incidence beginning in 2008 up to 2013 for patients aged 50 years or older were observed: annual prevalence from 28.9 (CI: 28.0, 29.8) per 100,000 in 2008 to 42.4 (CI: 41.2, 43.5) per 100,000 in 2013; incidence from 18.2 (CI: 17.2, 19.2) per 100,000 in 2008 to 26.9 (CI: 25.8, 28.0) per 100,000 in 2013. During this time period, males had 15% to 32% higher annual prevalence and 10% to 31% higher incidence rates compared to females. Similar trends were also observed using the "broad" definition, albeit at higher numbers.

Conclusions: This study showed an increase in IPF incidence and prevalence in the US from 2008 to 2013, particularly for patients aged 50 years or older regardless of definition. Additional studies are needed to better understand this increasing trend of IPF, including risk factors and the impact of available treatments.

187. Influence of Age and BMI on Risk of Venous Thromboembolism: A Meta-Analysis of 246,513 Women Using Combined Oral Contraceptives Based on 521,516 Women-Years

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Background: Women experiencing VTE under combined oral contraceptive (COC) use have multiple predisposing factors including advancing age and obesity. The independent effects of obesity and age have been

previously reported. It is not known if these two factors have a multiplicative effect.

Objectives: To determine if age and BMI interact when modelling the risk of VTE among users of COCs.

Methods: A meta-analysis of five prospective, transatlantic, observational cohort studies with primary endpoints of venous thromboembolism in women using COCs (IOC, TASC, ISCO, IFOC, LASS). Studies were conducted between 2007 and 2016 using similar methodology. 246,513 women with an observation time of 521,516 women-years were included. Inclusion criteria was prescription of a new COC, with no specific exclusion criteria. Women from the United States and Europe were followed for 3-5 years.

Main outcome measures: Age categorization was <25 years, 25-29, 30-39, and >40 years. BMI was defined dichotomously: $<35\,kg/m^2$ and $>35\,kg/m^2$. Smoking (y/n) and family history were cofactors included in final analysis.

Analysis: Poisson and Cox regression models were used to show the effect of age and BMI on VTE risk. The relative risk due to interaction (RERI) was calculated as described by Li et al. (2007). Interaction was defined as departure from the additive model (RERI = HR11 - HR10 - HR01 + 1). A RERI >0 or <0 indicates a super-additive or sub-additive effect.

Results: Poisson and Cox regression models show significant independent effects of age and BMI. Increasing age (ordinal scaled) was significantly associated with an increased VTE risk. The HR was observed between 1.15 and 1.70. The HR(BMI) ranged from 1.06 to 5.11. Results suggest a strong homogeneous effect of both factors HR(age) = 1.55 (1.44-1.68) and HR(BMI) = 2.09 (1.53-2.87). We observed a positive value for RERI in almost all categories tested, but significance based on normal approximation ($\chi 2$ test) could not be determined.

Conclusions: Age and BMI act as independent factors contributing to the risk of VTE. Their effect is additive, with no positive or negative interaction.

188. Body Mass Index and Cause-Specific Mortality: Population-Based Study Among 2 Million UK Adults Using Electronic Health Records Linked to National Mortality Data

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Background: Body mass index (BMI) is associated with all-cause mortality, but few large studies have explored associations with death from specific causes.

Objectives: To investigate associations between BMI and specific causes of death.

Methods: We used primary care data from the UK Clinical Practice Research Datalink, linked to national mortality data. Those with a valid BMI record were included; follow-up started 5 years later to avoid reverse causality. Outcomes were underlying causes of death: circulatory, cancers, respiratory, digestive, mental health, nervous system, genitourinary, endocrine/nutritional/metabolic, external, infections, musculoskeletal, and other. Associations with BMI were estimated using Cox models with cubic splines to capture non-linearity, adjusted for confounders. Cumulative incidences for each cause of death were calculated within BMI categories, with other causes as competing risks. Analyses were repeated among never-smokers in case of residual confounding.

Results: 2.0 million people and 129,671 deaths were included. There was a U-shaped association between BMI and all-cause death (among never-smokers, HR compared with healthy weight =1.58, 95% CI 1.49-1.67 for underweight; 1.01, 0.99-1.03 for overweight; 1.29, 1.26-1.32 for obese). BMI was strongly associated with each cause of death category (all $p<0.001$); positive associations were seen for cancer, genitourinary and endocrine/metabolic causes of death; inverse associations were seen for mental health, nervous system, and external causes of death; and U-shaped associations were seen for circulatory, respiratory, digestive, musculoskeletal, infections and "other" causes of death.

From estimated cumulative incidences, the probabilities of eventual cause of death being circulation-related were 29%, 35%, 38% and 39% among underweight, healthy weight, overweight and obese individuals respectively.

Conclusions: BMI was strongly associated with all categories of cause of death, with varying patterns of association. Results for more specific causes will also be presented.

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189. Natural History Of Primary Sclerosing Cholangitis – A Study Using the UK Clinical Practice Research Datalink (CPRD GOLD)

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Background: Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease with limited natural history data.

Objectives: To describe PSC natural history in CPRD GOLD.

Methods: Incident PSC patients in 1998-2014 and age-, sex-, and general practice (GP)-matched non-PSC patients were identified in CPRD through January 2015. Patients meeting all of the following criteria were included: a PSC diagnosis without a secondary sclerosing cholangitis diagnosis at any time; acceptable patients with at least 1 year of registration before the index PSC or cohort entry; patients who were registered with a GP that permits linkage to HES-ONS mortality data; patients who were eligible for HES-ONS linkage and had overlapping follow-up time in CPRD and HES data. Standardized difference (std diff) of 0.1 was used as threshold for baseline characteristics. Incidence rates ratios (RR) and 95% CI were calculated.

Results: Of 869 PSC patients, 250 were eligible and matched with 1250 controls (mean age 54 ± 18 years, men 63.2%). A total of 1272 person-years and 7410 person-years were respectively followed for PSC and controls. A higher percentage of PSC patients had inflammatory bowel disease (IBD, 54% vs 2%), cholangitis (40% vs 0%), gallstones (18% vs 3%), bile duct strictures (15% vs 0%) and biliary cirrhosis (6% vs <1%) than that of controls (std diff > 0.1). During a median follow-up of 5 years, new cases of liver failure (n = 11), liver transplant (13), and cholangiocarcinoma (9) were found in PSC, but none in the controls. At least 10 new cases were identified in PSC for portal hypertension, biliary cirrhosis, and hepatobiliary cancer, compared with < 5 new cases in the controls for each, with all RRs > 30 and 95% CI not including 1. In addition, incidence rates (per 1000 person-years) of IBD (61.0 vs 4.3, RR = 14.1, 95% CI 8.1-24.5) and gallstones (14.6 vs 3.4, RR = 4.3, 95% CI 2.1-8.6) were higher in PSC patients. A quarter of PSC patients and 10% of controls died, with the mortality rate (per 1000 person-years) higher in PSC (49.5 vs 16.1, RR = 3.1, 95% CI 2.2-4.2).

Conclusions: Compared with the general population, incident PSC patients had worse health outcomes.

190. Statin Use and Risk of Gallstone Disease in Switzerland - A Case-Control Study Based on Swiss Claims Data

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Background: Gallstone disease is a heavy economic burden in the Western world. Use of statins has previously been associated with a lower risk of developing cholesterol gallstones. So far, no studies on this association have been conducted using data from the Swiss ambulatory setting.

Objectives: To examine the association between use of statins and the risk of cholecystectomy.

Methods: We conducted a matched case-control study using claims data from the Helsana Group, a large Swiss health insurance provider, to identify cases with cholecystectomy (as proxy for gallstone disease) between 2013 and 2014. We identified four random controls for each case, matched on age, sex, index date and canton. Every patient was required to be enrolled with the Helsana Group constantly from 2008 on. We categorized patients into current (last prescription recorded within 180 days prior to the index date) or past statin use (last prescription recorded more than 180 days prior to the index date). Additionally, we categorized medication use by duration of use prior to the index date (short-term, 1-4; medium-term, 5-19; long-term, ≥20 prescriptions). We applied conditional logistic regression analysis to calculate relative risk estimates as odds ratios (ORs) with 95% confidence intervals (CIs). We adjusted the ORs and CIs for

history of diabetes, ischemic heart disease, stroke and transient ischemic attack, use of opposed or unopposed oestrogens, use of fibrates and other lipid-lowering agents.

Results: We identified a total of 2'220 cholecystectomy cases and 8'880 controls. Compared with non-use of statins, the adjusted OR (AOR) of undergoing a cholecystectomy was 0.85 (95% CI 0.74-0.99) for current statin users. Short-term current statin use was not associated with a statistically significantly altered risk estimate for cholecystectomy (AOR 1.34, 95% CI 0.99-1.83), while long-term use of statins was associated with reduced ORs (5-19 current statin prescriptions; AOR 0.77, 95% CI 0.65-0.92). The cholecystectomy risk was not affected either by short-term current statin use or by past statin use, irrespective of the duration of exposure.

Conclusions: Long-term use of statins was associated with a reduced risk of cholecystectomy.

191. Use of Angiotensin-Converting Enzyme Inhibitors and/or Angiotensin-Receptor Blockers and the Risk of Acute Kidney Injury After Colorectal Cancer Surgery: A Population-Based Cohort Study

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Background: Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin-receptor blockers (ARBs) are commonly used drugs with potential nephrotoxicity. It is unknown whether preadmission use of ACE-Is and/or ARBs has an impact on risk of acute kidney injury (AKI) after colorectal cancer (CRC) surgery.

Objectives: We assessed the impact of preadmission use of ACE-Is and/or ARBs on the post-surgical risk of AKI in patients undergoing surgery for CRC.

Methods: We used the Danish Colorectal Cancer Group Database to identify all CRC patients undergoing surgery between 2005 and 2011 in Northern Denmark. Based on reimbursed prescriptions, patients were characterized as current users of ACE-Is/ARBs (≥1 prescription within 90 days before surgery), former users (≥1 prescription in the period 90-365 days before surgery), or non-users (no prescriptions during 365 days before surgery). We assessed the outcome, AKI, using creatinine levels measured within seven days after surgery. We computed cumulative AKI risk with 95% confidence intervals for patients with current, former, or no use of ACE-Is and/or ARBs, and included death as a competing risk. Hazard ratios (HRs) were computed using Cox proportional hazards regression analysis, controlling for potential confounders and stratified by subgroups.

Results: Our analysis included 6,755 patients, of whom 20.3% were ACE-Is and/or ARBs users, 6.1% were former users, and 73.6% were non-users. The overall cumulative 7-day post-surgical risk of AKI for current users was 28.5 % (26.1-30.9 %), 26.0 % (21.9-30.3 %) for former users and 19.2 % (18.1-20.3 %) for never users. ACE-Is and/or ARBs was associated with an overall crude Hazard Ratio (HR) of 1.56 (1.39-1.76) for current users and 1.41 (1.16-1.72) for former users. The adjusted HRs were 1.10 (0.95-1.28) for current users and 1.02 (0.82-1.26) for former users, compared to never users within 7 days after surgery. The stratified analyses revealed similar estimates across subgroups.

Conclusions: The increased risk of AKI observed in users of ACE-Is and/or ARBs could be partially explained by confounding.

192. Prevalence of Crigler-Najjar in the Turkish Population

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Background: Crigler-Najjar (CN) is an autosomal recessive congenital non-hemolytic unconjugated hyperbilirubinemia caused by the deficiency of hepatic enzyme UDP-glucurunosyltransferase. The epidemiology of CN is poorly characterized, with few studies about the prevalence of this rare disease.

Objectives: To estimate the prevalence of Crigler-Najjar and its subtypes in the Turkish population.

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Methods: Using the Medula database, which covers approximately 80% of Turkish population, a retrospective claims study was conducted to determine the annual prevalence of CN, International Classification of Diseases, 10th Revision, Clinical Modification code E80.5, during the study period 01JAN2010-30SEP2014. Patients with >1 claim for CN at least 30 days apart and having continuous health plan enrollment in the calendar year were included. Once patients were counted as prevalent they were included in subsequent years as prevalent cases as long as were alive and continuously enrolled in the given year. CN patients were stratified as Type-1 (no claim for phenobarbital) and Type-2 (≥1 claim for phenobarbital within 9 months).

Results: The study period (2010-2013) included 86 patients with CN; the average age was 14 years. Number of patients in the Medula database ranged from 58,447,989 to 63,755,509 during the study period. Study findings revealed a range in CN prevalence by year (0.58 to 1.30 per 1,000,000) and a higher prevalence among patients aged 0-12 months, mostly males from the Black Sea region. More CN patients were classified as Type-1 compared with Type-2. Prevalence of Type-1 was highest among patients aged 0-12 months, ranging by year from 3.16 to 5.31 per 1,000,000 followed by patients aged 6-10 years (1.22 to 2.53 per 1000,000 during the study period. Prevalence of Type-2 was higher among patients aged 2-5 years during 2010 and 2012 (1.01 and 2.60 per 1,000,000), and higher among patients aged 0-12 months in 2011 and 2013 (1.57 and 2.90 per 1,000,000).

Conclusions: There is an increasing prevalence of CN in the Turkish population, with more patients classified as CN Type-1 compared with CN Type-2.

193. The Association Between Chronic Urticaria and Autoimmune Thyroid Disease: A Nationwide Population-Based Study in Taiwan

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Background: Chronic urticaria (CU) is defined as urticaria with a course longer than 6 weeks. The linkage of CU to autoimmune thyroid disease has been described but not fully characterized in the population-based study.

Objectives: To determine the association between CU and autoimmune diseases by utilizing a nationwide database in Taiwan.

Methods: This cross-sectional study was conducted using the 2000-2011 National Health Insurance Research Database (NHIRD, which contains administrative claims data from approximately 23 million enrollees under the National Health Insurance program in Taiwan. Patients of were included in the initial sample if they had as at least two diagnoses of CU (ICD-9-CM-CM: 708.1) within two years after the first observed urticaria diagnosis during 2000-2011. Each urticaria patient was matched to four non-urticaria patients on the same age and sex. The occurrence of autoimmune diseases, including thyroid disease was determined by respective ICD-9-CM coding.

Results: Totally, 16,152 patients, including 8,421 males and 7,731 females fulfilled the inclusion criteria of CU in our study period. The control group had 64,608 patients including 33,684 males and 30,924 females. Both the age at diagnosis and gender distribution were comparable between and urticaria and control group. As a whole, the CU patients owned an increased risk of the systemic autoimmune diseases when compared with the control group ($P < 0.001$). Among the systemic autoimmune diseases, lupus erythematosus had the highest risk ($RR = 5.2$) The results also showed that the thyroid disease was significantly enriched in the CU population. Looking into the specific thyroid diseases, hyperthyroidism but not hypothyroidism was more commonly seen in CU. Stratification by gender in the overall thyroid disease group revealed that the female was more prone to have hyperthyroidism ($RR = 1.55$, $P < 0.001$) while this risk was not significant in the male ($P = 0.056$).

Conclusions: Our study showed that CU owned a small risk for autoimmune thyroid diseases. Among the thyroid diseases, hyperthyroidism is significantly enriched in the female population.

194. Disease Severity and Characteristics of Patients with Atopic Dermatitis (AD) Investigated Using Administrative Claims Data

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Background: AD is a chronic inflammatory skin disease characterized by severe itching, sleep disturbances and widespread rash. Severity is not captured in most data sources, and characteristics of patients by severity are not well described.

Objectives: To define AD patient severity cohorts based on treatment received, and describe their characteristics, using claims data.

Methods: Adult patients (≥16 years) with ≥1 diagnosis of AD (ICD-9 CM codes 691.xx) between 1/1/2007 and 7/30/2013, 12 months pre and post-index continuous health plan enrollment, and ≥2 post-index dermatologist visits were identified from the US HealthCore Integrated Research Database (HIRD). They were assigned into severity cohorts defined by line of therapy in the pre-index period. Cohort 1: No prescriptions; 2: 1st line therapy (topical corticosteroids; TCS); 3: 2nd (topical calcineurin inhibitors); 4: 3rd (phototherapy); 5: 4th line (immunosuppressants); 6: biologics. All cohorts were evaluated for patient demographics and pre-index clinical characteristics (comorbidities, concomitant medications).

Results: Cohorts 1-6 included 19.4%, 73.5%, 4.7%, 1.2%, 0.6%, and 0.6% of a total of 55,858 patients, mean age across cohorts 42-54 years, 54-66% women.

Comorbidities generally increased with increasing cohort severity. Frequent comorbidities included asthma, allergic rhinitis, depression and anxiety.

Of cohort 2 patients, 49% were prescribed high / very high potency TCS. In cohorts 3-6, 69-75% of patients also claimed for TCS. Prescribed immunosuppressants in cohort 5 included: azathioprine (40%), mycophenolate mofetil (35%), cyclosporine (27%) and methotrexate (8.4%), all unapproved for AD. Biologics prescribed in cohort 6 may be for co-morbidities and/or for AD. Antihistamines were used by 25-27% of patients in Cohorts 3-6. In cohorts 4-6, anti-depressants were used by 27-34% and anxiolytics by 28-31%. Anti-asthmatic therapy increased notably with AD severity.

Conclusions: Disease severity cohorts were defined based on medication usage data. Findings suggest increased patient burden in adult AD with co-morbidities and additive, concomitant prescribing, including frequent use of TCS.

195. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Long-Term Sequelae Based on a 5-Year Follow-Up Analysis

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Background: Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN) is a rare, but severe cutaneous adverse reaction most often caused by drugs. Severity is determined by skin detachment related to the body surface area (BSA): SJS <10%, TEN >30%, and SJS/TEN-overlap 10-30% of BSA. The high mortality rate is due to severity as well as age of the patient. Survivors frequently suffer from long-term sequelae, particularly of the mucosa.

Objectives: To evaluate frequency and extent of late sequelae in patients with SJS/TEN.

Methods: A cohort study of patients with a validated diagnosis of SJS/TEN, who were included in the international Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) between 2003 and 2007, was performed. A specific follow-up questionnaire was developed and sent to the patients, who were asked to complete and return it.

Results: 112/233 completed follow-up questionnaires could be analyzed: 62 patients with SJS, 35 with SJS/TEN-overlap, 15 with TEN. The mean age is 44 years, and approx. 60% are women. More than 90% of the patients suffer from sequelae after 5 years, while the percentage increases with severity of the reaction. Less than 50% were able to completely return

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to their normal daily activities. Sequelae mainly affect skin (73%), mucosa (57%) and nails (52%). Chronic sequelae of the eyes (67%) are the main issue for the patients. They include increased photosensitivity, dry eyes, ingrowing eyelashes (trichiasis), excessive watery eyes (epiphora), inflammatory cicatrization up to blindness. Furthermore, patients describe sleep disturbances and nightmares (29%). In addition, they are afraid of drug use (65%), and 56% of the patients avoid taking drugs, leading to a potentially negative health impact.

Conclusions: The majority of patients who survived SJS/TEN suffer from long-term sequelae, often leading to disability. This is most important, since, first, SJS/TEN was formally thought to be an acute life-threatening but not a chronic disorder and, second, in only few countries compensation programs for patients with severe drug-induced adverse reactions are in place.

196. Atopic Diseases and the Risk of Developing Ulcerative Colitis

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Background: Although auto-immune diseases and atopic diseases seem to be caused by different malfunctions in the immunological pathways, there is an increasing body of evidence for cross regulation between the two pathways. Research showed that patients suffering from atopic diseases are at greater risk of developing for instance inflammatory bowel diseases.

Objectives: The aim of this study was to examine to what extent the risk of developing ulcerative colitis is increased in atopic patients.

Methods: We conducted a case-control study using data of patients, aged 18-50 years, from the prescription database IADB.nl. Cases were defined as new users of aminosalicylic acid preparations (ATC: A07EC); the first line treatment for ulcerative colitis. Controls were matched on gender and age at the index date. Excluded were rheumatic patients. Prevalence rates of atopic diseases were based on the use of either ≥2 prescriptions for dermal (atopic dermatitis), inhaled (asthma) or nasal (allergic rhinitis) corticosteroids within 12 months before the index date. Logistic regression analysis was used to estimate odds ratios (OR) and their corresponding 95% confidence intervals (95% CIs).

Results: A total of 2022 cases and 202200 controls were included in the study (38.4% male; mean age 36.3 years). All three atopic diseases, asthma, allergic rhinitis, and atopic dermatitis were associated with ulcerative colitis with ORs of 3.11 (2.66-3.64), 2.69 (2.33-3.12), and 3.59 (3.23-3.99), respectively.

Conclusions: This study shows a clear increased risk of developing ulcerative colitis among patients receiving medication for atopic diseases.

197. Can Rheumatoid Arthritis Associated With Interstitial Lung Disease (RA-ILD) Be Classified As An Orphan Disease In The U.S.?

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Background: Rheumatoid arthritis (RA) is a systemic inflammatory disease that affects approximately 1% of the adult population and whose primary pulmonary manifestation is interstitial lung disease (ILD). Although RA is often diagnosed before the detection of ILD by the presence of articular manifestations, patients may present de novo with isolated pulmonary disease. The reported prevalence of ILD among patients with RA is highly variable, ranging from 3.6% to 42%, depending on detection methods and population evaluated.

Objectives: The prevalence and incidence of RA-ILD in routine clinical practice were estimated using the U. S. MarketScan database to determine whether RA-ILD should be classified as an orphan disease (i.e., rare disease that affects fewer than 200,000 people nationwide).

Methods: Adult (aged ≥18) patients from a 10% sample of the U.S. MarketScan database during 01 January 2008 through 31 December 2013 were included if they had at least one year of continuous enrollment. To identify RA-ILD patients, the same codes used by

Olson et al. (2011) were applied: at least one ICD-9 diagnosis code each for RA (714.0, 714.1, 714.2, 714.8, or 714.9) and for ILD (515, 516.3, or 714.81). Descriptive analyses were conducted using the Aetion Evidence Platform.

Results: Among 6,676,639 adults, the RA prevalence was 148.38 per 10,000 patients and increased with age. The overall RA-ILD prevalence was 5.27 per 10,000 patients in the general population (ranging from 0.59 among 18-39, to 18.23 among those ≥60 years of age), and was 355.00 per 10,000 patients among those who ever had RA. The RA-ILD incidence rate was 1.95 per 10,000 person-years. The majority of the prevalent RA-ILD patients were ≥60 years of age [59%; mean age (SD): 63 (13.5)] and female (70%).

Conclusions: Applying these findings to the U.S. Census Bureau estimate of 245,201,076 adults in 2014, the number of prevalent RA-ILD adult patients is approximately 129,000 in the U.S. This is less than the FDA threshold of 200,000 people nationwide, suggesting that RA-ILD is an orphan disease.

198. Claims-Based Prediction Models Are Unable to Accurately Predict Disease Activity for Rheumatoid Arthritis

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Background: Accurate methods to assess rheumatoid arthritis (RA) disease activity are needed to conduct observational research studies of RA in administrative databases.

Objectives: Develop predictive models using administrative claims data and evaluate the potential of these models to predict RA disease activity.

Methods: Veterans enrolled in the Veterans Affairs Rheumatoid Arthritis (VARA) registry without diagnoses of cancer, organ transplantation, or other autoimmune diseases were included. VARA sites collect data on the 28 joint count disease activity score (DAS28) and the clinical disease activity index (CDAI). Models were developed to predict the first recorded DAS28 or CDAI after 1-year of enrollment. We identified 1,275 variables possibly associated with disease activity. We also leveraged hierarchical classification systems for pharmacy, procedure and diagnostic codes for high-dimensional variable selection. The least absolute shrinkage and selection operator (LASSO) was used for variable selection and model development. Multiple models were tested that varied the independent variables with ≥1% prevalence. The approaches used clinically defined variables, a high-dimensional approach and separate prescreening for statistical association with DAS28 and CDAI. Predicated disease activity scores were categorized as high or low and accuracy was calculated to evaluate classification performance. The cut point for actual DAS28 was ≤3.2 and 10 for CDAI. Cut-points for predicted scores were optimized for classification accuracy.

Results: There were 1,582 and 1,563 Veterans who fulfilled inclusion criteria for DAS28 and CDAI, respectively. The adjusted r-square for the 6 models tested ranged from 0.20-0.24 for DAS28 and 0.17-0.24 for CDAI. Accuracy ranged from 61.8-64.3 for DAS28 and 61.2-63.1 for CDAI.

Conclusions: Models tested with independent variables limited to information obtainable in claims data yielded similar results and showed weak predictive accuracy with measured disease activity. Future research should investigate additional strategies to collect components of disease activity measures directly from medical records.

199. A Systematic Review of Population-Based Incidence and Prevalence Estimates of Axial Spondyloarthritis, Including Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis

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Background: The incidence and prevalence of axial spondyloarthritis (axSpA), ankylosing spondylitis (AS) and non-radiographic (nr-)axSpA have been investigated in multiple studies, though there is a paucity

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of population-level data. It is essential to understand factors influencing incidence rate (IR) and prevalence rate (PR) estimates to improve diagnosis and treatment of poorly understood and uncommon diseases, such as axSpA.

Objectives: To perform a systematic literature review (SLR) to identify publications reporting IRs or PRs of axSpA, AS or nr-axSpA, and to investigate factors affecting reported rates.

Methods: The SLR was performed in line with PRISMA guidelines. PubMed and Embase were searched and results reviewed vs eligibility criteria by 1 reviewer with second reviewer assistance where inclusion was uncertain. Eligible articles had to be published in English between 1Jan2000 – 30June2015, reporting population-based studies and providing IRs or PRs.

Results: 2,148 articles were identified; 19 fulfilled eligibility criteria (from 15 countries). IRs per 100,000 patient-years (PY) were reported in 5 AS studies and varied from 0.4 in Iceland to 15.0 in Canada. Reported PRs per 100,000 PY also showed considerable variation (4 axSpA studies: 130.0 [Norway] to 1400.0 [US]; 16 AS studies: 6.5 [Japan] to 540.0 [Turkey]; nr-axSpA: none reported).

PRs varied by classification criteria used and method used to estimate PR (ie diagnosis vs screening). Although AS PRs are known to vary by HLA-B27 status, only 4 studies reported this genetic marker.

Conclusions: This SLR highlights the impact of inconsistent disease classification criteria and definitions of source populations on IR and PR estimates, which hinders the understanding of disease burden. The SLR demonstrates the need to capture all relevant information (eg. HLA-B27 positivity) and to investigate under-reported populations (nr-axSpA; Southern Hemisphere countries). Future studies should aim to address these data gaps and provide accurate IR/PR estimates for the global axSpA population.

200. Pigmented Villonodular Synovitis (PVNS): Incidence, Patient Characteristics, Treatment and Recurrence: a Cohort Study in Denmark

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Background: PVNS is a rare benign proliferative and inflammatory disease of joints' synovia, bursae, and tendon sheaths, with an estimated annual incidence of 2-50/million. Surgery is the primary treatment for PVNS. Little is known about the characteristics, clinical course and long-term outcomes among patients with PVNS.

Objectives: To estimate incidence rate of PVNS in adults; to describe characteristics of patients with PVNS; and to examine treatment patterns and long-term risk of recurrence.

Methods: We conducted a registry-based cohort study in Denmark in 1997-2012, with follow-up through 2012, using data on diagnoses and procedures from hospital encounters or pathology examinations. In the absence of a validated algorithm to identify PVNS from routine medical data, we defined algorithms for localized and diffuse PVNS types (L-PVNS/D-PVNS), based on face value of the available diagnostic codes and clinicians' advice. For the two PVNS types, we estimated incidence rates, described patients' demographic and clinical characteristics, and estimated long-term risk of recurrence.

Results: There were 2,087 cases of L-PVNS and 574 cases of D-PVNS, with incidence rates (95% CI) of 30.4 (29.1 – 31.7) and 8.3 (7.7-9.1) per million person-years. Women comprised 61% of the L-PVNS patients and 51% of the D-PVNS patients; >70% of D-PVNS and L-PVNS cases were diagnosed at ages 20-59 years. Within up to 3 years before the diagnosis, patients with D-PVNS had a higher than patients with L-PVNS prevalence of a skeletal injury (17% vs. 9.7%), osteoarthritis (52% vs. 17%), or arthropathy (25% vs. 6.5%); were more likely to have used systemic corticosteroids or antiinflammatory drugs; and had greater health care utilization. Surgery assumed to be for PVNS within up to 30 days of the diagnosis was recorded for 43% of D-PVNS and 28% of L-PVNS patients. The 10-year risk of recurrence was 20% for D-PVNS and 10% for L-PVNS.

Conclusions: PVNS incidence rates were comparable with those previously reported. D-PVNS carries a greater burden of disease than L-PVNS, including a higher risk of recurrence.

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201. The Association Between Prior Appendicectomy and/or Tonsillectomy in Females and Subsequent Pregnancy Rate: A Cohort Study

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Background: The appendix and tonsils are secondary lymphoid organs and surgical procedures to remove them are amongst the most common operations, particularly in children and young adults. The increased pregnancy rate following appendicectomy might be related to reduced local inflammation or inflammatory adhesions in the vicinity of the pelvic fallopian tubes reducing their patency.

Objectives: To study if subsequent pregnancy rate is altered after appendicectomy and/or tonsillectomy.

Methods: A population based cohort study was conducted in UK Primary Care Patients registered on the Clinical Practice Research Datalink (CPRD). Female cohorts who underwent appendicectomy, tonsillectomy or both between 1987 and 2012 and appropriate comparators were followed up until first pregnancy. The association between appendicectomy, tonsillectomy or both and subsequent pregnancy was determined by Cox regression models.

Results: The analyses included 54,675 appendicectomy only patients, 112,607 tonsillectomy only patients, 10,340 patients who had both appendicectomy and tonsillectomy with 355,244 comparators matched for exact age and practice from the rest of female patients in the database. There were 29,732 (54.4%), 60,078 (53.4%) and 6,169 (59.7%) pregnancies in the appendicectomy only, tonsillectomy only and both appendicectomy tonsillectomy cohorts respectively vs 155,079 (43.7%) in the comparator cohort during a mean follow up of 14.7 (SD, 9.7) years. Adjusted hazard ratios (HRs) for subsequent birth rates were 1.34 (95% CI 1.32 to 1.35), 1.49 (95%CI 1.48 to 1.51) and 1.43 (95%CI 1.39 to 1.47), respectively. Time to pregnancy was shortest after both appendicectomy and tonsillectomy followed by appendicctomy only and then tonsillectomy only in comparison to the rest of the population.

Conclusions: Appendicectomy and/or tonsillectomy were associated with increased subsequent pregnancy rates and shorter time to pregnancy. The effect of the surgical procedures on the pregnancy outcome was cumulative.

202. Longitudinal Changes in Prevalence of Rare Diseases and Related Costs in Taiwan (2003-2014)

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Background: The definition of rare diseases differs from country to country, and management of these diseases and availability of orphan drugs also vary between countries. Little attention has been given to the epidemiology of rare diseases and their health related economic burden in Taiwan.

Objectives: This study aims to examine the trends in prevalence of rare diseases and their health related economic burden (including medication costs) in Taiwan.

Methods: We examined 2003-2014 (12 years) rare disease-related claims data from National Health Insurance Research Database. We used time series analysis to assess trends in prevalence of rare diseases, and overall healthcare use and expenditures, including drugs.

Results: During the 12-year study period, the estimated prevalence of rare diseases increased from 10.50 to 33.19 per 100,000 population, an average rate of 19.64% increase per year. Of note, prevalence of amyotrophic lateral sclerosis and multiple sclerosis increased by 28.58% and 14.74% per year respectively. Total health expenditures for treatment of rare diseases overall increased from US$15 million to US$139 million, which accounted for 0.68% of total national health expenditure in 2014. Among health expenditures, drug expenditures for treatment of rare diseases increased from US$10.87 million to US$123.48

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million, which accounted for 2.31% national drug expenditure in 2014. We found a 21-fold difference in average health expenditure and a 70-fold difference in average drug expenditure between patients with rare diseases and all patients.

Conclusions: Prevalence of rare diseases, and related health and drug expenditures have substantially grown in Taiwan over the past 12 years, and these trends are likely to continue. Drug expenditures accounted for almost 90% of health expenditures. Further analyses in underway to examine economic burden of individual rare diseases.

203. Time Trends And Patterns Of Prescriptions For Drug Pairs With A Serious Drug-Drug Interaction In UK Primary Care

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Background: Polypharmacy is increasing over time. There is a strong correlation between polypharmacy and co-prescribing drugs with a potential drug-drug interaction (pDDI). The trends in the prevalence of (pDDI) will be explored.

Objectives: 1. Describe the trend in absolute prevalence of pDDI in UK primary care from 1994 to 2014.
2. Describe the differences in trend by drug class.
3. Describe the relative prevalence of pDDI as a fraction of the prescriptions for each constituent drug.

Methods: The source population was the UK Clinical Practice Research Datalink (CPRD), a primary care electronic health records database. Serious drug-drug interactions are defined as those listed as serious in the British National Formulary (BNF). For each interaction we found the number of patients issued with same day prescriptions for both drugs by year. The prevalence of each pDDI was defined as the proportion of the active patients in the database. We broke this down by drug classes and we also found the relative trend in pDDIs as a proportion of the total number of prescriptions for the interacting drugs to determine if the rise in exposure to drug-drug interactions is out of proportion with the prescription trends for the constituent drugs.

Results: Preliminary results show 29% of patients in 2014 received a prescription with a pDDI. Excluding interactions between antihypertensives (usually intentionally co-prescribed), 13% of patients received a prescription with a pDDI. All subsequent figures refer to this subset.

From 1994 to 2014 there has been a 262% increase in the proportion of patients exposed to a pDDI. The majority are accounted for by relatively few drug pairs. 79% were accounted for by 50 drug pairs and 45% by just 20 drug pairs. The commonest drug pair was amlodipine and simvastatin.

We will present trends by drug class and compare the absolute number of patients exposed to a pDDI with the relative number as a proportion of those that received either interacting drug.

Conclusions: There has been a large increase in the number of patients exposed to pDDIs. A small number of drug pairs account for the majority.

204. A Systematic Review and Methodological Framework for Estimating Prevalence of Rare Diseases

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Background: Accurate, population-based estimates of rare disease prevalence are necessary for regulatory and reimbursement decision making and to understand the burden of illness and establish networks for patient support and physician expertise. While considerable progress has been made in establishing rare disease registries, gaps in case ascertainment and estimation of denominator populations make accurate estimation of prevalence a challenge.

Objectives: 1) To systematically identify approaches currently being used by researchers to estimate rare disease prevalence, and 2) To create a framework to identify suitable methods for prevalence estimation.

Methods: We conducted a systematic literature review for 2005-2015 using Embase and Medline with free text and indexed search terms for rare diseases and prevalence. Data relating to the methodological approach, jurisdiction, and data sources were extracted and summarized. In parallel, we reviewed the methodological literature and developed a framework to

estimate rare disease prevalence, identifying key determinants of appropriate methodology.

Results: Our search returned 1280 hits, and we identified 80 relevant studies. Data sources used to identify prevalent cases included disease registries or clinical/administrative databases (n = 34), medical record reviews (n = 14), or surveys of relevant health-care professionals (n = 7). A third of the studies combined multiple approaches or incorporated mathematical models to estimate prevalence. The population at risk was most commonly based on census data, regional/national statistics or catchment areas of relevant healthcare institutions. Our conceptual framework focused on characteristics of the disease, jurisdiction, and available data. For each category, we created levels relating to the completeness of the data source for both numerator and denominator, and evaluated the suitability of the identified methods for prevalence estimation.

Conclusions: This review and framework will serve as a useful resource for those considering how to produce accurate estimates of prevalence, particularly when faced with imperfect data sources.

205. Mortality Rates in People with Intellectual Disabilities

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Background: A growing body of evidence highlights a disparity in mortality rates for people with intellectual disability (ID) compared with the general population. However, national data for England is lacking.

Objectives: Provide evidence on mortality rates in people with ID.

Methods: Patients registered for at least a day during 04/01/10-03/31/14 at a GP practice contributing to the Clinical Practice Research Datalink (CPRD) and consenting to linkage were included. Patients with ID were identified via Read codes. Date and cause of death were identified using linked Office of National Statistics mortality data. Crude mortality rates, life expectancy and indirectly age/sex standardised mortality ratios (SMR) were calculated with 95% confidence intervals (CI), overall, by ICD-10 chapter, for frequently occurring causes, and those classified as avoidable.

Results: 11 million person-years were included (0.5% for patients with ID) and 98,035 deaths occurred (0.7% in patients with ID). The mortality rate for patients with ID was 11.2 per 1,000 population, 1.3 times the rate for those without ID, with an associated SMR of 3.2 (95% CI 2.9-3.4). Life expectancy was 65.5 years (95% CI 61.9-69.2) for patients with ID and 85.3 years for those without (95% CI 85.2-85.4). Mortality rates were higher in patients with ID in all age/sex groups, with larger differences for younger ages. Patients with ID had higher cause-specific mortality rates across all ICD-10 chapters, with highest SMRs for congenital malformations (72.9, 95% CI 55.1-94.7), nervous system diseases (9.8, 95% CI 7.8-12.1) and mental disorders (5.4, 95% CI 3.9-7.3). Circulatory deaths were the most frequent, with ischaemic heart disease (SMR 2.2, 95% CI 1.6-2.8) and cerebrovascular disease (SMR 3.3, 95% CI 2.3-4.5) most prominent. A higher proportion of deaths were classified as avoidable for patients with ID (44.7%, 95% CI 41.0-48.5%) compared to those without (21.0%, 95% CI 20.7-21.3).

Conclusions: National English data confirm that patients with ID have higher mortality rates than those without. Mortality rates for patients with ID were higher across all age/sex groups and causes, with almost half of deaths classified as avoidable.

206. Use of FDA Approved Stents Intended for Adults for the Treatment of Pulmonary Artery Stenosis in Children

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Background: Treatment of branch pulmonary artery (BPA) stenosis with stents, widely considered standard practice by the pediatric interventional cardiology community, has not been approved by the Food and Drug Administration (FDA) in children.

Objectives: To evaluate the advisability of approving this use of stents, we conducted a systematic literature review.

Methods: PubMed was searched for clinical articles published on or after 2000, on the treatment of BPA using stents in children. Three outcomes were evaluated at baseline (BL) versus immediately post-stenting, and at follow-up (FU, usually 1-2 years) when available: diameter of the stenotic lesion; pressure gradient across the lesion, and; the ratio of right ventricular to systemic pressure.

Results: Twenty-three studies met the criteria for inclusion. In all 21 studies that assessed lesion diameters there was an increase in diameter from BL to immediately post-treatment, which averaged approximately 100%. In the studies that assessed FU results, the average diameters were midway between BL and immediately post-treatment.

All 17 studies that assessed pressure gradient showed a decrease of about 70% from BL to immediately post-treatment. The general pattern was a reversion of the pressure gradient over time towards BL levels; immediate post-treatment values were greater.

Seven of the 10 studies that assessed the ratio of right ventricular to systemic pressure showed a significant decrease from BL to immediately post-treatment. Of the 4 studies that assessed FU of the ratio, 3 showed little change from post- initial treatment.

Conclusions: This evidence indicates excellent immediate results from the use of stents to treat BPA stenosis in children. The literature shows increased post-stent arterial diameter and decreased pressure gradient, and decreased right ventricular to systemic pressure ratio to a lesser extent. FU assessment showed varying degrees of restenosis (often successfully re-treated), but generally substantially less stenosis than what was seen prior to the initial stent treatment.

207. Magnetic Resonance Imaging Examination in People with Cardiac Implantable Electronic Devices

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Background: Magnetic resonance imaging (MRI) is an important diagnostic tool. The presence of cardiac implantable electronic devices (CIED) (i.e. permanent pacemakers, cardiac resynchronisation therapy and implantable cardioverter defibrillators) has been considered a contraindication to MRI due to potential life-threatening interactions. MRI compatible CIEDs that are not affected by the MRI are now available. It is not clear how many patients with CIED undergo MRI examinations and whether this is associated with adverse events.

Objectives: To determine number of people with CIED undergoing MRI examinations and subsequent adverse events.

Methods: A retrospective cohort study using data from the Australian Government Department of Veterans' Affair claims database was conducted. People who received a CIED between 2004 and 2015 were evaluated. Exposure was outpatient MRI examination. Outcome was hospitalisations within 30 days of the MRI for device infection, venous thromboembolism, stroke, myocardial infarction, heart failure, lead displacement/failure, pneumothorax, pulmonary embolism and cardiac tamponade or death.

Results: A total of 20730 people were included. Of these, 60 (0.3%) people had at least one MRI, 18 (30%) people with non-compatible CIED and 42 (70%) people with compatible CIED. In the group with non-compatible CIED, there were 27 MRIs in 18 individuals. Of the 18 individuals with non-compatible CIED, 4 (22%) had a hospital admission in the following 30 days of having the MRI. Two hospitalisations (9 and 10 days after MRI, respectively) were for heart failure and the other two were unrelated to the outcome events. In the group with MRI compatible CIED, 3 (7%) hospitalisations occurred, one for heart failure, one for endocarditis and one for infection due to the CIED. There were no deaths within 30 days of undergoing an MRI in either group.

Conclusions: In this large cohort of people with CIED only a few MRI examinations were undertaken. Further studies are required to ascertain the risk of adverse

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events following MRI, both in people with compatible and with non-compatible CIED.

208. Spinal Degenerative Disc Disease Procedure Trends in the United States Using the National Inpatient Sample (2008-2012)

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Background: Degenerative disc disease (DDD) is an important contributing factor to morbidity, lifetime disability, health care utilization, quality of life and time lost from work in United States. The reported prevalence for the DDD in patients widely varies among studies, and it ranges anywhere from 0% - 86% in both asymptomatic and symptomatic patients. Surgery for DDD is recommended if conservative treatment fails to provide relief within two to six months. Within the past few years changes in coverage decisions by public and private insurers, along with rapidly evolving and available technologies have undoubtedly changed the landscape of procedures done to treat DDD.

Objectives: This study was conducted to provide an overview of national estimates of trends in incidence, revision surgeries, demographics, and cost of surgical procedures for DDD in the United States from 2008 to 2012 using the National Impatient Sample (NIS).

Methods: Analysis of Spinal Procedure Trends was done using data from the National Impatient Sample (NIS) from the years 2008 – 2012. Patients who underwent spinal fusions, laminectomies and disc excision were identified using the CCS (Clinical Classifications Software) codes. Procedures were further broken down and described using ICD-9 procedure codes that allowed for further granularity. National estimates and trends across procedures were then described and analyzed across the study time period with total cost, average length of stay, and other demographics described per procedure category.

Results: Overall there were 649,559 discharge records for patients undergoing spinal procedures during the years 2008 to 2012. This translated into a national estimate of 3,119,083 spinal procedures being performed in the US during the study period or 1.66% of all US hospital admissions from 2008-2012. There were considerable differences in trends in specific procedures over time. Cost and average length of stay also changed considerably for several procedures.

Conclusions: Far more patients are undergoing surgery to treat DDD and most recently far more patients are undergoing fusion than other procedures compared to earlier years.

209. The Impact of Channelling Bias in Device Epidemiology: Assessing Metal-on-Metal Total Hip Arthroplasty Implants

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Background: Channelling bias (CB) is a common challenge in post-marketing drug studies. To our knowledge CB has not been described in the comparative assessment of orthopaedic implants.

Objectives: To assess baseline characteristics and 5-year outcomes among patients undergoing a new metal-on-metal (MoM) total hip arthroplasty (THA) compared to those receiving an older ceramic-on-polyethylene (CoP) THA. And to assess whether propensity score adjustment can minimise CB-related confounding.

Methods: We included all consecutive primary elective THAs, operated upon in the Geneva arthroplasty registry in 2002-2007 with the same surgical approach, cup design and head size (28 mm), but receiving either 1.a MoM (new) or 2.a CoP ("old" implant) bearing. We assessed baseline characteristics. Secondly, we studied differences in 5-year outcomes (HHS absolute values and improvement) after propensity score adjustment.

Results: 634 MoM THAs and 867 CoP THAs were included. MoM recipients were significantly younger (64 vs. 74 yrs), more likely men (55% vs. 39%), had less comorbidities (≥3 comorbidities: 16% vs. 23%),

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better functional status, less pain, and more often private insurance. Five years after surgery, 91% MoM patients and 87% CoP patients were satisfied (OR 1.6, 95% CI 1.02-2.4). MoM had significantly higher absolute HHS (91.8 ± 11.5 vs. 87.2 ± 13.7; unadjusted mean difference 4.6 (95% CI 2.9-6.2)), but improvement was similar (36.8 ± 16.7 vs. 39.3 ± 18.9; effect size 0.14). Differences in satisfaction and HHS were attenuated and no longer significant after propensity adjustment (satisfaction: adjusted OR 1.3, 95% CI 0.8-2.2;HHS adjusted mean difference 0.6, 95% CI -1.4 to 2.6).

Conclusions: We have demonstrated the presence of CB in the comparative assessment of a new THA implant. Differences in satisfaction and absolute HHS scores 5 years after surgery favored the new implant, but these disappeared after propensity adjustment. Our findings illustrate both the need for and the usefulness of advanced methods to deal with CB in comparative device assessment studies.

210. Withdrawn by Author

211. Nationwide Knee Arthroplasty in France Between 2008 and 2013: Characteristics of the Patients, Implants and Procedures

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Background: Knee arthroplasty is performed to replace native articulation. Main indication is knee arthritis. Technical choices regarding type of replacement, total or unicompartmental knee arthroplasty (TKA/UKA respectively) and fixation method, cemented, uncemented or hybrid (partly cemented) are still subject of debate. Several countries with a registry, particularly in Nortern Europe, have shown an increase in the volume of knee arthroplaties, together with variability in the implanted population and implantation practices across countries.

Objectives: Our aim was to describe the characteristics of performed knee arthroplasties, of implanted devices and population, over several years in France.

Methods: We used "Système National d'Information Inter-Régimes de l'Assurance Maladie" (SNIIRAM), the French National Health Insurance Information System. All subjects having undergone unilateral knee arthroplasty in France between 1 January 2008 and 31 December 2013 were comprehensively included. Patients, hospital stay, procedures and implants characteristics were described over the 6 years inclusion.

Results: Mean age was 71+/-9 years; 63.5% were women; overall, 18% of the patients were obese (13.9% in 2008, 20.0% in 2013) and 16.8% diabetic (15.6% in 2008, 17.1% in 2013).

Over the six-year period, 472,600 knee arthroplasties were performed (among which 7% were revisions), with a 33% increased between 2008 (67,628) and 2013 (89,899); 89.8% were TKA, 8.5% UKA and 1.7% uni-component implantation; 49.8% were both-sides cemented, 34.6% uncemented and 15.6% hybrides (cemented tibial component, uncemented femoral component).

Conclusions: The results of our study evidenced a substancial increase in the number of knee arthroplasties between 2008 and 2013 in France, consistently with findings from the Swedish and Australian knee replacement registries. Knee replacements performed were mainly cemented TKA and women were more often implanted, whatever the year; the proportion of obese implanted patients raised by 6 points over the period. It will be of great interest to study the survivorship of these implants overtime.

212. Multiple Circular Stapler Use During Left-Sided Colon Resections as a Surrogate Measure of Procedural Complexity

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Background: A single circular stapler device is necessary for creating a bowel anastomosis (reconnecting bowel) after colon resections. Multiple circular devices can represent increasing procedural complexity (multiple bowel anastomoses or revision of an inadequate anastomosis--possibly due to device failure).

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Objectives: To evaluate the feasibility of identifying multiple circular stapler device use as a surrogate for procedural case complexity and the effect on resource utilization in left-colon resection.

Methods: All left-hemicolectomy and sigmoidectomy procedures from the Premier Perspective® Database from 2009-2014 were identified. Only procedures where at least one circular stapler device could be identified in the hospital billing record were evaluated. Differences in resource utilization parameters such as Operating Room Time (ORT) (mins), LOS (days), laparoscopic conversion to open surgery, and hospital cost (2014 US-Dollars) between procedures with single (SINGLE) versus multiple (MULTI) circular devices were evaluated using Generalized Estimating Equations (GEE) models controlling for patient demographics, provider and procedural characteristics, comorbidities, and hospital clusters.

Results: A total of 19,666 procedures were identified: left hemicolectomy (15.6%) and sigmoidectomy (84.0%) with 17,245 (87.7%) SINGLE and 2,421 (12.3%) MULTI procedures. Adjusted resource utilization was higher for MULTI compared to SINGLE across all outcomes: MULTI LOS was 6.8 days (SE = 0.1) compared to SINGLE 6.5 (SE = 0.1, $p < 0.001$), MULTI ORT was 244mins (SE = 6.6) verses 226mins (SE = 5.0 ,$p < 0.001$) for SINGLE, laparoscopic conversion was higher in MULTI (20.32%) versus SINGLE (14.09%) $p < 0.001$, and MULTI total cost was $20,665 (SE = 419) versus $18,974 (SE = 262, $p < 0.001$) for SINGLE.

Conclusions: Use of multiple circular staplers was associated with higher LOS, ORT, increased laparoscopic conversion to open surgery, and total hospital costs. Identification of multiple staplers appears feasible for characterizing increasing procedural complexity.

213. Analyses of Surgical Adverse Events – The Importance of Procedure Modifiers

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Background: Adverse events (AEs) rates requiring additional procedures, admissions or diagnoses can often be estimated from claims databases. Procedural complexity is one of the most important considerations when estimating AE rates. Primary procedure codes alone may not provide a sufficiently granular understanding of the index procedure for adequate risk adjustment. Additional procedural information from CPT modifiers or concurrently coded procedures is important.

Objectives: Evaluate the role of procedural complexity and procedure modifiers in understanding AE rates using the example of cerebrospinal fluid (CSF) leak following sinus surgery.

Methods: All patients from the MarketScan Commercial Claims and Encounter Database with sinus surgery CPT codes (31254, 31255, 31256, 31267, 31287, 31288) from 2003 to 2013 were identified. All patients had at least 12 months of continuous eligibility post-index. Index surgery was categorized based on reported sinus type (i.e.; frontal vs sphenoid vs maxillary vs ethmoid) and procedure modifier (modifier 50 and concurrent "R" and "L" indicative of bilateral procedures). CSF leaks were queried using CPT-4 codes indicative of CSF leak repair (62272, 31290, 31291 or 61619) or ICD-9 codes for CSF leak (349.81) or meningitis (320.X) within 12 months post-index. Rate of CSF leak following sinus surgery was analyzed and compared to index surgery category.

Results: From 2003 to 2013, the rate of patients with CSF leak increased non-significantly from 0.17% to 0.23%. However, the percentage of frontal and sphenoid sinus approaches increased significantly (patients undergoing frontal approaches in 2003: 25.7% - in 2013: 42.5%, $p < 0.05$) whereas overall percentage of patients undergoing maxillary and ethmoid approaches remained stable. In addition, bilateral vs unilateral procedures also increased significantly (bilateral frontal: 8.00% in 2003 – 23.70% in 2013, $p < 0.05$).

Conclusions: Heterogeneity of surgeries adds complexity in analyzing and interpreting AE rates. In our study, AE rates remained stable whereas surgical complexity increased significantly, thus highlighting the role for systematic procedural analyses in the evaluation of AE rates.

214. Research Using Claims Databases to Evaluate Adherence to Medical Guidelines: The Case of Tympanostomy Tube Insertion in the United States

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Background: Clinical guidelines help identify appropriate candidates for medical treatments, and thus may play a role in quality of care. The role of healthcare database research in evaluating adherence to medical guidelines is unclear.

Objectives: Evaluate the appropriateness of research using claims database in estimating adherence to medical guidelines in the case of tympanostomy tube insertion (TTI) for treatment of otitis media.

Methods: All patients within the MarketScan Commercial database with a CPT-4 code for tympanostomy requiring insertion of ventilation tube (CPT 69433: under local anesthesia, 69436: under general anesthesia) in 2011 were identified. All patients had ≥2 years continuous enrollment pre-TTI. From this initial cohort, a random 5,000 patient sample matched for age and gender was identified. All pre-operative diagnoses and procedures leading to TTI were evaluated and compared to the guidelines which require all surgical candidates to experience bilateral otitis media (OM) with effusion for ≥3 months along with hearing/quality of life (QoL) impairments. In our study, a diagnosis of ear pain was assumed to be a proxy for QoL impact.

Results: Within the random cohort, 90.7% patients had evidence of OM for ≥3 months prior to surgery. Of these, 42.5% had hearing/speech impairment. Of those patients without hearing/speech impairment, 53.3% experienced pain. Within the 9.3% patients with ≤3 months of OM, 26.0% had hearing/speech impairment and 27.5% had pain. Thus, whereas only 38.5% patients had the exact clinical presentation required by the guideline, 67.1% had OM with either speech impairment or diagnosed pain.

Conclusions: For patients with ≥2 years continuous medical enrollment, adherence to medical guideline could be ascertained using standard methodologies in 38.5% patients. When pain was used as a proxy for QoL impairment, adherence was approximated to 67.1% patients. Without patient-reported outcomes and better assessments of disease impact on QoL, use of claims databases to validate clinical guidelines remains challenging.

215. Combining Observational Data from Multiple Databases: Comparison of Individual Patient Data and Aggregate Data Meta-Analysis in the CARING Study

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Background: Combining multiple databases is valuable for analysing rare exposures and outcomes. In the CARING (CAncer Risk and INsulin analoGues) project, data from National Health Registers (NHR) in Denmark (DK), Finland, Norway (NO) and Sweden (SE) were combined with data from the United Kingdom Clinical Practice Research Datalink.

Objectives: To evaluate the use of individual patient data (IPD) as compared with aggregate data (AD) meta-analysis combining three of these databases (DK, NO and SE).

Methods: Population-based cohort studies of incident insulin users aged 18+ with no history of cancer were conducted using NHRs in DK, NO and SE. Based on the first dispensing, patients were classified as exposed to human insulin (N = 98,154), glargine (N = 12,529), detemir (N = 5,252) or other insulin types (N = 57,601). Poisson regression was used to estimate incidence rate ratios (IRR) of colorectal cancer, breast cancer and prostate cancer, comparing different insulins. Analyses were performed on a common dataset with IPD from all countries (adjusted for common covariates) and separate datasets for each country (adjusted for all available covariates, country-

optimized), pooling estimates using fixed and random effects models.

Results: In IPD analyses of colorectal, breast and prostate cancer, IRR (95% CI) for glargine vs. human insulin were 0.86 (0.66 to 1.14), 0.87 (0.59 to 1.30) and 1.07 (0.83 to 1.38), for detemir vs. human insulin 0.76 (0.47 to 1.22), 0.40 (0.16 to 0.98) and 0.91 (0.57 to 1.44). Fixed and random effects meta-analyses gave similar results. The AD meta-analysis did not include the NO cohort for most comparisons because of few outcome events whereas the IPD meta-analysis used all available data. Country-optimized adjustment was comparable to adjustment for common covariates.

Conclusions: No consistent differences in risk of the cancers investigated between different insulins were found. Low power in individual cohorts and uniform distribution of available covariates between cohorts favored the use of IPD over AD meta-analysis in this specific case.

216. Analytical Issues Faced When Analysing Recurring Events Over Multiple Treatment Patterns

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Background: Using observational data to analyse rates of repeat events with time-varying exposures is challenging. We intended to study possible toxicity of methotrexate (MTX) plus proton pump inhibitors (PPI), but faced problems of interpretation when considering just MTX data.

Objectives: To describe the statistical issues faced when examining risk of recognised MTX-associated AEs using routine primary care data.

Methods: This was a retrospective cohort study of rheumatoid arthritis patients in the Clinical Practice Research Datalink. Incidence rates for AEs with MTX were compared to those with exposure to no disease modifying antirheumatic drugs (DMARD), and HRs estimated using the Cox model.

Results: Initially, all study time with time-varying exposure and repeat AEs was analysed to maximise power for rarer events. Not all estimated HRs were consistent with crude RRs, implying possible non-proportional hazards and, counterintuitively, suggested that patients on MTX had lower rates of many MTX-associated AEs. It was hypothesised that the risk in subsequent episodes of the same treatment was likely lower due to depletion of susceptibles. When using first treatment episode only, results mostly showed significantly higher AE rates with MTX vs. no DMARD. Analyses were stratified into 6 month intervals within treatment groups to reduce the impact of non-proportionality. This analysis mostly generated HRs consistent with crude rates. Yet for some events higher rate of AEs was observed in no DMARD group. We noted that both MTX-naïve subjects and those who had stopped a DMARD contributed to the unexposed group. AE rates were mostly higher in those who had come off a DMARD possibly due to repeated AE recordings that had led to stopping treatment or reflecting a cohort of 'sicker' patients. 6 month HRs comparing MTX users with DMARD naïve reference group were in line with expectations.

Conclusions: Unexpected results in preliminary analyses of MTX toxicity led to significant changes in our approach and a sacrifice of statistical power to reduce bias. This highlights the need to fully explore complex data before embarking on elaborate study designs to explore the impact of drug interactions.

217. Heterogeneity in Treatment Effect: Dabigatran vs. Warfarin in Patients with Atrial Fibrillation

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Background: Anticoagulants are highly effective at preventing thromboembolic events (TE) among patients with atrial fibrillation (AF) but are known to increase risk of major bleeding (MB). Risk scores such as the CHA2DS2-VASc and HAS-BLED stratify patients on baseline risk of TE and MB but not on anticipated benefit or harm under treatment with alternative anticoagulation agents.

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Objectives: To identify subgroups with potential greater benefit or harm with dabigatran vs. warfarin for treatment of AF and validate findings in an external cohort.

Methods: We identified initiators of warfarin or dabigatran with non-valvular AF, CHA2DS2-VASc ≥2 and for whom propensity score overlap suggested "clinical equipoise" in treatment selection from the Optum Clinformatics and Truven MarketScan databases. We fit generalized boosted models in the Optum cohort for TE and MB, allowing pairwise interactions between exposure and risk factors in CHA2DS2-VASc or HAS-BLED respectively. We identified subgroups in Optum based on the interaction with the strongest H-statistic for each outcome. We estimated subgroup rate differences in the Truven cohort with stabilized inverse probability of treatment weights to adjust for confounding.

Results: In Optum, the strongest exposure interaction for TE was prior TE and for MB it was renal disease. In Truven, the rate of TE in patients with prior TE (secondary prevention) was reduced by 3.6 (95% CI, 0.2 to 6.4) per 100 patient-years for dabigatran compared to warfarin initiators; in patients without prior TE (primary prevention) the rate was reduced by 0.8 (95% CI, 0.3 to 1.2) per 100 patient-years. The reduction of TE was greater for secondary vs. primary prevention in 93% of bootstrap samples, difference 2.8 (95% CI, -0.5 to 5.4). In Truven, the annual rate of MB was reduced by 1.6 (95% CI, 0.7, 2.4) per 100 patient years without evidence of variation in patients with renal disease.

Conclusions: Dabigatran's superiority to warfarin at prevention of TE may be greater among higher risk secondary prevention patients. Lack of differences in effect on MB by renal disease status may be related to use of lower dabigatran doses in patients with impaired renal function.

218. Comparing Decision Tree and Logistic Regression Methods to Identify Factors Affecting the Choice of ACEI/ARB Dose Among Elderly Patients After Acute Myocardial Infarction (AMI)

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Background: Studies attempting to identify determinants of treatment choice abound in the epidemiological literature. Often, crucial multi-way interactions are omitted from traditional models while real-world clinical decisions can be hierarchical in nature. Decision tree analysis detects complex relationships existing in the data allowing for a simple and visual interpretation of the underlying interactions.

Objectives: To identify factors associated with receiving ACEI/ARB dose therapy recommended by RCT, and to describe potential variable interactions using logistic regression and decision tree analysis.

Methods: Medicare data for years 2007-2010 were used to identify patients who experienced AMI in 2008 or 2009. Index admission was defined as first AMI in 2008 or 2009. Eligible patients were 66 years of age; enrolled in Medicare parts A, B and D for at least a year prior to and at least 30 days after index date; survived at least 30 days after index admission; and filled a prescription for ACEI or ARB. We identified factors associated with the use of ACEI/ARB RCT dose using logistic regression and two methods of regression tree analysis: classification and regression trees (CART) and conditional inference trees.

Results: In this cohort of 101,588 patients, using a priori knowledge, we tested and found the following significant interactions: age and gender, age and baseline diabetes, age and hyperlipidemia, age and chronic kidney disease (CKD), hypertension and gender, hypertension and race, hypertension and diabetes, hypertension and hyperlipidemia, and hypertension and CKD using the approach of logistic regression. Both decision tree methods identified hypertension as the most important predictive factor, followed by diabetes and type (sub-endocardial) and site (anterior wall) of the index AMI.

Conclusions: While the decision tree approach might not be an ideal substitute for conventional logistic regression models, it can provide additional benefits in quantifying the order of importance of risk factors, and identifying valuable variable interactions that otherwise might be omitted.

219. Cumulative, Weighted Exposure for Modelling the Association Between Metformin and

Heart Failure Exacerbation in Patients with Diabetes and Pre-Existing Heart Failure

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Background: Controversy has existed on how best to control blood glucose in patients with diabetes and heart failure (HF).Currently, metformin is considered first line therapy, however, research conducted to date has failed to account for duration, timing and intensity of metformin exposure on HF risk.

Objectives: To compare alternative, flexible methods for modelling the association between metformin and HF exacerbation to conventional methods in patients with diabetes and HF.

Methods: Using a US claims database, 7,620 subjects with diabetes and incident HF were identified and followed from January 1, 2004 until death, termination of medical insurance, or December 31, 2010.The association between use of metformin and risk of HF hospital admission was assessed using conventional multivariable time varying Cox Proportional Hazards models, as well as a novel weighted cumulative use model which assigns weights based on past metformin exposure and risk of HF hospital admission up to a given point in time.All adjusted models accounted for demographic and clinical data as well as cardiovascular and antidiabetic drug use.

Results: Average age was 56 (SD 8) years and 60% were male.Conventional time-varying models suggested a substantial reduced risk of HF exacerbation with metformin use compared to non-use (3% vs 16%, adjusted Hazard ratio [aHR] 0.67 [95% CI 0.50-0.90]).Weighted cumulative use in the 30 days prior to censoring attenuated the relationship which was no longer statistically significant (aHR 0.77, 95% CI: 0.53-1.01).Subsequent analyses indicated that any benefits of metformin were attenuated within 2 weeks following discontinuation of the drug.Indeed cumulative weighted metformin use within 60 or 90-days indicated further non-significant 17% and 4% decreases in HF related hospital admission respectively.

Conclusions: Conventional analyses suggest metformin is associated with decreased risk of HF exacerbation; however, when the weighted, cumulative nature of metformin use was accounted for, no benefits were observed suggesting the choice of modelling strategy to represent metformin exposure is important.

220. Application of Marginal Structural Models to Data from Interval and Clinical Cohorts: A Simulation Study

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Background: Marginal Structural Models (MSMs), a class of structural causal models, are being increasingly used in the analysis of complex longitudinal health data because of their ability to give unbiased effect estimates of a time-varying treatment in the presence of time-varying confounding/mediating covariates. However, MSMs have shown good performance to settings where observations occur at regularly separated time points for all patients, whereas in "real-life" health record data, different patients are commonly seen and measured at different and irregular time points. In addition, the frequency with which a patient is seen may well be related to their health status. The impact of irregular, but more realistic, data on the performance of MSMs is unknown.

Objectives: To evaluate the performance in effect estimation of inverse-probability-weighted MSMs in balanced and unbalanced longitudinal data.

Methods: We conducted a simulation study to compare treatment effect estimates from inverse-probability-weighted MSM, adjusted and unadjusted generalised estimating equation (GEE) models. Irregular longitudinal data was generated by sampling time between consecutive visits for an individual from an inverse Gaussian distribution. Binary treatment was sampled from a Bernoulli distribution with likelihood of getting treated dependent on the confounder level, and dichotomous confounder values were sampled from a Bernoulli distribution. Continuous outcome

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values were simulated from a Normal distribution. Data simulation and analysis were carried out using R software.

Results: This simulation study showed that inverse-probability-weighted MSMs outperform stratification based estimation methods (adjusted and adjusted regression models) when time between visits is either regular (interval cohort) or irregular (clinical cohort).

Conclusions: Inverse-probability-weighted MSMs can give unbiased causal estimates when data is from either an interval cohort or a clinical cohort.

221. Optimal Treatment Strategies For Patients With Newly Diagnosed Type 2 Diabetes: An Application Of Dynamic Marginal Structural Models in the Clinical Practice Research Datalink

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Background: For patients with newly diagnosed type 2 diabetes (T2DM), UK guidelines advocate a glycated-haemoglobin level (HbA1c) of greater than 6.5% as the threshold for treatment initiation; but it is not clear whether this is optimal for minimising the risk of adverse clinical outcomes, such as cardiovascular (CV) events. There are a lack of trial data comparing different treatment strategies, but large observational data sources such as the Clinical Practice Research Datalink (CPRD), a UK primary care database, can provide detailed longitudinal information on patients with T2DM, including medication and HbA1c levels. An individual's adopted treatment strategy may depend on factors which themselves affect risk of future outcomes; so comparing the causal effects of different strategies on such outcomes using observational data is complex.

Objectives: Identify the optimal HbA1c threshold for treatment initiation with either metformin or sulfonylurea monotherapy in newly diagnosed T2DM patients in terms of risk of future CV events.

Methods: Dynamic Marginal Structural Models (dMSMs) are a class of causal models that reweight data to estimate the risk of an outcome under the assumption that all patients follow a particular treatment strategy, adjusting appropriately for prior treatment and covariate history. The optimal strategy may be identified by comparing outcomes under a range of strategies; for example: "start treatment when HbA1c reaches x," where x takes the values 6%, 6.5%, 7% etc. HbA1c thresholds from 6-9.5% will be compared with respect to future risks of MI, stroke, CV death and all-cause mortality.

Results: Initial investigations in CPRD show a wide variation in the HbA1c level at which patients are initially treated (1st percentile = 5.8%, 99th percentile = 13.8%), suggesting that comparisons of different thresholds is feasible. dMSMs will be implemented using data from ~57,000 patients with incident T2DM, with a median follow up of 4 years (IQR 1.8, 6.9).

Conclusions: This analysis may inform future guidelines for T2DM patients to reduce the risk of CV events in the short or long term.

222. Modeling Adverse Events Associate with Two Successive Treatments During Chronic Disease

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Background: Patients with a chronic disease have a long-term medical management, during which they can change of drug one or several times. When an adverse event occurred, most of the time the last prescribed treatment is accused, but it might be wrong.

Objectives: Our aim is to develop a statistical approach to estimate the risk of the same type of adverse events associated with each drug when two drugs were successively prescribed during a chronic disease, taking into account time-varying doses, cumulative effect of past prescriptions and the follow-up time.

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Methods: We propose to model each drug exposure with a weighted cumulated exposure (WCE) variable:

$$WCE(u) = \Sigma(t = max(1, u-a), t = u)\, w(u-t)T(t)$$

$T(t)$ is the dose at time t and $w(u\text{-}t)$ is a weight function giving the remaining effect at time u of a dose taken at time t. Function w is defined on a window period a. As the true w function is unknown, it should be estimated using cubic B-splines.

Then, the risk of adverse event can be estimated using a Cox's PH model, where each time-dependent treatment is represented by its WCE variable.

Monte Carlo simulations were performed to evaluate bias, coverage and power of this modeling approach in several scenarios defined by sample size, number of events, drugs effect on risk of adverse event and window a.

Two indicators are proposed to help identifying the most deleterious treatment, one at the subject level (based on hazard ratios), and one at the population level (based on attributable risk).

Results: When window a uses in estimations is the same as in simulated data or bigger, we observed small bias and a good coverage, but not when window is smaller. B-splines led to correct estimations of all w function. Results were similar for models with one or two treatments.

Indicators allowed finding the most deleterious treatment when two treatments compete.

Conclusions: WCE approach allowed modelling the risk of adverse event in a wide variety of scenarios involving two successive treatments. Simulations show good performances of estimators. The proposed indicators allowed making decisions at the subject or the population level.

223. Use and Effectiveness of Instrumental Variable Analysis: A Review of SEER-Medicare Studies

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Background: Instrumental variable analysis (IVA) is used increasingly in observational research to control for confounding (endogeneity) in treatment comparisons. It is thought to be particularly useful as a method to mitigate selection bias, since it adjusts for both observable and unobservable characteristics.

Objectives: To identify and assess IV's applied in published studies using Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data, which is commonly used for observational research on cancer in the US.

Methods: Using a PubMed search, we identified and reviewed published observational studies using linked SEER-Medicare data. We extracted the types, attributes, and performance of IV's used in IVA. For the latter, results from IVA were compared to traditional multivariate (MVA) and propensity score (PSA) analysis, and to clinical trial results (if reported).

Results: Our search resulted in 22 publications that performed IVA in SEER-Medicare, which were all published between 2008-2015. In total, 23 IV's were used in these studies (one study used two IV's), of which only 6 were unique. The most commonly used IV was region-based treatment rate. Among these IV's, 15 (65%) were region-based treatment rates, 4 (17%) were distance to provider, 1 (4%) was regional availability of hospice care, 1 (4%) was provider experience, 1 (4%) was provider preference for treatment, and 1 (4%) was region-based specialist visit rates. Six of these publications also performed a MVA and/or PSA in addition to IVA, and compared adjusted results to those in relevant clinical trials. In these 6 publications, 1 of 5 MVA results, 1 of 3 PSA results, and 6 of 7 IVA results (one study performed two IVA's) were similar to those in clinical trials.

Conclusions: In SEER-Medicare, a selection of IV's is available for IVA. Region-based treatment rate has been the most favored IV. Our analysis of the relatively few comparative published studies also suggests that in SEER-Medicare, IVA results are more comparable to clinical trial results than other methods of statistical control, such as MVA and PSA.

224. Bootstrap-Based Inference for the Effects of Changes in Epidemiologic Design and Analysis

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Background: Many methodological studies in epidemiology assess the effects of changes to study design,

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statistical model choice, or variable selection on study results. Yet the effects of these methodological changes are typically reported anecdotally, rather than as explicit parameter estimates with confidence intervals (CI).

Objectives: In the context of a study on the safety of opioids in hemodialysis (HD) patients, we estimated the effect of two different variable selection approaches for a propensity score (PS) model and computed a 95% CI for this difference using a resampling-based approach.

Methods: We identified a new user cohort of opioids and NSAIDs initiators using clinical data linked with claims data from a population of HD patients. To assess the effects of the different PS model specifications, we drew 500 bootstrap samples with replacement from the original cohort. Within each bootstrap sample, we estimated two PS models: one contained only variables derived from claims; and the second model augmented the first with clinical and laboratory variables. Each estimated PS was used to compute a 90-day mortality risk difference (RD) using an inverse-probability-of-treatment weighted Kaplan-Meier estimator. We graphically depicted the marginal and joint distribution of the RD estimators, computed marginal 95% CIs for each estimate, and a 95% CI for the difference between the two estimators.

Results: We identified 5,113 new users, of which 67% received an opioid. Under the first PS model, opioid use was associated with 2.2% (95% CI 1.0, 3.3%) increased risk of 90-day mortality. Under the second model, the RD was attenuated to 1.8% (95% CI 0.8%, 3.0%). Although the marginal confidence intervals overlapped heavily, the two estimators were highly correlated. The estimate of the difference between the two estimators suggested that the full model would result in a decrease in the RD of 0.4% (95 CI% 0.2, 0.8%).

Conclusions: In studies comparing different study designs or analytic methods, the bootstrap can be used to make inferential statements about the effects of changes in methodology.

225. The Regression Discontinuity Design in Epidemiology

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Background: The Regression Discontinuity Design (RDD) is a quasi-experimental design that aims to estimate the causal effect of a treatment through the exploitation of naturally-occurring treatment rules. Since its introduction the RDD has successfully been applied in educational research economics, politics, psychology and other areas. However RDD has only recently been applied in medical research.

Objectives: To demonstrate the use of the RDD in establishing causal effects in an observational drug treatment setting and also to extend and complement the knowledge provided by randomised controlled trials.

Methods: The RDD can be applied in any context where a particular treatment is administered according to a rule defining a threshold for a continuous variable: e.g., a drug may be prescribed if a biomarker is above a certain level. The RDD assumes that subjects with measurements within a bandwidth around the threshold belong to a common population in terms of the variables that inform their treatment and determine the outcome of interest. Thus the threshold can be seen as a randomizing device that assigns treatment to those individuals who fall just above the threshold and withholds treatment from those individuals who fall just below the threshold. There are two types of RDDs. A sharp RDD is possible when the guidelines are adhered to strictly. In the majority of medical applications this is not the case: in a fuzzy RDD the treatment might be assigned to or withhold from patients on both sides of the threshold, although with different probabilities.

Results: We provide examples of how the RDD can be applied in electronic health records and population registry data to evaluate the effect of statins on LDL cholesterol level in UK primary care, as well as the impact of metformin initiation on a range of adverse diabetic outcomes using data from Danish population registries. We discuss some of the challenges and limitations of RDD in the evaluation of drug treatments.

Conclusions: Regression Discontinuity Designs offer the opportunity to evaluate causal effects of drug initiations, but there are challenges in identifying settings

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where the assumptions for the RDD are met in clinical practice.

226. The Firth Correction: A Simple Solution When Parameter Estimates Diverge to Infinity

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Background: In certain data, the likelihood for the Cox regression model can converge even though one or more parameter estimates diverge to infinity. This can arise when the sample size is small, when a large proportion of subjects are censored, or when strong covariates, especially dichotomous covariates, are present. A common example occurs when a given level of a covariate has no events in the reference group. Sometimes the problem is readily apparent, but in other analyses there may be no evidence, e.g., no count of events tabulated for the treatment groups, to indicate that a potentially meaningful discrepancy exists between groups. Indeed, some analyses exclude such scenarios a priori.

Objectives: To increase awareness of a simple solution to the problem of infinite estimates when fitting a Cox regression model.

Methods: Originally developed to reduce bias in maximum likelihood estimates, the Firth correction (Firth, 1993) was adapted by Heinze & Schemper (2001) to address the current scenario. It permits the computation of a finite parameter estimate by penalizing the likelihood for very large values of the estimate. It is easily implemented in SAS through the 'firth' option in the proc phreg model statement:

```
e.g., proc phreg data=mydata;
model Time*Status(0)=Var1 Var2 Treatment / firth
risklimits=pl;
run;
```

Results: Finite hazard ratio estimates of treatment effects can be obtained by using the penalized maximum likelihood estimation provided by the Firth correction. Profile penalized likelihood confidence intervals and penalized likelihood ratio tests can also be computed for inference and statistical testing.

Conclusions: We recommend that the Firth correction be considered routinely when fitting Cox proportional hazards models under conditions that may lead to infinite parameter estimates.

227. Performance of Machine Learning Algorithms in Statistical Modeling of 30 Day Heart Failure Readmissions Risks Using Automated and Investigator-Specified Covariates

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Background: Including different covariate sets from claims data or using more complex statistical algorithms may increase the performance of Heart Failure (HF) prediction models.

Objectives: The objectives were to examine the impact of covariate sets and statistical algorithms on the performance of HF prediction models.

Methods: Using Marketscan Commercial claims database (2008-10), we defined the patient population and readmission outcome following the CMS HF readmissions measure specifications. Data were classified into a training and a test set. 10 fold cross-validation was used on the training set, and predictive performance was measured by the c-statistic on the test set. Four covariate sets were utilized for the primary analysis: 1) CMS set contained variables used in the CMS-risk adjustment model for HF readmissions, 2) Investigator-specified (IS) set contained variables related to clinical conditions, previous healthcare utilization, and previous medication adherence, 3) High-dimensional Propensity Score (HdPS) set contained the top 500 variables selected by the HdPS macro, and 4) Hybrid set contained variables from both the IS and HdPS set. As sensitivity analysis, the principal components (PCs) of these covariate sets were used. Logistic Regression (LR), Logistic Regression with elastic net Regularization (LRR), Support Vector Machines (SVM), Random Forests (RF), and stochastic Gradient Boosted Machines (GBM) were used on all covariate sets.

Results: For covariate sets, the IS set generally had the best predictive performance, followed by the CMS, hybrid, and HdPS sets. For statistical algorithms, GBM had the best predictive performance on the test

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set, followed by LRR, RF, LR, and SVM. C statistics for the best, baseline, and worst performing model were 0.66 (GBM on IS set), 0.64 (LR on CMS set), and 0.60 (LR on hybrid set) respectively. Using the PCs of the covariate sets resulted in less over-fitting in the training set, and similar performance on the test set.

Conclusions: Machine learning algorithms provide a robust alternative to traditionally used statistical models.

228. Risk Period Selection on Performance of Self Controlled Case Series (SCCS) Method for Signal Detection in Observational Data

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Background: In a drug safety signal detection framework, appropriate risk period (RP) selection may differ from a formal hypothesis-testing study in epidemiology (EPI). There has limited literature on the impact of such selection on method performance for signal detection, although Observational Medical Outcomes Partnership (OMOP) conducted some initial evaluation.

Objectives: Assess the impact of risk period selection on the performance of Self Controlled Case Series (SCCS) method for signal detection.

Methods: Two approaches to risk period selection are compared. 1). "OMOP": Risk period is exposure duration plus a variable subsequent period (0, 30, 60 or 90 days); all other time is considered baseline. 4 risk periods are selected. 2). "EPI": Risk period is exposure duration. Three 30 day washout periods (1-30, 31-60, 61-90 days) after end of exposure are analyzed separately. Risk and washout periods are each compared with the same baseline to obtain incidence rate ratio (IRR) estimates. Humira-6 outcomes and Lexapro-5 outcomes are selected respectively in the analyses using Optum, a US claims database and THIN, a UK EHR database.

Results: In Humira analysis, compared to "OMOP" risk period using exposure duration, "EPI" generated consistently higher estimates for the risk period across 6 drug-outcome pairs and highlighted one more significant pair. Compared to all 4 OMOP risk periods, "EPI" generated consistently higher estimates for the 1st washout period across 6 drug-outcome pairs. Three out of 6 pairs highlighted by "EPI" had IRR > 2 while no pair with IRR >2 was found using "OMOP". Overall, the estimates for 4 EPI periods varied more than those from "OMOP"; wider 95% confidence intervals of the estimates in the 3 washout periods were observed due to fewer events. Similar patterns were seen in the Lexapro analysis.

Conclusions: EPI risk period selection offers potential for signal detection. OMOP approach could lead an attenuated or diluted risk estimation when a risk period includes unexposed time, or baseline includes time where drug effect persists. The observed differences, however, are not substantial and may vary by the choice of database.

229. Probabilistic Bias Analysis in Pharmacoepidemiologic Studies

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Background: Probabilistic bias analysis can quantify systematic error when bias parameters are not known with certainty. How these analyses are reported in pharmacoepidemiologic literature is unknown.

Objectives: To systematically review pharmacoepidemiologic studies using probabilistic bias analysis.

Methods: A keyword search in PubMed and Scopus and citation search using Web of Science and Google Scholar identified articles published in English between January 2010-October 2015 with 1) a pharmaceutical, medical device, or medical procedure exposure and a health outcome; 2) an observational study; and 3) used probabilistic bias analysis. The purpose and implementation of probabilistic bias analysis including probability distributions assigned to and sources for bias parameters, the number of simulated iterations, sensitivity analyses and diagnostics implemented, interpretation, and the extent to which effect

estimates changed was extracted. Three reviewers performed data extraction.

Results: Nine studies simulating unmeasured confounding and 6 simulating misclassification were included. The majority simulating an unmeasured confounder did not specify the range of plausible estimates for the bias parameters; it was unclear if the full extent of uncertainty was incorporated. Studies simulating misclassification reported the probability distributions assigned. Key details including the number of simulated iterations and type of probability distributions assigned were not consistently reported. Few provided details on diagnostics or sensitivity analyses. Effect estimates changed by ≥10% in 8 studies and ≥30% in 4 studies.

Conclusions: Probabilistic bias analysis was not widely used in pharmacoepidemiologic studies despite concern of bias. The quality of reporting varied and was often unclear. Continued dissemination of probabilistic bias analysis and development of reporting guidelines is warranted.

230. Competing Risks Modelling of Time-Varying Drug Exposures

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Background: We propose a new method to address two important challenges of population-based pharmaco-epidemiological studies. (1) One is related to the need to account for time-varying exposures and possible cumulative effects of past drug use. (2) Another one is related to possible multitude of adverse events (e.g. MI vs stroke) that may be associated with the use of a given drug, each possibly involving a different biological mechanism.

Objectives: To simultaneously address both challenges, we develop, and validate in simulations, a new approach that combines (1) flexible modelling of the cumulative effects of time-varying exposures, with (2) competing risks methodology.

Methods: In particular, we use the Lunn-McNeil data augmentation approach to separate the effects of the same drug exposure on different outcomes (e.g. adverse events A vs B), within a competing risks extension of the Cox proportional hazards model. We then rely on flexible weighted cumulative exposure (WCE) methodology to model the cumulative effects of past drug use, as the weighted sum of past doses, with weights that reflect relative importance of doses taken at different times in the past. We also propose likelihood ratio tests (LRT) to test if the cumulative effects of past exposure on the hazards of different adverse events are the same or different. In simulations, we evaluate the accuracy of the (event-specific) WCE estimates, as well as type I error or power of the LRT.

Results: In simulations, the estimated weight functions are able to capture the shapes of the true weight functions for each of the two 'competing' events, under different assumptions concerning whether the two effects are different or not in terms of (a) their strength, and (b) the way the effects of past doses cumulate over time.

Conclusions: The propose method can help understanding potential impact of drug use on alternative health outcomes.

231. Simulation Study of Statistical Models for the Analysis of Clustered Length of Stay (LOS) Outcomes

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Background: Analyses of length of stay (LOS) are important for assessing inpatient interventions, but may pose analytic challenges when data are clustered by site. Commonly used models include generalized linear mixed models (GLMM), generalized estimating equations (GEE), or fixed effects (FE) models. However, they may become problematic depending on link-error assumptions or because of small or highly imbalanced samples.

Objectives: To determine the validity of several different methods for analyzing clustered LOS outcomes characterized by a small number of sites, imbalanced comparison groups, and variability of sample size per site.

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Methods: The cohort comprised 4784 patients receiving one of two knee replacement devices at 37 sites. Mean LOS was 3.0 days (SD = 1.3; range = 1 to 27). The number of patients ranged from 3 to 579 per site, and the percent in one device group from 10% to 90%. We conducted simulations using the existing design to determine the empirical Type I error ($\alpha = .05$) and precision of the effect estimates. We evaluated linear-Gaussian (LG), log-Poisson (LP), log-truncated-Poisson (LTP) and log-quasi-Poisson (LQP) link-error families due to under-dispersion. We used GLMM, GEE and FE to account for correlation within site.

Results: With regard to the LG link-error family, the Type I error was unbiased for GLMM (.046) and FE (.05), but slightly anti-conservative for GEE for model based (.069) and empirical (.081) standard errors (SEs). With regard to the LP family, the Type I error was very conservative for GLMM (.0055) and FE (.0095), while GEE was slightly anti-conservative (.07) for model SEs and empirical SEs (.082). For the LTP family, the Type I error was conservative for GLMM (.018) and FE (.012) and for the LPQ family, the Type I error was unbiased for FE (.055). With regard to precision of the estimates, the GLMM models resulted in the lowest mean squared error (MSE) and the FE models the highest MSE.

Conclusions: Overall the GLMM models and FE models performed best with the GLMM models showing the lowest MSE. GEE performed best with the model based SEs but was slightly anticonservative.

232. Detecting Suicidal Outcomes: A Power Analysis

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Background: Suicidal outcomes, including ideation, attempt, and completed suicide, are an important drug safety issue, as evidence by boxed warnings for some antidepressants and other medications. However, suicidal outcomes are difficult to ascertain in observational study.

Objectives: To estimate the ability of clinical trials to detect association with suicidal outcomes.

Methods: Stone et al. (2009) performed a meta-analysis of the association between antidepressants and suicidal outcomes which encompassed 372 clinical trials including 99,231 participants with 15,505 patient-years of follow-up finding increased risk of suicidal outcomes in patients aged 25 and younger and a protective effect among patients aged 65 and older. We used data from Stone et al., assuming average study sample size, follow-up, and event rates from the high-risk subgroup (under age 25), to perform power and sample size calculations to estimate the ability of trials included in the meta-analysis to detect statistically significant associations between antidepressants and suicidal outcomes.

Results: An average trial included in Stone et al. had only 5.1% power to detect an incidence rate ratio (IRR) of 2.0 for suicidal behavior and would have required an IRR of 10.9 to detect a signal with 90% power. A trial would have needed 1,304 person years of follow-up, compared to an average follow-up of approximately 42 person years per study observed by Stone et al., to detect an IRR of 2.0 with 90% power. The detection of smaller effects would require exponentially more follow-up.

Conclusions: Our calculations demonstrate that even in an at-risk psychiatric population many clinical trials are not powered to measure associations with suicidal outcomes. Trials including subjects from broader age groups would have less power to detect increased risk of suicidal outcomes among younger patients and less power to detect the strong protective effect observed among patients over age 65. Our findings underline the importance of developing new methods to measure suicidal outcomes in pharmacoepidemiological studies.

233. Methods of Defining the Noninferiority Margin: A Systematic Review

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Background: Noninferiority trials are conducted to investigate whether the efficacy of the test drug is not worse than the active comparator based on a pre-

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defined noninferiority margin. There is no consensus on a preferred method for defining the noninferiority margin, and previous studies showed that the rationale for its choice is often not reported.

Objectives: To investigate how the noninferiority margin is defined in the published literature, and whether its reporting has changed over time.

Methods: A systematic PubMed search was conducted for all published randomized, double-blind, noninferiority trials from January 1, 1966, to February 6, 2015. The time trend of defining the margin since the first published noninferiority trial was analyzed using Poisson regression analysis. The impact of the 2010 US Food and Drug Administration (FDA) draft guidance for noninferiority clinical trials on the choice of the margin, and the impact of the extension of the Consolidated Standards of Reporting Trials (CONSORT) Statement on the reporting of noninferiority margins were analyzed using generalized estimating equations to account for the clustering of the margins within articles.

Results: We included 275 articles, which account for 283 trials and 328 noninferiority margins. The rationale for the choice of the margin was not reported for 191 margins (58.2%). The under-reporting of the rationale for the choice of the margin has not improved neither since the first published noninferiority trial in this review in 2000 (P = 0.86), nor since the publication of the extension of the CONSORT Statement in 2006 (P = 0.96). The other 137 margins were mainly defined based on the historical evidence of the active comparator (n = 56) or subjectively based on expert opinions (n = 46). There was a 3.5-fold increase in the use of the fixed-margin method, the recommended method by the FDA to define the margin, after the publication of the FDA draft guidance (from 2.6% to 9%, P = 0.04).

Conclusions: Margins in noninferiority trials are poorly reported and this has not improved over recent years. Authors, reviewers, and editors need to take notice of reporting this critical information to allow for better judgment of noninferiority trials.

234. Real Time Aggregate Clinical Safety Monitoring Methodology-Evaluation of Multiple Quantitative Methods

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Background: To date, there is no consensus on how to assess and interpret periodically the aggregate safety events in individual and combined studies during clinical development.

Objectives: Develop and test statistical inference methodology to assist the safety assessment teams evaluate and interpret safety data from both blinded and unblinded randomized clinical trials.

Methods: Blinded periodic aggregate analysis was done on a hypothetical clinical trial dataset using sequential probability ratio test (SPRT) and Bayesian critical value approach considering both binomial and Poisson models. We unblinded the same trial data and used Bayesian method to evaluate the probability of exceeding pre-specified risk difference or risk ratio.

Results: Safety boundary using Wald SPRT and Bayesian methods were created for blinded analyses using both Binomial and Poisson models. Unblinded analyses were done using Bayesian Method.

Conclusions: This presentation summarizes a number of methodologies that can be applied to aggregate safety data which will enhance early identification of signals in clinical trials.

235. Improving Short-Term Mortality Prediction Using Timing of Acute Comorbidities During Lookback

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Background: A defined lookback period is often used to assess comorbidities for confounding control. Hazard functions for the outcome of interest can vary after an acute comorbid event, therefore individuals will be at different points on that curve as follow-up starts. Predictive models may need to account for the timing of events during lookback but little attention has been given to this issue.

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Objectives: To assess how the timing of hospitalization for pneumonia during the lookback period affects short-term mortality prediction.

Methods: Using U.S. Medicare claims data from 2009-2011, a cohort of older adults was identified by indexing beneficiaries on a randomly selected outpatient visit or prescription fill during 2010, as long as the beneficiary was ≥66 years old and had 360 days of continuous Parts A, B, and D coverage prior to the index date. This fixed lookback period was used to assess hospitalizations with a primary discharge diagnosis of pneumonia, coded as: 1) one indicator for the entire period, 2) 12 monthly indicators, and 3) 12 indicators identifying month of last hospitalization (if any) during lookback. The hospitalization variables, age, sex, comorbidities of the Charlson score, and index month were used in logistic regression models to predict 30-day all-cause mortality.

Results: The cohort included 2,337,652 beneficiaries and 1.4% died during the 30-day follow-up. Overall, 1.59% were hospitalized for pneumonia during the 12-month lookback and 0.13% were hospitalized ≥2 times. With a single 12-month indicator, the odds ratio(OR) was 1.75(95% CI:1.67-1.83). With monthly indicators, the ORs ranged from 3.51(3.18-3.88) in the most recent period to 1.11(0.93-1.32) in the earliest. Restricting to only the most recent hospitalization resulted in ORs ranging from 3.84(3.48-4.23) in the most recent period to 1.14(0.93-1.39) in the earliest. The c-statistic did not change appreciably across models.

Conclusions: A clear trend was seen between the timing of hospitalization for pneumonia and short-term mortality, with ORs decreasing with temporal distance to the index date. Short-term mortality prediction was unchanged when taking timing of baseline events into account.

236. Predicted Rates of Thromboembolism and Major Bleeding with Dabigatran or Warfarin in Patients with Atrial Fibrillation: Randomized Controlled Trials versus Routine Care

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Background: Risk scores such as CHADS2 and HAS-BLED for patients with atrial fibrillation (AF) on baseline risk of thromboembolic (TE) or major bleeding (MB) guide whether to initiate anticoagulation therapy. Randomized controlled trials (RCT) help guide treatment choice by providing stratified estimates under treatment with alternative anticoagulants. However, estimates based on highly selected RCT participants may not reflect risk in routine care patients.

Objectives: To compare the accuracy of predicted rates of TE and MB from RCTs and models developed in observational data for patients initiating dabigatran or warfarin in routine care.

Methods: We identified initiators of dabigatran (n = 3,995) or warfarin (n = 9,629) with non-valvular AF from the Optum Clinformatics database (2009-2013) and predicted TE and MB rates using components of CHADS2 and HAS-BLED. RCT estimates for TE were obtained from the RE-LY trial of dabigatran vs. warfarin. Due to lack of information on stratified MB rates in RE-LY, we obtained stratified estimates for warfarin from ARISTOTLE (apixaban vs. warfarin) and applied the hazard ratio from RE-LY to estimate MB rates in dabigatran initiators. We used 10-fold cross validation to compare the performance of RCT and model based prediction in terms of discrimination and calibration.

Results: Annual rates were 2.1 and 5.0 per 100 patients for TE and MB respectively. Calibration for TE was similar for RCT and models; however, RCTs underestimated the rate of MB in high risk patients treated with warfarin in routine care by up to 4.0 per 100 patient years. Across outcomes and exposure, discrimination was lower for RCT (c-indices 0.55- 0.59) than models in validation data (c-indices 0.55-0.72).

Conclusions: RCT estimated rates of TE under treatment with dabigatran or warfarin were close to observed rates in routine care patients; however rate of MB was underestimated. Models developed in routine care patients provided accurate, tailored estimates of risk and benefit under alternative therapies. Such estimates can facilitate informed decision-making and improve patient-centered care.

237. Development and Validity of a Checklist Assessing the Risk of Bias of Randomized Trials, Observational Studies and Systematic Reviews Analyzing Drug Adverse Events

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Background: In systematic reviews analyzing drug adverse events, the risk of bias of included studies must be carefully considered. Currently, there exists no standard method that is specific to studies analyzing drug adverse events and applicable to common study designs.

Objectives: To develop and validate an adequate tool to evaluate the risk of bias of randomized trials, observational studies and systematic reviews assessing adverse events of drugs.

Methods: Based on existing tools, literature and guidelines, a pilot version of a structured risk-of-bias checklist was developed as to be applicable to randomized trials, cohorts, case-control and nested case-control studies, and systematic reviews. Face and content validity was judged by three experienced reviewers. The checklist was revised and they all approved the final version as valid approach to measure risk of bias. Inter- and intra-rater reliability was determined using 20 studies, randomly selected from the PROTECT project database (4 for each design), assessed by 3 independent reviewers including one performing a 3-week retest. Kendall's W was used to measure agreement.

Results: The final version of the checklist was structured in 8 domains: study design and objectives; selection bias; attrition; adverse events information bias; other information bias; statistical methods to control confounding; other statistical methods; and conflicts of interest. Risk of bias was assessed ("Low", "Unclear" or "High") for all domains and for the whole study. The total number of questions varied from 10 to 32 depending on the study design. Inter- and intra-rater agreements were fair with Kendall's W of 0.70 ($p < 0.001$) and 0.74 ($p < 0.001$), respectively. Median time to complete the checklist was 8.5 minutes (Q1-Q3: 6-15).

Conclusions: The developed checklist proved to be a valid and acceptably reliable instrument to assess the risk of bias for studies analyzing adverse events of drugs. Hence, it might be considered as a novel useful tool for systematic reviews and meta-analyses focusing on adverse effects of drugs.

238. Probabilistic Bias Analysis for Unmeasured Confounders in a Study of Users of Topical Tacrolimus, Pimecrolimus and Corticosteroids (JOELLE) Study

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Background: Topical tacrolimus (TAC) is indicated for the treatment of moderate to severe atopic dermatitis (AD), and topical pimecrolimus (PIM) for mild to moderate AD. Severity of AD could confound the association between the risk of lymphoma and skin cancer and the use of these medications. We used type of prescriber of first prescription (TPFP) as a proxy for AD severity in a study where information on AD was available in two of the four databases used.

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Objectives: To use probabilistic bias analysis to correct partially adjusted incidence rate ratios (IRR) of lymphoma and skin cancer comparing new users of TAC and PIM with users of moderate- to high-potency topical corticosteroids (TCS).

Methods: Cohort study in the PHARMO Database Network (Netherlands), the Danish and Swedish national registers, and the Clinical Practice Research Datalink (CPRD) (United Kingdom), with RTI-HS acting as coordinating/pooled analysis center. We used available information on TPFP in PHARMO and Sweden to estimate input parameters for probabilistic bias analysis to correct IRRs and 95% confidence intervals (CIs) in Denmark and CPRD.

Results: We included 19,948 children and 66,127 adults treated with TAC matched with 79,700 children and 264,482 adults treated with TCS and 23,840 children and 37,417 adults treated with PIM matched with 90,268 children and 149,671 adults treated with TCS. The corrected IRR (95% CI) for lymphoma comparing TAC vs. TCS in children decreased by 28.9% from 5.26 (1.14-24.29) to 3.74 (1.00-14.06). The corrected IRR for cutaneous T-cell lymphoma (CTCL) comparing TAC vs. TCS in adults decreased by 35.1% from 2.71 (1.35-5.44) to 1.76 (0.81-3.79). For PIM, the corrected IRR for lymphoma in children decreased by 40.9% from 1.81 (0.41-8.02) to 1.07 (0.25-4.60), and the corrected IRR for CTCL in adults increased by 18.0% from 1.11 (0.28-4.32) to 1.31 (0.33-5.14). Smaller IRR reductions were observed for skin cancer for both TAC and PIM.

Conclusions: Probabilistic bias analysis for unmeasured confounders led to noticeable corrections of the effect of TAC and PIM on lymphoma and skin cancer.

239. Potential Effects of Medicare Payment Policy Changes on Hospitalization-Based Outcomes Research

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Background: The US Centers for Medicare and Medicaid Services instituted new readmission reduction policies in 2011 designed to help improve quality of care and reduce costly rehospitalizations using hospital penalties. We sought to understand the effect that these penalties may have had on hospital admission practices and their implications for research on hospitalization-based outcomes using Medicare data. We illustrate one potential challenge in the interpretation of results using a recent study of changes in erythropoiesis stimulating agent (ESA) prescribing practices following a labeling change and its putative effects on hospitalization-based outcomes in the end-stage renal disease (ESRD) population.

Objectives: To examine rates over time of hospitalization for stroke and heart failure (HF) among ESRD patients on dialysis, and separately, among non-ESRD Medicare patients.

Methods: We evaluated inpatient rates for stroke and HF among annual cohorts of patients on dialysis from 2005-2012. We selected a 5% non-ESRD Medicare population as our control population and evaluated the same outcomes.

Results: Each annual ESRD cohort included $>$ 235,000 and each non-ESRD Medicare cohort had $>$1.3 M patients. In dialysis, rates of HF and stroke decreased consistently from 2005-2011, with a more abrupt decline evident in 2012 (2005-2011, HF:16.9-13.2/100 pt-years (PYs), stroke: 4.3-3.4/100PYs; 2012, HF: 11.8/100PYs, stroke: 3.1/100 PYs). In the non-ESRD Medicare population, the trends were similar (2005-2011, HF:2.4-2.0/100 PYs, stroke: 1.2-1.1/100 PYs; 2012, HF: 1.9/100 PYs, stroke: 1.0/100 PYs).

Conclusions: Analyses limited to the dialysis population might appear to indicate that the drop in HF and stroke hospitalization in 2012 was attributable to ESA labeling changes. However, similar trends in the non-ESRD population, one unaffected by ESA label revisions, implies that there was confounding introduced by general Medicare payment policies. Payment policy revisions can have important effects on

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administrative data, and must be considered to ensure valid conclusions.

240. New Policies, New Sources of Error: Impact of Recent Medicare Policies on Database Research

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Background: Medicare has recently instituted new rules and provider incentives that can affect how information is captured in data. Researchers should understand the potential biases introduced by these changes so that they can be appropriately addressed in the design and/or analysis of observational research.

Objectives: To describe potential sources of error introduced by end-of-year claims processing as well as changes in coding of Medicare data.

Methods: Using Parts A/B Medicare files (2005-2012) for patients receiving maintenance dialysis, we defined annual cohorts of patients who were alive on January 1 of each calendar year, had been receiving dialysis for ≥9 months and had Medicare as their primary payer. We used inpatient and outpatient claims to assess comorbidity, and inpatient claims for identifying major cardiovascular (CV) outcomes. To generate valid estimates of event rates over time, we considered two potentially important sources of error: 1) an increase in the number of diagnosis fields on Part A claims from 9 to 25 implemented in 2010; and 2) hospitalization events bridging two consecutive calendar years.

Results: There were ~250,000 patients in each cohort. The mean number of diagnosis codes per inpatient claim was 8.5 before 2010, and 9.2, 14.9, and 15.6 for 2010, 2011, and 2012, respectively. Using only the first 9 codes, the percent with a coronary atherosclerosis-related hospitalization, as an example, decreased gradually from 19.0-17.4 from 2010-2012; using all codes, rates increased from 2010-2012 (19.0, 19.8, and 21.9% for 2010, 2011 and 2012, respectively). For hospital admissions occurring in December, final adjudication of the event did not occur until the following calendar year in ~20% of cases. For example, not accounting for subsequent year adjudications led to an underestimation of event rates of myocardial infarction: 7/100 patient-years in Dec 2012 vs 9.3/100 when accounting for events adjudicated in the subsequent year.

Conclusions: Failure to understand and account for how data are coded and structured over time may bias results and lead to invalid conclusions.

241. Exposure Misclassification Due to Household Availability of Prescription Medications

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Background: The new-user design is commonly used in pharmacoepidemiology, but the household context within which medications are initiated has not been examined. Given high rates of prescription drug sharing, high levels of household use will lead to misclassification of new drug exposure.

Objectives: To describe prevalent household utilization of prescription opioids and prescription non-steroidal anti-inflammatory drugs (NSAID) among prescription opioid and prescription NSAID initiators.

Methods: A retrospective cohort study of prescription opioid and prescription NSAID initiators and their households was conducted in a random sample of Truven Health's MarketScan Commercial Claims and Encounters Databases, 2000-2013. Initiators were identified using outpatient pharmacy billing claims with a 180-day washout period. We restricted to initiators enrolled with at least one other household member who could be identified through records and evaluated outpatient pharmacy claims for all

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household members during baseline to determine prevalent household use.

Results: We identified 218,594 prescription opioid and 114,767 prescription NSAID initiators between 2000-2013. Of these initiators, 160,404 (73% opioid) and 82,359 (72% NSAID), respectively, were enrolled within a household. Household size (median: 3 members, interquartile range (IQR): 2-4) and age of household members (median: 21 years, IQR: 12-45) were similar in both treatment groups. Prevalent household use of prescription opioids was 27% (95% confidence interval (CI): 27-28) among opioid initiators and 24% (95% CI: 24-24) among NSAID initiators. Prevalent household use of prescription NSAIDs was 20% (95% CI: 19-20) among NSAID initiators and 18% (95% CI: 17-18) among opioid initiators.

Conclusions: In our new user cohort, we observed high levels of prevalent household opioid use among both treatment groups. Comparative safety studies should consider the household availability of medications as a potential source of exposure misclassification which may introduce prevalent-user bias into new-user designs.

242. Assessment of Channelling Bias Among Initiators of Glucose Lowering Drugs - A Cohort Study

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Background: Channelling bias may occur when a newly marketed drug and an established drug, despite similar therapeutic indications, are prescribed to patients with different prognostic characteristics (also known as confounding).

Objectives: To investigate channelling bias and its impact on estimated effectiveness of GLP1 and DPP4, compared to basal insulin and sulfonylurea (SU), respectively.

Methods: We used CPRD data to include patients with T2D, initiating treatment (6 months drug-free) between 2007 (when GLP1 and DPP4 were approved by EMA) and 2015. All analyses were split in 7 time blocks of 365 days each. The characteristics of patients initiating GLP1 versus basal insulin, and DPP4 versus SU were compared over time. After propensity score matching (based on sex, age, BMI, diabetes duration, Charlson comorbidity score, use of other glucose-lowering drugs, use of anti-hypertensives, statins, anti-coagulants and diagnoses of hypertension, renal disease, myocardial infarction, and stroke), relative effectiveness on 6 month changes in HbA1C (%) was estimated.

Results: In total, 8,398 GLP1, 14,807 insulin, 24,481 DPP4, and 33,505 SU initiators were identified. Time trends for GLP1 and DPP4 showed that use of anti-hypertensives decreased among GLP1 initiators, and increased among DPP4 initiators. Use of other oral glucose-lowering drugs decreased, BMI decreased, and use of statins increased among DPP4 initiators. For other characteristics the difference between comparison groups were small and did not indicate channelling.

Propensity score matched analyses included 4,072 pairs of GLP1 and insulin initiators, and 10,620 pairs of DPP4 and SU initiators. For both comparisons relative effectiveness was similar across different time blocks: GLP-1 vs. insulin 0.14% [95%CI: 0.05;0.23], DPP4 vs. sulfonylurea -0.34% [-0.39;-0.29] (relative effect pooled across time blocks).

Conclusions: Channelling was not widespread and relative effectiveness appeared constant since launch of the drugs. It was possible to match many patients, which allowed for assessing relative effectiveness even in the early years after drug launch.

243. Matching on the Disease Risk Score vs the Propensity Score

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Background: Choosing an appropriate caliper distance is essential for achieving covariate balance and

obtaining valid effect estimates when matching on the propensity score (PS). While many studies have discussed and evaluated the performance of matching within specified caliper distances on the PS, there remains little discussion on the performance and choice of caliper distances when matching on the disease risk score (DRS).

Objectives: To evaluate the performance of DRS matching vs PS matching over a range of causal scenarios and caliper distances.

Methods: We simulated the outcome as a function of 80 binomial and 20 normally distributed baseline variables. We considered scenarios that varied in sample size (n = 1,000 to 20,000), treatment prevalence (10% to 50%), outcome incidence (10% to 50%), and the strength and direction of confounding. We matched on the estimated PS or DRS using 1-1 nearest neighbor caliper matching without replacement. We considered caliper distances ranging from 0.1 to 1.5 standard deviations of the logit of the respective PS or DRS distribution.

Results: When there was a strong correlation between the PS and DRS, matching on the DRS was essentially equivalent to matching on the PS with percent bias ranging from <1% to 3% and standard errors ranging from 0.02 to 0.07. As the correlation decreased, the overlap in DRS distributions across treatments increased compared to the overlap in PS distributions. For larger calipers, increases in overlap corresponded with less bias when matching on the DRS versus the PS <1% to 3% for DRS vs. 2% to 5% for PS). As calipers were reduced to those commonly recommended, PS and DRS matching both produced approximately unbiased effect estimates, but DRS matching resulted in improved precision (standard errors ranging from 0.01 to 0.05 for DRS matching vs. 0.02 to 0.07 for PS matching).

Conclusions: Commonly recommended logit-based PS matching calipers also perform well for DRS matching. When the correlation between the PS and DRS is moderate to weak, a larger proportion of individuals can be matched on the DRS compared to the PS, resulting in improved precision for DRS matching.

244. Improving Variable Selection for High-Dimensional Propensity Scores

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Background: The high-dimensional propensity score (HDPS) is a widely used automated variable selection algorithm in medical studies involving electronic healthcare datasets. While studies have demonstrated that the HDPS often improves confounding control when used to complement expert knowledge for variable selection, there remains the challenge that investigators must determine the number of variables to include in the HDPS model a priori. The Super-Learner and collaborative targeted maximum likelihood estimation (CTMLE) are recently developed methods for prediction modeling and causal inference that can potentially be combined with the HDPS to improve variable selection for PS models. CTMLE is computationally intensive, but one can obtain a scalable CTMLE for large datasets by enforcing an ordering of the variables.

Objectives: To evalluate data adaptive approaches for determining the optimal number of variables to include in an HDPS model.

Methods: We used a plasmode simulation where empirical data is incorporated into the simulation structure. We simulated the outcome as a function of 200 baseline variables and considered scenarios that varied in sample size, outcome incidence, and treatment prevalence. We fit 6 HDPS models, each controlling for a different number of variables, then used the Super-Learner to find the optimal combination of the predicted values in terms of minimizing the cross-validated negative log-likelihood. We also used the HDPS algorithm to pre-order 1000 variables based on their potential for bias, then used CTMLE to determine the number of variables to control for in the study analysis and estimate the treatment effect.

Results: Combining the Super-Learner with the HDPS resulted in the least biased effect estimates with percent bias ranging from <1% to 4%. Combining CTMLE with the HDPS was less consistent with the percent bias ranging from 1% to 7%. The two methods had similar standard errors (ranging from 0.01 to 0.03).

Conclusions: The Super-Learner can improve the robustness of HDPS analyses in high-dimensional covariate spaces. Combining the HDPS with a scalable

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version of CTMLE may also be promising, but can be sensitive to how the variables are pre-ordered.

245. Methods to Detect Misspecification in Propensity Score Models

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Background: Whilst it is known that a correctly specified propensity score model can eliminate confounding by the variables included in the model, there is little help in the literature for deciding if a propensity score model is correctly specified.

Objectives: To develop statistics that will identify misspecification of a propensity score model.

Methods: The Hosmer-Lemeshow test compares the observed and predicted prevalence of exposure in 10 groups defined by predicted probability of exposure. Grouping by a given continuous predictor would also provide a $\chi 2$ test, but specifically testing whether the log-odds of exposure is linear in that particular predictor. Alternative tests could be performed by calculating the predicted and observed cumulative prevalence of exposure as a continuous predictor changes, and considering the maximum difference (analogous to the Kolmogorov Smirnov statistic), the mean difference or the mean squared difference between them.

These new statistics were tested by applying them to simulated data. An baseline scenario in which the log odds of exposure was a linear function of 3 continuous and 4 categorical predictors was simulated. Then a set of 5 additional scenarios, each adding a single quadratic or interaction term to the linear predictor with sample sizes of 500, 1000, 2000, 5000 and 10000, and 1%, 2%, 5%, 10% and 20% of the variance in the log-odds of exposure due to the non-linear or non-additive effects were simulated. 1,000 simulations were performed in each case.

Results: The ability to detect misspecification improved with increasing sample size and increasing proportion of variance due to non-linearity. For all scenarios, the C-statistic reached 1 when at least 10% of the variance was explained and the sample size was at least 5000. In all cases, the $\chi 2$ statistic had the lowest c-statistic, the area between the curves had the highest.

Conclusions: These statistics provide a powerful means of identifying terms that need to be added to a propensity score to balance covariates appropriately, for modest misspecification and sample sizes. Their routine use will provide greater assurance that a propensity score model has removed the confounding due to the observed covariates.

246. Reporting of the Trimmed Population in Propensity Score Analyses

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Background: In nonrandomized studies examining treatment comparisons, propensity scores (PS) are frequently used to account for measured confounding. As part of this methodology, the PS distribution is typically reviewed, and patients with a PS in the areas of nonoverlap and/or with extreme PS values may be excluded with aim of improving validity; a practice commonly referred to as "trimming." In studies examining safety events, trimming can lead to an incomplete safety profile of the treated patients and reduce the generalizability of results. It is recommended that information on treated patients who were excluded from the analysis (i.e., trimmed) be presented to provide a more complete understanding of the study population (Sturmer et al. 2010).

Objectives: By performing a targeted literature review, we aim to quantify the PS methods used in nonrandomized safety cohort studies in recent years and determine if summary information is provided on the trimmed patients.

Methods: Articles published during 2014 and 2015 in six leading pharmacoepidemiology journals were identified in PubMed using the keyword "propensity score." Articles were required to be nonrandomized cohort studies with the primary objective of examining treatment safety. Two independent reviewers examined each article to determine eligibility and classification.

Results: Of the 59 articles identified in the PubMed search, the majority were methods articles, reviews, or editorials and were excluded. The 18 eligible articles used the following PS methods: 9 matching, 2 inverse probability weighting, 5 regression (covariate),

and 2 stratification. A total of 12 studies trimmed patients from the overall sample. Researchers commonly reported information on the overall sample and the analysis sample. However, none of the 12 articles presented summary information on the trimmed patients.

Conclusions: When PS trimming is conducted in safety cohort studies, researchers often report information on the overall and analysis sample without presenting information on the excluded patients, thus missing an important piece of information when evaluating the study's generalizability and a treatment's safety profile.

247. Effectiveness of Triple Therapy with Direct-Acting Antivirals for Hepatitis C Genotype 1 Infection: Application of Propensity Score Matching in a National HCV Treatment Registry

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Background: Observational studies have become increasingly important for assessing the effectiveness of therapeutic regimens in the real world setting. Non-randomisation in these studies can result in confounding or selection bias. Propensity score matching is one of a number of statistical tools that can be used to mitigate the effects of confounding in observational studies.

Objectives: To assess propensity score matching as a tool to report the adjusted outcomes for patients treated with direct-acting antiviral regimens for HCV genotype-1 infection using data from a national HCV registry.

Methods: The Irish national HCV treatment registry utilizes a prospective, longitudinal, observational methodology. We analysed the data of 338 patients who underwent triple therapy treatment with telaprevir, boceprevir or simeprevir, in combination with peg-interferon and ribavirin for HCV genotype-1 infection between June 2012 and December 2014. Three approaches to propensity score matching were used. Adjusted sustained-virological response rates, odds ratios, p-values and 95% confidence intervals were calculated from the three PS matched dataset.

Results: Prior to matching, the unadjusted SVR24 rates were 74%, 61% and 45% for telaprevir/PR, boceprevir/PR and simeprevir/PR, respectively. The odds of SVR in a patient treated with telaprevir/PR were 1.8 times greater than the odds of SVR in a patient treated with boceprevir PR (OR = 1.8, 95% CI 1.08-3, p = 0.025). After matching, adjusted SVR rates ranged between 73%-74% and 60%-61% for telaprevir/PR and boceprevir/PR, respectively. There was no statistically significant difference in the odds of SVR in telaprevir/PR-treated patients compared with boceprevir/PR patients.

Conclusions: This study illustrates how confounding in observational studies can be mitigated by propensity score matching. There was no significant change in SVR rates of the telaprevir/PR and boceprevir/PR groups prior to, and after, matching. The p-values after matching indicated that there was no statistically significant difference in the SVR rates between the two treatments.

248. Utilizing the Present on Admission (POA) Variable for Risk Adjustment with the Elixhauser Comorbidity Index: A Case Study in Thoracic Lobectomy

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Background: The Elixhauser Comorbidity Index (ELIX) is a commonly used measure for patient risk adjustment for outcomes such as cost. However, when ICD-9 diagnosis date is not available, it can be difficult to discern complications from comorbidities. The Present on Admission (POA) variable is useful for differentiating these concepts.

Objectives: Examine the impact of POA adjustment (POA-ADJ) on ELIX and its effect on total hospital costs.

Methods: All open thoracic lobectomies from 2008-2014 were identified in the Premier Perspective® Database. ELIX were computed with and without POA-

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ADJ (if POA was "No" then excluded from ELIX, if missing no adjustment). Generalized Estimating Equations (GEE) models controlling for patient demographics (age, gender) and hospital clusters were created to examine the impact of ELIX (with and without POA-ADJ) on total hospital cost (2014USD).

Results: A total of 14,833 lobectomies were identified. POA-ADJ reduced mean ELIX from 3.86 (SD = 1.93) to 3.42(SD = 1.69) and the percentage of patients with scores of ≥5 from 32.8% to 23.6%. POA-ADJ led to large decreases in ELIX categories that may capture acute complications: cardiac arrhythmia (28.62% vs. 13.85%), fluid electrolyte disorders (21.71% vs. 6.93%), and blood loss anemia (1.23% vs. 0.42%). Chronic comorbidities such as alcohol abuse (3.63% vs. 3.55%), hypertension (54.73% vs. 54.1%), and diabetes (18.77% vs. 18.22%) had little change. Results of the GEE analysis indicated that patients with POA-ADJ ELIX = ≥5 had 40.5% higher costs compared to those without any ELIX comorbidities. Patients without POA-ADJ ELIX = ≥5 had 62.9% higher costs compared to those without any comorbidities. This higher impact of non POA-ADJ ELIX on costs was consistently observed across all ELIX categories.

Conclusions: Using ELIX as a baseline risk adjustment variable without POA adjustment may lead to biases in estimates due to potential inclusion of complications in addition to comorbidities. POA adjustment should be considered, especially in cross sectional databases. Replication in other procedures and outcomes is required to confirm these findings.

249. Better Alternatives to Existing Methods to Take into Account Prognostic Scores in Observational Studies

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Background: Introduced by Hansen to account for confounding in observational studies, the PGS are presented as 'the prognostic analogue of the propensity scores' (PPS). The notion of 'analogy' should imply that they lead to the same type of estimation of the treatment effect. But if the most used PPS-based methods estimate the marginal (as opposed to conditional) treatment effect, the vast majority of simulation studies evaluating the performances of PGS-based methods used a collapsible measurement of the treatment effect, a situation where, by definition, the theoretical conditional and marginal effects are equal.

Objectives: The objectives of this Monte Carlo simulation study are:to compare the performances of existing PPS and PGS-based methods when the OR (non-collapsible estimator) is used to measure the treatment effect on a binary outcometo compare their performances with 3 new PGS-based methods.

Methods: 3 types of treatment effect were considered: the marginal OR on the overall population ('Average Treatment Effect' ATE)the marginal OR on the treated subjects ('Average Treatment Effect on the Treated' ATT)the conditional OR ('Conditional Treatment Effect' CTE)

We randomly generated datasets according to various scenarios and analysed them using PPS methods (matching, weighting using ATE weights or ATT weights), conventional PGS methods (matching, adjustment, or stratification) and 3 new PGS methods that we have developped for each with a specific measure in mind (either CTE, ATE or ATT).

Results: 1) Among conventional PGS methods, only matching estimated a marginal effect (ATT).

2) The performances of PGS adjustment and stratification for CTE estimation were heavily influenced by the treatment prevalence, with coverage rates far below 95% for the highest prevalences.

3) The new PGS methods resulted to unbiased estimations of the treatment effect for which they were respectively designed, with correct coverage rates. Overall, they outperformed conventional PGS methods, and PPS methods especially for the lowest treatment prevalences.

Conclusions: We propose 3 new PGS-based methods, easily implementable and more efficient than conventional PGS-based methods.

250. Predicting Chronic Medication Count in Veterans with and without HIV Infection

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Background: Polypharmacy (5 or more medications) is common, increases with age and likely associated with adverse events (AE) including falls and mortality. Because patients on more medications are generally sicker than those on fewer, accounting for expected count is necessary before exploring associations with AEs.

Objectives: To predict non-ARV medication count in patients receiving care from the Veterans Health Administration (VA), using electronic health record and pharmacy fill data.

Methods: We identified patients from the Veterans Aging Cohort Study who filled at least one prescription in 2008 and had a visit in 2009. We excluded those with cancer or detectable HIV RNA. We defined chronic use as 90 consecutive days, allowing gaps up to 30 days between fills. We used linear regression to model square root of medication count, separately by HIV status. Regression equations were solved and squared to get actual count for reporting. Predictor variables included demographics, chronic conditions, visits to primary care and specialist providers, and laboratory values. We tested for interaction by HIV in a combined model, for the strongest predictors.

Results: Among 10,556 HIV+ and 44,822 uninfected, median age was 56 years (IQR 50-61), 97% were male, 41% white and 47% black. For HIV+ and uninfected respectively, median non-ARV count was 4 (2-8) and 6 (3-9), model r2 was 0.48 and 0.46, correlation between observed and predicted count was 0.70 and 0.68. Although base values of non-ARV count were lower for HIV+ (0.9) than uninfected (1.7), significant ($p < 0.001$) positive interactions with HIV were found for age, hypertension, hyperlipidemia, pain-related diagnosis and mental health clinic visits. Predicted non-ARV count in a 50 year old with hypertension was 2.5 if HIV+ and 3.3 if uninfected. At age 70, it would be 3.4 and 3.9, showing additional interaction with age.[2]

Conclusions: We propose using predicted count analogously to propensity score to adjust for confounding by indication when exploring associations with polypharmacy. Given most HIV+ use 3 ARVs, total medication count is higher in HIV+ than uninfected.

251. Missing Cause Approach to Detect and Reduce Unmeasured Confounding Bias in Pharmacoepidemiology

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Background: Instrumental variables (IV) offer a rare opportunity to correct for unobserved confounding in pharmacoepidemiology but IV estimates suffer from serious variance inflation, with very wide confidence intervals (CI) making their interpretation difficult.

Objectives: To reduce the variance of the estimates, we propose a new method for reducing the impact of unobserved confounding in pharmacoepidemiology, validate it in simulations and apply it in a real-life drug safety study.

Methods: Under standard IV assumptions, our new "missing cause" method relies on estimated discrepancies between a) treatment actually received by individual patients and b) treatment they would be expected to receive based on their observed characteristics and their physicians' prescribing preferences. We use the treatment-by-discrepancy interaction, in the outcome model, to test for presence of unmeasured confounding and correct the treatment effect estimate for the resulting bias. Similar to IV analyses in pharmacoepidemiology, we implement the method within risk difference (RD) multivariable linear regression modeling of the effect of a binary exposure on a binary outcome. In simulations, we compare our missing-cause estimates with (i) conventional estimates, adjusted only for measured covariates, and (ii) IV estimates. We apply the method to compare gastrointestinal (GI) safety of COX-2 inhibitors vs. traditional NSAIDs in a large cohort of elderly in Quebec, Canada.

Results: In simulations, our estimates had four times smaller bias than conventional estimates, much smaller variance than unbiased but unstable IV

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estimates, and uniformly best overall accuracy (lowest mean square error). Our method suggested a slight reduction of GI risks for COX-2 inhibitors: adjusted RD = -2.6% (-8.4%, 3.2%), in contrast to risk increase suggested by IV estimates, with much wider CIs: RD = +3.3% (-12.7%, 19.3%).

Conclusions: Our "missing cause" method provides an efficient alternative to IV approaches for reducing unmeasured confounding bias in pharmacoepidemiology. Further research is necessary to adapt and assess this method for logistic and Cox regressions.

252. Predictability of Electronic Medical Record (EMR)-Based Patient Characteristics Using Health Care Utilization Data in Patients with Type 2 Diabetes Mellitus (T2DM) Initiating Glucose-Lowering Agents

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Background: Administrative databases are increasingly used to assess the comparative effectiveness and safety of diabetes medications in T2DM patients. However, they do not often contain important clinical information typically present in EMR such as body mass index (BMI), duration of diabetes, hemoglobin A1c (HbA1c), and estimated glomerular filtration rate (eGFR).

Objectives: To assess the extent to which EMR-based characteristics relevant to T2DM treatment can be predicted by administrative data.

Methods: Within a large, US health insurance database (MarketScan), we identified T2DM patients who initiated a non-insulin glucose lowering agent between May 2011-December 2012 and linked a subset of these patients to EMR. Within this subset, we built regression models to predict the actual value and missingness of each EMR-based characteristic (i.e. BMI, diabetes duration, HbA1c, and eGFR), using available claims-based covariates as predictors.

Results: We identified 166,613 T2DM patients who initiated a glucose lowering agent between May 2011-December 2012, and among those, a subset of 7,219 T2DM patients were linked to EMR. The linear models predicting the value of continuous EMR-based covariates, had higher predictive accuracy for eGFR (R-squared = 0.5358), than for BMI (R-squared = 0.1753), HbA1C (R-squared = 0.1539) or duration of diabetes (R-squared = 0.0858). The logistic models aimed at predicting the missingness of each EMR-based characteristic (1 = "Missing" Vs. 0 = "Non-missing"), had low to moderate predictive accuracy ($0.597 < c\text{-statistic} < 0.699$), suggesting considerable randomness in the mechanism underlying the missingness.

Conclusions: In the context of moderate ability of administrative data to approximate the actual value of important EMR-based characteristics through diagnostic, procedural and prescription claims, study design strategies (e.g. using a new user design and choosing appropriate comparison groups), may overcome this limitation and successfully address confounding associated with unmeasured information in comparative effectiveness research on diabetes therapy.

253. Combining Different Health Care and Health System Registries to Identify Diseases for Research and Health Policy Purposes: The Danish Registry of Selected Chronic Diseases

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Background: In epidemiological research, different methods are applied to identify and analyze outcomes. Outcome i.e. a specific disease is often selected from specific coding in one register and a study population is identified based on the coding to analyze a hypothesis. Another approach is a population-based study (i.e. CPRD) using algorithms combining information from databases included in the study containing a variety of different health data information regarding the specific population. In Denmark, we have an opportunity to combine registries for a whole population. Identifying diseases based on algorithms using information from different registries can be used as a standard for research and public health policy.

Objectives: To establish a registry that can be used for a broad variety of public health policies as well as in epidemiological and pharmacoepidemiological research.

Methods: We have combined data from the Danish heath care databases with information on drug use (Register of Medicinal Product Statistics) and hospital admissions (National Registration of Patients, The Danish Psychiatric Central Research Register). Algorithms are based on guidelines for treatments. Specialist and medical societies have been invited and have participated to develop algorithms for chronic diseases.

Results: Algorithms for the following diseases have been developed: type 1 and 2 diabetes, Heart Failure, COPD, Asthma, Osteoporosis, Rheumatoid Arthritis, Schizophrenia and Dementia. For the first time we have separated type 1 and type 2 diabetes based combining information from registries.

Conclusions: An increasing interest in chronic diseases and the growing burden on the health care systems from an aging population with chronic diseases will be met with this registry.

254. Complementary Observational Studies Assessing the Incidence of a Rare Cancer Outcome by Linking State Cancer Registry Data to Large Pharmacy Claims Databases in the United States

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Background: There are many challenges to conducting traditional post-marketing surveillance studies for rare cancer outcomes including precise case identification; exposure assessment; longitudinal follow-up; and sufficient study size. Using two large pharmacy claims databases to identify exposure and linking to cancer registries to determine outcome is one novel approach currently being implemented in an ongoing safety surveillance program.

Objectives: To describe methods using two pharmacy claims databases linked to state cancer registries to assess the incidence of osteosarcoma, a rare bone cancer, among patients taking teriparatide and a comparison group.

Methods: Two population-based pharmacy claims databases, a Federal health insurance program and a commercial outpatient pharmacy database, are used to identify drug exposure and assemble the appropriate study cohorts. Cancer diagnosis information is obtained by linking the cohorts with state cancer registry databases who use the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) codes. Incidence of cancer among the exposed and unexposed cohorts will be estimated and compared.

Results: Approximately 30 different state cancer registries initially agreed to participate in these linkage studies. The process for conducting the linkages between two different pharmacy claims databases and individual state cancer registries must be tailored to meet data privacy and other local requirements for all data sources. For one pharmacy claims database, a deterministic linkage using a direct identifier will be implemented either through a trusted third party or by the individual registry. For the other pharmacy claims database, linkage will be conducted using deidentification technology.

Conclusions: Using large pharmacy claims databases to obtain drug exposure information and linking with cancer registries to determine cancer outcomes minimizes the possibility of misclassification of the tumor type and has the potential to improve monitoring for patient safety without imposing burden on the patient.

255. Identification of Associations Between Prescribed Medications and Cancer: A Nationwide Screening Study

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Background: Pharmaceutical agents may possess carcinogenic or chemopreventive properties. Such effects are not captured via conventional pharmacovigilance approaches.

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Objectives: We present a large-scale systematic screening for identifying associations between prescribed drugs and cancer risk using the high quality nationwide health and demographic registries in Denmark.

Methods: We identified all patients (cases) with new primary invasive cancers in Denmark during 2000-2012 (n = 278,485) and matched each case on gender, age and calendar time to 10 cancer-free controls. Complete prescription histories since 1995 were extracted from the Danish Prescription Registry. In a two-phase case-control approach, we screened prescription drugs for associations with 99 different cancer types. In the first phase, we identified single drugs or drug classes associated with an increased or decreased risk of cancer. In the second phase, we further evaluated potential associations by examining specificity and dose-response patterns.

Results: A total of 22,125 drug-cancer pairs underwent evaluation in the first phase. Of 4,561 initial signals (i.e. drug-cancer associations), 3,541 (78%) failed to meet requirements for specificity and dose-response patterns, leaving 1,020 eligible signals. Of the 510 signals involving the use of single drugs, 33% (166 signals) suggested a reduction in cancer risk and 67% (344 signals) an increase. A large proportion of the signals were attributable to confounding by indication. The screening algorithm was successful in identifying well-established causal associations, e.g., between female hormone therapy and risk of breast cancer, as well as several new signals that deserve further study.

Conclusions: Our results provide the basis for future targeted studies of single associations to capture novel carcinogenic or chemopreventive effects of prescription drugs.

256. Semi-Automatic Coding of Case Definitions

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Background: Collaborative epidemiological studies require the combination of evidence from electronic health record databases using various coding systems. The mapping of a case definition into codes of the coding systems is largely a manual process and poses a bottleneck to the rapid implementation of such studies. The Accelerated Development of Vaccine Benefit-Risk Collaboration in Europe (ADVANCE) aims to create a framework to provide robust data on vaccine benefits and risks for accelerated decision making. CodeMapper was developed within this framework.

Objectives: To present the application CodeMapper that supports the creation of code sets from a textual case definition in multiple coding systems simultaneously, and to evaluate the effectiveness of the operations provided by the application.

Methods: The workflow of CodeMapper has three phases: identifying medical concepts in a case definition, revising the concepts, and retrieving the code sets for the selected coding systems, while retaining a history of all revision steps. The revision operations include the adding and removal of concepts and the expansion to more general or more specific concepts.

CodeMapper was evaluated by applying the expansion operators on the concepts identified in a case definition, and including expanded concepts if they contributed codes to the reference mapping. Expansions are applied to the mapping in consecutive steps. The performance of each step is measured by the sensitivity and positive predictive value (PPV) of the generated codes in comparison to manually created reference code sets.

Results: Automatic concept identification has a sensitivity of 0.297 and a PPV of 0.570. The sensitivity increases to 0.851, 0.921 and 0.940 after one, two and three steps of expansion, whereas the PPV increases first to 0.600 and decreases then to 0.539 and 0.534.

Conclusions: Automated concept identification in the case definition alone is insufficient for generating code sets, but the expansion to more general or more specific concepts is an effective means. The history of operations recorded in CodeMapper documents the mapping process in a transparent and reproducible manner.

257. Identifying the Prescribing Physician in US Healthcare Claims Data

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Background: In many healthcare claims databases, a unique physician identifier (PI) that spans all parts of the database (e.g., pharmacy claims (PC) and medical services claims (MSC)) is not available. Therefore, identifying the physician responsible for prescribing a patient's drug may be challenging.

Objectives: To identify the most likely match between the DEA and PROV and to assess the association between the match and characteristics of the providers/medical encounters in the United Healthcare (UH) database, which has PIs coded by a drug enforcement administration (DEA) variable in PC and a provider (PROV) variable in MSC.

Methods: All unique DEAs in a cohort of new users of osteoporosis (OP) medications were identified from women >=55 years old (2008-11). For each DEA, all new prescription (Rx) fills for any drug during the study period were obtained and the PROVs on MSC within 7 days prior to each new Rx were identified. The proportion of times each unique PROV appeared at least once in this time window out of the total # of new Rxs for each DEA was calculated and the PROV with the highest proportion was classified as the most likely match to the DEA. Subsetting to PROV and DEA #s that occurred together >=80%, a logistic regression model was built with characteristics of providers/medical encounters as explanatory variables and the match as the dependent variable.

Results: We identified 66,125 new users of OP medications with 38,810 unique DEAs on the PC of their index Rxs. There were 1,014,354 unique PROVs which appeared in the 7 days prior to the new Rxs of these DEAs during the study period. The strongest predictor of matching (c-statistic: 0.78) was physician specialty (OR=7.70, 95% CI:5.87, 10.10), followed by outpatient office visit (OR=2.61, 95% CI:1.71, 3.99), OP diagnosis (OR=2.39, 95%CI:1.45, 3.94), and DXA scan (OR=0.97, 95% CI:0.59, 1.60).

Conclusions: In the UH database, the association between physician/medical encounter characteristics and a DEA-PROV match was evaluated. The predicted model could be used in other databases to facilitate the linkage of prescriber information from different parts of the database, allowing for the investigation of physician prescribing patterns over time.

258. Evaluation Of Different Missing Data Strategies In Propensity Score Analyses

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Background: Propensity scores are used to adjust for confounding. However, data on confounders is often not fully available. Different techniques are available to handle missing data, but there is little data available about the relative performance of missing data methods within the context of propensity score analyses.

Observational studies have shown decreased risks of fracture with use of statins while large randomized clinical trials (RCTs) found a relative risk of 1.0. BMI is an important confounder with often incomplete data and this might explain the differences between the results of the RCTs and the observational studies.

Objectives: To explore the sensitivity of estimated treatments effects to the missing data approach used.

Methods: A retrospective cohort study using data from the UK Clinical Practice Research Datalink (CPRD) (1992-2014) was conducted. Statin users, aged 50 years or older, having at least one statin prescription since 1992 were selected and matched 1:1 by year of birth, sex and practice to non-users. Cox regression models were used to estimate the hazard ratios (HR's) of hip fracture in statin users versus non-statin users. Missing data were handled by complete case (CC) analysis, adding an indicator (IND) and multiple imputation (MI). Adjustments by propensity scores (inverse probability weighting) were compared to adjustments including confounders in the regression model.

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Results: The confounder adjusted methods showed all a decreased risk of hip fracture for statin users as compared to non-users (CC: HR 0.92 95% CI (0.85 – 0.99); IND: HR 0.92 (0.86 – 0.99); MI: HR 0.92 (0.86 – 0.99)). Propensity score adjusted models showed no association in the CC analysis (HR 0.98 95% CI: 0.93 – 1.02), whereas the IND and MI analysis showed a decreased risk of hip fracture with statin use (IND: HR 0.94 (0.91 – 0.98); MI: HR 0.95 (0.91 – 0.99)).

Conclusions: The point estimates of the three different missing data techniques did not differ much, suggesting that the different techniques used in the present study did not greatly influence the estimated treatment effect.

259. Agreement Between ICD-9 Codes and Laboratory Results Indicative of Myelosuppression (MS) in Patients with Longer-Term Exposure to Linezolid in a Claims Database

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Background: Linezolid is indicated for treating antibiotic resistant skin and soft tissue infections often occurring in immunocompromised patients, particularly infections caused by Gram-positive bacteria. There have been reports of MS events associated with long exposure >14 days) to linezolid.

Objectives: This study assessed the agreement between ICD9 codes and lab data for MS events in a claims database.

Methods: Adults exposed to linezolid were selected from a claims database and followed 42 days past the end date of linezolid prescriptions. Patients were required to be in the health plan at least 180 days prior to the initial prescription of linezolid. MS was defined using either ICD-9 codes or lab values by the occurrence of at least one of the following: anemia (AN), thrombocytopenia(TH), or neutropenia (NU). MS lab-based definitions were: hemoglobin <9.5 g/dL), neutropenia <1000/mm3) and platelet count <75,000 platelets/ mm3). Cohen's kappa was computed to assess chance-corrected agreement between ICD-9 and lab based outcomes.

Results: A total of 15,908 patients were identified with linezolid exposure (82% <14 days) from 2000-2014. 1,889 events of MS (11.9%) were observed using ICD-9 definition. Lab values were available in 5,058 patients (32%). For overall MS, AN, TH and NU events there were 4917, 4877, 4939 and 4636 patients who had both an ICD-9 diagnosis and lab values for the respective outcomes. Kappas (95% CI) were .05 (0-.12), .13 (.03-.23), .22 (.17-.26) and .23 (.18-.28) for NU, TH, MS, and AN, respectively.

Conclusions: Agreement between ICD-9 and lab values was poor. Lack of agreement may be negatively affected by missing data. Missing lab values may be due to patients receiving labs from out of network labs. Lab results may not make their way into the patient records after the medical decision is made to continue therapy. Similarly, healthcare providers may not record an ICD-9 code of a MS event once the lab result has been reviewed and course of action taken. Further research is needed to investigate the impact of this missing information on algorithms assessing MS events.

260. Use of Electronic Healthcare Records to Identify Complex Patients with Atrial Fibrillation for Targeted Intervention

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Background: Practice guidelines recommend anticoagulation for patients with atrial fibrillation (AF) and risk factors putting them at higher risk of stroke. However, many high-risk patients remain undertreated, in part due to concerns regarding major bleeding as an adverse effect of anticoagulation.

Objectives: To develop and validate algorithms using electronic healthcare record (EHR) data to identify patients with atrial fibrillation (AF) and determine the presence or absence of known risk factors for stroke and major bleeding.

Methods: We developed and tested the performance of multiple algorithms using EHR data from the Partners Healthcare System to identify patients with AF and 16 other conditions included as risk factors in the CHA2DS2-VASc and HAS-BLED scores for stroke and major bleeding. Algorithms were based on information contained in problem lists, billing codes, laboratory data, prescription data and clinical notes. Performance of candidate algorithms in 1000 bootstrap samples was compared to a gold standard of manual chart review by resident physicians.

Results: Resident physicians reviewed a sample of 480 patient charts to determine presence or absence of each condition. We tested and chose algorithms that maximized positive predictive value (PPV) and specificity. The median PPV of the selected algorithms was greater than 0.90 in 1000 bootstrap samples for 11 conditions; the remaining conditions had a median PPV between 0.53 and 0.89. Median specificity was greater than 0.92 in 1000 bootstrap samples for 14 conditions; the remaining conditions had a median specificity between 0.52 and 0.83. When using these algorithms to identify patients with CHA2DS2-VASc ≥ 2 or HAS-BLED ≥ 3 in 1000 bootstrap samples, the median PPV was 1.00 and 0.93, while median specificity was 0.93 and 0.77, respectively.

Conclusions: We developed a set of algorithms to identify patients with AF and known risk factors for stroke and major bleeding using EHR data. Algorithms such as these can be built into EHR systems to focus population health management efforts on patients with the greatest need for preventive anticoagulation therapy and lowest risk of adverse effects.

261. Validity of Claims-Based Definitions for Hospitalized Volume Overload Among Hemodialysis Patients

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Background: Hospitalizations attributed to volume overload are critical outcomes when evaluating the comparative effectiveness of fluid management therapies in hemodialysis (HD) patients. Despite growing interest in the use of administrative data to study such outcomes, validated claims-based definitions for hospitalized volume overload in the HD population are lacking.

Objectives: To validate administrative claims-based definitions for hospitalized volume overload in the HD population.

Methods: We randomly sampled medical records of HD patients (n = 200) admitted to a large U.S. academic medical center from 2011-2012. We applied a diagnostic algorithm that included symptoms, physical exam findings, imaging and clinical impression to data abstracted from medical charts to adjudicate the presence of volume overload at admission. Seven claims-based definitions of volume overload were constructed using ICD-9 discharge diagnosis codes obtained from the medical center's billing data. We estimated the sensitivity (SE), specificity (SP), positive predictive value (PPV) and corresponding 95% confidence intervals (CIs) for each claims-based definition using clinically adjudicated volume overload as the gold standard.

Results: Forty-two admissions (21%) were clinically adjudicated as hospitalized volume overload. Sensitivity (SE range: 0.07-0.55), SP (SP range: 0.95-0.98) and PPV (PPV range: 0.43-0.84) varied across the 7 claims-based definitions. Hospitalized volume overload defined as the presence of ICD-9 discharge diagnosis codes of fluid overload, pulmonary edema or pleural effusion listed in any position had a SE = 0.55 (CI: 0.38, 0.70), SP = 0.95 (CI: 0.90, 0.98) and PPV = 0.74 (CI: 0.55, 0.88). Narrowing the definition to only include fluid overload ICD-9 codes reduced SE (SE = 0.38; CI: 0.24, 0.54) but improved SP (SP = 0.98; CI: 0.95, 1.00) and PPV (PPV = 0.84; CI: 0.60, 0.97).

Conclusions: The claims-based definition of a fluid overload ICD-9 discharge diagnosis code present in any position had excellent SP and a high PPV, supporting its use as an outcome definition in comparative effectiveness studies of HD patients.

262. Do Hemoglobin Lab Test Results Increase Detection of Upper Gastrointestinal Bleeding (UGIB)?

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Background: Studies that evaluate UGIB in electronic healthcare data typically rely on inpatient diagnostic codes for outcome identification. Use of hemoglobin (HGB) lab test results might increase detection of UGIB that do not lead to hospitalization.

Objectives: To evaluate whether use of HGB test results increases UGIB identification using non-steroidal anti-inflammatory drugs (NSAIDs) as a test case.

Methods: From the Mini-Sentinel distributed database, we identified patients ≥18 years old who initiated prescription NSAIDs in 3 Data Partners between January 2008-April 2013. Availability of HGB test results was examined before and after NSAID initiation. Numbers of events and cumulative incidences within 30 days after NSAID initiation were calculated for 4 mutually exclusive outcome definitions: (1) inpatient UGIB diagnosis (standard claims-based definition without lab test results); (2) non-inpatient UGIB diagnosis AND ≥3 g/dL decrease in HGB; (3) ≥3 g/dL HGB decrease alone without UGIB diagnosis in any clinical setting; (4) non-inpatient UGIB diagnosis, without ≥3 g/dL HGB decrease. In secondary analyses, we reviewed all coded diagnoses in patients with outcome 3 to scan for codes indicative of potential UGIB and assessed distributions of specific UGIB diagnoses in patients with outcomes 1, 2, and 4.

Results: We identified 2,289,772 NSAID initiators; 45% had ≥1 HGB result available within 365 days before or 30 days after NSAID initiation. Only 7% had results before and after. Of 7,637 potential outcomes identified from all 4 definitions, outcome 1 accounted for 22%, outcome 2 for 1%, outcome 3 for 34%, and outcome 4 for 43%. Potential cases identified by outcome 3 were mostly associated with codes for non-UGIB or other non-hemorrhagic conditions. Outcomes 1, 2, and 4 were associated with similar distributions of specific UGIB codes.

Conclusions: Using HGB result values in combination with UGIB diagnoses identified few additional potential UGIB cases and with unknown specificity. The use of HGB result values alone did not improve identification of potential UGIB events. The use of non-inpatient diagnostic codes may increase UGIB outcome detection, but would require validation.

263. Cancer Recording In Patients With Type 2 Diabetes In Primary Care And Hospital Admission Data

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Background: Electronic health records are increasingly used to investigate associations between antidiabetic therapy and cancer. Misclassification can impact results, especially if differential between comparators.

Objectives: Estimate cancer misclassification when using primary care or hospital data alone.

Methods: Adults aged ≥40 years with an insulin or oral antidiabetic prescription in Clinical Practice Research Datalink (CPRD) primary care data at least a year after start of data collection, and no record of type 1 diabetes, were included. Patients were matched by year of birth (stepwise within 5 years), sex and GP practice to up to 1 non-diabetic patient. The cohort was restricted to those eligible for Hospital Episode Statistics (HES) linkage with follow-up during the study period (04/01/97-12/31/06). Follow-up started at the maximum of the registration date with the practice, practice up-to-standard date (a CPRD quality metric), and start of study period. Follow-up ended at the minimum of when the patient left the practice, the date CPRD last collected data from the practice, and end of study period. Cancer was identified in CPRD via Read codes and in HES via ICD-10 codes. For each cancer case in CPRD, analysis evaluated whether there was a corresponding record in HES coded with same, different or unspecified site. Analysis was repeated for cancers identified in HES.

Results: 53,585 diabetic patients were matched to 47,435 non-diabetic patients. 83% of cancer cases in CPRD had a corresponding record in HES (78% with the same type). Misclassification varied by cancer site, ranging from 3% (stomach cancer) to 57% (non-melanoma skin cancer). 83% of cancer cases in HES had a

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corresponding record in CPRD, with all misclassification rates <20%.

Conclusions: A good level of concordance and low level of misclassification of cancer exist between CPRD primary care data and HES. The value of linking these data for establishing cancer outcomes lies more in the complimentary variables held than in reducing misclassification.

264. Authenticity Validation of Lung Cancer Records from a Standardized Inpatient EMR Database in China and Comparison of Different Methods

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Background: Information from pathology reports and discharge diagnoses in Electronic Medical Records (EMR) are frequently used to identify lung cancer patients. Their validity has not been fully assessed in China.

Objectives: To assess the accuracy of the identification of lung cancer inpatients using standardized EMR data from our hospital (The first affiliated hospital of Guangzhou medical university, China).

Methods: The de-identified EMR data from the hospital was transformed into a common data model. Patients with an inpatient lung cancer diagnosis, pathology diagnosis, or discharge diagnosis of lung cancer between January 1, 2012 and September 30, 2015 were identified. Both ICD-10 code and description in free text were used. A random sample of 300 lung cancer inpatients was selected, and their medical records were reviewed and adjudicated by an experienced physician who was blinded to the diagnosis. Positive predictive values (PPV) were calculated as the proportion of lung cancer inpatients in the EMR database that were correctly identified based on the physician assessment.

Results: There were 6862 possible lung cancer inpatients identified per discharge diagnosis, of whom 2703 patients did not have a pathology diagnosis (group i). There were 5274 cases identified according to pathology reports, of whom 1115 did not have a corresponding discharge diagnosis (group ii); 4159 cases were categorized into group iii (patients with both pathology and discharge diagnoses). The PPV for group i was 85% (95% CI, 77.6%–92.4%), which was lower than the 90% (95% CI, 84.1%–95.9%) for group ii. Patients with both lung cancer pathology and discharge diagnoses (group iii) yielded the highest PPV, 99% (95% CI, 97.1%–100.0%). There were more male and older patients in group i, which may be due to a higher number of pre-existing lung cancer patients who did not have pathology records within the predefined period.

Conclusions: In this study, the PPV is highest when cases are identified using both lung cancer pathology and discharge diagnoses. In China, free text analysis alone is not sufficient to identify true cases; combined method is encouraged.

265. Ascertaining Pulmonary Hypertension and Other Conditions in Claims Databases

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Background: Epidemiological studies using claims databases often rely on diagnostic codes for case identification. For certain diseases, this may result in misclassification.

Methods: In the context of a study to estimate the incidence and prevalence of pulmonary arterial hypertension in a US pediatric population, 2010-2013 using MarketScan claims data we identified all potential cases of pulmonary hypertension (PH). Initially, a case was defined as a patient with ≥2 claims for PH that were at least 1 day apart, or ≥1 claim for PH plus ≥1 prescriptions for PH treatment (definition A). Later, we redefined the inclusion criteria to require ≥1 prescriptions for PH treatment for all cases (definition B). We evaluated the impact of each definition as the ratio of both incidence and prevalence of PH using each definition. We searched the literature on other

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diseases to assess the impact of requiring drug treatment as part of the case definition in claims data.

Results: Using definition A, the annual incidence of PH in the US ranged between 21 and 29 and the prevalence ranged between 57 and 63 cases per million children in 2010-13. When restricting to definition B, the incidence ranged between 5 and 7 cases per million children and the prevalence between 26 and 33. On average, the incidence was 5 times lower using definition B and the prevalence was half of that from definition A. Other studies showed a similar pattern for conditions such as venous thromboembolism where the PPV increased after inclusion of anticoagulant therapy in the case definition without jeopardizing sensitivity, and for asthma the PPV increased from 67% to 95% after including asthma therapy in addition to asthma claims.

Conclusions: Including PH treatment in the case definition for PH ascertainment resulted in outcomes more consistent with previous reports from European registries. Including targeted therapy in the case definition may increase the validity of the study outcome and prevent misclassification. This is especially relevant for diseases that require medical intervention and have few therapeutic options which, in turn, have few indications.

266. Validation of a Case-Finding Algorithm for Symptomatic Uterine Fibroids

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Background: Comparing Options for Management: Patient Centered Results for Uterine Fibroids (COMPARE-UF) is a voluntary registry of women with symptomatic uterine fibroids (UFs) from 9 clinical centers in the U.S. At the UNC-Chapel Hill clinical center, the Carolina Data Warehouse for Health (CDW-H) contains billing and electronic health records (EHR) data and will be used to identify eligible participants. Diagnosis codes for UFs may not be specific in identifying women with clinically relevant UFs since most UFs are asymptomatic and do not require treatment. Use of treatment procedural codes would exclude symptomatic patients who prefer medical management or watchful waiting.

Objectives: To test the positive predictive value (PPV) of an EHR-based phenotyping algorithm (computable phenotype) to identify women with symptomatic UF in the CDW-H.

Methods: To be detected by the algorithm, patients were required to (1) be between 18 and 54 years of age, (2a) have an ultrasound or MRI report containing the words "fibroids", "leiomyoma", or "myomata" with no preceding negation OR (2b) a billing code for UF (ICD-9-CM 218.0-218.9), and (3) no hysterectomy claims or mention of prior hysterectomy in their chart. Natural language processing (NLP) was used for both 2a and 3. A random selection of 150 charts was reviewed to calculate PPV.

Results: The algorithm identified 4,342 patients. Ultrasound evidence of UF was found for 139 (93%), and 71 (47%) were symptomatic cases eligible for the COMPARE-UF registry. The PPV for symptomatic UF was 47% (95% CI: 39-56%) for the overall algorithm, 46% (95% CI: 35-58%) for patients with imaging reports and claims, 57% (95% CI: 42-70%) among women with UF billing codes only, and 15% (95% CI: 2-45%) for those with imaging reports only. The low PPV for symptomatic cases was driven by a high number of women for whom UF was an incidental finding during treatment for other gynecologic conditions, pregnancy, or abdominal pain.

Conclusions: While most patients with billing codes and/or NLP evidence of UF do in fact have UF, most are not symptomatic and would not be eligible to participate in a registry for UF treatments.

267. Development and Validation of an Algorithm to Identify Endometrial Adenocarcinoma in US Administrative Claims Data

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Background: Endometrial adenocarcinoma is an important endpoint in safety monitoring of estrogen and progestin (E + P) hormone therapy (HT) products.

The performance of diagnostic codes to identify endometrial cancer, however, is uncertain.

Objectives: To develop and validate an algorithm for identifying endometrial adenocarcinoma using health insurance claims.

Methods: Published literature and medical consultation were used to develop an algorithm requiring at least one inpatient diagnosis or at least two outpatient diagnoses of endometrial adenocarcinoma (ICD-9-CM 182.xx) to identify potential cases among women who used E + P HT in the HealthCore Integrated Research Database (HIRD). We then obtained medical records that were adjudicated by two clinical experts to determine case status and estimated the positive predictive value (PPV) of the algorithm.

Results: The algorithm's PPV was 88.2% (95% CI 83.1 – 92.2). Potential cases who after review of medical records were found not to have endometrial adenocarcinoma, had alternative diagnoses such as uterine sarcoma, rhabdosarcoma of the uterus, endometrial stromal sarcoma, ovarian cancer, fallopian tube cancer, endometrial hyperplasia, leiomyosarcoma and colon cancer. Because the initial screening algorithm performed well, further refinements using the adjudicated cases status were not necessary.

Conclusions: In this validation study, we found that ICD-9-CM diagnosis codes for endometrial adenocarcinoma performed well in terms of PPV. Although some misclassification remained, the extent of outcome misclassification can inform bias analyses in the future.

268. Development and Validation of an Algorithm to Identify Endometrial Hyperplasia in US Administrative Claims Data

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Background: Endometrial hyperplasia is an important endpoint in safety monitoring of estrogen and progestin (E + P) hormone replacement therapy (HRT) products, especially as a precursor to endometrial cancer. Diagnostic codes to identify endometrial hyperplasia, however, have poor specificity (Reed, et al, 2009) making this endpoint challenging to study in automated databases.

Objectives: To use medical records and predictive models to develop and validate an algorithm for identifying endometrial hyperplasia accurately using health insurance claims.

Methods: We used information obtained from the literature and consultation with clinical experts to develop an initial screening algorithm that we applied to women who were new users of E + P HRT in the HealthCore Integrated Research Database (HIRD). We then obtained medical records that were adjudicated by two clinical experts to determine confirmed case status. After estimating the positive predictive value (PPV) for the screening algorithm, we used lasso logistic regression to predict the probability of being a confirmed case, which assigned weights to specific hyperplasia diagnosis types and other variables identified in the administrative claims data. We used Receiver Operating Characteristic (ROC) curves to select a probability threshold and cross-validation techniques to optimize and estimate PPV.

Results: We reviewed 363 medical records for women who met the screening algorithm, which had a PPV of 34.2% (95% CI 29.0-39.7). The lasso logistic regression model with a probability threshold of 0.6 gave a cross-validated PPV of 81.6% (95% CI 80.0-83.2). This probability threshold correctly excluded 95% (197/208) of false positives, and is where incremental gains in PPV leveled off.

Conclusions: Inaccurate diagnostic codes can introduce outcome misclassification and bias in administrative database studies. In this validation study, we confirmed a previous finding of limited performance of diagnosis codes for endometrial hyperplasia. Incorporating regression modeling with validation produced an algorithm with markedly increased PPV.

269. Can Population-Based Incidences Help Define Bladder Cancer Outcomes in a Medicare Cohort?

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Background: Using administrative claims to identify cancers, such as bladder cancer (BC), can be challenging due to the lack of pathological reports. Comparing event rates using differing claims-based algorithms to define outcomes can detect coding variation and programming errors in an individual study, but is limited without external validation.

Objectives: Compare BC rates in Medicare cohorts initiating pioglitazone (PIO) and dipeptidyl-peptidase-4 inhibitors (DPP) using various outcome algorithms with age- and sex-standardized population-based incidence rates from Surveillance, Epidemiology, and End Results (SEER).

Methods: We identified cohorts aged >65 with new claims for PIO or DPP 2008-2012. BC events were defined using various combinations of diagnosis claims (ICD-9: 188.X, 233.7) and procedure claims for BC-related diagnostic workup (i.e. cystoscopy) or treatment (i.e. cystectomy, chemotherapy instillation). Age- and sex-specific exposed person-time was multiplied by corresponding SEER rates to estimate standardized morbidity ratios (SMRs) and 95% CIs for BC.

Results: Cohorts included 63,897 patients and ~166,800 person-years leading to ~191 expected BC events. SMRs were 2.43 [2.21,2.65] for any diagnosis, 1.51 [1.34,1.68] for 2 diagnoses within 60 days, 1.27 [1.11,1.43] for 1 diagnostic procedure followed by 2 diagnoses within 3 months, and 1.11 [0.96,1.26] for 1 diagnosis followed by treatment within 3 months. Extending the interval between claims from 3 to 6 and 12 months did not appreciably alter SMRs.

Conclusions: We anticipated events observed in these diabetic cohorts to be 40-50% higher than the general population. Requiring only 1 diagnosis clearly had low specificity, likely due to rule-out. Requiring 2 diagnoses within 60 days, previously validated by Setoguchi et al., yielded the most plausible incidence rates, but this could be due to a balance of false positives and false negatives. This definition may be combined with treatment within 3 months to increase specificity, as evinced by the lowering of the SMR. Routine comparison of events observed with those expected is recommended to guide algorithm choice for defining outcomes in the absence of validation data.

270. Agreement Between Hospital Diagnosis Codes and Medical Records to Identify Metastatic Colorectal Cancer and Comorbidities in Elderly Patients

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Background: Pharmacoepidemiological research using French healthcare reimbursement and hospital databases is developing. Hospital data from the Programme de Médicalisation des Systèmes d'Information (PMSI) could be useful to identify cancer patients and comorbidities but have been little investigated with this respect.

Objectives: This study aimed to compare medical records and PMSI coding regarding diagnosis of metastatic colorectal cancer (mCRC) and comorbidities in elderly patients.

Methods: From 01/01/2013 to 30/06/2014, 74 patients aged ≥65 years at mCRC diagnosis were identified in Bordeaux university hospital. Data on mCRC and comorbidities were collected from medical records. All diagnosis codes (main, related and associated) registered from the mCRC diagnosis into the PMSI were extracted for each patient. The agreement between both sources was evaluated using the percent agreement for mCRC diagnosis and the kappa (K) statistic for comorbidities.

Results: The agreement for primary CRC and mCRC was higher considering all diagnosis codes related to the 1st hospitalization for mCRC than exclusively the

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main diagnosis codes (respectively 95% vs 53% for primary CRC and 91% vs 24% for mCRC). The agreement between both sources was substantial (K 0.65) for cardiovascular diseases, notably atrial fibrillation (K 0.77) and hypertension (K 0.68). It was moderate (K 0.48-0.55) for psychiatric disorders, and respiratory diseases although, within this class, chronic obstructive pulmonary disease had a good agreement (K 0.75). Within the class of endocrine, nutritional and metabolic diseases (K 0.55), agreement was substantial for diabetes (K 0.91), obesity (K 0.82) and hypothyroidism (K 0.72) and moderate for malnutrition (K 0.42) and hypercholesterolemia (K 0.51). The agreement was poor (K<0.25) for digestive, neurological diseases, and other cancers.

Conclusions: Results are reassuring with regard to the detection from PMSI data of primary CRC and mCRC if all types of diagnosis codes are considered. They are also useful to better choose comorbidities in elderly mCRC patients that could be well identified through hospital diagnosis codes.

271. Adding of CPT Codes Improves Classification of Type of Bowel Resection Based Only on ICD-9-CM Procedure Codes

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Background: To gauge the feasibility of a pediatric trial of a drug to prevent post-operative ileus, we sought to estimate the number of children who underwent bowel resection with a primary anastomosis. We initially queried the Kids' Inpatient Database (KID), the largest all-payer pediatric inpatient care database in the US. While KID can provide population-based estimates, it can only identify surgical procedures using ICD-9-CM codes (hereafter ICD-9), and a substantial proportion of bowel resections could not be fully characterized. To better characterize these procedures, we sought to extrapolate from a claims database that included the more granular CPT codes, in addition to ICD-9 procedure codes.

Objectives: Among patients for whom ICD-9- procedure codes indicated only nonspecific small or large bowel resection, to determine the proportion of surgeries that CPT codes could reclassify as involving a primary anastomosis.

Methods: We used the inpatient admissions data from the MarketScan® Commercial Claims and Encounters database, which includes both ICD-9 and CPT procedure codes. Pediatric patients <19 years of age) admitted and discharged in 2012 with an ICD-9-CM procedure code for bowel resection but without any additional code to distinguish primary anastomosis from diverting ostomy were included. For each eligible bowel resection procedure, we further assessed the type of surgery based on CPT codes.

Results: Of 1,174 pediatric patients who had bowel resection surgery based on ICD-9 procedure codes, we could not determine whether 802 (68.3%) procedures involved primary anastomoses vs. diverting ostomies. Using information from CPT coding, 274 (34.2%) bowel resection surgeries could be further classified as primary anastomoses and 194 (24.2%) as ostomies.

Conclusions: Bowel resection procedures that involve primary anastomoses are incompletely identified in children in administrative data using only ICD-9 procedure codes. Use of CPT codes improves classification. Our results suggest that when ICD-9 procedure codes failed to specify the type of bowel resection, about one-third of patients actually had a primary anastomosis.

272. Validation of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Diagnoses in the Clinical Practice Research Datalink

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Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions to drugs.

Objectives: To evaluate the validity of recorded diagnoses of SJS and TEN, requiring secondary care, in the Clinical Practice Research Datalink (CPRD).

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Methods: We identified patients of any age with a diagnosis for SJS or TEN between January 1995 and June 2014. Of those, we extracted information on all patients with a recorded referral to a secondary care unit within 30 days before or after the first SJS/TEN diagnosis, from information recorded in CPRD longitudinal patient profiles, additionally including free text or in-hospital episode statistics (HES) data. Two specialized clinicians and two epidemiologists abstracted and reviewed the patient files (CPRD gold including free text) and classified patients as probable, possible, or unlikely SJS/TEN cases. We calculated a positive predictive value (PPV) for all patients categorised as probable/possible SJS/TEN cases, using diagnoses made in secondary care as the gold standard.

Results: We identified 1324 patients with an incident diagnosis of SJS or TEN during the study period, among whom 640 had a recorded secondary care referral. A total of 569 patients were classified as probable or possible SJS/TEN patients after classification based on expert review of patient records. Of those, "gold standard" diagnoses were available for a representative subsample of 109 'possible or probable' SJS/TEN patients, within which we calculated a PPV of 0.90 (95% CI, 0.83-0.95). After excluding 10 false positive patients, our final study population consisted of 559 SJS/TEN patients.

Conclusions: We established a population-based SJS/TEN study population of high diagnostic validity from a large electronic database, by extracting SJS/TEN patients who required secondary care and by additional expert evaluation of available information.

273. Comparing Instant Health Data and SAS for Evaluation of Incidence Rates in Multiple Sclerosis Using MarketScan

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Background: Recently there is an increasing need for fast, accurate and user friendly analytical platforms for epidemiological and health outcome research.

Objectives: By using SAS programming method and an analytical tool, Instant Health Data (IHD), the incident rates (IRs) of multiple outcomes in Multiple Sclerosis (MS) patients by US MarketScan database were compared to demonstrate the performance of the IHD tool. The outcomes measured included depression, diabetes, sepsis, pneumonia, non-infectious colitis and convulsions.

Methods: The study was conducted using both SAS and IHD. MS population was identified from MarketScan Commercial and Medicare databases from 1/1/2009 to 6/30/2014. The first MS diagnosis date was defined as the index date. The patients were at least 18 years old and had the second diagnosis of MS at least 30 days apart after index date. The outcomes were defined by ICD-9 CM codes in any inpatient diagnosis fields. IRs measured overall and by age group and gender were calculated in each cohort, while any cases with an outcome diagnosis code within 183 days prior to index date were excluded.

Results: Using similar measurements and algorithms between SAS and IHD, the setup and execution of the studies on IHD was 80-90% faster. There were 79,274 patients identified in IHD vs. 78,899 in SAS. Comparing IHD to SAS results, the mean age in years was 48.1(±12.7) vs. 48.5 (±12.2). Both had 23.8% male and 76.2% female. Across the six outcomes, ratios of IRs ranged from 1.01 to 1.08. Pearson's correlation coefficient (r) between IRs by the two methods was 0.9996 ($P<0.0001$). The average ratios of the number of patients and the average follow-up time were 1.00 (r: 0.9999) and 1.02 (r: 0.9971). The ratio of the total number of cases varied from 1.04 to 1.11 (r: 0.9996). Some variations in the methods (e.g., facility header file was included in the IHD analysis but not in SAS) could explain the differences observed.

Conclusions: This evaluation study suggests that the results produced by IHD platform were very close with the ones by SAS. Meanwhile, much less time was needed using IHD to perform the same data management and analysis tasks.

274. Medications Prescription at Hospital Discharge in Patients with Validated Diagnosis of Dementia

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Background: Health databases may be used to assess cases of dementia (D), among the main causes of morbidity in the elderly, if the data are accurate.

Objectives: We present the preliminary results of a cohort study aimed at assessing a) validity of discharge diagnosis of D; b) medication prescribed at discharge; c) prescription redemption after discharge, through record-linkage with outpatient prescription database.

Methods: Sources of Data: Friuli Venezia Giulia (FVG), Italy, Regional Health Database of Hospitalizations and hospital electronic medical records (HEMR).

Study population: all records of discharge from the Udine University Hospital (FVG) 2012-2014 with International Classification of Diseases, 9th Revision Clinical Modification (ICD-9-CM) code for D (senile, presenile, vascular 290.0-290.43; degenerative 290.9; alcohol persistent 291.2; drug persistent 292.82; D in other diseases 294.1-294.8; frontotemporal 331.0-331.19; Lewy body 331.82; Creutzfeldt Jakob 046.1) in any position were selected from the Hospitalizations Database. The diagnosis was confirmed through HEMR review by trained Medical Doctors. Case confirmation required a written diagnosis of D and/or severe cognitive deficit. Reasons for not confirmation included wrong code, evidence of another disease.

Statistical analysis: Positive Predictive Value (PPV), with Wilson 95% Confidence Interval (95%CI), as the ratio of confirmed to potential cases.

Results: From 1 July to 31 December 2014, 445 hospitalizations with discharge code for D occurred, for 424 (94.4%) the information in HEMR was complete, in 404 of these the diagnosis was confirmed (PPV 96.2%; 95%CI 94.4-98.0). The most common diagnoses were the senile 290.0, (N = 186, 46.0%), vascular 290.4X, (N = 158, 39.1%) and presenile 290.1X, (N = 26, 6.4%) D subtypes. Proton pump inhibitors (A02BC, N = 210, 52.0%), Platelet aggregation inhibitors (B01AC, N = 166, 41.1%) and Antipsychotics (N05A, N = 141, 34.9%) were the most prescribed medications.

Conclusions: Consistently with prior studies, codes for D showed high validity. Review of hospital charts is required when the information in HEMR is lacking.

275. Comparing Methods Generating Drug Exposure Time From Prescription Register Data

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Background: Methods using fixed time windows, DDD or tablet dosage assumptions are widely used in pharmacoepidemiological research. There is a lack of knowledge how different methods perform with different drugs.

Objectives: To investigate the correctness of drug use times produced with different modelling methods.

Methods: Design: Drug purchases from Finnish Prescription register during 1995-2012 as part of nationwide register-based MEDALZ (Medication use and Alzheimer's disease) study including community-dwelling older persons. Drug use periods were modelled from drug purchases with one tablet and one DDD per day with grace periods of 0-180 days, fixed time windows of 90-360 days and PRE2DUP which is a mathematical modelling method taking account on individual variation in drug purchases and is tailored according to drug and packaged information.

Setting: 100 randomly selected purchase histories of each drug were modelled with different methods and resulting drug use periods were evaluated by two independent reviewers. The methods were randomized and the order of the methods blinded for each evaluation.

Exposure: Purchase histories of warfarin, bisoprolol, simvastatin, risperidone and mirtazapine were evaluated. Grace periods were not included at the end of drug use period.

Main outcome measure: The correctness of drug use periods included if correct purchases were included and was the duration of the last purchase correct.

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Statistical analysis: Confidence intervals and Kappa values of two expert's opinions.

Results: Kappa values describing agreement between two reviewers were between 0.88 and 0.98. The proportion of correct solutions was 0-41% with DDD methods, 0-73% with tablet methods, 0-22% with fixed time windows and 70-94% with PRE2DUP for different drugs. PRE2DUP had higher correctness for all drugs compared to any other method.

Conclusions: Fixed DDD and time window methods performed poorly, tablet methods moderately and PRE2DUP well. Only PRE2DUP performed reasonably with all drugs. It is important to select methods and parameters that produce correct drug use times for the drug(s) in question.

276. A Summary of Clinical Coding Systems by Different Clinical Settings in Healthcare Databases in the US and UK

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Background: Clinical coding systems are complex, and vary significantly by inpatient and outpatient settings in claims and electronic medical record (EMR) databases, which may be unclear to observational researchers. It is imperative that researchers understand key elements of coding systems and in which settings they are captured before defining clinical exposures and outcomes in databases.

Objectives: To summarize inpatient and outpatient clinical coding systems used in claims and EMR databases in the US and UK.

Methods: We reviewed clinical coding systems employed in a total of 10 major claims and EMR databases in the US and UK, with special focus on diagnoses, procedures, medications and laboratory tests. We summarized coding systems by countries, databases, and different clinical settings (inpatient vs. outpatient).

Results: In the US, ICD-9-CM was used to record diagnoses before 2015, and ICD-10-CM is currently in use in both inpatient and outpatient settings in all databases. ICD-9 or ICD-10-PCS is used to record hospital inpatient procedures; while HCPCS/CPT is used for procedures submitted by physicians in both inpatient and outpatient settings. Medication information is mainly captured in the outpatient setting using NDC, GPI or ATC systems. As with medication data, laboratory test information is only available in certain outpatient databases, and can be identified by LOINC codes. In the UK GP databases (outpatient), diagnoses, procedures and laboratory tests are all recorded by READ/OXMIS codes and medications are coded using BNF or ATC for high level drug classes and Gemscript/Multilex for individual drugs. In the UK hospital database (inpatient), ICD-10 is used to record diagnoses and OPCS-4 is used to record procedures, with no medication data available.

Conclusions: Having a better understanding of complex international coding systems used in databases will help researchers identify exposures and outcomes more accurately. Future research needs to be done to thoroughly compare contents of different coding systems and their implications in observational research.

277. Standardizing Diversity of Event Definitions in Federated Networks of Heterogeneous Health Data Sources: The "*Component Algorithm Strategy*"

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Background: Heterogeneity of European health data sources hampers the execution of high quality multinational, multi-data source observational studies.

Objectives: To describe the algorithm standardization strategy developed within the *European Medical Information Framework* (EMIF) project using 3 examples.

Methods: To identify cases of *type 2 diabetes* (T2DM), *dementia* (DEM) and *acute myocardial infarction* (AMI) in the *EMIF-Platform*, a federated network of heterogeneous data sources, standard algorithms (*components*) for case-identification were generated using a top-down/bottom-up iterative approach. Each component was based on records from one single data domain among *diagnoses*, *drugs*, *procedures*, *diagnostic test utilization* and *test results*. The Unified Medical Language System was used for semantic harmonization. All components were extracted separately so that any *logical combination* (*AND*, *OR*, *AND NOT*) was allowed.

Results: For T2DM/DEM/AMI, a set of 9/6/6 data sources was respectively used. Overall, 16/7/11 components per event were generated. All events had diagnoses-based components (7/3/5); T2DM and DEM had 4 drug-based components each; DEM had neither components based on test utilization or test results; AMI was the only event with procedure-based components (n = 2). Diagnoses-based components were subclassified by setting of data collection (e.g. AMI diagnoses in primary, secondary, inpatient care or death registry). Components from the remaining data domains were subclassified according to the pattern of the selected records (e.g. for DEM: ≥1 memantine drug prescription; ≥2 memantine drug prescription in 1 year). For T2DM, component-level benchmarking showed similar results from drug-based components across 6 of 9 data sources.

Local experts could choose one *data source-tailored logical combination of components* per event as the preferred case-finding algorithm.

Conclusions: The "*component strategy*" allows building data source-tailored extraction algorithms in a standardized fashion and facilitates both benchmarking and interpretation of study results across heterogeneous data sources.

278. Designing Medical Record Abstraction Forms for Retrospective Chart Review Studies: Considerations and Recommendations

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Background: Retrospective chart review (RCR) studies are commonly conducted to obtain evidence on treatment patterns, resource utilization, adverse events, and clinical outcomes. Accurate and efficient data collection from patient charts requires a thorough and well-developed medical record abstraction form. Yet there is limited methodological guidance available on designing medical record abstraction forms.

Objectives: To present a conceptual framework outlining pertinent considerations and recommendations for researchers throughout the process of designing a medical record abstraction form for a RCR study.

Methods: We conducted a targeted review of the methodological literature on published guidance for developing abstraction forms for RCR studies. Sources identified from this search were reviewed, and constructs relevant to the development of abstraction forms were identified. Key considerations and recommendations deemed relevant by the abstract authors were highlighted for each construct. The resulting information was synthesized into a methodological framework for the development of abstraction forms.

Results: Limited guidance exists on best practices for developing medical record abstraction forms for RCR studies. From the publications found, four constructs were identified for the framework: design, abstraction form format, data definitions, and pilot testing. For each construct, we highlighted elements to be considered throughout the design of an abstraction form, including: ensuring the data to be collected is aligned with research objectives, early involvement with study sites, pre-defining variables and plausible answers, designing the form to secure patient privacy, and pilot

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testing the abstraction form to confirm the reliability of data collection.

Conclusions: The conceptual framework discussed serves as a tool to enhance the quality and accuracy of data collected from patient medical charts. This framework can also serve as a starting point for the development of formal methodological guidelines specific to RCR studies.

279. Validity of the Prescriber Information in the Danish National Prescription Registry

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Background: The variable denoting the prescriber in the Danish National Prescription Registry (DNPR) holds important information which has great potential in drug utilization studies. However, the validity of the variable has been questioned.

Objectives: The aim of this study was to measure the validity of the prescriber information recorded in the DNPR.

Methods: The prescriber information recorded in the single pharmacy's electronic dispensing system was considered to represent the prescriber information recorded in the DNPR. Further, the problem of validity of the prescriber information pertains only to non-electronic prescriptions, as these are manually entered into the electronic dispensing system. The recorded prescriber information in the electronic dispensing systems was thus validated against information from a total of 2,000 non-electronic prescriptions at five Danish community pharmacies. The validity of the recorded prescriber information was measured at the level of the individual prescriber and the prescriber type, respectively.

Results: The proportion of non-electronic prescriptions with incorrect registrations in the pharmacies' electronic dispensing systems was 22.4% (95% Confidence Interval (CI): 20.6-24.3) when considering individual prescriber identifiers and 17.8% (95% CI: 16.1-19.5) when considering prescriber type. When excluding prescriptions specifically registered as 'missing prescriber identifier', the proportions decreased to 9.5% (95% CI: 8.2-11.0) and 4.1% (95% CI: 3.2-5.1), respectively. The positive predictive values for the classification of prescriber types were in the range 94.0%-99.2%, while the sensitivity ranged between 64.6%-91.8%. With a maximum of 14% non-electronic prescriptions of all prescriptions in the DNPR in year 2015, this corresponds to correct classification of prescriber types in the DNPR of at least 97.5%.

Conclusions: The prescriber information in the DNPR was found to be valid, especially in recent years. Researchers should be aware of the low sensitivity towards prescriptions from private practicing specialists.

280. Validation of the Recording of Key Medical Conditions in General Practice Data

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Background: In a proactive vaccine pharmacovigilance strategy a range of serious conditions that might be reported in temporal association with the vaccine are pre-identified and evaluated from the start of a new programme using sequential monitoring. In order to place spontaneous reports into context, age and gender specific background event rates are needed. Electronic healthcare record databases can be used to estimate these.

Objectives: To assess the completeness and validity of the recording of key conditions of interest for vaccine pharmacovigilance in general practice data.

Methods: The conditions of interest were Guillain-Barre syndrome (GBS), facial palsy, chronic fatigue syndrome (CFS), encephalitis, optic neuritis, myasthenia gravis, transverse myelitis, narcolepsy and vasculitis. Using the cohort of patients with linked integrated Hospital Episode Statistics (HES) data and primary care data from the Clinical Practice Research Datalink (CPRD), incident cases for each condition were identified in HES 10/1998- 09/2011 and in CPRD 04/1998-03/2012. The proportion of patients with an event recorded in HES who had a corresponding CPRD record, and vice versa, was stratified by age and year and the distribution of times between the two records summarised.

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Results: Over 48,000 incident events were identified in HES and over 47,000 in CPRD. CPRD identified more cases than HES of Bell's palsy, CFS and optic neuritis only. Myasthenia gravis, GBS, and transverse myelitis were the most commonly validated events in both data sources. Just 10% of CFS cases identified in CPRD were found in HES while 9% of narcolepsy cases and 4% of encephalitis in HES had a corresponding CPRD record. GBS, Bell's palsy, and encephalitis were the events most commonly recorded on the same day in the two databases although for all events a high proportion had differences in the date of recoding of 3 + months.

Conclusions: There is considerable variation in the completeness of CPRD recording in comparison to HES. The process by which each medical condition presents and is investigated and diagnosed at different ages plays a part in establishing which data source would be most suitable in estimating background event rates.

281. Claims-Based Algorithms Greatly Impact the Estimated Incidence of Serious Angioedema Among Heart Failure (HF) Patients in the United States (US)

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Background: How outcomes are defined can greatly impact their estimated incidence. We explored how different algorithms for serious angioedema varied its estimated incidence within a population of HF patients using a US claims database.

Objectives: To assess how the estimated incidence of serious angioedema in HF patients can vary using three different claims-based algorithms.

Methods: We conducted a cohort study of adult HF patients using the PharMetrics Plus claims database from 1 January 2007 to 31 March 2015. Follow-up began on the index HF date (i.e., the earliest of either a hospitalization or the first of at least 2 outpatient visits with a HF diagnosis) and ended on the earliest occurrence of a serious angioedema event (identified by a hospital discharge ICD-9 code 995.1 for angioedema,), loss to follow-up, or study end. We estimated crude incidence rates using three algorithms based on the position of the angioedema diagnosis code on the hospital discharge claim and presence of procedure codes indicative of airway obstruction: 1) diagnosis code only in the primary position, 2) diagnosis code only in any position, and 3) diagnosis code in any position with a procedure code indicative of airway obstruction.

Results: The study included 117,882 HF patients (mean age: 59.5 years; 55.5% male) with an average follow-up time of 31.6 months. The incidence of serious angioedema was 0.28 (95% confidence interval [CI], 0.23–0.35) per 1,000 patient-years (PYs) when diagnoses in the primary position were considered, 0.60 (95% CI, 0.52–0.69) per 1,000 PYs when diagnoses in any position were considered, and 0.54 (95% CI, 0.46–0.63) per 1,000 PYs when diagnoses in any position with a procedure code were considered.

Conclusions: Our results show that the estimated incidence of serious angioedema among HF patients can vary by over two-fold when different claims-based algorithms are used. Given the estimates considering diagnosis codes in any position or incorporating a procedure code, we suggest using a broad algorithm to capture more potential cases. Case validation should also allow for a more robust incidence estimate.

282. Patterns and Predictors of Having a Colonoscopy Following Drug Initiation in Older US Adults with Diabetes

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Background: Drug initiation is a complex decision process involving healthcare system encounters and evaluation of patients' health status. This could lead to screening and diagnostic work ups with increased cancer incidence following drug initiation. Assessing

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colonoscopy patterns following drug initiation is important in cancer comparative effectiveness studies.

Objectives: To assess the trend and predictors of colonoscopies following drug initiation among older US adults initiating two second line antihyperglycemic drug classes, dipeptidyl peptidase-4 inhibitors (DPP-4i) and thiazolidinediones (TZD).

Methods: Among Medicare beneficiaries with parts A, B and D coverage, we identified a cohort of diabetic patients initiating DPP-4i and TZD from 2007-2013, requiring a 12 month washout period. Initiators with any cancer related claims or colonoscopies during these 12 months were excluded. Patients were required to survive for 6 months following drug initiation. We assessed monthly probabilities of first colonoscopy in the six months following drug initiation and compared probabilities between drug classes using log binomial regression adjusting for demographics, clinical and health care characteristics.

Results: Monthly risks for colonoscopy were highest in the first post-index month (0.84%) and lowest in the third (0.71%). The probability of colonoscopy during the first post-index month was slightly lower in DPP-4i (0.79%) than TZD initiators (0.92%). The trend remained for the first 6 months. The overall 6 month risk of colonoscopy was 4.3% in DPP-4i versus 4.6% in TZD initiators with adjusted relative risk 1.00 (95% CI: 0.93, 1.09). Black versus white race, baseline hospitalization, gastrointestinal diseases and fecal occult blood testing were associated with higher post-index colonoscopy risk.

Conclusions: In diabetic patients requiring a second line treatment, the probability of having a colonoscopy is highest in the first month after drug initiation and essentially the same between DPP-4i and TZD initiators. Understanding screening or diagnostic procedures after drug initiation is important to avoid potential detection bias in comparative effectiveness research.

283. Feasibility of Using Procedural Code Combinations for Identifying Conversion from Video Assisted Thoracic Surgery (VATS) to Thoracotomy

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Background: Surgical conversion in approach is an important surgical outcome in thoracic lobectomy and is strongly correlated with increasing operating room time(ORT), length of stay(LOS), and hospital costs. Currently only a diagnosis code(V64.42) exists which may be underutilized.

Objectives: To evaluate the feasibility of procedure code combinations to identify conversions in lobectomy.

Methods: All elective lobectomies from 2008-2014 were identified in the Premier Perspective® Database. The lobectomies were categorized by approach: OPEN (thoracotomy only), VATS-SUCCESS (VATS without VATS-CONVERSION), and VATS-CONVERSION (either the presence of V64.42 or the simultaneous combination (COMBO) of both VATS and OPEN lobectomy). Incidence of VATS-CONVERSION was calculated for all non-OPEN procedures. ORT(mins), hospital costs(2014USD), and LOS(days) differences between VATS-CONVERSION identification methods, COMBO and V64.42, in reference to OPEN and VATS-SUCCESS, were evaluated using Generalized Estimating Equations (GEE) models controlling for patient demographics and hospital clusters.

Results: A total of 22,947 patients were identified: OPEN(13,114), VATS-SUCCESS(8,500), and VATS-CONVERSION(1,333). VATS-CONVERSION incidence was 13.5%(11.2% V64.42, 2.3% COMBO). Mean ORT was 241.0mins (SD = 167.1). Adjusted mean ORT for COMBO(266.6) was significantly different than other approaches but had a smaller difference compared to V64.42(281.3) as opposed to OPEN (248.1) and VATS-SUCCESS (240.7). Overall mean costs were $26,778 (SD = 81,324). Adjusted costs were significantly higher for COMBO($31,376) compared to VATS-SUCCESS($25,759); however, there was no difference to V64.42($30,951, $p = 0.80$) or OPEN($27,834 $p = 0.05$). Adjusted mean LOS for COMBO(8.3, SE = 0.5) was significantly longer than VATS-SUCCESS(6.3; $p < 0.01$) and no different than V64.42 (8.6; $p = 0.60$) or OPEN(8.3; $p = 0.90$).

Conclusions: Identification of conversion based on procedure code combinations appears feasible based upon similarities with V64.42 on cost and LOS while

small differences were seen in ORT. Advanced classification methods are needed to confirm these initial findings.

284. Influenza Vaccine Effectiveness Estimates in the Dutch Population from 2003 to 2014: The Test-Negative Design Case-Control Study with Different Control Groups

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Background: The influenza vaccine effectiveness (IVE) varies each year and for the different circulating virus (sub)types/lineages. A commonly used study design to obtain IVE estimates is the test-negative design (TND) case control study, however there is no consensus about the definition of the control patients.

Objectives: To estimate the IVE over eleven seasons in the Netherlands (from 2003/2004 through 2013/2014) using the three most commonly applied definitions of TND control groups.

Methods: We conducted a TND study using the Dutch Sentinel Practices Primary Care Database hosted by the NIVEL which includes data from patients who consulted the GP for an episode of influenza-like illness (ILI) or acute respiratory infection (ARI) with known influenza vaccination status. Cases were patients who tested positive for influenza virus A or B by PCR, and controls were grouped into those who tested (1) negative for influenza virus, (2) negative for influenza virus, but positive for respiratory syncytial virus, rhinovirus or enterovirus, and (3) negative for these four respiratory viruses. Using the three different control groups we estimated the IVE over all seasons, pooled VE for influenza vaccine partial/full matched and mismatched seasons and the individual seasons using generalized linear mixed model and multiple logistic regression models.

Results: The for age, ILI/ARI diagnosis, chronic disease and respiratory allergy adjusted IVE over all seasons was 29% (95% CI 10 – 45), 54% (95% CI 35 – 67) and 22% (95% CI -1 – 39) for control group 1 to 3, respectively. In subgroup analyses IVE estimates were in general the highest when using control group 2, which is in line with findings of previous effectiveness studies.

Conclusions: When using the control group 2 definition, IVE estimates are more consistent with previous evidence, likely due to limiting false-negative controls.

285. Study Design and Analytic Approach for Research on the Effectiveness of Childhood Vaccine Schedules

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Background: Important questions exist regarding the real-world effectiveness of childhood vaccine schedules. However, optimal approaches to studying this complex issue are unclear.

Objectives: In the context of a study of the 3-dose pentavalent rotavirus vaccine (RV), we describe a possible design and analytic approach to estimate the effectiveness of different RV schedules.

Methods: Using a large US claims database (2007), we performed an observational study to emulate a hypothetical randomized trial comparing infants randomized to 3 different RV protocols: 1) no RV; 2) partial RV series; or 3) full RV series. We identified infants who received dose #1 of DTaP between 38-92 days of age; requirement of timely administration of DTaP, which has high coverage rates (≥95%), aims to minimize unmeasured confounding. We excluded infants with RV prior to DTaP. We created 3 separate cohorts (C1-C3) to correspond to the 3 protocols. Initially, infants contributed person-time to each cohort. Censoring occurred when RV receipt or non-receipt deviated from the cohort-specific protocol. Infants receiving RV within 1-14 days after DTaP could be censored from C1 or reassigned to C2, at the risk of

selection bias. Informative censoring was addressed with inverse-probability of censoring weighted (IPCW) estimation.

Results: Among 148,608 infants who received DTaP, 91,041 (61.3%) received RV on the DTaP date, 331 (0.2%) received RV within 1-7 days after DTaP, and 208 (0.1%) received RV within 8-14 days after DTaP. Infants who did and did not receive dose #1 of RV differed by maternal age, sibling number, provider type, health plan, and geographical area. During follow-up, 4138 infants in C1 were censored at dose #1 of RV; 79,815 infants in C2 were censored at dose #2 of RV; and 19,101 infants in C3 were censored when they did not receive dose #2 or #3 of RV by 153 or 214 days of age, respectively. The percentage of infants censored from C3 was sensitive to these dates.

Conclusions: Innovative study designs informed by sensitivity analyses are needed to examine the effects of complicated childhood vaccine schedules. IPCW estimation is a possible analytic approach that warrants further study.

286. Investigating the Assumptions of the Self-Controlled Case Series Method

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Background: The self-controlled case series (SCCS) method is used when temporal association and control of fixed confounders are relevant.

Objectives: Two key assumptions of the SCCS method are that events do not influence subsequent exposures and the length of observation periods. We aim to provide tests to investigate the robustness of results obtained using SCCS when the validity of these assumptions are questionable.

Methods: For the assumption that events do not influence subsequent exposures, we propose fitting standard SCCS models with and without a 'risk' period prior to exposure, of varying lengths, and comparing via a likelihood ratio test. This allows the length of dependence to be explored. Tests are applied to data on mumps, measles, rubella (MMR) vaccination and idiopathic thrombocytopenic purpura (ITP).

For the assumption that events do not influence the length of observation periods, we propose that cases who died within the planned observation period are identified using an indicator variable. Then standard SCCS models may be fitted with and without interaction terms using this indicator and compared using a likelihood ratio test. The test is applied to data on antipsychotics and stroke.

We also explore the use of graphical displays.

Results: We will present results of simulation studies that demonstrate when violation of these assumptions make an important difference to study results.

For the MMR and ITP data, the tests provided weak, but not significant, evidence that hospital admission for ITP delays subsequent MMR vaccination for up to 2 months. This did not have a major impact on the results, or on the conclusion that MMR vaccination is positively associated with ITP.

For the antipsychotics and stoke data, the test showed that there is evidence of event-dependent observation periods. However, this does not always impact and alter conclusions.

Conclusions: If SCCS study results are not found to be robust to key assumptions, extensions to the SCCS method may be applied in certain circumstances, though these are complex. Some simple methods to test the validity of key assumptions of the SCCS model have been developed that can easily be implemented within the standard SCCS framework.

287. Withdrawn by Author

288. Effect-Modifiers of Antipsychotic Drugs Effect, in Schizophrenia Treatment

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Background: An efficacy-effectiveness gap may exist when effect-modifiers of the treatment ("drivers of effectiveness" – DOE) fail to be adequately captured in

clinical trials. These DOE should be explored to better design clinical trials.

Objectives: To identify effect-modifiers of antipsychotic drugs, in schizophrenia treatment.

Methods: Data were retrieved from the CGS observational cohort study, including 1859 schizophrenia inpatients and outpatients aged 15-65 years old through 177 centres in France. Patients were followed-up at 3, 6, 9 and 12 months.

Patients who initiated or switched APD were identified and schizophrenia symptoms evolution was measured 3 to 6 months later, using the BPRS-18 scale (ΔBPRS).

First, potential DOE of APD were identified through a focused literature search, which was reviewed by 3 schizophrenia specialized psychiatrists. Five DOE were short-listed: (1) shorter duration of illness, (2) higher level of negative symptoms, (3) poor adherence, (4) cannabis/drug use and (5) tobacco use.

Effect modification was assessed using sub-group analyses, with comparisons of the ΔBPRS in the 2 strata of each DOE. Two-sided Welch t-tests were used with a "non-conservative" type-I error $\alpha = 0.2$. Multivariate analyses were not performed due to limited sample size.

Results: Out of 1859 schizophrenia patients, 116 patients initiated drug B, 272 patients initiated drug D and 204 patients initiated drug K. Other drugs were initiated by too few patients. The mean decreases in BPRS were: -7.2 points (SD = 16.3) in "drug B initiators", -7.5 points (SD = 15.3) in "drug D initiators" -3.9 points (SD = 14.1) in "drug K initiators". The level of symptoms improvement was higher in patients with a "higher level of negative symptoms" for all drugs ($p < 0.012$) and "poorer adherence", for drugs D and K ($p < 0.013$). The level of symptoms improvement was also better in patients who did not smoke, however not significantly. Cannabis use was not an effect-modifier, in all drugs.

Conclusions: Overall, "adherence", "tobacco smoking" and "negative symptoms" may be drivers of effectiveness. These factors should be adequately captured and explored in pre-launch clinical trials to avoid an efficacy-effectiveness gap.

289. A Systematic Literature Review on the Efficacy-Effectiveness Gap: Comparison of Randomized Controlled Trials and Observational Studies of Glucose-Lowering Drugs

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Background: Beneficial effects of drugs can be divided into efficacy and effectiveness. An understanding of the efficacy-effectiveness gap is important for patients, health care professionals, payers, regulators and the pharmaceutical industry to provide effective treatments.

Objectives: to identify a potential efficacy-effectiveness gap, and possible explanations (drivers of effectiveness) for differences between results of randomized, controlled trials (RCTs) and observational studies investigating anti-diabetic drugs.

Methods: A systematic literature review of studies comparing glucagon-like peptide-1 analogues (GLP-1) with insulin or comparing dipeptidyl peptidase-4 inhibitors (DPP-4i) with sulfonylurea, all with change in glycated haemoglobin (HbA1c) as outcome. Information on baseline characteristics of the study population, publication year, study duration, number of patients and quality of observational studies were extracted.

Results: Twelve RCTs and six observational studies comparing GLP-1 with insulin, and 19 RCTs and four observational studies comparing DPP-4i with sulfonylurea were finally included. No differences were observed in baseline characteristics of the study populations (age, sex, BMI, time since diagnosis, HbA1c) or effect sizes across study designs. No patterns were observed when plotting effect estimates against baseline characteristics of the study population, publication year, study duration or number of patients, neither within nor across RCTs and observational studies. The quality of the identified observational studies was generally low.

Conclusions: Neither potential drivers of effectiveness nor an efficacy-effectiveness gap were identified. However, the low quality of the identified observational studies may have hidden a true efficacy-effectiveness gap.

290. Interim Analyses in Prospective Observational Studies of Medical Product Safety

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Background: Interim analyses are playing an increasingly important role in prospective observational studies of medical product safety. Based on the interim analysis results[1] of a study on the risk for bladder cancer with pioglitazone, FDA issued a safety communication[2] and updated the label in 2011, advising against use of pioglitazone in patients with active bladder cancer.

Objectives: To discuss methods and key considerations for conducting interim analyses in prospective observational studies to improve study design and facilitate regulatory decision-making without compromising study integrity.

Methods: The goals of interim analyses include (1) to determine whether the study can or should stop early due to an emerging safety signal, or be extended or expanded due to low statistical power, and (2) to facilitate the re-evaluation of the feasibility of a study with a specific design. Blinding in observational studies refers to blinding to study outcomes by treatment group throughout the study period among investigators, stakeholders and regulators. We discuss the advantages and disadvantages of various approaches to interim analyses. We use a study on the risk of acute nonarteritic anterior ischemic optic neuropathy with phosphodiesterase type 5 inhibitors[3] to illustrate how the pre-defined goals can determine the frequency, blinded vs. unblinded, study power and type 1 error adjustment of the interim analyses. Given the nature of the study (rare study outcome and unique case crossover design), the goal of the interim analyses was to re-evaluate the exposure rate in the control window which determined study power and sample size needed. Though blinded analyses maintain study integrity, they cannot meet such goal. Unblinded interim analyses were properly used; and appropriate access to the unblinded interim results was carefully considered to ensure study integrity.

Conclusions: The goals and methods of interim analyses in prospective observational studies are to be planned with care as they can impact study integrity and their contribution to the total body of evidence on medical product safety.

291. Incorporating Clinical Factors That Are Inconsistently Recorded in Electronic Health Records to Improve Confounding Adjustment in Claims-Based Comparative Effectiveness Research

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Background: Measurement of patient clinical characteristics can help control residual confounding in observational comparative effectiveness research (CER), but electronic health record (EHR) data are challenging to incorporate in claims-based analyses due to inconsistently recorded confounding factors.

Objectives: The aim of this study was to determine the impact on confounding control when EHR covariates subject to missing data are incorporated into propensity score (PS)-adjusted analyses using two example cardiovascular disease cohorts.

Methods: In two separate claims-derived cohorts (statin and antiplatelet initiators), we computed the PS using claims covariates and complete EHR data elements in validation subsets, then added EHR covariates that were partially missing and multiply-imputed. We measured the improvement in exposure prediction and in EHR covariate balance by incorporating the imputed EHR data in the PS. We compared hazard ratios obtained from PS-calibrated analyses with and without addition of these covariates.

Results: Treatment prediction and EHR covariate balance both improved with the addition of multiply-imputed EHR covariates. Compared to an observed null association with a PS using only fully-observed claims

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and EHR covariates, we observed a protective association of combination statin therapy after including imputed values of missing clinical covariates (hazard ratio of 0.82). There was no change in the observed null association in the antiplatelet cohort.

Conclusions: Similar to results from the recent IMPROVE-IT trial, we uncovered an apparently protective association of combination statin use (ezetimibe plus simvastatin) versus statin monotherapy when incorporating missing EHR covariates. The value of incorporating highly missing EHR covariates to improve confounding adjustment in claims-based studies is questionable.

292. Withdrawn by Author

293. Withdrawn by Author

294. Early Life Antibiotic Exposure Is Associated with an Increased Risk of Atopic Eczema and Hay Fever

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Background: Several studies suggested that early life exposure to antibiotics is associated with an increased risk of developing allergies later in life, but results are inconsistent.

Objectives: We aimed to systematically review and quantify the relationship between early life exposure to antibiotics and the risk of atopic eczema (dermatitis) or hay fever (allergic rhinitis).

Methods: PubMed and Web of Science databases were searched for observational studies published from January 1966 through November 11, 2015. Studies were included that assessed the association between antibiotic consumption during the first 2 years of life and the risk of later eczema or hay fever. Separate meta-analyses were performed to assess the risk estimates for cohort studies, cross sectional studies and case control studies. Furthermore, in subgroup analyses the effect of child's age at the time of antibiotic use/diagnosis of allergies have been analyzed.

Results: Twenty-two studies (including 394,517 patients) were selected to study the risk of eczema and 22 studies (including 256,609 patients) to study the risk of hay fever. In all separate meta-analyses of the distinct study designs, those who were exposed to antibiotics early in life were found to have a statistically significantly increased risk of eczema and hay fever. The summary ORs for risk of eczema were 1.24 (95% CI, 1.09-1.41; I2: 60.0%) in the meta-analyses of the cohort studies (n = 50,824); 1.41 (95% CI, 1.33-1.49; I2: 0.0%) in the cross sectional studies (n = 217,752), and 1.15 (95% CI, 1.01-1.42; I2: 79.5%) in the case control studies (n = 125,941). The summary ORs for risk of hay fever were 1.18 (95% CI, 1.01-1.37; I2: 74.3%) in the cohort studies (n = 46,540); 1.56 (95% CI, 1.29-1.90; I2: 63.6%) in cross sectional studies (n = 27,608), and 1.14 (95% CI, 1.04-1.26; I2: 64.8%) in the case control studies (n = 182,461). In subgroup analyses, there was no statistically significant effect of the patient's age at both time of antibiotic use and time of allergy diagnosis on these associations.

Conclusions: Early life exposure to antibiotics is related to an increased risk of both atopic eczema and hay fever later in life.

295. Withdrawn by Author

296. Analysis of Splitting Sustained-Release, Enteric-Coated Drugs in Pediatric Patients: HIRA-PPS

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Background: Even though decreased efficacy or unsure safety and stability of specific formulation, some prescriptions which need to split and grind tablets are prescribed. This could be unsafe and uneffective if those tablets or capsules are sustained-release (SR) and enteric-coated (ER) forms.

Objectives: This study was performed for giving information about the splitting SR and ER drugs in pediatric patients in Korea to physician in order to prescibe appropreate dosage and drug form.

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Methods: This study is to analyze of frequency of once dose, diagnosis, medical departments for splitting prescriptions of SR and ER drugs using by Health Insurance Review Assessment Service (HIRA) pediatric sample data 2011.

Results: Among 3,343 of prescriptions in 40 kinds about SR drugs, most frequently splitting prescription was clarithromycin 500 mg ER with 2,331 cases (69.7%), followed by acetaminophen ER 650 mg ER with 362 cases (10.8%). The proportion of antibiotics are occupied very high at 72.7%. Among 11,768 of prescriptions in 14 kinds about enteric-coated (EC) drugs, most frequently splitting prescription was bromelain 45 mg EC with 7,390 cases (62.8%), followed by bromelain 100 mg EC with 3,529 cases (30.0%). Compared once dose, 0.50 splitting dose was most high in toddler, child, and adolescent patient groups, 0.33 splitting dose was most high in infant. Most frequently diagnosis for splitting prescription was acute bronchitis with 3,725 cases (13.7%). The principal diagnosis of accumulated percentage at 72.1% was different types of upper respiratory infections, asthma, and pneumonia. Most frequently department for splitting prescription was pediatrics with 5,693 cases (37.7%), followed by otolaryngology 3,154 cases (20.9%), internal medicine 2,516 cases (16.7%) respectively.

Conclusions: There is a lot of splitting prescription of SR and ER drugs, because of lack of alternative agent in pediatric patients, and absence of adequate review of drug using evaluation. For more effective and safe use of pediatric medications, it is necessary to development of DUR system, as well as education for physicians, pharmacists and pediatric patients.

297. Differences Between Genders in Antipsychotic Medication Among Children and Adolescents – Patterns in Use and Underlying Mental Disorders

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Background: The prevalence of antipsychotic drug use among children and adolescents has increased during the last 10-20 years. Antipsychotic drugs have different indications but there is lack of knowledge on the disorders underlying antipsychotic drug use in the pediatric population.

Objectives: To study prevalence of antipsychotic drug use, type of prescribed drugs and presence of mental disorder diagnoses among 0-18 year old boys and girls in Norway in 2010.

Methods: Linked data from nationwide health registries on prescription drugs in 2010 (Norwegian Prescription Database) and mental disorder diagnoses in 2008-2012 (Norwegian Patient Register) were used to study prevalence of antipsychotic drug prescriptions, type of drugs, underlying diagnoses, and distribution of drugs per diagnostic category and gender.

Results: A total of 2,008 (0.17%) children and adolescents were prescribed antipsychotic drug during 2010. Of these, 92.4% had at least one mental disorder diagnosis. Risperidone was the most frequently prescribed drug among boys (57.4%) and girls (32.3%). In girls quetiapine (27.4%) was nearly as prevalent as risperidone, while aripiprazole was the second most prescribed drug to boys (19.4%). Hyperkinetic (49.9%) and autism-spectrum disorder (27.1%) were the most common mental disorder diagnoses among boys using antipsychotics. Anxiety (41.5%) and depressive disorders (33.6%) were the most common in girls. A diagnosis of schizophrenia-like psychosis was the underlying diagnosis in 11.1% of the boys and 18.2% of the girls. More than half of boys who used risperidone or aripiprazole were diagnosed with hyperkinetic disorder. More than half of girls who used quetiapine had a diagnosis of either anxiety and/or depressive disorder.

Conclusions: The prevalence of antipsychotic drug use among children and adolescents is low, and the drugs are primarily used for non-psychotic mental disorders such as hyperkinetic, anxiety or depressive disorders.

298. Psychiatric Medication Use Before and After the Onset of Type 1 Diabetes in Children and Adolescents: A Population-Based Cohort Study

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Background: Several studies showed a bidirectional association between type 2 diabetes and psychiatric disorders in adults. There is limited information available about the association of type 1 diabetes (T1D) and psychiatric disorders in children and adolescents.

Objectives: To assess the extent of psychiatric medication use before and after the onset of T1D in children and adolescents compared with a reference cohort without T1D.

Methods: A population-based cohort study was conducted in the Dutch PHARMO Record Linkage System. All children and adolescents < 19 years) with at least two insulin dispensings between 1999 and 2009 were identified as a T1D cohort (N = 925) and matched with an up to four times larger diabetes-free reference cohort (N = 3591) by age and sex. The period prevalences of psychiatric medication use (psycholeptics (ATC N05) and psychoanaleptics (ATC N06)) were calculated by dividing the number of patients with at least one dispensing by the number of patients available in the cohort during that time. Prevalences were calculated from 5 years before until 5 years after the onset of T1D (the index date in both cohorts) and stratified by age, sex, medication subgroup, and before/after the onset of T1D.

Results: The mean age of the study participants was 10.1 years and 51% were boys. The 5-year prevalence of psychiatric medication use before the index date was significantly higher in the T1D cohort than in the reference cohort (7.2 vs. 4.7%, respectively, p = 0.002). The same pattern was observed for the period after developing T1D (10.4 vs. 7.9% in the T1D and reference cohort respectively, p = 0.015). In both cohorts adolescents (15-19 years) and boys had higher prevalences of psychiatric medication use. This increased prevalence of psychiatric medication use both before and after the index date in T1D cohort was mainly driven by an increased use of psycholeptics (mainly anxiolytics).

Conclusions: Children with T1D were more likely to use psychiatric medication in the years before and after the onset of type 1 diabetes. This increased use was mainly driven by psycholeptics both before and after onset of T1D.

299. Withdrawn by Author

300. Antidepressant Drug use Among Adolescents in Norway from 2004 to 2013- A Population-Based Register Study

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Background: After the warnings in 2004 that use of antidepressants may increase suicide risk in adolescents, the use of drugs to treat depression in this age group has been debated. However, there have been few studies of time trends in use and psychiatric morbidity.

Objectives: To study trends and patterns in use of antidepressants among adolescents, including contact with specialist health care, and use of other psychotropic drugs in incident users.

Methods: The 1-year prevalence of antidepressant drug use among 13–17 year olds in Norway during 2004–13 was analyzed using data from the nationwide Norwegian Prescription database. Use of other types of psychotropic drugs and registered contacts with specialist health care, as registered in the Norwegian Patient Register, were analyzed for incident antidepressant users in 2012.

Results: The 1-year prevalence of antidepressant drug use increased from 6.4/1000 to 9.1/1000 during 2004–13, with the steepest increase from 2010 onwards, particularly among girls. The highest prevalence was found in 17-year-old girls (27.5/1000 in 2013 - an increase from 16.7/1000 in 2009). Of incident users in 2012, 78.4% were prescribed a selective serotonin reuptake inhibitor. Of incident antidepressant drug users in 2012, 78.7% had received a diagnosis of a mental disorder and/or were registered for child and adolescent specialist mental health care.

The most common types of psychotropic co-medications were melatonin (24.6%), antipsychotic drugs (13.2%), stimulants (8.8%) and anxiolytics (6.0%).

Conclusions: Use of antidepressants among adolescents has increased over the last 3–4 years, particularly among 16- to 17-year-old girls. Three out of four incident antidepressant users in 2012 had been referred to

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specialist mental health care, which indicates that antidepressant drug therapy is used by the most severe cases.

301. Proceedings of a Workshop from the USFDA: Evaluation of Long-Term Neurocognitive Development in Pediatrics

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Background: Safety information derived from adults on the effects of products on neurocognitive function lack information from pediatric clinical trials about the exposure of a rapidly developing brain to therapy. This workshop discussed the identification of signals from animals and pediatric clinical trials that warrant further clinical investigation and the selection of assessment tools that may be predictive of neurocognitive and behavioral outcomes in children.

Objectives: The goals of this workshop were to:

1. Inform investigators of the potential utility of existing measurement standards.
2. Promote further research and development of animal models to predict and assess possible medical product related neurocognitive and behavioral changes.
3. Discuss strategies to improve the evaluation of neurocognitive outcomes in long-term safety studies.

Methods: Experts in the field of pediatric neurocognitive development and evaluation participated in an FDA-sponsored public workshop held on April 16-17, 2015.

Results: A consensus emerged concerning challenges in the evaluation of pediatric long-term neurocognitive and behavioral outcomes. Challenges in identifying appropriate norms for tools to assess neurocognitive and behavioral development in childhood were identified. The NIH Toolbox is an example of an attempt by researchers to select a standardized battery of assessment tools to facilitate cross-study comparisons. A paucity of pediatric neuropsychologists or developmental psychologists have been trained in clinical trial methodologies. A future goal is to better reconcile results from neuroimaging, genetic research, and biomarkers with cognitive test performances in children. Safety signals from nonclinical animal studies will be important to include in future safety assessments.

Conclusions: Reliable and valid tools and biomarkers to assess pediatric neurocognitive and behavioral development are needed. Development of standardized measurements and tools in the assessment of neurocognitive and behavioral development in infants and children should be an important priority for stakeholders involved in drug and biological product development.

302. Drug Utilization Among Norwegian Children Diagnosed with Chronic Fatigue Syndrome / Myalgic Encephalomyelitis

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Background: Chronic fatigue syndrome (CFS), or myalgic encephalomyelitis (ME), is a debilitating disorder with unknown disease mechanisms.

Objectives: To describe dispensed drugs for children diagnosed with CFS/ME before and after their diagnosis.

Methods: We identified 1686 children (age < 18 y) with a specialist health care diagnosis of CFS/ME by means of data from the Norwegian Patient Register (NPR) 2008-2014. The NPR is a mandatory register covering all Norwegian hospitals. For each child with CFS/ME we randomly selected 20 children matched for sex, birth year, and county from the National Registry. We used the date of the CFS/ME diagnosis as index date for each case/control set. Information on all dispensed antiinfectives for systemic use (ATC code J01) and psychoactive prescription drugs (ATC code N) before and after the index date was obtained from the Norwegian Prescription Database. We used conditional logistic regression to obtain odds ratios (ORs), using children in the control group as reference.

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Results: In the 1 year period leading up to the index date, antiinfectives were dispensed for 39.7% of children in the CFS/ME group and 17.0% of children in the control group (OR 3.4, 95% CI: 3.0-3.8). Corresponding figures for psychoactive drugs were 32.4% and 7.2%, respectively (OR 6.5, 95% CI: 5.8-7.2). In the 1 year period after the index date, antiinfectives were dispensed for 29.9% of children in the CFS/ME group and 18.1% of children in the control group (OR 2.0, 95% CI: 1.8-2.3). Corresponding figures for psychoactive drugs were 42.4% and 8.5%, respectively (OR 8.5: 95% CI: 7.7-9.5). The most frequently dispensed psychoactive drug in CFS/ME was melatonin (13.6% before the index date and 27.0% after). This drug was rarely dispensed in the control group <1%) (before: OR 17.6, 95% CI: 14.6-21.1, after: OR 35.2, 95% CI: 30.0-41.3).

Conclusions: Children with CFS/ME are far more often prescribed antiinfectives and psychoactive drugs than children without CFS/ME. Melatonin was dispensed to more than a quarter of patients with CFS/ME, but rarely used among children without CFS/ME.

303. Attention Deficit Hyperactivity Disorder (ADHD) in Under 19 s: Prevalence and Predictors of Medication Use in Primary Care

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Background: Pharmaceutical treatment for ADHD is not appropriate in all cases and should not be commenced without specialist input. However, rising prescription rates have raised concerns that ADHD is being treated pharmaceutically as a matter of course in UK primary care.

Objectives: The study assessed what proportion of children and adolescents diagnosed with ADHD received a primary care prescription for a licensed ADHD medication. It also determined the average time between ADHD diagnosis and the start of pharmaceutical treatment in primary care, and sought to identify predictors of pharmaceutical treatment.

Methods: The study used electronic health records from the Clinical Practice Research Datalink (CPRD). The study cohort comprised patients with a documented diagnosis of ADHD before the age of 19, between 1/1/2004 and 31/12/13. Treated patients also had a documented prescription for an ADHD medication during this period. The time between diagnosis and first treatment was calculated for each treated patient. Logistic regression assessed if patients' probability of receiving pharmaceutical treatment was influenced by gender, deprivation level, the nation in which their general practice was based and their age at diagnosis.

Results: Only 56.5% of patients with a diagnosis of ADHD had a documented primary care prescription for a licensed ADHD medication. The median interval between diagnosis and first prescription for an ADHD medication was 84 days (IQR = 21-258 days, range = 0-3433 days). Scottish patients had significantly higher odds of receiving treatment than English patients (OR 1.54 [95% CI 1.33 – 1.79]), and patients' age at diagnosis and deprivation level also impacted their odds of receiving medication in primary care. However, the difference in treatment rates between the least deprived and most deprived patients was not statistically significant. Gender did not significantly influence patients' odds of receiving medication.

Conclusions: A diagnosis of ADHD was not always followed by a prescription for a licensed ADHD medication. Several factors appeared to influence patients' odds of receiving pharmaceutical treatment in primary care.

304. Out of Hospital Cardiovascular Medication Use in Children with Congenital Heart Defects

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Background: Clinical trials on cardiovascular drugs form a particular challenge in children. Thus, many drugs used to treat children with congenital heart defects (CHD) are used off-label. Few data exist on the out of hospital use of cardiovascular medication in children with CHD.

Objectives: To determine the proportion of children with CHD who at some point uses cardiovascular medication in an out of hospital setting.

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Methods: We used data from population-based medical registries covering all Danish hospitals to identify all subjects who were born and diagnosed with CHD in Denmark between 1995 and 2012, and who received a diagnosis of CHD before the age of 15. Unique personal identifiers permitted unambiguous data linkage and complete follow-up. Out of hospital cardiovascular medication use (ATC code: C0x) was identified from nationwide prescription data, covering all prescriptions filled at Danish pharmacies since 1995. Follow up was continued from birth until filling of a prescription for cardiovascular medication, death, emigration, or Jan. 1, 2013, whichever came first. We computed cumulative incidences of first time cardiovascular medication use before age 15 years, overall and for medication subtypes.

Results: We identified 11,101 individuals with CHD. The overall cumulative incidence of cardiovascular drug use by age 15 was 25% (95% CI: 24-26). Diuretics (ATC code: C03x) were the type of cardiovascular drug at some point used by most children with CHD, with a cumulative incidence of 19% (95% CI: 18-20). Beta blocking agents (ATC code: C07x) were used by 2.3% (95% CI: 1.9-2.7) and calcium channel blockers (ATC code: C08x) by 0.9% (95% CI: 0.6-1.2). Cardiac therapy (ATC code: C01x) was used by 1.4% (95% CI: 1.1-1.7).

Conclusions: A substantial proportion of children with CHD are at some point using cardiovascular medication, most commonly diuretics. We need more understanding of the benefits and harms of these medications, when used in children with CHD, to ensure optimal patient care.

305. Obesity Predicts Shorter Time to First Exacerbation in Pediatric Patients with Uncontrolled Mild to Moderate Asthma

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Background: Although childhood obesity has been linked to poor asthma control, other studies have refuted this claim. Such inconsistencies may be due to the lack of clinical severity indicators and asthma diagnosis ascertainment in administrative databases; thus, the effect of weight status on asthma control remains to be elucidated in children using clinical data.

Objectives: To assess if BMI percentile is a significant predictor of time to first exacerbation among children with mild to moderate uncontrolled asthma.

Methods: We conducted a retrospective cohort study from clinical data linked to health and drug administrative databases. The cohort consisted of children aged 5-18 years with confirmed asthma, followed by the Montreal Children's Hospital's Asthma Center (AC) from January 1 2000 to September 31 2007 in QC, Canada. Patients were included at cohort entry if they were newly stepped-up to a higher-dose inhaled corticosteroid (ICS) monotherapy (MT) or ICS combination therapy (CT),i.e. with Long-Acting Beta2-Agonists or Leukotriene Receptor Antagonists as add-on therapies, from a low-dose ICS regimen. Exclusion criteria were: bronchopulmonary dysplasia, cystic fibrosis, or not covered by the public drug insurance plan. Patients were followed until the date of first exacerbation, lost-to-follow-up or end of 1-year follow-up, whichever occurred first. Age- and sex-specific BMI percentiles were computed using the WHO growth charts at cohort entry and subsequent AC visits. Exacerbation was defined as any ED visit, hospitalization, or use of oral corticosteroids for asthma. A Cox model was used to determine the effect of time-varying BMI percentile on hazard of first exacerbation.

Results: The final sample consisted of 355 children newly stepped-up to ICS MT (N = 252) or ICS CT (N = 103), with 234 (65.9%) events during follow-up. For every 10 unit increase in BMI percentile, the hazard of exacerbation increased by 31% (HR 1.31, 95% CI 1.20-1.43), after adjusting for confounders.

Conclusions: Excess weight is an important predictor of exacerbation-free time in pediatric asthma. Further research is warranted to understand the pathology of obese-asthma in children.

306. Childhood Obesity in Relation to Poor Asthma Control and Exacerbations

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Background: The relationship between obesity and asthma severity in children is inconsistent across studies.

Objectives: To estimate the association between obesity and poor asthma control/ risk of exacerbations in asthmatic children and adolescents, and to assess whether these associations are different by gender.

Methods: A meta-analysis was performed on unpublished data from three North-European pediatric asthma cohorts (BREATHE, PACMAN and PAGES) and 11 previously published studies. Body mass index (BMI) was classified as obesity (BMI≥95th percentile) and non-obesity <95th percentile). Outcomes were poor asthma control (Asthma Control Questionnaire score (ACQ) ≥ 0.75 or Asthma Control Test scores (ACT) ≤19 or meeting at least three criteria of the NHLBI guidelines on asthma control) and exacerbations rates (asthma-related visits to the emergency department, asthma- related hospitalizations and/or use of oral corticosteroids). Overall pooled estimates of the odds ratios (ORs) were obtained using fixed or random-effects models.

Results: In 52,140 asthmatic children and adolescents, there was no statistically significant association between obesity (BMI≥95th percentile) and poor asthma control (OR: 1.17, 95% confidence interval (CI): 0.95-1.45, p-value, 0.15). However obese children compared with non-obese peers had a small but significant increased risk of asthma exacerbations (OR: 1.13, 95% CI: 1.00-1.28; p-value, 0.04). After stratification for gender, the differences in ORs for girls and boys were similar, yet no longer statistically significant.

Conclusions; In asthmatic children, obesity is associated with a minor increased risk of asthma exacerbations but not with poor asthma control. Gender does not appear to modify this risk.

307. State Register of Medicinal Products of Russian Federation as a Source of Information About Age Restrictions for Drug Prescription

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Background: State Register of Medicinal Products of Russian Federation (SRMP) is a information system, which contains data about authorized medicinal products (MP) and pharmaceutical substances. It is only regularly updated source of officially approved instructions for medical use in the country.

Objectives: Our goal was to analyse instructions available in SRMP and evaluate presence, content and quality of recommendations for use of MP in pediatrics.

Methods: We used manual search of age restriction in the text of instruction provided by SRMP. Due to permanent process of Register update we constrict our search to SRMP content issued in 03.01.2015, when we started our work. We saved our results to own database called "KORDAG Nucleus".

Results: We analyzed 19131 records of SRMP (69.4% of all records). 4403 (23%) records were excluded from analysis because contains data about substances, in-bulk products, allergen kits, diagnostic tests, etc. In 14728 records included in manual search only 10151 (76.1%) contains strictly defined contraindication for use in different age groups. 4577 (23.9%) records contain fuzzy recommendations. From them only 1496 (7.8%) allow use of drug in any age period, 1050 (5.5%) do not contain any information on this issue and 2031 (10.6%) contain uncertain recommendations, which lead doctors into error. Usually, the uncertainty of recommendations is caused by differences in age periods definitions, i.e. MP may be "contraindicated in small children" or "allowed for adolescents". Another problem is no strictly defined place of age restriction in the text of instruction, it may be found in part of indications, contraindications, dosing or special warnings. In addition, we revealed that 4830 records were dublicates and 2758 were out-of-date.

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Conclusions: We revealed that SRMP is not a source which is comfortable for use by doctors or patients. It contains 40.6% of useless records. we also found that only 8% of registered MP may be prescribed in children of any age, 5.5% do not contain any information about use in children and 10.6% mislead consumers and increase risk of unappropriate use of the MP.

308. Quality of Pediatric Pharmacoepidemiological Safety Studies Published from 1979 to 2013

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Background: Pharmacoepidemiological safety studies in children can yield important evidence for better drug use in pediatrics but validity of study results are limited by various challenges.

Objectives: To assess the quality of published pharmacoepidemiological safety studies in children and its association with characteristics related to the design, conduct and reporting of studies.

Methods: Relevant articles from inception to 2013 were retrieved from Embase.com and Medline. We sequentially screened titles, abstracts and full texts, with independent validation. We systematically evaluated the quality of retained studies by applying a modified Newcastle-Ottawa-scale (maximum score = 9) and derived a summary quality score for each study. We estimated the median (p25; p75) score. By applying Kruskal Wallis H (KWH) or Mann Whitney U (MWU) tests, we tested the association between quality and several characteristics including year of publication (categorised according to introduction of drug legislations), geographical setting, study funding, type of journal, type and mode of data collection, design, age of the study population and type of exposure.

Results: Out of 4825 retrieved (unique) articles, 259 full texts were evaluated; 54.4% pertained to drugs, the remainder to vaccines. Generally, study quality was high (median score = 7; p25 = 6; p75 = 8). The following characteristics were significantly associated with quality: year of publication (KWH p-value = 0.01), geographical setting (KWH p-value = 0.04), study funding (KWH p-value $<$ 0.01), type and mode of data collection (KWH p-value $<$ 0.01), design (KWH p-value $<$ 0.01) and type of exposure (MWU p-value $<$ 0.01). Self-controlled case-series studies (median score = 7; p25 = 7; p75 = 8) of vaccine exposures (median score = 6; p25 = 7; p75 = 8) performed in North America and Europe (median score = 6; p25 = 7; p75 = 8), based on retrospectively collected secondary data and published from 2010 with specified funding source were the best. The results were adjusted for confounding.

Conclusions: Published pediatric pharmacoepidemiological safety studies showed good quality which improved over time and was associated with geographical setting, design, conduct and reporting of results.

309. Use of Copay as an Instrumental Variable for Adherence in Comparative Effectiveness and Safety Research

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Background: There is substantial interest in assessing the effects of improved medication adherence on health outcomes. However, as a behavior, adherence cannot be easily studied in randomized experiments, and observational studies can be challenging because of confounding. Copay has been previously used as an instrumental variable (IV) for studying the effects of adherence.

Objectives: To evaluate the use of copay as a potential IV for a study of the effect of cinacalcet adherence on health outcomes in hemodialysis (HD) patients.

Methods: We conducted a retrospective cohort study of cinacalcet initiators using data from the US Renal Data System (2006-2011). Our cohort included HD patients aged ≥18 years, with continuous Medicare part A, B and D coverage and no low income subsidy in the 6-month baseline period. Copay of the first prescription cinacalcet fill was evaluated as an IV. Adherence to cinacalcet was defined as percentage of days covered (PDC) in the first 12 months after the first month covered by the index prescription. To evaluate copay as an IV for adherence, we

examined (1) the baseline patient demographic and clinical characteristics across copay groups and (2) the relationship between distributions of PDC and copay categories.

Results: We categorized 3,460 cinacalcet initiators into four groups based on their copay levels (≤$30, $30< - $45, $45< - $195 and >$195). Baseline characteristics were similar across patient groups, with exception of slightly higher proportion of patients with longer vintage and high parathyroid hormone values in the highest copay group. Mean PDC was the highest among patients with copay >$195 (0.44, SD 0.33), followed by patients with copay ≤$30 (0.41, SD 0.32) suggesting a U-shaped relationship between copay and adherence.

Conclusions: Copay was not found to be a good IV in this setting, as suggested by the absence of a monotonic association between copay and adherence which might be due to a self-selection process by disease severity. The use of copay as an IV for adherence needs to be carefully assessed in other settings.

310. Positive Predictive Value of Antidiabetic Agent Exposure from EHR Prescribing Data Relative to Pharmacy Dispensing Data in the OptumLabs™ Data Warehouse

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Background: Electronic health records (EHRs) permit observational research with clinical and laboratory data more granular than health insurance claims data.

Objectives: The study objective was to determine the period positive predictive value (period PPV) of classifying antidiabetic agent (ADA) exposure using EHR Rx data relative to pharmacy dispensing data.

Methods: The study population included patients from the OptumLabs™ Data Warehouse (OLDW), which includes claims data for more than 150 million privately insured and Medicare Advantage (MA) enrollees, as well as electronic medical record data from a nationwide network of provider groups. Included patients had linked claims and EHR data and an office visit in 2012 (the index date). We compared ambulatory EHR Rx data to pharmacy dispensing data for each of the following ADAs separately: metformin (M), sulfonylurea (SU), DPP4 inhibitors, GLP-1 RAs, basal insulin (BI), and short-acting/mixed insulin (SMI). The 12 month period PPV was calculated as the number of patients with ≥ 1 pharmacy dispensing among all patients with an EHR Rx in the 12 months following the index date. We also evaluated periods of 1, 3, and 6 months.

Results: The 12 month period PPVs for M, SU, DPP4, GLP1, BI, and SMI were 81, 84, 77, 82, 85, 65%, respectively. For all ADAs, the period PPV was 5-15% less for patients with an incident EHR Rx and for patients with Medicare insurance. The 1 month period PPVs ranged from 48% for SMI to 64% for GLP1 RAs; however, the period PPVs were consistent from 3-12 months.

Conclusions: For the ADAs we evaluated, the period PPV increased with the duration of the period, but stabilized around 80% with a 3 month period. In order to increase the validity of classifying ADA exposure using EHR Rx data, researchers should use at least a 3-month period; they should also be aware of the lower period PPV for patients with an incident EHR Rx and Medicare insurance.

311. Primary Non-Adherence Associated with Antidiabetic Agents (ADAs) from Electronic Health Record Prescribing Data (EHRx) in the OptumLabs™ Data Warehouse

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Background: Primary nonadherence (PNA) is a significant therapeutic problem among patients with diabetes. PNA occurs when patients are prescribed a medication but fail to fill the medication at the pharmacy. The linkage between electronic health records

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(EHR) prescribing (Rx) data and pharmacy claims data provides a unique opportunity to study PNA.

Objectives: The purpose was to describe the proportion of patients with an ambulatory antidiabetic agent EHRx where there is no corresponding pharmacy dispensing claim.

Methods: The study population was extracted from the OptumLabs™ Data Warehouse (OLDW), which includes de-identified claims data for more than 150 million privately insured and Medicare Advantage (MA) enrollees, as well as electronic health record data from a nationwide network of provider groups. We included patients who had linked claims and EHR data in 2012. Among patients with an ambulatory ADA EHRx, we determined the probability of not having a pharmacy claim within 3 and 12 months following the last ADA EHRx in 2012. The index date was the last EHRx for: metformin (M), sulfonylurea (SU), DPP4 inhibitors, GLP-1 RAs, basal insulin (BI), and short-acting/mixed insulin (SMI).

Results: PNA at 3 months was 28, 26, 32, 26, 25, and 44% for M, SU, DPP4, GLP-1, BI, and SMI, respectively. PNA at 12 months was 20, 18, 27, 20, 16, and 36% for M, SU, DPP4, GLP-1, BI, and SMI, respectively. PNA at 3 and 12 months was 5-10% higher when the index EHRx was an incident prescription. For all ADAs, PNA was higher for patients ≥65 years.

Conclusions: One quarter to 44% of patients do not fill their ADA prescription within 90 days. By 12 months 15-36% still had not filled their prescription. Older patients and those with a new ADA prescription are less likely to fill their medication. Healthcare providers may seek to better understand reasons for delayed medication fills. Researchers using EHRx data to classify ADA exposure should consider methods to account for PNA and potential misclassification.

312. Medication Possession Ratio Associated with Antidiabetic Agents from Electronic Health Record Prescribing Data (EHRx) in the OptumLabs™ Data Warehouse

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Background: Medication possession ratios (MPR) are used to quantify medication exposure and adherence. MPR is the percentage of time a patient possesses a supply of a medication. MPRs are difficult to determine with EHR Rx data alone due to limited or no ascertainment of pharmacy dispensing and medication discontinuation data. The linkage between EHR Rx and pharmacy claims data provides a unique opportunity to study medication exposure and adherence associated with EHR Rx data.

Objectives: The purpose was to describe the MPR for antidiabetic agents (ADAs) following an electronic health prescribing record (EHRx).

Methods: We conducted a retrospective cohort study among patients with linked claims and EHR data using the OptumLabs™ Data Warehouse (OLDW). This database includes claims data for more than 150 million privately insured and Medicare Advantage (MA) enrollees, as well as electronic medical record data from a nationwide network of provider groups. The index date was the date of the last EHRx in 2012 for: metformin (M), sulfonylurea (SU), DPP4 inhibitors, GLP-1 RAs, basal insulin (BI), and short-acting/mixed insulin (SMI). The MPR was calculated as the number of days covered (classified using pharmacy dispensing data) in the 12 months following the index date.

Results: The median MPRs were 64, 71, 33, 41, 49, and 25% for M, SU, DPP4, GLP-1, BI, and SMI, respectively. The proportion of patients with a MPR ≥ 80% were 35, 40, 23, 20, 19, and 12%. The MPRs for patients with an incident EHRx were 12-40% lower than for patients with a prevalent EHRx. The MPRs increased by 10-30% when ≥1 additional EHRx was observed in the 12 month period.

Conclusions: Medication exposure and adherence following an EHRxs for ADAs vary widely with M and SU having the highest median MPR and DPP4 inhibitors and SMI having the lowest median MPR. Given the potential for exposure misclassification, researchers using EHRx data should be aware of the limitations of EHRx data and use methods to mitigate exposure misclassification. To improve the validity of medication exposure classification, researchers may consider requiring multiple EHRxs.

313. Withdrawn by Author

314. Patient Adherence to Treatment After Discharge for Acute Coronary Syndrome in Vietnam: A Prospective Observational Study

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Background: The long-term benefits of using secondary prevention medications for post-acute coronary syndrome are proven, but little is known about patient adherence to treatment in Vietnam.

Objectives: To determine the extent of patient adherence to treatment for acute coronary syndrome (ACS) in the first 3 months after hospital discharge and to identify factors correlated with non-adherence and clinical outcomes.

Methods: We conducted a prospective observational study on all local residents with ACS discharged from two public hospitals in Can Tho city, Vietnam between January and October 2015. Patients with cognitive impairment or patients who died within 1 month of discharge were excluded. Patients were interviewed at 1 and 3 months after discharge. Adherence was measured using the Morisky Medication Adherence Scale - 8 items (MMAS-8). Adherence to treatment was defined as returning for their scheduled outpatient appointments and having all MMAS-8 scores of > 5 during follow-up. Factors correlated with patient non-adherence and 3-month readmission or death were identified using logistic regression.

Results: Overall, 101 patients were included (mean age 65.7 (SD 13.4) years, 59% male); 35% had more than 2 comorbidities; 83% hypertension, 43% peptic ulcer, 31% dyslipidemia, 30% diabetes. A total of 79% of patients were adherent to treatment. Older patients were less likely to be adherent (OR 0.96; 95% CI 0.92-1.00). The 3-month readmission rate was 26%, and 2% died during follow-up. Patients with more than 2 comorbidities had a higher risk of 3-month readmission or death (OR 2.66; 95% CI 1.05-6.7), but there was no correlation between patient non-adherence and 3-month readmission or death.

Conclusions: Adherence to treatment in the first 3 months after discharge among ACS patients in Vietnam was relatively high. Older patients were less likely to be adherent.

315. Impact of Hospitalization Periods on the Calculation of Adherence Measures

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Background: Pharmacy claims data are commonly used to assess medication adherence. However, many claims databases lack information on inpatient drug use. It is unclear how different approaches to handling hospitalizations compare to the gold standard of using both outpatient and inpatient drug claims data.

Objectives: To compare various approaches to handling hospitalizations when measuring drug adherence.

Methods: We identified 2 cohorts of patients in the population-based Taiwan database, which includes indicators of inpatient drug use: β-blocker initiators after myocardial infarction and all statin initiators (with or without prior hospitalization). We measured adherence

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to -blockers or statins during a 1-year follow-up period using the proportion of days covered (PDC). PDC was calculated in 3 ways using only outpatient pharmacy claims: ignoring hospitalizations (PDC1); subtracting hospitalization days from the denominator (PDC2); and assuming drug use on all hospitalized days (PDC3). We compared these to the gold standard approach that incorporated inpatient drug use (PDC4).

Results: A total of 1,729 β-blocker initiators and 69,435 statins initiators were identified, with 54% and 16% of patients hospitalized during follow-up. Overall, mean PDC was 74% for β-blockers and 44% for stains, which varied little across approaches (range = 73.1-74.9% for β-blockers; 43.5-44.0% for statins). As mean length of hospitalization increased, differences in methods became apparent. For patients hospitalized for >28 days (6.8% and 1.6% in each cohort, respectively), the mean differences between PDC3 and PDC1 were >15% in both cohorts (64.7% vs. 49.0% for β-blockers; 52.7% vs. 35.3% for statins). PDC3 always yielded the highest value and PDC1 the lowest. The relative performance of the approaches compared to PDC4 depended on total days supply from outpatient prescriptions and mean length of hospitalization.

Conclusions: Different approaches to handling hospitalizations lead to adherence estimates that were very similar to the gold standard of incorporating inpatient drug use. When patients have many hospitalization days during follow-up, the choice of approach should be tailored to the specific setting.

316. Prior Medication Adherence As A Strong Predictor Of Future Adherence

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Background: Medication non-adherence is a widespread problem. Identification of patients who are likely to be non-adherent can guide targeted interventions and improve the design of comparative effectiveness studies.

Objectives: We examined multiple measures of patients' prior medication adherence for predicting adherence to newly initiated statins in a large US administrative claims database.

Methods: We identified a cohort of patients initiating statins and measured their prior adherence to chronic preventive (non-statin) medications during a 365-day baseline period, using metrics such as proportion of days covered (PDC), lack of second fills, and number of dispensations. We measured adherence to statins during the year after initiation, defining PDC≥80% as "high adherence". We used logistic regression models to predict high adherence in a random 50% sample and tested their discrimination using c-statistics in the other 50%. We also assessed the association between prior adherence and subsequent statin "high adherence" by fitting a modified Poisson model from all relevant covariates + prior mean PDC categorized as <25%, 25-79%, ≥80%.

Results: We identified 89,490 statins initiators. A prediction model including only demographic variables had a c-statistic of 0.578 (95% confidence interval: 0.573-0.584). A combined model adding information on patients' comorbidities, health services utilization, and medications used resulted in a c-statistic of 0.665 (0.659-0.670). Models with each of the prior medication adherence measures as the only explanatory variable yielded c-statistics ranging between 0.533 (0.529-0.537) for lack of 2nd fill, and 0.665 (0.691-0.701) for median PDC. A model adding median PDC to the above combined model yielded a c-statistic to 0.695 (0.690-0.700). Patients with prior mean PDC<25% were half as likely to show high adherence to statins compared to those with prior mean PDC≥80% (risk ratio: 0.49 [95% confidence interval: 0.46-0.50]).

Conclusions: Including measures of prior medication adherence yields better prediction of future statin adherence than standard baseline clinical measures that are typically used in claims-based studies.

317. Reliably Estimating Adherence to Therapy in Chronic Patients from Italian Administrative Databases

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Background: In previous studies we observed that sensitivity of the best case-finding algorithms for type 2 diabetes (T2DM) and ischemic heart disease (IHD) in Italian Administrative Databases (IAD) is between 50 and 75%, and positive predictive value (PPV) is between 73% and 85%. On the contrary, PPV of case-finding algorithms for T2DM and IHD in primary care medical records (MR) was higher than 97%.

Objectives: To assess how estimates of adherence to therapies for patients with T2DM or IHD from IAD compare with estimates from MR.

Methods: We selected 24 clusters of subjects living in different areas of Italy. All the subjects in a cluster were in charge to the same General Practitioner. For all patients both IAD and MR were collected. In all clusters we estimated adherence to statins in T2DM patients, and adherence to ACE inhibitors (ACEi), antithrombotics, beta-blockers (BB) and statins in IHD patients, as the age-standardised proportion of subjects with ≥2 prescriptions during a year of follow-up. Each proportion was computed both from IAD and MR. Average value according to IAD (AI) with interquartile range (IQR) and median difference within pair of measures (MDW) were computed. Each pair was labelled as *discordant* if the two proportions were significantly different at the 0.05 level, as *concordant* otherwise.

Results: 32,687 subjects entered the study. The average size of clusters was 1,362. Average prevalence (AP) of T2DM in the clusters was 8% (IQR 7-9) in MR and 7% (IQR 6-8) in IAD, concordance measured with Cohen's kappa (K) was 78%. AP of IHD was 4% (IQR 3-5) in MR and 3% (IQR 2-3) in IAD, K was 58%. All 24 pairs were concordant in estimating adherence to statins in T2DM patients, AI was 52% [46-60] and MDW was 3. Adherence to ACEi, antithrombotics, BB and statins in IHD patients was concordant, respectively, in 20 (AI 68% [61-76], MDW 4), 20 (AI 82% [77-90], MDW 5), 21 (AI 62% [55-73], MDW 8) and 17 (AI 72% [71-78], MDW 9) of the 24 pairs.

Conclusions: Even though IAD validity in detecting cases was not optimal, estimates of adherence to recommended therapies in patients with T2DM or IHD were similar to estimates from MR.

318. The Use of New Oral Anticoagulants in Patients with Atrial Fibrillation in Scotland – A Population-Based Drug Utilisation Study

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Background: Atrial fibrillation (AF) is a common arrhythmic disorder and a major risk factor for stroke. Anticoagulants are widely used as a preventative measure; in addition to warfarin, three new oral anticoagulants (NOACs) – dabigatran, rivaroxaban, and apixaban – have been introduced for this purpose in Scotland since 2008.

Objectives: To examine the uptake and use of NOACs in patients with a diagnosis of AF, confirmed in secondary care, in Scotland.

Methods: Patients with a diagnosis of AF who have been treated with NOACs between January 2009 and June 2014 have been identified using data from the Scottish Morbidity Records (SMR) linked to the

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Prescribing Information System (PIS). Yearly incidence and prevalence of NOAC use have been calculated based on mid-year population estimates; adherence to drug treatment has been analysed by calculating duration of treatment and number of days' supply (first up to, but not including last refill), and medication refill adherence (MRA), defined as total days' supply divided by total days of study participation.

Results: Between January 2009 and June 2014, 5769 patients with a confirmed diagnosis of AF received at least one prescription for any NOAC. 53.7% of patients were male, and the mean age at time of first prescription was 74.8 years (SD 11.3). Prevalence of NOAC use increased from 0.2 patients/100,000 population in 2009 to 63.5 patients/100,000 population in 2013; incidence per 100,000 population in 2013 ranged from 7.6 (dabigatran) to 33.2 patients (rivaroxaban). Among patients treated exclusively with NOACs who received at least two prescriptions (n = 2000), mean duration of treatment and mean days' supply dispensed were 235.0 and 235.4 days, respectively (SD 206.3; 201.4); MRA was 100.4% (SD 42.2).

Conclusions: The findings suggest that AF patients are increasingly prescribed NOACs, including a substantive number of patients previously treated with warfarin. Overall adherence to NOACs among AF patients in Scotland seems to be satisfactory, yet additional information regarding persistence to and discontinuation of treatment is needed for a better understanding of NOAC utilisation.

319. Non-Adherence to Methotrexate in Rheumatoid Arthritis; a Prospective Cohort Study (RAMS)

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Background: Methotrexate is the firs-line treatment for rheumatoid arthritis (RA) in the UK, and non-adherence partially explains poor response. In order to optimise MTX use it is crucial to identify the reasons for non-adherence and those patients at risk of non-adherence.

Objectives: 1) To determine the rate and reasons for MTX non-adherence during the first six months, 2) To identify predictors of non-adherence.

Methods: The rheumatoid arthritis Medication Study (RAMS) is a 12 month prospective study of incident MTX users with RA recruited from 35 secondary care settings across the UK. At baseline clinical, demographic and psychological data were collected. To measure non-adherence over 6 months patients completed a weekly MTX diary. Non-adherence was defined as ≥1 week MTX was missed against medical advice, and the proportion of non-adherent weeks were calculated. To identify potential baseline predictors of non-adherence univariate logistic regression analyses were conducted, predictors were entered/retained in the multivariate logistic model adjusted for age and gender if $p<0.1$, odds ratios and 95% confidence intervals are reported.

Results: In total 1000 patients were recruited between 31/08/08 and 30/05/14, 809(81%) remained in the study at six months and 605(75%) returned a MTX diary. The diary sample were predominantly female (69%), median age 60(IQR51-70) years, with a median disease activity score (DAS28) of 4.2 (IQR3.5-5.2). Overall proportional non-adherence was 2%. This corresponds to 157(26%) being non-adherent, of those 71% were intentionally so. Twelve baseline variables were entered into multivariate analysis, and DAS28 OR 1.2(.98,1.4) fatigue OR1.1(.99,1.1), having >1 co-morbidity OR 2.0(1.1,3.4), the Beliefs in Medicines Questionnaire Necessity-Concern Differential OR .95(.92, .99) and being an ex-smoker OR .71 (.46,1.1) predicted non-adherence (ROC analysis AUC = .63).

Conclusions: Given that patients with high disease burden and high MTX concerns are at risk of early non-adherence, and non-adherence is primarily intentional, modifying MTX beliefs may optimise MTX use.

320. Persistence to Anti-Osteoporosis Treatments in Primary Care Patients Recorded in the Spanish Electronic Database BIFAP

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Background: A lack of persistence to anti-osteoporosis drugs (AOM) has been reported.

Objectives: We aimed to estimate the persistence of AOM use in Spanish primary care.

Methods: A cohort study was performed using anonymized electronic primary care records for 4 million people (BIFAP database). Participants entered the study when aged ≥50 years in 2001-2013 and with ≥1 year of data available. Users of AOM in the previous year were excluded. Six cohorts of AOM new users were identified according to first prescribed AOM: alendronate, other oral biphosphonates (OB), SERM, strontium ranelate (SR), teriparatide (TE), and denosumab (DE). AOM users were followed from initiation to cessation (90 days refill gap), AOM switching, drop-out, death, or December 2013. Sensitivity analysis using 180 and 30 days of gaps were also performed. First-year cessation proportion was estimated using life tables.

Results: Overall, 95,057 new AOM users were identified (90.7% women; mean age 67.46 S.D. + -10.30), 36 182 AL, 37 594 OB, 11 723 SERM, 7,978 SR, 1,287 TE, and 293 DE. First-year cessation were 51% overall. Cessation was 68%, 45% when using 30 or 180 days gap respectively. Cessation was highest for strontium (62-81%), and lowest for denosumab (25-33%) for the 3 gap defined.

Conclusions: Half of the patients initiating AOM therapy ceased treatment for at least 90 days during the first year, with strontium being the most commonly stopped drug. Few patients re-started the treatment in following months. For AOM therapy, 90 days seems to be more accurate to define cessation than 30 days, since more patients cessing 30 days than 90 days, re-started the treatment in following months.

321. Associations Between Personality Traits and Adherence to Antidepressants Assessed Through Self-Report, Electronic Monitoring, and Pharmacy Dispensing Data

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Background: Treatment with antidepressants is often compromised by substantial non-adherence. To understand non-adherence, specific medication-related behaviors and beliefs have been studied, but less is known about broader and temporally stable personality ´traits´. Furthermore, adherence has often been assessed by a single method, most of the time self-report.

Objectives: To investigate the associations between the Big Five personality traits and adherence where adherence is assessed by self-report, electronic drug use monitoring, and dispensing data.

Methods: Using the Big Five Inventory, we assessed the personality traits 'Openness', 'Conscientiousness', 'Extraversion', 'Agreeableness', and 'Neuroticism' of adult patients treated with antidepressants who were randomly selected from five Dutch community pharmacies. Self-reported adherence was assessed with the Medication Adherence Rating Scale (score >24), electronic monitoring with Medication Event Monitoring System (MEMS) devices (therapy days missed ≤ 10% and <4 consecutive days missed), and dispensing data (Medication Possession Ratio ≥ 80%). Associations between adherence and the Big Five Factors were examined using multiple logistic regression models and presented as odds ratios (OR) with 95% Confidence intervals (CI). Personality traits were divided into quartiles to examine if these were differentially associated with adherence.

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Results: The study population included 137 patients of whom 75.9% were women with a mean age of 51.0 (standard deviation 14.0) years. The majority (73.7%) received therapy due to depression and paroxetine was the most frequently prescribed antidepressant (38.6%). Logistic regression analysis revealed that the 3rd and 4th quartiles of 'Conscientiousness' were associated with better self-reported adherence (OR = 3.63, 95%CI:1.34-9.86 & OR 2.97, 95CI%: 1.09-8.08; P-values $\leq$ 0.05). No clear relationships were found between personality traits and adherence assessed through electronic drug use monitoring or dispensing data.

Conclusions: Adherence to antidepressant therapy seems to be largely unrelated to personality traits.

322. Impact of Pharmaceutical Care on Medication Adherence, Hemoglobin Levels and Interdialytic Weight Gain Among Hemodialysis Patients – A Multicentric Trial

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Background: Poor adherence to complex multimodal therapies is a widely recognized problem among hemodialysis (HD) patients, contributing to morbidity and mortality.

Objectives: To assess the impact of pharmaceutical care on medication adherence, hemoglobin (Hb) levels and interdialytic weight gain (IDW) among hemodialysis patients.

Methods: Open-label randomized control trial was carried out at 3 different HD centres of teaching, government and corporate hospitals. The patients were randomized into two groups [Usual Care Group (UC) and Pharmaceutical Care Group (PC)]. The customized care plan was designed and delivered to the patients on monthly basis based on the condition and need of the patient by WHO-FIP Pharmaceutical care model. The outcome of the study include medication adherence, Hb levels and IDW. The assessment was done at baseline, 6th and 12th months. The repeated measures of analysis was performed for the analysis of change in the outcomes in the two groups.

Results: At the end of the study, 153 patients were followed. Out of 153 patients, 75 from UC group and 78 from PC group. The PC (4.13 –3.5 – 3.46) group had significantly reduced its IDW (L) levels in comparison to UC (3.94 – 4.09 – 3.97) group at different time intervals with a statistical significance of F (1.460, 220.502) = 71.166, $p < 0.001$. There was a significant increase in Hb (g/dl) levels noticed in PC (9.17- 9.4.47- 9.75) group compared to UC (8.96 – 8.69 – 9.22) group with a statistically significance of F (1.932, 291.657) = 5.867, p = 0.004. There was a statistically significant improvement in medication adherence rate scores observed in PC (4.58 – 5.88 – 6.04) group compared to UC (4.42 – 4.59 – 4.65) group F (1.809, 273.137) = 43.321, $p < 0.001$.

Conclusions: The 'WHO-FIP Pharmaceutical Care' plan model delivered by the registered pharmacist had positive impact on medication adherence, Hb levels and IDW. However, a significant increase was noticed in the medication adherence rate scores but the overall medication adherence rate was moderate.

323. Male Breast Cancer and Adherence to Adjuvant Endocrine Therapy

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Background: Most male breast cancers are estrogen receptor-positive and adjuvant endocrine therapy (AET) greatly improves survival rates when adhered to for 5 years.

Objectives: We aimed to evaluate adherence to adjuvant endocrine therapy (AET) in men diagnosed with breast cancer in comparison with women for two years after AET initiation and examine characteristics associated with adherence to AET in men with breast cancer compared to female breast cancer cases.

Methods: We performed a retrospective cohort study of patients treated with AET using the Truven Health MarketScan database. Men and women diagnosed with breast cancer who initiated either tamoxifen,

anastrozole or letrozole treatment between 2009 and 2013 were identified. We collected information on patient demographics and medication use for 12 months prior to and two years following AET initiation. Adherence to AET was measured as medication possession ratio (MPR) for the first and second years since AET initiation. Multivariable generalized estimating equation (GEE) models were used to examine associations between patient characteristics and AET adherence (MPR ≥0.80) among all breast cancer patients and in stratified analyses by gender.

Results: 165 male and 37,486 female breast cancer patients were included in our analysis. Compared to women, more men were diagnosed at an older age (Median 62 vs. 58 years), had higher levels of comorbidity (Charlson score of 1+: 48% vs. 29%), were treated with adjuvant chemotherapy (40% vs.25%) and initiated treatment with tamoxifen over aromatase inhibitors (78% vs. 39%). In multivariable GEE models, we found strong evidence to suggest that men were less likely to be adherent to AET over time compared to women (OR = 0.64, 95% CI: 0.48-0.84). Concurrent use of lipid-lowering medications was associated with adherence to AET in all breast cancer cases (OR = 1.29, 95% CI: 1.23-1.35) and in analyses of men only (OR = 2.05, 95% CI: 1.09-3.83).

Conclusions: The findings in this study corroborate other studies that report significant tamoxifen-related side effects in men that may contribute to treatment non-adherence. Future efforts to improve AET adherence in men with breast cancer may result in better outcomes.

324. Alternative Data Processing in the Culig Adherence Scale

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Background: Perseverance in taking therapy is an important determinant of its success, but the evaluation of patient adherence is extremely complex. The Culig scale with 16 questions of perseverance is used in Croatia.

Objectives: The determination of psychometric properties of the Culig questionnaire of perseverance, in which the individual results are formed in an alternative way.

Methods: Raw values of each indicator, 68 of them, are processed, instead of the original 16 composite variables of the Culig scale. At the same time, reactions on certain indicators are normalized by the inverse integral of the standard normal distribution, after which the data are standardized. After the data are processed, results are formed for each subject as factor scores on the first main component of the inter-correlation matrix of indicators. Such a procedure allows calculation of the contribution of individual indicators to the overall results on the scale, and with the method of the factor analysis it is possible to accurately show the interconnection of individual indicators, as well as their possible groupings.

Results: Scale reliability (Cronbach alpha = 0.94) becomes significantly higher than in classical procedures. The first factor is defined by the highest number of individual indicators and represents the main subject of the whole scale measurement; indicators with the highest saturation are connected to the perseverance in taking the drug and to the indicators of the subjects' mood, with an emphasis on the sad and depressed mood. Interestingly, the indicators of the relationship of the patient with the doctor or the pharmacist were not significantly associated with indicators of perseverance in taking the drug, but are on an independent dimension.

Conclusions: Alternative methods of processing the individual results and psychometric properties determined by that process are presented in the Culig questionnaire of perseverance. These kind of properties are better than those that are usual of certain conventional ways of processing. Such a process opens the possibility for a multivariate analysis of the results in the questionnaire, which is important for further research.

325. Predicting Refill Adherence from Alternative Data Sources: Claims, Structured Electronic Health Record Data, and Physician Notes

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Background: Prediction of medication adherence from healthcare claims has typically had poor accuracy. Electronic health records (EHRs) offer a promising alternative data source with rich clinical detail that may lead to more accurate predictions, especially when timely access to claims data is not available.

Objectives: To evaluate the use of claims, structured EHR data, and unstructured EHR physician notes for predicting medication refill adherence.

Methods: We used a linked de-identified database of complete claims and EHR data from patients enrolled in a Medicare Advantage plan and receiving care at a community-based medical group. We identified patients who filled a prescription for a statin, antihypertensive, or oral antidiabetic during 2010-2011. We measured adherence to the index medication from claims during the year following the index fill and categorized it into 5 groups based on a group-based trajectory model. Potential predictors of adherence were extracted from each data source using data accrued during the year before the index fill. For the unstructured EHR data, variables were extracted using natural language processing algorithms. Boosted multinomial logistic models were fit to predict adherence group, and we measured prediction accuracy using 10-fold cross-validated C-statistics.

Results: There were 7,783, 10,122, and 1,936 statin, antihypertensive, and antidiabetic users, respectively. Accuracy of predicting consistently poor adherence from claims varied across cohorts (C = 0.89, 0.72, and 0.68). An indicator of prior gaps in medication use was the strongest claims predictor. Prediction from structured EHR data was lower, but still comparable with prediction models currently in use (C = 0.71, 0.62, and 0.62). Prediction from unstructured EHR data alone was poor (C = 0.56, 0.57, 0.53). Combining EHR and claims predictors did not meaningfully impact predictions.

Conclusions: Highly accurate predictions from claims alone relied on the inclusion of prior adherence information. EHR data alone achieved moderate prediction accuracy and may be useful for targeting patients for intervention in the absence of available claims data.

326. Pharmacy Inducement Programs Associated with Better Medication Adherence: A Cohort Study

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Background: Many community pharmacies in Canada use inducement programs to promote customer loyalty; however, the clinical effects of these programs are unknown.

Objectives: This study examined relationships among inducement programs, medication adherence, and health outcomes. We hypothesized that patients using pharmacies with inducement programs to obtain their statin prescription refills would have better adherence and a lower risk of acute coronary syndrome (ACS) events compared to patients using pharmacies that do not have inducement programs.

Methods: Residents of Alberta, Canada with at least one physician visit for diabetes or hypertension between April 2008 and March 2014 were eligible for this study. Subjects were included if they were new statin users and alive at least 455 days after the first statin dispensation. Subjects were assigned to the 'inducement' or 'non-inducement' group if they obtained all statin dispensations in the first year from pharmacies with or without inducement programs, respectively. Discontinuation was defined as no statin dispensation record between 275 and 455 days after the first statin dispensation. Hospitalizations or deaths attributable to an acute coronary syndrome (ACS) event were identified between 456 days and 3 years after the first statin dispensation. Multivariable regression analyses were conducted to examine relationships among inducement programs, discontinuation, and ACS event.

Results: There were 159,998 new statin users; mean age 60.2 (±13.7) years, and 67,534 (42%) were women. Statin discontinuation occurred in 22,455

(28.9%) of 77,803 inducement group subjects and 25,816 (31.4%) of 82,195 non-inducement group subjects (aOR 0.88; 95% CI 0.86-0.90). Risk of an ACS event was similar for inducement and non-inducement groups (aHR 1.00; 95% CI 0.92-1.08); however, discontinuing statin therapy was associated with a higher risk of an ACS event (aHR 1.27; 95% CI 1.15-1.39).

Conclusions: Inducement programs are associated with better adherence and not directly associated with risk of health outcomes.

327. New Self-Questionnaire Way To Measuring Adherence To Medication

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Background: Nonadherence to medication is a growing concern to healthcare systems, physicians and other stakeholders because of mounting evidence that it is prevalent and associated with adverse outcomes and higher costs. Self-report scales have the benefits of being cheap and easy to administer.

Objectives: The objective of the paper is to check the basic metric characteristics of the Culig scale, in an alternative way.

Methods: Design: The cross-sectional study

Setting: 223 patients in Zagreb pharmacies

Main outcome measures: Cronbach's coefficient valid for results formed as a projection of the results of each of the respondents to the first main object of measurement questionnaire, which is defined as the factor score on the first principal component intercorrelation matrix.

Statistical analysis: Student's t-test and Chi-square test with a significance level of $p <= 0.05$ were used when appropriate for the evaluation of the results.

Results: Culig self-questionnaire was administered to a sample of 223 respondents, with 59 indicators, and reliability coefficient α in this measurement is 0.92, what is essential higher than in a conventional way (0.89).

Conclusions: There are many self-report scales for measuring medication adherence and their derivatives (or subscales). The used alternative processing methods of individual results by Culig questionnaire and some psychometric properties are defined. The results in this way are significantly better than those in certain conventional way of processing. The 16-item Culig scale with very good internal consistency reliability (Cronbach's alpha = 0.89) has been inaugurated in Croatia. Such analysis opens the possibility of multivariate analyses of the results, what is important for further research.

328. The Quality of Prescribing in Type 2 Diabetes Mellitus After Intervention of Evidence-Based Drug Formulary in a Private Hospital in Indonesia

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Background: Type 2 diabetes mellitus accounts for 90 % of all diabetes. Most current therapies for this disease were developed. Quality prescribing of antidiabetic drugs is recommended as it results in greater improvement in glycaemic control.

Objectives: To evaluate quality of prescribing in type 2 diabetes mellitus after intervention of evidence-based drug formulary in a private hospital in Indonesia.

Methods: Design: A quasi-experimental study, pre-post test design

Setting: Data was extracted from electronic patient records from the medical record before intervention (2010-2011 data, 297452 prescriptions) and after intervention (2012-2013 data, 126124 prescriptions) in the private hospital

Exposures or interventions: The implementation of an evidence-based drug formulary in a private hospital

Main outcome measures: The main antidiabetic drugs prescribed, average number of antidiabetic drugs prescribed per prescription, the proportion of generic drugs prescribed, average drugs cost per prescription before and after intervention.

Statistical analysis: The in-hospital prescribing before and after the intervention was compared using t-test, with the significance level of 0.05.

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Results: Antidiabetic drugs were prescribed more often after the intervention (2.1% vs. 4.7%, $p<0.05$). The main antidiabetic drugs prescribed before and after intervention was same (metformin, glimepiride and piogliglitazone). The average numbers of antidiabetic drugs prescribed per prescription was slightly increased after the intervention (1.25 vs. 1.56, $p<0.05$). However, the proportion of antidiabetic generic drugs prescribed was increased significantly (38.0% vs. 62.0%, $p<0.05$), mostly driven by metformin and glimepiride. Average antidiabetic drugs cost per prescription was 25.36% lower after the formulary implementation ($p < 0.05$); mostly due to metformin (11.15% vs. 4.4%), glimepiride (37.53% vs. 23.83%) and pioglitazone (39.65% vs. 23.42%).

Conclusions: Prescribing quality of antidiabetic drugs was improved by implementation of evidence-based hospital drug formulary in a private hospital in Indonesia.

329. New Glucose Lowering Drugs (Gld) Usage in Portugal: Results of an Intensive Monitoring Study in Real-Life Conditions

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Background: We investigated the trends in the utilization of GLD in Portugal (2004-2013) and we found that even though new GLD drugs are being used in large numbers of patients, unlike other European countries, evidence supporting its use with respect to routine clinical practice data is limited. By pharmacy based tracking of patients, we implemented an intensive monitoring (IM) model that is actively focused on gathering post-authorization data, aiming to fill the gap between clinical trials, database studies and spontaneous reporting data. Baseline results are here described.

Objectives: To describe the patterns of usage and population under treatment of new GLD in PT.

Methods: IM is defined as an inception cohort of subjects exposed to drug of interest. All adult type 2 diabetics initiating: DPP-4, glucagon-like peptide-1 (GLP-1) and sodium-glucose co-transporter 2(SLGT2) inhibitors, that consented to participate were consecutively recruited through pharmacies (Nov14-Apr15). Data was collected at baseline by a pharmacist during a face-to-face interview (socio-demographic, anthropometrics and self-reported health characteristics, drug utilization patterns). Data analysis comprised descriptive statistics.

Results: 385 out of 670 pharmacies that accepted to participate recruited 1333 eligible subjects and 231 refused to participate(similar age group and gender distribution, $p>0.05$). The mean age was 64.0 yrs, 50.5% were female, median age at diabetes diagnosis was 54 yrs, 88.8% had other chronic disease, 24.3% had diabetes related complications, 94% used concomitant medication (68.6% renin-angiotensin system acting agents, 63.2%statins and 33.9%antithrombotic). About 64% initiated DPP-4, 23.3% SLGT2, 11.2% GLP-1 and 2.0% more than one monitored drug. 70.7% were currently using other GLD(mean = 2.4 diff. GLD per subject), 27.7% of them were using insulin. 65.3% discontinued at least one GLD prior to recruitment.

Conclusions: Approx. 9% of patients were newly diagnosed (duration <= 6 months). Results suggest an approach that favours the intensification of GLD treatment. IM can play an important role in the frame of real-world practice evidence generation data.

330. Utilisation of Once Weekly Exenatide (Bydureon®) for Type 2 Diabetes Mellitus (T2DM): Interim Results from an Observational Cohort Study in England

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Background: Bydureon®, licensed in 2011, is indicated for treatment of T2DM in combination with metformin (MET), sulphonylurea (SU), thiazolidinedione (TZD), MET + SU or MET + TZD for patients (pts) with inadequate glycaemic control on maximally tolerated doses of these therapies alone. A post-marketing

safety study is underway as part of the EU Risk Management Plan.

Objectives: To describe pts characteristics and utilisation of Bydureon® at interim (once 2500 pts accrued).

Methods: An observational, population-based cohort study in primary care. Pts were identified from dispensed prescriptions (Rx) issued by GPs Sep 2011-Sep 2015 (interim datalock). Questionnaires were sent to GPs 12 months after each pts' 1st Rx for additional exposure, outcome and risk factor information for selected outcomes of interest recorded in medical charts. Summary descriptive statistics were calculated. A final cohort of 5000 pts is desired.

Results: Interim evaluable cohort = 2538 pts; 1410 (55.6%) males; median age 57 years (IQR: 50, 65). At baseline, 91.5% (n = 1984) of pts were obese (BMI>30.0 kg/m2) and 50.0% (n = 810) had HbA1c>9%, representing very poor diabetes control. A number of pts were diagnosed with T2DM >10 years (42.6%, n = 1054) prior to treatment. Prior exposure to exenatide (Byetta®) was reported in 33.2% (n = 826) pts. Bydureon® was prescribed in primary (50.2%, n = 1245), secondary (46.3%, n = 1146) and intermediate (2.9%, n = 73) care settings. Bydureon® was used predominantly as 2nd (30.9%, n = 744) or 3rd line co-therapy (66.6%, n = 1601). MET (85.5%, n = 2170) and SU (49.7%, n = 1260) were frequently co-prescribed antidiabetics at index. A total of 1752 pts (69.0%) continued treatment to the end of the 12-month observation period.

Conclusions: These interim results suggest Bydureon® is largely used in obese pts, suggesting possible channelling by prescribers to pts who are obese and/or have poor control of their diabetes. Bydureon® is largely prescribed as 2nd line co-therapy with MET or SU or 3rd line co-therapy with MET + SU, as per NICE guidelines. This interim analysis will be superseded once cohort accrual and final analysis are complete.

331. How To Use Pharmacy Dispensing Data To Measure Adherence And Identify Nonadherence With Oral Hypoglycaemic Drugs

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Background: Adherence calculations are often based on information of automated databases and require a number of methodological choices. A framework was available to assess adherence with oral hypoglycaemic agents (OHA) by health insurance claims data. Pharmacy dispensing data are useful to identify non-adherent (NA) patients for pharmaceutical care and need additional methodological categories.

Objectives: The objective was to examine the influences of different parameter values within a framework expanded for the use of dispensing data in estimating OHA adherence.

Methods: The following adherence measures were calculated for OHA use in the study period between July 2013 and July 2014: 1. The average medication availability (AMA), 2a. the percentage of patients with an AMA $\geq$ 80% (MRAP80) and 2b. the mean number of NA patients per pharmacy. Consequences from variation on parameter values for the adherence measures were compared to a base case scenario.

Results: Data were available for 604,500 OHA users in 1,737 Dutch community pharmacies. Adherence scores were for the base case an AMA of 88.3% and a MRAP80 of 80.3%, corresponding with 69 NA patients per pharmacy. Parameter variation resulted in scores for the AMA between 85.0 and 91.8%, the MRAP80 between 75.3 and 86.1% and between 49 and 92 NA patients per pharmacy.

Conclusions: Adherence scores by pharmacy dispensing data were relatively robust to parameter value variation within a methodological framework for relative OHA outcomes but differed substantially for absolute numbers of NA patients per pharmacy.

332. Factors Associated with T2DM Treatment Choice Across Europe

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Background: National guidelines for type 2 diabetes mellitus (T2DM) differ in treatment recommendations with regard to choice of antidiabetic drug classes.

Objectives: To explore demographic and clinical factors associated with T2DM treatment at time of treatment intensifications across Europe.

Methods: Antidiabetic drug prescription records were obtained from electronic medical record databases for a 5-year study period (2007-2011/2008-2012) in the Netherlands (NL), Italy (IT), Spain (ES) and the United Kingdom (UK). Oral monotherapy was defined as first line, oral dual therapy as second line, >2 oral treatments or oral combined with an injectable as third line and an injectable only as fourth line treatment. Treatment intensification was defined as first initiation of a higher line of treatment. Potential associated factors included general characteristics, comedication, comorbidities and clinical parameters and were evaluated using multivariate logistic regression.

Results: We included 48,479 (NL), 67,751 (IT), 348,572 (ES) and 152,544 (UK) patients. First line SU was associated with age >75 years (RRs from 2.04 (ES) to 3.66 (IT)) and with renal comorbidity (RRs from 1.36 (NL) to 2.65 (UK)), but inversely associated with BMI ≥25 kg/m2 in UK (RRs from 0.42 (UK) to 0.68 (ES)). For second line, age >75 years was associated with metformin + SU (RRs from 1.04 (ES) to 1.34 (IT)), and renal comorbidity with SU + DPP4 in UK (RR 1.26) and NL (RR 2.31). BMI ≥30 kg/m2 was associated with metformin + TZD (RRs from 1.26 (ES) to 1.79 (NL)) and with metformin + DPP4 in NL (RR 1.34) and UK (RR 2.38). For third line, age >75 years (RRs from 2.60 (ES) to 3.56 (UK)) and renal comorbidity (RRs from 1.61 (ES) to 3.45 (UK)) were associated with SU + insulin. BMI ≥30 kg/m2 decreased the probability of receiving metformin + SU + TZD as third line in UK (RR 0.90), but increased the risk in IT (RR 1.34) and ES (RR 1.51). High BMI was also inversely associated with any third line containing insulin. For fourth line women were more likely to receive GLP-1 in UK and ES.

Conclusions: The results from this study suggest that age and renal comorbidity were the predominant factors associated with the choice of T2DM treatment intensifications.

333. Comparison of Glucose Lowering Drugs Usage Between Portugal and 6 European Countries, in 2014

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Background: Portugal has one of the highest prevalence of type 2 diabetes in Europe hence this is a national health priority area. Drugs used in diabetes represent 20.1% of total pharmaceutical expenditure. National guidelines recommend metformin as first-line product of choice and the use of insulin exclusive or in association is possible in any stage of the disease.

Objectives: To perform a cross-country comparison of GLD utilization patterns between PT and six European countries focusing on quality prescribing indicators (e.g. metformin uptake and insulin usage) and a cost-saving scenario analysis using potentially more rational prescribing patterns in PT.

Methods: Cross-national GLD (ATC: A10A, A10B) utilization comparison of 2014 data from: Portugal, Denmark, England and Wales, Finland, the Netherlands, Norway and Sweden. Data from Portugal was retrieved from hmR Pharmacy Sales Information System, a nationwide database with representative ambulatory data. Data from other countries was selected from open-access databases in each country. Consumption data was expressed in defined daily doses (DDD) per 1000 habitants per day (DHD) using the ATC/DDD system for each country. Proportion of insulin utilization in total GLD market was calculated. Cost-saving analysis was performed using the mean cost/DDD in Portugal as reference.

Results: PT had a higher consumption rate of dipeptidyl peptidase 4 (DPP-4) inhibitor fixed-dose combinations (high cost/DDD) than the studied countries. Conversely, PT had the lowest intake of metformin alone (33.6%; 0.14€/DDD), half than Sweden, and the lowest insulin consumption rate (16.2%), 2.3 times lower than Norway. If PT had the same Dutch GLD (excl. insulins) consumption pattern (% in DDD) an expenditure

reduction of 118.7 M€ would had been achieved, corresponding to a decrease of 62.3% in total costs.

Conclusions: Portugal had the highest use of combinations with DPP-4, the lowest intake of oral first-line agents and insulin consumption rate. Increased use of first line agents can result in significant savings for patients, payers, and the health care system.

334. Medication Use and Potentially High Risk Prescribing in Older Patients Hospitalised for Diabetes: A Missed Opportunity to Improve Care?

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Background: The care of older people with diabetes is particularly challenging; half have three or more comorbid conditions and over 60% are likely to have a treatment conflict with the potential to cause poor health outcomes. Little is known about the influence of hospitalisation for diabetes on the prevalence of potential medicine conflicts or inappropriate prescribing in older people.

Objectives: To examine the appropriateness of medicine use, and extent of treatment conflicts and potentially high risk prescribing in older people prior to, and after hospitalisation for diabetes.

Methods: A retrospective cohort study was conducted between 1st Jan 2012 – 31st Dec 2012 among patients hospitalised for diabetes, using administrative data from the Australian Government Department of Veterans' Affairs. Clinical guidelines and Beers criteria were used to determine appropriateness of medicine use, and potentially high risk prescribing, including hyper-polypharmacy, treatment conflicts and inappropriate medicine use. Relative differences and 95% CI for changes in medicine supply 120 days before and after hospitalisation were calculated. McNemar's binomial test was used to compare changes.

ResultsA total of 876 subjects were hospitalised for a diabetes-related complication. Four months prior, 25% were not dispensed an anti-diabetic medicine and 25% had not had their HbA1c measured. Use of anti-diabetic medicines increased to 85% after hospitalisation, with a 25.6% relative increase (95% CI 10.9-42.1) in the those dispensed insulin. High risk prescribing prior to admission was high; 70% had more than 10 medicines dispensed, a third had at least one treatment conflict and half were dispensed a potentially inappropriate medicine. Little change in this high risk prescribing were observed following discharge.

Conclusions: This study identified high risk prescribing in older people hospitalised for diabetes. While diabetes medicine use improved following hospitalisation, there was limited change in potentially inappropriate medicine use suggesting an opportunity to improve medication use in this vulnerable population has been missed.

335. The Application of the HAS-BLED Criteria within Post Authorisation Safety Studies to Characterise Anticoagulant New User Patients with Non-Valvular Atrial Fibrillation (AF): Interim Results from a Specialist Cohort Event Monitoring (SCEM) Study

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Background: The Rivaroxaban Observational Safety Evaluation (ROSE) SCEM study is being conducted as part of a risk management plan to monitor short-term (first 3 months) safety and utilisation of rivaroxaban (Riv). A contextual comparator of new user patients (pts) prescribed best practice standard care (warfarin-War) is also being identified. Study objectives include advancing the understanding of the pt population prescribed Riv in the secondary care setting.

Objectives: An interim analysis to evaluate use of HAS-BLED to characterise baseline bleeding risk of pts with AF treated for prevention of stroke/systemic embolism with Riv or War.

Methods: An observational, population-based cohort study. The interim cohort was identified through a specialist network from Sep13 to Mar15 (datalock), supported by UK Clinical Research Networks. Data collected via a questionnaire from consenting pt medical charts by specialists incl. baseline pt

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characteristics within HAS-BLED. Descriptive statistics & univariate analyses [OR(95%CI)] were calculated (% denominator assumes no missing data).

Results: Interim AF cohort; Riv = 641, 53% male; War = 477, 56% male. Riv pts were more likely than War pts to have a stroke history [39% vs 26%;OR 1.8(95%1.4,2.3)], but less likely to have renal disease [1% vs 4%;OR 0.2 (95%CI0.1,0.6)] or use drugs predisposing to bleeds [2% vs 5%;OR 0.3 (95% CI0.2,0.7)]. Non-significance differences in baseline prevalence were observed of uncontrolled hypertension (3% vs 4%), abnormal liver function (0.5% vs 1%), predisposition to bleeds (4% vs 4%), excess alcohol use (2% vs 2%) and age 65+ yrs (84% vs 83%), respectively.

Conclusions: This SCEM study shows that HAS-BLED criteria can provide a framework for systematic collection of baseline bleeding risk data. In this interim analysis, some differences were observed between the Riv and War AF cohorts in the reported prevalence of baseline bleeding risk factors. Findings from this interim analysis will become obsolete when all available data are analysed for the final report.

336. Characteristics of Patients at Initiation of Treatment for Primary Chronic Immune Thrombocytopenia

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Background: It is recommended that patients with primary chronic immune thrombocytopenia (cITP) with platelet values over 30*109 /L without symptoms of bleeding can be left without any treatment. However, other factors such as age, comorbidity and co-medications can influence prognosis of the disease and might be considered in decision making for start of treatment.

Objectives: To study demographical and clinical characteristics of patients with cITP at initiation of ITP-treatment.

Methods: We identified 1,756 adults (18 years or older) with a diagnosis of primary cITP between 2009 and 2014 using the Swedish Patient Register. Codes D69.3 and D69.4 from the Tenth Revision of the International Classification of Diseases were used to identify patients. Data on platelet levels, treatments, comorbidity and co-medication were retrieved from medical records and the national registries.

Results: In total 824 (47%) patients were treated for their cITP during the study period, from those 485 were treated for the first time. There was no sex difference for those who were treated and their mean age was 56 years (SD=21). Median value for platelet counted within 10 days preceding the first treatment was 18*109 /L (IQR 7-35*109) and mean value was 30*109 /L (SD=40*109). A second treatment was received by 255 patients from which 104 (41%) were add-on treatments. Median value for platelet count before the second treatment was 19*109 /L (IQR 7-44*109), and mean value was 41*109 /L (SD=64*109). Mean number of treatments for each case during the study period was 4 (SD=9), and the most common drugs were corticosteriods, IVIg and rituximab. Platelet value at initiation of treatment was similar in those with or without comorbidity. Bleedings requiring hospital contact during the same year as treatment (45% at first and 48% at second treatment) were mostly epistaxis, petechiae and hematoma. The rates and patterns of comorbidity, other than bleeding, were similar before the first and second treatment episodes.

Conclusions: Patients with cITP have their first treatment according to the international recommendations. However, those receiving a second treatment had higher platelet counts.

337. Factors Associated with Rivaroxaban Prescribing in Specialist Care Setting: Interim Results from the Rivaroxaban Observational Safety Evaluation (ROSE) Study

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Background: Increasingly choice of medicines is guided by published guidelines. ROSE is being conducted as part of a risk management plan to monitor short-term (first 3 months) safety and utilisation of rivaroxaban (Riv). A contextual comparator cohort of

new user patients (pts) treated via standard care (warfarin-War) is also being identified. Study objectives include advancing the understanding of use of Riv in the secondary care setting.

Objectives: An interim analysis of treatment setting and factors influencing anticoagulant prescribing decisions.

Methods: An observational, population-based cohort study. The interim cohort was identified through a specialist network from Sep13 to Mar15 (data lock date), supported by UK Clinical Research Networks. Data collected via a questionnaire from consenting pt medical charts by specialists included reasons for prescribing such as guidelines. Descriptive statistics were calculated (% denominator assumed no missing data; sub-cohorts were pooled by indication: treatment/prevention of DVT/PE; prevention of stroke/systemic embolism in pts with non-valvular AF).

Results: Interim cohort = 2022 (54% Riv vs 46% War); median age 71 yrs (IQR 59, 80); 56% (1131) male; 59% (1193) were outpts; AF cohort =1118: Riv (59%), War (51%) and the DVT/PE cohort =860: Riv (39%), War (46%). Irrespective of indication, the most frequently provided prescribing reason was clinical judgement [Riv (98%), War (82%)]. Other reasons were NICE guidance [Riv (25%), War (40%)], lifestyle impact [Riv (29%), War (3%)] and formulary guidelines [Riv (15%), War (28%)]. Similar patterns were observed when data were stratified by indication group.

Conclusions: This interim analysis shows that in UK secondary care clinical practice, prescriber clinical judgement is the overriding factor affecting treatment choice. Whilst guidelines are important, their influence on prescribing decision differs between the two drugs. Non-clinical lifestyle considerations appear to be more important for patients treated with Riv than War. A formal multi-level analysis of determinants of prescribing is planned for the final analysis.

338. Cohort Characteristics and Determinants of Prescribing Rivaroxaban in Primary Care in England: Interim Results from a Post Authorisation Safety Study (PASS)

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Background: A UK PASS is being conducted as part of a risk management plan to monitor the safety and use of rivaroxaban (Riv) as prescribed for medical conditions requiring anticoagulation. Increasingly, patient (pt) prescribing is influenced by published guidelines. One study objective was to evaluate Riv prescribing in real-life clinical practice in primary care in England.

Objectives: A planned interim analysis to describe cohort characteristics and determinants of prescribing.

Methods: An observational cohort study. Interim cohort was identified from dispensed prescriptions of Riv in England from Dec 2011 to Jul 2015 (datalock). Questionnaires requesting information on drug utilisation were sent to prescribing general practitioners (GPs) at ≥3, and ≥12 months after 1st Riv prescription issued for each pt. Summary descriptive statistics were calculated; % denominator where response given; pts with single indications reported were analysed within mutually exclusive groups.

Results: Interim evaluable cohort = 8372 pts (median age 75 years (IQR 64-83)); 4223 (50.5%) female; indication of non-valvular atrial fibrillation (AF) reported for 4764 pts (56.9% cohort) and venous thromboembolism (VTE) for 2286 pts (27.3% cohort). More than half of pts (4862, 59.4%) were initiated on 20 mg od. Riv was initiated more frequently in secondary vs. primary care setting (4467, 55.3% vs. 3530, 43.7%). Recommendation from a specialist was the most frequent reason for prescribing (4509, 56.3%), followed by clinical judgement (2029, 25.3%), lifestyle/anticoagulation monitoring needs (1695, 21.1%) and recommendation by guidelines (1073, 13.4%).

Conclusions: The interim analysis reveals that Riv is largely prescribed within the licensed indications of AF and VTE. In terms of GP prescribing determinants, recommendation from a specialist would appear to be most influential, however approximately one fifth of GPs cite pt lifestyle factors (anticoagulation monitoring needs) as critical to the decision to prescribe. These results will become obsolete when further evaluation and validation are complete for the final report.

339. Characterisation of Baseline Risk Factors for Bleeding Outcomes in Patients with Non-Valvular

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Atrial Fibrillation (AF) Prescribed Rivaroxaban in Primary Care in England: Interim Results from a Post Authorisation Safety Study (PASS)

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Background: Rivaroxaban, first approved in the EU in 2008, is one of the novel oral anticoagulants. To advance the understanding of the safety and use of rivaroxaban, a UK PASS is being conducted in primary care as part of a risk management plan. Study objectives include characterisation of baseline risk of bleeding in patients (pts) with AF.

Objectives: To characterise baseline risk factors for bleeding in pts prescribed rivaroxaban in primary care in England.

Methods: An observational cohort study. Interim cohort identified from dispensed prescriptions of rivaroxaban in England from Dec 2011- Jul 2015. Risk factors for bleeding were collected from prescribing general practitioners (GPs) via questionnaires sent ≥3, and ≥12 months after 1st prescription issued for each pt. Summary descriptive statistics were calculated (% denominator is of interim AF cohort assuming no missing data; pts with other or multiple indications excluded).

Results: The interim evaluable 3-month AF cohort consisted of 4764 pts [median age 77 years (IQR 69-84)]; 2316 (48.7%) female). Relevant risk factors reported at baseline included: age>65 yrs (4193, 88.0%), stroke history (662, 13.9%), history of bleeding (114, 2.4%), excessive alcohol intake (85, 1.8%), uncontrolled hypertension (40, 0.8%), renal disease (38, 0.8%), medication use predisposing to bleeds (26, 0.6) and abnormal liver function (20, 0.4%). 4198 (88.2%) pts had a HAS-BLED score of 1 (3490, 73.3%) or 2 (708, 14.9%). 88 pts (1.9%) had a score of ≥3 indicating high risk of bleeding.

Conclusions: The results from this interim analysis show that the prevalence of stroke history is very common in patients with AF starting rivaroxaban, followed by a history of bleeding and excessive alcohol intake. A HAS-BLED score necessitating caution or regular review (i.e ≥3) was reported in 1.9% of the cohort. These results will be superseded after validation and follow-up are complete for the final analysis.

340. A Retrospective Analysis in a Local Health Authority in Northern Italy to Evaluate the Utilization of Oral Anticoagulants

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Background: Oral anticoagulants modify blood clotting capacity and are widely used for long-term prevention or treatment of thrombosis. The traditional drugs are vitamin K antagonists, while the new agents target either factor Xa or thrombin.

Objectives: To evaluate utilization pattern of anticoagulants in province of Cremona.

Methods: Data were retrieved from administrative databases; they included the register of residents in the province of Cremona, dispensed drugs, hospitalizations and outpatient care. A retrospective drug utilization study was conducted, enrolling subjects≥40 years old with at least one prescription of drugs with ATC codes B01AA, B01AE or B01AF during the period January 1st, 2013 – September 30th, 2015. Prevalence and volume of use were estimated. Frequency analyses by sex and age were performed. Incident users during the study period were identified, hospitalization and outpatient data were analyzed and used as proxy to define the indication for use. Switching patterns between traditional (TAO) and new oral anticoagulants (NAO) were explored.

Results: A total of 10,206 patients received at least one prescription of anticoagulants during the study period: 83% were TAO users and 37% were naïve users. Overall, 83,590 prescriptions of oral anticoagulants were cashed, 87% of which for TAO. The most used TAO was warfarin (88% of all TAO), while dabigatran was the most prescribed NAO (55% of all NAO). Overall, 17.0% were NAO users, for an estimated average 381.3 DDD, against a mean of 310.6 DDD for TAO. Incident anticoagulant users were prescribed TAO in 71.5% of cases, almost totally warfarin (95%). Approximately 35% of subjects was treated

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for nonvalvular atrial fibrillation (NVAF), 10% for pulmonary embolism and deep vein thrombosis. Switching between anticoagulants was not frequent, occurring only in 1.8% of users.

Conclusions: Traditional oral anticoagulants are frequently dispensed in the province of Cremona; switching between traditional and new anticoagulants is not so common yet.

341. How Complete Are Primary Care and Cardiologist Data in Germany for Research of Oral Anticoagulants in Non-Valvular Atrial Fibrillation?

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Background: In Germany, patients can move between primary care physicians (PCPs) and do not need referral to specialists, potentially affecting continuity of care and data quality e.g. availability of medical history and complete prescription data.

Objectives: To investigate the completeness of PCP and cardiologist data in Germany and impact on estimates of oral anticoagulant (OAC) persistence in patients with non-valvular atrial fibrillation (NVAF).

Methods: Patients with NVAF who were newly treated with an OAC (index prescription) between Dec-2012 and Oct-2014 in Germany were selected from IMS Disease Analyzer (DA). PCP and cardiologist panels from IMS DA were assessed separately. The completeness of both datasets was assessed by estimating median [1st-3rd quartiles] number of physician visits during the year prior to index date and regularity of such visits. "Regular" was defined as those who visited a physician in every quarter of the prior year and had ≤4 months between visits. Cumulative incidence [95% confidence intervals] of persistence to OAC therapy (i.e. no switch/discontinuation) at 6 months after OAC initiation were calculated separately in each panel. Patients could have initiated multiple OACs therefore analysis was conducted for each newly prescribed OAC exposure.

Results: Of 22,151 OAC exposures in the PCP data, median number of visits during the prior year was 16 [9-24] and 73% had regular visits in the data. Of 2,584 OAC exposures prescribed by cardiologists, median number of visits was 2 [1-4] and 9% had regular visits. 6-month OAC persistence rates were higher in the PCP data (novel OACs [NOACs] 68% [67-68] & vitamin K antagonist [VKA] 71% [70-72]) than the cardiologist data (NOACs 44% [41-46] & VKA 29% [24-35]).

Conclusions: Patients from the PCP panel had a higher number of visits and more regularly visited their physician, which may have had an impact on the observed higher persistence compared to patients from the cardiologist panel. Continuity of care was not observed in the cardiologist panel, highlighting the importance of quality assessments in specialist data.

342. Compliance and Persistence to Anticoagulation Therapy: A Retrospective Analysis in a Local Health Authority in Northern Italy

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Background: Oral anticoagulants modify blood clotting capacity and are widely used for long-term prevention or treatment of thrombosis. The traditional drugs are vitamin K antagonists, while the new agents target either factor Xa or thrombin.

Objectives: To analyze adherence and persistence of traditional (TAO) versus new (NAO) oral anticoagulants.

Methods: Data were retrieved from administrative databases; they included the register of residents in the province of Cremona, dispensed drugs, hospitalizations and outpatient care. A retrospective drug utilization study was conducted, enrolling subjects≥40 years old with at least one prescription of drugs with ATC codes B01AA, B01AE or B01AF during the period January 1st, 2013–September 30th, 2015. Compliance was measured as medication possession ratio (MPR); optimal compliance was defined at MPR ≥80%. Persistence, measured with Kaplan-Meier curves, was defined as time on therapy to discontinuation; patients who stopped

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treatment for 60 days were considered "non persistent". Adherence and persistence were estimated for three categories of users: "new" (who used only NAO), "old" (only TAO), and switch who used both TAO and NAO.

Results: A total of 10,206 patients received at least one prescription of anticoagulants during the study period, the 37% were naïve-to-treatment. Adherence for new users was about 63.9% [61.5%-66.3%], for switch 69.41% [67.7%-71.1%] and for old 42.4% [42.0%-42.95%]. The MPR grew if subjects with almost two prescriptions were considered, overall for new user reached the 85.9% [84.11%-87.6%]. Adherence is rather similar between gender. Kaplan-Meier curves showed more persistence for new users after about 150 days of treatment, before old users were more persistent than others. Wald-Test underlined that the difference between curves were statistically significant ($p<0.001$).

Conclusions: New oral anticoagulants users are better compliant and persistent, with an optimal MPR among those with at least two prescriptions.

343. Determinants of Blood Pressure Control Among Ambulatory Hypertensive Patients: A Cross Sectional Study in Ethiopia

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Background: Achieving tight blood pressure (BP) control has repeatedly shown to improve cardiovascular outcomes, but implementation remains a challenge. Africa experiences an epidemiological transition from infectious diseases to chronic non-communicable diseases such as hypertension. So far, little is known about treatment of hypertension.

Objectives: To investigate determinants for BP control and treatment intensification in Ethiopian ambulatory hypertensive patients.

Methods: A cross-sectional study was conducted in 6 public hospitals in Ethiopia. Hypertensive patients included were aged ≥18 on prior antihypertensive medication. The main outcome measures were controlled BP (SBP/DBP < 140/90 mmHg) and treatment intensification for those patients with uncontrolled BP. Multivariable logistic regression was used to identify determinants (sociodemographics, disease and treatment characteristics) for BP control and treatment intensification.

Results: We recruited 966 patients of which 93% had BP record at baseline. The mean age was 57 (SD14) years, 63% were females, and 35% had ≥ 1 cardiometabolic comorbidities. Overall, 335 (37%) patients had controlled BP. Treatment was intensified for 123 (23%) of 562 patients with uncontrolled BP. Determinants positively associated with achieving target BP were treatment at a general hospital (adjusted odds ratio 95% CI; 1.72 [1.17; 2.54]), treatment regimens with beta blockers (1.61 [1,07;2.44]), and a longer treatment duration (1.04 [1.02;1.07]), while negatively associated determinants were previously uncontrolled BP (0.37 [0.27;0.51]), treatment regimens with diuretics (0.66 [0.47;0.92]), older age (0.99 [0.98;1.00]), and longer refill period (0.86 [0.74;1.00]). The only significant determinant for treatment intensification in our multivariable model was longer duration of therapy (1.03 [1.00;1.05]).

Conclusions: The level of BP control in our study is similar to that described in European countries. Intervention programs to improve BP control should target previously uncontrolled patients, those who are elder or visit specialised hospitals. Programs should also address specific drug regimens and aim for frequent refills.

344. Adherence to Lipid-Lowering Therapy in Elderly – A Pharmacy Database Study in Bulgaria

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Background: Patients with dyslipidemia are at high risk for cardiovascular diseases. Adherence with prescribed therapy can considerably mitigate this risk and is important in these patients.

Objectives: The aim of this study is to evaluate adherence to lipid-lowering therapy in patients over 65 years old using pharmacy dispensing records and define predictors of non-adherence.

Methods: This retrospective study examined the refill patterns of 341 patients diagnosed with hyperlipidemia (ICD code E75.8) from their automatic pharmacy dispensing records for a period of 24 months. Adherence was measured as proportion of days covered by each one month interval following enrolment in study. Patients were considered adherent if they had filled prescriptions no later than 5 days after due date. Age, sex, comorbidities, generic/brand medicines were evaluated as potential predictors of adherence.

Results: Two-year adherence rates were 70% for women and 64% for men. Lower copayments were associated with higher levels of adherence for both groups. After adjustment for age, sex, comorbidities and other potential predictors, patients were more likely to be adherent if they were female, age 65-75 years old and with a history of coronary heart disease.

Conclusions: Elderly patients have low rates of adherence to lipid-lowering therapy. This suggests that they receive limited benefit from their therapy.

345. The Association Between Statin Therapy and Neovascular Age-Related Macular Degeneration

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Background: Statins may inhibit atherosclerotic process, an essential pathophysiologic manifestation in neovascular age-related macular degeneration (nAMD). However, little is known on the preventive effect of statin therapy on nAMD.

Objectives: The study aimed to investigate the relationship between statin therapy and nAMD.

Methods: A case-control study was conducted by using the Taiwan's National Health Insurance Research Database (NHIRD), containing 1 million beneficiaries who were randomly sampled in 2005. The cases were defined as patients with diagnosis of nAMD (ICD9 of 362.52) from 2000 to 2010. The index date was set as the first date of nAMD diagnosis. The control group was selected from the non-AMD cohort, which excluded AMD patients (ICD9 of 362.5x), by matching on age, sex, and the index year. The statin use was defined as at least 1 prescription of statin (ATC code of C10AA). Odds ratio for the association between statin use and nAMD was calculated by logistic regression model, adjusted for socioeconomic status, past history of eye diseases, co-medications for eye diseases, and other comorbidities and co-medications.

Results: 1048 cases were identified and matched to 1048 controls. The mean age of cases was 64.58 year old, and 52.2% (547/1048) cases are female. Among cases, 15.07% (158/1048) had at least 1 prescription of statin, while 15.27% (160/1048) controls had exposure to statin. The crude odds ratio for the association between statin use and nAMD is 0.98 (95% CI 0.81-1.12). The association remained insignificant after adjustment by multiple logistic regression (OR 0.95, 95% CI 0.91-1.22).

Conclusions: The statin use was not associated with the development of nAMD. Additional prospective studies would be needed to determine the preventive effect of statin on nAMD.

346. Association Between Exposure to Evidence-Based Heart Failure Drug Treatment and All-Cause Hospitalization and All-Cause Mortality

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Background: According to evidence-based consensus clinical guidelines, patients suffering from heart failure (HF) should be treated with the HF evidence-based drug treatment (i.e. bisoprolol, metoprolol or carvedilol + an ACE inhibitor, an angiotensin receptor blocker or hydralazine + isosorbide dinitrate).

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Objectives: To assess the association between exposure to HF evidence-based drug treatment and 1) all-cause hospitalization and 2) all-cause mortality, among people newly diagnosed for HF.

Methods: We conducted two nested case-control studies using Quebec (Canada) medico-administrative data. We selected cases and controls in a cohort made of Quebec residents ≥ 18 years who had a first diagnosis of HF between 01/01/2000 and 12/31/2009 and who did not use HF evidence-based drug treatment before their diagnosis. Cases were those hospitalized or who died during follow-up. Each case was randomly matched to 4 to 10 controls using incidence density sampling. Exposure to HF evidence-based treatment was assessed using the proportion of days covered (PDC). Adjusted odds ratios (OR) were calculated using conditional multivariable logistic regressions.

Results: Among the 125,622 individuals in the cohort, 96,794 (77.1%) were hospitalized and 52,064 (41.4%) died during follow-up. Only 8.8% of hospitalization cases, 10.8% of their controls, 9.1% of death cases and 12.4% of their controls had a PDC ≥ 80%. Compared to those with a PDC ≥ 80%, patients who had a PDC > 0% and < 80% (OR = 1.30 (95% CI = 1.25-1.34) or a PDC = 0% (OR = 1.41 (1.37-1.45) were more likely to be hospitalized. Similarly, compared to those with a PDC ≥ 80%, patients who had a PDC > 0% and < 80% (OR = 1.46 (95% CI = 1.41-1.52) or a PDC = 0% (OR = 1.64 (1.58-1.70) were more likely to die during their follow-up.

Conclusions: Exposure to HF evidence-based drug treatment is suboptimal. A low exposure could increase the risk of hospitalization and have a detrimental effect on survival of HF patients.

347. Classification of Drugs Implicated in Cases of Proarrhythmia: Results from the Drug-Induced Arrhythmia Risk Evaluation (DARE) Study in England

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Background: Several drugs have been withdrawn due to QT prolongation (QTp) or Torsade de Pointes (TdP). The DARE study aimed to improve knowledge of the epidemiology of proarrhythmia [documented TdP, ventricular fibrillation (VF) or polymorphic/non-polymorphic VT (non-QTp); exacerbation of pre-existing proarrhythmia, newly documented proarrhythmia or conversion of unsustained proarrhythmia to sustained; severe >500 ms) or moderate (450 ms male/470 ms female) QTp with past medical history (PMH) of presyncope or syncope] by identifying a cohort of cases.

Objectives: Characterise cases and estimate contribution of individual drugs to risk of proarrhythmia.

Methods: Self-reported data on demography, symptoms, PMH and drug history (DH) were gained for proarrythmia cases referred by cardiologists in England 2003-2011. PMH/DH were verified from hospital notes. Implicated drugs were adjudicated by 2 cardiologists and classified (ATC system). Proarrythmia risk and cytochrome (CYP) P450 activity were categorised using CredibleMeds; potential drug-drug interactions were identified using Medscape Drug Interaction Checker. Analysis comprised descriptive statistics and radar plots.

Results: Of 124 cases, 95 (77%) were QTp-related and 29 (23%) non QTp-related; mean age 62 yrs [SD 15]; 63% female; PMH: 66 (53%) high blood pressure, 90 (73%) heart rhythm problems, 34 (27%) heart valve problems; 33 (27%) hypokalaemia at presentation. Of 166 implicated drugs, 70 (42%) were antiarrhythmics (C01B) [40 amiodarone; 23 flecainide]. A single drug was implicated in 90 (73%) pts and multiple drug combinations in 32 (26%) pts [27 >1 CYP inhibitor]. Potential drug-drug interactions were QTp (19), cardiotoxic (5), conditional (6), other (1). Drugs with known/possible/conditional QTp risk were implicated individually in 88 (71%) pts or in combination in 24 (19%) pts.

Conclusions: Antiarrhythmics, non-cardiac drugs and drug combinations were implicated in the 124 clinically-validated proarrhythmia cases. Underlying cardiovascular disease was present in most cases. Selection bias is possible due to referral and adjudication by cardiologists only.

348. Characterization of New Users of Cilostazol in the United Kingdom, Spain, Sweden, and Germany

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Background: Cilostazol is indicated in Europe to improve walking distances in patients with intermittent claudication. The European Medicines Agency evaluated the benefit/risk of cilostazol and recommended labeling changes, including addition of unstable angina, recent myocardial infarction, or recent coronary intervention as new contraindications.

Objectives: To describe the characteristics of new users of cilostazol in Europe to support evaluation of its benefit/risk as used in regular clinical practice before the implementation of new contraindications.

Methods: New users of cilostazol were identified in five automated health databases—United Kingdom (THIN), Spain (IACS-EpiChron and SIDIAP), Sweden (National Registers), and Germany (GePaRD)—between 2002 and 2013. New users were characterized according to the prevalence of cardiovascular disease and other comorbidity, concurrent use of interacting medications, new contraindications, duration of use, and potential off-label prescribing.

Results: We identified 22,593 new users of cilostazol. Characteristics of users varied across databases. Median age in years ranged from 68.0 (SIDIAP) to 73.7 (Sweden). Between 74.5% (IACS) and 95.7% (GePaRD) of users had cardiovascular disease other than peripheral arterial disease, 78.8% (GePaRD) to 91.6% (THIN) were treated with interacting medications, and 2.7% (Sweden) to 22.3% (THIN) were treated with potent CYP3A4 or CYP2C19 inhibitors. Prevalence of new cardiovascular contraindications ranged from 1.5% (THIN) to 11.6% (GePaRD), and concurrent use of two or more antiplatelet drugs ranged from 6.3% (SIDIAP) to 13.5% (IACS). Between 39.4% (Sweden) and 52.9% (THIN) of users discontinued cilostazol in the first 3 months. Between 41.0% (SIDIAP) and 93.4% (THIN) of users were considered to have received cilostazol according to the labelling.

Conclusions: This collaborative European study showed that most cilostazol users were elderly patients with a high prevalence of comorbidity, particularly of cardiovascular diseases, high concurrent use of interacting drugs, and high discontinuation rates in the first 3 months of treatment.

349. Physician Adherence to Acute Coronary Syndrome Prescribing Guidelines in Vietnam: A Prospective Observational Study

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Background: Acute coronary syndrome (ACS) is a leading cause of death in Vietnam, guidelines describe the essential role of medications in treatment, but little is known about actual prescribing patterns.

Objectives: To determine the extent of physician adherence to ACS prescribing guidelines at hospital discharge and to identify factors correlated with adherence and clinical outcomes.

Methods: We conducted a prospective observational study on all patients with ACS discharged from two

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public hospitals in Can Tho city, Vietnam between January and October 2015. Patients who were transferred to another institution or who discharged home without a prescription were excluded. Data were collected from medical records and telephone interviews with patients at 1 month after discharge. The extent of physician adherence to guidelines was defined as the percentage of eligible patients receiving guideline-recommended medications at discharge. Factors correlated with physician adherence and 30-day readmission or death were identified using logistic regression.

Results: Overall, 550 patients were included (mean age 68.5 (SD 13) years, 55% male). Anti-platelet agents and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers were prescribed for 94%; beta blockers for 64%; statins for 95%; and all 4 medications for 53% of eligible patients. Patients were more likely to receive all 4 medications at discharge when undergoing an invasive procedure (OR 5.2; 95% CI 2.7-10.3) or not having health insurance (OR 2.3; 95% CI 1.1-4.8). Patients had a higher risk of 30-day readmission or death when having diabetes (OR 3.5; 95% CI 1.6-7.4), estimated glomerular filtration rate (eGFR) $<$ 60 mL/min (OR 2.7; 95% CI 1.4-5.2), or not receiving all 4 guideline-recommended medications at discharge (OR 3.7; 95% CI 1.9-7.2).

Conclusions: In general, physicians closely adhered to ACS prescribing guidelines in Vietnam. But prescribing of all 4 guideline-recommended medications could be improved, especially for patients with insurance.

350. Lipid Profile and Patient Characteristics Prior to Initiation of Niaspan (Extended Release Niacin) Therapy: Analysis of a Large Electronic Medical Record Database

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Background: The combination of high TG and low HDL-C is recognized as a lipid risk factor for the development of atherosclerotic cardiovascular disease. Niaspan's indications include its use as monotherapy for the treatment of very high TG levels and for the raising of HDL-C. The patient characteristics and lipid profile, prior to initiation of therapy, in the real world clinical setting has not been well documented.

Objectives: The objective of this study was to evaluate the lipid values, particularly TG and HDL-C levels, as well as prevalence of CHD/CHD risk equivalent prior to starting Niaspan therapy in the General Electric (GE) outpatient population.

Methods: Using electronic medical record data of outpatient care in GE system, all adult (age≥18 [thinsp]years) patients with a first prescription of Niaspan (defined as the absence of any previous prescription of Niaspan/Niaspan combination products for at least six months) were identified between July 1 2000 and June 30 2013. Patients were categorized based on lipid values into three groups: (a) high TG (≥200 mg/dL) or low HDL-C values <40 mg/dL in men, <50 mg/dL in women) or combination of the two; (b) normal TG and HDL-C values (TG $<$ 200 mg/dL and HDL-C $\geq$ 40 mg/dL in men/≥50 mg/dL in women) (3) Others.

Results: There were 89,091 new users, 65.0% were men, and 94.2% above 40 years old, 77% (n = 68,538) had HDL-C or TG levels measured within 6 months prior to initiation of therapy. Mean (± SD) values for TG, HDL-C, and LDL-C for females were 221.6 ± 139.7 mg/dl, 46.4 ± 15.8 mg/dl and 123.5 ± 46.2 mg/dl respectively. Mean values for men were 213.3 ± 145.9 mg/dl, 36.4 ± 10.9 mg/dl, and 99.7 ± 37.9 mg/dl respectively. Overall, 77% had either TG and or HDL-C abnormality and 34% had abnormality of both TG and HDL. Among abnormal TG and HDL group the ratio of TG to HLD-C was very high among younger age group. More than a third of the patients had diagnosis of CHD or CHD risk equivalent prior to starting Niaspan.

Conclusions: Drug utilization analysis demonstrates that the majority of Niaspan users had high TG and/or low HDL-C. TG/HDL-C ratios was higher in younger population.

351. The Temporal Trend of the Prevalence of Heart Failure Hospitalization Prior to Dispensing of Dronedarone

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Background: Dronedarone is an antiarrhythmic drug approved by the US Food and Drug Administration in 2009. Dronedarone is contraindicated in and has a boxed warning for patients with symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure. Accordingly, a risk evaluation and mitigation strategy has been in place to prevent the use of dronedarone in such patients.

Objectives: To examine the temporal trend of the prevalence of heart failure hospitalization within 30 days prior to dispensing (initiation or refilling) of dronedarone.

Methods: Dispensing of dronedarone between July 2009 (launch date in the US) and December 2013 and heart failure hospitalizations within 30 days prior to each dispensing were identified using the Clinformatics DataMart and the MarketScan databases. In each database, the prevalence of heart failure hospitalization within 30 days prior to dispensing of dronedarone was calculated for each quarter starting with the third quarter (Q3) of 2009.

Results: A total of 9,474 and 46,759 dronedarone users who had at least 30 days of continuous enrollment in databases prior to the dispensing of dronedarone were identified in Clinformatics and MarketScan, respectively. The quarterly prevalence of heart failure hospitalizations within 30 days prior to each dispensing ranged from 0.6% (10/1,766; 95% confidence interval (CI): 0.2 – 0.9%) in Q3 2013 to 3.1% (30/964; 95% CI: 2.0 – 4.2%) in Q4 2009 in Clinformatics and from 1.2% (117/9,631; 95% CI: 1.0 - 1.4%) in Q3 2013 to 5.0% (74/1,491; 95% CI: 3.9 - 6.1%) in Q3 2009 in MarketScan. There was a statistically significant downward trend in prevalence in both databases ($P < 0.001$).

Conclusions: The prevalence of heart failure hospitalization prior to dispensing of dronedarone was low and there was a significant downward trend over time in 2 claims databases in US. The results suggest that the risk evaluation and mitigation strategy is effective in limiting the use of dronedarone in patients with recent heart failure hospitalization.

352. Patterns Of Statin Initiation And Continuation In Cancer Patients Towards End-Of-Life

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Background: Statins are widely used in the prevention of cardiovascular disease. The potential benefit of statin use in those with reduced life expectancy may be limited to high-risk cardiovascular patients, and may be considered for discontinuation otherwise. Studies investigating statin exposure and cancer outcomes, not accounting for these changes in statin use towards end-of-life, may be subject to reverse causation. A method for dealing with this is lagging drug exposure, which requires information on how statin exposures change prior to death.

Objectives: The aim of this study was to longitudinally describe changes in statin exposure prior to death, in patients with breast or colorectal cancer.

Methods: This study was carried out using linked national cancer registry and pharmacy claims data. Patients who died of their breast or colorectal cancer (cases) were matched (by cancer type, tumour stage, age at diagnosis, gender, and pre-diagnostic statin use) to patients who survived (controls), and the probability of initiating statin, or continuing statin use was estimated in the five years prior to a cancer-specific death (cases) or index date (controls). Conditional binomial models were used to estimate relative risks and risk differences for associations between statin initiation/continuation and cancer-specific death/index date with 95% confidence intervals (CI).

Results: In breast cancer cases (N = 1,055) matched to controls (N = 1,577), and colorectal cancer cases (N = 1,668) matched to controls (N = 1,668), we observed no difference in statin initiation, approaching cancer death/index date. The probability of continuing statin use appears to decline in the year prior to a breast or colorectal cancer death. In the week prior to death, the probability of continued statin use was 45.7% for breast cancer cases, compared to 76.5% of breast cancer controls (RD -0.30 95%CI -0.38, -0.23); and 30.8% for colorectal cancer cases, versus 77.4% for controls (RD -0.47 95% CI -0.55, -0.38).

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Conclusions: A significant proportion of patients cease statins in the time prior to a cancer specific death. This has implications for epidemiological studies that investigate statin-use and cancer mortality.

353. Continuity of Prescribing and Medication Adherence in Patients with Schizophrenia and Cardiometabolic Comorbidities

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Background: Patients with schizophrenia often have comorbid cardiometabolic conditions that increase risk for morbidity and mortality. Given the prevalence of comorbidities in this population, there is the potential for patients to have prescribing by more than one provider resulting in disruptions in continuity of care.

Objectives: Our objectives were to examine continuity of prescribing in patients with schizophrenia and one or more comorbid cardiometabolic conditions (hypertension, hyperlipidemia, and/or diabetes) and its effect on medication adherence.

Methods: In a retrospective cohort study using 2010 data, we examined whether medication adherence differed by the number and type of providers managing patients from 4 U.S. Medicaid programs. The exposure of interest was a count of the number of Primary Care Providers (PCPs) and number of Psychiatric Specialists involved in the prescribing of medications for each patient in 2009. We hypothesized that having a single PCP and single psychiatric specialist would result in the highest proportion of days covered (PDC) measure of medication adherence to antipsychotic, oral diabetes, statins for hyperlipidemia, and antihypertensive medications.

Results: Among the 4236 patients with schizophrenia and one or more cardiometabolic conditions; 2189, 3277, and 2181 had diabetes, hypertension, and/or hyperlipidemia respectively and19.36% of patients had all three comorbidities. The PDC for antipsychotic medications and medications for cardiometabolic conditions was relatively unaffected by the number of PCP prescribers involved in patient care. However, increasing the number of psychiatric specialty prescribers from one to three or more was associated with higher antipsychotic adherence (76.4 vs 83.1%) but poorer cardiometabolic medication adherence (62.8% vs 56.5% for diabetes, 71.7% vs 70.1% for hypertension, and 60.1 vs 51.6% for hyperlipidemia).

Conclusions: Continuity of prescribing appears to influence adherence to mental health and cardiometabolic conditions differently. Additional analyses are needed to control for the severity of illness in this population to inform interventions to improve medication use.

354. Time-to-Treatment In The Management Of Relapsing/Remitting Multiple Sclerosis

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Background: Despite drug therapy for multiple sclerosis (MS) having a critical role in in slowing disease progression and alleviating sympotms, many patients appear to delay onset of treatment.

Objectives: The aim of this study was to explore the time-to-treatment in a longitudinal cohort of MS patients and identify factors associated with delay in treatment initiation.

Methods: Data from a longitudinal patient cohort of all patients treated at a specialist MS clinic in Sydney, Australia was used. All patients with relapsing remitting disease, treated at the clinic between June 2008 and September 2015 were included in the study. Time to treatment initiation was calculated as the number of days between the first date of documented definitive diagnosis, and the date that the drug therapy treatment was first prescribed. Cox regression survival analysis was used to identify factors associated with time to initiation.

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Results: The cohort comprised 109 patients of whom 84.4% initiated treatment in the study period. Interferons (1alpha, 1beta and pegylated, 62.0%, n = 57/92) were most commonly the first agent commenced. The median time-to-initiation was 62 days (IQR 7-142 days). Almost one fifth (19.5%) commenced treatment on the day of diagnosis and 34.8% commenced within a month. Only commencement of interferon 1 alpha was associated with significant delays in time to treatment (OR = 5.089, 95%CI 1.044-24.791). No clinical factors including age, gender, level of disability, quality of life, lesion load at diagnosis, and fatigue, were significant in predicting delays treatment initiation.

Conclusions: While many patients are treated within weeks of receiving a diagnosis of MS, many patients experience significant delays in the commencement of therapy. Some differences in time to treatment were observed for the different drug classes used but further work to better understand these delays are needed to ensure patients receive optimal care.

355. Potentially Inappropriate Prescriptions for Stimulant Medication for Treatment of Attention Deficit Hyperactivity Disorder Among Canadian Adults

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Background: There is increasing awareness of attention deficit hyperactivity disorder (ADHD) in adults and a corresponding increase in prescribing of ADHD medications in this population. The prevalence of potentially inappropriate prescriptions (PIP) for stimulant ADHD medications has not been documented in Canada.

Objectives: To describe the rate of PIP of stimulant ADHD medications among adults across Canada overall and stratified by province and age group.

Methods: We used data from public drug programs across Canada (except Quebec) to investigate PIP of stimulant ADHD medications among adults aged 18 years of age or older in 2013 and 2014. In order to define PIP of stimulant ADHD medication, we identified prescriptions of at least 30 units. PIPs were then defined as subsequent prescriptions that were dispensed within 1-7 days of the initial prescription by a different physician and different pharmacy. Proportions of PIP were calculated as the number of prescriptions that were potentially inappropriate among all stimulant ADHD medications prescribed. Analyses were stratified by province and age group (18-25, 26-35, 36-64, 65+).

Results: The rate of PIP for stimulant ADHD medications was low <0.3%; N = 2,574) across all provinces. Overall, Ontario had the highest rate of PIP followed by Alberta and British Columbia (range from 0.2-0.5%). In Manitoba, Newfoundland and Labrador, and Saskatchewan the rate of PIP was highest among those aged 18-25, whereas in Alberta, British Columbia, and Ontario the highest rate of PIP was among those aged 26-35.

Conclusions: The rate of PIP for stimulant ADHD medications in adults across Canada was low overall, highest in Ontario, and highest in individuals aged 18-35.

356. Psychotropic Medication Use in Patients with Eight Major Cancers in Japan: A Retrospective Descriptive Study Using a Health Insurance Claims Database

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Background: Although psychiatric comorbidity is common among cancer patients, no study has examined the use of psychotropic drugs at a national level in Japan.

Objectives: To investigate the prevalence and prescription patterns of the use of psychotropic drugs among patients with any of the eight major cancers after an initial diagnosis using a health insurance claims database in Japan.

Methods: A retrospective descriptive study was performed using a health insurance claims database consisting of approximately 300 million patients' medical fee receipts provided by over 50 health

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insurance societies across Japan. We extracted data of newly diagnosed patients aged 18 to 74 years with any of the eight major cancers (breast, colorectal, liver, lung, ovary, pancreas, prostate, and stomach) between July 2009 and May 2014. We calculated the percentages of the psychotropic drug prescriptions given within 13 months of an initial diagnosis of any of the cancers. Psychotropic drugs were defined by the Anatomical Therapeutic Chemical (ATC) classification system codes N03 to N07.

Results: A total of 25,148 patients (56.6% female) with a mean (± standard deviation) age of 53 (±10.54) years were included. The cohort consisted of patients with eight types of cancer (breast, 24.7%; colorectal, 21.9%; stomach, 15.1%; ovary, 13.7%; lung, 9.9%; prostate, 3.5%; liver, 3.9%; and pancreas, 3.5%). Of these, 55.7% were prescribed at least one psychotropic drug; the highest proportion was 66.3% in pancreatic cancer patients, while the lowest was 43.6% in prostate cancer patients. Benzodiazepines (BZDs), the most commonly prescribed psychotropic drugs, were prescribed to 45.2% of patients. More than half of the patients with any of the five major cancers (colorectal, liver, lung, pancreas, and stomach) received BZDs, while the proportion in patients with the other three cancers was approximately 30%.

Conclusions: In Japan, psychotropic drug prescription is common among patients with any of the eight major cancers. The most frequently prescribed psychotropic drugs were BZDs, and the prevalence of the prescription varied according to the type of cancer.

357. Utilization of Psychosocial Services After Initiation of Antipsychotics in High Risk Youth

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Background: Concomitant management with psychosocial services (PS) in youth treated with antipsychotics (ATPs) is considered a quality of care indicator. Despite the evidence on the benefits of PS, patterns of PS use following ATP initiation are unknown, especially among high risk youth.

Objectives: To explore patterns and likelihood of PS utilization after ATP initiation, comparing sub- groups of youth defined by prior psychotropic use history.

Methods: A retrospective cohort of Medicaid-insured youth, <21 years, in foster care for at least 1 year during 2010-2014, from a mid-Atlantic U.S. state, who initiated ATPs after a 6 month washout, was identified using Child Welfare linked to Medicaid Administrative claims. Psychotropic use was defined as having a prescription for stimulants, antidepressants or mood stabilizers. Youth were classified based on psychotropic use in the 12 months prior to initiation as non-users [NP] (no use of any psychotropics), past-ATP [P] users (prior to washout) and users of any psychotropics (except ATP). PS were defined as any outpatient psychotherapy visit after ATP initiation. Quarterly probabilities PS were compared across user types using proportion differences. Hazard Ratios (HRs) with 95% confidence intervals (CI) were estimated using a multivariate counting process Cox regression, to compare the risk of PS receipt across subgroups.

Results: We identified 730 initiators of whom 178 (24%) were past ATP users, 339 (46%) had other use and 214 (29%) had no use. Eighty-one percent (n = 598) of youth had a PS visit during follow-up, with 48% of those (n = 292) only having one. The quarterly probability of a PS visit within 3 months of initiation ranged from 65% to 80%, being lowest in the P group. P users were less likely to have a PS visit during follow up when compared to NP (HR 0.83 CI 0.75, 0.92) or other users (HR 0.90 CI 0.38, 2.17). No differences were observed between other and NP users (HR 1.04 CI 0.96, 1.14).

Conclusions: Our findings suggest that use of concomitant PS in youth is low and varies by history of psychotropic use. Variability in the utilization of recommended practices could differentially affect outcomes in this population.

358. Correlates of In-Patient Initiation of Antipsychotics Among Elderly Patients Discharged to Nursing Homes

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Background: Antipsychotics are often initiated in the hospital setting for elderly patients discharged to nursing homes. The extent to which initiation of antipsychotics varies across hospitals has yet to be explored.

Objectives: To describe hospital-level variation of in-patient antipsychotic initiation and to identify patient-level and hospital-level correlates of initiation among elderly patients discharged to nursing homes.

Methods: Using an extract from the US Cerner HealthFacts database (74 acute care hospitals), we identified 31,272 hospitalizations in 2012 without documentation of an antipsychotic medication on the day of admission among 24,907 unique patients aged ≥ 65 years without schizophrenia, Tourette's syndrome, or Huntington's disease and discharged to nursing home. Initiation of antipsychotics was defined as presence of an in-patient medication record after admission date. Correlates of initiation of use at the patient-level (e.g. age, sex, race, diagnoses) and hospital-level (e.g. teaching hospital, bed size) were estimated using hierarchical models.

Results: Six percent had antipsychotics initiated during the hospital stay (hospital-specific estimates ranged from 0% to 15.4%). Women were less likely than men to have antipsychotics initiated (Odds Ratio (OR): 0.76; 95% CI: 0.69 – 0.83). Patients with delirium were at greatest risk for initiation (OR: 7.78; 95% CI: 6.56 – 9.21). The estimated variance of the hospital intercepts was 0.17 (standard deviation: 0.05) indicating a significant hospital effect on antipsychotic initiation. Bed size of the hospital facility was the strongest observed facility-level correlate of antipsychotic initiation (e.g. OR<99 beds versus >500: 0.37; 95% CI: 0.24 - 0.57).

Conclusions: The observed hospital-level variation in antipsychotic initiation and correlates of initiation suggests that hospitals (as the point of initial prescribing of antipsychotics) may offer a new target for intervention to reduce antipsychotic use in nursing homes.

359. Prevalence and Associated Factors of Psychotropic Medication Use: A Cross-Sectional Study of the Mexican Teacher Cohort

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Background: Depression is the second leading cause of disability globally and among the top ten causes of disability in Mexico.

Objectives: To study the prevalence of psychotropic medication use in female teachers in Mexico with severe symptoms of depression and associated factors including comorbidities, place of living, lifestyle activities and daily life stressors.

Methods: We used first follow up cycle data (2011-2013) of the Mexican Teachers' Cohort and extracted the records of those teachers with completed information on the Patient Health Questionnaire (PHQ9) form, from a 12-state area in Mexico. Using multivariate analysis, we assessed the differences between severe vs mild-no depression in terms of any use of psychotropic medication, comorbidities, age, region, residential area, amount and intensity of weekly physical activity, stress, alcohol consumption and smoking status.

Results: Out of 43,845 teachers with available PHQ9 scores, 7,026 teachers had a score compatible with moderate-severe depression. The prevalence of severe depression was 16%. Only nineteen percent of those with a PHQ9 score suggesting severe depression received medication, while teachers with a previous diagnosis of depression reported using medication 60% of the time. Adjusted results showed an increased medication use in the group with severe depression (OR 2.52, CI:2.29-2.72), more than three comorbidities (OR 2.50, CI:2.18-2.87), higher levels of couple, family and work stress ($p < .0001$), consumption of more than 4 glasses of alcohol a month (OR 2.33, CI:1.93-2.81) and cigarette consumption (OR 1.44, CI:1.30-1.59). Teachers located in North and Center rural residencies were more likely to report severe depression compared to their urban counterparts.

Conclusions: Less than a fifth of teachers without a formal depression diagnosis but consistent clinical signs of depression are using psychotropic medication.

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The regional drivers of higher proportions of depressed teachers in rural areas in the north and center states in Mexico warrant future studies to explore possible barriers to care.

360. Drug-Drug Interactions at Increased Risk of Adverse Effects for Antipsychotic Users in France from 2007 to 2012: A Population-Based Study

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Background: Data on antipsychotic (AP) use in patients with underlying conditions that increase the risk of adverse effects, such as concomitant use of drugs at risk of interactions, are lacking.

Objectives: To estimate the prevalence of drug-drug interactions (DDIs) in AP new users in France. This study was part of the DRUGS-SAFE program, funded by the French Medicine Agency (ANSM).

Methods: A yearly repeated cross-sectional study was conducted from 2007 to 2012 within the French national healthcare insurance system. DDIs, as defined in APs Summary of Product Characteristics, were explored in new users (no AP reimbursement in the year prior to the first dispensing of AP over each studied year). Reimbursements of concomitant drugs during a 60-day period (30 days before and 30 days after the first dispensing) were used to identify DDIs. Prevalence of DDIs was also measured for 2007 and 2013 (at least one AP reimbursement during the year).

Results: From 2007 to 2012, 86% to 88% of AP new users had at least one concomitant drug at increased risk of adverse effects at treatment start. In 2012, enhanced CNS-depression due to concomitant use of other sedatives was common (70%), and higher in patients treated with the most sedative APs [1] such as chlorpromazine and clozapine >80%). An increased risk of arrhythmias related to the concomitant use of drugs that prolong the QT interval, or that induce hypokalemia or bradycardia was found in 40% of AP new users. An increased risk of atropinic effects due to concomitant use of other atropinic drugs was found in 29% of new users. Concomitant use of drugs known to induce orthostatic hypotension was found in 40% of new users (52% for chlorpromazine, an AP with high risk of hypotension); concomitant use of drugs lowering seizure threshold was observed in 41%. Similar results were found in prevalent users both in 2007 and 2013.

Conclusions: DDIs at-risk of adverse effects were very common at AP treatment start, and may persist all along treatment duration. These results emphasize that more education on rational prescribing in AP users is required.

1. Leucht, *et al. Lancet* 2013; **382**: 951–962.

361. Antipsychotic Medication Treatment of New Depressive Episodes in the US Medicaid Population

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Background: Several antipsychotic medications (APMs) are FDA approved as adjunctive treatments for depression after insufficient response to antidepressants (ADs). The role of APMs in the community treatment of depression, however, remains poorly understood.

Objectives: To characterize the role of APMs in the community treatment of adult depression.

Methods: We identified all new episodes of adult (25-64 years) depression in national US Medicaid data from 2001 to 2010 (n = 2,041,372). Episodes with pre-existing alternative APM indications, such as schizophrenia or bipolar disorder, were excluded. Each episode was followed for 1 year to characterize APM and AD treatment and emerging alternative APM indications. APM initiators without emerging APM indications through day 45 following APM initiation were presumed to have initiated the APM for treatment of depression. Among this group, we determined whether APM initiation was preceded by minimally adequate AD treatment, defined as active AD treatment for ≥30 days prior to and including the day of APM initiation.

Results: Within 1 year following onset, 14.1% (n = 287,085) of new depressive episodes included an APM initiation (mean time from diagnosis to APM initiation: 99.4 days). 41.5% (n = 119,026) of APM initiators developed an alternative APM indication through day 45 of APM initiation (predominantly bipolar disorder or depression with psychotic features) leaving 58.5% (n = 168,059) who presumably initiated APMs for nonpsychotic depression. APM doses were generally in line with recommendations for adjunctive treatment in depression. 73.3% (n = 123,160) of patients initiating an APM for depression did not have minimally adequate AD treatment prior to APM initiation.

Conclusions: APMs are commonly used to treat patients with new episodes of depression. In approximately 60% of cases APMs appeared to be intended for the treatment of depression. While APM dosing patterns were in line with recommendations, almost 3/4ths of the APM-treated patients did not receive even minimally adequate AD treatment prior to APM initiation, indicating potentially premature initiation of a drug class with substantial adverse effects and medical risks.

362. Potentially Inappropriate Medications in Elderly Patients: Prevalence and Changes During Hospital Stay

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Background: Inappropriate prescribing in older patients is a major cause of preventable adverse drug events. At the time of hospital admission, there is an opportunity to stop potentially inappropriate medications (PIMs).

Objectives: To estimate the prevalence of PIMs upon admission and describe changes made during hospitalization.

Methods: We conducted a prospective cohort study of patients seen at the McGill University Health Center in Montreal, Quebec, Canada from May 2014-October 2015 who were over the age of 65. Medications patients were taking upon admission to hospital were obtained from drugs dispensed in the past 3 months retrieved from the provincial pharmanet system as was their reconciliation action. The STOPP criteria were utilized to identify PIMs effecting the central nervous system (CNS) and included use of 1st generation antihistamines & prolonged use (≥4 weeks) of benzodiazepines, tricyclic antidepressants (TCA's) & antipsychotics since they are commonly prescribed in this patient population.

Results: Among the 2,042 included patients, mean age (SD) was 77 (8), and 44% were female. Patients were admitted to hospital with a total of 19,282 drugs (9 on average per patient). A total of 718 CNS drugs were considered to be potentially inappropriate; 570 (28%) patients were admitted with at least one PIM. Of the 718 inappropriate medications at admission, 417 (58%) were benzodiazepines, 221 (31%) were antipsychotics, 30 (4%) were antihistamines and 50 (7%) were TCA's. Within the subgroup of patients (n = 742) for which we had information on medication reconciliation actions, 29% of PIMs present at admission were stopped upon discharge from hospital; antihistamines were the least likely to be discontinued (36%) while antipsychotics were the most likely (22%). Additionally, 31% of benzodiazepines were discontinued.

Conclusions: The prevalence of treatment with PIMs was high in elderly patients upon admission to hospital with the most common PIMs including benzodiazepines. The majority of PIMs were not discontinued at discharge, therefore future research should evaluate interventions to increase the discontinuation of PIMs during the hospital stay.

363. Initiation Of Strong Prescription Opioids In Australia: Cohort Characteristics And Factors Associated With The Type Of Opioid Initiated

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Background: Although the patterns and harms of increasing opioid use have been well documented in several countries, there is limited research on opioid initiation.

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Objectives: To describe the characteristics of Australians initiating strong opioids and examine the factors associated with the type of opioid initiated.

Methods: National dispensing records were used to form a cohort from a 10% sample of people who initiated a strong opioid (buprenorphine, fentanyl, hydromorphone, morphine, oxycodone) between 29 September 2009 - 31 December 2013 (90-day strong opioid-free window). We restricted the cohort to concessional beneficiaries so that all dispensed medicines could be ascertained. Socio-demographic characteristics, previous dispensing histories and index opioid use were examined. Multinomial logistic regression was used to calculate adjusted relative risk ratios (aRRRs) and 95% confidence intervals (CIs) to determine the factors associated with the type of opioid initiated, relative to oxycodone.

Results: A total of 125,335 concessional beneficiaries initiated a strong opioid: 58.3% were female and 63.7% were aged ≥65 years. The most commonly initiated strong opioid was oxycodone (72.8%), usually 5 mg immediate-release tablets (76.1%). Compared to people aged 18-44 years, those ≥85 years were 14.18 times as likely (95% CI 12.67-15.87) to initiate morphine than oxycodone. Compared to people with no previous anti-cancer medicine dispensing, those dispensed an anti-cancer medicine were 2.34 times as likely (95% CI 2.11-2.60) to initiate morphine than oxycodone.

Conclusions: The most commonly initiated strong opioid was oxycodone, usually at lower strengths. Those who initiated oxycodone were more likely to be younger with no previous dispensing of an anti-cancer medicine. As these are high-risk characteristics for potential harms, a judicious approach when initiating strong opioids for this group is necessary.

364. Alcohol and Illicit Drug Use and Their Association with Prescription Opioid Misuse Among Undergraduate and Postgraduate Medical Students in Greece

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Background: Medical students may be at a higher risk for substance use and this behaviour can create unfavourable patterns and affect their professional life in the future.

Objectives: To investigate the prevalence of illicit drug use and the correlations with alcohol and the non-medical use of opioid painkillers among medical students in Northern Greece.

Methods: 657 undergraduate and postgraduate medical students from the Faculty of Medicine of the Aristotle University of Thessaloniki participated in the study completing a self-administered web survey. The survey included questions regarding: i) prevalence of illicit (e.g marijuana, heroin, cocaine, ecstasy, amphetamines, LSD, mephedrone) and licit drug use (opioid painkillers that were used without physicians consent) and ii) the CAGE questionnaire, a widely used screening test for potential alcohol problems iii) a question investigating binge drinking behaviour. All statistical analyses were performed using Statistical Package for Social Science (SPSS) v. 22.0.

Results: Overall, 657 students completed the survey. The mean age of the participants was 22.2 ± 2.3 years and 90% were undergraduate students. Lifetime use of illicit drugs was 23,9% (157/657). The mostly used substance was marijuana (21%) followed by cocaine (2.3%), ecstasy (2.3%), LSD 2%, ketamine (2%), and amphetamines (1.8%). The prevalence of lifetime opioid misuse was 19.6% (129/657). 6.2% of the participants scored positive in the CAGE scale and 22.2% in the binge drinking scale. In the multivariate model illicit drug use was significantly correlated with number of cigarettes ($p<0.001$), binge drinking ($p<0.001$) and also the study level (undergraduate/postgraduate, $p=0.014$). There was no significant correlation with opioid misuse and the other factors (gender, study year, CAGE).

Conclusions: Approximately one quarter of the participants reported use of illicit drugs and several factors are independently associated. Further research is needed to investigate the prevalence, the motivation and also the impact of this risky behaviour among medical student population.

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365. Drug Utilization Study for Lisdexamfetamine Dimesilate in Australia

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Background: Attention Deficit Hyperactivity Disorder (ADHD) is a developmental disorder primarily characterized by the co-existence of attentional problems and hyperactivity. Lisdexamfetamine dimesilate (LDX) was authorized for treatment of ADHD in Australia in 2013.

Objectives: The overall objective of the study is to provide utilization data for LDX in Australia.

Methods: This is a cross-sectional study which includes longitudinal patient level prescription data (IMS® LRx database) and de-identified patient data from a survey among physicians known to treat patients with ADHD. The study was conducted in an outpatient setting across Australia. Here, data from 01 September 2013 to 31 August 2015 are shown.

Results: Data from 101 patients in the survey and from 1,701 LDX prescriptions in the database for 471 patients were analysed. 76% of the patients documented in the survey were male. One patient (1%) was younger than 6 years, 70 patients (69.3%) were between 6 and 17 years. 30 patients (29.7%) were adults. No patient was older than 55 years.

All patients had a documented diagnosis of ADHD. For all but one patient, ADHD was documented as the main indication for prescribing LDX.

The average daily dose (ADD) prescribed by the physicians in the survey was between 10 mg to 140 mg, with a mean around 41.9 mg per day. Recommended daily dose of 70 mg was not exceeded in 99% of patients in the physician survey. Mean ADD derived from IMS® LRx data was 44.6 mg, with 97% within the recommended range.

Conclusions: Overall, the findings indicate that LDX is prescribed mainly within the label. That is, to the indicated age group and without exceeding the recommended dosage.

366. Use of Benzodiazepines in Circumstances at Increased Risk of Adverse Effects in the French Population

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Background: Prevalence estimates of benzodiazepine (BZD) use in patients with underlying conditions that increase the risk of CNS or respiratory depression are lacking.

Objectives: To estimate the overall prevalent use of BZD and their use in circumstances at increased risk for BZD adverse effects in the French population. This study was part of the DRUGS-SAFE program, funded by the French Medicine Agency (ANSM).

Methods: A cross-sectional study was performed using data from the French national healthcare insurance system. Prevalence of use was estimated by considering as users patients who had at least one BZD reimbursement during the year 2013. The explored at-risk circumstances for BZD use were: i) drug-drug interactions at risk for sedation and respiratory depression; ii) comorbidities at risk for adverse respiratory effects, or for falls or fracture.

Results: The prevalence of BZD use in France in 2013 was estimated at 13.8% (95%CI: 13.7-13.8); it was higher among women and increased with age. This prevalence was 10.6% (10.5-10.7) for anxiolytic BZD, and 6.1% (6.0-6.1) for hypnotic BZD. Roughly half of BZD users (48.1%; 47.8-48.5) were in at least one circumstance at increased risk for BZD adverse effects at index date; this proportion increased with age. Drug-drug interactions represented the most prevalent at-risk circumstance; it concerned 39.3% (38.9-39.6) of BZD users. The drugs most frequently involved were opioids: analgesics (15.9%; 15.6-16.2) and antitussives (6.8%; 6.6-6.9). Comorbidities at increased risk for adverse respiratory effects were found in 11.3% (11.1-11.6) of BZD users (13.9% in those aged

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65-69; 13.4-14.5) and comorbidities at increased risk for falls or fracture in 7.0% (6.8-7.2) of BZD users (13.4% in those aged ≥80; 12.7-14.0).

Conclusions: This study identified a high prevalence of at-risk circumstances in BZD users, most commonly related to drug-drug interactions. These findings are concerning, given that benzodiazepines are frequently used especially among the elders.

367. Misuse of Benzodiazepines in the French Population: A Cohort Study in the Echantillon Généraliste de Bénéficiaires Between 2007 and 2012

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Background: Benzodiazepines are commonly used in France. A recent study performed by the health authorities has reported that 17% of the population had a benzodiazepine dispensation at least once in 2012. Studies have shown that benzodiazepine use and especially misuse is associated with risks (falls, bone fractures, dementia, road traffic accidents, etc.).

Objectives: Estimate of benzodiazepine misuse in France using a French insurance claims database (EGB, Echantillon Généraliste de Bénéficiaires).

Methods: Between 2007 and 2012, every subject contributing to the EGB with a first benzodiazepine dispensation (hypnotics including derivatives, i.e. zopiclone, zolpidem, and anxiolytics). The date of first dispensation was the index date. Misuse criteria: i/ frequency of concomitant dispensations of 2 benzodiazepines of the same type within 30 days following the index date; ii/ frequency of index dispensations covering more than 4 weeks of treatment for hypnotics and more than 12 weeks for anxiolytics; iii/ frequency of at least 1 new dispensation of a hypnotic or anxiolytic over the 2 mths following the end of the treatment coverage period.

Results: About 28 000 subjects were identified between 2007 and 2012 as new users of benzodiazepines (about 10 000 hypnotics and 18 000 anxiolytics each year). According to the year of inclusion, 27% to 30% of hypnotic users and 17% to 20% of anxiolytic users had at least one misuse criterion. The most frequent misuse criterion was renewal of the first dispensation over the 2 mths following the end of the treatment coverage period, which varied between 2007 and 2012 from 19 to 22% for hypnotics and from 10 to 12% for anxiolytics. Misuse by a treatment covering more than 4 wks for hypnotics varied from 14 to 16%, and covering more than 12 wks for anxiolytics varied from 11 and 19%. Misuse by concomitance varied from 4 to 6% for both hypnotics and anxiolytics.

Conclusions: According to the considered criteria, one third of hypnotic users and one fifth of anxiolytic users in France presented with misuse of benzodiazepines. Actions to improve good prescription and use of benzodiazepines are still needed.

368. Characteristics of Opioid Maintenance Therapy (OMT) Prescribers and Their Distribution Among OMT Patients in Ontario

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Background: Opioid maintenance therapy (OMT) such as methadone and buprenorphine is the standard of care for opioid dependency in Canada. As the opioid epidemic grows worldwide, a better understanding of OMT prescribing and its physicians is of the utmost importance.

Objectives: To describe OMT prescribers in Ontario and to determine the clustering of OMT patients among them.

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Methods: We conducted a population-based, cross-sectional study examining physicians who prescribed methadone or buprenorphine for OMT to individuals eligible for publicly funded drug coverage in Ontario, Canada between January 1, 2014 and December 31, 2014. We determined the distribution of OMT patients and urine drug screen (UDS) billings among these prescribers using linked administrative data housed at the Institute for Clinical Evaluative Sciences. Clustering of patients among prescribers was estimated using Lorenz curves and Gini coefficients. Baseline physician characteristics were summarized among low, medium and high volume prescribers.

Results: We identified 565 methadone prescribers and 635 buprenorphine prescribers for OMT in Ontario in 2014. Physicians were predominantly male (67%) with a median age of 50 years. We found that the top 10% of methadone prescribers were treating 48% (N = 28 533) of methadone patients in Ontario (Gini = 0.73) and the top 10% of buprenorphine prescribers were treating 43% (N = 3876) of buprenorphine patients (Gini = 0.73). The highest volume methadone prescribers saw an average of 467 patients and billed and average of 14 147 UDS in 2014, compared to only 140 patients and 2396 UDS among medium volume prescribers.

Conclusions: The results show an unequal distribution of patients among OMT prescribers, with a small proportion of physicians caring for the majority of patients. It is uncertain whether this may impact the quality of primary care provided, therefore these results will be used in future studies to determine the quality of care of OMT prescribers in Ontario. Ultimately, this will inform OMT policy decisions.

369. Detection of Aberrant Opioid Use in Prescription Claims Data: Comparison and Validation of Five Algorithms

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Background: Given the soaring rates of prescription opioid abuse and overdose in the US, there is growing interest in applying algorithms to prescription claims data to identify aberrant behaviors, such as misuse, abuse, and diversion. Yet the relative performance of available algorithms has not been evaluated.

Objectives: To compare and validate five previously published algorithms to detect aberrant opioid use: the Opioid Misuse Score, Controlled Substance-Patterns of Utilization Requiring Evaluation (CS-PURE), Overutilization Monitoring System, Katz, and Cepeda algorithms.

Methods: Claims data for incident prescription opioid users were extracted from the Medicaid Analytic eXtract (MAX) for 2000-2010 and United Healthcare for 2004-2013. Patients were followed for 1 year after their first opioid dispensing, and aberrant opioid behavior was defined according to each of the five algorithms. Cohen's kappa was calculated to assess algorithm agreement. Unadjusted risk differences (RD) between the identified aberrant and non-aberrant users were also calculated to assess risk of an opioid-related adverse event (defined as an ICD-9 code for opioid abuse, overdose, or dependence) for each algorithm.

Results: There were 3.7 million eligible individuals in MAX and 4.3 million in United who received at least one new opioid prescription. Algorithms ranged from flagging potential aberrant behavior in 0.02% to 12.8% of patients in MAX and 0.01% to 7.9% of patients in United. Kappa values were poor to moderate (0.01 to 0.50 in MAX; 0.01 to 0.30 in United). Algorithms varied substantially in their ability to predict opioid-related adverse events; the Overutilization Monitoring System had the highest RD (14.8% in MAX; 13.4% in United) and the Katz algorithm had the lowest (1.03% in MAX; 0.47% in United).

Conclusions: In large cohorts of publicly and commercially insured patients, we demonstrated that algorithms differed substantially in agreement and performance. Further evidence-based improvements to existing algorithms may be possible.

370. Prescription Opioid Access Patterns in Australia: A National Observational Cohort Study

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Background: Prescription opioid use has increased 15-fold in Australia in the past two decades; yet there is limited understanding about individual opioid access patterns and the factors associated with increased access.

Objectives: Examine associations between patient and clinical factors and increasing opioid access patterns as measured by number of prescribers, pharmacies and dispensings.

Methods: We used Pharmaceutical Benefits Scheme (PBS) dispensing history of a 10% random sample of persons aged ≥18 years, with complete ascertainment of PBS drugs, commencing a strong opioid treatment episode (no evidence of strong opioid dispensing for 3 months) between July 2010 and December 2012. We used separate zero-truncated negative binomial regressions to explore factors associated with increased access patterns. Persons were censored 365 days after their index opioid or at death, whichever came first.

Results: 70809 persons commenced a new strong opioid treatment episode; they were predominantly female (60%) with a median age of 72 (interquartile range [IQR]:59-81). Over 1-year they had a median of two opioid prescribers (IQR:1-3), one dispensing pharmacy (IQR:1-2) and three dispensings (IQR:1-10). Eleven percent of the cohort had access patterns in the upper quartile across all outcomes, i.e. ≥3 prescribers, ≥2 pharmacies and ≥10 dispensings. Being male (IRR: 1.14[1.12-1.17]), history of pain management (IRR: 1.72[1.67-1.77]), history of cancer therapy (IRR: 1.70[1.58-1.82]) and higher overall disease burden (≥6 conditions IRR: 1.75[1.68-1.82]) were all associated with increased dispensings. We found similar patterns for the two other outcomes with the exception that increasing age was positively associated with increased dispensings and negatively associated with increased prescribers and pharmacies.

Conclusions: We demonstrated the complexities of prescription opioid access patterns. The three outcomes used in this study are often dichotomized in the literature, with higher access representing 'misuse'. However, our study shows that Australian patients access multiple prescribers, pharmacies and dispensings which may be a marker more severe illness, not necessarily inappropriate use.

371. Withdrawn by Author

372. Association Between High Risk Opioid Prescribers and Patients

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Background: Despite epidemic rates of injuries and deaths associated with prescription opioids, little is known regarding the degree to which high-risk patients are concentrated within high-risk prescribers.

Objectives: To describe patterns of opioid prescribing and utilization stratified by prescriber and patient risk levels.

Methods: We used IMS Health LRx all-payer, longitudinal pharmacy claims, to characterize patients and prescribers into high and low risk groups. We focused on 821,125 patients in Florida from July 2010 to Jun 2011. Patients were classified as high risk if they: (1) filled more than 14-days of concomitant opioids and benzodiazepines in a year (concomitant users), or (2) used more than 100 morphine milligram equivalents per day for more than 90 days (chronic users). Prescribers were classified as high risk if they comprised the highest fifth percentile of opioid volume for four consecutive calendar quarters. Among patients who

saw both low and high-risk prescribers, we calculated the differences in opioid dispensing between high and low risk prescribers for every eligible patient, and evaluated if such differences were statistically different from zero using the Wilconxon Signed Rank Test after accounting for patient comorbid burden using the Chronic Disease Score. We performed multiple sensitivity analyses that varied these assumptions.

Results: A total of 12.1% (concomitant users) and 2.7% (chronic users) of patients were classified as high-risk. Approximately 17%-28% of opioid volume and 20%-46% of all opioid prescriptions prescribed to high-risk patients originated from low-risk doctors. After accounting for patient comorbid burden, patients were more likely to receive higher doses, longer days supply, greater opioid volume and more opioid prescriptions when they saw high-risk prescribers instead of low-risk prescribers; these effects increased with patient comorbid burden.

Conclusions: High-risk prescription opioid users obtain a substantial proportion of their opioids from low risk prescribers. The persistence of differences in prescribing patterns holding patient factors constant suggests the importance of interventions targeting prescriber behavior.

373. The Influence of Concomitant Opioids on Opioid Utilisation for Tramadol Users – A Retrospective Cohort Study in the UK Primary Care Setting

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Background: Tramadol was re-classified as a Class C /Schedule III controlled drug in the United Kingdom (U.K) from June 2014 because of the potential for misuse and harm. However, the therapeutic role in relation to other opioids in the general practice is still under studied.

Objectives: This study aimed to assess the influence of combining opioids on daily consumption of opioid analgesics in tramadol users.

Methods: This retrospective cohort study used the U. K Clinical Practice Research Datalink database from 2000 to 2010. Adults (≥18 years) initiated tramadol during study period and had ≥2 tramadol prescriptions were included. The duration from the first tramadol prescription to the date when no further tramadol was prescribed in 60 days was defined as the first tramadol spell. Patients concurrently received other opioids in the first spell were defined as combine groups. Mean daily dose (MDD) of tramadol and all opioids (including tramadol) in the first spell were measured in oral morphine equivalent dose (OMEQ). Descriptive statistics were used to summarise patients' baseline characteristics and compare the MDD of all opioid between combine and non-combine groups. The association between baseline characteristics and opioid utilisation with MDD of all opioids was tested by multiple linear regression.

Results: Of the 261906 included tramadol users (mean age 57.7 ± 17.4 years), 60.2% were female and 69.7% had multiple spells. The median duration and the MDD of tramadol in the first spell were 40 days and 48.9 ± 100.4 mg of OMEQ. Of the 60,441 (23.1%) tramadol users classified as combine group, their MDD of all opioids (56.7 ± 110 vs. 36.5 ± 81, $p<0.001$) in the first spell were lower than the non-combine group; and the MDD of all opioids was significantly associated with the MDD of other opioids during combination (coefficient: 0.24, 95% confidence interval: 0.23, 0.24; $p<0.001$).

Conclusions: Many tramadol users received several spells of tramadol prescriptions. Dose of opioids is the main reason of increasing opioid daily consumption for new tramadol users. The safety and appropriateness of such combination need further evaluation.

374. The Difference in Baseline Characteristics Between Persistent Tramadol Users Defined by Different Criteria

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Background: Although several algorithms have been developed to identify persistent opioid users in

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literature, there is no consensus on a common criterion to define tramadol persistent users.

Objectives: This study compared the characteristics of tramadol users to explore the feasibility of defining persistent tramadol use by a modifying and existing algorithm for persistent opioid use.

Methods: The retrospective cohort study used the UK Clinical Practice Research Datalink from 2000 to 2011. Adult patients (≥18 years) who were prescribed with tramadol in primary care during the study period followed from index date (first tramadol prescription) to the end of registration or end of study. The persistence of tramadol was defined by annual consumption (AC), number of prescriptions (NP) and number of quarters covered (NQC) in the first patient-year. Patients were categorised into 'strict' (AC≥60000 mg, NP≥10 and NQC = 4) and 'wide' (AC≥15000 mg and NQC≥3) groups of persistent use. Patients' disease history, demographics, and medication use in 6 months prior to index date were measured. Descriptive statistics and univariate analysis were used to assess the differences in baseline characteristics between strict and wide tramadol persistence groups.

Results: Overall, 18.5% and 5.2% of the 524583 patients were categorised in the wide and strict persistence groups. The proportion of female was similar in both groups (58.8% vs. 59.3%). The mean age was slightly higher (59.2 ± 0.1 vs. 58.9 ± 0.1 years, $p = 0.0359$) but the proportion of patients with cancer diagnosis was significantly lower (6.7% vs. 7.8%, $p < 0.001$) in strict definition group. Higher proportion of patients in the strict definition group used antidepressants (33.8 vs. 31.1%, $p < 0.001$) and benzodiazepine (15.3% vs. 13.7%, $p < 0.001$) and received ≥1125 mg oral morphine equivalent dose of weak opioids (2% vs. 1.2%, $p < 0.001$) prior to tramadol initiation.

Conclusions: There was marked variation in patient characteristics among persistent tramadol users. The impact of the variation in baseline characteristics should be considered when exploring the association between persistent tramadol utilization and its safety outcome.

375. Monitoring of Medication Uptake in Difficult Asthma

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Background: Poor compliance with prescribed medicines has been identified as a significant contributing factor for difficult asthma.

Objectives: To determine qualitatively the acceptability of using details of medicines dispensed in primary care to inform the treatment of patients with difficult-to-treat asthma.

Methods: Consultant respiratory physicians' access to a summary of all relevant medicines dispensed from community pharmacies to patients attending a difficult asthma clinic was piloted in 2015 (therapy review). Patients consented to this and the summary was used to assess compliance with therapy and inform future management.

Semi-structured interviews were conducted with 8 patients who had received a therapy review within a difficult asthma clinic and 8 respiratory physicians: 2 with access to the summary and 6 without. The interviews aimed to highlightthe experiences of patients and physicians on the utility of therapy reviewsthe views of physicians without access to summaries on the prospective use of therapy reviews.

With the participants' consent, interviews were recorded and transcribed. Thematic analysis of responses from each group was conducted with the use of NVivo software.

Results: All consultants agreed that poor compliance remains a significant concern when treating patients with difficult asthma. Physicians with experience of therapy reviews supported their use. Advantages were reliability over current methods of assessing compliance; ability to inform future treatment and assist in the discussion of medicine use. This was reflected in the opinions of other physicians. There was concern that use may lead to confrontation: reflected in the experience of one patient who expressed that use of the review discouraged them from improving compliance. Additional intervention is needed to improve compliance. Opinions from other patients were positive and supported the inclusion of therapy reviews as part of a consultation.

Conclusions: This demonstrates the positive impact of using primary care dispensed medicine data in secondary care to assess medicine compliance and inform a patient's future treatment, but highlights that

continued investigation and action is required to lead to an improvement.

376. Oral Corticosteroids in Asthma Exacerbations: Differences Between Patient-Reported Data and Proxies from Claims Data

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Background: In claims data, asthma exacerbations are approached by proxies based on new dispensations of oral steroids (OCs). However, it is unclear how OCs dispensations match with the use of OCs courses for asthma declared by patients.

Objectives: We compared OCs dispensations with OCs courses for asthma reported by patients. The patterns of use of patient-reported OCs courses for asthma exacerbations were also described.

Methods: Persistent asthma patients (age 6-40) with at least 6 months of prescribed therapy by ICS and/or LABAs were prospectively followed up to 24 months, with data collected on asthma exacerbations by computer-assisted telephone interviews every 4 months and monthly text messages. Patient-reported data were individually linked to claims data. The percentage of patients presenting ≥ one dispensation of OCs during the first 12 months of follow-up (study period) was compared to patients' declared OCs courses.

Results: Among 363 asthma patients with a complete 12-month follow-up (mean age 22 years, 47% females), 27% reported ≥ one OCs course for asthma during the study period. A majority of OCs courses (53%) coincided with an unscheduled medical contact. Compared to patient-reported OCs courses for exacerbations, the presence of OCs dispensations during the study period showed sensitivity and specificity rates of 70% and 71%, respectively. After discarding OCs dispensations associated exclusively to non-respiratory drugs and those filled ≥ 2 days after prescription, the specificity raised to 86%.

Conclusions: OCs dispensations in claims data match only partially with patient-reported OCs courses for asthma exacerbations. Specificity increased with an algorithm linking OCs to respiratory therapy and early refill of prescriptions. OCs courses for asthma exacerbations are often associated with unscheduled medical care, suggesting an emergency context and possibly inappropriate patients' training on disease self-management.

377. Excess Dosing and Knowledge About Currently Used Acetaminophen-Containing Products

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Background: Acetaminophen is contained in hundreds of OTC and Rx products; lack of knowledge of product ingredients and dosing instructions may increase the risk of overuse.

Objectives: Examine the relation of knowledge about current acetaminophen medications to excessive dosing.

Methods: Adult subjects were enrolled from internet panels from 2012 through 2014. Each recorded their medication use daily for 7 days. Acetaminophen products taken were identified from a comprehensive list. An exit survey elicited knowledge of product ingredients and dosing directions for currently used medications. "Complete" knowledge was defined as knowing that all products taken during the week contained acetaminophen and that >1 product should not be used concurrently, and for all OTC products, the correct dosing amount and interval between doses.

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The prevalence of complete knowledge and unadjusted odds ratios (OR) with 95% confidence intervals were calculated for various groups of users. We also examined the relation of individual types of knowledge to specific deviations from label directions, e.g., knowledge of minimum dosing interval in subjects who redosed too soon.

Results: Among 7222 acetaminophen users, 481 exceeded the maximum recommended 4 g dose on ≥1 day. Only 2.5% of the latter had complete knowledge, and the OR was 0.2 (0.1-0.4) relative to those who had taken ≤4 g. This relation was attenuated among users of 2 or more products (OR, 0.4; 0.2-0.8), primarily due to decreased knowledge in users who did not exceed 4 g. Although the overall prevalence for individual knowledge types (maximum 1-time dose, minimum dosing interval, and avoiding concomitant use) varied from 21-84%, >4 g users were approximately 60% less likely to know each of these metrics. Each specific knowledge type was inversely associated with the corresponding deviation, with ORs of 0.2 for maximum 1-time dose, and 0.5 for the two other types.

Conclusions: There is substantial room for improving knowledge about safe use of acetaminophen-containing products. However, a few individuals exceed maximum daily dose recommendations despite complete knowledge.

378. Withdrawn by Author

379. Antibiotics Resistance Pattern and Prevalence of Urinary Tract Pathogens in Malaysia

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Background: Antibiotics resistance is a daunting problem for the treatment of urinary tract infections (UTIs) worldwide.

Objectives: The aim of this study was to investigate antimicrobial resistance patterns and prevalence of urinary tract pathogens (UTPs) in Malaysia.

Methods: Positive urine culture samples were collected and studied between July 2014 and July 2015. All urine samples were cultured on different mediums i.e. blood agar and EMBs. Colonies were counted after 24 hours at 37C and samples having colony count more than 100 000/mL were considered as positive. BD Phoenix 100 were used for bacterial identification and antimicrobial susceptibility. Statistical software package was used for analysis.

Results: A total of 158 urine samples were found to be culture positive. 95 patients (60.12%) were female while 63 (39.88%) were male. The mean age of the patients was 46.2. The following three most common organisms isolated were: Escherichia coli (55.5%), Klebsiella pneumoniae (24.5%) and Pseudomonas aeroginosa (17.8%). E. coli was found to have higher resistance against ciprofloxacin (44.2%), ampicillin (28.8%), gentamicin (28.8%) and no resistance to imipenem (0%) and meropenem (0%). Ampicillin-resistance was also highest in Klebsiella spp. (47.1%) and Enterococcus spp. (31.9%).

Conclusions: This study showed low antibiotic resistance which may be because of the limited usage of wide spectrum antibiotics in Malaysia, but still accurate choice of antimicrobials and antibiotics is crucial to obtain optimal outcomes. More studies are also needed to explore whether this resistance pattern will change in the following years.

380. Antibiotic Use Practices By Pharmacy Staff: A Cross-Sectional Study in Saint-Petersburg, Russia

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Background: The global emergence and spread of antimicrobial resistance remain a major infection control challenge and a predominant reason for therapy failure. Non-prescription access to antimicrobials is

common and self-prescribing is increasingly popular in Russian society.

Objectives: The aim of this study was to assess attitudes of community pharmacists related to antibiotics use and self-medication.

Methods: We conducted a cross-sectional study of community pharmacists in Saint-Petersburg and Leningrad region, Russia (n=410). The final sample comprised of 316 pharmacists. A self-administered questionnaire was used and included the following categories: attitudes and behaviours towards antibiotic use and self-medication; information on the types of involved diseases, knowledge of antibiotic use and resistance, and source of antibiotic knowledge; personal and professional information. To evaluate the influence of attitudes, behaviour, knowledge and demographics on self-medication with antibiotics, univariable logistic regression analyses were performed. Association between demographic characteristics and attitude towards antibiotics use was tested using Pearson chi-squared tests.

Results: Of the total of 316 pharmacists (77.07%) who completed the questionnaire, 241 (76.3%) self-medicated with antibiotics. Antibiotics were mostly used to self-treat upper (53.3%) and low (19.3%) respiratory tract infections relying on own knowledge (81.5%), previous treatment experience (49%) and patients' prescriptions (17%). The most commonly used antibiotics were macrolides (33.18%). The probability of self-medication increased for those who felt ill (CI 95% 0.23-0.71), used antibiotics as per the leaflet (CI 95% 1.25-3.49), got new information on antibiotics through learning paths such as training courses (CI 95% 0.31-0.88) or special literature (CI 95% 0.26-0.77). Self-medication was strongly associated with all levels of education.

Conclusions: The study confirms that self-prescribing of antibiotics is a common practice amongst pharmacists in Saint-Petersburg. Pharmacists' personal and professional characteristics strongly associated with self-medication were identified.

381. Withdrawn by Author

382. Prevalence and Predictors of Post-Discharge Antibiotic Use Following Mastectomy

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Background: Discontinuation of prophylactic antibiotics within 24 hours of surgery is recommended by the CDC, but antibiotics are frequently overused peri- and post-operatively.

Objectives: Determine use and independent predictors of post-discharge prophylactic antibiotic utilization after mastectomy with and without immediate breast reconstruction.

Methods: We established a retrospective cohort of women 18–64 years old with ICD-9-CM procedure or CPT-4 codes for mastectomy from 1/2004–12/2011 using commercial claims data. Women with a wound complication or septicemia during the mastectomy hospitalization were excluded. Prophylactic antibiotics were identified 0–30 days post-discharge and prior to coding for an infectious or noninfectious wound complication or septicemia. Predictors of prolonged prophylactic antibiotic utilization were identified in women with one year of prior health insurance enrollment, and relative risks (RR) were calculated using a generalized estimating equations model.

Results: 12,455 inpatient mastectomy procedures were identified, with immediate reconstruction in 7,877 (63.2%) procedures. Prophylactic antibiotics were used post-discharge in 5,458 (69.3%) procedures with immediate reconstruction, and 1,673 (36.5%) mastectomy only procedures ($p < 0.001$). Cephalosporins were the most commonly prescribed antibiotic class (61.8%), followed by fluoroquinolones (16.4%) and penicillins (6.7%). Independent predictors of prophylactic antibiotic use post-discharge were implant (RR 1.73) or autologous flap reconstruction (RR 1.38), bilateral mastectomy (RR 1.04), rheumatologic disease (RR 1.16), hypertension (RR 1.11), surgery at an academic hospital (RR 1.12), and receipt of post-operative home health care (RR 1.07).

Conclusions: Post-discharge prophylactic antibiotic use in the absence of infectious or noninfectious wound complications is very common after mastectomy and is more likely among women with

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immediate breast reconstruction and some underlying comorbidities. Efforts to limit prophylactic antibiotic use after hospital discharge are needed to avoid the development of antimicrobial resistance and other adverse events.

383. Utilization of Antibiotics with QT Prolongation Potential in the United States

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Background: The association between QT prolongation with macrolide and fluoroquinolone antibiotics has been further evaluated in recent studies.

Objectives: To describe patterns of outpatient prescriptions for macrolide and fluoroquinolone antibiotics in a large, national administrative claims database.

Methods: Utilization was assessed in the Optum Clinformatics Data Mart database from 2010 to 2012. Our analysis was limited to first fills of oral dosage forms of study antibiotics in the outpatient setting only. Topical, optical, and ophthalmic dosages were excluded. We calculated prescriptions filled per 1,000 unique persons with medical claims for each quarter.

Results: Macrolide utilization demonstrated a seasonal trend, with utilization 44% higher from October through March than April through September (Q1, Q4: 96.2 vs Q2, Q3: 61.4 average prescriptions per 1,000 unique persons with medical claims). Azithromycin was the most commonly prescribed macrolide in all 12 quarters, which accounted for more than 90% of all macrolide use. Azithromycin use increased 15% from Q3 of 2011 to Q3 of 2012 and increased 10% from Q4 of 2011 to Q4 of 2012. Clarithromycin use accounted for less than 10% of all macrolide use and erythromycin was rarely used. Seasonal patterns were less pronounced with fluoroquinolones (Q1, Q4: 42.1 vs Q2, Q3: 37.4) and utilization was stable over the study years. Ciprofloxacin was the most commonly used fluoroquinolone, which accounted for more than 50% of all fluoroquinolone use, followed by levofloxacin (33%) and moxifloxacin (6%).

Conclusions: From 2010 through 2012, fluoroquinolone utilization was relatively stable between seasons and year-to-year. Azithromycin and ciprofloxacin were the most commonly prescribed macrolide and fluoroquinolone antibiotics, respectively. Despite warnings of potential negative cardiovascular outcomes with azithromycin, which received national attention in May of 2012, utilization actually increased from the previous year in the last two quarter of 2012.

384. The Practice Pattern of Initial DMARDs Treatment and Hepatitis Screening in Rheumatoid Arthritis Patients: A Cross-National Comparison Between USA And Taiwan

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Background: Hepatitis B screening is a proven strategy that can prevent hepatitis B reactivation in patients receiving immunosuppressive therapies. However, the screening rates and patterns in rheumatoid arthritis (RA) patients starting DMARDs have not been well studied.

Objectives: To compare the practice pattern of initial DMARDs treatment and hepatitis B screening in USA and Taiwan RA patients.

Methods: We conducted a retrospective cohort including RA patients starting their first DMARD in USA (Nationwide commercial health plans: 2001-2013) or Taiwan (National claims database: 2001-2010). The first date patients received any DMARD was defined as the index date. Hepatitis B screening was defined as any of the following tests 1 year before or after index date: HBsAg, HBsAb, HBcAb, HBeAg, HBeAb or HBV DNA. We calculated the screened rate by year and used Poisson regression to generate the screening rate ratio and test the country-difference.

Multivariable logistic regression models were constructed to investigate predictors of screening, adjusting for demographic variables, combined comorbidity score and initial DMARDs.

Results: There were 14,568 and 46,265 RA patients in USA and Taiwan in the study cohort. Methotrexate or hydroxychloroquine monotherapy was the most prevalent initial treatment in USA; in contrast, hydroxychloroquine or sulfasalazine was the most frequently choice in Taiwan. Over all, the screening rate was 20.3% in USA and 24.5% in Taiwan, and it increased over time. More than 70% of screened patients received screening before DMARD initiation. HBsAg and HBsAb were the most frequent screening tests in both countries. Results of Poisson regression found Taiwan had a 17% higher screening rate over USA during follow-up period (crude rate ratio: 1.17; 95% CI 1.12-1.22). We also found the followings correlated to Hepatitis B screening: male gender, diagnosis of HBV or HCV, and more baseline health resource utilization.

Conclusions: We found there were disparities in initial treatment strategies in USA and Taiwan, and there is still room for improvement in hepatitis B screening for patients starting DMARDs.

385. Perceptions of Oncology Practitioners Towards Off-Label Use of Anti-Cancer Medicines

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Background: Prescribing drugs outside regulatory recommendations is known as off-label use. Studies have reported widespread off-label drug use in oncology practice. The clinical, economic and humanistic outcomes for such practice are often uncertain. Perceptions with current practice of off-label use are not well understood from oncology practitioners' perspective.

Objectives: The objective of the study is to explore perceptions of oncologists, pharmacists and nurses on off-label use in oncology.

Methods: This study employed a cross-sectional design implemented in the form of a pre-validated, self-administered questionnaire at National Cancer Centre Singapore where more than 70% cancer patients of the country are treated. Data collected were analysed using Chi-square or Fisher's exact test.

Results: Eighty-one practitioners involving nurses (38%), medical oncologist (37%) and pharmacists (25%) were surveyed. Majority of practitioners (70%) agreed that off -label use as integral part of cancer therapy. Main reasons cited include advanced cancers where standard lines of treatment are exhausted (58%), lack of alternative approved drug (43%) and rare tumours (47%). There was difference in opinion between oncologists and non-oncologists in evidence supporting off-label use ($p<0.05$). Oncologists viewed Phase 2 (73% versus 31%) and conference abstracts (56% versus 23%) as sound evidence for off-label use. Major concerns include lack of efficacy (62%), inadequate patients understanding (54%), uncertain safety (52%) and out-of-pocket cost (49%) associated with off-label use. Most viewed need for obtaining informed consent (86%) and institutional guidance (75%) as important elements in practice framework.

Conclusions: The study provides an insight about off-label use practice and establishes need for robust clinical guidance. More comprehensive research is required in this area to warrant off-label use in oncology.

386. The Relationship Between Patient Safety Culture and Medication Errors Among Healthcare Professionals in Private and Public Hospitals in Nigeria

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Background: A positive patient safety culture can improve health care, but there is a dearth of information on how patient safety culture affects medication errors in developing countries, including Nigeria.

Objectives: To assess the patient safety culture of healthcare professionals working in public and private healthcare institutions in Nigeria and to determine the

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relationship between their patient safety culture and their behaviour towards medication errors.

Methods: This was a cross-sectional survey of health care professionals from private and public hospitals in Oyo State, Nigeria. Safety culture was assessed using the Safety Attitudes Questionnaire (SAQ) which contains six subscales. Scores were computed between 0 and 100 with higher scores representing more positive safety attitudes. Knowledge, behaviour and attitude about medication errors was assessed using open questions. The relationship between safety culture and the behaviour towards medication errors was assessed using logistic regression.

Results: A total of 617 healthcare professionals completed the questionnaires. The overall scores for each subscale were between 55.3 ± 29.3 and 88.8 ± 12.7 for private hospitals and 52.4 ± 29.9 and 88.8 ± 21.8 for public health centres. Stress recognition was low across both categories of health institution with its lowest SAQ score as 57.5 ± 27.2. Overall, 70% of the respondents were unaware of a reporting system for medication errors. Less than a quarter of respondents had ever reported a medication error (23% public, 28% private), but the willingness to report medication errors was high (87% in public health centres and 91% in private hospitals). There was no statistically significant relationship between the healthcare professional's behaviour of reporting medication errors and the SAQ questions on perception of medication errors.

Conclusions: The healthcare professionals in both public and private hospitals had relatively positive patient safety attitudes, but knowledge of medication errors was poor surprisingly, we found no relationship between patient safety culture and behaviour towards medication errors.

387. Drug Utilization Study: Evaluation of the Use of Nepafenac in the Netherlands and Denmark

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Background: Nevanac 1 mg/ml and Nevanac 3 mg/ml are available in the EU for prevention and treatment of postoperative pain and inflammation after cataract surgery, for the first 2 weeks of the postoperative period. Treatment can be extended to the first 3 weeks of the postoperative period as directed by the clinician. In 2011, Nevanac 1 mg/ml was approved for reduction in risk of postoperative macular edema associated with cataract surgery in adult patients with diabetes, for up to 60 days after surgery. This study aimed to address the European Medicines Agency concern about potential off-label use.

Objectives: To quantify and describe use of nepafenac with reference to the approved indications.

Methods: Using data from the PHARMO Database Network (The Netherlands, 2008 to 2013) and the National Health Databases (Denmark, 2008 to 2014), we created cohorts of nepafenac users starting with the first prescription. Some underrecording of cataract surgery is present in both databases.

Results: The Netherlands contributed 9,530 users (12,691 therapy episodes); mean age, 71 years; 60% women; 17% diabetic. Of all episodes, 79% did not have recorded cataract surgery; 19% of these had cataract diagnoses. Of 2,266 episodes in adult nondiabetic patients with cataract surgery, 40% had more than one bottle dispensed >21 days). Of 441 episodes in adult diabetic patients with cataract surgery, 10% had more than two bottles dispensed >60 days)

Denmark had 60,403 nepafenac users (73,648 therapy episodes); mean age, 72 years; 58% women; 59% did not have recorded cataract surgery. Of 26,649 nepafenac episodes in adult nondiabetic patients with cataract surgery, 8% had more than one bottle dispensed >21 days). Of 3,458 episodes in adult diabetic patients with cataract surgery, 0.2% had more than two bottles dispensed >60 days)

Pediatric use was 0.3% in both populations.

Conclusions: Nepafenac use in pediatric patients was minimal. In adults, more than half of therapy episodes were not related to cataract surgery, and around 10% were for longer use than approved. Underrecording of ophthalmic conditions and procedures challenges research in this area and can result in overestimation of this off-label use.

388. Dispensing Patterns of Ophthalmological Products in Community Pharmacies in South Africa: A Pharmacoepidemiological Study

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Background: Ophthalmic conditions and visual impairment pose a significant burden on both individuals and society. Studies on the prescribing patterns of ophthalmological products are limited. Only one previous study on the general prescribing patterns of ophthalmological products in South Africa was found in the literature.

Objectives: The primary aim of the study was to determine the prescribing patterns of ophthalmological products in a community pharmacy patient population.

Methods: A retrospective, cross-sectional drug utilisation study was conducted on a 2013 community pharmacy dispensing database representing 327 pharmacies in South Africa. Both products reimbursed by private health insurance schemes and private purchases were included in the study. All records for ophthalmological products (ATC group S01) were extracted and analysed. Basic descriptive statistics were calculated.

Results: A total of 320 246 patients (56.36% females) received 552 816 ophthalmological products at a cost of approximately R54 million. Patients were dispensed on average 1.73 (SD = 2.31) products during the year. The average age of patients was 46.63 (SD = 15.69) years. Half of the patients were between 30 and 49 years of age. Decongestants and antiallergics (ATC group S01G) represented 50.82% of all products dispensed (26.96% of total cost), followed by antiglaucoma preparations and miotics (ATC group S01E) at 19.26% of dispensing volume, costicosteroids and anti-infectives (11.16%), and anti-infectives (10.06%). One specific trade name eye drop (an over-the-counter eye drop containing tetryzoline and antazoline) accounted for 16.58% of all products dispensed. The most expensive products dispensed were antineovascularisation agents (specifically, ranibizumab 10 mg/ml intravitreal injection) at an average cost of R6026 per prescription.

Conclusions: A limitation of the study was the lack of specific diagnoses and prescribing for co-morbid conditions were also not investigated. There is need for more studies on the prescribing and utilisation of ophthalmological products to establish a baseline of the treatment of ophthalmological conditions in South Africa.

389. Cyproterone/Ethinylestradiol And Concomitant Use Of Other Hormonal Contraceptives In The Netherlands

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Background: Cyproterone acetate combined with ethinylestradiol (CPA/EE) is indicated for moderate to severe acne and/or hirsuitism in women of reproductive age. In 2013 the European Medicines Agency (EMA) concluded the benefits of CPA/EE outweigh the risks, provided that several measures are taken to minimize the risk of thromboembolism. One of the recommendations was that CPA/EE should not be used in combination with other hormonal contraceptives, as this will expose women to a higher dose of oestrogen and increase the risk of thromboembolism.

Objectives: To assess concomitant use of CPA/EE and other hormonal contraceptives (HC) among new CPA/EE users in 2011, 2012 and 2014.

Methods: In this observational study, new CPA/EE users in 2011, 2012 and 2014 were identified in the PHARMO Out-patient Pharmacy Database and followed from first prescription until database exit or end of index year. Concomitant use of other HC (28-day cycle HC or long-acting reversible contraceptive) was defined as overlapping prescriptions of CPA/EE and other HC. A distinction was made between overlap during expiration of the first drug (potential concomitant use; likely a switch because no refill of the first drug was observed) and overlap with refill prescriptions of the first drug while the second was already prescribed (concomitant use).

Results: New users of CPA/EE represented 2.8, 2.6 and 0.7 per 1,000 women in 2011, 2012 and 2014, respectively. Their mean (±SD) age was 25 (±9) in 2011 and 2012 and 29 (±9) in 2014. Among 7,876 (2011), 7,562 (2012) and 1,401 (2014) new CPA/EE users concomitant use of other HC was observed for 2-3% of users and for a median duration of 78 days. Another 25% had potential concomitant use for a median duration of about 60 days.

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Conclusions: The overall use of CPA/EE in the Netherlands strongly decreased between 2011 and 2014. Concomitant use of CPA/EE and other HC was low and might be due to multiple treating physicians. Additional potential concomitant use was observed; however these were likely switchers. Most women were prescribed CPA/EE in accordance with the recommendation of use.

390. Cyproterone/Ethinylestradiol Use and Indications in the Netherlands

Irene D. Bezemer[1], Lisa Smits[1], Fernie J. A. Penning-van Beest[1], Alex Asiimwe[2] and Ron M. C. Herings[1]

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Background: Cyproterone acetate combined with ethinylestradiol (CPA/EE) is indicated for moderate to severe acne and/or hirsuitism in women of reproductive age. In 2013 the European Medicines Agency concluded that the benefits of CPA/EE outweigh the risks, provided that several measures are taken to minimize the risk of thromboembolism. One of the recommendations was to emphasize the approved indications of use in order to limit use outside the label.

Objectives: To assess recent diagnosis of acne or other reasons for CPA/EE use among new users in 2011, 2012 and 2014.

Methods: New CPA/EE users in 2011, 2012 and 2014 were identified in the PHARMO Out-patient Pharmacy Database and linked to the General Practitioner (GP) Database. Records of users captured by both databases were searched for information on diagnoses and treatment of acne, other hyperandrogenic conditions, menstrual problems and GP consultations for contraceptive management in the year prior to starting CPA/EE.

Results: New users of CPA/EE represented 2.8, 2.6 and 0.7 per 1,000 women in 2011, 2012 and 2014, respectively. A total of 1,415 (2011), 1,359 (2012) and 321 (2014) users with pharmacy as well as GP data were included; mean (±SD) ages were 24 (±8), 25 (±9) and 28 (±8). A recent acne diagnosis was observed for 12-17% of users and 35-38% of users had recently received acne treatment without a diagnosis: in total 772 (55%) users in 2011, 703 (52%) users in 2012 and 150 (47%) users in 2014 had a recent record of acne diagnosis or treatment. GP consultations for other hyperandrogenic conditions (3%), menstrual problems (3%) or contraceptive management (12-15%) were also observed. The remaining 36-44% of users had none of the selected diagnoses or treatments prior to initiating CPA/EE.

Conclusions: The overall use of CPA/EE strongly decreased between 2011 and 2014. About half of the new CPA/EE users had a recent record of acne diagnosis or treatment. Few additional users had diagnoses of other hyperandrogenic conditions. Potential non-labeled use was also observed; however note that concomitant diagnoses and treatment were identified rather than actual reasons of drug prescription.

391. Incidence of and Factors Associated with Anticholinergic Drugs Among Women with Urinary Incontinence: A Population-Based Cohort Study

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Background: Very little data exist on factors associated with the prescription of anticholinergic drugs to women with urinary incontinence.

Objectives: To investigate the prescription pattern of anticholinergic drugs and factors associated with the commencement of such therapy in a community-based population.

Methods: In this cohort study, information from the Norwegian Prescription Database (NorPD) on the prescription of anticholinergic drugs was linked at an individual level to data from the Nord-Trøndelag Health Study 3 (HUNT3). Logistic regression was used to investigate whether commencement of treatment with an anticholinergic drug was associated with variables such as type and severity of urinary

incontinence, lifestyle factors, socio-demographic factors and health status.

Results: Among the women having urinary incontinence in HUNT3, 4.5 % had been prescribed an anticholinergic drug during the previous 12 months. Prescription was most frequent in women with urge incontinence (10.5 %) and mixed incontinence (7.0 %). Of women having urinary incontinence without being treated with an anticholinergic drug, 1.8 % filled such a prescription during the following year, corresponding to 3.1 % of women with urge incontinence and 3.0% of women with mixed incontinence. Characteristics significantly associated with commencement of treatment were age above 50 years, urge or mixed urinary incontinence and having severe or very severe symptoms. Consumption of four or more cups of coffee per day was weakly associated with being prescribed an anticholinergic drug, whereas no association was found with marital status, parity, smoking, alcohol intake or anxiety/depression.

Conclusions: In this population-based study, 10.5 % of women having urge incontinence were prescribed an anticholinergic drug. The 12-month incidence of receiving a new prescription when having urge incontinence was 3.1 %. Age above 50 years and severe symptoms were the factors most clearly associated with commencement of treatment.

392. Retention in Methadone Maintenance Treatment (MMT) in Primary Care: National Cohort Study Using Proportional Hazards Frailty Model for Recurrent MMT Episodes

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Background: Retention in MMT is associated with reduced mortality. Few studies account for patient's movement in and out of treatment.

Objectives: Identify determinants of time to discontinuation of MMT across multiple treatment episodes in Primary Care using a new-user design.

Methods: Cohort study of opioid dependent persons experiencing ≥ 1 MMT episodes in primary care between 1st August 2004 and 31st December 2010, excluding episodes which were ongoing at the start of follow-up. Record linkage of national methadone treatment register, primary care methadone dispensing records (Methadone Treatment Scheme (MTS)), and co-prescriptions in the General Medical Services pharmacy claims database. Length of a treatment episode was based on the coverage of each methadone prescription. Retention in treatment classified as no interruptions in treatment coverage lasting > 7 days. Treatment episodes that were ongoing at the end of follow-up were right-censored.

Outcome: Time to discontinuation from recurrent MMT episodes.

Exposures: Median daily methadone dose and proportion of methadone scripts per treatment episode which were dispensed under supervised consumption. Age, gender, and comorbidities included as potential confounders.

Statistical analysis: proportional hazards gamma frailty model of time to discontinuation from recurrent MMT episodes.

Results: 6,393 patients experienced 19,715 treatment episodes. Compared to 60 mgs, median daily doses > 60 mgs (60-120 mg: hazard ratio (HR)=0.47, 95% CI 0.45 – 0.50); >120 mgs: HR=0.62, 95% CI 0.53 – 0.72), and having greater than 20% of methadone scripts dispensed as supervised consumption (compared to <20%) were associated with longer treatment episodes (20-39% of scripts: HR=0.36, 95% CI 0.33 – 0.38); 40-59% of scripts: HR=0.24, 95% CI 0.22–0.27; 60-79% of scripts: HR=0.25, 95% CI 0.22–0.27; >80% of scripts: HR=0.28, 95% CI 0.26–0.30). Patients experiencing multiple treatment episodes stayed in treatment for progressively longer periods of time.

Conclusions: The prescription of higher daily doses of methadone, and regular supervised consumption can increase MMT retention.

393. Quality Use of Medicines Among Makkah Community

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Background: Quality Use of Medicines (QUM) is one of the central objectives of Patient quality of life. Within the context of QUM framework, it is crucial to get current data from the general population in order to assess their understanding on issues related to rational use of medicines.

Objectives: To explore attitude of Makkah community about use and provision of drugs.

Methods: Face to face interview was used to administer questionnaires among patients from two tertiary care hospitals and four primary care centers dealing with patients from rural and urban areas in Holly Makkah region.

Results: A total of 554 patients were enrolled while majority of them were lived urban areas (n=457,82%). 419 (76%) responder were females and 531(96%) were living with their family and had up to collage education (n=174,31%).We found that most of respondents were diabetic (185,33%) and hypertensive (n= 172,31%). More than half of the patients (77%) claimed that they will consult government doctor first if they experienced any health problems and obtain their medicines from governmental hospitals (n=536,97%) but they had trouble reading labels for medicine supplied from them (n=98,18%). We found (n=156,28%) of patients can differentiate whether the medicine name is the name of active ingredient and (n=218,39%) of patients aware about drug-food interactions. Also 73 % of respondents were aware about drug-drug interactions. More than half of the participants (n=353,64%) claimed that they will consult the doctor if they experience any health problems and 285 (51%) get information easier from the government doctor. Most of the consumers (207,37%) stated that they preferred to get drug information from health care professional.

Conclusions: This periodic mapping of pharmaceuticals use among consumers in Saudi Arabia is indeed an important effort to explore issues on quality use of medicines and make plans for future interventions and policies.

394. Off-Label Use of the Expensive Orphan Drug Eculizumab in France 2009-2013 and the Impact of Literature: Focus on the Transplantation Field

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Background: The study of the use of medicines for off-label indications is of key interest, as it can represent mainly a suboptimal (or irrational) use of a drug, or a new use of a drug that can have an added benefit or address an unmet medical need. The orphan drug eculizumab is one of the most expensive in the world and based on expenditures is classed among the highest in France, a scenario suggestive of off-label use. Given its pharmacological properties, it is likely to be used in organ transplantation.

Objectives: Our purposes were to describe the consumption trends of eculizumab for off-label indications overall and in the organ transplantation field and to assess the impact of publications on the latter use.

Methods: We carried out a temporal ecological study within the French national hospitalization database (PMSI). First, the trend of eculizumab consumption (2009-2013) was compared to our estimate of the maximum on-label consumption (overall and for transplantation). Second, we evaluated the impact of the publications supporting the effectiveness of eculizumab in the transplantation field on temporal trends of eculizumab consumption.

Results: Eculizumab total consumption exceeded our estimate of the maximum on-label consumption since

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the end of 2011 and increased until the end of the study. Compared to Denmark and Norway, total eculizumab consumption per habitant in 2013 in France was remarkably high, with respectively 534, 627 and 1785 DDD/1Mo Habitants. We estimate that off-label use represented at least 50% of the drug consumption. The off-label consumption in organ transplantation also increased since 2011. The amount of publications grew trough the study period but overall the evidence level remained low. Statistically, publications were not associated with the drug consumption for transplantation.

Conclusions: Eculizumab started being notably used for off-label indications in France since the end of 2011 and this use increased until the end of the study. We found only low level evidence concerning the off-label use of eculizumab in transplantation field trough the studied period.

395. Assessment of Vaccine Cold Chain Management Status at Service Delivery Health Facilities in Dawro Zone, South West Ethiopia

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Background: The 'vaccine cold chain' is the system of transporting and storing vaccines within the safe temperature range, which is +2°C to + 8°C for refrigerator vaccines and -15°C to -25°C for freezer vaccines. It begins from the time the vaccine is manufactured, continues through to the region or territory vaccine distribution centres and ends when the vaccine is administered.

Objectives: To assess vaccine cold chain management status at service delivering health facilities in Dawuro zone, South West Ethiopia.

Methods: A facility based cross-sectional descriptive study design was employed. Both quantitative and qualitative methods were used to collect data from February 30-March 20 2015. Data were collected from 24 facilities, 24 vaccine handlers, and 12 key informants. Descriptive analysis was done using SPSS version 16.0.Chi-square was employed to test presence of association between dependent and independent variables. Data from in-depth interview were analyzed by thematic content analysis technique.

Results: From 24 public health facilities visited, 4 (16.7%) and 20(83.3%) had medium and poor availability of cold chain equipment respectively to store and transport vaccines. From 24 vaccine handlers interviewed, 7(29.2%), 8(33.3%) and 9(37.5%) had good, medium and poor knowledge level respectively on vaccine cold chain management system. In addition, out of 24 facilities assessed regarding vaccine handling and storage practice, 6(25%), 10(41.7%) and 8(33.3%) had good, medium and poor practice level respectively. Work experience and types of training on vaccine cold chain had a statistically significant association with knowledge and practice levels of vaccine handlers (p-value$<$ 0.05). This result is also supported by the majority of key informants.

Conclusions: Vaccines in a half of the facilities found to be at a high risk of losing their potency. There is an urgent need to distribute Equipment; improve knowledge, and practice on cold chain management through supportive supervision and training.

396. Are Multiple Interventions Needed To Influence Physician Prescribing Behaviour: Implications For The Future?

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Background: Resources must be found to cover costs of new innovative medicines addressing significant unmet need. Successful approaches include models to optimise their prescribing and enhancing prescribing of generics.

Objectives: Analyse the impact of different interventions among different medicine classes to increase rational use and savings.

Methods: Appraisal of published drug utilisation studies including those conducted by the co-authors.

Results: a) Supply and demand-side measures needed to increase prescribing of generics and save costs; supply side measures alone not sufficient to contain costs; (b) Generics vs. originators: (i) lowest generic prices where highest volumes; (ii) educational initiatives successfully addressed concerns with generics and misinformation, e.g. clopidogrel; together with other measures achieve high INN prescribing - up to 98% in Scotland; (iii) compulsory generic substitution accepted in Sweden with monthly auctions further lowering generic prices; (c) generics vs. patented products: (i) limited change without multiple measures; alternatively, increased prescribing of patented medicines, e.g. PPIs and statins in Ireland, ARBs in Portugal; (ii) patient co-payments appreciably influence prescribing; however, considerable care where affordability is an issue; (iii) health authorities can successfully initiate therapeutic switching programmes without compromising care; (iv) prescribing restrictions can significantly impact on utilisation – however care with enforcement and timing; (v) multiple demand-side measures have a similar impact on prescribing as restrictions; (vi) delisting patented medicines from a class has the greatest influence on prescribing; (vii) recognised difficult for health authorities to influence physician prescribing in certain classes, e.g. anti-psychotics; (d) programmes can be instigated to ensure correct dosing, e.g. statins.

Conclusions: Multiple measures appreciably impact on physician prescribing, with health authorities already learning from each other. This will continue. Without these measures, authorities will struggle funding new valued medicines and increased demand with ageing populations.

397. Utility of Prescription Drug Monitoring Data for Policy Analysis in a State Medicaid Program

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Background: Administrative claims data fail to capture prescription that are filled but paid for with a cash (as opposed to insurance-based) transaction. The emergence of state prescription drug monitoring programs (PDMP) offers the opportunity to make a more comprehensive assessment of opioid filling patterns.

Objectives: To evaluate the epidemiology of potential cash payments and contrast the effects of using PDMP data for an opioid-related high dose policy in a state Medicaid program.

Methods: Using Oregon Medicaid claims and PDMP data, we created a linked dataset for a cohort of Medicaid beneficiaries between 2012 and 2013. Data on all filled opioids were obtained the PDMP database and then matched to claims data based on national drug code, quantity, and date. PDMP fills that did not have a corresponding Medicaid pharmacy claim were assumed to indicate a cash payment. To evaluate the impact of using PDMP versus claims data for program evaluation, we examined the impact of a high dose opioid prior authorization (PA) policy implemented in 2012.

Results: Of the 464,277of opioid fills, 79,437 (17.1%) could not be matched to a Medicaid claim. Methadone (23.0%) and fentanyl (22.4%) were the most likely to not match to a corresponding claim. Fills lacking a corresponding claim were significantly more likely to be present as part of specific indicators of opioid misuse. Of fills involved in an indicator for pharmacy shopping, 24.0% could not be matched to a corresponding claim, compared to 16.6% of fills that were not involved in pharmacy shopping ($p<0.001$). A similar pattern was observed for overlapping opioids (18.1% vs 16.5%; $p<0.001$) and benzodiazepine overlap (18.7% vs 16.8%; $p<0.001$). An analysis of the high dose PA found a 16.2 mg net reduction in MED using Medicaid claims. Using PDMP fill data, the net reduction was only 8.1 mg MED.

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Conclusions: A substantial proportion of opioid fills are not captured in Medicaid administrative data. Missing opioid claims, presumably paid with cash, are associated with several indicators of opioid misuse. Missing claims also overestimate of the impact of opioid policies.

398. Medicine Utilisation Capabilities in Africa: Current Status, Implications and Future Prospects

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Background: Understanding medicine utilisation patterns alongside on-going policies is essential to improve their rational use. Little is known about such capabilities among African countries. This needs to be addressed, especially for high priority areas such as infectious diseases.

Objectives: To undertake a qualitative study of medicine utilisation capabilities among private and public sectors in Africa.

Methods: Qualitative survey among MURIA (Medicines Utilisation Research in Africa) members (http://muria.nmmu.ac.za/).

Results: Currently very variable capabilities among African countries, ranging from access to patient level data in ambulatory care among private insurers in Botswana and Namibia as well as among individual private insurers in South Africa, to currently no consolidated databases. However, there can be specific databases, e.g. HIV patients in Botswana and Swaziland. Self-medication data is also challenging to collect, necessitating qualitative interviews as recently undertaken in Uganda. Specific country examples include Kenya where currently no longitudinal databases in ambulatory care; however, community pharmacy data is available to track utilisation and expenditure. Similarly in hospitals, utilisation and expenditure data is available for research. Aggregated reimbursed utilisation data is available on a monthly basis in both ambulatory care and hospitals in Namibia. However, there is currently no longitudinal databases in the public sectors in Botswana, Nigeria, Tanzania and South Africa. Utilisation and expenditure data in the private sector is not readily available in Nigeria and Tanzania, with utilisation and expenditure data more readily available in public versus private sectors in Zimbabwe. Programmes are ongoing among African countries to rectify this, especially regarding antibiotic consumption including point-prevalence studies in hospitals. The findings will form the basis of future interventions.

Conclusions: Currently variable capabilities across Africa. This is changing with increasing need to document utilisation and expenditure patterns to improve future planning, especially in high priority areas such as infectious diseases.

399. Defining Prescription Quality Indicators at Primary Care Level in Portugal

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Background: Prescribing quality indicators (PQI) have been used to assess quality, safety and appropriateness of drugs. However, consensus about which PQI are more adequate and feasible at primary care (PC) level is scarce.

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Objectives: To define a valid and consensual list of PQI to be implemented in quality assessment programs at Portuguese PC level.

Methods: A systematic review was performed in PubMed, Science Direct and Web of Knowledge databases, for studies published between 01APR1998 and 31JAN2015 with "prescri*", "quality", "indicator" and "valid*" in the Title/Abstract. Two investigators reviewed selected studies and developed a list of PQI, grouped in four dimensions: safety, indication, necessity/adequacy and cost. The list was submitted to a two rounds Delphi panel, with 36 experts (31 family physicians and 5 clinical pharmacologists). The adequacy of each indicator was rated, from 1=totally inadequate up to 9=totally adequate. PQI were included if scored ≥7 by at least 69% experts. Included PQI are being applied to 2014 prescription data from two Portuguese PC Health Units, corresponding to 50109 prescriptions from 16508 patients.

Results: From 2082 articles, 200 were selected for detailed review. A total of 94 PQI were identified from the review, and additional 4 proposed by the investigators. Experts' response rate was 72.2%. After the first round, 46 PQI were included and 8 indicators reformulated after experts' comments. In the second round, 47 PQI were rated as valid, distributed in the dimensions safety (8), indication (7), necessity/adequacy (27) and cost (5). When applied to prescription data, preliminary results show that all PQI seem to be feasible except one safety PQI: no cases were identified for the indicator "pediatric antitussives' use".

Conclusions: A total of 34 PQI were validated by a panel of family physicians and clinical pharmacologists, covering the most relevant domains of prescription decision, namely necessity/adequacy, safety, indication and cost. Validated indicators were pretested in real-world data and seem to be feasible for assessing quality of prescribing at PC level in Portugal.

400. An European Repository for Electronic Selection of Explicit Criteria of Potentially Inappropriate Prescriptions (PIPs) in Old Age

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Background: Lack of computerization of electronic assessment of medication lists in electronic health records is a barrier for more generalized use of PIP-lists, designed for older adults in primary care.

Objectives: Constructing a European repository for selection of explicit criteria on PIPs, suitable for electronic assessment, and identifying possible limitations.

Methods: Criteria from EU(7)-PIM list, STOPP/START criteria and a subset of BEERS 2015, were entered in a specific frame with four main categories: PIP description, Medication data, Clinical data, and Evidence related information. In all lists, some of the criteria were excluded, and a number of criteria were divided for more operable use.

Results: Total of n=692 criteria were entered, of which n=279 (40.3%) from EU(7)-PIM, n=233 (33.7%) from Beers and n=180 (26.0%) from STOPP/START list. Identification of the medication was possible with ATC for practically all criteria, except for n=24 (3.4%). Of all the criteria, 76.8% were identifiable with one code at ATC 5 level. For 16.7% one code of a higher level was required, and 2.8% needed complex combination of codes. A total of n=429 (62.0%) criteria needed medication information only. In 53.8% of the criteria, identification of the active substance(s) was the only medication data requirement, and 8.2% needed additional information (dose, duration, route of administration). Clinical information was required for 38.0% of the criteria, 16.0% requested disease information only, and 22.0% needed additional information such as specific indication, history of diseases, lab results or severity of diseases. All the criteria that pertained to underuse (8.4%), required clinical information.

Conclusions: Construction of an electronic repository combining 3 PIPs lists is feasible, although requires precise definition of medication and clinical data. In the future, developers of new lists of PIPs should consider the suitability for electronic use and semantic interoperability.

401. Evolution of the Medication Use in a Cohort of Newly Admitted Nursing Homeresidents (Ageing@NH): Report of the First Follow-Up Observations

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Background: Quality of pharmacotherapy in old age is major issue, but there is a limited number of long term studies, following residents and their medication use from entering in a nursing home (NH) until death.

Objectives: This study describes the evolution of the medication use one year after entering a NH, compared to the baseline observations.

Methods: We used data from the Ageing@NH study, an observational prospective study based on a inception cohort of newly admitted residents at NHs in the Dutch speaking part of Belgium (65+), selecting those consenting, with medication chart available. Information about socio-demographic, clinical and functional characteristics, as well as medication use, was collected at baseline and at one year follow-up. The comparison was done for participants with available medication information for both years.

Results: From a total of n=1065 residents at baseline, n=743 consented and had available medication information (mean age 83.9, 65% female). Hospitalization rate in the year before admission was 68.5%, with mean number of 43.1 days. Polypharmacy (≥5 medications) was present in 51.1% of the patients, with excessive polypharmacy (≥10 medications) in 32.3%. Mean number of chronic medication was 8.1. Most commonly used groups were neurological (85%), as well as the alimentary (83.1%) and cardiovascular (81.6%) medications. At the follow-up, information for medication use for both years was available for n=414 residents. Hospitalization rate decreased significantly (35%, p-value<0.001). The number of chronic medications increased to 8.7 (p-value <0.001). Extreme polypharmacy increased significantly to 41.8% (p-value=0.003). The largest increase was noted for the respiratory group of medications (from 21.3% to 28.5%, p-value=0.003), and for Proton Pump Inhibitors (from 40.1% to 47.3%, p-value=0.034).

Conclusions: After one year of follow-up, the number of chronic medications increased, especially in respiratory medications and Proton Pump Inhibitors. Significant increase of extreme polypharmacy was noted, prompting systematic appraisal of the quality of pharmacotherapy in this frail population.

402. Antidepressant Medication and the Risk of Pregnancy-Induced Hypertension

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Background: Increased activity of the sympatic nervous system could possibly cause pregnancy-induced hypertension (PIH). Previous studies have suggested that antidepressants could contribute to this increased activity.

Objectives: To examine whether the use of antidepressants during pregnancy increases the risk of developing pregnancy-induced hypertension.

Methods: This retrospective cohort study was conducted using the prescription database IADB.nl among nulliparous women with singleton pregnancies between 1994 and 2014 in the Netherlands. Exposure was defined as at least one dispensing record of an antidepressant (AD; ATC-code N06A) during the first 20 weeks of gestation. Excluded were women using antithrombotic agents, antidiabetic drugs, antimigraine drugs, and antihypertensive drugs during six months before pregnancy till twenty weeks of gestation. The outcome, PIH, was defined as at least one dispensed record of an antihypertensive drug (methyldopa, nifedipine, labetalol, ketanserin, nicardipine) after 20 weeks of gestation till 14 days after delivery. Odds ratios (OR) and their corresponding 95% confidence intervals (95%CIs) were estimated using logistic regression analysis, adjusting for maternal age, benzodiazepine and antibiotic use. Subanalyses were conducted for class of AD, duration of use of AD (1-30, ≥ 31 Defined Daily Doses (DDD)), and maternal age. As the exact duration of gestation was unknown, all analysis were conducted for 3 theoretical gestational ages (35, 37, 39 weeks).

Results: 28020 women were included, of which 539 (1,92%) used antidepressants (gestational age 39 weeks). The risk of pregnancy induced hypertension doubled for women using an antidepressant (aOR [95%CI] 2.00[1.30-3.18]). Significant associations (OR [95% CI]) were also found for the subgroup SSRI

(2,12 [1.28-3,50]), ≥ 31 DDDs (2.53 [1.58-4.85]) and maternal age of 30-34 years (2,59 [1,35-4,98]). Decreasing the theoretical gestational age showed comparable results.

Conclusions: Use of ADs during the first 20 weeks of gestations appeared to be associated with an increased risk of developing PIH. When balancing the benefit and risks of using these drugs during pregnancy, this should be taken into account.

403. Gestational Exposure to SSRIs and Risk of Preeclampsia in Pregnancy: A Study from the Norwegian Mother and Child Cohort Study Accounting for Time-Varying Severity of Depressive and Anxiety Symptoms

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Background: The risk of preeclampsia after gestational exposure to selective serotonin reuptake inhibitors (SSRIs) is not yet elucidated.

Objectives: To explore whether SSRI use in pregnancy may increase the risk of preeclampsia, with the attempt to account for time-varying severity of depressive and anxiety symptoms during pregnancy.

Methods: The Norwegian Mother and Child Cohort Study and the Medical Birth Registry of Norway constituted the data source. The analysis cohort was restricted to 5850 pregnant women reporting depression six months before and/or during pregnancy. Information about preeclampsia (i.e. proteinuria with gestational hypertension after gestational week 34) stemmed from the Medical Birth Registry of Norway. Symptoms of depression and anxiety were measured at gestational weeks 17 and 30 via the short versions of The Hopkins Symptom Checklist-25. A Generalized Estimating Equations (GEE) analysis was conducted to determine adjusted relative risk (RR) and 95% confidence interval (CI) for preeclampsia. A Marginal Structural Model (MSM) analysis was conducted to account for time-varying exposure and confounding factors (i.e., depressive/anxiety symptoms and comedications).

Results: In our analysis cohort, 611 (10.4%) women reported use of SSRIs in pregnancy, whereas 5130 did not use any antidepressant. In the GEE adjusted model, the RR of preeclampsia for 2nd trimester SSRI-exposed was 1.30 (95% CI: 0.65-2.59) and for 3rd trimester SSRI-exposed was 1.55 (95% CI: 0.79-3.04), compared to non-exposed. In the MSM model, the RR of preeclampsia was 0.92 (95% CI: 0.44-1.92) for 2nd trimester SSRI-exposed, and 1.57 (95% CI: 0.70-3.53) for 3rd trimester SSRI-exposed, compared to non-exposed.

Conclusions: Among this Norwegian cohort of pregnant women, 2nd trimester use of SSRIs did not confer an increased risk of preeclampsia, especially after accounting for time-varying confounders. Although the association between 3rd trimester SSRI-exposure and preeclampsia was not statistically significant, a moderate increased risk of preeclampsia could not be ruled out.

404. Continuation of Atypical Antipsychotic Medications During Pregnancy and the Risk of Gestational Diabetes

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Background: Gestational diabetes mellitus (GDM) is a serious complication of pregnancy that can lead to adverse outcomes. Some atypical antipsychotics (AAP) are associated with weight gain and insulin resistance, which are risk factors for GDM. There is lack of evidence to inform the decision about whether to discontinue AAP during pregnancy due to this concern.

Objectives: To examine the risk of GDM associated with continuation of aripiprazole (ARI), olanzapine (OLZ), quetiapine (QTP), risperidone (RSP), or ziprasidone (ZIP) through the first half of pregnancy compared to discontinuation prior to pregnancy.

Methods: We conducted a cohort study using Medicaid data (2000-2010) from non-diabetic women with a live-born infant who had ≥ 1 AAP dispensing during the 3-months prior to pregnancy. For each AAP, we compared women with ≥ 2 dispensings (continuers) to women with no dispensing during the first half of pregnancy (discontinuers). GDM was defined using previously validated algorithm in claims data. We used a generalized linear model and propensity score stratification to obtain absolute and relative risks (RR), adjusting for confounders including psychiatric diagnoses and duration of AAP use before pregnancy.

Results: Among 1,543,334 pregnancies, the number of baseline AAP users was 1,924 for ARI, 1,425 for OLZ, 4,533 for QTP, 1,824 for RSP, and 673 for ZIP. The proportion of continuers ranged between 20% and 34%, depending on the drug. Continuers generally had higher comorbidity and longer baseline AAP use compared to discontinuers. The crude risk of GDM for continuers vs. discontinuers, respectively, was 4.8% vs.4.5% for ARI, 12.0% vs. 4.7% for OLZ, 7.1% vs. 4.1% for QTP, 6.4% vs. 4.1% for RSP, and 4.2% vs. 3.8% for ZIP. The adjusted RRs were 0.80 (0.48-1.33) for ARI, 1.86 (1.22-2.83) for OLZ, 1.31 (1.02-1.68) for QTP, 1.37 (0.84-2.25) for RSP, and 0.93 (0.34-2.54) for ZIP.

Conclusions: Our results suggest that compared to discontinuation, continued use of OLZ, QTP, and possibly RSP during the first half of pregnancy is associated with an increased risk of GDM. ZIP and ARI, the newer AAPs with less weight gain potential, were not associated with an increased risk.

405. Is There a Dose-Response Relation Between the Use of Lithium in Early Pregnancy and the Risk of Cardiac Malformations?

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Background: It is acknowledged that the use of lithium (Li) in early pregnancy increases the risk of Ebstein's anomaly, a right ventricular outflow obstruction defect, and potentially other congenital cardiac defects. Animal studies have shown that Li may have a dose-related teratogenicity, but the dose-response relation between Li and the risk of cardiac malformations in humans remains largely unexplored.

Objectives: To evaluate whether the association between Li use in early pregnancy and the risk of cardiac malformations is dose-dependent.

Methods: Our population included 1,357,551 women who delivered a live-born infant during 2000-2010 and were enrolled in Medicaid from 3 months before conception to 1 month after delivery. We examined the risk of cardiac defects (identified with validated claims-based algorithms) associated with first trimester (T1) use of Li in monotherapy, according to daily dose tertiles of the first prescription filled during T1. The comparator group consisted of women unexposed to Li or other mood stabilizers during T1 or the 3 months before conception. Fine stratification on the propensity score was used to control for indications and other potential confounders. Relative risks (RR) and 95% confidence intervals (CI) were estimated using generalized linear models.

Results: There were 663 women who filled at least one Li prescription during T1: 305 at low dose (≤600 mg/day), 235 at medium dose (600-900 mg/day), and 123 at high dose (≥900 mg/day). Overall, 1.2% of unexposed births were diagnosed with cardiac defects, compared with 1.6% of births exposed to low dose Li, 2.1% to medium dose, and 4.9% to high dose. The adjusted RR was 1.10 (95% CI 0.46-2.64) for low dose Li, 1.59 (0.67-3.79) for medium dose, and 3.21 (1.47-6.99) for high dose. All right ventricular outflow obstruction defects occurred in association with medium or high doses, with an overall RR=2.65 (1.00-7.04). Results were consistent in secondary analyses that used tertiles of the highest dose filled during T1.

Conclusions: Results from this study suggest that the teratogenic effect of Li in causing cardiac malformations in humans may be dose-dependent.

406. Associations Between Treatment with Selective Serotonin Reuptakeinhibitors (SSRIs) Before and After Pregnancy

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Background: Depression is common in women of child bearing age and selective serotonin reuptake inhibitors (SSRIs) are among some of the most commonly prescribed medicines. However, four out of five women stop treatment in pregnancy and limited information is available on how many take up SSRI treatment after delivery.

Objectives: To examine the association between SSRI treatment before pregnancy and after delivery.

Methods: Using data from The Health Improvement Network (THIN) UK primary care database from 2000 – 2014 we identified women who had given birth and randomly selected one pregnancy per woman (n = 246,612). We estimated the number of women who had received SSRI treatment: (1) 18 to 6 months before pregnancy and/or (2) 0 to 12 months after giving birth. We estimated the 'Relative Risks' (RR) of receiving SSRIs after birth given prior treatment and vice versa using Poisson regression.

Results: There were 19,452 (7.9 %) pregnancies where the women received at least one SSRI prescription in the 18 to 6 months before pregnancy start. Of these 49% also received SSRIs 0 to 12 months after they have given birth. There were 32,294 (13.1%) women who received SSRIs 0 to 12 months after delivery and of these 30% had received treatment in the 18 to 6 months before the pregnancy. The RR for SSRI treatment after birth was 4.95 (95%CI 4.87 to 5.08) for women who had received SSRIs prior to pregnancy. Conversely the RR for having had SSRI treatment prior to pregnancy was 6.49 (95%CI 6.31 to 6.68) for women who had received SSRIs after delivery.

Conclusions: Although there is a very strong association between SSRI treatment before pregnancy and after delivery only half of the women treated before pregnancy restarted SSRI after delivery and less than a third of those receiving SSRI postnatally received treatment 18 to 6 months before pregnancy. This suggest postnatal SSRI treatment is not just a continuum of previous episodes of SSRI treatment and further work is needed to identify women in need of postnatal treatment.

407. Risk Of Neurodevelopmental Disorders Following Prenatal Valproate Exposure: An Observational Cohort Study Using The Health Improvement Network

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Background: Prenatal exposure to valproate containing antiepileptic drugs has been linked with specific congenital malformations and, more recently, neurodevelopmental disorders such as autism.

Objectives: To investigate the association between valproate treatment in pregnancy and the risk of neurodevelopmental disorders in children.

Methods: This was a comparative cohort study in the United Kingdom using The Health Improvement Network (THIN) general practice database. From an established cohort of child-linked pregnancies, we identified women who received valproate treatment in pregnancy (n=217), women who received treatment with other antiepileptic drugs in pregnancy (n=808), women who discontinued antiepileptic drug treatment before pregnancy (n=1,247) and women not treated with antiepileptic drugs before or during pregnancy (n=256,317). Cox regression models were used to estimate the hazard of neurodevelopmental disorders in the children of women who received valproate treatment in pregnancy relative to the three other treatment groups, adjusting for a range of potential confounders.

Results: Women who received valproate treatment in pregnancy were more likely to be deprived, to have an epilepsy diagnosis, and to give birth to a boy than women in the other three exposure groups.

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Independent of these differences in measured characteristics, children born to women who received valproate treatment in pregnancy had a more than two-fold higher risk of neurodevelopmental disorders than women not treated with antiepileptic drugs (HRadj 2.29 CI95 1.59 to 3.31), women treated with other antiepileptic drugs in pregnancy (HRadj 2.07 CI951.29 to 3.34) and women who discontinued valproate treatment before pregnancy (HRadj 2.77 CI951.52 to 5.06).

Conclusions: Valproate treatment in pregnancy is associated with a doubling in the risk of neurodevelopmental disorders. These associations should be taken in to account when considering the risks and benefits of prenatal valproate treatment.

408. Frequency and Predictors of Analgesic Prescribing in US Nursing Home Residents with Persistent Pain

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Background: Inadequate treatment of persistent pain affects quality of life for many elderly residents in nursing homes.

Objectives: To quantify prescription analgesic use among elderly nursing home residents with persistent non-cancer pain and to identify individual and facility traits associated with the absence of such treatment.

Methods: This was a cross-sectional study sourced from Linked Minimum Data Set (MDS) assessments; Online Survey, Certification and Reporting (OSCAR) records; and Medicare Part D claims. From a cross-section of all long-stay US nursing home residents in 2008 with an MDS assessment and Medicare Part D enrollment, we identified individuals ≥65 years old with moderate-to-severe, daily pain on consecutive assessments at least 90 days apart, but without dementia, severe cognitive impairment or receipt of hospice care. We quantified Part D claims for an opioid or non-steroidal anti-inflammatory drug (NSAID) within 30 days following persistent pain onset. We obtained resident and facility characteristics from MDS and OSCAR records. We estimated associations of patient and facility attributes and pain treatment from multilevel mixed effects logistic regression analyses.

Results: Among 18,526 residents with persistent pain, 3,094 (16.7%) did not receive prescription pain medicine; 12,815 (69.2%) received an opioid; 485 (2.6%) received a prescription NSAID, and 2,132 (11.5%) received an opioid and prescription NSAID. In the adjusted analysis, residents ≥95 years old (compared to 65-74 years old, odds ratio (OR)= 2.06, 95% confidence interval (CI) = 1.70-2.49), or with moderate-to-severe cognitive impairment (compared to no cognitive impairment, OR=2.12, 95% CI = 1.71-2.62), were less likely to receive a prescription pain medicine.

Conclusions: Pain remains incompletely treated in US nursing homes, especially among certain subpopulations of residents such as those with cognitive impairment. Changes in pain management practice and policies may be necessary to target these more vulnerable residents.

409. Prevalence and Trends of Analgesic Medication Utilisation in Patients Undergoing Total Joint Replacement Surgery

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Background: Globally the use of opioids has increased since the 1990s, in part due to the relaxing of prescription restrictions and regulations and changes in guidelines for non-cancer chronic pain. In Australia there has been a 15 fold increase in the use of opioids in the general population. Candidates for total joint replacement (TJR) surgery are recommended comprehensive pharmacological pain management prior to surgery due to their disabling joint conditions. How the changes in opioid regulations and general use have affected pain management strategies of patients undergoing TJR surgery is not well understood.

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Objectives: Our study evaluated trends in prevalence and rate of change in analgesic medication prescription in patients prior to joint replacement.

Methods: Using the Australian Department of Veterans' Affairs data a population based epidemiological study was conducted. Opioids, NSAIDs, corticosteroid injections, neuropathic pain medication, hypnotics, and muscle relaxants supply one year pre-total knee replacements (TKR, n=15517) and total hip replacements (THR, n=10018) was assessed (2001-2012). Adjusted prevalence rate ratios (PRR), accounting for patient characteristics and surgical indication, and 95% confidence intervals (CI), are provided.

Results: From 2001 to 2012, the prevalence of opioid use prior to surgery increased from 37% to 49% in TKRs (PRR=1%, 95%CI 0-2%, p=0.04) and from 44% to 54% in THRs (PRR=1%, 95%CI 0-2%, p=0.007). Neuropathic pain medication use increased from 5% to 13% in TKRs (PRR=6%, 95%CI 4-8%, p<0.0001) and from 6% to 12% in THRs (PRR=7%, 95%CI 5-9%, p<0.0001). The NSAID use decreased from 76% to 51% in TKRs (PRR=4%, 95%CI 4-5%, p<0.0001), and 80% to 47% in THRs (PRR=5%, 95%CI 5-6%, p<0.0001). Corticosteroid injections prevalence decreased from 21% to 17% in TKRs (PRR=3%, 95%CI 2-4%, p<0.0001) and 19% to 17% in THRs (PRR=3%, 95%CI 2-4%, p<0.0001).

Conclusions: Utilization of pain medication prior to a patient's TJR surgery has changed significantly in this national cohort of Australian patients during the 2000s, despite the underlying reason for surgery remaining the same across the time period.

410. Global Utilization of Attention Deficit Hyperactivity Disorder Medications – Preliminary Results

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Background: The global epidemiology of attention deficit hyperactivity disorder (ADHD) medication use varies by region and measurement methods. Increasing ADHD medication prevalence is evident in North America and Europe but has not been assessed in Asia.

Objectives: To determine overall and subgroup-specific prevalence of ADHD medication use in children 3-18 years of age in 4 countries, with particular focus on relative trends in prevalence of medication use over time.

Methods: We conducted an observational study using population-based electronic health databases from Hong Kong (HK, 2001-2015), Taiwan (TW, 2000-2013), Japan (JP, 2010-2015) and the province of Quebec, Canada (QC, 2001-2009), using a common protocol approach to estimate use of licensed ADHD prescribed/dispensed medication (identified by ATC classification codes). Annual prevalence (/1000 children) with 95% confidence intervals (CI) of ADHD medications were calculated within available years in each country between 2000-2015, stratified by age group (3-5, 6-11, 12-18 years) and gender over time.

Results: Prevalence of any ADHD medication (/1000 children age 3-18(95%CI)) varied between 0.5 (0.5-0.6) to 21.5 (21.2-21.8) in HK, 3.0 (2.8-3.3) to 12.4 (11.8-12.9) in TW, 2.9 (2.7-3.1) to 5.4 (5.2-5.6) in JP and 0.2 (0.1-0.4) to 17.6 (17.0-18.3) in QC. ADHD medication prevalence increased over available study period in all countries: increased 41 times in HK, 4.1 times in TW, 1.9 times in JP and 73 times in QC. Similar trends were observed in males and females. The male/female ratios in prevalence were 5.0 (HK, 2015), 3.5 (TW, 2013), 2.9 (JP, 2015) and 2.2 (QC, 2009). The age group with highest ADHD medication prevalence was age 6-11 compared to other available age groups: 39 (HK, 2015), 30 (TW, 2013), 6.4 (JP, 2015) and 19.6 (QC, 2009). Methylphenidate was the most commonly used ADHD medication in all countries: 94.9% (HK, 2015), 96.1% (TW, 2013), 55.6% (JP, 2015) and 62% (QC, 2009). Results from 13 additional countries, including adult estimates, are in progress.

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Conclusions: Use of a common protocol and standard medication measurements indicate large increases in ADHD medication use over time in these 4 countries.

411. Prescribing Trends of Attention-Deficit Hyperactivity Disorder (ADHD) Medications in UK Primary Care, 1995-2015

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Background: In the past decades, an increased prevalence of Attention-Deficit Hyperactivity Disorder (ADHD) and use of ADHD medications has been observed in several countries, raising concerns about a possible over-diagnosis and inappropriate prescription of ADHD medications. However, longitudinal trends of ADHD medications have not been updated recently. Also, despite a growing interest in adults with ADHD, most studies have been restricted to children and little is known about the prescribing patterns of ADHD medication in adults.

Objectives: To describe the prescription of medications for Attention-Deficit Hyperactivity Disorder (ADHD) in the UK between 1995 and 2015.

Methods: Using the Clinical Practice Research Datalink (CPRD), we defined a cohort of all patients aged 6 to 45 years, registered with a general practitioner between January 1995 and September 2015. All prescriptions of methylphenidate, dexamphetamine/lisdexamphetamine, and atomoxetine were identified and annual prescription rates of ADHD were estimated using Poisson regression.

Results: Within a cohort of 7,432,735 patients, we identified 698,148 prescriptions of ADHD medications during 41,171,528 person-years of follow-up. Usage was relatively low until the year 2000 during which the prescription rate was 42.7 (95% confidence interval (CI) 20.9 to 87.2) prescriptions per 10,000 persons, increasing to 394.4 (95% CI 296.7 to 524.2) in 2015, corresponding to an almost 800% increase (rate ratio 8.87; 95% CI 7.10 to 11.09). The increase was seen in all age groups and in both sexes but was steepest in boys aged 10 to 14 years. The prescription rate in males was almost 5 times that of females. Methylphenidate remained the most prescribed drug during the 20-year study period, representing 88.9% of all prescriptions in the 6-24 years old, and 63.5% of all prescriptions in adults (25-45 years old).

Conclusions: Prescription rates of ADHD medications have increased dramatically in the past two decades. This may be due to both an increase in the number of patients diagnosed with ADHD over time and a higher percentage of those patients treated with medication.

412. Drug Utilization of Lisdexamfetamine Dimesylate in European Countries

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Background: Attention Deficit Hyperactivity Disorder (ADHD) is a developmental disorder primarily characterized by co-existence of attentional problems and hyperactivity. Lisdexamfetamine dimesylate (LDX) has been authorized for ADHD treatment since 2013 in Europe.

Objectives: The objective of this study is to provide utilization data for LDX in European countries.

Methods: This is a multi-country drug utilization study based on a retrospective database analysis. Longitudinal electronic medical records databases (Germany: IMS Disease Analyzer; UK: CPRD), National Registries (Denmark, Sweden), prescription databases (Switzerland: IFAK/New Index) and prescription data derived from prescriber panels (Spain, Switzerland: IMS Prescribing Insights) were used.

The study includes all patients who have been prescribed LDX at least once during the study period (March [first EU launch] 2013 – December 2014).

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Results: Overall, 11,369 patients with 40,374 prescriptions were included in the analysis.

The majority of patients treated with LDX were males: Germany (78%), UK (82%), Spain (87%), Denmark (63%), Sweden (60%) and Switzerland (75%).

Less than 1% of all patients were < 6 years. Proportion of patients >18 years with LDX was 4% in Spain, 9% in Germany, 12% in UK, 45% in Denmark, 60% in Sweden and 70% in Switzerland.

For 78% (Sweden) or ≥90% of patients (Germany, Spain, UK) an ADHD diagnosis was documented in the medical history in all countries with available information in the database.

Prescribed average daily dose (ADD) of LDX was within recommended range (30-70mg) for 97% to 100% of patients, with a mean ADD of 41mg in Spain, 44mg in Germany, 48mg in UK and about 45mg in Sweden. In Denmark and Switzerland recommended dose was not available in the database.

Conclusions: Findings indicate that LDX is mainly prescribed label compliant with respect to targeted patient group and dose regimen. Adult use is more common in Denmark, Sweden and Switzerland where use of LDX is licensed for adults.

413. Treatment Patterns in Adults with Newly Treated Attention Deficit/Hyperactivity Disorder

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Background: Previous studies on treatment patterns of adult ADHD patients are scarce, which has not been examined in Medicaid beneficiaries.

Objectives: To examine the treatment patterns in adults with newly treated ADHD, including discontinuation, dose escalation, augmentation and switching.

Methods: We used Medicaid Analytic eXtract files of 29 states to identify adult beneficiaries in Fee-for-Service plans in 2000-2010. Eligible patients had to be 18-64 years at the time of their first prescription for an ADHD medication. They had at least 12-months continuous eligibility with no ADHD medication dispensing records before the first prescription, and at least 1 in- or 2 outpatient ADHD diagnoses at any time during the study period.

We examined treatment patterns including: 1) discontinuation - if no refill occurred within 90 days after the end of estimated days' supply of the last pharmacy dispensing claim; 2) dose escalation - if the total dose of the initial medication in any of the 90-day follow-up segments increased compared to the baseline dose in the first 90 days; 3) augmentation -if a second medication was added to the initial one; 4) switching - if a second medication occurred when the initial medication had no active days' supply, and the initial medication did not show any refills after the first claim of the new medication. Using the Kaplan-Meier method, we plotted the time to each endpoint.

Results: Across all states we identified 25,407 eligible beneficiaries. The average follow-up time to discontinuation was 53.9 days. The majority of discontinuation occurred within the first 100 days after treatment initiation. About one-third of patients had dose escalation, most of which happened within 180 days after initiation. The average follow-up time to switching was 366.2 days while the average follow-up time to augmentation was 421.0 days.

Conclusions: Most patients discontinued their medication within the first three months after initiation. About one-third of patients increased the dose of the initially prescribed medication by the end of follow-up. The rates of switching and augmentation were very low, which is consistent with other reports and clinical experience.

414. Psychotropic Medicine Use in Australia (2006 to 2014); Annual Incidence, Prevalence and Patterns of Use

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Background: There are international concerns regarding the quality of psychotropic drug use.

Objectives: To examine annual incidence and prevalence of psychotropic medicine use and details of individual treatment episodes and relate these to prescribing quality.

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Methods: We use individual-level dispensing claims from 10% random sample of Australians receiving government-subsidized drugs between 2006 and 2014. We measure incident and prevalent use at the drug, subclass and class levels, stratified by year. We calculate the estimated period of exposure (EPE) after a single dispensing for each medicine as the time interval at which 75% of people receive a subsequent dispensing of the same medicine. We use EPE to categorise incident treatment episodes in 2007 and 2013 into continuous (C), multiple continuous (MC), multiple non-continuous (MNC) and one-off (O) use and determine the median annual durations of exposure within each category.

Results: Overall, incidence dropped (160-117/1000pop) and prevalence remained stable (350/1000 pop). Incidence of antidepressant use decreased (245-222/1000pop) but prevalence increased (626-750/1000pop); driven by an increase in the number C and MC exposures. The incidence and prevalence of benzodiazepine use decreased (293-231 and 575-501/1000pop respectively) due to decreases in C and O temazepam exposure but there were increases in persons exposed and duration of exposures to all other benzodiazepines. 20% and 30% of antipsychotic and benzodiazepine exposed persons had MNC and O episodes, respectively. Incidence and prevalence of antipsychotics increased (45-51 and 146-200/1000pop respectively), driven by increases in quetiapine use and exposure.

Conclusions: Although new use of antidepressants is decreasing, they are being used continuously and for longer periods. This may represent improved adherence but also a degree of over-treatment. While benzodiazepine use is decreasing overall, the use of most benzodiazepines for extended periods is increasing, out of keeping with current guidelines. Antipsychotics appeared to be used in a similar way to benzodiazepines, possibly indicating significant off label use.

415. Incidence of Mood and Anxiety Disorders and Psychotropic Use in Spouses of Dementia Patients: A Population-Based Study

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Background: The risk of developing psychiatric morbidity as a result of having a spouse with dementia is poorly defined.

Objectives: This study aimed to quantify the incidence of mood and anxiety (MAD) disorders, as well as the incident use of psychotropic drugs in spouses of dementia individuals in the community setting.

Methods: In this population-based, matched cohort study using the Manitoba administrative databases between April 2000 and March 2015, spouses of dementia individuals were identified using household unique registration numbers in the provincial health insurance database. Each dementia spouse was then matched to three comparison spouses based on age, sex and geographic region. Applying a 3-year washout period, clinical cases of depression, anxiety and other stress-related disorders were captured using established medical billing codes. Incidence of MAD and psychotropic use was estimated using cox-proportional hazards models, adjusting for matching variables, socioeconomic status and comorbidities.

Results: Over a median follow-up period of 3.4 years (IQR 1.3 to 6.7 years), we observed 2,768 cases of MAD among 13,463 dementia spouses, and 5,432 cases among 42,264 comparison spouses. Crude incidence rate was 47.2 (95% CI 46.3 – 48.0) per 1000 person-years and 29.0 (95% CI 28.8 – 29.3) per 1000 person-years for dementia spouses and non-dementia spouses, respectively; the adjusted HR was 1.63 (95% CI 1.56 0 1.71; $p<0.0001$). Incident use of psychotropic drugs was 84.5 (95% CI 82.9 – 86.1) per 1000 person-years and 57.3 (95% CI 56.7 – 57.9) per 1000 person-years for dementia spouses and non-dementia spouses, respectively, with an adjusted HR of 1.48 (95% CI 1.42 – 1.53; $p<0.0001$). Incident uses for antidepressants, mood stabilizers, benzodiazepines and other sedatives were all significantly higher for dementia spouses.

Conclusions: A higher risk of psychiatric morbidity and psychotropic drug use can be attributed to having a spouse with dementia.

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Healthy Living and Seniors, or MCHP is intended or should be inferred.

416. Sustained Use of Benzodiazepines and High Dose Escalation in a Canadian Population

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Background: Anti-benzodiazepine campaigns have been conducted worldwide to limit prescribing because of concerns about inappropriate use and addiction. Causal relationship between long-term use and high dose escalation has not been proven.

Objectives: This study assessed the extent of dose escalation in individuals on long-term use of benzodiazepines or Z-hypnotics.

Methods: population-based study was conducted in the Canadian province of Manitoba using administrative databases housed at the Manitoba Centre for Health Policy (MCHP). Sustained use was defined as continuous use for at least 2 years (N=12,598). Dose escalation, measured in Diazepam Milligram Equivalents (DME)/day over 6-month interval observations, was assessed using latent-class trajectory analysis (LCTA). Descriptive statistics was used to characterize individuals with sustained use. Chi-square tests (categorical variables) and t-tests (continuous variables) were used to compare the younger (0-64 years of age) to the older (≥65 years of age) segments of the population.

Results: LCTA revealed 4 distinct groups. Two groups <8% of the cohort) show dose escalation to high doses (over 40 DMEs). More than 55 % of high-dose escalators belonged to the 0-44 years of age group; 75% lived in urban areas and 78% had a diagnosis of depression. Clonazepam was the drug most commonly involved with dose escalation; among individuals escalating to doses higher than 60 DME, 91% were using clonazepam. Elderly individuals were generally treated with lower doses and had lower concomitant use of opioids. Younger individuals showed more "doctor shopping"/"pharmacy hopping" compared to older adults and had higher use of concomitant antidepressant therapy.

Conclusions: A limited segment of a population that receives benzodiazepine prescriptions can be classified as sustained users and a small number ever escalates to doses higher than those recommended by product monographs and clinical guidelines.

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417. Antidepressant and Benzodiazepine Co-Initiation and Subsequent Long-Term Benzodiazepine Use in Adults with Depression, United States 2001-2014

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Background: Short-term co-initiation of antidepressants (AD) and benzodiazepines (BZD) has been used for patients with depression, particularly when anxiety or insomnia is present. However, BZDs are associated with risks including dependency, which may take only a few weeks to develop.

Objectives: To describe BZD+AD co-initiation over time among adults with depression initiating ADs and to estimate the proportion of co-initiators with long-term BZD use.

Methods: Our population included adults (18-64 years) with a recent inpatient/outpatient depression diagnosis (ICD-9-CM code) who initiated an AD between 2001-2013, MarketScan Commercial Claims database. AD initiators were naïve to both AD and

BZD at AD initiation (no dispensed prescriptions in prior year). Co-initiation was defined as a BZD prescription fill the same day as AD initiation. Long-term BZD use was defined as continuing BZD therapy 180+ days after co-initiation; BZD discontinuation was defined as no BZD prescription fill 30 days after the last prescription's days supply ran out. We described co-initiation across time and, in adults with 6-months of follow-up, estimated long-term BZD use, using adjusted Poisson regression with robust variance to evaluate factors associated with long-term BZD use.

Results: Overall 10% (n=62,142) of 650,671 adults initiating an AD co-initiated BZD. Co-initiation increased from 5% in 2001 and peaked at 12% in 2012, similar trends by age group and provider (psychiatry: 8% to 15%, family practice: 4% to 12%). In co-initiators with follow-up, 63% discontinued BZD use after initial fill; still, 11% (n=5,272) exhibited long-term BZD use. Long-term BZD use was more likely in males (RR=1.3, 1.2-1.4), patients with a higher initial BZD days supply (22-35 days vs. 1-7, RR=2.8, 2.4-3.3), and depression diagnosed by a psychiatry provider vs. family practice (RR=1.4, 1.3-1.5).

Conclusions: Co-initiation with BZD peaked in 2012 among AD initiators, we will evaluate if the 2012 plateau continues through 2014. Over 10% of co-initiators became long-term BZD users. Given risks associated with BZDs, co-initiation requires careful balance of benefit and harm.

418. Benzodiazepines and Mortality: A Marginal Structural Model (MSM) Application in Claims Data

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Background: Multiple studies have suggested benzodiazepines (BZD) are associated with an increased mortality risk (up to 4.5-fold). An important challenge for research in this area is the selection of an appropriate reference group. While use of an active referent coupled with an as-treated analysis is typically preferred, this approach can be biased by non-random discontinuation or switching of treatment (informative censoring). MSMs address this problem through the creation of a pseudo-population in which there is no association between measured confounders and treatment, including discontinuation or switching, at any time during follow-up.

Objectives: Use MSM to estimate the effect of BZD on mortality using antidepressants (AD) as the active referent.

Methods: We defined a cohort of 1:1 propensity score (PS) matched initiators of BZD or AD nested in the Optum data from 2004-2013. The outcome was 12-month mortality. At each month of follow-up, the patients' exposure was re-classified based on the treatment actually received (BZD, AD, both, none) and 52 time-varying covariates were measured, including comorbidities, concomitant medications, and healthcare utilization. Stabilized inverse-probability-of-treatment (SIPT) weights were used to create the pseudo-population. We estimated the hazard ratio (HR) for death using an SIPT weighted pooled logistic model.

Results: The cohort comprised 901,712 matched pairs. Overall, the 12-month mortality risk was 6.3 per 1,000. The HR was 2.88 (95%CI, 2.71-3.06) in the unmatched cohort, and 1.64 (1.52-1.77) in the PS-matched cohort, using a Cox model with censoring at treatment switch or discontinuation. Time on treatment was shorter for BZD users (median: 42 days) than for AD users (median: 92 days). Patients staying on BZDs longer tended to be sicker. The mean of the weights was 1.0. The MSM resulted in a HR of 1.17 (1.13-1.22).

Conclusions: Our findings suggest that previously estimated large mortality risks associated with BZDs are very sensitive to unlikely assumptions about switching and discontinuation and that BZDs are associated with a very small increase in risk at most. These analyses illustrate the value of MSM in claims data.

419. Impact of Paliperidone Palmitate versus Oral Atypical Antipsychotics on Healthcare Resource Use and Costs in Veterans with Schizophrenia with Limited Antipsychotic Exposure in the Prior 12 Months

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Background: Studies examining the impact of paliperidone palmitate (PP) in schizophrenia patients with limited antipsychotic (AP) exposure in the prior 12 months are few.

Objectives: Compare healthcare resource utilization and costs in veterans with schizophrenia treated with PP versus oral atypical antipsychotics (OAA) who were exposed to 0 or 1 AP in the prior 12 months.

Methods: Veterans Health Administration electronic health record data were used to conduct a retrospective longitudinal study in veterans with schizophrenia newly treated with PP or OAA between 1/1/10-6/30/15 (first dispensing defines the index date), with ≥12 months of enrollment prior to treatment initiation (i.e., baseline), and with exposure to 0 or 1 AP and ≥1 Global Assessment of Functioning (GAF) score during baseline. Inverse probability of treatment weighting (IPTW) was used to adjust for baseline differences. Weighted regression models were used to estimate adjusted cost differences (CD) and incidence rate ratios (IRR) for the effect of PP versus OAA on all-cause healthcare costs and resource utilization during the 12 months post-index.

Results: Of 6,441 veterans included in the study, 590 (9%) and 5,851 (91%) were treated with PP and OAA, respectively. The distribution of baseline covariates between cohorts was balanced after applying IPTW. After adjustment, PP was associated with fewer inpatient (IRR=0.90, $p<0.001$), mental health (IRR=0.80, $p<0.001$), and long-term care stays (IRR=0.55, $p<0.001$), but a greater number of mental health intensive case management (MHICM) visits (IRR=1.10, $p<0.001$) compared to OAA. Reductions in resource utilization associated with PP resulted in lower average annual inpatient stay costs (CD=-$15,454, $p<0.001$), which offset higher average annual pharmacy costs (CD=$3,498, $p<0.001$), resulting in annual total cost savings (CD=-$10,042, $p=0.032$) for PP users relative to OAA users.

Conclusions: Treatment with PP was associated with significant cost savings relative to OAA due to fewer hospitalizations in patients with schizophrenia who received 0 or 1 AP agent during baseline.

420. Final Results of a Large Multi-National Postmarketing Safety Study Evaluating Use of the Oral Anti-Diabetic Drug Saxagliptin and Risk of Five Outcomes

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Background: The safety profile of saxagliptin compared to other oral anti-diabetics (OADs) has not been studied in real-world settings.

Objectives: To evaluate the risk of major adverse cardiovascular events (MACE), infection, acute kidney injury (AKI), acute liver failure (ALF), and severe hypersensitivity reactions in adult patients with type 2 diabetes newly prescribed saxagliptin compared to those initiating OADs in classes other than dipeptidyl peptidase-4 inhibitors.

Methods: We conducted cohort studies within US Medicare, the HealthCore Integrated Research Database, Clinical Practice Research Datalink, and The Health Improvement Network from 2009-2014. Follow-up began at initial prescription/dispensation of the index OAD and continued until study outcome (each evaluated separately), drug discontinuation, DPP-4 initiation, or end of study, whichever occurred first. Outcomes were hospitalized MACE, AKI, ALF, infections, and severe hypersensitivity events, all evaluated using diagnostic coding algorithms and medical records. Within each data source, Cox models were used to determine hazard ratios (HR) with 95% CIs of each outcome in saxagliptin versus other OAD initiators, adjusted for propensity scores of saxagliptin initiation. Meta-analysis of each outcome across data sources was performed as data permitted.

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Results: We identified 427,576 saxagliptin initiators and 3,535,010 other OAD initiators. There were no increased incidence rates or risk of MACE, infection, AKI, ALF, or severe hypersensitivity reactions between saxagliptin initiators and other OAD initiators within each data source. Meta-analyses resulted in no increased risk of hospitalization/death from MACE (HR, 0.91 [95% CI, 0.85-0.97]), hospitalization for infection (HR, 0.97 [95% CI, 0.93-1.02]), or hospitalization for AKI (HR, 0.99 [95% CI, 0.88-1.11]) among saxagliptin initiators. ALF and hypersensitivity events were too rare to permit meta-analysis.

Conclusions: Saxagliptin initiation was not associated with significantly increased incidence rates of MACE, infection, AKI, ALF, or severe hypersensitivity reactions.

421. Use of Incretin Agents and Risk of Acute and Chronic Pancreatitis: A Population-Based Cohort Study

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Background: Incretins are new therapeutic agents for the treatment of Type 2 Diabetes Mellitus (T2DM), and are a subgroup of the Non-Insulin Antidiabetic Drugs (NIAD). Although incretin agents have demonstrated efficacy for T2DM, they have been associated with pancreatitis. Recent literature shows limited and conflicting evidence for the association between incretin agents and the risk of acute pancreatitis. Furthermore, the risk of chronic pancreatitis with the use of incretin agents has not been investigated.

Objectives: To determine the association between the use of incretin agents and the risk of acute and chronic pancreatitis.

Methods: A retrospective population based cohort study, using data from the Clinical Practice Research Datalink (CPRD) (2007–2012), was conducted. Patients (N=182,428) with at least one NIAD prescription and aged 18+ during data collection, were matched to one control patient without diabetes. Multivariable Cox proportional hazards models and a new user design were used to estimate the hazard ratio of (acute, chronic and any) pancreatitis in incretin users (N=28,370) compared with non-diabetics and other NIAD-treated patients. Time dependent adjustments were made for age, sex, life style, comorbidities and drug use.

Results: Current NIAD use was associated with acute, chronic and any pancreatitis. This risk increased among current incretin users, as compared to non-diabetic controls. However, only any pancreatitis was associated with incretin use when compared to other NIAD-treated patients (HR=1.47, 95% CI 1.06–2.04). Pancreatitis risk was higher among younger patients (age 18-≤59 years), those with a BMI <25 kg/m2, or those using DPP4-Is compared to other NIAD-treated patients. In the new user design cohort, the association between incretin use and acute and any pancreatitis doubled compared to the prevalent cohort.

Conclusions: Incretin use was associated with an increased risk of any pancreatitis. Moreover, risk of pancreatitis was higher among incident incretin users. Further research is necessary regarding the need for clinical consensus between the association of pancreatitis and incretin use in T2DM patients with a history of pancreatitis.

422. Use of Non-Insulin Blood Glucose Lowering Drugs and the Risk of Acute Pancreatitis

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Background: Use of non-insulin blood glucose lowering drugs (NIBGLD) has been associated with acute pancreatitis (AP). For newer NIBGLDs, including GLP-1 based drugs, evidence for such risk is conflicting.

Objectives: To estimate the risk of AP for NIBGLD in databases (DB) participating in the SAFEGUARD project.

Methods: Case-control study was performed nested in a cohort of new NIBGLD users. Incident AP cases were matched with up to 5 controls on DB, sex, cohort entry (±3 months) and date of birth (±1 year) using risk set sampling. Data were retrieved from 7 DBs from Europe (Netherlands: PHARMO; Spain: BIFAP; Germany: GePaRD; Italy: Health Search, Regional DBs of Lombardy and Puglia; United Kingdom: CPRD) and USA (Medicare). Adjusted odds ratios (ORs) and 95% confidence intervals (95%CI) were estimated per DB, comparing current use of metformin +sulfonylureas (reference) with each monotherapy, dual therapy of metformin plus another NIBGLD (not SU) and other combinations. One (ORpool) and two stage (OR meta) pooling was used to combine the database specific data.

Results: In total 3,990 incident AP cases were matched to 19,543 controls. Majority of subjects were male. Drugs known to be associated with AP (class 1), gallstones and alcohol abuse increased risk of AP. Metformin monotherapy was associated with a decreased risk of AP (ORpool 0.88 95%CI:077-1.00; ORmeta 0.84; 0.73-0.96). Regarding GLP-1 based drugs, we observed a statistically non-significant risk for sitagliptin monotherapy (ORpool 1.53; 0.88-2.64; ORmeta 1.29; 0.64-2.58). Monotherapy of glimepiride (ORmeta 1.02;0.84-1.24) and glibenclamide (ORmeta 1.16;0.68-1.97) did not yield an increased risk. Current use of any other NIBGLDs or combinations was not associated with an increased risk of AP in any of the databases (ORpool 1.1; 0.94-1.34; ORmeta 1.01; 0.85-1.20). Recent and past use of any NIBGLD were not associated with an increased or decreased risk of AP (ORmeta 1.10; 0.88-1.36 and 0.93; 0.80-1.09, respectively).

Conclusions: Monotherapy of metformin was associated with a decreased risk of AP, while sitagliptin monotherapy was associated with a statistically non-significant increased risk while a risk≥2.6 could be excluded.

423. Metformin and Cancer Risk in Type 2 Diabetes: An Application of Marginal Structural Models with Inverse Probability of Treatment Weights in the Clinical Practice Research Datalink

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Background: Previous studies provide conflicting evidence on whether metformin is protective against cancer. The effect of time-varying confounders that affect treatment, such as HbA1c, may not have been adequately accounted for. However, such variables may act as both confounders and causal pathway variables, so cannot be handled by standard regression models. Marginal structural models (MSMs) with inverse probability of treatment weights (IPTW) can correctly adjust for such time-varying confounders by creating a pseudo population in which confounders are balanced across treatment groups through time.

Objectives: To estimate the effect of metformin on cancer risk compared to diet alone, using MSMs with IPTW to correctly adjust for time-varying confounding.

Methods: Patients with incident T2DM were identified in the Clinical Practice Research Datalink

(CPRD), a UK primary care database. Patients entered the study when they had complete confounder data. Follow-up was split into 1 month intervals. Logistic regression was used to calculate IPTW; then the effect of metformin on cancer risk was estimated via pooled logistic regression in the weighted population.

Results: 55,629 patients were alive and cancer free at study entry; 2530 cancer diagnoses were observed during a median follow-up time of 4 years. After adjustment for baseline confounders only, the HR for cancer comparing metformin with diet only was 0.95 (95% CI, 0.86–1.05); the HR estimate was similar in a weighted MSM adjusted for time-updated confounding (HR=0.97, 0.84–1.13). Results were robust to a range of sensitivity analyses.

Conclusions: We found no evidence for a protective effect of metformin on cancer. Results are consistent with previous studies at low risk of bias, and suggest that time dependent confounding between post baseline treatment and cancer is of low importance in this context.

424. Impact of Glycaemic Control on Risk of Infections in 69 318 Patients with Type 2 Diabetes: A Population-Based Cohort Study

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Background: Infections are a major clinical challenge for type 2 diabetes patients, but little is known about the impact of glycaemic control on infection risk.

Objectives: To examine the effect of short- and long-term glycemic control on risk of infections in type 2 diabetes.

Methods: We identified 69 318 patients with an incident diagnosis of diabetes defined as a first glucose-lowering drug prescription or first inpatient or outpatient hospital contact with diabetes in individuals >30 years recorded between 2000 and 2012. We followed these individuals for subsequent hospital contacts for infection and receipt of antibiotic prescriptions in primary care. We examined the association between first HbA1c value after diagnosis of diabetes (baseline) and time-varying updated HbA1c values and rate of infections, using Cox regression to compute adjusted hazard ratios (HRs).

Results: The rate of infections was 401/1000 patient-years. The adjusted HRs for infection associated with every 1% increase in HbA1c level were 1.00 (95% confidence interval [CI] 0.99–1.00) for baseline HbA1c level, 1.01 (95% CI 1.01–1.02) for updated mean HbA1c level, 1.02 (95% CI 1.01–1.03) for updated time-weighted mean HbA1c level, and 1.03 (95% CI 1.02–1.04) for the latest updated HbA1c level. Patients with a latest updated HbA1c value of ≥10.5% were 1.64-fold (95% CI 1.51–1.79) more likely to get hospitalised for infection and 1.15-fold (95% CI 1.09–1.21) more likely to fill an antibiotic prescription, compared to patients with a latest updated HbA1c value of 5.5%–6.5%. Current hyperglycaemia – defined by latest updated HbA1c value – was associated particularly with risk of abscesses, skin infections, fungal infections, viral infections, septicaemia, urinary tract infections, and tuberculosis, and with filled prescriptions for cephalosporins, quinolones, dicloxacillin/flucloxacillin, and animycobacterials.

Conclusions: Current hyperglycaemia is associated with infection risk in patients with type 2 diabetes.

425. Estimated Effects of Treatment Changes on Emergency Care Utilization in a Cohort of Patients with Type 1 Diabetes

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Background: Initiation of continuous subcutaneous insulin infusion (CSII), also known as an insulin pump, and continuous glucose monitoring (CGM) has been shown to improve glycemic control in patients with type 1 diabetes mellitus (T1DM). However the effects of these treatments on emergency care utilization are not well known.

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Objectives: To estimate the effects of initiation of CSII and/or CGM on emergency care utilization in a cohort of patients with T1DM.

Methods: This study was performed using data from the US Department of Defense Military Health Systems database between October 2007 and September 2013. A validated claims algorithm with high accuracy was used to identify T1DM patients age ≤ 18. Study follow-up began one year after first T1DM diagnosis to create a cohort with established (post-honeymoon) T1DM. A zero-inflated Poisson model estimated the effects of switching insulin delivery method from multiple daily injections (MDI) to CSII and/or augmenting treatment with a CGM on emergency care utilization. Emergency care was defined as a day with an ambulance, emergency room, or inpatient hospitalization encounter.

Results: The cohort consisted of 3,138 patients with T1DM (44% female; mean age 13.8 years at presentation) using conventional therapy (MDI and self-monitoring of blood glucose). During follow-up, 62.6% (n=1,964) of patients remained on conventional therapy and 37.4% (n=1,174) changed treatment. Patients had 21,371 total emergency care days during 9,940 patient years of follow-up (an average of 2.15 total emergency care days per patient year). Patients who initiated CSII (RR=0.81; [95% CI, 0.78–0.84]) or CGM (RR=0.88; [0.80–0.96]) experienced fewer days with emergency care. Patients who initiated both CSII and CGM (RR=0.85; [0.79–0.90]) did not experience further reduction in emergency care utilization from multiple treatments.

Conclusions: Patients who changed treatment from conventional therapy to CSII and/or CGM experienced a statistically significant reduction in the number of days with emergency care.

426. 35-Year Trends in First-Time Hospitalizations for Hip Fracture and Subsequent 0-30 and 31-365 Days Mortality: 1980-2014

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Background: Change in comorbidity over time, and its impact on mortality following hip fracture surgery, has not been examined in population-based settings.

Objectives: To examine trends in hip fracture incidence rates in Denmark from 1980 through 2014, and subsequent mortality.

Methods: Using prospectively collected data from population-based registries, we included 262,437 first-time hospitalizations for hip fracture from 1980 through 2014. We calculated the age- and sex-standardized incidence rates of hip fracture and mortality within 30 days and 31-365 days after hip fracture. Comorbidity was assessed by the Charlson Comorbidity Index (CCI) score and classified as no, moderate, severe, and very severe.

Results: The overall hip fracture incidence rates decreased by 23% from 1980 to 2014, only among women. The overall rates decreased in all age groups. The proportion of patients with severe and very severe comorbidity increased from 9.8% and 5.6% in 1980-1984 to 18.8% and 26.5% in 2010-2014, respectively. Mortality rate ratios (MRRs) adjusted for comorbidity, age and sex were 0.7 (95% confidence interval (CI): 0.6-0.7) within 30 days and 0.6 (CI: 0.6-0.7) within 31-365 days of hip fracture in 2010-2014 compared with 1980-1984. Stratified analyses on CCI revealed reduction in mortality from 1980 to 2014 in both patients without and with different levels of comorbidity. Compared with patients with no comorbidity, hip fracture patients with severe comorbidity had adjusted MRRs of 1.7 (CI: 1.7-1.8) and 2.0 (CI: 1.9-2.0) within 30 days and 31-365 days post hip fracture, respectively, while patients with very severe comorbidity had adjusted MRRs of 2.5 (CI: 2.4-2.6) and 2.8 (CI: 2.7-2.9) during these follow-up periods, respectively.

Conclusions: We found a decrease in incidence rates of hip fracture in Denmark in women and all age groups. The proportion of patients with comorbidity increased over time. Still, 30-day and 31-365-day mortality decreased by 30% to 40% since 1980. The decrease in mortality over time was seen in patients without and with comorbidity before hip fracture.

427. Association of Gout Diagnosis with Increased Risk of Joint Replacement: A Population-Based Cohort Study of Older Adults

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Background: Gout is the most common inflammatory arthritis in men and older women. There are few studies on joint replacement rates among patients with diagnosed gout compared to those without gout.

Objectives: To assess risk of joint replacement among patients with diagnosed gout compared to patients without gout diagnosis, and associated predictors.

Methods: In this population-based cohort study of older adults, we identified all subjects aged >66 years between Jan 1, 1995 and Dec 31, 2009. A study cohort of 252,255 individuals was reconstructed using the Quebec RAMQ and MedEcho administrative databases. Patients with a gout diagnosis were included only if they met all of the following criteria: 1) gout defined by ICD-9 or ICD-10 or exposure to specific gout treatment. Date of cohort entry of patients with gout was defined as the first date of established gout during follow-up. Primary outcome was incident joint replacement rate defined by a composite endpoint representing patients with a medical procedure in the hip, femur and basin, knee, ankle/foot, hand/finger, shoulder/humerus, forearm/elbow, or wrist. Potential predictive factors examined included gout diagnosis, dementia, diabetes, and cardiovascular, cerebrovascular, peripheral vascular, kidney, pulmonary, rheumatic, and gastrointestinal diseases.

Results: The incident rate of joint replacement was at 2.67 (95% CI: 2.57-2.77) and 1.92 (1.90-1.94) per 100 person-years among patients with and without a gout diagnosis, respectively ($p<0.0001$). Major predictors of total joint replacement were gout diagnosis (31%), advanced age (42%), cerebrovascular disease (13%), acute renal failure (10%), respiratory disease (12%), rheumatic disease (43%), and gastrointestinal disease (10%). Significant predictors of drug exposure are NSAIDs, intra-articular corticosteroids and narcotic use. Noted limitations included the limited ability to adjust for clinical severity and potential of residual confounding factors.

Conclusions: Gout disease was associated with a significant, 31% increase risk of joint replacement in older adults. Further research should be conducted to confirm this potential associated risk.

428. Validation of Fracture Risk Assesment Tool Using Real-World Data

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Background: A fracture risk assessment model (FRAX) was recently constructed for Israel using national hip fracture rates.

Objectives: To evaluate the predictive performance of FRAX using real-world patient-level data.

Methods: A retrospective cohort study was conducted utilizing the central database of a large Israeli health fund (both insurer and provider of healthcare services). Patients with electronically recorded bone mineral density (BMD) measured at age 50 or above at the year 2006 or earlier were eligible. First available BMD test defined the index date. Patients with less than 10 years follow-up after index (for reasons other than death) were excluded. A major osteoporotic fracture (MOF) was determined by clinical diagnoses or specific procedures of hip, spine, Colles' or humerus fractures occurring at age 50+ for women or 60+ for men, excluding motor vehicle accidents. FRAX scores at index were obtained using the web-calculator for a random sample of patients, and compared to actual fractures observed during the following 10 years. Area under receiver operating characteristic curve (AUC) was computed as a measure of discriminative strength, and calibration was assessed by Hosmer-Lemeshow goodness-of-fit.

Results: A total of 10,700 eligible patients were identified. Study sample included 6,000 patients (mean ±SD age=61±8 years), of whom 94% women, and 56% treated for osteoporosis for at least 3 years. Median (IQR) 10-year FRAX scores were 6.5% (4.4-9.9%) and 1.4% (0.7-3.0%) for any MOF and hip fracture, respectively, whereas observed events rates were 20% and 3% for MOF and hip fracture, respectively. While the AUC of BMD alone was 0.55 (95% CI: 0.53-0.57) for MOF and 0.31 (95% CI: 0.27-0.35) for hip, the AUC of FRAX score was 0.62 (95% CI: 0.60-0.64) for MOF and 0.78 (95% CI: 0.74-0.81) for hip fracture.

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Conclusions: Among this Israeli cohort of middle-aged community dwelling patients with measured BMD, the FRAX calculator exhibited a clear added value over using BMD alone, a reasonable predictive value for hip fracture incidence, yet a limited calibration for other major fractures. Incorporating FRAX into intervention allocation strategies would largely impact detection and intervention rates.

429. Total Hip and Knee Replacement Among Incident Osteoarthritis and Rheumatoid Arthritis Patients Within the UK Clinical Practice Research Datalink (CPRD) Compared to Hospital Episode Statistics (HES): A Validation Study

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Background: The UK CPRD is a rich source of primary care health data and has been previously used to research total hip replacement (THR) and total knee replacement (TKR) among arthritis patients and in the general population.

Objectives: We aimed to validate primary THR and TKR Read code definitions in CPRD against the HES dataset. HES contains all admissions data from NHS hospitals in England.

Methods: Patients with HES linkage and a first diagnosis of rheumatoid arthritis (RA), hip osteoarthritis (OA) or knee OA between 1995-2014 were identified in CPRD using pre-defined Read code lists. Exclusion criteria were age<18 years, GP practice outside England, prevalent arthritis or multiple types of arthritis during follow-up (hip and knee OA allowed). Subsequent primary THR and TKR events among each arthritis cohort were similarly identified. THR and TKR in HES were identified using OPCS4 codes. We compared THR and TKR events in CPRD to HES (considered as gold standard) by calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Events in HES were not counted if event was present in both datasets but with more than a 60 day interval.

Results: Of 24,435 patients identified in CPRD with hip OA, 10,059 had a THR of which 7,320 also had a THR in HES: sensitivity = 86.6%, specificity 82.9%, PPV = 72.8% and NPV = 92.1%. Of 51,696 patients identified in CPRD with knee OA, 8,937 had a TKR of which 6,663 also had a TKR in HES: sensitivity = 88.0%, specificity 94.8%, PPV = 74.6% and NPV = 97.9%. Of 14,979 patients identified in CPRD with RA, 630 had a THR of which 426 also had a THR in HES: sensitivity = 81.6%, specificity = 98.6%, PPV = 67.6% and NPV = 99.3%. 811 RA patients had a TKR in CPRD of which 574 also had a TKR in HES: sensitivity = 85.3%, specificity 98.3%, PPV = 70.8% and NPV = 99.3%.

Conclusions: Primary THR and TKR can be identified among OA and RA patients in CPRD with a high degree of agreement with HES. This confirms the validity of using the CPRD to study THR and TKR in these populations.

430. Modular versus Monobloc Neck Stems Primary Total Hip Arthroplasty Survivorship. Result of a Prospective Series of 324,108 THA at 6-Years Follow-Up

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Background: Modular neck stems were introduced in Total Hip Arthroplasty (THA) to improve restoration of joint biomechanics (restoring anteversion, offset and limb length) and reduce dislocation-rates. On the other hand, neck modularity has also been reported to result in adverse effects and this option has become more and more discussed.

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Objectives: Our aim was to find out if neck modularity represents a class issue regarding THR survivorship, exploiting the French national health insurance databases.

Methods: All French patients aged 40 years or older, having undergone primary THR from January 1, 2009, through December 31, 2012 were included. Outcome of interest was THR revision, including any surgical procedure in which the implant or any component was changed or removed. Follow-up started the day the primary THR was performed. Observations were right-censored on December 31, 2014, if neither revision nor death had yet occurred. THR survivorship was assessed according to type of neck - modular or monobloc - in univariate and multivariate Fine and Gray competing risks regression models.

Results: The study cohort comprised 324,108 individuals: mean age at baseline, 76.5 years; women, 62.3%; implanted for traumatic resaon: 23.8%.

Modular neck THRs proportion was 2.8%. Regarding bearing surface, 32.3% were ceramic-on-ceramic, 17.3% ceramic on polyethylene, 47.8% metal on polyethylene and 2.7% metal on metal. Regarding fixation, 10.6% were cemented, 71.3% uncemented, 16.5% hybrid and 1.6% reverse hybrid.

During the median 45-month follow-up, 11,968 individuals underwent prosthetic revision. At 6-years follow-up, cumulative revision incidence was 7.0% for modular neck THRs versus 5.1% for monobloc neck THRs ($p<0.001$). Adjusted hazard ratios for modular neck THRs was 1.26 (1.14-1.38; $p<0.001$), compared to monobloc neck THRs.

Conclusions: Modular neck THRs had a poorer survivorship, independently of other prosthetic revision risk factors. Accordingly, expected anatomical and functional benefits should be carefully assessed before choosing this design.

431. Incidence and Trends in ACL Reconstruction Among Commercially-Insured Individuals in the United States, 2002-2013

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Background: Tears of the anterior cruciate ligament (ACL) are one of the most debilitating knee injuries and typically result in pain, mobility limitations, reconstructive surgery, extended rehabilitation (up to 6 months), and accelerated progression to post-traumatic osteoarthritis over the ensuing decade.

Objectives: Describe incidence and trends in ACL reconstruction among commercially-insured individuals in the United States from 2002-2013 by gender and age.

Methods: Incidence rates were estimated using the Truven Health Analytics MarketScan Commercial Claims and Encounters database (2002-2013), which includes privately-insured individuals <65 years old. ACL reconstructions were identified as arthroscopically aided ACL reconstruction or knee ligamentous reconstruction (CPT codes: 29888, 27428) with diagnosis of new or prior ACL tear (ICD-9 codes: 717.83, 844.2). Only one ACL reconstruction per person per month was included. Annual denominators for the incidence rates reflected person-time at risk for all individual person-months enrolled in a health insurance plan covered by the database.

Results: During the study period, there were 253,544 ACL reconstructions and 345,817,834 person-years at risk. The rate of ACL reconstruction per 100,000 person-years increased from 61.0 in 2002 to 77.3 in 2013, a 27% increase. However, among patients <13 years old, the rate rose 138% over the study period (1.2 in 2002 to 2.9 in 2013). Patients aged 13-17 years had the highest rates of reconstruction (207.4 per 100,000 person-years). Rates remained relatively stable over time for patients 18-40 years old. Males had higher rates of ACL reconstruction than females (86.9 vs. 60.6).

Conclusions: The incidence rate of ACL reconstruction among commercially-insured individuals in the United States has increased rapidly in recent years in younger age groups. This may be secondary to increased injury rates and/or greater perceived benefit from surgical intervention in younger age groups.

432. A Comparison of Methods for Estimating Values for Sparse and Irregularly Spaced

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Continuous Outcome Measures in Electronic Health Record (EHR) Data

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Background: A common primary outcome in healthcare studies is change in continuous variables over prespecified time periods. Measurements using data collected as part of routine clinical practice recorded in EHRs depend on when patients visit their clinician resulting in data that can be sparse and irregularly spaced. Measuring change at prespecified time points is therefore challenging. Various methods exist for estimating missing values including computationally simple approaches e.g. last observation carried forward (LOCF) and more complex techniques e.g. functional principal component analysis (FPCA).

Objectives: To compare the performance of five methods to estimate known, but hidden, haemoglobin A1c (HbA1c) values in a cohort of diabetic patients: 1) linear interpolation, 2) simple linear regression, 3) arithmetic mean, 4) random effects modelling and 5) FPCA.

Methods: For 16,034 diabetic patients identified in the UK's CPRD, with at least two measures in a 30-month period, HbA1c was estimated after temporarily omitting i) the final and then ii) the middle known values using all five estimation methods. Performance of each method was assessed using mean prediction error and mean squared prediction error. The influence on predictive accuracy of 1) more homogeneous populations and 2) number and range of known HbA1c values was explored.

Results: The predictive accuracy of FPCA and LOCF was highest when estimating the last observation, with more than half the predicted values within 0.4 units, equivalent to laboratory measurement error. Predictive accuracy improved generally when estimating the middle observation with almost 60% predicted values within 0.4 units for FPCA. These patterns persisted with more homogeneous populations. High variability in HbA1c and fewer data points led to lower predictive accuracy with all approaches where modelling methods such as FPCA did not convincingly produce better results.

Conclusions: For sparse longitudinal data, estimation of change from baseline to specified time points in EHR data can be achieved just as accurately with simpler approaches as with more complex modelling techniques.

433. A Comparison Of Structured Data Query Methods Versus Natural Language Processing To Identify Metastatic Melanoma Cases From Electronic Health Records

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Background: With the wide-spread adoption of electronic health records (EHR) and advances in the nature language processing (NLP) technology, analyzing unstructured data (e.g. narrative medical reports) becomes feasible and affordable. It is an alternative way other than structured data query to identify clinical events of interest in large populations.

Objectives: To evaluate the performance of unstructured data analysis using NLP relative to structured data query in identifying metastatic melanoma patients in a large EHR database.

Methods: A retrospective study was conducted using the Indiana Network for Patient Care (INPC) database. The target population included all patients of age 21 years or older who had any clinical records between January 1, 2005, and December 31, 2013. Metastatic melanoma cases were identified by two methods separately: 1) NLP algorithms applied to text reports, and 2) structured data query of diagnosis codes. Manual

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chart reviews established the "gold standards" for estimating positive predictive values (PPVs). Each identified case was classified as "definite positive," "definite negative," "unsure but possible", or "unsure, but unlikely." The Indiana Tumor Registry served as an external source of true metastatic melanoma cases for estimating the sensitivities.

Results: NLP of text report and structured data query identified 1,727 and 607 metastatic melanoma cases, respectively. A total of 512 cases were identified by both methods. Using "definite positive" from medical chart review as the gold standard, the PPVs of these two methods were 74% vs. 83%. When "unsure but possible" was added to the gold standard, the PPVs slightly increased to 80% vs. 84%. The NLP method had much higher sensitivity than the structured data query method, which was 67% vs. 35%.

Conclusions: The NLP method identified metastatic cancer cases nearly three folds as many as structured data query, although the chance of false positive result was slightly higher. It is a useful tool to use alone or together with structured data query in EHR database research.

434. Additive versus Multiplicative Survival Models: Prediction and Understanding of Effect Modification

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Background: Additive interaction is highly relevant for assessing treatment effect heterogeneity because it directly quantifies the public health impact of treatment across patient subgroups. However, in part due to ease of statistical modeling, multiplicative interaction is more often reported. Either additive or multiplicative survival models may be useful for identifying treatment effect heterogeneity via predicted individual effects if they can accurately model outcome risk within treatment groups, but prediction accuracy of these models has not been evaluated.

Objectives: To fit additive and multiplicative survival models in an applied example and compare predictive performance in validation data.

Methods: We identified a cohort of dabigatran (n = 59,125) or warfarin (n = 109,822) initiators in Medicare (2010-2012). The outcomes of interest were ischemic stroke - IS (n = 723) and major bleeding - MB (n = 4,108). We fit Cox proportional hazard and Aalen additive hazard models using exposure and risk factors in the CHA2DS2-VASc or HAS-BLED scores as predictors. We fit models without interactions as well as up to 3-way interactions with lasso penalization for variable selection. We compared discrimination and calibration in 10-fold cross-validation.

Results: Discrimination in validation data was similar across models and outcomes (c-index 0.65-0.67). Additive models with lasso selected interactions had good calibration of predicted to observed rates in validation data ($p > 0.10$) but models with main terms only fit poorly ($p < 0.01$). Multiplicative models with only main terms were well calibrated in validation data for both outcomes ($p > 0.25$).

Conclusions: In our examples, predictive performance of multiplicative models with main terms only was as robust as additive models with many interactions in validation data. Additive models can provide insight on how risk factors work together to change baseline risk, but numerous interactions can be challenging to interpret and easy to overfit. While main terms for multiplicative models had readily interpretable relative effects, variable absolute treatment effect in patients with distinct patterns of comorbidity was obscured.

435. Validity of Cardiac Examination, Procedure, and Surgery Codes in the Danish National Patient Registry

Kasper Adelborg[1,2], Jens Sundbøll[1,2], Troels Munch[1], Trine Frøslev[1], Henrik T. Sørensen[1], Hans E. Bøtker[2] and Morten Schmidt[1]

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Background: Danish registries are widely used for cardiovascular research. Validation of registry codes is necessary to ensure high data quality.

Objectives: We calculated positive predictive values (PPVs) of codes for cardiac examinations, procedures, and surgeries registered in the Danish National Patient Registry (DNPR), to evaluate their potential use for research.

Methods: We randomly selected 1239 patients from one university hospital and two regional hospitals in the Central Denmark Region (2010-2012). All codes were validated using medical record review as gold standard.

Results: A total of 1233 medical records were available and reviewed (99% of the total sample). The PPVs ranged from 83% to 100% (median of 98%). For examinations, the overall PPV was 98%, which included PPVs of 97% for echocardiography, 97% for right heart catheterization, and 100% for coronary angiogram. The overall PPV was 98% for procedures; specifically the PPVs were 98% for thrombolysis, 92% for cardioversion, 100% for radiofrequency ablation, 98% for percutaneous coronary intervention, and 100% for both cardiac pacemakers and implantable cardiac defibrillators. The overall PPV was 99% for cardiac surgery, represented by mitral and aortic valve surgery (100% and 99%), coronary artery bypass graft surgery (98%), and heart transplantation (100%). The validity of the codings were consistent within age-, sex-, and calendar year categories. The completeness of the variables was not examined, but assumed high owing to the diagnosis related group system as a prospective reimbursement system for all Danish hospitals since 2002.

Conclusions: Cardiac examinations, procedures and surgeries in the DNPR are accurately recorded in the DNPR and thus valuable data for cardiovascular research.

436. Validity of Cardiovascular Diagnoses in the Danish National Patient Registry

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Background: Only few cardiovascular diagnoses have been validated in the Danish National Patient Registry (DNPR).

Objectives: We aimed to conduct a comprehensive validation study on cardiovascular diagnoses in the DNPR.

Methods: The study was conducted in the Central Denmark Region between 2010 and 2012. Using medical record review as the reference standard, we examined the validity of cardiovascular diagnoses in the DNPR according to the International Classification of Diseases, 10th revision (ICD-10). For each cardiovascular diagnosis, we randomly selected up to 100 patients from one university hospital and two regional hospitals. Three physicians reviewed discharge summaries and medical records to verify the diagnoses, and computed the positive predictive values (PPVs) as the proportion of confirmed diagnoses with 95% confidence intervals (CI).

Results: A total of 2153 (97% of the total sample) were available for review. The PPVs ranged from 64% to 100% with a median PPV of 90% (interquartile range 80–95). The PPVs were ≥90% for first-time myocardial infarction, stent thrombosis, stable angina pectoris, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, takotsubo cardiomyopathy, arterial hypertension, atrial fibrillation/flutter, cardiac arrest, mitral valve insufficiency/stenosis, aortic valve insufficiency/stenosis, pericarditis, hypercholesterolemia, aortic dissection, aneurysm/dilatation, and arterial claudication. Apart from myocarditis (PPV 64%) the remaining PPVs were between 80%-90% for recurrent myocardial infarction, unstable angina pectoris, pulmonary hypertension, bradycardia, ventricular tackycardia/fibrillation, endocarditis, cardiac tumours, first-time venous thromboembolism and between 70%-80% for first-time and recurrent admission for heart failure, dilated cardiomyopathy, restrictive cardiomyopathy, and recurrent venous thromboembolism. The validity of the codings was consistent within age-, sex-, and calendar year categories.

Conclusions: The validity of cardiovascular diagnoses in the DNPR was high for the vast majority of diseases and thus valuable data for research.

437. Validation of Cardiovascular Events and Covariates in CPRD GOLD Using Questionnaires to General Practitioners (GPS)

Andrea V. Margulis[1], Cristina Varas-Lorenzo[1], Christine L. Bui[2], Lisa J. McQuay[2], Ryan Ziemiecki[3], Maria Reynolds[3], Cristina Rebordosa[1], Manel Pladevall-Vila[1], Joan Fortuny[1], Elena Rivero-Ferrer[1], Estel Plana[4], Willem Jan Atsma[5], Kwame Appenteng[6], Billy Franks[5], Stefan de Vogel[5], Milbhor D'Silva[6], Susana Perez-Gutthann[1] and Alejandro Arana[1]

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Background: Reliable assessment of events and covariates is needed for valid study results.

Objectives: To evaluate a process to identify and verify cases of cardiovascular (CV) events and patient characteristics within a study of CV safety in users of overactive bladder (OAB) drugs in the CPRD.

Methods: We identified a cohort of new OAB-drug users aged ≥18 years in 2004-2012. Epidemiological definitions for acute myocardial infarction (AMI) and stroke were used. Events and patient characteristics in cases were compared, in a sample, against information from questionnaires sent to GPs.

Results: A total of 5,593 CV events were identified in CPRD GOLD via algorithms. GPs' response rate was 81%. Positive predictive values (PPVs) and 95% confidence intervals: definite AMI, 98% (94%-100%); probable AMI, 92% (86%-96%); possible AMI, 92% (73%-99%); definite stroke, 92% (85%-96%); probable stroke, 79% (69%-87%); and possible stroke, 84% (70%-93%).

The negative predictive value (95% CI) was 99% (95%-100%) for noncases that were alive at the end of follow-up and 84% (77%-90%) for noncases who died during the study.

In CPRD GOLD, smoking information was available for 1728 of 1731 patients with questionnaire information on smoking; on the closest day before the event, 17% of patients were current smokers, 41%, former smokers, and 42%, never smokers. Of patients identified as current smokers in GOLD, 84% were also current smokers according to GP questionnaires; likewise, 77% of former smokers and 97% of never smokers were confirmed.

In CPRD GOLD, information on obesity (BMI ≥ 30 kg/m^2) was present in 74% of the 1713 patients with questionnaire information on obesity. Of the patients classified as obese in CPRD GOLD, 82% were confirmed through GP questionnaires; of patients classified as not obese, this was confirmed for 92%.

History of AMI was confirmed in 70% of the cases, and history of stroke in 44%. Of patients assumed to be premenopausal, 12% were confirmed and 77% were reported as having gone through menopause by their GPs.

Conclusions: AMIs, definite strokes, smoking status and obesity identified via electronic algorithms in CPRD GOLD could be confirmed in most cases.

438. Calcium Intake and 10 Year Risk of Incident Coronary Artery Calcification in the Multi-Ethnic Study of Atherosclerosis

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Background: A number of reports suggest that there is an increased level of cardiovascular events among participants who had a high level of calcium intake, especially when this calcium intake is derived from calcium dietary supplements.

Objectives: To assess the association between calcium intake, from both foods and supplements, and incident coronary artery calcification (CAC) as a measure of atherosclerotic burden in a longitudinal cohort study.

Methods: The study included 5448 (51.7% women) participants in the Multi-Ethnic Study of Atherosclerosis (MESA), aged 45 to 84 years, of four race/ethnicity groups, and free of clinically diagnosed cardiovascular disease at baseline. Baseline measurements in 2000-2002 include dietary calcium, CAC, and calcium supplements. CAC measurements obtained by computed tomography were repeated in 3100 participants in 2010-2012. Total calcium intake consisted of diet (as assessed using a food frequency questionnaire) and calcium supplements (as assessed by a medication inventory).

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Results: At baseline, the median calcium intake quintiles were 323.3, 541.8, 783.0, 1160.4, and 1919.0 mg/day. Women had higher total calcium intakes than men. After adjustment for potential confounders (including supplement use), among 1567 participants without baseline CAC, the relative risk (95% confidence intervals) of developing an incident CAC score >0 by quintile 1 to 5 of calcium intake were 1.00 (reference), 0.95 (0.79-1.14), 1.02 (0.85-1.23), 0.86 (0.69-1.05), and 0.73 (0.57-0.93). In this model, calcium supplement use had a RR=1.22 (1.07-1.39) and 75% of participants in Q5 were supplement users. Excluding calcium supplement use from the statistical model removed any protective association between quintile 5 of calcium intake and CAC.

Conclusions: These results suggest that any protective association is only for participants with high dietary calcium intake, possibly as a marker of higher quality diets. While, consistent with randomized trials on cardiovascular events, we see some risk of incident atherosclerosis with supplement use, yet no increased risk of incident atherosclerosis with high dietary calcium intake.

439. Model Observational Bridging Study on the Effectiveness of Ezetimibe Upon Cardiovascular Outcomes

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Background: The Model-Observational-Bridging Study (MOBS) on ezetimibe (EZE) was planned to address the request from French authorities to EZE manufacturer to conduct a long-term, real-life cohort study on the health impact following marketing approval of the drug in France.

Objectives: To estimate the number of non-fatal and fatal cardiovascular events (CVE) prevented by ezetimibe in real life.

Methods: 48-month prospective, nationwide cohort study conducted between 2008 and 2013 in France. Over 700 physicians recruited 3,395 patients with hypercholesterolaemia started on ezetimibe for less than three months at enrolment. Follow up consisted of a telephone interview every six months and annual visits to the physician.

MOBS leveraged EZE data to evaluate its effect on cardiovascular morbidity and mortality over 5 years using longitudinal predictive modelling. Discrete event simulations incorporated information from clinical trials, baseline and follow-up EZE data, and literature-based risk equations to estimate the NNT with ezetimibe to prevent a CVE. Model predictions were validated by CVE observed in the EZE cohort through doctor and patient's reports and hospital discharge letters.

Results: A total of 112 CVEs were observed, 96 non-fatal (myocardial infarction, stroke, acute coronary syndrome, coronary bypass surgery and angioplasty) and 16 fatal, for a rate of 12.02 events per 1 000 person-years. This rate was higher in men (1.72, 95% CI 1.08 - 2.74) and in patients >70 years (1.77, 95% CI 1.17 - 2.68). The relative risk of CVE was 3.35, 95% CI 2.09 - 5.36 in patients from secondary prevention compared with primary prevention patients. Ezetimibe plus a statin can prevent 12 CVE per 1000 patients over 5 years compared to statin alone. NNT, respectively with and without previous lipid-lowering therapy residual effect, were 143 and 110 to prevent one non-fatal CVE, and 1,345 and 964 for one fatal event.

Conclusions: The MOBS methodology succeeded in efficiently combining predictive modelling and parsimonious data collection to allow for robust assessment of impact upon public health.

440. Clinical Impact of an Interaction Between Clopidogrel and Selective Serotonin Reuptake Inhibitors

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Background: Clopidogrel is a pro-drug that requires activation by the cytochrome P450 (CYP) enzyme system. Patients receiving clopidogrel are often treated with selective serotonin reuptake inhibitors (SSRIs) for co-existing depression. SSRIs that inhibit the CYP2C19 enzyme have the potential to reduce the effectiveness of clopidogrel; however the clinical outcomes of this interaction have not been examined.

Objectives: To assess clinical outcomes following initiation of clopidogrel among patients treated with an SSRI that inhibits CYP2C19.

Methods: Using five US databases (1998-2013), we conducted a population-based cohort study of adults who initiated treatment with clopidogrel while treated with an SSRI. Patients were variable ratio matched by propensity score (PS) and followed for as long as they were exposed to both clopidogrel and the index SSRI group (CYP2C19- inhibiting SSRIs (fluoxetine and fluvoxamine) vs non-inhibiting SSRIs) in the primary analysis and for 180 days (intention to treat approach) following clopidogrel initiation in a sensitivity analysis. Primary outcomes included a composite ischemic event (myocardial infarction, ischemic stroke, or a revascularization procedure) and a composite major bleeding event (gastrointestinal bleed or hemorrhagic stroke).

Results: The PS-matched cohort comprised 9,281 clopidogrel initiators on CYP2C19-inhibiting SSRIs and 44,278 patients treated with non-inhibiting SSRIs. As compared to those treated with a non-inhibiting SSRI, patients on a CYP2C19-inhibiting SSRI had an increased risk of ischemic events (hazard ratio [HR], 1.12; 95% confidence interval [CI], 1.01-1.24) following clopidogrel initiation. The increase in risk was more pronounced in patients 65 years of age and older (HR, 1.22; 95% CI, 1.00-1.48). The HR for major bleeding was 0.76 (95% CI, 0.50-1.17).

Conclusions: Initiation of clopidogrel while treated with a CYP2C19-inhibiting SSRI may be associated with decreased effectiveness of clopidogrel. Treatment with an SSRI that does not interact with clopidogrel should be considered.

441. Effectiveness of Recommended Drug Classes in Secondary Prevention of Acute Coronary Syndrome in France

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Background: Guidelines for cardiovascular secondary prevention are based on evidence from relatively old clinical trials and need to be evaluated in daily clinical practice.

Objectives: To evaluate effectiveness of the recommended drug classes after an acute coronary syndrome (ACS) for secondary prevention of cardiovascular diseases and all-cause mortality.

Methods: This cohort study used data from a representative sample of the French national healthcare insurance system database (EGB). Patients hospitalised for an incident ACS between 2006 and 2011, and aged $\geq$ 20 years at time of ACS were included in the study. Patients non-exposed to any of the four recommended drug classes (beta-blockers, antiplatelet agents, statins, and angiotensin-converting-enzyme inhibitors, ACEI, or angiotensin II receptor blockers, ARB) in the first 3 months following ACS or who died during this period were not included in the cohort. Exposure status was determined daily during follow-up. Effectiveness of the four therapeutic classes in preventing the composite outcome ACS, transient ischemic attack, ischemic stroke, or all-cause-death was estimated using a time-dependent Cox proportional hazards model, which was adjusted for time-fixed confounders measured at baseline (general characteristics and characteristics of the initial ACS) and time-dependent confounders during follow-up (co-morbidities and co-medications).

Results: Of the 2874 patients included in the study, 33.9% were women and the median age was 67 years (interquartile range, IQR: 56-77). The median time of

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follow-up was 3.6 years (IQR: 2.2-5.3). The risk of the composite outcome decreased with use of antiplatelet agents (adjusted hazard ratio (aHR) 0.76, 95% confidence interval (CI) 0.63; 0.91), use of statins (aHR 0.71, 95%CI 0.57; 0.87), and use of ACEI/ARB (aHR 0.67, 95%CI 0.57; 0.80). Use of beta-blockers was not associated with a lower risk of the composite outcome (aHR, 0.90, 95%CI 0.74; 1.09]).

Conclusions: Use of antiplatelet agents, statins, and ACEI/ARB after an ACS, but not beta-blockers, was associated with a lower risk of cardiovascular morbidity and all-cause mortality.

442. Treatment with Carvedilol, Bisoprolol or Metoprolol Tartrate and the Risk of Mortality and Hospital Readmission Among Older Adults with Heart Failure

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Background: The long-term use of ß-blockers has been shown to improve the outcomes of patients with heart failure (HF). However, it is still disputed whether this is a class effect, and whether carvedilol or bisoprolol are superior to metoprolol tartrate.

Objectives: To compare the effectiveness of ß-blockers for older patients following a primary hospital admission for HF.

Methods: We conducted a cohort study using Quebec administrative databases to identify patients who were prescribed the ß-blockers, carvedilol, bisoprolol or metoprolol tartrate after the diagnosis of HF. We characterize the patients by the type of ß-blocker prescribed at discharge of their first HF hospitalization. To control for differences among patient characteristics, a multivariate Cox proportional hazards model was used to compare the primary endpoint of all-cause mortality and the secondary endpoint of HF readmission. We conducted analyses by matching for a propensity score for initiation of β-blocker therapy.

Results: Of the 3197 patients with HF with a median follow-up of 2.8 years, the crude annual mortality (per 100 person-years) was 16, 14.9 and 17.7 for metoprolol tartrate, carvedilol, and bisoprolol, respectively. After controlling for covariates, we found that carvedilol (HR 0.92; 0.78-1.09) and bisoprolol (HR 1.04; 0.93-1.16) were not superior to metoprolol tartrate in improving survival. After matching for propensity score, carvedilol and bisoprolol shown no additional benefit on all-cause mortality and HF readmission compared to metoprolol tartrate.

Conclusions: We suggest that there is no evidence of a differential effect of β-blockers on all-cause mortality and HF readmission in older patients with HF.

443. Real-Life Statin Use and LDL-Cholesterol Reduction in a General Population: A Retrospective Study of Primary Care Electronic Medical Records

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Background: Guidelines on management of dyslipidemia recommend statins based on their capacity to lower LDL-C levels. However, these recommendations are mainly based on clinical trials. Observational studies of the general population describing real-life statin use, in terms of potency and adherence, are scarce.

Objectives: To describe the effect of statin potency and adherence on LDL-C reduction in a general population from a primary care electronic medical record database.

Methods: Retrospective cohort study of 322,283 statin new users (53.37% women), aged 35 to 74y. Inclusion criteria: one LDL-C measurement without statin treatment in the previous 6 months and a second LDL-C measurement after statin initiation. Exposure: statin potency and MPR (≤50, 50-70, >70). Outcome: relative LDL-C reduction. Total LDL-C measurements: 1,461,936. Study period: 2006-2014.

Results: Regimes of potency use were 3.08% (low), 68.72% (moderate), 25.6% (high) and 2.52% (very high);6-month mean MPR: 60.89%, 65.16%, 66.20%

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and 68,13%, respectively. Relative reductions in LDL-C within MPR ≤50: 11.02% (10.46-11.56,low potency), 20.53% (20.39-20.66.moderate), 26.57% (26.30-26.84, high), 34.48% (33.53-35.42, very high). Relative reductions within MPR >50-70: 20.31% (19.33-21.28, low), 30.00% (29.81-30.19, moderate), 36.65% (36.30-37.01, high), 42.91 (41.60-44.19, very high). Relative reductions within MPR >70: 25.98% (25.48-26.48, low), 35.91 (35.82-36.00, moderate), 42.56 (42.40-42.72, high), 48.40% (47.87-48.92, very high).

Conclusions: The observed LDL-C reductions in real-life did not achieve the expected reductions in any of the statin potency groups, even for individuals of MPR>70. The statin capacity reduction decreased by between 30% and 57% in individuals of MPR≤50 compared to those of MPR>70, depending on their statin potency group. Similar relative LDL-C reductions were observed in the moderate potency group of MPR >70, high potency group of MPR >50-70 and very high potency group of MPR ≤50. Thus, strategies to improve statin effectiveness in prevention of cardiovascular diseases should focus on improving adherence.

444. Psychotropic Medications and the Risk of Neonatal Withdrawal

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Background: The potential for neonatal withdrawal after in-utero exposure to specific medications such as opioids and benzodiazepines has been well documented, but evidence for other psychotropic agents is weaker. In 2011, FDA changed the label for all antipsychotic medications (APM) to reflect the potential risk for extrapyramidal or withdrawal symptoms as noted in 69 newborns after 3rd trimester exposure. Case reports of withdrawal have also been described for gabapentin (GBP). In both instances, confounding by other factors was a concern.

Objectives: To assess the risk of neonatal withdrawal associated with in-utero exposure to APMs or GBP.

Methods: We linked a cohort of Medicaid-eligible pregnancies in 2000-2010 to live-born infants. Exposure was defined as filling a prescription for an APM or GBP during the last 90 days of pregnancy, versus no dispensing. Withdrawal was defined based on the presence of ICD-9 code 779.5x in medical claims during the first 30 days of life. Maternal covariates, medications and healthcare utilization were assessed during pregnancy and used for propensity score (PS) estimation. Adjusted relative risks (RR) were estimated using fine stratification on the PS.

Results: The source cohort consisted of about 4 mln pregnancies, of which 7780 were exposed to atypical APMs, 1400 to typical APMs, and 1976 to GBP. The risk of withdrawal in the reference group was 3.3/1000 births. In unadjusted analyses, all exposures were associated with large increases in risk: RR of 13.9 (95%CI, 12.5-15.4) for atypical APMs, 8.2 (6.0-11.3) for typical APMs, 22.1 (18.9-25.8) for GBP. These associations were markedly attenuated in PS-stratified analyses: RR of 1.5 (1.3-1.6) for atypical APMs, 0.9 (0.7-1.3) for typical APMs, and 2.3 (2.0-2.7) for GBP. Similar associations were observed in secondary analyses assessing exposure in the last 45 days of pregnancy and in analyses restricted to women without exposure to opioids or benzodiazepines. An association was observed for most individual atypical agents.

Conclusions: Our findings suggest an increased risk of withdrawal for atypical APMs and GBP, but not for typical APMs. Further analyses should focus on characterizing the severity of the withdrawal symptoms.

445. Channeling Bias in a Comparative Effectiveness Study of a Newly Launched Antipsychotic

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Background: Channeling bias may be problematic in comparative effectiveness studies of psychiatric

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medications when the ability to assess psychiatric symptom severity is limited.

Objectives: To assess the ability to adjust for channeling bias when comparing the effectiveness of a newly launched antipsychotic to other antipsychotics for schizophrenia treatment using claims data.

Methods: Schizophrenia patients dispensed antipsychotics were identified from Danish National Registries (2004-2012). Anticipating channeling bias, the analysis was restricted to later years since risperidone long-acting treatment (RLAT) market entry (2010-2012), while remaining powered to detect differences in psychiatric hospitalization rates. To investigate channeling, we derived yearly propensity scores. Rates of hospitalizations for RLAT vs. oral antipsychotic exposure were compared using a GEE-Poisson model; adjusted models included disease severity proxies.

Results: Between 2004 and 2009, 17,770 patients were included (mean age, 44.8 years; male, 59.3%) with a hospitalization rate of 44.4 per 100 person-years; size and composition of the 2010-2012 cohort was similar. In 2004, patients with ≥1 suicide-attempt (OR=1.14, 95% CI: [1.03-1.27]), with 1 (OR=1.26 [1.10-1.44]) or ≥2 (OR=1.32 [1.16-1.51]) past-year psychiatric hospitalizations, hospitalized 1-30 (OR=2.27 [1.97-2.62] or >30 days (OR=3.55 [3.10-4.06]) or with 1 (OR=2.22 [2.01-2.45) or ≥2 (OR=2.51 [2.27-2.77]) past-year antipsychotic therapy changes were more likely to receive RLAT than oral antipsychotics. By 2009, the strength of these predictors of RLAT receipt diminished or disappeared; the c-statistic decreased from 0.76 in 2004 to 0.67 in 2009. Crude and adjusted relative hospitalization rates were 1.91 (1.61-2.26) and 1.26 (1.11-1.43) in 2004 compared to 1.16 (1.02-1.32) and 1.08 (0.99-1.18) in 2010-2012, respectively.

Conclusions: More severe patients received RLAT shortly after launch. Due to limitations in measuring disease severity, restricting to 7 years after launch and adjusting for proxies of disease severity was unlikely to have fully accounted for confounding by severity and the lingering effects of channeling.

446. Mortality Risk of Second-Generation Antipsychotic (SGA) Augmentation for Adult Depression

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Background: Randomized controlled trials have demonstrated >50% increased all-cause mortality in elderly patients with dementia treated with SGAs. SGAs are also prescribed for depression in >2 million US office-visits/year. Because approval trials for SGA augmentation in depression were not powered for rare outcomes, it is unknown whether the risk associated with SGAs in elderly patients with dementia generalizes to less frail non-elderly patients who use SGAs as augmentation for depression.

Objectives: To examine all-cause mortality risk of SGA augmentation for adult depression.

Methods: Using national US Medicaid data from 2001-2010, we examined all-cause mortality risk in a retrospective cohort of adults (25-64 years) diagnosed with depression (ICD-9-CM 296.2, 296.3, 300.4, 311.x) who, after ≥3 months of antidepressant (AD) monotherapy, initiated either a SGA or a second AD. Patients with alternative SGA indications, such as schizophrenia or bipolar disorder, were excluded. Cox proportional hazards models stratified by propensity score (PS) deciles after asymmetric PS trimming assessed mortality risk of SGA augmentation compared to AD augmentation (referent). Follow-up was censored at day 365, discontinuation of the index drug, loss of Medicaid eligibility, or on 12/31/2010. PSs were calculated from a broad set of demographic, clinical, and utilization variables assessed during the 180-day pre-index period.

Results: 52,728 individuals (76.3% female, mean age 44.7 years) initiated augmentation with either an SGA (n=30,177) or a second AD (n=22,551) and accrued 17,913 person years of follow-up. Mean follow-up duration was 125.7 days (SGA) and 121.8 days (second AD). 300 cohort members died during follow-up (SGA 202; second AD 98). Unadjusted (HR 1.50, 95%CI 1.18-1.90) as well as PS-adjusted analyses (HR 1.33, 95%CI 1.03-1.72) indicated an increased mortality risk for SGA augmentation. Results were robust across numerous sensitivity analyses.

Conclusions: These preliminary results suggest that physicians managing adults with depression should carefully weigh the potential increased mortality risk associated with SGA augmentation against its potential benefits.

447. Comparative Safety of Antipsychotic Medications in Hospitalized Myocardial Infarction Patients

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Background: Both haloperidol (HDL) and second-generation antipsychotics (SGA) are frequently used to treat delirium-related agitation. While outpatient studies suggest a higher risk of death associated with HDL compared to SGA, the evidence is limited in hospital settings.

Objectives: We compared HDL to SGAs (olanzapine, quetiapine, risperidone) with regard to in-hospital mortality in non-surgically treated myocardial infarction (MI) patients, in whom delirium is commonly observed.

Methods: We conducted a cohort study of patients over age 18 with a primary diagnosis of MI, who initiated an oral antipsychotic during their hospital stay using the Premier Research Database (2003-2009). We obtained hazard ratios (HR) of in-hospital death comparing HDL use to SGA use, using Cox regression and 1:1 propensity score matching. Patients with psychiatric disorders were excluded to ensure the drug was used for delirium symptoms. In the intention-to-treat (ITT) analysis, patients were followed from initiation to death or discharge. In the per-protocol (PP) analysis, patients were censored when they discontinued or switched to the other antipsychotic class or to non-oral antipsychotics.

Results: Among 3,530 MI patients included in the study with a mean age of 76 years, 26.7% initiated HDL and 73.3% initiated SGAs. The time from admission to initiation and length of stay was similar, but the median treatment duration was 1 day (Interquartile range 1-3) for HDL initiators and 2 days (IQR 1-5) for SGA initiators. 106 (11.2%) of HDL initiators and 261 (10.1%) of SGA initiators died in hospital. In ITT analyses, the unadjusted HR of death comparing HDL to SGA was 1.15 (95% Confidence interval 0.91-1.44) and the adjusted HR was 1.23 (0.93-1.63). In PP analyses, the unadjusted HR was 1.99 (1.39-2.84) and the adjusted HR was 1.73 (1.12-2.67).

Conclusions: Our results raise the possibility of an increased risk of in-hospital death associated with HDL compared with SGA when it was used to treat delirium-related agitation in non-surgically treated MI patients. This suggests acute harmful effects of HDL, but residual confounding cannot be excluded. Further research is needed to confirm our findings.

448. Examining the Impact of UK Drug Safety Warnings on Antipsychotic Drug Prescribing to Older People with Dementia

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Background: The risks of prescribing antipsychotic drugs to people with dementia are well-known. In March 2004 the UK Committee for the Safety of Medicines (CSM) warned that risperidone or olanzapine should not be used for the treatment of behavioural symptoms of dementia.

Objectives: To describe the time trends from 2000 to 2014 and characteristics of patients and practices at increased risk of potentially inappropriate prescribing of antipsychotic drugs and quantify the impact of the UK drug safety updates.

Methods: Data from 694 UK general practices contributing data to the Clinical Practice Research Datalink were analysed. The prevalence of patients aged over 65 with a diagnosis of dementia (and without a psychosis diagnosis) receiving at least 2 repeat prescriptions of an antipsychotic drug within a six month time period was measured. Temporal trends in prevalence, and the impact of patient and practice level

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variables on prevalence, were examined using a multilevel logistic regression models. The impact of drug safety warnings were examined using a before and after experimental design.

Results: Potentially inappropriate prescribing of antipsychotic drugs to older patients with dementia had a prevalence of 12% in 2000 and 7.5% in 2014. Younger patients (aged 65 to 75) were more likely to be prescribed antipsychotic drugs compared with older patients (75+, OR 0.65; 95% CI 0.53 to 0.79). Patients with polypharmacy were also more likely to be prescribed antipsychotic drugs (10+ repeated prescriptions in 12 months, 3.94; 3.23 to 4.79). The 2004 CSM warning coincided with a drop in potentially inappropriate prescribing for Risperidone (0.32; 0.31 to 0.33) and Olanzapine (0.50; 0.47 to 0.52) but there was a concomitant increase in the use of Queitiapine (3.06; 2.91 to 3.22) and Amisulpride (3.61; 3.25 to 3.99).

Conclusions: Despite the decrease in potentially inappropriate prescribing of antipsychotic drugs to older patients with dementia, high levels of prescribing persist. When drugs are specified in safety warnings greater consideration may be needed to avoid the possibility of switching prescribing to alternative drugs within the same class.

449. Antipsychotic Use, Frailty and Health Outcomes Among Residents of Assisted Living

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Background: Relative to long-term care (LTC), few studies have examined the prevalence or outcomes of antipsychotic use within assisted living (AL). AL residents often present with dementia and frailty however they receive less clinical oversight than those in LTC.

Objectives: We examined the prevalence of antipsychotic use and associated 1 year health outcomes (hospitalization & mortality) in a large AL cohort (2006-09) and explored the role of two distinct frailty measures as possible effect modifiers of outcome associations.

Methods: Prospective cohort study of 1,089 residents (mean age 85; 77% female; 57% with dementia) from 59 AL facilities in Alberta, Canada. Research nurses completed resident assessments at baseline and 1 year. Frailty was assessed using the Cardiovascular Health Study (CHS) criteria and an 86-item Frailty Index (FI). Hospitalization was determined via linkage with the provincial discharge abstract database. Risks of first-event hospitalization and mortality were examined using multivariable Cox proportional hazards models, adjusted for age, sex, outcome-relevant covariates, and clustering and stratified by frailty measures.

Results: The prevalence of antipsychotic use was 26% (94% atypical). Over 1 year, 39% were hospitalized and 13% died. Frailty prevalence was 27% and 19% with the FI and CHS, respectively. Frailty was significantly associated with antipsychotic use (FI), hospitalization [FI: HR (95% CI) 1.33 (1.02-1.75); CHS: HR 2.12 (1.54-2.92)] and mortality [FI: HR 2.21 (1.37-3.57); CHS: HR 3.00 (1.72-5.22)] in adjusted analyses. Antipsychotic use was not significantly associated with mortality or hospitalization; however, hospitalization risk varied by frailty status. Among robust residents, antipsychotic users were significantly less likely to be hospitalized than non-users [FI: HR 0.63 (0.39-1.00); CHS: HR 0.63 (0.41-0.96)] whereas among frail residents, antipsychotic use was significantly associated with hospitalization [FI: HR 1.55 (1.01-2.37)].

Conclusions: Our preliminary findings highlight the importance of considering frailty in drug benefit/risk decisions across care settings.

450. Medication Taking Behaviour and Adverse Health Outcomes in Community Dwelling Older Patients

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Background: Medication taking behaviour (MTB) is an important aspect in the treatment of chronic conditions but despite its importance, rates of non-adherence with any medication treatment may vary from 15% to 93% with an average estimated rate of 50%.

Objectives: To determine the association between MTB and adverse drug events (ADEs), health related quality of life (HRQOL) and hospitalisation in older community dwelling patients.

Methods: A retrospective cohort study of 855 patients aged ≥70 years from 15 general practices in Ireland

Medication non-adherence was measured by: (i) Medication Possession Ratio (MPR) using national pharmacy claims data; and (ii) self-report using the Morisky Medication Adherence Scale.

ADEs and hospitalisation were measured by patient medical record and self-report for the previous 6 months. HRQOL was measured using EQ-5D. Multilevel Poisson and linear regression were used to examine how the number of ADEs, utility and hospitalisation varied by non-adherence after adjusting for covariates; socioeconomic status, practice deprivation, co-morbidity, number of drugs, functional disabilities, social support and health insurance.

Results: 263 (31%) patients were non-adherent based on pharmacy claims data (MPR<80%) and 302 (35%) self-reported non-adherence to their medication. Non-adherence (MPR<80%) was not significantly associated with any ADEs but self-reported non-adherent patients had an increased risk of any ADEs (IRR 1.18; 95% CI 1.05, 1.33, $p<0.01$). Non-adherent patients had a significantly lower mean HRQOL utility (MPR coefficient, -0.11, SE 0.03, $p<0.001$; self-report coefficient, -0.06, SE 0.01, $p<0.001$) and an almost two-fold increased risk in the expected rate of any hospitalisation (MPR IRR 1.75; 95% CI 1.42, 2.15, $p<0.001$; self-report IRR, 1.53; 95% CI 1.16, 2.01, $p<0.01$) compared to adherent patients.

Conclusions: Non-adherence was significantly associated with adverse health outcomes. Developing methods to assist older adults in managing their medications may increase their quality of life.

451. Adherence to Anti-Hypertensive Medication in the Elderly: A Prospective Cohort Study

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Background: Poor adherence to antihypertensive therapy is a potential cause for uncontrolled hypertension.

Objectives: To estimate the prevalence of adherence to anti-hypertensive medication and identify predictors of adherence to anti-hypertensive medication at 12 months.

Methods: 1562 older adults >65yrs) were recruited from 106 Irish community pharmacies. Each pharmacy recruited 15 consecutive community dwelling patients, filling a prescription for antihypertensive medication. Patients completed a structured telephone interview which was linked to their pharmacy records. Participants were followed up at 12 months and were invited to attend the pharmacy for BP measurement.

Adherence was measured using the 8-item Morisky Medication Adherence Scale (MMAS-8) and the Medication Possession Ratio (MPR). Determinants of adherence recorded from interview data included sociodemographics, and beliefs about medication using a structured questionnaire (BMQ); medication regimen and polypharmacy were determined from the pharmacy records. Multivariate logistic regression was used to identify predictors of adherence at 12 months as measured by MMAS-8 and MPR. The study has 95% power to detect a factor which reduces or increases adherence by 10%.

Results: At baseline self-reported adherence using the MMAS-8, 57.0% of participants were high adherers, 32.1% were medium adherers and 10.9% were poor adherers. Prevalence of poor adherence calculated as the MPR <0.8) from pharmacy dispensing records was 10.1%. 78.8% of participants completed the

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follow-up interview. High, medium and low adherence by self-report adherence at 12 months was 50.3%, 37.2% and 12.5% respectively. Low adherence by MPR was 10.0%. Higher concerns about antihypertensive medication at baseline increased the risk of low adherence by self-report (OR 2.02, 95% CI 1.48-2.78).

Conclusions: Negative patient beliefs about medication were found to influence poor adherence and are potentially modifiable and could be targeted in interventions to improve adherence.

452. Too Many, Too Few, Or Too Unsafe? Impact Of Inappropriate Prescribing On Mortality, And Hospitalisation In Community-Dwelling Adults, Aged 80 And Older

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Background: Little is known on the impact of Inappropriate Prescribing (IP) in community-dwelling adults, aged 80 and older.

Objectives: To assess the prevalence of IP (polypharmacy, underuse, and misuse) at baseline (Nov 2008 – Sep 2009) and impact after 18 months on mortality, and hospitalisation in a cohort of community-dwelling adults, aged 80 and older (n=503).

Methods: Screening Tool of Older People's Prescriptions (STOPP, misuse) and Screening Tool to Alert to Right Treatment (START, underuse) criteria were cross-referenced and linked to the medication use (in Anatomical Therapeutic Chemical-coding) and clinical problems. The Belfrail-Med cohort was used, in which general practitioners recruited a sample of community dwelling adults, aged 80 years and older, and not in palliative care. Index date was the date of baseline assessment. Survival analysis until death or first hospitalisation was performed at 18 months after inclusion using Kaplan-Meier. Cox regression analysis was used for risk assessment and to control for covariates.

Results: Mean age was 84.4 years (range 80 – 102). Mean number of medications prescribed was 5 (range 0 – 16). Polypharmacy (≥5 medications, 58%), underuse (67%), and misuse (56%) were high. Polypharmacy, underuse and misuse coexisted in 34%, and were absent in 9% of the population. A higher number of medications was correlated with more misused medications (rs=.51, $p<.001$), and with more underused medications (rs=.26, $p<.001$).

Mortality and hospitalisation rate were 8.9%, and 31.0% respectively. After adjustment for number of medications and misused medications, there was an increased risk of mortality (HR 1.39; 95%CI 1.10 – 1.76), and hospitalisation (HR 1.26; 95%CI 1.10 – 1.45) for every additional underused medication. Associations with misuse were less clear.

Conclusions: Inappropriate prescribing (polypharmacy, underuse and misuse) was highly prevalent in adults, aged 80 and older. Underuse and misuse were highly correlated and coexisted in almost half of the population. Surprisingly, underuse and not misuse, had strong associations with mortality and hospitalisation.

453. Is Hospitalisation Associated with the Unintentional Discontinuation of Appropriate Long-Term Medication in the GP Prescribing Record Post Discharge?

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Background: Medication errors at transitions of care are common. Previous studies have reported that prescription errors and omissions occur at hospital discharge. These have the potential to impact a patient's health following discharge if not subsequently identified and corrected.

Objectives: The objective of this study was to determine the association between discontinuation of evidence-based long term medication in general practice prescriptions and hospitalisation.

Methods: A retrospective cohort study was undertaken of patients ≥65 years in 41 Irish general practices using the Irish Primary Care Research Network. Prescription data was obtained from GP electronic records and hospitalisation exposure data via discharge message notification. Four cohorts were

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defined by patients continuously prescribed antiplatelets/anticoagulants, statins, thyroid medication and respiratory inhalers over a one-year period. Discontinuation was defined as the absence of the specified chronic medication in the six-months post discharge for the hospitalised group, and the absence of the specified chronic medication over a random six-month period post enrolment for the non-hospitalised participants. Multilevel logistic regression was used for all analyses, with adjustments made for relevant confounders such as age, multimorbidity and potentially inappropriate prescribing (PIP).

Results: 17,487 patients were enrolled: 3,058 (17.5%) had experienced hospitalisation. The odds of discontinuation for two groups (antiplatlets/anticoagulants (OR 1.24, 95%CI (1.03, 1.49), p=0.02); statins (1.44, (95%CI (1.20,1.73), p<0.001)) were significantly higher among those who had been hospitalised than those who had not. These effects remained after adjusting for confounding variables. Increasing age (p<0.001) was also associated with the odds of discontinued medication.

Conclusions: Medication discrepancies may occur among older patients requiring long-term medication. Such discrepancies may affect patients and future demand for services. Further research is examining the potential impact of discharge medication notes on medication discontinuity.

454. Reducing Patients' Cumulative Exposure to Anticholinergic and Sedative Medication With Medication Reviews: A Randomized Controlled Trial

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Background: Older people commonly use medications with anticholinergic or sedative effects despite their negative benefit risk profile in many patients (e.g. risk of falling, worsening of cognitive impairment). The Drug Burden Index (DBI) is a quantitative measure of a patient's cumulative burden of anticholinergic and sedative medication.

Objectives: We evaluated whether medication reviews provide an effective intervention to reduce a patients' DBI.

Methods: A randomized controlled single blind trial was conducted in 15 community pharmacies in the Netherlands from December 2014 until October 2015. Community-dwelling patients aged ≥ 65 years, using ≥ 5 medications for ≥ 3 months including at least one medication with an ATC code from the groups N05 or N06 and having a DBI ≥ 1 were included in the study. The intervention was a medication review by the pharmacist in cooperation with the patient's general practitioner. Data were collected at baseline and 3-months follow-up. Primary outcome was the difference in proportion of patients having a decrease of DBI ≥ 0.5 between the intervention and control arm at follow up. Secondary outcomes were anticholinergic and sedative effects, falls, cognitive function, activities of daily living, quality of life, hospital admission and mortality.

Results: A total of 157 participants were included in the analysis (4.3% drop-out). Participants in both allocation arms were comparable, main characteristics: 70.9% female, mean age 75.5 years, mean DBI 2.6 and a mean of 8.9 medications used ≥ 3 months. Multilevel analysis showed no significant difference in the proportion of participants having a decrease in DBI ≥ 0.5 between intervention- and control arm (14.7% versus 15.9%, OR=0.91, 95% CI [0.38-2.18], p=0.836). No significant difference was found in secondary outcomes except for intervention patients reporting fewer sedative effects (p=0.002).

Conclusions: Our intervention was not effective in reducing the DBI in this frail group of older people. Preventive measures against development of high DBI and persuasive strategies to increase patients' willingness to change their medication may be ways forward.

455. Treatment Association with Preventable Hospitalizations in Older Adults with Serious Mental Illness

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Background: Serious mental illness (SMI), including bipolar disorder, schizophrenia, and major depressive

disorders, is known as a risk factor for preventable hospitalization. However, few studies had examined SMI pharmacological treatment association with preventable hospitalizations.

Objectives: To quantify the effect of SMI treatment on preventable hospitalizations in older adults.

Methods: Using 2006-2012 Medicare administrative and claims data, this retrospective cohort study identified fee-for-service beneficiaries aged >64 and newly-diagnosed with SMI. SMI treatment initiation was defined as any prescription fill for medications indicated for the index SMI condition(s) in the 12 months after diagnosis (no evidence of prior use in the 6 months before initiation). Preventable hospitalization rates were measured by count of hospital or emergency department admissions related to ambulatory care-sensitive conditions (e.g., diabetes, cardiovascular and respiratory conditions etc.) during the same follow-up period and compared between SMI treatment initiators and nonusers using generalized linear mixed models. Covariates included patient demographics, comorbidities, health services utilization, regional physician supply, and spatial clustering of SMI treatment incidence (identified using local indicator of spatial autocorrelation [LISA]).

Results: A total of 38,421 older adults newly-diagnosed with SMI were identified. The sample was predominantly female (74.0%) and white (85.1%), with a mean age of 78.5 years. Almost 65% initiated SMI treatment. LISA results returned highly localized treatment incidences: hot spots in Midwest and upper Pacific West, and cold spots in West South Central and lower New England. Compared with SMI treatment nonusers, treatment initiators showed reduced risk for preventable hospitalizations after SMI diagnosis (RtR 0.88, 95% CI 0.84-0.93).

Conclusions: The majority of older adults initiated relevant pharmacological treatment after SMI diagnosis, although treatment initiation rates varied by location. After adjusting for patient characteristics and regional health resources, SMI treatment was associated with lower preventable hospitalization risk.

456. Acetaminophen Overdose-Related Morbidity and Mortality in Canada

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Background: Acetaminophen is widely used for treating pain and fever, however, it is also the leading cause of acute liver failure in many developed countries.

Objectives: The objective of this study was to investigate the Canadian incidence of acetaminophen overdose-related medical incidents, hospitalizations and deaths, using several data sources from 2006 to 2012.

Methods: Data sources included: (i) utilization data from IMS Health Canada Inc (ii) hospitalization data from the Canadian Institute of Health Information's Discharge Abstract Database and Hospital Morbidity Database-Québec (iii) deaths occurring outside of hospital settings from the Canadian Coroner and Medical Examiner Database and (iv) spontaneous adverse drug reaction reports from the Canada Vigilance database. All data extracted were analyzed by year, age, gender and intentionality. Trends in incidence rates were examined.

Results: More than 4,000 hospitalizations for acetaminophen related overdoses occur each year in Canada of which 20% are due to unintentional overdoses. The incidence rate of unintentional overdoses has been rising steadily since 2006. From 2006 to 2010, 236 deaths were identified from the coroners database as being associated with acetaminophen overdose, 46% of which were related to unintentional poisoning. Adverse reaction data indicate that nearly 20% of spontaneous case reports for acetaminophen-induced liver injury involve doses within the therapeutic range (4g/day). These results are in the context of more than 4 billion doses of acetaminophen being sold annually across Canada and a population of 35 million.

Conclusions: This is the first national study to assess acetaminophen overdose-related injury from a variety of Canadian data sources and will be valuable in informing Health Canada in addressing the risk of injury associated with acetaminophen overdose.

457. Comparative Hepatotoxicity of Echinocandins in Hospitalized Patients (pts): A Retrospective Cohort Study

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Background: Anidulafungin (ANF), caspofungin (CSP), and micafungin (MCF) are echinocandins for treating invasive candidiasis. Of these, ANF is the only antifungal not metabolized by the liver. Comparative rates of severe hepatic adverse events are of interest within this class.

Objectives: To compare rates of severe hepatotoxicity in hospitalized pts treated w/ ANF vs CSP or MCF and in pts w/ normal or mild/moderately elevated baseline liver function tests (LFT).

Methods: Humedica (2007-2013) and Cerner (2006-2013) hospital databases were used. Study pts had LFT values, graded per modified CIT-TCAE criteria, before and after treatment (tx) initiation. A subgroup w/ normal or mild/moderately elevated pre-tx LFT (i.e. grade $\leq$2) was identified. Severe hepatotoxicity post-tx was defined as elevated LFT grade $\geq$3. Incidence rate ratios (IRRs) of severe hepatotoxicity were estimated for ANF vs CSP and MCF using negative binomial regressions, adjusting for demographic, baseline LFT, other labs, and clinical covariates.

Results: Of 12,678 eligible pts, 13%, 35% and 52% received ANF, CSP and MCF, respectively; of whom 9,161 patients had normal or mild/moderately elevated LFT at baseline. Compared to CSP and MCF pts, in the pre-tx period, ANF pts had significantly ($p < .05$) more elevated LFT grade $\geq$3 (40% vs. 26%, 26%), critical care admissions (75% vs. 53%, 49%), use of central venous catheters (44% vs. 13%, 19%), and immunosuppressive drugs (15% vs. 4%, 6%), and higher rates of comorbidities. After adjusting for confounders, IRRs of severe hepatotoxicity for ANF vs CSP were 1.43 (95% CI: 1.14-1.79) overall and 1.46 (0.91-2.37) among the subgroup w/ normal or mild/moderately elevated LFT; while the corresponding IRRs for ANF vs MCF were 1.19 (0.92-1.54), and 1.62 (0.95-2.77), respectively.

Conclusions: This real-world hospital practice data analysis demonstrates confounding by indication due to channeling of ANF to pts w/ significantly impaired liver function. While this bias is notoriously difficult to adjust for, when considering only patients w/ normal or mild/moderately elevated baseline LFT, the risk of severe hepatotoxicity was similar in pts receiving ANF vs CSP or MCF.

458. Detection and Quantification of Flucloxacillin-Induced Liver Injury: A Population-Based Cohort Study

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Background: The antibiotic flucloxacillin is an established cause of liver injury. A number of studies of flucloxacillin-induced liver injury have been performed, with age over 60, prolonged use, and gender identified as possible risk factors for increased susceptibility. Despite this, there are a lack of published data on the incidence of flucloxacillin-induced liver injury within these subgroups.

Objectives: To measure the association between flucloxacillin and liver-injury when compared with oxytetracycline. To quantify the risk of symptom-defined and laboratory-confirmed injury within both the general population and subgroups at potentially increased risk.

Methods: We performed a cohort study between the 1st January 2000 and the 1st January 2012 using the UK Clinical Practice Research Datalink, including 1,046,696 people (861,959 exposed to flucloxacillin). 1-45 day risks of symptom-defined and laboratory-confirmed liver injury were estimated, before using Poisson regression to compare the 1-45 day rate in each exposure group.

Results: The 45-day risk of laboratory-confirmed liver injury was 6.15 per 100 000 users (95% CI 4.61 – 8.04), increasing to 14.15 per 100 000 users (95% CI 11.75 – 16.90) if relying soley on symptoms for case-classification. The multivariable adjusted rate ratio for laboratory-confirmed injury was 3.79 (95% CI 1.19 – 12.13). Those in the highest age group (70+) who received more than two consecutive prescriptions had the greatest risk of laboratory-confirmed injury (72.78 per 100 000 users, 95% CI 19.87 – 185.96).

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Conclusions: The risk of laboratory-confirmed flucloxacillin-induced liver injury is particularly high within those over the age of 70 who receive more than two consecutive flucloxacillin prescriptions. The risk of symptom-only defined jaundice associated with flucloxacillin suggests that incidence figures based upon laboratory-confirmed injury from UK primary care data underestimate the true frequency of injury.

459. Diagnosis-Based Cohort Augmentation Using Laboratory (lab) Data in the FDA Sentinel Initiative: The Case of Chronic Kidney Disease (CKD)

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Background: Cohort selection in drug safety research using electronic data is often limited to coded diagnoses.

Objectives: To assess how augmenting a diagnosis-based CKD cohort with patients identified through lab results impacts cohort characteristics.

Methods: Using data from two Data Partners within the FDA's Sentinel Distributed Database, we identified patient's first 'indication' of CKD in 2012 as their index date. Characteristics were collected over a baseline of 365 days, prior to and including index. The first indication was either 1) an ICD-9 code for CKD, or 2) a low estimated glomerular filtration rate (eGFR; <60ml/min/1.73m2) from lab data. Patients with an ICD-9 code for CKD during baseline formed the DxGroup. Among those without a code for CKD we used National Kidney Foundation criteria to define CKD based on 2 low estimated glomerular filtration rates (2-LabGroup) during baseline, and a group with only their single low index eGFR (1-LabGroup). We compared the DxGroup to the Lab Groups on demographic, clinical and utilization characteristics using standardized differences (significance level 0.2).

Results: A total of 228,827 patients were identified; 107,607 in DxGroup (47%), 33,542 in 2-LabGroup (15%), and 87,678 in 1-LabGroup (38%). Patients in both Lab Groups were significantly different from the DxGroup on CKD Stage [DxGroup worse <2% Stage 4 in Lab Groups vs 10% in DxGroup)] and diabetes (23% in 1-LabGroup, 32% in 2-LabGroup, and 46% in DxGroup). The 2-LabGroup had fewer Black patients than the DxGroup (5% vs. 10%). The 1-LabGroup was younger vs. DxGroup (mean age 69 vs. 73), and fewer had congestive heart failure (8.6% vs 17%) and hypertension (64% vs 84%).

Conclusions: Augmenting a CKD cohort based on diagnostic codes with lab data more than doubled the cohort size, but the diagnostic-based cohort was significantly sicker on characteristics related to CKD development and poor outcomes. Our findings suggest that drug safety researchers should consider whether the method of cohort identification contributes to generalizability of safety findings.

460. Development of Risk Model to Predict Drug Induced Acute Kidney Injury in Hospitalized Patients

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Background: Acute kidney injury (AKI) following nephrotoxic drug is associated with an increased risk of prolonged hospital stay or mortality. A risk model can identify patients at higher risk for drug induced AKI and facilitate preventive strategies. While successful risk models have been developed, none has used fully automated electronic health record (EHR) data to predict drug induced AKI.

Objectives: This study aimed to identify a set of risk factors for AKI, and develop a dynamic risk model specific to inpatients on nephrotoxic drugs using EHR.

Methods: We established a retrospective cohort obtained from EHR for patients aged ≥18 who are

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admitted to two UF affiliated hospitals from Jan 1, 2012, to Dec 31, 2013. We identified risk factors from the published literature, guidelines, and drug monographs; risk factors were operationalized allowing for an automated retrieval from EHR. For each patient exposed to nephrotoxic drugs, we used multivariate logistic regression to calculate risk scores predicting stage 2 AKI. Stage 2 AKI was defined as a ≥ 2.0 times increase of serum creatinine (SCr) from baseline within 5 days after an administration of any nephrotoxic drug, provided no dialysis dependence. Hospital day 1 through day 5 were modeled separately. Backward elimination was used in order to select final variables included in models; We internally validated the daily models with 1,000 bootstrap samples. The C-statistics was computed to assess the performance of the risk models. We used SAS v 9.4 for all analysis.

Results: A total of 2,535 outcomes occurred in at-risk days during the study period (1.44 cases/100 person-day). Strong predictive risk factors across the daily models included 1) stage 1 AKI, 2) use of vancomycin and piperacillin-tazobactam, 3) oliguria, 4) receiving cardiac surgery, and 5) total number of nephrotoxic medications/day. The C-statistics were between 0.79 and 0.82.

Conclusions: The risk model showed good predictive performance in identifying patients with manifestation of stage 2 AKI. Once prospectively implemented in EHR systems to flag high-risk patients the risk models may facilitate pharmacist intervention surrounding preventive strategies.

461. Evaluation of the Risk of Acute Kidney Injury (AKI) Associated With Vancomycin Plus Piperacillin-Tazobactam (VPT) Compared With Vancomycin Plus Cefepime (VC)

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Background: Recent studies found a possible association between piperacillin-tazobactam (PT) when added to vancomycin (Vanco) and AKI risk with odds ratios of 2.48-5.67 compared to Vanco monotherapy. They were limited by small sample size or confounding by indication. A formal comparative safety study in a larger study population is warranted.

Objectives: To compare the risk of VPT on the development of AKI with VC and to examine whether pre-existing renal impairment mediates this risk.

Methods: This was a retrospective matched cohort study using electronic health records (EHR) for patients admitted to two UF Health hospitals between Jan 2012 and Dec 2013. We included patients who received IV Vanco at least 72hrs followed by either PT or cefepime (Cef) between the first Vanco and 72hrs of the last Vanco. Patients were excluded if they received both PT and Cef or had severe blood loss, AKI, or end stage renal disease on admission. VPT patients were matched with VC patients, based on their time between Vanco start and PT (or Cef) start. Baseline covariates obtained within ±24 hours of index date, the first day of PT or Cef, were summarized in a propensity score. The outcome was defined as an increase in serum creatinine (SCr) of ≥0.3 mg/dl or 50% from baseline. We stratified patients by level of estimated CrCl > or ≤60 ml/min. We used Cox proportional hazard regression for analysis. Censoring was PT or Cef discontinuation for >3 days, discharge or death, whichever occurred first.

Results: A total of 4,903 patients received VPT or VC. We identified 819 (17%) cases; 545 cases (20%) in 2,777 patients with CrCl ≤60 and 274 cases (13%) in 2,126 patients with normal renal function. VPT was associated with a higher risk of AKI relative to VC, with hazard ratios of 1.31 (95% CI, 1.13-1.52) in the total population, 1.73 (1.33-2.26) in patients CrCl >60 and 1.15 (0.96-1.39) in patients with CrCl ≤60.

Conclusions: Using a large inpatient EHR, we found VPT was associated with a higher risk of AKI relative to VC. The association was true in patients with normal renal function and to a lesser extent in renal impairments.

462. The Risk of Hospitalized Infection Associated with New Use of Abatacept versus TNF Inhibitors in Juvenile Idiopathic Arthritis

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Background: Infection is the most common serious adverse event associated with biologic agents in the treatment of juvenile idiopathic arthritis (JIA). The comparative risk of infection with the newer biologic abatacept (ABA) versus tumor necrosis factor inhibitors (TNFi) is not known.

Objectives: To compare rates of hospitalized infection among JIA patients initiating ABA or TNFi.

Methods: We combined results from 2 data sources: U.S. Medicaid claims from 2000-2010 inclusive and MarketScan claims from 2010-2014 inclusive. New use of TNFi and ABA was defined by a 6 month baseline period of non-use. New users with a physician diagnosis code for JIA prior to new use were included. Follow-up began on the day of the new prescription fill or infusion claim. Outcome was hospital discharge with any infection as the primary diagnosis. We calculated crude infection rates per 100 person-years and stratified results according to clinical factors during the baseline period (use of oral glucocorticoids, use of a different biologic agent, inpatient or outpatient infection) and likely systemic JIA (SJIA) based upon claims. Multivariable regression analyses were precluded by few observed outcomes.

Results: We identified 91 and 8 infections following 5,933 and 257 initiations of TNFi and ABA, respectively. The overall crude rates were 1.50 [1.22-1.85] for TNFi and 4.14 [2.07-8.28] for ABA. SJIA was strongly associated with ABA (13.6% vs 7.7% for TNFi; p=0.0001). SJIA contributed to higher infection rates among ABA users (23.45 [8.80-62.49] vs 2.27 [0.85-6.05] for non-SJIA) and to a lesser extent among TNFi users (2.23 [1.16-4.29] vs 1.45 [1.17-1.80] for non-SJIA). Recent infection was a strong risk factor for the outcome, but not a clear confounder or effect modifier; all 8 patients with infection outcomes following ABA had infections during the baseline.

Conclusions: Crude infection rates for ABA were significantly higher compared to TNFi. The increase may be attributable to greater use of ABA in patients with SJIA. The role of prior infection is less certain. Safety evaluation of second-line biologics requires careful consideration of prescriber channeling.

463. In Search of Predictors of Erythropoiesis-Stimulating Agents (ESAs) Resistance: A Population-Based Study

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Background: A preliminary multicenter cohort study conducted in the context of the "Assessment of short and long term risk-benefit profile of biologics through healthcare database network in Italy" project and funded by Italian Ministry of Health, showed no difference on the effectiveness of biosimilar vs originator erythropoiesis-stimulating agents (ESAs), while around 20% of ESA users seemed to be ESA resistant. Very limited post-marketing data exist on the predictors of ESA resistance.

Objectives: To identify predictors of ESA resistance in patients affected by chronic kidney disease (CKD) or cancer in routine care.

Methods: A population-based nested case-control study was conducted during the years 2009–2014 using administrative database of Treviso Local Health Unit. Among incident ESA users, the difference between the hemoglobin (Hb) value registered within 30 days prior to the first ESA dispensing (index date, ID) and another one between 60 and 90 days after ID, defined as delta Hb (ΔHb), was calculated. Cases were defined as all ESA resistant users (ΔHb≤0 or ΔHb<2 with at least one transfusion). For each case, up to 3 controls were randomly matched by age, sex, strength and duration of treatment. A multivariate regression model was performed, including all potential known predictors of ESA resistance and stratifying by indication for use.

Results: Overall, 365 incident ESA users (CKD: 214, 59.7%; cancer: 151, 40.3%) were identified. Cases did not reach the target Hb (CKD=10.2±1.0; Cancer=9.9 ±1.7) compared to controls (CKD=11.9±1.4; Cancer=12.1±1.7). Type of dispensed ESA (biosimilar or originator) was not a predictor of ESA resistance, which was instead 3.5-fold increased by a previous history of ischemic heart disease (Odds Ratio: 3.5, IC95%: 1.3-9.7; p-value= 0.015) in CKD patients.

Conclusions: No difference on the short-term effects on ESA resistance between users of either biosimilar or originator ESAs was observed in an outpatient setting from Northern Italy. Previous history of ischemic heart disease is a potential predictor of resistance to ESA. Further analyses are required to identify other potential predictors of ESA resistance.

464. Comparative Effectiveness and Safety of Erythropoiesis-Stimulating Agents (Biosimilars versus Originators) in Clinical Practice: A Population-Based Cohort Study

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Background: The erythropoiesis-stimulating agents (ESAs) play a major role in the management of anaemia both in the nephrology and oncology settings. The ESA biosimilars are available since 2007, although their take up is low due to the lack of comparative effectiveness and safety data when used in real life as well as on skepticism on regulatory pathways for their approval.

Objectives: We aimed at evaluating the benefit/risk profile of epoetin alpha biosimilar with the ESA originators when administered to in naïve patients from current clinical practice.

Methods: In an observational cohort study, data on ESA use were collected among 13 470 subjects with chronic kidney disease (CDK) or cancer from the regional Electronic Therapeutic Plan register between 2012 and 2014. The outcomes defined according to the International Classification of Diseases (9th revision) were retrieved from health information systems; outcomes were related to the effectiveness (all-cause mortality and blood transfusion) and safety (major cardiovascular events, blood dyscrasia), throughout six months follow-up. A composite outcome including all-cause mortality, blood transfusion and major cardiovascular events was predefined. Hazard Ratios of any outcome were estimated through Cox regression.

Results: Overall, baseline characteristics of patients using biosimilars and all originators can be considered comparable although in the CKD setting patients starting biosimilars were less severe.

We found no differences between patients on biosimilars or all originators on the composite outcome in the CKD setting (biosimilars versus epoetin alpha originators: HR=1.02, 95% CI 0.78 to 1.33; biosimilars versus other originators: HR=1.09, 95% CI 0.85 to 1.41). Comparable risk estimates were observed in the oncology setting.

Conclusions: Our findings are suggestive of no difference between biosimilar and originators on relevant effectiveness and safety outcomes.

465. Comparative Safety and Effectiveness of Denosumab versus Zoledronic Acid in Patients with Osteoporosis: A Cohort Study

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Background: Denosumab is the first biologic agent approved to treat osteoporosis. Zoledronic acid is an intravenous bisphosphonate thought to have similar efficacy compared to denosumab. However, limited head-to-head comparative safety or effectiveness data exist between denosumab and alternative bisphosphonate in real-world healthcare.

Objectives: We examined the safety and effectiveness of denosumab compared to zoledronic acid for serious infection, cardiovascular disease (CVD) and osteoporotic fracture in patients with osteoporosis.

Methods: We conducted a cohort study using claims data (2009-2013) from a US commercial health plan. We included patients aged 50 years or older who newly initiated on denosumab or zoledronic acid. Patients with malignancy or use of chemotherapy

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during the 455-day baseline period were excluded. The outcomes of interest were 1) hospitalization for serious infection, 2) composite CVD endpoint including myocardial infarction, stroke, coronary revascularization, and heart failure and 3) non-vertebral osteoporotic fracture including hip, wrist, forearm and pelvic fracture. To control for potential confounders, we used propensity score matching with a 1:1 ratio. Cox proportional hazards model compared the risk of serious infection, CVD and osteoporotic fracture within 365 days after initiation of denosumab with zoledronic acid.

Results: The cohort included 2,760 denosumab and 5,210 zoledronic acid users. After PS matching, a total of 2,467 pairs of denosumab and zoledronic acid initiators were selected with a mean age of 63 years. When compared with zoledronic acid, denosumab was not associated with an increased risk of serious infection (HR 0.81, 95% confidence interval [CI] 0.55-1.21) or CVD (HR 1.11, 95% CI 0.85-1.26). Similar results were obtained for each component of CVD. The risk of osteoporotic fracture was also similar between groups (HR 1.21, 95% CI 0.84-1.73).

Conclusions: This large population based cohort study show that denosumab and zoledronic acid have comparable clinical safety and effectiveness with regard to the risk of serious infection, CVD and osteoporosis fracture in osteoporosis patients.

466. A Real World Comparison of Methods for Assessing Dosing Patterns of Biologic Therapies for Psoriasis

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Background: Biologic therapies for psoriasis may require changes in dosage regimen which may affect clinical & cost effectiveness, & likelihood of adverse events. There is lack of consensus on the optimal method to evaluate dosing patterns.

Objectives: To compare different analytic methods to evaluate dosing patterns for adalimumab (ADA), etanercept (ETN) & ustekinumab (UST) using the British Association of Dermatologists Biologic Interventions Register.

Methods: Patients were included if they were followed-up for ≥12-months & had complete records of dosing information. Five methods for assessing dosing patterns were compared descriptively: last vs. index dose (ID; dose of biologic therapy at enrolment); average vs. recommended dose; multiple instances of subsequent doses different from the ID; subsequent doses different from ±30% of the ID; & time-trend method comparing the annual cumulative dose (CD) received to the recommended CD.

Results: Overall 2980 patients (ADA:1675; ETN:996; UST:309) were included. Estimates of dose escalation (DE) were lowest for all drugs using the last vs. ID method (ADA,1%; ETN,4%; UST,15%) while the average dose method gave the highest estimates (ADA,5%; ETN,12%; UST,26%). In contrast, the average dose method gave the smallest estimates of dose reduction (DR) for all drugs (ADA,1%; ETN,1%; UST,25%) while the time-trend method gave the highest rates (ADA,3%; ETN,5%; UST,30%). The multiple incidences & the threshold approaches yielded similar findings for both DE & DR for all drugs. These rates were also similar to those determined using the last vs. ID method for ADA & ETN, but differed for UST. In all but one case, higher rates for changes in utilisation of UST were due to differences with administration intervals rather than prescribed dose.

Conclusions: Different methods yielded diverse estimates using the same data, but consistently gave the same overall finding that UST patients had higher rates of change in dosing patterns, regardless of the method. The time-trend method provided the most comprehensive measure on usage patterns taking account of both

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frequency & timing of changes in regimen, which differed from the other approaches.

467. Trends in the Utilization of Biologics for Inflammatory Bowel Disease in the United States

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Background: Increasing incidence of inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC) are seen in the United States. In recent years several biologic drugs have been approved for the treatment of IBD, and demonstrate effectiveness in achieving and maintaining remission of IBD, in randomized clinical trials and observational studies.

Objectives: This study aims to describe the utilization trends of biologics in the treatment of inflammatory bowel disease in the United States.

Methods: A retrospective cross-sectional analysis was conducted in the Truven Health MarketScan® Commercial Claims and Encounters Database 2008-2013. The index date was defined as the date of first occurrence with an ICD-9 code for IBD in each calendar year. Patients were required to have at least 3 healthcare contacts for IBD on separate days within two years or one IBD medication use (aminosalicylics, budesonide, methotrexate, thiopurine or any biologics) within 30 days after the index diagnosis. Patients were excluded, if not continuously enrolled in the health plan for two years after the index date. Biologics including infliximab, adalimumab, certolizumab, golimumab and natalizumab were identified using NDC and HCPCS codes. Descriptive analysis was conducted to compare biologics use across years for both CD and UC patients.

Results: 82,332 patients with CD, and 85,054 patients with UC were identified. For patients with CD, the proportion of biologics users increased from 36% in 2008-2010 to 42% in 2011-2013. Similarly, among UC patients, the proportion of biologics users increased from 16% in 2008-2010 to 20% in 2011-2013. Among biologics users, a decreased use of infliximab and increased use of adalimumab was observed for CD and UC patients. A slightly increased use of certolizumab and golimumab was observed for CD patients.

Conclusions: The analysis of a large US administrative claim database showed an increased penetration of biologics in the treatment of Crohn's disease and ulcerative colitis from 2008 to 2013.

468. Baseline and Time-Varying Determinants of Statin Adherence

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Background: Statin adherence may be better understood by examining both baseline and time-varying covariates.

Objectives: The objectives of the study were to determine the factors associated with statin adherence over time, and to use adjusted group based trajectory models to characterize subgroups of adherence trajectories.

Methods: We used Marketscan commercial claims data from 2008-2013. Adults who newly initiated statins (no statin in one-year lookback period), and had 3 years of continuous enrollment post statin initiation were included in the study. This 3 year follow-up time was divided into 12 periods of 90 days, and a period was classified as adherent if the patient was exposed to statins for 80% of the days. Baseline covariates included age, sex, and history of congestive heart failure (CHF), hypertension (HTN), stroke, asthma, chronic obstructive pulmonary disease (COPD), depression, and diabetes (DM). Time varying covariates included new onset of clinical conditions (same conditions as baseline plus liver dysfunction and myopathy) and average non-statin daily pill burden in a period <1, 1-2, or >2 pills/day). Generalized estimating equations (GEE) were used as primary analysis. We estimated Group Based Trajectory Models (GBTM) while adjusting for all baseline and time-varying covariates as secondary analysis.

Results: 252,272 patients met the inclusion criteria. For the GEE analysis, patients having a history of COPD (adjusted odds ratio [OR] 0.88, $p<0.05$) or new onset of depression (OR 0.78, $p<0.05$) were most likely to be non-adherent to statin therapy. The GBTM analysis identified the 5 group model as the best model. We found significant interactions between the covariates and the identified subgroups of adherence

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in the GBTM. For instance, in the highest adherence subgroup, new onset of myopathy was associated with highest decrease in adherence (OR 0.73, $p<0.05$), while for the non-adherent groups, new onset of stroke was associated with highest increase in adherence (OR 2.25, $p<0.05$).

Conclusions: Compared to baseline covariates, time varying covariates had greater magnitudes of effect and therefore may be more important in determining longitudinal medication adherence.

469. Determining Prescription Durations from the Parametric Waiting Time Distribution

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Background: Assigning exposure duration to single prescriptions is a prerequisite for determining drug exposure status. The waiting time distribution (WTD) has been suggested for this, but length bias must be accounted for.

Objectives: To estimate prescription durations based on the WTD which appropriately accounts for length time bias.

Methods: We develop a new estimation algorithm based on maximum likelihood estimation of a parametric two-component mixture model for the WTD. The distribution component for prevalent users estimates the so-called forward recurrence density (FRD), which is related to the distribution of time between subsequent prescription redemptions – the so-called interarrival density (IAD) – for users in continued treatment. Length bias governs the relationship between the FRD and the IAD and is well-understood in the theory of renewal processes. We exploit this to estimate percentiles of the IAD by inversion of the estimated FRD, and define the duration of a prescription as the time within which 80% of current users has presented themselves again. The statistical properties are examined in simulation studies and we apply the method to four model drugs: non-steroidal anti-inflammatory drugs (NSAIDs), warfarin, bendroflumethiazide, and levothyroxine.

Results: Simulation studies found negligible bias when the data-generating model for the IAD coincided with the FRD used in the WTD estimation (Log-Normal). When the IAD consisted of a mixture of two Log-Normal distributions, but was analyzed with a single Log-Normal distribution, relative bias did not exceed 9%. The root mean square error did not exceed 5.5 days in the considered scenarios. Using a Log-Normal FRD, we estimated prescription durations of 117, 91, 137, and 118 days for NSAIDs, warfarin, bendroflumethiazide, and levothyroxine, respectively. Based on a Weibull FRD, estimates were 130, 91, 138, and 118 days.

Conclusions: The algorithm allows valid estimation of single prescription durations when the WTD reliably separates current users from incident users. It does not require a run-in period and may replace ad-hoc decision rules in automated implementations.

470. Assessing and Reducing the Impact of Drug Exposure Measurement Errors Due to Non-Adherence: A Simulation Study

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Background: Pharmacoepidemiological studies of drug effectiveness and safety often rely on large administrative databases, which record prescriptions filled by patients rather than their actual use of the drugs. Many patients may only partially adhere to prescribed medication. Thus, the amount of drug actually taken and the timing of actual exposure cannot be accurately evaluated, inducing exposure measurement errors that affect the accuracy of the analyses.

Objectives: We use simulations to: 1), assess the impact of ignoring medication non-adherence in the time-to-event analyses of adverse drug effects with time-varying exposure and 2), explore methods to correct for the resulting bias.

Methods: In simulations, we generate various time-varying patterns of both the prescribed treatment and the non-adherence, reported in literature, and examine the impact of resulting measurement errors on the estimated treatment, effects under different assumptions about true exposure-outcome associations. We then use Continuous Single/Multiple interval medication availability (CSA/CMA) to quantify non-adherence

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and apply these measures to correct for the exposure errors with: 1) Simulation-Extrapolation (SIMEX); 2) Imputation of 'true exposure'.

Results: In all simulations, ignoring non-adherence induced bias towards the null. Proposed methods generally reduced the bias but their accuracy depended on the true exposure-outcome association. The imputation method worked better when the outcome was associated with current exposure, reducing relative bias from around 70% to 15%. The SIMEX methods procedure was more accurate when the past exposures had cumulative effects, reducing relative bias from >20% to 6%.

Conclusions: Medication non-adherence may substantially reduce the accuracy of pharmacoepidemiological analyses. Various methods may be used to reduce the impact of the resulting exposure measurement errors, but further evaluation of their performance is needed.

471. Performance of the Propensity Score in the Presence of Nondifferential Exposure Misclassification: A Simulation Study

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Background: Propensity score (PS) methods are often employed in administrative claims data and drug registries, where misclassification of the exposure is likely. Despite this, the extent to which PS reduces bias in the presence of nondifferential exposure misclassification is unclear.

Objectives: To compare bias and variance obtained from 3 common PS implementations for varying degrees of nondifferential exposure misclassification using realistic parameters based in the pregnancy medication exposure literature.

Methods: Data were generated using estimates selected based on the literature on analgesic use during pregnancy and birth weight. Five independent confounders were simulated, and a dichotomous exposure variable, A, was generated conditional on these confounders. A normally distributed outcome variable, Y, was generated conditional on A and the set of confounders. The true unbiased treatment effect was a mean difference in birthweight of 200g, and the true confounded treatment effect was a mean difference of 220g. Exposure was misclassified using sensitivity/specificity combinations (1.00, 0.99, 0.95, 0.90, 0.80, 0.70). We examined bias and coverage probability associated with each sensitivity/specificity combination, for PS matching, stratification by quintiles, and adjustment.

Results: Low specificity had greater impact on effect estimates than low sensitivity. PS adjustment had the lowest overall bias (average bias: -68.0 across all scenarios) and highest coverage probability, followed by stratification (-74.5) and matching (-80.1). In cases where sensitivity was moderate to high and specificity was high, all methods performed well.

Conclusions: PS adjustment may result in less bias due to exposure misclassification compared to matching or stratification in instances of nondifferential exposure misclassification.

472. Exposure Misclassification and Inverse Probability Weighting: A Plasmode Simulation

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Background: If exposure is misclassified, individuals in the tails of the propensity score (PS) distribution may appear to be treated contrary to indication. Inverse probability of treatment weighted (IPTW) analysis may amplify this error as these individuals are upweighted.

Objectives: Compare bias and precision of IPTW and PS matched analyses under exposure misclassification.

Methods: We used NHANES participants, 1999-2012, age 40-79, with lab data and no reported statin use (n=5,245) as the source population for a plasmode simulation. We randomly sampled with replacement to populate 2,000 cohorts, each n=10,000. We simulated statin exposure as a function of demographics and cardiovascular risk factors and outcomes as a function of

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10-year CVD risk score and a protective effect (rate ratio [RR]=0.5) of statins. We misclassified exposure at random for 20% or 40% of 1) the entire cohort, 2) truly exposed, and 3) truly unexposed. We also induced exposure misclassification that increased with the true PS (e.g. truly unexposed with high PS more likely to have a statin which they did not take). We evaluated median bias and standard error (SE) of RRs estimated using IPTW and PS matching.

Results: When 20% of observations were misclassified at random, the crude, IPTW, and matched RRs were 1.12, 0.72 and 0.71, respectively, vs. the true effect of 0.5. Predictably, as misclassification increased to 40%, IPTW and matched RRs approached the null. The median SEs (2.5th, 97.5th percentiles) were larger in the matched analysis; crude: 0.093 (0.086, 0.101), IPTW: 0.098 (0.091, 0.107), and matched: 0.104 (0.097, 0.115). When misclassification was related to the PS, bias increased. The crude, IPTW, and matched had log-scale bias of 0.99, 0.66 and 0.64, respectively. When misclassification only affected exposed (perfect specificity) or unexposed (perfect sensitivity), the SEs of IPTW estimates exceeded those of corresponding matched analyses in some instances.

Conclusions: Exposure misclassification appears to have a similar effect on bias and precision of rate ratios estimated by IPTW vs. matching. Bias was greatest when misclassification was related to the PS, a more plausible form of misclassification.

473. Evaluation of the Two-Stage Residual Inclusion Method for Instrumental Variable Estimation in Survival Analysis: A Simulation Study

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Background: Instrumental variable (IV) analysis can reduce bias in observational studies even in the absence of information on important confounders. However, IVs are difficult to implement in survival analysis.

Objectives: We assessed the performance of the two-stage residual inclusion (2SRI) method that extends traditional IV analyses to survival analysis.

Methods: We simulated associations between a binary exposure, a binary or continuous IV, and a binary unmeasured confounder and time to event (outcome). The exposure-IV association was modeled with linear or logistic regression and its strength was quantified through squared partial correlation. Then using the 2SRI method, the exposure-outcome association was estimated through a Cox model that included additionally the response, Pearson or deviance residuals from the exposure-IV model. We compared bias, variance and mean squared error (MSE) of the 2SRI estimates with those based on the conventional Cox model. Finally, we applied the SRI method to compare the risk of gastrointestinal (GI) complications between users of COX-2 inhibitors vs. traditional NSAIDs.

Results: Even when the association between exposure and IV was weak (partial $r2 \leq 0.013$), the 2SRI IV estimates were less biased (2-4%) than the conventional estimates (17%), but had higher variance and MSE. For stronger IVs and a linear or logistic regression as the first stage of 2SRI analyses, the estimates were less biased (0-2%) and had smaller variance when we used response rather than Pearson (2-3%) or deviance (4-6%) residuals. In real-life analyses of GI risk, the 2SRI estimate using a linear model for the exposure-IV association yielded a protective effect of COX-2 inhibitors vs. traditional NSAIDs (HR: 0.74, 95% CI: 0.25 – 1.66) compared to the conventional estimate (HR: 0.99, 95% CI: 0.87 – 1.13).

Conclusions: The 2SRI method provides approximately unbiased IV estimates, if a valid IV is available.

474. New Statistical Methods for Using Validation Subsamples to Adjust for Time-Dependent Unmeasured Confounders in Marginal Structural Cox Models

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Background: Many pharmacoepidemiologic cohort studies rely on large administrative databases which often lack information on important confounders, and thus unmeasured confounding is a common problem.

Several methods have been suggested which combine use of these databases with confounder information from clinical datasets in order to control for unmeasured confounders, but none have been extended to deal with unmeasured time-varying confounders which also act as possible mediators of the treatment effect.

Objectives: To develop and compare methods which adjust for unmeasured confounding in marginal structural Cox models (Cox MSM) in large administrative databases, using data from smaller clinical cohorts with information on additional confounders.

Methods: We propose and compare three methods which attempt to adjust for unmeasured confounding when fitting a Cox MSM by inverse probability of treatment weighting (IPTW). Similar to propensity score (PS) calibration, Method 1 uses regression calibration to correct the PS, which is then used to estimate corrected IPT weights. Methods 2 and 3 are based on our expectation that the martingale residual (MR), obtained from a Cox model, may be informative about the values of unmeasured confounders and, thus, may help correct the weights. Method 2 simply includes the MR in a measurement error model for regression calibration of the weights. Method 3 uses the MR to impute unmeasured confounders, and then estimates IPTW using the imputed values. We compare the methods under various scenarios in simulations.

Results: All three methods reduced confounding bias over naive methods. Methods 1-3 reduced relative bias of naive methods by 54%, 78% and 63% respectively. MR-based methods 2 and 3 yielded lower bias and better overall accuracy, with lower mean squared error (MSE) than method 1. Method 3 had higher variance, leading to higher MSE than method 2.

Conclusions: Using the proposed methods to extract confounder information from small cohorts largely reduced bias over standard methods of fitting Cox MSM. Using martingale residuals further enhanced the accuracy of the estimates.

475. Perspectives from Causal Inference in the Era of Big (Healthcare) Data

Susan Gruber[1], Michele Jonsson Funk[2], Robert Platt[3], James M. Robins[4], Mireille Schnitzer[5], Til Stürmer[2] and Alexander M. Walker[6]

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Background: Administrative claims and electronic health records are an important source of information for evaluating the benefit and harm of medical products in real-world settings. However, the lack of randomization and imperfect capture of data on exposures, outcomes, and confounders pose serious challenges to obtaining unbiased effect estimates. Secondary analyses of these "big data" provide an opportunity to evaluate risks involving rare exposures or outcomes, but are further complicated by informative loss to follow-up, non-random patterns of missing data, and non-standard coding practices.

Objectives: To examine and discuss ways in which tools and methods from causal inference can improve the reliability and interpretability of pharmacoepidemiologic research.

Description: Dr Gruber will present a motivating example (10min) from the pharmacoepidemiologic literature which panelists will use as a reference point for their remarks. The panelists will discuss (10min each) specific challenges and how they would approach the design and analysis for this application according to a causal inference perspective.

Dr. Stürmer will discuss considerations for defining a study population, and the implications this has for effect estimation and interpretation. Dr. Walker will discuss how a causal perspective can inform the development of case definitions used to identify patients who experienced an outcome from claims or electronic medical records. Dr. Platt will discuss how causal thinking can improve study design by identifying the parameter most relevant to the scientific question of interest, and ways in which the available data can serve as proxies for unmeasured confounders. Dr. Jonsson Funk will discuss the challenges of estimating meaningful causal effects of chronic treatments in which the disease itself, patient response and adherence vary over time. Dr. Robins will describe an alternative study design and analyses ideally suited to evaluate risks and benefits of drugs in complex, longitudinal real-world settings.

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Drs. Gruber and Schnitzer will moderate a discussion (30min) in which panelists respond to questions from the audience, moderators and each other.

476. Making Optimal Use of Routinely Collected Data from United Kingdom Electronic Health Records

Ian J. Douglas[1], Stephen J. Evans[1], Laurie Tomlinson[1], Rohini Mathur[1], Krishnan Bhaskaran[1], Caroline Minassian[1], Sara Thomas[1], Rachel Williams[2], Wilhelmine Meeraus[2], Jenni Quint[3], Janet Valentine[2] and Liam Smeeth[1]

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Background: Databases of Electronic Health Records (EHR) are continually developing. Availability of novel information within a database and linkages between databases provides a dynamic and rich resource for researchers. However, each new improvement or linkage presents a steep learning curve in order to evaluate its utility and to optimise its research applications. For this symposium we focus on making the best use of developments, taking as an example the United Kingdom Clinical Practice Research Datalink (CPRD) and linked data sources.

Objectives: To describe rigorous approaches for utilising recent developments with UK EHR data. Researchers wanting to learn about, and discuss approaches to the use of EHRs in an era of rapid data developments will benefit from attending this symposium.

Description: Researchers with direct experience of turning database developments into improved research quality will describe approaches using fully worked examples, each followed by short audience discussion. Four main themes will be explored:

1) Approaches to identifying and utilising phenotypes: e.g. pregnancy can be difficult to ascertain using EHRs. A new algorithm using CPRD data seeks to refine the identification of pregnancies by maximising the use of antenatal, delivery and postnatal records relating to the timing and duration of pregnancy and the outcome; live birth, stillbirth or pregnancy loss.
2) Newly available data and its utility will be described: For example novel linkage between primary care and outpatient Hospital Episode Statistics data; the ability to combine both Vision and EMIS practice data.
3) EHRs provide a valuable resource in which to study long term conditions. However, there are multiple ways of coding for diseases, coding practices change over time, making accurate identification challenging. Amongst other examples, asthma and COPD validations will be described; identification of stable diseases and ascertainment of acute events associated with both conditions.
4) Novel approaches to prospective study design (e.g. real time identification of research participants and direct electronic data collection; the latest on randomised or prospective studies).

477. Using "Big Data" in Early Safety Evidence Gathering and Targeted Surveillance for Newly Launched Medicines: Is It the Right Time Now?

Hu Li[1], Andrew Bate[2], Joshua Gagne[3], Jim Slattery[4], Ken Hornbuckle[1] and Stephen Motsko[1]

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Background: Early understanding of the safety profile for newly launched products using "big data" (EMR, claims, etc.) has attracted increased attention. Despite regulatory agency efforts (FDA Sentinel), broad initiatives (IMI PROTECT, EU ADR), and industry's efforts exploring the opportunity of leveraging "big data" for early safety evidence gathering and targeted surveillance, there is a lack of consensus on needs and approaches. Furthermore, various analytic methods continue to evolve to facilitate valid observational studies that use large electronic medical data systems. While the approaches that underlie these methods have been widely used to refine and evaluate safety signals, such approaches have not yet been fully explored and optimized to detect or continuously monitor potential safety concerns for newly launched products. An optimal approach to detecting, monitoring, and managing safety signals generated from "big data" requires coordination among industry, regulatory agencies, and academic researchers. This symposium is designed to provide a focused discussion on the options that can be used to exploit the wealth of available "big data," the development and adoption of new methods to harness these growing data, and opportunities and challenges of conducting early evidence gathering and targeted surveillance activities.

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Objectives: To discuss and debate the various approaches in early safety evidence gathering and targeted surveillance:

1. Provide an overview of the new methodologies (Joshua Gagne)
2. Discuss potential challenges from the lessons learned and real-world experience (Andrew Bate);
3. Discuss business operation opportunities for application and integration (Stephen Motsko); and
4. Provide a regulatory perspective of best practice recommendations and future direction (Jim Slattery).

Description: The session will focus on evidence gathering, continuous safety monitoring for newly launched medicines, and sharing cutting-edge methodology. Topics will be presented via real-world lessons learned applications, and will provide perspectives from business operation and from a European regulatory agency.

478. What's in a Code? Algorithm Validation in Drug Safety Studies

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Background: Electronic healthcare databases can offer highly informative real-world data for drug safety studies, but diagnosis codes are not always valid.

Objectives: To provide an overview of validation methods in studies using claims-based electronic healthcare databases on drug safety, share important lessons learned from conducting validation studies, and discuss current topics related to validation in drug safety. Researchers involved in observational drug safety studies and individuals in healthcare or regulatory professions who draw from observational studies would benefit from attending.

Description: The following topics will be discussed:

1 What is algorithm validation in the context of drug safety studies using claims-based electronic healthcare databases, and why is it important?
2 How can algorithms best be validated, including choice of gold standard data, selection of events to validate, and performance assessment?
3 What lessons have we learned from the planning, design, and conduct of validation studies, and what impact can algorithm validation have on the conclusions of a drug safety study?
4 What are the current considerations of study validation in the regulatory environment?
5 How should an algorithm with established validity be used, and how far can a validated algorithm be generalized, into other databases or over time?

Each topic will be presented as a brief overview, with a focus on relevant examples from prior studies. Questions will be posed to the audience at several points during the session, to inspire an engaging discussion on successes and failures they have had with validation, and to explore and remedy misconceptions that may exist around the validation of database algorithms.

479. The Epidemiological Approach to Rare Disease Research: Challenges and Opportunities

Mary E. Ritchey[1], Jessica J. Jalbert[2], Alicia Gilsenan[1], Theodore Lystig[3], Michael Peng[4], Tzuyung D. Kou[5] and William Blumentals[6]

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Background: There are over 6000 rare diseases which affect approximately 8% of the global population. Up to 80% of rare diseases may result from a genetic anomaly. Interest in precision medicine has led to an increase in the number of clinical development programs focused on rare diseases. This has led to many promising drugs, biologics, and devices that are either in the pipeline or currently available to patients with these conditions. Despite the large number and variation in types of rare diseases, there is a common theme in epidemiologic research on rare diseases: small numbers issues are compounded by a lack of suitable, contemporaneous comparators necessitating creative approaches to traditional epidemiologic questions.

Objectives: The objective of this symposium is to discuss a range of regulatory, methodological, and strategic topics, as they apply to epidemiologic research on

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rare diseases. These topic areas represent unique challenges and opportunities for any rare disease development program.

Description: Regulatory landscape and traditional epidemiological approach (Ritchey, 15 min):
- Overview of definitions and regulatory environments for rare disease therapeutic products
- Traditional approach for rare disease products with a focus on disease registries for natural history and product safety registries for safety and longer-term outcomes
- Challenges with traditional approach

Methodological approaches (Lystig, 15 min):
- Extrapolation of data from alternative/related populations, including pediatrics
- Leveraging Bayesian approaches for small numbers
- Opportunity for innovative approaches in data collection (Peng, 15 min):
- Case identification and choice of comparator through linked electronic healthcare record data and use of natural language processing

Integration of epidemiology findings into a clinical development program (Kou, 15 min):
- Focus on patient journeys and leveraging their experience to better understand recruitment and retention
- The role of epidemiology throughout the product development program

Final thoughts (Blumentals, 15 min)
- Future directions for rare disease research

Panel discussion moderated by Gilsenan/Jalbert, 15 min.

480. The Role of Evidence Synthesis in Drug Safety Evaluation and Regulation

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The regulatory landscape has evolved recently with increasing use of synthesized evidence, either being from clinical trials or observational studies, in drug safety evaluation and regulation. Relevant guidance to govern the role of meta-analysis of clinical trials in drug safety assessment is being finalized by the CIOMS X Expert Working Group in 2016. For observational studies, the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) published guidance in 2015 on the role of systematic reviews and meta-analysis of observational studies in the evaluation of drug safety (http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml). This symposium will focus on (i) the recently published CIOMS and ENCePP guidance for the design and conduct of meta-analysis in drug safety, and (ii) the role of synthesis of trials and observational data in drug safety regulation.

This 90-minute symposium will consist of four 15-minute presentations followed by 30 minutes of panel discussion and audience Q&A. Presentations will address (1) the CIOMS X guidance for the design and conduct of meta-analysis in drug safety (15 minutes), as well as the role of synthesis of trials and of observational studies in regulatory decision making in the (2) Food and Drug Administration, Center for Drug Evaluation and Research (15 minutes), (3) the European Medicine Agency (15 minutes), and (4) the Medicines Evaluation Board in Netherlands (15 minutes).

Questions for Panel Discussion: The panel will consist of representatives of regulatory agencies and industry. Panelists will be asked to discuss the following

1. Factors influencing how synthesis of trials and real world data are used in drug safety evaluation and regulation
2. How synthesis of evidence from trials and observational studies fit into the hierarchy of evidence in drug safety evaluation and regulation
3. Future vision of the use of synthesis of trials and observational studies in drug safety evaluation and regulation

481. A Discussion of Data Requirements and Methodologic Considerations for Evaluating the Real-World Effectiveness and Safety of Biosimilar Medicines

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Background: A biosimilar is a medicine that has demonstrated similarity to an already licensed biological medicine in terms of quality, efficacy and safety. Interchangeability and automatic substitution are important scientific and policy issues regarding the introduction and use of biosimilars. The economic savings could lead to better access to these life-altering therapies. Switching between biological products, including reference product to biosimilar, is heavily discussed in medical literature and treatment guidelines at this moment.

Objectives: The objective of this symposium is to highlight important methodological considerations, review and clarify legislation around interchangeability, discuss results from European studies, and offer recommendations for future opportunities to study substitution, and switching to biosimilars when using real world data. Researchers and other stakeholders involved in biosimilar development, research and policy would benefit from this symposium.

Description: This symposium includes pharmacy, regulatory, industry and academic perspectives and will be moderated by the ISPE Biologics SIG chairs Dr. Veronique Kugener and Dr. Amanda Golembesky. Dr. Jaclyn Bosco will introduce the symposium and provide an overview of biosimilars with regard to interchangeability and considerations for pharmacoepidemiology studies. Dr. Thijs Giezen will present the EU regulatory and pharmacy perspectives about interchangeability. Dr. Gianluca Trifirò will summarize main results of European observational studies concerning biosimilar use and switching in routine care. Specific considerations will be made about definitions of biologically naive and switchers.

Drs. Kelsh and Bradbury will discuss data requirements and other methodologic considerations when designing real-world biosimilar effectiveness and/or safety studies.

482. Dabigatran versus Warfarin in Patients with Non-Valvular Atrial Fibrillation: A Population-Wide Cohort Study in Chinese Patients

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Background: Dabigatran, a direct thrombin inhibitor, was the first new oral anticoagulant approved for use as an alternative to warfarin in patients with non-valvular atrial fibrillation (NVAF). However, the effectiveness and adverse events concerning the use of dabigatran are not well described outside the clinical trial setting, especially among Asian population.

Objectives: To compare the effectiveness and safety of dabigatran and warfarin in patients with NVAF in the real-life clinical setting.

Methods: Patients newly diagnosed with NVAF from 2010 through 2013 and received dabigatran or warfarin were identified from the Clinical Data Analysis and Reporting System (CDARS), a population-wide database managed by the Hong Kong Hospital Authority. Cox proportional-hazards regression was used to compare the risk of ischemic stroke, intracranial hemorrhage (ICH), gastrointestinal hemorrhage (GIH), and all-cause mortality between treatment groups with 1:1 propensity-score (PS) matching. Patients with a history of any outcomes of interest were excluded.

Results: Preliminary results indicated that 4049 and 1281 eligible patients with NVAF receiving warfarin and dabigatran were identified in CDARS respectively. Of these, 2522 PS-matched patients were included in the analysis. Compared to warfarin, the use of dabigatran was associated with a reduced risk of ICH (hazard ratio [HR]=0.25; 95% confidence interval [CI]=0.07-0.89) and all-cause mortality (HR=0.58;95%CI=0.37-0.92); but a comparable risk of GIH (HR=1.08;95%CI=0.63-1.86) and ischemic stroke (HR=0.86; 95%CI=0.51-1.47). In the subgroup analyses for those aged≥75 years with 1324 PS-matched patients, similar results were found for ICH (HR=0.17;95% CI=0.04-0.75), all-cause mortality (HR=0.39;95% CI=0.22-0.68), GIH (HR=1.56;95%CI=0.83-2.93), and ischemic stroke (HR=0.58;95%CI=0.28-1.22).

Conclusions: In this Chinese population, the use of dabigatran was associated with a lower risk of ICH and all-cause mortality; and similar risk of GIH and ischemic stroke as compared to warfarin. Similar findings were also observed in those aged≥75 years.

483. Evaluation of Clinical and Genetic Risk Factors in the Development of New-Onset Diabetes Mellitus in Malaysian Post-Renal Transplant Patients

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Background: New-onset diabetes after transplantation (NODAT) is a major metabolic complications after renal transplantation with reduced overall patient and graft survival.

Objectives: To determine the clinical and genetic risk factors of NODAT in Malaysian renal transplant patients.

Methods: This is a retrospective study involving adult renal transplant patients without diabetes who were followed-up at two major Malaysian transplant centres from 1st January 2000 to 31st December 2014 (n=177, 61% males). Those who developed NODAT (n=30) were compared to those without NODAT as controls (n=147). Three single nucleotide polymorphism (SNPs); IL7R (rs1494558), CAT (rs1001179), and MBL2 (rs2232365) were genotyped. The relationship between patients' clinical covariates including genetic polymorphisms and NODAT were examined using multivariate logistic regression.

Results: Twenty-nine percent of patients developed NODAT within 1-year of transplantation. Significantly higher mean age at transplantation (40.29±10.71 vs 34.83±12.48 years, p=0.02) and mean daily prednisolone dose at 1-year post-transplant (14.54±3.16mg vs 12.58 ±3.73mg, p=0.01) were observed in NODAT patients compared to controls. Daily dose of prednisolone at 1-year post-transplant was significantly associated with NODAT (OR=1.88, 95% Confidence interval 1.15-3.06 per mg increase, p=0.01). Gender, ethnicity, primary kidney diseases, pre-transplant dialysis period, types of donor (living or cadaveric), body mass index, creatinine levels and types and dosage of calcineurin inhibitors (tacrolimus or cyclosporine) as immunosuppressants were not associated with increased risk of NODAT. No significant differences in the frequency of the three SNPs were found between the two groups.

Conclusions: Dosage of corticosteroids was associated with increased risk of NODAT amongst Malaysian renal transplant patients.

484. Association of Aspirin Use and Age-Related Macular Degeneration in Taiwan

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Background: Aspirin is commonly used for primary or secondary prevention of cardiovascular diseases. Although the bleeding side effect in gastrointestinal tract is well noted, its effect on eye is still unknown. The results from randomized control studies and observational population-based studies were controversial.

Objectives: To assess if aspirin users have higher risk to develop age-related macular degeneration (AMD).

Methods: We conducted a population-based retrospective cohort study by using Taiwan National Health Insurance Research Database. We included patients aged more than 45 years-old and initiated aspirin therapy during 2001-2010 and followed till 2013. The comparison group was selected by age and gender-matched to the aspirin users with 10-20 to 1 frequency matching. The outcome of interest was AMD defined by ICD-9 code 362.50, 362.51, 362.52 or 362.57. We used propensity score matching to balance the characteristics of patients between groups to estimate the hazard ratio.

Results: We included a total of 65,859 patients who were aspirin new users and found 2,211 (3.36%) cases of AMD. While in the comparison group, there were 533 (0.32%) cases of AMD in 164,063 patients. The incidence of these 2 groups was 14.76 and 1.57 per thousand person-year, respectively. After propensity score matching, the hazard ratio was 2.07 (95% CI, 1.88 - 2.28).

Conclusions: Aspirin users had higher risk compared to non-user in developing AMD. Though the incidence is low, physicians should be aware and indicate patients for eye examination if any signs of AMD occurs.

485. Risk Factors of Trastuzumab Related Cardiotoxicity in Taiwanese Breast Cancer Women

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Background: Trastuzumab (TRA) has a major role in treatment women with HER2-overexpressed breast tumors and but its use is associated with an increased risk of cardiotoxicity. Age and use of anthracycline were 2 significant risk factors for TRA-related heart failure and/or cardiomyopathy (HF/CM) in Western population. Few data are available regarding the risk factors of TRA related HF/CM in Asian women.

Objectives: To identify risk factors of TRA related HF/CM within a year after TRA initiation among Taiwanese women with breast cancer (BC).

Methods: We identified TRA users from the entire Taiwan female BC cohort with the Registry for Catastrophic Illness Patient Database between 2006 and 2012. We included women who survived at least a year after TRA initiation. We estimated the risk factors of HF/CM (ICD9-CM-code: 402.x1, 402.x3, 404.x1, 404.x3, 425, 428, and 785.51) within a year after TRA initiation with a multivariate logistic regression model. We included age at diagnosis, cardiovascular specific comorbidities and related medication records a year prior TRA, surgery history, types of diagnostic imaging, outpatient visit counts a year prior BC diagnosis, BC screening records 2-year prior BC diagnosis. Radiotherapy (RT) and chemotherapy (CT), including anthracyclines, taxanes and cyclophosphamide prior TRA initiation were also involved in the analytic model. All statistical analyses were performed using SAS software 9.4.

Results: Among 6,407 TRA users, 132 (2.14%) women had HF/CM within a year after TRA initiation. In multivariate model, compared with users under 45 years of age, 55 to 64 year-old women were more likely to have HF/CM during treatment (OR: 2.15, 95% CI: 1.14-4.04) and the risk further increased in women older than 75 years of age (OR: 3.82, 95% CI: 1.59-9.15). Other risk factors of TRA HF/CM included diagnosed as hypertension (OR: 1.53, 95% CI: 1.00-2.55) and arrhythmia (OR: 3.01, 95% CI: 1.52-5.98) prior TRA initiation. RT and CT prior TRA did not impact significantly on HF/CM risk.

Conclusions: Risk factors of HF/CM were different between Asian TRA users and women of Western countries. Further studies are needed to explore such population discrepancies.

486. Antipsychotic Polypharmacy of Schizophrenia Treatment – a Database Approach in China

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Background: Although antipsychotic monotherapy is consistently recommended as the main treatment for schizophrenia, antipsychotic polypharmacy (APP) is common in practice. Longitudinal data on treatment patterns and APP in schizophrenia is limited.

Objectives: Describe antipsychotic treatment patterns and APP in the treatment of schizophrenia by utilizing an de-identified electronic medical records (EMR) database in China.

Methods: The EMR database was from a major mental health hospital, which provides integrated mental healthcare in Beijing, China. Schizophrenia patients who received continuous care (had at least 3 consecutive visits) and antipsychotics between 1/1/2010 and 12/31/2014 were included in the cohort. An antipsychotic new-user sub-cohort was also analyzed. APP was defined as having more than one antipsychotic overlapping for at least 7 days or 60 days for inpatient or outpatient treatment, respectively.

Results: The study cohort contained 8,812 patients with the initial treatment mostly monotherapy (83.8%) and single oral atypical (76.2%). The prevalence rate of APP was 16.2% and mostly (68.7%) from outpatient. The incidence rates of APP were 12.6% (95% CI: 11.8%-13.3%) or 12 (95% CI: 11-13)/100 pys (patient-years). The mean (SD) and median time to switch were 287.2 (308.8) days and 166 days, respectively. The incidence rate decreased from 39/100 pys in the youngest age group to 4/100 pys in the

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oldest age group. The new-user sub-cohort (1,352) showed similar demographic characteristics, comorbidity, treatment pattern, and inverse age distribution with APP. The incidence rates of APP were 8.8% (95% CI: 7.2%-10.6%) or 12 (95% CI: 10-14)/100 pys in the sub-cohort.

Conclusions: The APP rates were lower than those reported in previous publications in China or in Asia. It's probably due to the longitudinal approach to exclude transient overlapping or drug titrations. Most schizophrenia patients can be well-maintained on monotherapy and switching to APP likely occurred within the first year. Those who were younger were more likely to switch and tended to switch to APP earlier, which may reflect the different characteristics of disease management and courses.

487. Statin Induced Diabetes Mellitus in Cardiovascular Patients: A Multicentric Observational Study of Hospital Databases in South Indian Tertiary Healthcare Facilities

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Background: Stain use and its potency are associated with increased risk of new-onset diabetes (NOD). Asians phenotype, especially South-Indians with certain unique features, present a higher likelihood for NOD risk for statins.

Objectives: To assess the effect of statins on development of NOD when used for secondary prevention of CVD) and investigate relationship between the duration and potency of statin use with development of NOD.

Methods: A multi-centric retrospective cohort study was conducted in 6 hospitals from 4 South-Indian states by using the hospital databases of patients admitted for secondary prevention of CVD. The study population was patient aged $\geq$ 30 years, without any previously diagnosed or treated for diabetes, and hospitalization for a major cardiovascular event. Based on inclusion and exclusion criteria 2422 patients were identified for the study. The primary outcome was incident diabetes, defined as a diagnosis of diabetes in the hospital databases.

Results: There is a increased incidence of NOD among statin exposed group (42.6%) compared to non-exposed group (36.7%). There is a statistically significant association between statin exposure and diabetes (p=0.026; chi2=4.96). Risk estimation showed a significant risk of NOD in statin exposed group (OR=1.28; RR=1.162). Analysis showed that age was not a confounding factor for NOD after statin therapy (p=0.034; MH Chi2=4.49).Higher potency statin users have increased incidence of NOD (57.3 %) compared moderate potency statin users (42.7%) as well as low potency statin users (21.9%). There was a significant association between statin potency and NOD (p=0.0001).There was no statistically significant association between duration of statin exposure and NOD (p=0.468; chi2=0.526). Duration of statin use was not a risk factor for NOD (OR=0.936;RR=0.963).The number needed to harm (NNH) was 17.

Conclusions: There is a harmful association between statin use and NOD in patient's treated for secondary prevention of CVD in our population. Higher potency statin use is associated with increase in the risk of NOD compared with lower potency statin.

488. Incidence and Medical Resource Utilization for Cardiovascular Events in Asia

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Background: Cardiovascular events are the leading cause of mortality and morbidity in United States (US) and other industrialized countries. However, little is known about trends in the incidence and resource utilization of these conditions in Asia as life-style have westernized.

Objectives: To describe the incidence (IR) and medical resource utilization of cardiovascular events among the study population in Hong Kong (HK), Taiwan (TW), Japan (JP) and US from 2006-2013.

Methods: We utilized the OMOP common data model in the AsPEN converted from a 1% random sample of Hong Kong Clinical Data Analysis and Reporting System (CDARS), a 5% random sample from Taiwan National Health Insurance Research Database (NHIRD), Japan Medical Data Center Database (JMDC), and 5% sample from the US Medicare database. Hospitalization and length of hospital stay for myocardial infarction (MI) or acute coronary syndrome (ACS) were identified from the databases. Comorbidities and concurrent medications for the patients at the time of the MI/ACS were assessed.

Results: The age-gender adjusted IR (per 100 persons) for MI/ACS were 0.2 in HK, 0.1 in JP and TW, and 0.9 in US. Average number of hospitalizations increased from 4.7-15.2 in HK, 0.8-1.1 in JP, 4.5-7.0 in US but slightly decreased in TW (10.8-10.0) over the study period. Average length of stay was increased by 14.5%-107.9% across the four countries. Congestive heart failure and hypertension were the most common comorbidities in these patients. Medications used after MI/ACS were quite different across sites: 93% of HK and 63% of TW patients started antiplatelet after MI/ACS vs. only 14% patients in JP and 0.1% in US. 61% patients in HK started renin-angiotensin system (RAS) inhibitors after diagnosis, whereas 22.1% and 38.3% patients in TW and US started the same treatment.

Conclusions: The IR of MI/ACS were similar among different Asian sites but were higher in US. An increasing number of hospitalizations and length of stay suggested an increasing disease burden. Discrepancy in recommended drug use after MI/ACS provides additional insights into the variation across countries in treatment patterns that must be appreciated when undertaking multinational studies.

489. Epidemiology in Asian Pharmacoepidemiology Network (AsPEN): Study in Surveillance of Health Care in Asian Network (SCAN)

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Background: The purpose of SCAN is to gain a better understanding of the health and health care utilization of the population covered in each participating sites from the AsPEN.

Objectives: To investigate the prevalence of clinically recognized disease among the study population in Hong Kong (HK), Taiwan (TW), Japan (JP) and the United States (US).

Methods: We utilized the OMOP common data model in the AsPEN converted from a 1% random sample of Hong Kong Clinical Data Analysis and Reporting System (CDARS), a 5% random sample from Taiwan National Health Insurance Research Database (NHIRD), Japan Medical Data Center Database (JMDC), and 5% sample from the US Medicare database. Prevalence rates (per 100 persons, age-gender adjusted) of 33 clinically recognized diseases were evaluated.

Results: 6,476,773 individuals were identified in 4 databases, 47% were male. Hypertension is the most common disease in HK, TW and US and ranked fourth in JP with the prevalence of 2.6, 7.9, 59.6 and 4.6 respectively. Diabetes ranked third in HK (1.3), fourth in TW (3.8), fifth in JP (3.7) and third in US (23.3). Hyperlipidemia is the second most common in TW (5.1), JP (4.9) and US (51.6) and seventh in HK (0.8). Obstructive chronic bronchitis is the third most common disease in TW and JP (4.6 for TW, 4.8 for JP, 0.7 for HK, 9.1 for US). Asthma is the most common disease in JP (7.6) but not in other sites (0.5 for HK, 2.3 for TW, 5 for US). Prevalence of cancers were similar among Asian sites ranging from 0.1-0.5 but were lower than US (0.4-2.2). Similar pattern was observed in psychiatric disorders; Prevalence of depression and schizophrenia were 0.4-1.6 and 0.4 in Asian

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sites whereas 4.4 and 1 in US. US has the highest prevalence in most of the diseases.

Conclusions: US has the highest age-gender adjusted prevalence across most of the diseases but the discrepancy was much less in non-CV diseases. This may be due to the difference in diet and lifestyle as well as in health care system and coding between Asian countries and US. Understanding the underlying prevalence of disease across standardized database representations is important when undertaking multi-national studies.

490. European Healthcare Professionals' Familiarity with and Perceived Usefulness of Safety Communications on Medicines

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Background: Effective communication of drug safety information to healthcare professionals (HCPs) is essential for achieving the objectives of pharmacovigilance. The most commonly used safety communication tools are Direct Healthcare Professional Communications (DHPCs), national competent authority (NCA) communications, but educational materials (EMs) are also increasingly used.

Objectives: To determine HCPs' familiarity with and perceived usefulness of DHPCs, NCA communications and EMs in nine European (EU) countries.

Methods: Within the SCOPE project (www.scopejointaction.eu), a web-based survey was distributed to HCPs (mainly GPs and pharmacists) in Norway (NO), Sweden (SE), Denmark (DK), Ireland (IE), the United Kingdom (UK), the Netherlands (NL), Spain (ES), Italy (IT) and Croatia (HR). HCPs were recruited through direct e-mail or information on websites or newsletters. Chi-square statistics were used to test for differences between countries; $P < 0.001$ was considered statistically significant for multiple comparisons.

Results: Of the 3625 respondents (61% females), 16% were from NO, 3% from SE, 2% from DK, 12% from IE, 18% from UK, 4% from NL, 30% from ES, 10% from IT and 5% from HR. HCPs were familiar with DHPCs (91%) but there were differences among the countries (77% in NO to 97% in IE, $P<0.001$). Those familiar with DHPCs considered them useful (85%; 61% in SE to 97% in IT, $P<0.001$). Most HCPs (87%) were also familiar with NCA communications. Differences in familiarity were larger between countries (28% in NL to 96% in ES; $P<0.001$). HCPs familiar with NCA communications generally found them useful (94%; 77% in NL to 98% in ES and IT, $P<0.001$). A lower number of HCPs were familiar with EMs (66%; 60% in ES to 79% in IE, $P<0.001$) however, those familiar evaluated these materials as mostly useful (84%; 64% in NL to 95% in IT and HR; $P<0.001$).

Conclusions: HCPs are generally familiar with the safety communication tools, especially with DHPCs and NCA communications. These tools are considered useful, however, the variation between EU countries suggests that country-specific strategies are needed to further improve safety communication on medicines.

491. A Number Needed to Treat Test

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Background: The Number-Needed-to-Treat (NNT) statistic gives the number of patients who need to be exposed to an intervention in order to prevent one event. Historically, we calculate the NNT only after a statistically significant study has been completed.

Objectives: To demonstrate a method of directly testing a cohort to determine the degree to which a particular NNT is supported by the data.

Methods: The NNT test is explained and then demonstrated using the CRISTAL randomized trial, which examined whether colloids versus crystalloids for fluid resuscitation improved mortality in intensive care patients with hypovolemic shock. To apply the test, the physician first states the NNT treatment goal (=15 in the example), the value of which is used to form the alternative hypothesis of the test. In addition, a quasi-indifference factor, τ, is specified to be 0.2. τ serves a role similar to that of a type II error (β) in a conventional hypothesis test. A risk difference is then

calculated from the data. A likelihood ratio is estimated to compare the relative plausibility of the null and alternative hypotheses. Finally, the likelihood ratio is used in a written statement of evidence.

Results: After 90 days in the CRISTAL trial there were 927 deaths among the 2857 patients randomized to one of the two treatments (colloids n=1414, deaths=434; crystalloids n=1443, deaths=493). Using the alternative hypothesis treatment goal of NNT=15, and τ=0.2, a likelihood ratio comparing an alternative hypothesis of 15 to 18 patients compared to a null hypothesis was estimated to be 0.285. The interpretation of this LR is that treating 15 to 18 patients with Colloids instead of Crystalloids is 0.284 times as likely to have no additional benefit as it is to prevent one additional event after 90 days.

Conclusions: Clinical significance is addressed directly in the NNT test rather than in an informal sense post-hoc of a small p-value. As such, there is no opportunity to confuse statistical significance for clinical significance. The test provides a structured and quantitative alternative to informally combining the p-value or confidence interval with a notional NNT. In this regard, nothing should be sacrificed by using the NNT test in lieu of those other measures.

492. Additional Risk Minimisation Measures Targeting Patients in the PRAC Era: A Qualitative Review of the European Public Assessment Report Database

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Background: Additional Risk Minimisation Measures (aRMM) are imposed as a condition for the safe and effective use of approximatelly 25% of medicinal products centrally authorised in the EU. Among others, the Patient Alert Card (PAC) is a widely used aRMM. The EU pharmacovigilance legislation in force since July 2012 established the Pharmacovigilance and Risk Assessment Committee (PRAC) with the mandate to advice on all aspects of therapeutic risk management. Good Vigilance Practice guidance (GVP Module XVI) was released in 2013 to support the development of aRMM and the evaluation of their effectiveness.

Objectives: This review describes the use of PAC as aRMM in 2013-2015.

Methods: We reviewed the EPAR database to identify medicinal products centrally authorised in EU between 1/1/2013 and 31/12/2015. The number of products targeting patients with PAC and other tools were computed and grouped by chracterizing variables. Measures of effectiveness were also reviewed.

Results: During the study period 201 non-generic products were centrally authorised in EU, including 53 products with aRMM, 27 of which consisted of educational tools targeting patients. Tools included educational material (n=7) and patient cards (n=20) of which 11 (5% of all authorised medicines) were described as PAC. Only 2 products included the PAC in the label to address the risks of bleeding and hypersensitivity. Main safety concerns targeted with PAC included infections (n=5), drug-drug interactions (n=2) and pregnancy prevention (n=2). In line with GVP guidance, in all but 2 instances patients were required to carry the PAC with them at all times.Measures of effectiveness of aRMMs targeting patients were planned through drug utilisation studies (n=5), registry (n=8) or PASS not otherwise specified (n=5). In one third of products metrics were limited to routine phararmacovigilance (n=5) or were not specified (n=4). No process measurements (e.g. survey) were planned.

Conclusions: This review shows that between 2013 and 2015 PAC were imposed for 5% of centrally authorised medicines in EU. Characteristics of the PAC appeared to be in line with GVP guidance.

493. Evaluating Physician Knowledge of Risks and Safe Use of Xarelto (Rivaroxaban)

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Background: Rivaroxaban is an oral direct Factor Xa inhibitor approved in Europe in 2011 for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation and treatment of

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deep vein thrombosis (DVT), and for prevention of recurrent DVT and pulmonary embolism following an acute DVT in adults. As part of a safety risk management plan revision, a prescriber guide (PG) and patient alert card (PAC) were distributed in Europe to provide education on key safety information.

Objectives: To measure whether prescribers received and used the PG and evaluate their knowledge of the key safety messages.

Methods: This study was conducted in the United Kingdom, Germany, France, and Spain. Physicians who had prescribed rivaroxaban in the past 6 months were recruited from a web panel to complete a survey on their knowledge of key safety information for rivaroxaban.

Results: A total of 1,224 physicians (9% of the total invited) completed the questionnaire. More than half (56%) of physicians reported that they used the PG as a source of information. Approximately half (47%) reported they received PACs, and 80% of these reported they provide it to most or all of their patients. Physician knowledge was high on the overall risk of bleeding $>$ 90% correct) as well as on the risks for populations with contraindications and populations at increased risk of serious side effects (66%-91%). A lower percentage of physicians (59%) were aware that rivaroxaban should be taken with food. The lowest percentages of correct responses related to converting to and from vitamin K antagonist, monitoring, and dosing. In general, neurologists, cardiologists, and haematologists had higher levels of knowledge. Physicians responsible for initiating or converting treatment had higher knowledge than those who were responsible only for maintenance treatment. Physicians who reported receiving information from the PG consistently had higher knowledge than those who did not.

Conclusions: Physicians' knowledge was highest on the most important risks and lower on more complex aspects of safe use that lend themselves to consultation of the PG and/or label rather than reliance on recall.

494. Semi-Quantitative Benefit-Risk Assessment for Dengvaxia

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Background: Dengue disease is a major public health concern in endemic countries. There is no specific treatment available and vector control is not fully effective. Dengvaxia, a Dengue tetravalent vaccine (live, attenuated), has recently been approved in some first countries including Mexico, Philippines, Brazil and El Salvador, for the prevention of dengue disease of any severity caused by serotypes 1, 2, 3 or 4 with a 3 doses schedule 6 months apart in individuals 9 through 45 years of age living in endemic areas.

Objectives: A benefit/risk analysis was performed in individuals aged 9-60 years before registration.

Methods: In the absence of alternative vaccine or treatment, benefits and risks were assessed using the PrOACT-URL method. Favorable and unfavorable effects at individual and population levels were established, using i) data from 13 completed and ongoing clinical studies in more than 20,000 subjects aged 9-60 years who received at least one dose of Dengvaxia, and ii) hypotheses considering what we know from other vaccines.

Results: Overall, identified and potential favorable and unfavorable effects were considered, e.g. protection against symptomatic dengue disease (with a pooled efficacy of 65.6% [95% CI 60.7-69.9] during the first 25 months after first vaccination for those aged 9 years or above), protection against hospitalization, protection against severe disease, potential risk of increase in severity of dengue disease, potential risk of allergic reactions. For each of them, we attributed a probability of occurrence with associated uncertainty, and a qualitative ranking in terms of impact at the individual and population levels (from low to very high).

Conclusions: The benefit/risk balance of the dengue vaccine appears positive for the prevention of dengue disease in individuals aged 9-60 years living in endemic areas.

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495. Traditional vs. HIV-Specific Cardiovascular Disease Risk Scores in Persons Living with HIV

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Background: Cardiovascular disease (CVD) risk scores are used to guide treatment decisions for lipid-lowering drugs. Most risk scores are based on HIV-uninfected cohorts and do not include HIV-specific risk factors or include outdated antiretroviral medications without potentially more relevant factors such as CD4 count.

Objectives: Determine if including HIV-specific risk factors can improve discrimination for a CVD risk score.

Methods: Observational study of persons living with HIV (PLWH) at 5 US sites in the CNICS cohort. PLWH were followed until type I or II myocardial infarction (MI), death, loss to follow-up or administrative censoring. MIs were centrally adjudicated and the risk score endpoint was fatal and non-fatal MIs, both type I and II. The sample was split into training and test sets. The 2013 AHA/ACC Pooled Cohort Equation (PCE) was calculated and 2 new scores were generated in the training set from traditional CVD risk factors and HIV viral load (VL), CD4 count, antiretroviral use, and protease inhibitor (PI) use. The first score (C-Lasso) used lasso and ridge regression and the second (C-BMA) used Bayesian model averaging and Cox models to select variables and find coefficients. Scores were evaluated in the test set by calculating the Harrell's C (HC) and Hosmer-Lemeshow (HL) goodness of fit tests.

Results: 15849 PLWH (mean age 40, 79% male, 39% black race) had 353 MIs during a mean 4.8 years of follow-up. PCE had a HC of 0.71 (95% confidence interval 0.67,0.75) and a HL test statistic of 214 ($p<0.01$). C-lasso included all potential covariates and several interactions, and the HC was 0.74 (0.70,0.77). C-BMA included black race, hypertension medication, PI use, diabetes, age, smoking, HDL, systolic blood pressure, VL, and CD4 and had a HC of 0.72 (0.68,0.76). The HC of the 2 new scores were not significantly higher than that of PCE. The HL test statistics of the new scores were 45 for C-lasso and 27 for C-BMA, and all scores showed significant lack of fit.

Conclusions: PCE showed good discrimination in CNICS and the scores with HIV-specific risk factors did not improve prediction in this population. PCE is probably acceptable for determining CVD risk in PLWH.

496. Quantitative and Qualitative Methods to Support Therapeutic Risk Minimization Efforts

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Background: A comprehensive approach to therapeutic risk management ranges from assessing the need for additional Risk Minimisation (RM) to evaluating their effectiveness. Communication is a key tool for Pharmacovigilance and RM. While pharmacoepidemiology remains invaluable for risk quantification and safety outcome evaluation, complementary approaches, including qualitative research methods are needed to ensure effective RM.

Objectives: To describe qualitative research methods applied to RM.

Methods: Usability Testing (UT) and Linguistic Validation (LV) are applied to RM efforts. UT uses iterative interviews of target individuals to identify and rectify vulnerabilities in written communication. Open-ended questions are scored against pre-defined indicative answers, while semi-structured questions yield qualitative feedback. LV ensures culturally adaptation and validation of questionnaires used in RM surveys. The procedure includes concept elaboration and pilot testing in the form of cognitive debriefing interviews.

Results: We developed a stepwise model for RM including: to assess the need for additional RM, select

and design RM tool(s), distribute the tools and evaluate their effectiveness with process and safety outcome metrics. Case studies will show the model and how UT and LV can optimize RM efforts. For instance, UT was conducted to confirm format and structure validity of a prescriber guide developed as additional RM tool. Iterative interviews of 5 physicians led to format and words changes. At round 2 of testing, all information items on the guide passed the testing criteria: At least 90% of participants could find each item; of these at least 90% understood it correctly. Questionnaires were developed ad hoc to run a healthcare professional and patient survey in 6 EU countries. LV was conducted to ensure translations were adapted to cultural differences across countries. Minor adjustments were required in all languages. Overall respondents were able to understand the questions in all languages.

Conclusions: RM requires a combination of methodologies, including qualitative research methods to reach effective communication and appropriate evaluation of RM interventions.

497. Additional Risk Minimisation Measures to Prevent Medication Error in the EU

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Background: Medication Error (ME) is an unintended failure in a treatment process that may lead to patient harm. ME can relate to prescribing, storage, dispensing, preparation and administration of medicines. ME represents a public health and financial burden in EU. The EU pharmacovigilance legislation of 2010 includes legal provisions for the reporting, evaluation and prevention of ME. Good Vigilance Practice (GVP) guidance was released late in 2015 to support legislation implementation and to guide ME management. This analysis provides an overview of additional Risk Minimisation Measures (aRMM) addressing ME, since therapeutic risk management was first introduced to date.

Objectives: To describe aRMM imposed to prevent ME in the period 2006-2015.

Methods: We reviewed the European Public Assessment Reports (EPAR) database to identify medicinal products first authorised between 1/1/2006 and 31/12/2015. The number and percentage of products with aRMMs targeting ME, as defined in the GVP, were computed by calendar year and stratified by target population and scope of intervention. Measures of effectiveness were also reviewed.

Results: The EPAR database included 550 non-generic products, of which 144 had aRMM. In 32 products (22.2%), aRMM were imposed to prevent or minimise ME. The yearly frequency increased during the study period up to 66.7% (n=8) and 31.6% (n=6) in 2014 and 2015 respectively. The aRMM addressing ME were more prevalent among products in the ATC category of nervous system (6/32), alimentary tract (5/32) and antineoplastic and immunomodulators (5/32).

Additional RMM consisted of educational tools targeting prescribers/nurses (29/32), patients (14/32) and pharmacists (4/32). ME were mostly potential risks (22/32) and included failure of administration devise (n=5) or misreading of diagnostic images (n=3). Effectiveness of aRMMs were described for 13/32 products, and included surveys (n=6) and drug utilisation studies (n=4).

Conclusions: This review shows that over 20% of aRMM imposed between 2006 and 2015 targeted ME. This frequency increased over time, most notably in 2014 and 2015. Further analyses will be needed to monitor any impact of the most recent GVP guidance on ME.

498. Utilization Heterogeneity of Aromatase Inhibitor Agents for Breast Cancer Treatment in a US Medicare Population

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Background: Third generation aromatase inhibitor (AI) agents approved for post-menopausal breast cancer(BC) treatment in United States have unknown clinical differences. Heterogeneity in individual AI agent utilization remains poorly characterized.

Objectives: Elucidate potential utilization heterogeneity of individual AI agents for BC treatment by clinical and population characteristics.

Methods: Female BC patients, aged 65 and older, with Medicare Part D benefits, newly diagnosed breast cancer in 2007, and antiestrogen BC therapy

utilization were identified(n=5,587) in a SEER-Medicare linked United States(US) 6 state sample. Median (range) age at diagnosis was 74(65–90) with 28(0-35) months of observation following BC diagnosis. The majority (82.8%) of patients were Caucasian. Patient exposure to individual AI agents exemestane, anastrozole, and letrozole were the outcomes of interest, instances of overlap were removed from the cohort. Utilization heterogeneity was evaluated using chi-square analysis of US state of residence, tumor stage, zip code density, and zip code median income. Density and income measures were stratified across all zip codes contained within a 5% control sample corresponding to sampled US states.

Results: AI agent utilization for exemestane 25(15-369), anastrozole 258(194-3,536), and letrozole 134 (64-1,271) varied by state. Significant AI agent heterogeneity by state was observed for exemestane ($\chi2=11.6$,$p=0.041$), anastrozole($\chi2=18.6$,$p=0.002$), and letrozole($\chi2=24.7$,$p<0.001$). Tumor stage was associated($p<0.001$) with all AI agents utilization. Zip code density was associated($p<0.005$) with anastrozole and letrozole. State, tumor stage, and zip code density were associated($p<0.005$) with anastrozole and letrozole utilization in an additive age-adjusted model.

Conclusions: While potential generalizability is limited to an aged Caucasian US population of post-menopausal women, anastrozole and letrozole utilization appears to vary by US state, population density, and tumor stage. AI agent utilization heterogeneity appears to be potentially attributed to both clinically relevant and population characteristics.

499. Does Concordance with Fixed-Dose Combination (FDC) Treatment Guidelines Improve Persistence? An Australian Population Based Cohort Study

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Background: In Australia, FDC products are not recommended for first-line hypertension therapy. While the use of FDCs has increased substantially in recent years, there is little information about how their use in routine care compares to Australian guidelines.

Objectives: We investigated how first-line antihypertensive therapy followed Australian recommendations, and the impact of initiation outside recommendations on treatment discontinuation in the first year.

Methods: We performed a population-based retrospective cohort study using dispensing data for a 10% sample of Australians (2005-2014). Among incident users of antihypertensive medicines, we identified whether the choice of antihypertensive adhered to Australian recommendations. We used logistic regression to determine whether adhering to guidelines at initiation was associated with discontinuation of initial therapy, and discontinuation of any therapy in the first year of treatment.

Results: In our sample of 55 937 persons initiating therapy, 5.0% initiated on a FDC. Persons initiating FDCs had a higher median initiating defined daily dose (DDD) for angiotensin-converting-enzyme inhibitors/angiotensin II receptor antagonists (2 vs 1, $p<0.001$), but a lower median DDD for thiazide diuretics (0.5 vs 1, $p<0.001$). In the first year, 47.5% of those who used a FDC were dispensed at least one of the individual medicines that formed part of the FDC prior to switching; only 1.7% were dispensed both (as recommended). After adjusting for covariates (including dose), persons initiating on FDCs were more likely to discontinue their initial therapy (OR=1.20, 95% CI 1.09-1.32) as well as all antihypertensive drug treatment (OR=1.42, 95% CI 1.30-1.55) in the first year compared to persons treated according to the recommended monotherapy.

Conclusions: In Australia, FDCs are being used outside guideline recommendations and often start with higher doses. Initiation on FDCs and other non-recommended treatments was associated with lower persistence on antihypertensive therapy in the first year. Long term effectiveness and outcomes may be enhanced by initiating with low dose monotherapy.

500. Characterization Of Pregnant Women With Pre-Gestational Diabetes In the UK

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Background: Around 3% of pregnancies are affected by pre-gestational or gestational diabetes. However, little is known about the pharmacologic management of diabetes and glycaemic control during pregnancy in clinical practice.

Objectives: To describe both the prescription patterns of antidiabetic medications by general practitioners and the glycaemic control in pregnant women with pre-gestational diabetes in the UK.

Methods: We used electronic medical records from The Health Improvement Network (THIN) database from January 1995-June 2012 to identify the first pregnancy in women 15 to 45 years of age with pre-gestational diabetes type 1 or type 2. Information on prescription of specific antidiabetic medications as well as glycaemic control measures (HbA1c) was obtained from primary care provider records. Glycaemic control was categorized according to HbA1c units as good <=7%) or poor >7%). We evaluated treatment patterns within 90 days before the last menstrual period (LMP) and per trimester of pregnancy, and HbA1c during the year before pregnancy and per trimester.

Results: In a cohort of 1511 pregnant women with pre-gestational diabetes, 60% had type 1 and 40% type 2. The prevalence of antidiabetic medication prescriptions was 76% during the pre-pregnancy period and 80% during the 1st trimester (69% received insulin and 19% oral antidiabetics with or without insulin). Among those treated at LMP, 6.8% discontinued while 35% of those non-treated initiated treatment by the 1st trimester. The proportion of women with at least one HbA1c value recorded within the year prior to LMP were 76% for type 1 and 70% for type 2. Among women with recorded HbA1c, the prevalence of HbA1c>7% before pregnancy was 74% for type 1 and 48% for type 2. Those proportions remained similar in the 1st trimester but came down to 35% in the 2nd and 33% in the 3rd trimesters for both subgroups.

Conclusions: The majority of women received treatment before and during pregnancy. Glycaemic control was worse among women with type 1diabetes and, although it improved during pregnancy, one third of women still had at least one elevated HbA1c measurement throughout pregnancy.

501. Patient Characteristics Associated with Persistent Tramadol Use for Patients with Chronic Non-Cancer Pain in U.K. General Practices

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Background: The persistent use of tramadol in patients with chronic non-cancer pain (CNCP) has been suggested to be associated with increased tramadol-related deaths in the United Kingdom (U.K.). However, no study has explored factors associated with persistent tramadol use in CNCP patients in the U.K.

Objectives: This study aimed to identify factors associated with persistent tramadol utilisation for patients with CNCP in U.K. general practices.

Methods: Retrospective cohort study used the Clinical Practice Research Datalink from 2000 to 2011. Adult patients (≥18 years) prescribed tramadol during study period with no cancer diagnosis before index date (first tramadol prescription) were included and followed from index date to the end of registration or end of study. Persistent tramadol use was defined as a patient received tramadol at least 3 quarters and more than tramadol 15000 mg in the first patient-year. Demographics, disease history, medication use in 6 months prior to index date and persistency of tramadol use of each patient were measured. Logistic regression was used to assess the association between patients' characteristics and tramadol persistent use, the results were presented as odds ratio (OR) and 95% confidence interval (CI).

Results: Overall, 81414 of 383725 (21.2%) tramadol users were persistent tramadol users. Male (OR: 1.25; 95%CI: 1.17, 1.33; p<0.001) patients and those aged 40-65 years (OR: 1.21; 95%CI: 1.07, 1.36; p=0.002) were more likely to use tramadol regularly.

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Patients with arthritis (OR: 1.34; 95%CI: 1.23, 1.48; p<0.001) were more likely to become persistent tramadol users when compared with patients with low back pain. Patients taking higher dose of weak opioids (OR ranged: 1.56, 5.6; all p<0.001) and tricyclic antidepressants (OR ranged: 1.32, 2; all p<0.001) prior to tramadol initiation had an increased odds of using tramadol persistently.

Conclusions: Patients with arthritis and those taking weak opioids or tricyclic antidepressants were more likely to become persistent tramadol users. Further research is needed to evaluate tramadol related deaths and adjusting for these baseline characteristics.

502. Patterns of Tiotropium Dispensing in the United States and Impact of FDA Drug Safety Communications

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Background: Tiotropium is indicated for chronic obstructive pulmonary disease (COPD). The FDA issued two drug safety communications (DSCs) related to the cardiovascular safety of tiotropium, one in March 2008 warning of a potential increase in stroke risk and a follow-up communication in January 2010 informing of an absence of a strong signal related to cardiovascular events based on findings from a large trial.

Objectives: To evaluate the impact of the two safety communications in a large US claims database.

Methods: Monthly dispensing rates for tiotropium initiators among 103,063 COPD patients ages 40 years and older were calculated from 2006-2012 using the IMS LifeLink database. Dispensing rates for long-acting β-agonist (LABA) initiators were also evaluated to explore product switching. The characteristics of patients starting treatment around the FDA safety communications were examined. Patterns in dispensing rates in the two treatment groups were examined and changes in trend before and after the safety communication dates were evaluated using interrupted time-series analysis (ITS). Subgroup analyses of patients with greater cardiovascular (CV) risk (e.g., CV comorbidity and patients 65 years and older) were performed.

Results: A decreasing trend in dispensing rates was present prior to the initial DSC in 2008. ITS analyses suggest the early DSC caused an immediate 2.8% (p-value=0.02) reduction in tiotropium initiation with a continuous decreasing trend (-0.09% per month) until the second DSC. The dispensing rate increased 2.5% (p-value=0.03) immediately after the second DSC, reducing the overall decline in rate and stabilizing the trend. Dispensing patterns in LABA initiators suggest potential product switching. No significant changes in dispensing level or trend were observed among COPD patients with CV comorbidity (p-values>0.05).

Conclusions: Decreased tiotropium dispensing was detected immediately following the initial DSC; however, the second DSC was associated with a reversal of the decline. Future studies are needed to evaluate the patterns among older populations and within-patient treatment patterns.

503. In-Hospital Antipsychotic Use Among Elderly Patients Discharged to Nursing Homes

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Background: High antipsychotic use persists in nursing homes (NHs) despite federal intervention including boxed warnings from the Food and Drug Administration (FDA) and prescribing regulations from the Centers for Medicare and Medicaid Services (CMS). Nearly half of NH residents on antipsychotics initiate therapy before the NH admission. No estimates of initiation in hospital settings exist.

Objectives: To estimate trends in the prevalence and incidence of antipsychotic use among elderly patients in hospital settings between 2000 and 2012.

Methods: We identified 297,127 hospitalizations from 189,225 unique patients aged ≥ 65 years without schizophrenia, Tourette's syndrome, or Huntington's

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disease discharged from 104 hospitals in the United States to nursing homes between 2000 and 2012 using Cerner HealthFacts data. We estimated the prevalence of antipsychotic use on the day of hospital admission. Among those without an antipsychotic medication recorded on the day of admission, we estimated the proportion with a medication record for an antipsychotic at some point later in the hospital stay. A random effects logistic model was used to test for trends while adjusting for clustering of patients within hospitals.

Results: On the day of admission, 15.3% received an antipsychotic. Yearly estimates varied through time (13.7% in 2000, 19.7% in 2007, 12.6% in 2012). Haloperidol was most commonly prescribed (47%), followed by quetiapine (18%), and risperidone (10%). Nine percent initiated an antipsychotic during the hospital stay (range: 17.1% in 2000 to 6% in 2012; (p for monotonic trend < 0.0001)). Once initiated, 70% had orders for an antipsychotic on the day of hospital discharge.

Conclusions: In a frail population of elderly persons discharged to NHs, antipsychotic use was common at admission, and commonly initiated in this setting. CMS efforts to develop a hospital-based quality indicator to address the concern of initiation of antipsychotics in hospital are warranted.

504. Use of New Oral Anticoagulants in the Secondary Care Setting vs Primary Care in the UK: Interim Results from Two Post-Authorisation Studies

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Background: The Risk Management Plan for rivaroxaban (Riv) included studies on the utilisation and safety monitoring of Riv prescribed in primary care (a Modified Prescription-Event Monitoring (M-PEM) study; all indications) and secondary care (a Specialist Cohort-Event Monitoring (SCEM) study; selected indications incl. prevention of stroke and systemic embolism in non-valvular atrial fibrillation (AF)).

Objectives: An ad hoc interim analysis to describe the baseline bleeding risk characteristics of two interim study Riv cohorts with AF.

Methods: Both studies used an observational cohort design. Data (incl.selected pt baseline characteristics as per HAS-BLED) were collected from forms sent to specialists in secondary care Sep 2013 to Mar 2015 (datalock) and General Practitioners (GPs) in primary care Dec 2011 to Jul 2015 (datalock). Descriptive statistics & univariate analyses [OR (95%CI)] were calculated (% denominator assumes no missing data). AF cohorts exclude pts with >1 indication.

Results: Interim AF cohort; SCEM=641, 53% male; M-PEM=4764, 52% male. SCEM pts were more likely than M-PEM pts to have a history of stroke [39% vs 14%; OR 3.9 (2.3,4.7)], uncontrolled hypertension [3% vs 1%; OR 3.8 (2.2,6.6)], clinical predisposition to bleeds [4% vs 2%; OR 1.7 (1.1, 2.7); or use drugs predisposing to bleeds [2% vs 1%; OR 3.5 (1.7,6.9)]. Baseline prevalence of abnormal liver function, renal disease, excess alcohol use & age 65+ yrs in the 2 cohorts were similar. The HAS-BLED score distribution differed (ranksum $p<0.001$); HAS-BLED$\geq$3 [6%vs 2%; OR 3.3 (2.3, 5.0)].

Conclusions: In this ad-hoc analysis, SCEM AF pts appeared to have a higher burden of baseline bleeding risk factors than M-PEM AF pts. This appears to be as expected within healthcare systems, where complex pts with multiple morbidities may be managed by specialists in secondary care. Considerations include differences in the recording of data in medical records held by specialists compared to GPs and interim cohort sample size. Nevertheless, these findings support the need for systematic surveillance across healthcare settings to evaluate full spectrum of pts at risk.

505. Poor Adherence With Non-Vitamin K Oral Anticoagulant (Dabigatran, Rivaroxaban) Among Patients With Nonvalvular Atrial Fibrillation Initiating Anticoagulant Therapy In 2013 In France. A Cohort Study On The French Healthcare Databases

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Background: As a more convenient alternative to Vitamin K antagonists (VKA) for which poor adherence is a common problem, non-VKA Oral Anticoagulants (NOAC), dabigatran and rivaroxaban, have been

promoted for the prevention of stroke in patients with nonvalvular atrial fibrillation (nv-AF).

Objectives: To describe adherence rates of nv-AF patients to dabigatran and rivaroxaban in the year following treatment initiation.

Methods: This study included VKA-naïve patients with nv-AF who initiated dabigatran (110mg/150mg) and rivaroxaban (15mg/20mg) between 2013 January 1st and June 30th; using data from the French National Health Insurance databases (SNIIRAM-PMSI) general scheme (almost 50 million people, 75% of the French population). Patients presenting a contraindication or discontinuous enrollment were excluded. One-year adherence was defined using the proportion of day covered (PDC, ratio of total days supplied divided by 360-day follow-up duration after treatment initiation) of 80% or more. Sub-group analyses were performed after excluding patients who i) died; ii) died or switched to VKA or another NOAC, during the 360 day-follow-up period.

Results: Study included 11,742 patients treated with dabigatran (men: 52%, mean age: 73.7±11.0 years, 80 and over: 34.5%) and 11,710 with rivaroxaban (men: 54%, mean age: 73.7±11.1y, 80 and over: 34.3%). During follow-up, switch towards VKA was observed in 14.5% dabigatran and 11.7% of rivaroxaban patients; 10.2% and 5.9% switched towards another NOAC (including apixaban); 4.4% and 4.3% died, respectively. The proportion of adherent patients was 51.8% (i: 53.8%; ii: 67.6%) in dabigatran- and 58.3% (i: 60.6%; ii: 70.5%) in rivaroxaban-treated patients.

Conclusions: One-year adherence to NOAC therapy is poor in French nv-AF patients initiating anticoagulant treatment. Reinforced teaching of both patients and prescribers regarding the benefits of optimal adherence may help to guarantee translation of trials results to clinical practice.

506. Neurodevelopmental Problems At 18 Months Among Children Exposed To Paracetamol *In Utero* – A Propensity Score Matched Cohort Study

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Background: Prior studies showed that children exposed to paracetamol during fetal life might have an increased risk of neurodevelopmental problems. Since paracetamol is one of the most commonly used medications during pregnancy, even small increases in the risk of neurodevelopmental problems may have considerable implications for public health.

Objectives: To examine associations between prenatal paracetamol exposure and neurodevelopmental problems among children at 18 months.

Methods: Using data from the Norwegian Mother and Child Cohort Study, we applied propensity score (PS) matching to examine associations between prenatal paracetamol exposure and neurodevelopmental problems among children at 18 months. Paracetamol use was classified into short-term <28 days) and long-term (≥28 days) exposure.

Results: Of the 51 200 pregnancies included in our study, 40.5% of mothers (n=20 749) used paracetamol at least once during pregnancy. In the PS-matched analyses, long-term paracetamol exposure during pregnancy was associated with communication problems (OR: 1.38, 95% CI 0.98-1.95) and delayed motor milestone attainment (OR: 1.35, 95% CI 1.07-1.70). We did not observe increased risks after short-term exposure. Sensitivity analyses for several indications showed similar effects as the PS-matched analyses, suggesting no confounding by indication.

Conclusions: Long-term exposure to paracetamol *in utero* was associated with modestly increased risks of motor milestone delay and impaired communication skills among children at 18 months. Caution is warranted when considering long-term use of paracetamol during pregnancy; however, women with severe pain

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conditions should not be deprived of appropriate pharmacotherapy.

507. Mood Stabilizer Use and Risk of Ischemic Placental Disease

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Background: Anticonvulsant use in pregnancy is increasing, particularly for treatment of bipolar disorder. Some animal and human studies have raised concerns of fetal growth restriction following pregnancy exposure, which may be a manifestation of ischemic placental disease.

Objectives: To determine if the use of mood stabilizers (lithium and specific anticonvulsants) in pregnancy are associated with increased risk of ischemic placental disease and its components (preeclampsia, placental abruption, growth restriction).

Methods: A cohort study was carried out using the Medicaid Analytic eXtract (MAX) data for pregnant women linked to live born infants enrolled in Medicaid, 2000-2010. We assessed the exposure to monotherapy of the following medications during the first 20 weeks of pregnancy: lithium, carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproate. The reference group did not use an anticonvulsant or lithium during the three months prior to conception or the first half of pregnancy. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated using log-binomial regression with propensity score weights to control for confounding.

Results: Among 1,472,672 included deliveries, 10,690 (0.7%) were exposed to mood stabilizer monotherapy. Potential indications for monotherapy were bipolar disorder (39%), migraine (32%), epilepsy (26%), and neuropathic pain (7%); each was associated with all outcomes studied in the untreated. Unadjusted models suggested increased risks of ischemic placental disease, RR (95% CI) 1.33 (1.25-1.41) for any mood stabilizer monotherapy (ranging from 1.16 to 1.54 for each drug), and all individual outcomes. However, results were strongly attenuated with confounder adjustment; adjusted RR for ischemic placental disease 0.90 (0.85-0.97) for any mood stabilizer (ranging from 0.88 to 1.01 for each drug). Null results were seen for all individual drugs and specific outcomes in adjusted models, except for a slight negative association for preeclampsia with any mood stabilizer and valproate monotherapy.

Conclusions: This study suggests that mood stabilizers are not associated with an increased risk of ischemic placental disease after accounting for confounding by indication.

508. Maternal and Infant Characteristics – Differences and Similarities Between the Nordic Countries and the United States

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Background: Data from the Nordic health care registers have been of great value in perinatal epidemiological research. It has been assumed that findings in the Nordic population (Denmark, Finland, Iceland, Norway, and Sweden) are applicable to other populations, such as the population of the United States (US).

Objectives: To describe and compare maternal and infant characteristics between the Nordic and the American populations as recorded in the official statistics.

Methods: This population-based study included data on all women who gave birth, and their infants, in the Nordic countries and the US. The data was obtained from the US National center for Health Statistics and the official statistics from the Nordic countries and included births from 2006 to 2010.

Results: The mean maternal age at delivery was lower in the US than in the Nordic countries (27.5 versus 30.3 years). Cesarean sections (32.2 versus 17.9 percent), low birth weight (8.2 versus 4.8 percent), and preterm birth (12.3 versus 5.9 percent) were more common in the US than in the Nordic countries.

Smoking during early pregnancy was slightly less common in the US compared to the Nordic countries (9.8 versus 11.2 percent). Restricting the data from the US to women with a university degree, characteristics such as age at delivery, birth weight, and preterm deliveries were more in alignment with the Nordic data.

Conclusions: There are differences in some key maternal and neonatal characteristics between the Nordic countries and the US. However, some characteristics are related to socioeconomic status and the Nordic data seems to be applicable to the part of the population in the US with higher SES.

509. Preconception Use of Pain Relieving Medication and Time to Pregnancy: A Prospective Study

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Background: Reproductive-aged women in the United States commonly use pain relieving medications. However, the effects of these medications on fecundability are unknown.

Objectives: To evaluate the association between fecundability and preconception use of pain medications.

Methods: Data were analyzed from Pregnancy Study Online (PRESTO), a North American preconception cohort study. A total of 1763 female pregnancy planners were followed prospectively until self-reported pregnancy, initiation of fertility treatment, loss-to-follow-up, or 12 months, whichever occurred first. Past-month use of acetaminophen, aspirin, ibuprofen, naproxen, and opioids was reported at baseline and at each bimonthly follow-up. Multivariable-adjusted fecundability ratios (aFR) and 95% confidence intervals (CI) were calculated using proportional probabilities regression models. Models were adjusted for demographics, lifestyle and anthropometric factors, reproductive history, gynecologic morbidity, and indications for use of pain medications (e.g. endometriosis, migraine headaches, antibiotic use as a proxy for fever/infection).

Results: At baseline, 1279 (73%) women reported using ≥1 pain-relieving medication in the past month. When compared with non-use of pain relieving medications, use of naproxen (aFR: 0.76, 95% CI: 0.61-0.93) and opioids (aFR: 0.81, 95% CI: 0.59-1.10) was associated with reduced fecundability. There was little evidence of association between fecundability and acetaminophen, aspirin, or ibuprofen. Similar results were observed for baseline and time-varying analyses. Among women younger than 30, acetaminophen use reported at baseline was associated with a 23% increase in fecundability (95% CI: 1.03-1.48); a slight inverse association was observed among women ≥30 (aFR=0.87, 95% CI: 0.72-1.05).

Conclusions: Preconceptional use of pain-relieving medications may influence human fecundability, and associations may vary by active agent. Residual confounding by indication may partially explain these results, warranting further research.

510. A Systematic Review of Enrollment and Retention in US Pregnancy Exposure Registries and Corresponding Pharmacovigilance Systems

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Background: Pregnancy Exposure Registries (PER) and spontaneous reports (SR) are important tools to evaluate medical product safety in pregnancy.

Objectives: To contrast (1) enrollment and retention in PER and (2) capture of SRs for pregnancy exposure, in the context of pregnancy drug utilization data.

Methods: PERs for FDA approved drugs and biologics were identified in a previous systematic review (Jan 2014). A standardized information request (IR) obtained data on (1) enrollment and retention in PERs, capture of birth outcomes, child follow-up, and (2) SR

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for pregnancy exposures in the sponsors' worldwide pharmacovigilance databases. Drug utilization data among 1.9 million live birth pregnancies in the Sentinel Distributed Database were used to quantify real-world exposure of these products in pregnant women.

Results: We identified 37 registries and 34 (91.9%) completed the IR. Median (interquartile range, IQR) PER enrollment is contrasted with median (IQR) capture of SRs and is shown within categories of actual use data, defined as: 1) Not Rare, >20/100,000 Sentinel exposed pregnancies to registry product (n=7 registries): PER enrollment: 810 pregnancies (308-2419), SR: 1097 pregnancies (880-1423); 2) Rare, 0.5-20/100,000 Sentinel exposed pregnancies (n=14): PER: 50 (19-251), SR: 695 (221-2644); 3) Very Rare, ≤0.5/100,000 Sentinel exposed pregnancies (n=13): PER: 4 (2-20), SR: 47 (5-266). Among registries enrolling ≥10 pregnancies (n=23), median retention rate to childbirth was 88.4% (73.3-94.9). For registries with ≥10 children, median retention rate to achieve protocol specified follow-up of >1 day to <6 months (n=4) was 83.4% (47.5-79.23) and >6 months (n=11) was 57.1% (35.0-71.6).

Conclusions: Products with greater use among pregnant women in Sentinel had more successful PER enrollment. Products with rare or very rare use had a larger median number of SRs versus PER enrolled pregnancy exposures, suggesting these products especially may benefit from a comprehensive pregnancy surveillance system with multiple data streams. Most registries had acceptable capture of birth outcomes, although retention decreased with longer follow-up.

511. Antidepressant Use in Pregnancy and the Risk of Attention Deficit with or without Hyperactivity Disorder in Children

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Background: The association between antidepressant (AD) use during pregnancy and the risk of attention deficit with or without hyperactivity disorder (ADHD) in children is controversial.

Objectives: We sought to evaluate the risk of ADHD associated with overall and class-specific antidepressant exposure in-utero.

Methods: We performed a register-population based cohort study, using an ongoing population-based cohort, the Quebec Pregnancy/Children Cohort (QPC), which includes data on all pregnancies and children in Quebec from 1998-2009. Antidepressant exposure during pregnancy was defined according to trimester, and specific antidepressant classes. Children with ADHD were defined as those with at least one diagnosis of ADHD or prescription filled for ADHD medications between birth and the end of follow-up. Cox proportional hazards regression models were used to estimate crude and adjusted hazard ratios (HRs) with 95% confidence intervals.

Results: During 542,897.28 person-years of follow-up, 4564 infants (3.16%) were diagnosed with ADHD. The mean age at first ADHD diagnosis was 6.35 ± 2.33 years (median, 7.00 years) and the mean age at first ADHD medication was 7.00 ± 1.54 years (median, 7.03 years). AD use during the 2nd or 3rd trimester of pregnancy was significantly associated with an increased risk of ADHD (aHR= 1.28; 95% CI 1.03-1.59; 134 exposed cases)) event after adjusting for potential confounders, including maternal history of depression and ADHD; tricyclic ADs use was significantly associated with an increased risk of ADHD (aHR=1.76; 95% CI 1.01-3.06; 16 exposed cases); SSRI and SNRI use were increasing the risk of ADHD but estimates were non-statistically significant.

Conclusions: Our findings suggest that use of ADs during the 2nd or 3rd trimester of pregnancy, specifically tricyclic antidepressants, is an independent risk factor for ADHD in children above and beyond the risk associated with maternal depression or ADHD. Our results are suggesting that medications with serotonergic effect during pregnancy have an impact on the risk of ADHD.

512. Estimation of Gestational Age at Birth Using Claims-Based Algorithms in a Commercially Insured US Population

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Background: Gestational age at birth (GAB) is an essential variable for perinatal epidemiology, although unavailable in administrative claims data. Due to a lack of clinical data needed to estimate GAB, claims-based research has traditionally used a fixed-period of 270-280 days. Claims contain rich information about procedures used during pregnancy that may be leveraged to improve GAB estimation.

Objectives: To develop and evaluate algorithms for the estimation of GAB using claims data.

Methods: A retrospective cohort study was conducted among 28,889 deliveries identified from the HealthCore Integrated Research Database and linked to due date information from a care management program. Six algorithms for estimating GAB were built in a training cohort of 9,812 women and tested in a validation cohort of 19,077 women. Performance of algorithms including fixed-period and those estimated using dates of procedures targeted to specific gestational age intervals (4 algorithms described previously and 2 novel approaches) were compared graphically (plotting distributions of difference between claims-based and due date-based GAB) and by testing the difference in the proportion with claims-based and due date-based GABs within 1 week using McNemar's chi-squared statistic.

Results: The best performing algorithm, the 'weighted procedure date-based average' used procedure date information weighted according to the procedure's time period of recommended use to estimate GAB. The algorithm estimated 67% of all deliveries and 60% of preterm deliveries within 1 week of the due date-based GAB. The proportion of deliveries with estimated GAB within 1 week of due date-based GAB was statistically significantly greater than any other algorithm ($p<.001$ for all comparisons) although other procedure date-based algorithms also performed well.

Conclusions: Claims-based algorithms for estimating GAB based on procedure dates performed better than those assuming fixed-period GAB. In the absence of procedure date information, preterm delivery diagnosis codes should be used to flag preterm deliveries and fixed-periods of 35 weeks for preterm and 39 weeks for non-preterm deliveries should be used.

513. Risk of Infections During the First Year of Life After In Utero Exposure to Drugs Acting on Immunity: A Population-Based Cohort Study

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Background: Antenatal exposure to immunosuppressive drugs has been associated with the alteration of biological immunity parameters. Little is known, however, of the potential effects of in utero exposure to these drugs on the newborn's immunity.

Objectives: The aim of the study was to evaluate the association between in utero exposure to drugs that potentially exhibit immunosuppressive activity and occurrence of infections during the first year of life.

Methods: We conducted a cohort study on the prescription data of pregnant women and their children registered in the EFEMERIS cohort (France), during a one-year period. We classified in utero child exposure according to the number of reimbursements for immunosuppressive drugs during pregnancy. The number of infectious episodes during the first year of life was estimated through the number of anti-infective drugs dispensed. The association between the number of infectious episodes and in utero exposure to immunosuppressive drugs was estimated by a quasi-Poisson regression with adjustment for confounders.

Results: The study population consisted of 9,614 children, 3,141 of whom had been exposed to immunosuppressive drugs during pregnancy. The most frequently immunosuppressive drugs prescribed were corticosteroids. The mean number of infectious episodes during the first year after birth increased with the number of immunosuppressive drugs dispensed during pregnancy. After adjustment for potential confounders, in utero exposure to immunosuppressive drugs was significantly associated with the number of infectious episodes during the first year of life (adjusted RR 1 exposure VS 0 = 1•12, 95% CI 1•07 to 1•18 / RR 2 exposures VS 0 = 1•20, 95% CI 1•12 to 1•29 / RR 3 or more exposures VS 0 = 1•35, 95% CI 1•24 to 1•46).

Conclusions: Intrauterine exposure to potentially immunosuppressive drugs was associated with an increased susceptibility to infections in early childhood.

514. Predictors and Clinical Impact of Indeterminate QuantiFERON-TB Gold Testing in Inflammatory Bowel Disease

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Background: Prescribing guidelines recommend testing for latent tuberculosis prior to and intermittently during therapy with TNF-α inhibitors. Indeterminate (IND) QuantiFERON-TB Gold (QFTG) results are commonly encountered in clinical practice.

Objectives: To determine factors associated with IND QFTG results in inflammatory bowel disease (IBD) patients and whether IND results are associated with delays in therapeutic decision making and IBD-related morbidity.

Methods: This retrospective cohort study included patients with IBD who had QFTG testing from 2009 to 2014. All individuals with IND QFTG results and 2:1 negative controls were abstracted for evaluation. The association between demographic and clinical data at the time of QFTG testing and results was assessed using multivariable logistic regression. Inverse probability-of-treatment (IPTW) regression models were employed to assess the association between IND QFTG result and risk of delay in medication change, therapy interruption, hospitalization, or surgery.

Results: 411 patients with QFTG testing were identified, of which 80 were IND. No patient with an IND result subsequently had a confirmed LTBI. Hospitalization at the time of QFTG (OR 3.8, 95% CI 1.9–7.7) and systemic steroid use (OR 4.4, 95% CI 2.0–9.6) were associated with IND QFTG, but immunomodulator use (OR 3.1, 95% CI 0.9-9.8) and TNF-α inhibitor use (OR 0.9, 95% CI 0.2–4.6) were not. IND QFTG was associated with a 11.1% (95% CI 0.2–22.1%) greater probability of hospitalization or re-hospitalization in 60 days and a 18.1% (95% CI 8.8–27.4%) greater probability of a delay in planned initiation or change of TNF-α inhibitor therapy.

Conclusions: Systemic steroid use and hospitalization were associated with increased odds of an IND QFTG result, and IND QFTG results were associated with subsequent hospitalization and delay in initiation of TNF-α inhibitor therapy compared to negative results. Clinicians should consider earlier QFTG screening when possible to avoid such delays in care. Moreover, pre-test probability of tuberculosis exposure should be taken into account when interpreting IND results.

515. The Development And Evaluation Of A Dynamic Risk Model For Hospital Associated Hyperkalemia

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Background: Hyperkalemia is a common and potentially life-threatening adverse event in the hospital setting. Risk factors (RFs) for hyperkalemia are well-described. With the advancement of hospital electronic health record (EHR), it is of great interest to construct a fully-automated, score-based alert system that can extract known RFs directly from EHR to flag patients at highest risk of developing hospital associated hyperkalemia and at greatest need for intervention.

Objectives: To build a dynamic risk prediction model for hospital associated hyperkalemia and evaluate its predictive performance.

Methods: Our retrospective cohort included all admitted adults from the two largest UF affiliated hospitals between 1/1/2012-11/1/2013. Hyperkalemia was defined as (1) having two abnormal serum potassium values (≥5.5 mmol/L) within 6 hours or (2) having one abnormal value and subsequent medication treatment within 12 hours. 36 RFs identified from literature were operationalized using discrete EHR data elements. For each of the first 5 hospital-days, we modelled the probability of developing hyperkalemia at the subsequent hospital-day using logistic regression. Predictive performance of our model was

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validated with 100 bootstrap datasets and evaluated by c-statistics and Hosmer–Lemeshow (HL) test.

Results: The prevalence of hyperkalemia events across 262,314 hospital-days was 0.4% (1,042 events). The validated c-statistics for our models ranged from 0.81(Day2) to 0.89(Day1) and the HL test p values ranged from 0.037(Day2) to 0.089(Day1). For the Day1 prediction, 8.2% of patients with risk scores in the 95th percentile developed hyperkalemia and accounted for 63.9% of all events. Predictors that consistently remained significant ($p < 0.05$) across all modelling days included most recent highest potassium value, renal impairment, acidosis and use of vasoactive beta agonists.

Conclusions: Our model achieved excellent discrimination and adequate calibration ability. Once externally validated, this risk assessment tool could be used to prospectively identify individuals at risk for hyperkalemia and thus guide effective prevention.

516. Benefit-Risk of Artemether-Lumefantrine versus Artesunate-Amodiaquine for Uncomplicated Malaria in Under 5 Year Olds in Ghana Using the PhRMA BRAT Framework

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Background: Allopathic medicines are associated with both benefits and risks. These qualities need to be considered concurrently during the life cycle of all medicines. In sub-Saharan Africa there are regional differences in the choice of anti-malarials which are based exclusively on empirical information.

Objectives: To compare benefits and risks of artemether-lumefantrine (AL) and artesunate-amodiaquine (ASAQ), among under 5 years old children in Ghana using the PhRMA BRAT framework.

Methods: Design: The literature was reviewed for all clinical trials (randomized controlled trials) done in Ghana using the two drugs. Search engines used were Embase, Pubmed and Cochrane Library. Various such terms were used to extract publications. The inclusion criteria were a study looking at both medicines concurrently, done in Ghana, and that considered both benefits and risks.

Setting: Under 5 years old with uncomplicated malaria in Ghana.

Exposure: Treatment with AL or ASAQ.

Main outcome measure: The main outcome (benefit) of interest was absence of parasitaemia on day 28 post-treatment after adjusting for genotyping using PCR. Risks were the reported adverse events after treatment.

Statistical analysis: Tabular and graphical displays were generated. Value trees were made using the odds ratios of benefits and risks. This was followed by key benefit-risk summary tables and corresponding Forest plots using risk differences. All analyses were done using SAS version 9.3.

Results: Only one study satisfied all the inclusion criteria. For benefits the odds ratio (OR) comparing AL to ASAQ was 1.1 (95% CI 0.84 to 1.45); the risks identified comparing AL with ASAQ were anaemia (OR, 0.79 [95% CI 0.66 to 0.96]); respiratory symptoms (OR, 0.87 [95% CI 0.71 to 1.08]); gastrointestinal symptoms (OR, 0.79 [95% CI 0.58 to 1.07]); and dermatological symptoms (OR, 0.65 [95% CI 0.35 to 1.20]). Odds ratio for serious adverse reactions was 1.00.

Conclusions: Although AL shows better benefit-risk profiles compared to ASAQ according to this study, most of the associations are not significant. This may account for the regional choice differences.

517. Knowledge, Attitude, and Perception of Parents Towards Antibiotics Use for Upper Respiratory Tract Infections in Children in Holy Makkah, Kingdom of Saudi Arabia

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Background: Upper respiratory tract infection is most frequently reported among children. Majority of such infections are viral oriented and does not require antibiotics. Parent's attitude and perception may result to inappropriate antibiotics use, resulting to antimicrobial resistance in general.

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Objectives: Aim of this study was to study and analyze parental belief about antibiotics use for children with upper respiratory infections in Holy Makkah, Kingdom of Saudi Arabia, where most parents can access community pharmacy and obtain antimicrobials by pharmacist.

Methods: A knowledge attitude practice questioner was adopted from previous study conducted in Greece by Panagakou et al. Study was conducted during September till December 2015. The sample of the study contained parents from different areas of Makkah region. Simple random stratified sampling was used to select representative sample of parents.

Results: Five hundred & fifty six parents completed the questioner. Most of the mothers (95%) responded among parents. 67% were having no health insurance to cover medications costs. Most of them (74%) were related to medium income level. Seventy percent of the parents believed physicians as a source of information for judicious antibiotics use. Interestingly, only 8 percent were agreed that most of the upper respiratory tract infections are caused by viral reasons. Majority of Saudi parents (53%) expect pediatricians to prescribe antimicrobials for their children for symptoms like cough, nose discharge, sore throat and fever.

Conclusions: Majority of Saudi parents believe on pediatricians and use antibiotics on physicians advice. Most of them expect antibiotics from their physicians as primary treatment for upper respiratory tract infections. There is need of more educational activities to parents by pharmacist to prevent antibiotics overuse among children.

518. A Qualitative Study to Identify Interventions to Reduce Pain or Syncope Related to Adolescent Vaccination

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Background: There has been little research into the perspectives of patients, parents, and healthcare providers regarding recommended, but not widely implemented, strategies for pain management and syncope that may improve the adolescent vaccination experience and future receipt of vaccinations.

Objectives: To qualitatively assess patient, parent, and provider preference for and acceptance of strategies to reduce acute pain and syncope associated with adolescent vaccination.

Methods: We employed qualitative research methods to identify interventions for reducing pain and preventing syncope among adolescents undergoing vaccination at Kaiser Permanente Northwest (KPNW). We conducted focus groups with recently-vaccinated 11-17 year-olds and their parents to explore perceptions of adverse events associated with vaccination and receptivity to potential interventions. We interviewed clinical staff who provide patient care during vaccination. A qualitative methodologist conducted the focus groups and interviews and content analysis to identify promising interventions for presentation at a data synthesis workshop to identify approaches to be piloted in KPNW clinics.

Results: Patients, parents, and provider were generally receptive to recommended interventions. More specific feedback included:

- Willingness to use pre-visit education, breathing exercises, social support or distraction, and water consumption; interest in a list of options for interventions at start of visit
- Mixed reactions to topical anesthetics and negative reactions for caffeine consumption
- Need for verbal education and messaging about potential outcomes following vaccination
- Emphasis on identification of patients who are anxious about vaccination prior to visit
- Provider emphasis on interventions that could be conducted within limited clinical time.

Conclusions: Patients, parents, and providers acknowledged the value of interventions to reduce pain and syncope following adolescent vaccination. The results of the qualitative study are being vetted through a data synthesis workshop. Interventions developed in that workshop will be piloted at KPNW clinics.

519. Drug Safety of Macrolide and Quinolone Antibiotics in a Tertiary Care Hospital: Administration of Interacting Comedication and QT-Prolongation

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Background: Some macrolide and quinolone antibiotics (MQAB) are associated with QT-prolongation and life-threatening torsade de pointes arrhythmia (TdP). MQAB may also inhibit cytochrome P450 isoenzymes and thereby cause pharmacokinetic drug-drug interactions (DDI). There is limited data on the frequency and management of such risks in clinical practice.

Objectives: This study aimed to quantify co-administration of MQAB with potentially interacting drugs and associated adverse events.

Methods: We conducted an observational study within our pharmacoepidemiological database derived from electronic medical records of a tertiary care hospital. Among all users of MQAB associated with TdP we determined the prevalence of additional QT-prolonging drugs and risk factors for TdP, and identified contraindicated co-administrations of simvastatin, atorvastatin or tizanidine. ECG-monitoring and associated adverse events were validated in medical records.

Results: Among 3444 administered courses of clarithromycin, erythromycin, azithromycin, ciprofloxacin, levofloxacin or moxifloxacin there were 1332 (38.7%) with concomitant use of additional QT-prolonging drugs. Among those we identified 7 events of related QT-prolongation, but 49.1% had no ECG-monitoring. Of all MQAB users 547 (15.9%) had hypokalemia. Thirty-one MQAB users had contraindicated co-administrations of simvastatin, atorvastatin or tizanidine, and 3 of those related adverse events.

Conclusions: In the studied real-life setting we found a considerable number of MQAB users with additional risk factors for TdP but no ECG monitoring. However, adverse events were rarely found, and costs vs. benefits of ECG monitoring have to be weighted. In contrast, avoidable risk factors and selected contraindicated pharmacokinetic interactions are clear targets for implementation as automated alerts in electronic prescribing systems.

520. Media Monitoring Of The HPV Vaccines Debate – What The Public Wants To Know And Experts Should Address

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Background: Vaccine benefit-risk (BR) is debated in the media. Utility of media monitoring (MM) for ensuring that public concerns and information gaps are covered by BR assessment and communication is unclear.

Objectives: Use of EU review of adverse events (CRPS, POTS) with HPV vaccines as test for MM utility. Determine impact of media debate on spontaneous reporting. The test should also inform communication strategies for vaccine BR monitoring methods currently developed by ADVANCE.

Methods: Daily MM of worldwide online news in most EU languages Sep-Dec 2015 for HPV vaccines (Cision® software). Analyses of topics, concerns and information gaps; translation into virtual questions. 'All ADRs' reporting rates in EudraVigilance for HPV vaccines Jul-Dec 2015. Evaluation of MM utility for the European Medicines Agency (EMA).

Results: About 60-100 news items were identified daily. Weekly reports presented item numbers, geography, topics and considerations for communication. Topics varied geographically and were categorized in 17 positive or negative themes. 5 major peaks were related to certain news. ADR reporting rate in July, when EU review started, doubled vs monthly average in Q1/2 2015 and stayed significantly above this average in Q3/4. The public debate moved from personal stories to scientific points. The virtual questions behind public concerns and information gaps could be grouped into 12 question areas. The public had wide information needs about assessment scope, data, case definitions, underreporting, epidemiological methods, causal pathways, vaccine effectiveness, independence and legislation. MM helped assessors and decision-makers to ensure that public concerns were covered by the assessment and that adequate details in public statements and press briefings were provided about the PRAC outcome in Nov. MM predicted all questions journalists raised in the press conference.

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Conclusions: The test demonstrated MM utility. Media debate may increase spontaneous reporting. MM provides important feedback to medicines safety experts for researching and presenting what the public wants to know, to support trusted, safe and effective use of medicines.

521. Methodologies to Assess the Benefit and Risk Balances and Examples in Vaccines

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Background: The benefit and risk balance of a pharmaceutical product represents a key indicator for the decision-makers and the regulatory agencies. Based on an objective, transparent, evidence-based and critical appraisal of each component, a variety of methodologies have been developed in the last decades. However, the majority was designed for the benefit risk assessment of common drugs.

Objectives: To review the different methods, identify the vaccines-related variations and provide examples of the current methods used for vaccines.

Methods: An extensive literature review was performed in Medline, Embase and The Cochrane Library. All articles were scrutinized and selected if they presented a specific method or an example of benefit and risk assessment. A descriptive analysis of each method was carried out and published examples focused on vaccines were searched.

Results: In total, 29 methodologies for benefit and risk assessments were identified through the literature review. Most of them were focused on a quantitative approach only. Three recent methods consisted of a mixed framework including both quantitative and qualitative data: BRAT – ACIP GRADE and ProACT URL. Only two methods (NNV and ACIP GRADE approach) were specifically designed for vaccines. However, Decision Tree and NNT or NNV were the most commonly used estimates for assessing the benefits and risks associated with vaccines. Nevertheless these methods are either descriptive or quantitative; thus they do not allow obtaining the complete benefit risk assessment for one product.

Conclusions: Compared with other drugs, vaccines present specific characteristics including the administration to mainly healthy population, the herd effect, the benefits at population and individual levels, the immunization schedule and a potential rapid epidemiological impact. For all these particular properties, dedicated methodologies for benefit and risk assessment should be developed.

522. Digoxin Use After Diagnosis of Prostate Cancer and Survival: A Population-Based Cohort Study

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Background: Preclinical studies have shown that digoxin exerts anti-cancer effects on different cancer cell lines including prostate cancer. A recent observational study has shown that digoxin use was associated with a 25% reduction in prostate cancer risk.

Objectives: The aim of this study is to investigate whether digoxin use after diagnosis of prostate cancer is associated with decreased prostate cancer-specific mortality.

Methods: A cohort of 13,134 prostate cancer patients newly diagnosed from 1998 to 2009 was identified from English cancer registries and linked to the UK Clinical Practice Research Datalink (to provide digoxin and other prescription records) and to the Office of National Statistics mortality data (to identify 2,010 prostate cancer-specific deaths). Using time-dependent Cox regression models, unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CIs) were calculated for the association between post-diagnostic exposure to digoxin and prostate cancer-specific mortality.

Results: Overall, 701 (5%) prostate cancer patients used digoxin after diagnosis. Digoxin use was associated with an increase in prostate cancer-specific mortality before adjustment (HR=1.59; 95% CI 1.32-1.91), but after adjustment for confounders, the association was attenuated (adjusted HR=1.13; 95% CI 0.93-1.37) and there was no evidence of a dose response.

Conclusions: In this large population-based prostate cancer cohort, there was no evidence of a reduction in prostate cancer-specific mortality with digoxin use after diagnosis.

523. A Framework for the Evaluation of the Effectiveness of Risk Minimisation Measures Applied to Retrospective Danish Real-World Dabigatran Etexilate Data

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Background: Evaluating the effectiveness of risk minimisation measures is an evolving field within pharmacovigilance.

Objectives: To propose a framework for the evaluation of risk minimisation measures and review its features when applied to retrospective, real-world data following the introduction of dabigatran etexilate in Denmark for the prophylactic treatment of patients with non-valvular atrial fibrillation.

Methods: We propose a framework consisting of four domains: data, knowledge, behaviour and outcomes. It is suggested that four classes of variables be monitored: 1) Patient descriptors 2) Knowledge indicators 3) Behavioural indicators 4) Outcome indicators. The proposed framework was applied to retrospective Danish real-world data representing the period from August 2011 until June 2014. An interrupted time series (ITS) analysis was applied in order to evaluate the effect of a safety update issued by the European Medicines Agency on 18 November 2011.

Results: At the start of the observation period the overall mean age of incident users (a patient descriptor) was higher compared to patients included in the pivotal trial (74.6 yrs (SD 9.5) for Danish patients vs 71.8 yrs (SD 8.7) for patients in the RE-LY trial); however, the mean age declined over time. The proportion of users aged >75 years and prescribed 150 mg twice daily (a behavioral indicator) was initially 30% but later stabilised at around 15%. The quarterly number of major bleedings out of the total number of patients exposed (an outcome indicator) ranged from 0 to 0.5% with no clear trend over time. The ITS analysis was applied to the behavioral indicator as a "proxy" for the effect of the safety update. We observed a significant change in slope (less negative) of the estimated regression line ($p<0.001$), but no significant change in level at the intervention time point ($p=0.338$).

Conclusions: When applied to retrospective Danish real-world data our framework provided useful graphical displays and a statistical evaluation of a regulatory intervention. As a next step, the framework should be prospectively applied for the safety monitoring of a medicinal product.

524. The Association Between Statin Use And Kidney Stones In Adult Men: A Systematic Review To Evaluate The Available Evidence And Provide Benefit/Risk Assessment

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Background: Prevalence of kidney stones (KS) in men is estimated 10.8% in 2007, and cumulative annual KS incidence rose by 16% between 1997 and 2012 in the United States. Furthermore, being male was positively associated with a history of KS (OR: 1.59 [95% CI, 1.33-1.92]) . In parallel to the increasing rate of growth in the population of men aged 60 years and older, CDC estimates prevalence of overweight and obese men as more than 75%. A strong association between obesity and KS was established before. The prevalence of statin use is estimated 26.7%, among obese men.

Objectives: To determine the available risk and benefit of statins with respect to kidney stone formation among men aged 20 years or older in the United States with a systematic review.

Methods: A systematic review of studies examining the relationship between statin therapy kidney stones. Included studies were rated based on their methodological quality. A best evidence synthesis was used to summarise the results, and Bradford Hill criteria were used to assess causation.A qualitative evidence integration is used according to criteria by the BRACE white paper (PMID:26456379).

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Results: Statins are proposed to decrease kidney stone risk. However, the potency of statins and their dose must be carefully evaluated by the clinicians before application to specific group of patients such as those with chronic kidney disease (CKD) and other chronic or advanced conditions.

Conclusions: Statins could decrease Kidney Stones among adult men. The benefit could increase among obese men, however there could be severe risk among patients with CKD and other chronic conditions. Large and nationally representative studies and randomized controlled trials could clarify the surrounding controversy in this relationship.

525. Assessment of Effectiveness of Dronedarone Risk Minimization Measures Through a Drug Utilization Study in Two European Countries

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Background: Dronedarone is an antiarrhythmic drug, approved in Europe for maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation.

Objectives: A drug utilization study was conducted to measure the compliance of prescriptions of dronedarone to labeling recommendations as regards to its contraindications, and recommended patient monitoring.

Methods: This was a retrospective cohort study using patient level Electronic Medical Records and prescriptions databases in Germany and in Catalonia in Spain from Jan-2010 to Dec-2014. Two separate cohorts of "prevalent" and "new" users were set up among patients initiated on dronedarone in the outpatient setting before and after implementation of risk minimization measures (RMMs) that occurred in Nov-2011 in Germany and in Jan-2012 in Spain.

Results: In Germany, 675 new and 1,392 prevalent dronedarone users from the IMS® Disease Analyzer GP panel and 190 new and 654 prevalent users from the IMS® Disease Analyzer cardiologist panel and 18,127 new and 50,573 prevalent users from the IMS® LRx database were selected. The findings indicate an impact of the RMMs with regard to prescription of at least one contraindicated drugs from 12% to 10% as measured in the LRx databases, increase in performance of liver monitoring from 20% to 25%.

In Spain, 921 new and 1,319 prevalent users were selected from SIDIAP prescription database. Compliance with EMA recommendations was low but has improved since the implementation of RMMs with regards prescription of at least one contraindicated drugs from 19% to 14% and liver function monitoring in the first month from 14% to 22%.

Conclusions: This study using existing prescription records allowed describing improvement of prescription patterns as measure of effectiveness of minimization measures. This study was conducted in a large sample of patients without external intervention over a large period of time covering both prior and after implementation of measures periods.

526. Cardiovascular Disease, Medications, and Heat: What Precautionary Advice Is Available?

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Background: Global temperatures are rising, increasing the probability of population exposures to extreme heat events. Patients with cardiovascular disease may be at increased risk during extreme heat events, and cardiovascular medications may exacerbate this risk, for example, through dehydration and electrolyte imbalance - including hypnonatremia. Normal Cardiovascular adaptation to severe heat stress can involve an increase in cardiac output (CO) by up to 20L/min and a shift of heated blood from core to peripheral

circulation. An inability to increase CO results in impaired heat tolerance and increased susceptibility to heat stroke.

Objectives: To review commonly used health professional medical resources in relation to heat-related precautionary advice for cardiovascular disease management and people prescribed cardiovascular medications.

Methods: We conducted a content analysis of the following Australian

1. Therapeutic Guideline Cardiovascular Version 6
2. Australian Medicines Handbook 2015
3. Australian Heart Foundation Guidelines
4. Approved Product Information for specific drugs (i.e. atenolol, metoprolol, frusemide, spironolactone, glyceryl trinitrate, perindopril, irbesartan, amlodipine, atorvastatin).

These resources were searched manually for the following terms: "heat", "weather" and "season."

Results: No advice was found for health professionals regarding the potential effects of exposure to extreme heat in patients with cardiovascular disease, nor precautionary advice for people prescribed cardiovascular medications except for generic storage of medicines advice.

Conclusions: Precautionary advice regarding the effects of heat in patients with cardiovascular disease and use of cardiovascular medications is not generally available.

527. Improving a Drug Information Leaflet of Antihypertensives for Senior Citizens; Employing Performance-Based User-Testing

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Background: Written information could be helpful for senior population to adhere to complex medication therapies, but must be well prepared and empirically assessed to achieve such end.

Objectives: To develop a drug information leaflet for senior citizens.

Methods: We employed a user-testing, a mixed method to figure difficulties out with patients' leaflets from the user perspective. The cycle made of test and revision can be repeated as necessary. We recruited senior citizens with age of 65 or above who were taking antihypertensive medications at the point of participating and excluded the elderly who suffered illiteracy. We firstly rectified a drug information leaflet of antihypertensive medications for the general public distributed by the Korean authority based on focus group interviews (9 participants). The revised leaflets were tested four times with 8 ~ 12 participants in each round (41 seniors in total). We targeted to develop a leaflet which more than 80% of participants understood 10 key information. Main outcomes measures were to be able to find information and be able to understand information. This study was approved by the Yeungnam University Research Ethics Committee.

Results: Focus group interviews identified difficulties with small font of words, professional language, long information, and a poor structure. The leaflet was revised and in the first round questionnaire found problems with 4/10 information points; interviews disclosed all but one (normal blood pressure range) were ill-understood. The second round questionnaire and interview found fewer problems but the comprehensiveness of participants was still poor in several points. For the third and fourth rounds we revised the leaflets in the individual-targeted manner. Finally, the fourth round showed all key information found and understood by at least 80% of participants except one question about drug name.

Conclusions: The drug leaflets need to be developed in a personalized mode for the seniors. There was a limit for Korean seniors to understand nonproprietary name of their drugs because they used to producers' trade names which the Korean health system predominantly works with.

528. Evaluation of Physician Awareness of Risks Described in the SIMPONI (Golimumab, GLM) EU-RMP Educational Program

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Background: The overall goal of the GLM educational program is to increase GLM prescriber awareness of the risks as described in the RMP by providing appropriate tools to optimize the benefit/risk profile of GLM in RA, PsA, AS and UC.

Objectives: To measure the awareness of HCPs who are current or future prescribers of GLM on the risks associated with the use of GLM and on the requirements for handing out the patient alert card (PAC) as described in the GLM RMP educational program and to compare the results with the 2010 and 2012 surveys.

Methods: A structured, quantitative survey, hosted on the internet, was conducted in 2014 in 8 EU countries among HCPs who were current or future prescribers of GLM.

Results: The 393 current or future prescribers of GLM (685 HCPs surveyed) showed an awareness of each of the surveyed risks and of the requirements for handing out the PAC of at least 70% (70-98%). In comparison to the study in 2012, the overall risk awareness remained steady for GLM-prescribing rheumatologists and dermatologists in most statement categories. In 2014, the awareness of the GLM risks was higher among rheumatologists (69-99%) and gastroenterologists (72-99%) than among dermatologists (61-89%). The three risk statements that tended to have lower awareness were the following: GLM should be used with caution in patients with mild heart failure (71%); there is a risk of hypersensitivity in patients at the first dose of GLM (70%, added to the survey in 2012), and periodic skin examination is recommended for patients using GLM (73%, added to the survey in 2014). Overall, the awareness of the requirements for handing out the PAC remained steady in 2014 vs 2012 (82-90% vs 80-85%).

Conclusions: The results of the 2014 evaluation of the GLM educational program showed that the educational program remains effective overall as an additional risk minimization activity for the risks specified in the RMP of GLM, with a stable level of awareness when compared to results of previous surveys. The HCPs awareness of the requirements for handing out the PAC to patients treated with GLM also remained satisfactory when compared to results of previous surveys.

529. Evaluation of Risk Minimisation Activities for Cyproterone Acetate 2 mg/Ethinylestradiol 35 µg

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Background: Cyproterone acetate 2 mg/ethinylestradiol 35 µg (CPA/EE), an estrogen/progestogen drug indicated for dermatologic conditions shares thromboembolism risk with combined hormonal contraceptives. A "Dear health care professional" letter, patient information card, and prescriber checklist were distributed to physicians to increase awareness of this risk.

Objectives: To measure physician knowledge of thromboembolism risk by specialty and ascertain whether physicians received educational materials.

Methods: This cross-sectional, study was conducted in Austria, the Czech Republic, France, the Netherlands, and Spain. Recent prescribers of CPA/EE were recruited to complete a phone or web survey. Physician specialty was considered when selecting the sample based on country-specific prescribing patterns. Frequency and percentage of correct responses were calculated for 14 knowledge questions.

Results: The targeted 500 responses were achieved (9% [N = 559] of invited physicians), with 44.7% OB/GYNs, 33.6% GPs, and 21.6% dermatologists. 47.8% reported receiving at least one of the educational materials, and 73.5% to 79.3% of those reported the materials were helpful. Knowledge was highest (≥80%) for (1) symptoms of possible deep vein thrombosis, pulmonary embolism, and cerebrovascular accident; (2) most important risk factors for thrombosis; and (3) use in smokers. Knowledge ranged from moderate to high (≥61%) for approved indication and risky time periods/special situations. It varied for contraindications, symptoms of myocardial infarction, other risk factors for thrombosis, instructions related to immobilisation and selected concomitant medical conditions. Knowledge was ≤ 60% regarding prescribing CPA/EE for acne only after failure of topical therapy or systemic antibiotics. It did not vary by receipt of educational materials or physician specialty for most questions.

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Conclusions: Knowledge of thromboembolism risk was generally high. Knowledge varied for topics that were more complex or less frequently encountered in which physicians might consult additional references. The relatively low knowledge about prescribing after failure of other acne treatments was unexpected.

530. Assessment Of Pharmacist Mediated Education On Health Related Quality Of Life In Type 2 Diabetes Mellitus Patients In Rural India

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Background: Type 2 Diabetes Mellitus is slowly spreading from urban area to rural areas due to stressful life situations among people in rural India. This warrants the need for sensitization of individuals through education towards managing the early onset of Diabetes Mellitus and preventing the consequences of uncontrolled Diabetes Mellitus.

Objectives: To assess the influence of pharmacist mediated education on health related quality of life in rural patients with type 2 diabetes mellitus.

Methods: This is a prospective, randomised interventional study approved by institutional ethics committee. Eligible type 2 diabetic patients given written informed consent were enrolled and randomized into control and test group. Diabetic health profile 18 (DHP-18) questionnaire was administered on all patients at base line and three subsequent follow ups. Patients in the test group received structured education at every follow up whereas the control group patients received education only at the final follow up. SPSS software was used to evaluate the data.

Results: Among the 72 patients enrolled, 37 were randomized in to test and 35 were in to control groups. Majority study patients (65.2%) were males and in the age range of 30 to 72 years and were with school education (59.7%) and from agriculture profession. The mean BMI of the study patients was 25.01. At base line, the mean HbA1C value of patients was 6.48%±1.39 in the control group and 6.23%±1.16 was in test group. At the end of the study, a significant ($p<0.05$) improvement was observed in DHP-18 scores in test group patients compared to control group patients which was supported by statically significant ($p<0.05$) improvement in CBG values.

Conclusions: Pharmacist mediated structured education has shown a positive impact on health related quality of life of test group patients towards their disease management.

531. Programmatic Efficiency of a Pharmaceutical Risk Management Program: Outcomes from Diabetes Screening of Adults Receiving Antipsychotics

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Background: Programmatic efficiency of risk management programs using standard public health metrics is under-reported.

Objectives: To assess screening yield and number needed to screen to detect a new case of diabetes in a state Medicaid program that implemented a metabolic risk management program for adults receiving antipsychotics.

Methods: A retrospective cohort study was conducted among new users (ages 18-64 yr) of second-generation oral antipsychotics in Missouri Medicaid (N=4182 patients) using administrative claims data (2010-12). Annual glucose testing was identified using CPT codes. Diabetes status and number of American Diabetes Association type II diabetes risk factors (age, race/ethnicity, hypertension, dyslipidemia, heart disease) were identified using ICD-9 codes, pharmacy claims, and eligibility records. Age-adjusted rates (standard=2000 U.S. Census) and descriptive statistics are reported.

Results: Baseline diabetes prevalence was 12.3 % (US prevalence = 9.3%). 57.6 % of adults without diabetes had one or more type 2 diabetes risk factors. The screening program achieved a testing rate of 79.3% (86.4% among adults with one or more diabetes risk factors). 149 new cases of diabetes were identified (yield = 5.3%). 16.8% of new cases (n=25) were adults with no diabetes risk factors. 71.1% of new cases (n=106) were adults without schizophrenia or bipolar

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disorder (S/BP, subset targeted by U.S. NCQA HEDIS quality measures). New cases of diabetes were distributed across prescriber specialty-settings: 41.6% (n=62) behavioral health/Community Mental Health Centers, 25.5% (n=38) primary care; and 32.9% (n=49) other/unknown. The number needed to screen to detect a new case of diabetes was 20 (95% CI: 17-26) and 14 (95% CI:11-20) in patients with S/BP.

Conclusions: The low number needed to screen suggests good yield in this population-based risk management program relative to public health screening norms. Screening efficiency metrics, along with effectiveness in reducing morbidity/mortality, cost-effectiveness, and frequency of unintended harms, can be incorporated into routine risk management program evaluation.

532. Compliance with Renal Testing Recommendations for Fampridine Use in a German Population with Multiple Sclerosis

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Background: Renal insufficiency may increase the risk of seizures in patients taking prolonged release fampridine (FAMPYRA) 10mg bid. Due to kidneys excreting fampridine, renal function evaluation is recommended for multiple sclerosis (MS) patients treated with the drug; however, the level of adherence to this recommendation is unknown.

Objectives: To calculate the percentage of patients receiving renal function testing at fampridine initiation.

Methods: This was a retrospective, observational study of MS patients from the NeuroTransData (NTD) network, which consists of de-identified data from select neurology practices in Germany. The analysis included MS patients in the NTD who were treated with fampridine from 01 Sept 2011-30 Oct 2014. To ensure adequate coverage, all patients ≥65 years of age were included in the analysis; a random sample of 100 patients < 65 was conducted. The occurrence of renal testing within +/- 4 weeks of fampridine initiation was noted, and, where available, the actual serum creatinine values were identified. Descriptive statistics, including counts and percentages, were developed and, where possible, estimates were weighted for the underlying fampridine age distribution in the NTD.

Results: Among 1,118 fampridine users in the NTD, 122 (10.9%) were ≥65 years of age. Of the remaining patients, 102 patients <65 were randomly selected. After weighting for oversampling those ≥65 years, 65.0% of patients received renal testing within +/-4 weeks of fampridine initiation. Patients ≥65 years were less likely to receive testing (44.3%) compared to those <65 years (67.6%). Among the 64 patients who had serum creatinine clearance reported, 90.3% had normal (e.g. ≥80mL/min) renal function, after weighting to the NTD fampridine population. Only 50.0% of those ≥65 years with a reported serum creatinine value had normal renal functioning, while 95.2% of patients <65 years had normal renal functioning.

Conclusions: Renal testing occurred in 65.0% of patients within +/- 4 weeks of fampridine initiation; however, older patients were less likely to be tested. A small number of patients with known renal insufficiency (9.7%) continued to receive fampridine.

533. Usage Of Valproate In Women In The UK

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Background: In early 2015 the European Medicines Agency (EMA) strengthened their advice that valproate (VPA) should not be prescribed for epilepsy, bipolar disorder, or migraine in pregnant women, or in women who can become pregnant (unless other treatments are ineffective or not tolerated) due to concerns about neurodevelopmental problems in children following in-utero exposure.

Objectives: To examine patterns of use of VPA in women before and following communications and since the risk minimisation measures were introduced in the UK.

Methods: Women aged 14-45 years were identified. Prevalence and incidence prescribing rates for VPA were calculated over 6-month periods 01/01/2010-30/06/2015. Women were eligible for inclusion if they were in active follow up for the whole period. To identify incident prescriptions, a minimum of one year of follow up prior to the first prescription and relevant

six-month period was required. Possible indications of treatment were identified using relevant Read codes for epilepsy, bipolar disorder or migraine at any time in the medical record.

Results: The prevalence of VPA prescribing appears to have slightly declined in women over the period up to the end of June 2015; with a 17% decrease in VPA prevalence in the first half of 2015 compared to the first half of 2010 (0.28 vs. 0.23%). There was a general pattern of increased VPA prescribing in the second half of each year. Epilepsy was the most commonly recorded indication and had a reduction in use of 22%; smaller declines were seen for bipolar disorder and migraine (20% and 14% respectively) although overall levels of use for these indications were much lower. There was a 31% decline in patients newly starting VPA; however this was based on low absolute numbers.

Conclusions: In keeping with recent guidance; UK usage of VPA is decreasing in women. It is not yet possible to determine the full impact of the updated advice or risk minimisation measures. These data provide baseline figures to inform future studies investigating VPA usage and the effectiveness of the risk minimisation measures. Future work will also include prescribing patterns specifically in pregnant women.

534. Impact of an Opioid Risk Reduction Initiative on Motor Vehicle Crash Risk Among Chronic Opioid Therapy Patients

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Background: Though prescription opioids have been associated with higher motor vehicle crash (MVC) risk, it is unknown whether health system initiatives to better manage chronic opioid therapy (COT) can reduce MVC risk.

Objectives: To evaluate whether risk-reduction initiatives which substantially lowered opioid doses were accompanied by a reduction in MVC rates.

Methods: We conducted an interrupted time series study among patients from Group Health (GH), a mixed-model healthcare delivery system within Washington State, between 2006 and 2014. GH members aged 18 and older; continuously enrolled in the health plan for the entire quarter in which they received COT and the 3 quarters prior; and who received at least 70 days supply of opioids in the current quarter, were eligible for the study. Group practice COT risk reduction initiatives were evaluated in two phases: 1) altered prescribing expectations; and 2) multi-faceted initiatives. We also stratified on co-prescribed sedative/ benzodiazepines and evaluated the opioid dose-response relationship with MVC. We compared the quarterly rates of MVC between group practice with contracted-care patients using a modified Poisson regression model for a binary outcome to estimate adjusted trends over time in the two populations.

Results: 32,691 COT patients (27.4% from contracted care) met eligibility criteria between January 2006 and September 2014 and experienced a total of 1,956 MVCs during study follow-up (mean, 8.1 quarters per person), of which 810 were serious injury crashes. Crash rates were not significantly different between the patient groups within any of the time periods. Analyses stratified by concurrent prescription of a sedative hypnotic or benzodiazepine found no significant difference between the group practice and contracted care patients. There was a modest elevation of MVC risk for high dose patients relative to former COT patients who stopped receiving opioids.

Conclusions: The risk of MVC was not mitigated in a large cohort of COT patients exposed to a health plan policy initiative that substantially lowered mean opioid dose.

535. Inappropriate Fentanyl Prescribing Among Nursing Home Residents in the United States

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Background: Due to its risks, clinical guidelines and FDA warnings recommend that transdermal fentanyl

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be limited to individuals with prior opioid use and persistent pain.

Objectives: To quantify transdermal fentanyl prescribing in elderly nursing home residents without prior opioid use or persistent pain and the association of individual and facility traits with opioid-naïve prescribing.

Methods: This was a cross-sectional study sourced from Linked Minimum Data Set (MDS) assessments; Online Survey, Certification and Reporting (OSCAR) records; and Medicare Part D claims. From among a cross-section of all long-stay US nursing home residents in 2008 with an MDS assessment and Medicare Part D enrollment, we identified initiators of transdermal fentanyl, excluding those with dementia, severe cognitive impairment, cancer, hospice care, or age <65 years. We classified transdermal fentanyl initiators as "opioid-naïve" if they received no opioid prescriptions during the previous 60 days. We defined persistent pain as moderate-to-severe, daily pain on the last MDS assessments just prior to fentanyl initiation that were consecutive and at least 90 days apart. We obtained resident and facility characteristics from MDS and OSCAR records. We estimated associations of patient and facility attributes and opioid-naïve fentanyl initiation using multilevel mixed effects logistic regression analyses.

Results: Among 17,052 transdermal fentanyl initiators, 6,190 (36.3%) were opioid-naïve and 15,659 (91.8%) did not have persistent pain. In the adjusted analysis, residents who were ≥95 years old (compared to 65-74 years old, odds ratio (OR)= 1.69, 95% confidence interval (CI) = 1.46-1.95), or had moderate-to-severe cognitive impairment (compared to no cognitive impairment, OR=1.99, 95% CI = 1.73-2.29) were more likely to initiate transdermal fentanyl without prior opioid use.

Conclusions: Most nursing home residents initiating transdermal fentanyl did not have persistent pain and many were opioid-naïve. Changes in prescribing practices may be necessary to limit adverse effects, particularly for vulnerable subgroups such as the cognitively impaired.

536. Incidence of Opioid Overdose Among Patients Using ER/LA Opioid Analgesics Before and After Implementation of the Class-Wide Opioid REMS

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Background: Extended release (ER) and long-acting (LA) opioids are used for chronic moderate-to-severe pain. A Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioids was implemented in July 2012.

Objectives: To assess the impact of the REMS on the incidence of emergency department visits and hospitalizations for opioid overdose among patients prescribed ER/LA opioids.

Methods: This retrospective cohort study used HealthCore Integrated Research Database (HIRD) and US Medicaid data to compare the incidence of opioid overdose before and after implementing the REMS. We included patients with ≥1 ER/LA opioid prescription during the REMS pre-implementation period (July 2010 through June 2012), REMS implementation period (July 2012 through June 2013) and/or REMS active period (July 2013 through August 2014). We computed incidence rates as the number of overdoses observed during each REMS period divided by total person-time at risk. We compared the active period to the pre-implementation period using incidence rate ratios (IRR), controlling for demographic characteristics, pain conditions, psychiatric comorbidities and baseline medication use.

Results: Among commercially-insured patients, the IRR for opioid overdose among all users was 0.83 (95% CI 0.70–0.99), and the IRR for heroin overdose was 3.70 (95% CI 0.92–14.86). In new users, opioid overdose was stable (IRR 1.06, 95% CI 0.78–1.45). In the Medicaid population, the IRR was 0.81 (95% CI 0.59–1.18) for opioid overdose and 1.12 (95% CI 0.35–3.15) for heroin overdose.

Conclusions: Amidst previously increasing rates of opioid overdose, the decline in opioid overdose among all users of ER/LA opioid analgesics and leveling off among new users is consistent with a positive impact

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of the REMS on opioid overdose. Given many other ongoing initiatives, however, these findings cannot be attributed directly to the opioid REMS.

537. Experience from the Zyprexa Relprevv Patient Care Program: 2010-2015

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Background: The Zyprexa Relprevv Risk Evaluation and Mitigation Strategy (REMS) program includes Elements to Assure Safe Use (ETASU) and an implementation system. These are referred to as the Zyprexa Relprevv Patient Care Program (PCP). The goal of the PCP is to mitigate the risk of negative outcomes associated with post-injection delirium/sedation syndrome (PDSS). Zyprexa Relprevv is the only drug or biological product with all potential REMS elements as outlined in the Food and Drug Administration Amendments Act.

Objectives: The objective is to describe the PCP enrollment metrics and PDSS event rates from its launch on 26 January 2010 through 30 August 2015.

Methods: The PCP enrolls all key stakeholders: prescribers, patients, healthcare facilities (HCF) and pharmacy service providers (PSP) who are involved in the administration of Zyprexa Relprevv. The PCP follows and actively solicits information regarding the occurrence of signs and symptoms of PDSS. The PCP seeks to provide a complete denominator of Zyprexa Relprevv treated patients and number of injections and a complete numerator of cases of PDSS. All suspected cases of PDSS are adjudicated by an internal committee.

Results: From 26 January 2010 through 30 August 2015, there have been 4784 patients for a total of 71 593 injections, 1019 active HCFs, 1169 active PSP, and 1360 active prescribers. Using annual reporting period cut-offs, the largest number of active patients, prescribers, HCFs, and PSPs were enrolled from 31 August 2012 to 30 August 2013. Since that time period, the number of active stakeholders has steadily decreased. During the most recent annual reporting period, there were 1323 active patients, 414 active HCFs, 451 active PSPs and 557 active prescribers. Cumulatively, 72 PDSS events have been confirmed in 68 patients, for a per-injection and per-patient PDSS rate of 0.10% and 1.42%, respectively.

Conclusions: The per-injection rate of PDSS observed in the PCP was consistent with that observed in clinical trials and spontaneous reporting. Participation in the PCP has been declining since 2013.

538. Presentation of Stigma Associated with Mental Disorders in the News Media

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Background: The stigma of mental illness is a multifaceted phenomenon with affective, cognitive, and behavioural components but little is known about the problem in Singapore to reduce this stigma.

Objectives: To gather information on the features of stigma (including perception, emotions and implications) associated with mental disorders, and identify areas of involvement for healthcare professionals, particularly pharmacists, to destigmatise mental disorders.

Methods: A preliminary systematic search was conducted on archived Singapore news sources in Factiva database from 1989 to 2015, using combinations/variants of the search terms "mental health", "stigma" and "healthcare professionals". Inductive content analysis was carried out on selected articles with context of stigma associated with mental disorder(s). Descriptive statistics were generated to summarize the data.

Results: Of the 72 articles analysed, the majority (67%) were journalist articles and some (~20%) from forums. The general public formed the major source of stigma associated with mental disorders (72%), while some patients reported experiencing social stigma (26% of articles). There was strong negative public perception of mental patients reported in the articles, with the identified cause being the lack of awareness of mental disorders. This has implications on patients who delayed seeking drug treatment. While existing programmes are available to raise awareness and help destigmatise mental disorders, it was not evident nor clear how pharmacists were involved or can be engaged.

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Conclusions: Pharmacists can work collaboratively with other healthcare professionals (such as counsellors or psychiatrists) in programmes, and employ appropriate media for more effective public awareness and reduction of mental disorder stigma, thereby promoting public health.

539. Patient Preference (PP) Studies in Benefit-Risk Assessment (B-RA): Is There a Room for Improvement Through Good Pharmacoepidemiology Practices (GPP)?

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Background: One of the most important questions in patients' and prescribers' minds when using or prescribing a medicine is whether its benefits outweigh risks. To answer this question, stakeholders are taking a systematic approach through structured B-RA. While sponsors, regulators, and prescribers are conducting B-RAs for patients, patients themselves are increasingly taking a direct role in the B-RA process. To better understand and use PP in decision-making, PP studies are emerging as a way to gather valid, representative data to support evidence based B-RAs.

Objectives: To highlight lessons learned from conducting PP studies and the value GPP bring to PP study design, analysis, and reporting of results.

Methods: Systematic review of PP literature describes methods to collect and analyze patient perspectives in these studies including data on risk tolerance, risk preference, and B-R tradeoffs.

Results: PP methods provide information on the relative desirability and importance of B-R attributes. They also assess and quantify risk tradeoffs that patients are willing to take to gain benefits from a treatment. There are a variety of methods used to elicit preferences, and one important learning is that the method must match the study purpose. Other learnings include determining the best time in the lifecycle to perform the study; all stakeholders aligning early on study objectives; including patients in the study to ensure the appropriateness of the attributes; and ensuring that all stakeholders comprehend PP study terminology to interpret the study results. Our research suggests that GPP enhances PP studies through protocol development, study design, analysis, interpretation, and communication of results.

Conclusions: PP are becoming critical to the development, approval, and use of medicinal products. Use of GPP can further enhance the quality of such studies.

540. Review of the Pharmacoepidemiological Studies Using the Medical Information Databases in Japanese Hospitals

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Background: The Japanese MHLW announced a plan for the Sentinel Project in Japan (J-Sentinel). To achieve the goal of J-Sentinel, it is necessary to consider the pharmacoepidemiological methodology for useful mining of the medical information databases (MIDs).

Objectives: To examine the utilization possibility of the MIDs in Japan and to find issues to be solved for pharmacoepidemiological study, studies using the MIDs in Japanese hospitals were reviewed.

Methods: We conducted 4 pharmacoepiedemiological studies using Japanese MIDs via on-site research or distributed data approach, and issues raised during these studies were summarized.

Results: Of four studies, 3 of them were examined Detection algorithm of drug adverse events and another one was evaluation of impacts of regulatory actions, as follows; i) fluoroquinolones (FQs)-induced tendon disorders were detected 14 patients in 17,147 subjects (frequency: 0.082%). The risk ratio of a tendon disorder for FQ relative to cephalosporin was 6.29 (PDS, 2012; 21: 886-89). ii) The heparin-induced

thrombocytopenia (HIT) algorithm detected 47 patients in 2875 subjects and review of the medical records demonstrated the PPV for the algorithm was 87.2% (frequency:1.4%) (J Clin Pharm Ther, 2013; 38: 423-28). iii) Drug-induced liver injury (DILI) algorithm based on DDW-J, a Japanese clinical diagnostic criteria, identified antibiotic-induced liver injuries and risk factors (PDS, 2014; 23: 984-88). iv) a significant impact of a 'Dear Doctor' letter to restrict oseltamivir use in teenagers was demonstrated (J Clin Pharm Ther, 2014; 39: 361-67). Several issues were also raised during these studies, such as i) uniformity of diagnostic criteria for adverse events, ii) difficulties of detecting adverse reactions with very low incidence rate, iii) unavailability of all testing data for diagnostic criteria, vi) differences in testing methodologies or upper limit of normal values between the hospitals.

Conclusions: These studies supported the utility of MIDs in Japanese hospitals for pharmacoepidemiological study, although several limitations were also recognized.

541. Applying The Number Needed To Harm (NNH) to Benefit-Risk (BR) Assessments Of Drugs Withdrawn From The Market Due To Safety Reasons

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Background: BR assessments are based on the best evidence on the efficacy and safety of drugs. There are well-established methods for assessing efficacy, but not safety.

Objectives: The usefulness of the NNH was explored by studying the agreement between NNH values and decisions of withdrawing drugs from the European market due to safety reasons.

Methods: Drugs, identified in the EMA's website, were included if safety data was available in longitudinal controlled studies. Main data sources were EMA's assessment reports. Data on patient-years (PY) of exposure and adverse events was extracted. Incidence rates per PY were used to estimate NNHs (and 95% CIs) for withdrawn drugs vs. controls in pre- and post-marketing periods of time.

Results: Eleven drugs were included. Pre-marketing data could not be retrieved for almitrine, benfluorex and ketoconazole. The adverse events supporting the withdrawal of sibutramine and ximelagatran were not reported in pre-marketing studies. A reduction of the NNH (95%CI) from pre- to post-marketing period was seen for rofecoxib (1266, not statistically significant [NS] vs. 139 [80-527] for thrombotic events). Regarding niacin-laropiprant, a decrease was noted for myopathy (1011 [NS] vs. 770 [589-1177]), but not for new-onset diabetes (108 [57-1099] vs. 385 [264-770]. The NNH for myocardial infarction (MI) with rosiglitazone decreased from pre- (-1923 [NS]) to post-marketing setting, but statistically significance (SS) was noted only in 3 post-marketing cohort studies (53 [33-145]; 527 [323-1266]; and 60 [48-79] for a composite of MI, stroke, heart-failure or all-cause mortality). The NNH for liver-injury with lumiracoxib increased over time, but without SS (1695 [NS] vs. 2387 [NS]). The NNHs obtained for rimonabant (8 [7-10] vs. 6 [4-13]) and valdecoxib (1 [1-7] vs. 2 [1-3]) varied little over time.

Conclusions: The results preclude conclusions about the usefulness of the NNH in BR assessments. With the exception of rofecoxib, the results aren't in line with the decisions of withdrawing drugs from the market. Thus, the use of the NNH may not be applicable in all cases of BR assessments. Further research is needed.

542. Do Patients Store Their Oral Oncolytics According To Manufacturers' Storage Recommendations: An Observational Study Of Home Storage Temperatures

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Background: Patients receive oral and/or written instructions on how to store their oral oncolytics at home

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when medication is dispensed at the pharmacy. How well patients manage to comply with the manufacturers' storage recommendations is not known.

Objectives: To investigate the proportion of patients that store oral oncolytics according to manufacturer's storage recommendations.

Methods: Consenting adult patients from six Dutch outpatient hospital pharmacies using oral oncolytics (ATC groups L01XE) during Mar 2014 - Jan 2015 were included. The oral oncolytics were dispensed together with a validated temperature logger which was read out after the use of the oral oncolytic. Two types of oral oncolytics in this study required storage below 25°C and three below 30°C.Ten oral oncolytics were tested by manufacturers and found to be stable at temperatures ≥40°C, therefore not requiring special storage conditions. Primary outcome was the proportion of patients that stored oral oncolytics according to the recommended storage temperature, with no consecutive time of two hours or longer above 25°C or 30°C. The influence of ambient temperatures on mean daily storage temperatures of oral oncolytics was assessed by linear regression analysis.

Results: Of 121 patients, 90 (81.1%) patients (47.8% female, mean age 65.2 (SD; 11.1)) returned their temperature loggers to the pharmacy. 14.4% and 41.1% of patients received oral oncolytics that required storage below 25°C and below 30°C, respectively, of which 76.9% and 5.4% stored their oral oncolytic at temperatures higher than recommended by the manufacturer. Mean daily storage temperatures ranged from 17.4°C to 25.6°C with maximum temperatures up to 58.0°C. In the summer months (Jun 1st – Aug 31st), significant correlation was found between mean outside temperatures and mean daily storage temperatures (R^2=0.69, $p<0.001$).

Conclusions: The majority of patients using oral oncolytics that required storage below 25°C did not comply with the storage label recommendations. Daily storage temperatures often reach temperatures above 25°C and are influenced by ambient temperatures in the summer period.

543. Is There Scope for Rapid Implementation of Pharmacoepidemiology Findings Using Quality Improvement Methods?

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Background: The Scottish Patient Safety Programme – Pharmacy in Primary Care collaborative has developed High Risk Medicine (HRM) Care Bundles (CB). These CBs, which are interventions that improve care processes and outcomes, focus on clinical assessment and patient education. Using quality improvement methods, these have been implemented in 28 community pharmacies in four health service regions – two focus on Warfarin and two on non-steroidal anti-inflammatories. The intent is for national roll out of a HRM CB, where a standardised process may act as a platform to accelerate uptake of pharmacoepidemiology findings into routine practice.

Objectives: To develop a generic HRM CB process map to facilitate implementation.

Methods: Regional process maps were developed through data collection in four pharmacies, involving simulation of the CB process, staff interviews and documentation of resources. Following validation by the onsite pharmacist, commonalities among the process maps were collated to create a process map for each HRM. To develop a generic HRM process map, these were validated by 93% (n=26) of participating pharmacies.

Consent was gained throughout. Ethical approval was not sought as this was service evaluation.

Results: Although some regional variation existed, the validation identified six core stages required for successful CB delivery: patient identification, clinical assessment, patients' eligibility flagged, CB delivery, enrolling non-attending patients and documentation. The commonalities were sufficient to develop a generic process map encompassing staff and patients' journey, its integration into usual practice and resources utilised.

Conclusions: To maximise implementation success, the process map allows for targeted development of resources to facilitate each core stage. The feasibility of developing a generic process map suggests adaptability of the CB to varying clinical contexts, strengthening the CBs potential to facilitate national implementation of health informatics research. Safety

concerns highlighted by pharmacoepidemiology studies could be addressed by adapting the CBs' content, allowing seamless translation of evidence into practice.

544. Determinants for Healthcare Professionals to Take Action in Response to Safety Communications on Medicines

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Background: In the European Union (EU), new important safety information on medicines is mainly communicated to healthcare professionals (HCPs) via Direct Healthcare Professional Communications (DHPCs). However, information is lacking on how HCPs follow recommendations made in DHPCs.

Objectives: Determine the influence of HCPs' characteristics and views on the frequency of recommended actions taken in response to DHPCs.

Methods: A web-based survey was distributed to HCPs in 9 EU countries; Norway (NO), Sweden (SE), Denmark (DK), Ireland (IE), the United Kingdom (UK), Spain (ES), Italy (IT) and Croatia (HR) [SCOPE project: www.scopejointaction.eu]. HCPs were recruited via e-mail, websites and newsletters. Logistic regression was performed. HCPs' self-reported frequency on how often they took recommended action in a DHPC was used as categorical outcome measures (based on mean value). Determinants: gender, age, profession, years of accreditation, country, perceived usefulness of DHPCs, HCPs' view on the national competent authority (NCA) as a source of safety communications and on keeping up to date on safety of medicines via dedicated information in personalized letters.

Results: In total, 3625 HCPs responded (61% females). Those HCPs familiar with DHPCs (91%), reported on average to take the recommended action 77% of the time. General practioners and pharmacists more often took action than other HCPs ($P<0.05$). HCPs from DK, ES, IE, IT and NO took action more often than HCPs in the UK, whereas HCPs from NL took action less often (all $P<0.01$). Compared to a neutral opinion on their usefulness, a negative view of utility of DHPCs was associated with taking action less often ($P=0.005$) whereas a positive opinion with more actions taken ($P=0.000$). A positive view on the NCA ($P=0.012$) and on information in personalized letters ($P<0.001$) was associated with taking more often action than a neutral view.

Conclusions: HCPs reported to have taken action as recommended in response to three out of four DHPCs received. Perceived usefullness of the DHPC, trustworthiness of the NCA, and of information in personalised letters, profession and country influenced how often HCP took action.

545. Drug Promotional Activities in Nigeria: Impact on Prescribing Pattern and Practices of Medical Practitioners

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Background: The relationship between the pharmaceutical industry and medical practitioners continues to generate controversies worldwide. However, the relationship between Nigerian doctors and the drug industry and its impact on their prescription pattern and practice has not been well explored.

Objectives: The main objective of this study was to investigate the impact of drug promotion by the pharmaceutical industry on the prescribing pattern of medical doctors working in three healthcare facilities in Nigeria.

Methods: This cross-sectional questionnaire-based study was carried out among 250 medical doctors working in three tertiary healthcare facilities in Nigeria. The information obtained from the questionnaire

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was coded, entered and analyzed using IBM SPSS version 19.

Results: Majority (154/87.5%) of respondents had had drugs promoted to them within the preceding three months. Most of the encounters with pharmaceutical representatives was in the outpatient clinics (60.2%) and department clinical meetings (46%). The information provided during promotional activities included: brand name of the drug (79.5%), clinical indications (80.7%), contra-indications (54.5%), potential adverse effects (41.5%), reference materials (39.2%) and potential drug-drug interactions (27.3%). Most respondents (68.2%) had gifts distributed during these encounters with food items (70.5%) and souvenirs (68.8%) being the main forms of gratification. Majority (107/60.8%) of respondents felt motivated to prescribe the promoted drug afterwards. Factors that influenced respondents positively towards prescribing the promoted drugs were: information provided (63.6%), cost benefit analysis of the product, reputation of the drug company (28.4%) and gifts received (4.5%). Most respondents (64.8%) felt that the relationship between doctors and representatives of the pharmacological industry should have some form of regulation.

Conclusions: Drug promotional activities have some influence on prescribing pattern of Nigerian medical doctors. Gifts received during the promotional activities appeared not to have any significant effect on the decision to prescribe the marketed drug.

546. Regulatory Considerations for Knowledge, Attitude, and Belief Surveys: A Systematic Review of Physician Survey Response

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Background: Knowledge, attitudes and belief (KAB) surveys are key components of risk management program evaluations. Understanding factors affecting response rates (a potential source of bias) is needed to inform regulatory decision making using these data.

Objectives: To systematically review the literature on physician survey response and survey method factors affecting response.

Methods: A systematic review was conducted in PubMed using MeSH terms to identify surveys of healthcare providers on topics of prescriptions and pharmaceuticals in the US from Jan. 2000 to Oct. 2014 that reported response rates (RR). An abstract review was undertaken on resulting publications to identify articles addressing physician surveys of pharmaceuticals and reporting a response rate. Among eligible publications, full manuscript reviews were conducted to identify RR and survey method factors that could influence response: physician specialty, number of contact attempts, contact methods (e.g. mail, email), incentive, study design, and two proxies for level of engagement: survey sample size and data source. Pearson's correlation coefficients were calculated to examine relationships between response rates and numeric design factors. Unpaired t-tests were used to compare other design factors.

Results: MeSH search terms returned 164 publications. Abstract reviews identified 76 eligible papers. Mean RR=51% (median=48%;SD=22%). Correlations revealed that RRs were lower when a larger sample was contacted (r= -0.254) and higher with more contact attempts (r=0.265). Commercially-available sample lists had lower mean RR compared to internal lists (45% vs. 65%, p= 0.02). Population-based samples had higher mean RR than random sample (56% vs. 47%, p=0.09). Mixed contact methods yielded higher mean RR than mailed surveys alone (58% vs. 46%, p=0.02). Data reported on incentives was too sparse to review. No papers provided response bias analysis.

Conclusions: A broad range of physician survey response is reported in the medical literature. Survey design choices may influence response rates. Formal analysis of response bias should be part of standard regulatory reporting.

547. Use of Cognitive Testing to Optimize Questionnaire Wording and Mode of Administration in the Evaluation of Risk Minimization Activities

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Background: As part of the evaluation of risk minimization measures for aflibercept, for intravitreal injection, a questionnaire was developed to assess patient knowledge and understanding of key safety information contained in aflibercept's EU educational materials. Interviews were conducted to test the questionnaire with patients prior to the start of data collection.

Objectives: To ensure that patients understood and consistently interpreted the questions and response options and to determine the most appropriate mode of data collection given the potential for visual impairment in the target population.

Methods: Two rounds of interviews were first conducted in English (in the UK) with 11 patients to identify issues and optimize wording. Interviewers trained in cognitive debriefing methods asked patients to complete the questionnaire while describing their thought processes aloud. Additional probe questions elicited more information on how patients interpreted and chose their answers and the format and usability of the questionnaire. The questionnaire was revised after each round of interviews and translated into 4 additional languages (for France, Germany, Italy, and Spain). Cognitive interviews were then conducted with 4 patients per country to confirm wording and cultural acceptability.

Results: Across all countries, 56% of patients were aged 50 to 75 years, and 37% were 75 years or older. Early results indicated that some patients likely could have difficulty completing the questionnaire without support due to visual impairment and cognitive difficulties. Based on these findings, the questionnaire was shortened, the language simplified, and the format changed to be interviewer administered. Subsequent interviews in the UK and other countries supported the length and wording of the revised questionnaire, as well as the mode of administration.

Conclusions: Appropriate questionnaire design is essential to optimize data quality. Careful pretesting is critical to ensure appropriate wording and administration format, particularly when there is potential for visual and/or cognitive impairment within the target population.

548. A Cross-Sectional Study on the Adequacy of Product Information in Medical Advertisements Published in Print Media

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Background: Previous studies overseas reported that medical advertisements (MAs) contained unreliable information or unsubstantiated claims.

Objectives: To evaluate the adequacy of medical product information in MAs published in print media in Singapore.

Methods: A cross-sectional study was conducted on MAs (containing Health Sciences Authority advertisement permit numbers) in English-language newspapers and magazines. MAs were evaluated on (i) peripheral properties (using a 11-points scoring system); (ii) consumer education information (19-points scoring system) consisting of uses and benefits (6-point), risks (6-point), and consumer counselling (7-point); and (iii) credibility (claims substantiation). Statistical significance was set at <0.05.

Results: Of 37 unique-products advertisements evaluated, the scores for peripheral properties were comparable for all MAs [median (IQR) score: 4 (4, 5)]. The score for consumer education information was 5 (4, 7), with significant differences in scores between advertisements of pharmaceutical products and health supplements ($p=0.013$) and among advertisements of different sizes ($p=0.024$). Information on risks was found lacking in MAs, with median scores of 0 (0, 0), with only 2 MAs mentioning special precautions. Further analyses also revealed significant differences in scores for uses and benefits, and consumer counselling, with scores of 3 (3, 4), and 1 (1, 3), respectively.

Conclusions: Overemphasis on products benefits, deficiency of product risk information, compromised information adequacy due to size of advertisements, differential consumer counselling information in health supplement advertisements and lack of claims substantiation were potential gaps identified in local MAs. Adequacy of information provided in MAs can be improved to provide consumers with relevant product information against misleading advertising.

549. Content Analysis and Frequency of Direct-to-Consumer Advertising (DTCA) of Health Products on Television (TV) in Singapore

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Background: Advertisements can affect consumers' purchase decisions, and it is crucial to understand how advertisements are shown on television (TV) and the techniques used. However, little is known about direct-to-consumer advertising (DTCA) of health products on TV in Singapore.

Objectives: To gather information on the frequency and placement of health product advertisements on TV; and understand the types of persuasive techniques utilized in DTCA on TV.

Methods: TV programs on Channel 5 were recorded over 14-hours every day over a 3 months duration.

Advertisements with the Singapore Health Sciences Authority (HSA) advertisement permit number were included for content analysis, in terms of frequency and time of day of screening and their durations; the genres of TV programs that they were featured and also the persuasive techniques used in the DTCA. Descriptive statistics were generated to summarize the data.

Results: 1150 advertisements were recorded over the 3 month period, with 30 different advertisements showing 21 unique products from 4 categories. Most advertisements were 15s long (n=16, 53.3%). The occurrence of advertisements followed a cyclical pattern, peaking over the weekends. Typically, the average number of advertisements per hour decreased after mid-day. Most advertisements used positive valence as a persuasive technique and all advertisements showed the type of formulation of the product and its uses.

Conclusions: Many health product advertisements share similar characteristics in their advertising campaigns. Our findings provided fundamental understanding of how DTCA could be relevant to provide product information and influence the patients in self-treatment.

550. A Study of "Drug Entry Lags" Between Japan and the US: Compering the Timing of a New Drug Entry, Generic Entry and Market Exclusivity Periods

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Background: Very little is known about the timing of generic entry in different countries. No prior study has examined the influence of the market exclusivity period on launch times of generics.

Objectives: The market exclusivity period (MPE) which is between the timing of a new drug entry and generic entry were assessed in Japan and the US to compare the both time lags between the two countries in the period of 2007 - 2015.

Methods: New drug and generic drug approval/listed data were collected from notices of Ministry of Health, Labor and Welfare (MHLW) in Japan and the FDA Orange Book in the US. During the study period, 55 drugs were identified to compare MPE and the time lag of market entry in both countries. Analysis included generic drugs only of new moleculer entities at first MHLW/FDA approval and excluded having more than 25years market exclusivity. Descriptive, Spearman's rank-correlation analyses were performed, stratified by types of drugs (oral, injection and external).

Results: The timing of generic entry in Japan was later than that in the US by 3.25±3.86 (mean±SD) years, at a median of 2.41years (interquartile range 0.53, 5.34), and the timing of a new drug in Japan was also later by 3.25±3.86years, at a median of 2.98years (0.35, 4.38). Both time lags strongly correlate (ρ=0.6537, p=<.0001). The mean MEP in Japan was 12.53 ±3.26years, at median of 12.03 years (10.03, 14.08), while MEP in the US was 12.12±2.97years, at median of 12.65 years (9.86, 14.51). Both periods correlate (ρ=0.4456, p=0.0007). The mean MEP of oral (n=35), injection (n=15) and external (n=5) drugs in Japan was 11.94±2.68years, 14.70±3.68years, 10.08 ±2.61years, while MEP in the US was 11.66 ±2.70years, 13.44±3.03years, 11.41±4.01years respectively. The MEP in Japan had no correlation with generic entry lag in both countries, but strong correlation with new drug entry lag (ρ=-0.5123, p=<.0001). The MPE in the US had strong correlation with generic entry lag (ρ=-05055, p=<.0001), but no correlation with new drug entry lag.

Conclusions: The time lag of a new drug entry in both countries could directly influence on the time lag of generic entry.

551. Prevalence of Preexisting Diabetes in Pregnancy and Associated Prescribing Patterns

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Background: Diabetes mellitus (DM) is one of the commonest chronic conditions affecting pregnancy; 2-5% of pregnancies are affected, with increasing prevalence. Preexisting DM in pregnancy is related to adverse events for mother and baby, optimal glycaemic control prior and during pregnancy reduces the risk.

Objectives: Compare characteristics of pregnant women with and without DM. Examine time trends in the prevalence of: DM in pregnancy, and prescribing during pregnancy.

Methods: Pregnant women aged 16 years or over were identified as diabetic via diagnostic Read codes and prescriptions. Women were compared in terms of: age, body mass index (BMI), blood pressure, smoking status, social deprivation score and HbA1c. Prevalence of preexisting DM and prescriptions were calculated by calendar year and DM type between 1995 and 2012.

We used The Health Improvement Network (THIN) primary care database; a database of anonymised electronic general practice medical records.

Results: Data from 402,529 pregnancies suggest women with preexisting DM were: older (median: 30, 31 vs 29 years for type 1 (T1DM), type 2 (T2DM) and non-diabetic), had higher BMI (median: 25.9, 29.9 vs 24.1 kg/m2 for T1DM, T2DM and non-diabetic), and were registered with a general practice for longer than pregnant women without DM. Pregnant women with T2DM were more likely than T1DM to be: non-smokers (46% vs 43%) and had better glycaemic control prior to pregnancy (median HbA1c 37 vs 65mmol/L).

The prevalence of T1DM in pregnancy increased from 3.2 to 5.2 per 1000 pregnancies between 1995 and 2012 and for T2DM the increase was from 0.8 to 8.7 between 1995 to 2008 and then to 22.6 per 1000 pregnancies by 2012.

The prevalence of prescribing DM therapy in primary care during pregnancy increased for T1DM and decreased for T2DM between 1995 and 2012.

Conclusions: Women with T2DM had better glycaemic control prior to pregnancy than T1DM women. The prevalence of both T1DM and T2DM increased in pregnancy, prevalence of T2DM accelerated after 2008. The prevalence of prescribing during pregnancy increased in T1DM and decreased in T2DM pregnancies. It is likely that many pregnant women receive treatment in secondary care during pregnancy.

552. Safety Of Antidiabetic Drugs In A Cohort Of Pregnant Women With Pre-Gestational Diabetes

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Background: Women with insulin dependent diabetes are at an increased risk for miscarriage and several types of congenital malformations in their offspring. However, little is known about the comparative safety of oral antidiabetic medications.

Objectives: To evaluate the relative safety of antidiabetic treatments in pregnant women with pre-gestational diabetes.

Methods: We used The Health Improvement Network (THIN) database in the UK from January 1995-June 2012 to identify the first pregnancy in women aged 15-45 during the study period. Information on both diabetes diagnoses and prescription of specific antidiabetic drugs around conception was collected. An unexposed non-diabetic comparison cohort of 10,000 pregnancies was matched to 1511 women with pregestational diabetes on calendar time and maternal age. To study outcomes in the offspring, the cohorts were restricted to pregnancies linked to a live birth. The risk of major birth defects was estimated and compared with odds ratios (OR) and 95% confidence intervals (CI), using logistic regression.

Results: The risk of miscarriage was 10.5% in non-diabetic and 15.8% in diabetic women (17.4% in non-treated, 27.4% in oral treatment and 13.3% in insulin only users during the 1st trimester). Among completed pregnancies, the risk of major birth defects was 2.8%

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in non-diabetic vs. 7.4% in diabetic women (4.3% in non-treated, 1.9% in oral treatment, 8.9% in insulin users during the 1st trimester). The adjusted OR of major malformations for diabetes was 2.7 (95%CI 1.9-3.7) compared to women without diabetes. Restricting to women with diabetes, the ORs of major malformations were 2.2 (95%CI: 1.2-4.2) for type 1 compared with type 2, 3.5 (95%CI 1.3-10.1) for insulin use compared with oral antidiabetics during 1st trimester, and 2.8 (95%CI: 1.4- 5.6) for HbA1c >7% compared with HbA1c values <=7% before pregnancy.

Conclusions: Women with diabetes have a higher risk of adverse obstetric outcomes. Among women with pre-gestational diabetes, diabetes type 1, treatment with insulin or poor glycemic control were associated with a higher risk of major congenital malformations in the offspring.

553. Tocilizumab Use in Pregnancy: Analysis of a Global Safety Database Including Data from Clinical Trials and Post-Marketing Data

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Background: Tocilizumab is an anti-interleukin-6-receptor monoclonal antibody used for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. Published experience on tocilizumab use during pregnancy is very limited.

Objectives: Analyze the cumulative evidence for pregnancy outcomes after maternal exposure to tocilizumab.

Methods: We have analyzed 501 pregnancy-related reports documented in the Roche Global Safety Database until December 2014.

Results: After exclusion of ongoing pregnancies, duplicates, and cases retrieved from the literature, 399 women were found to have been exposed to tocilizumab shortly before or during pregnancy, with pregnancy outcomes being reported in 288 pregnancies (72.2%). Of these 288 pregnancies, 180 were prospectively reported resulting in 109 live-births (60.6%), 39 spontaneous abortions (21.7%), 31 elective terminations of pregnancy (17.2%), and 1 stillbirth. The rate of malformations was 4.5%. Comedications included methotrexate in 21.1% of the prospectively ascertained cases. Compared to the general population, an increased rate of preterm birth (31.2%) was observed.

Retrospectively reported pregnancies (n=108) resulted in 55 live births (50.9%), 31 spontaneous abortions (28.7%), and 22 elective terminations (20.4%). Three infants/fetuses with congenital anomalies were reported in this group.

No increased risks for adverse pregnancy outcomes were observed after paternal exposure in 13 pregnancies with known outcome.

Conclusions: No indication for a substantially increased malformation risk was observed. Considering the limitations of global safety databases, the data do not yet prove safety, but provide information for physicians and patients to make informed decisions. This is particularly important after inadvertent exposure to tocilizumab, shortly before or during early pregnancy.

554. Congenital Malformations and Maternal Use of Anti-Hypertensive Medication in the UK

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Background: Few studies have assessed the use of anti-hypertensives among women of child bearing age in the real world. Most studies have been unable to stratify anti-hypertensives to assess fetal outcomes and health risks per drug class, particularly angiotensin II receptor blockers (ARBs) and angiotensin-converting-enzyme inhibitors (ACEI).

Objectives: To evaluate adverse fetal outcomes (congenital malformation in live births or post-partum infant death) in women treated with anti-hypertensives.

Methods: Pregnant hypertensive women were included in this study from Jan 1, 1997 to Dec 31, 2014. The UK Primary healthcare data, Clinical Practice Research Data Link were linked with inpatient hospital episode statistics and the Office of National Statistics mortality data, to describe the potential fetal

effect from exposure to anti-hypertensives during pregnancy. Where possible, mothers were linked to records relating to their newborn. Pre-existing diabetes or heart failure, weight, age at pregnancy, smoking, and Index of Multiple Deprivation, were also analysed to understand the mother's risk profile impacting adverse fetal outcomes.

Results: Of 34701 pregnant hypertensive women with at least 1 live birth, 5437 (16%) were on anti-hypertensives at any time during their pregnancy, including beta blockers (69%) calcium channel blockers (14%) and diuretics (12%). ACEI were prescribed more frequently than ARBs 9.7% vs 2.7% and both were prescribed across all trimesters but less so as pregnancy progressed. Whether a mother is on an anti-hypertensive drug during pregnancy, 1 yr prior to pregnancy, or not on anti-hypertensive medication, there were no differences in adverse fetal outcomes, 7.4%, 7.1%, and 7.1%, respectively [X2=0.49, 2DF, p=0.78]. The most frequent birth defects were similar across exposure groups: Nevus, undescended testicle, Patent Ductus Arteriosus, and Ventricular Septal Defect.

Conclusions: Most children with mothers exposed to any anti-hypertensive during or 1 yr prior to pregnancy did not develop fetal abnormalities. Improved screening methods and more attentive care to high-risk mothers may further decrease the number of fetal malformations found in this study.

555. Use of Antihypertensive Drugs During Pregnancy in the Netherlands

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Background: Antihypertensive drugs are used during pregnancy for both chronic hypertension and gestational hypertension. Methyldopa, labetalol and nifedipine are considered safe for the fetus during pregnancy and are therefore recommended in the Dutch guidelines.

Objectives: To determine how often antihypertensive drugs are prescribed in pregnancy and whether recommended drugs are prescribed.

Methods: Using IADB.nl, a database with prescription records of 500,000 people in the Netherlands we investigated the use of antihypertensive drugs of women in the 273 days before the birth of their child.

Results: Antihypertensive drugs were used in 2.3% of the pregnancies. Of these 44% used a not recommended drug in the first trimester of pregnancy, 22% in the second trimester and 10% in the third trimester.

Of the pregnant women with chronic hypertension 49% used a recommended drug already before the pregnancy, 23% stopped using antihypertensive drugs during pregnancy and 17% switched to a recommended drug. 10% used a not recommended antihypertensive drug during the whole pregnancy.

Of the women who started an antihypertensive drug after the 20th week of pregnancy, probably the group with gestational hypertension, 94% used a recommended drug.

Conclusions: In most pregnancies antihypertensive drugs were used which are recommended as safe for the unborn child by the Dutch guidelines. In the first trimester 44% used a not recommended drug. Of the women with chronic hypertension 10% continued using a not recommended drug. More information to and education of women with chronic hypertension in the fertile age, by GP's and pharmacists could decrease these percentages.

556. Exposure To Thiocolchicoside During Pregnancy: First Clinical Data in EFEMERIS

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Background: Following a recent safety alert from the European Medicines Agency, thiocolchicoside, a colchicine derivative indicated for the treatment of painful muscular contractions, has been contraindicated during pregnancy. This decision was based on the experimental evidence of aneugenic properties of one of its metabolites. Aneuploidy is recognized as a potential risk factor for miscarriage and congenital birth defects. At the present time, human data concerning thiocolchicoside in pregnancy are not available in the literature.

Objectives: The objective of this study was to describe pregnancy outcomes of women having at least one prescription and dispensation of thiocolchicoside during pregnancy.

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Methods: We performed a descriptive study in EFEMERIS, a French database of pregnant women who delivered in Haute-Garonne and their outcomes (live birth or pregnancy loss). Between 2004 and 2013, 90,013mother-child (fetus) pairs were included.

Results: During the 9-year study period, 425 of fetus registered in EFEMERIS (0.5%) were exposed to thiocolchicoside during pregnancy: 302 during the first (71.1%), 95 during the second (22.4%) and 37 during the third (8.7%) trimester.

The outcome was a pregnancy loss (legal or therapeutic termination, miscarriage, stillbirth, and ectopic pregnancy) for 68 exposed women (16.0%). Eight cases of birth defects (1.9%), without any co-prescription for a mutagenic or teratogenic drug, were identified with 4 chromosomal abnormalities (0.9%): 3 trisomies 21 and 1 trisomy 18. In general population on the same geographical area (EFEMERIS data), the prevalence of these outcomes was the following: pregnancy losses 5.9% ($p<0.0001$), birth defects 2.1% ($p=0.8$) and chromosomal abnormalities 0.2% ($p=0.02$).

Conclusions: Women exposed to thiocolchicoside during pregnancy had a higher prevalence of pregnancy losses and chromosomal abnormalities than general population. These first epidemiological data on exposure to thiocolchicoside during pregnancy strengthens the recommendation that physicians must avoid prescribing this drug to women of childbearing age without effective contraception.

557. Venlafaxine Exposure in Pregnancy, A Multicenter ENTIS Study

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Background: Venlafaxine is a serotonin and noradrenaline reuptake inhibitor used for the treatment of depression and anxiety disorders. The experience with venlafaxine use in pregnancy is still limited compared to the selective serotonin reuptake inhibitors.

Objectives: The primary aim of this study is to assess the rate of major congenital malformation (MCMs). Secondary aims are pregnancy outcomes: spontaneous abortion, preterm delivery and birthweight.

Methods: This multicenter, prospective cohort study was performed using data from nine centers of the European Network of Teratology Information Services (ENTIS). Information about the exposure, pregnancy data and pregnancy outcome were collected after individual risk counseling. Standardized procedures for data collection and follow up were used by each center. Venlafaxine exposure is compared with a group of women not exposed to any known teratogen during pregnancy. Analysis was performed using logistic regression.

Results: Follow up data were collected on 732 pregnancies of women who used venlafaxine during gestation. In 655 (89.5%) cases the exposure was at least in the first trimester. In total there were 590 live births (5 twins), 85 spontaneous abortions, 57 elective terminations of pregnancy (ETOPs) and 5 stillbirths. In the comparison group were 656 live births (6 twins), 46 spontaneous abortions, 25 ETOPs and 3 stillbirths.

The overall rate of MCMs after first trimester exposure and excluding chromosomal and genetic disorders was 3.25% (17/523) in all live births/stillbirths and ETOPs with known MCM compared to 2.44% (16/656) in the comparison group, OR 1.34 (95% CI 0.67-2.69). The number of preterm deliveries was higher in the venlafaxine group, 62 compared to 36 in the comparison group. No statistical difference was found in the mean birthweight of live born singletons, 3240mg (venlafaxine group) and 3297mg (comparison group).

Conclusions: In this study venlafaxine was not associated with an increased rate of MCMs. The rate of

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spontaneous abortion and preterm delivery was higher in the venlafaxine group. Further analysis of the data is necessary to investigate the role of potential confounding factors.

558. Rates of Psychotropic Prescribing in Pregnancy

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Background: Perinatal mental illnesses are common, affecting 1 in 5 women at some point during pregnancy or up to one year after. However, there is uncertainty around using any type of pharmacological interventions during pregnancy and breastfeeding due to the possible risks to the fetus and nursed infant.

Objectives: To assess trends in annual levels of prescribing of psychotropic medication in pregnancy stratified by drug group and by type of mental illness.

Methods: The source population comprised of all acceptable female patients in the CPRD who were registered at an English practice contributing between 01/04/2007 and 31/03/2015. Pregnancies where a potential start and end data could be identified were evaluated. End of pregnancy was identified using Read codes suggestive of pregnancy outcomes (labor, stillbirth, delivery, miscarriage). If end of pregnancy dates were less than 90 days apart they were presumed to be part of the same pregnancy. Start of pregnancy was identified as the event furthest from the end of pregnancy date and within 280 days. Patients who had more than one pregnancy were included multiple times.

Psychotropic prescriptions which were up to three months prior to or during pregnancy were identified. Only one record per psychotropic category per pregnancy was counted. Where enough data was available pregnancies with a psychotropic prescription were stratified by mental health categories. Patients were followed until the earliest of 365 days post pregnancy or the end of their follow up for evidence of prescribing.

Annual rates of psychotropic prescribing were calculated per 100,000 pregnancies. 95% confidence intervals for rates were calculated using a binomial distribution. Pregnancies were counted in the year in which they ended.

Results: The prescribing of antidepressants in pregnancy has significantly increased over time (2007-14) with most recent estimates of the rates of SSRI's showing 5573.05 (95%CI 5234.71-5925.79) per 100 000 pregnancies.

Conclusions: Rates of antidepressant prescribing in pregnancy have increased despite NICE recommendations that psychological therapies should be first line treatment for most women presenting with mild or moderate illnesses.

559. Psychopharmacological Drug Utilization Patterns in Pregnant Women with Bipolar Disorder – A Nationwide Register-Based Study

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Background: Bipolar disorder is often associated with a lifetime indication for treatment with psychotropic drugs, thus pregnant women and women planning pregnancy face the dilemma whether to continue treatment or not. The therapeutic strategy is often determined by an individual risk-benefit analysis, balancing the potential teratogenic effects of the psychotropic drugs against the risk of relapses. Little is known about the actual treatment patterns in these women.

Objectives: To investigate the psychopharmacological drug utilization patterns before, during and after pregnancy among women with bipolar disorder.

Methods: We conducted a register-based cohort study among all Danish women aged 15-55 with a diagnosis of bipolar disorder registered in the Danish Psychiatric Central Research Register, who gave birth to their first and singleton child between January 1997 and December 2012. Psychotropic drug use was determined from 1 year preconception to 1 year postpartum by prescriptions obtained from the Danish National Prescription Registry.

Results: We included 336 women. The proportion of women redeeming prescriptions for any psychotropic drug decreased during pregnancy, from 54.8% in the 3 months preconception to 36.6% in the third trimester. Lithium dosing increased significantly during pregnancy. Antidepressants were the most commonly used psychotropic drugs before, during and after

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pregnancy. 41.2% of the women on psychotropic monotherapy (N= 85) and 50.0% of the women on psychotropic polypharmacy (N= 74) used an antidepressant without concomitant use of a mood-stabilizer at some time during pregnancy.

Conclusions: We found a decrease in the proportion of women redeeming prescriptions for psychotropic drugs during pregnancy. The high prevalence of antidepressant use without a mood-stabilizer, potentially putting women at risk for a switch to mania, calls for further investigation.

560. Impact of Evolution and Intensity of Prenatal Exposure to Anxiolytics and Hypnotics on Neonatal Health: A Study in EFEMERIS Using a Trajectory Method

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Background: The effects of exposure to anxiolytics and hypnotics during late pregnancy on the neonate are well-known. However, women can be differently exposed to the drugs and no data exist on the relationship between the characteristics of this exposure and neonatal health.

Objectives: To provide data on the potential risk for the newborn according to evolution and intensity of exposure to anxiolytics and hypnotics during pregnancy.

Methods: The study was performed in EFEMERIS (database of pregnant women) between 2004 and 2010. Individual trajectories of exposure to anxiolytic and hypnotic drugs were defined by both the evolution of exposure and the intensity of treatment (addition of DDD of anxiolytics and hypnotics (N05B, N05C)) during pregnancy. An implementation of the standard partitioning method K-means adapted to longitudinal data was used to classify these trajectories in clusters (profiles).(1)

Neonatal pathologies at birth were studied, using the following parameters as indicators: need of oxygen therapy, intubation, neonatal resuscitation or transfer at birth. The occurrence of these events was compared between the different clusters, using multinomial logistic regressions.

(1) Comput Stat 2009; 25: 317–32.

Results: Four clusters of pregnant women with homogeneous trajectories of exposure were identified: one with a low constant level of exposure (EA), one with an exposure decreasing during the first trimester of pregnancy and a low constant level thereafter (EB), one with a moderate constant level of exposure (EC) and one with a high level of exposure (ED).

A significant difference in the rates of neonatal pathologies was observed. Newborns of clusters EC and ED were more at risk of developing neonatal pathologies than newborns of cluster EA (ORC/A=2.1 [1.0-4.2] and ORD/A=8.1 [2.9-22.2]) or cluster EB (ORC/B=2.6 [1.2-5.7] and ORD/B=10.0 [3.5-29.4]).

Conclusions: The use of the trajectory method shows that a high anxiolytic-hypnotic burden throughout pregnancy may increase the risk of neonatal pathology. Other situations do not appear to be associated with such an increased risk.

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561. First Trimester Antidepressant Use in the National Birth Defects Prevention Study

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Background: As many as 18% of pregnant women are believed to have depression. Untreated depression is associated with an increase in several adverse pregnancy outcomes, making the management of depression during pregnancy critical. However, possible associations between antidepressant use in early pregnancy and birth defects have been reported.

Objectives: To describe the use of antidepressants during the first trimester of pregnancy.

Methods: We analyzed data from the 1997–2011 National Birth Defects Prevention Study (NBDPS), a population-based, multi-site, case-control study of

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birth defects, to estimate the proportion of mothers who reported antidepressant use in the first trimester of pregnancy (defined here as the period from 1 month before to 3 months after conception to account for uncertainty in conception dates). Analyses were restricted to mothers of live-born infants without major birth defects and to the NBDPS study sites that were collecting data both at the beginning and end of the study period (i.e., California, Georgia, Iowa, Massachusetts, New York, and Texas).

Results: Overall, 271 (3.7%) of 7343 mothers reported taking an antidepressant during their first trimester of pregnancy. Of these, 74.5% reported taking only selective serotonin reuptake inhibitors, 4.8% reported taking only serotonin-norepinephrine reuptake inhibitors, 3.7% reported taking only tricyclic antidepressants, 11.1% reported taking only antidepressants from among other types (i.e., bupropion, mirtazapine, nefazodone, or trazodone), and 5.9% reported taking more than one antidepressant class. First trimester antidepressant use increased during the study, peaking in 2010–2011 (6.1%). The most commonly reported antidepressants were sertraline, fluoxetine, paroxetine, bupropion, and citalopram.

Conclusions: Antidepressant use during the first trimester of pregnancy is common and these data suggest it was increasing at least until 2011. These findings support the need to evaluate the potential teratogenicity of these medications by assessing associations between maternal antidepressant use in early pregnancy and the risk for specific birth defects.

562. Withdrawn by Author

563. Should We Treat Or Not Mildly To Moderately Depressed Pregnant Women During Pregnancy?

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Background: Depression is prevalent in women of reproductive age and antidepressants (ADs) are widely used. Given that the majority of depressed pregnant women are mildly to moderately depressed, there is no current consensus on whether treatment with ADs is beneficial in this sub-group.

Objectives: This study aimed to investigate whether ADs use during pregnancy was associated with the risk of postpartum depression (PPD) in mildly to moderately depressed pregnant women.

Methods: A cohort study was performed using the Quebec Pregnancy Cohort (QPC). All pregnancies with a diagnosis of depression or anxiety, or exposed to antidepressants in the 12 months before pregnancy, and ending with a delivery were included. Exposure during pregnancy was classified in five groups (not exposed (reference); exposed throughout pregnancy; first trimester exposure only; second/third trimester exposure only; and intermittent). PPD was defined as having a hospital diagnosis from 1 month after delivery until 12 months postpartum. Cox proportional hazard models were used to estimate crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CI), adjusting for potential confounders including severity of the depression.

Results: 20,647 pregnancies met inclusion criteria. When adjusting for potential confounders, women exposed to antidepressants throughout pregnancy (aHR=1.59; 95% CI: 0.52-4.79; 4 exposed cases), those exposed in the first trimester only (aHR=1.90;95% CI: 0.86-4.22; 8 exposed cases), and those exposed in the second/third trimester only (aHR=1.72; 95% CI: 0.43-6.97; 2 exposed cases) were comparable to depressed pregnant women that did not take antidepressants during gestation in terms of their risk of PPD. However, pregnancies with intermittent exposure were at higher risk of PPD when compared to non-exposures (aHR =2.85; 95% CI: 1.31-6.21; 10 exposed cases).

Conclusions: This study showed that antidepressant use in mildly to moderately depressed pregnant women was not associated with lower risk of PPD compared to non-use. Women with intermittent exposure, however, were at higher risk of PPD, suggesting potential residual confounding by severity of depression in this sub-group.

564. Maternal Depression and Use of Antidepressants During Pregnancy Increase the Risk of Adverse Pregnancy Outcomes: An IPD Meta-Analysis

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Background: Recent systematic reviews and meta-analyses examining the adverse effects of maternal depression and the use of antidepressants during pregnancy show inconclusive results. As a result, prospective parents, prenatal care providers, general practitioners, and psychiatrists cannot make evidence-based decisions on treatment possibilities.

Objectives: Therefore, we performed an individual patient data (IPD) meta-analysis on the associations between non-pharmacologically managed maternal depression or antidepressant use during pregnancy and the occurrence of preterm birth, low birth weight, small for gestational age (SGA), and poor Apgar scores.

Methods: A systematic literature search was conducted until February 2015. For eligible publications (n=201), the methodological quality was independently assessed with the Newcastle-Ottawa Scale by two reviewers. All authors that could be traced were invited to share their original data. These individual patient data were used in a 1-stage random-effect meta-analyses based on logistic regression models.

Results: So far, data from 125.095 individual patients have been collected out of 28 studies. The preliminary analyses showed adjusted odds ratios for self-reported symptoms of depression ranging from 1.24 (1.06-1.45) for preterm birth and 1.36 (1.19-1.55) for low birth weight to 1.82 (1.38-2.40) for poor Apgar scores at 5 minutes. Adjusted odds ratios for antidepressant use during pregnancy ranged from 1.02 (0.68-1.53) for SGA and 1.43 (1.01-2.04) for low birth weight to 2.07 (1.58-2.72) for preterm birth.

Conclusions: So for all pregnancy outcomes studied, associations were observed with self-reported symptoms of depression and antidepressant use, except for SGA and antidepressant use. This IPD meta-analysis overcomes the inconclusive results of other systematic reviews and meta-analyses and provides evidence-based information on the potential adverse effects of maternal depression and use of antidepressants during pregnancy on several pregnancy outcomes.

565. The Risk Of Specific Congenital Anomalies In Relation To Newer Antiepileptic Drugs; A Literature Review

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Background: Anti-epileptic drugs (AEDs) are used by women of fertile age. Of the newer AEDs more information is needed about possible associations between the use in the first trimester of pregnancy and specific congenital anomalies of the fetus.

Objectives: We performed a literature review to find signals indicating the association of newer AEDs and specific congenital anomalies.

Methods: Pubmed and Embase were searched to find studies with pregnancies exposed to newer AEDs and detailed information on congenital anomalies. The specific congenital anomalies in the studies were classified according to the congenital anomaly subgroups of European Surveillance of Congenital Anomalies (EUROCAT). We compared the prevalence of specific congenital anomalies of fetuses exposed to individual AEDs of the combined studies to the prevalence of the general population in a reference database. A significant higher prevalence based on three or more cases among the exposed fetuses was considered as a signal.

Results: Four signals were found indicating the association of exposure to either lamotrigine or topiramate monotherapy in the first trimester of pregnancy and a specific congenital anomaly. Of levetiracetam, gabapentin and oxcarbazepine no signals were found. The possible associations of topiramate and cleft lip with or without cleft palate and hypospadias were noted in the conclusion of the articles.

Conclusions: Concerning the association of monotherapy of a newer AED in the first trimester of pregnancy and a specific congenital anomaly the

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signals of topiramate and cleft lip with or without cleft palate and hypospadias should be investigated further.

566. Prenatal Exposure to Non-Steroidal Anti-Inflammatory Drugs and Child Behavior at 36 Months: Birth Weight and Gestational Age as Mediators

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Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are analgesic medications that are used by approximately 10% of pregnant women. No prior studies have investigated effects of prenatal NSAID exposure on neurodevelopment, although several have observed low birthweight and gestational age.

Objectives: To examine the direct and indirect effects of NSAIDs on child neurodevelopment, using causal mediation analysis.

Methods: The Norwegian Mother and Child Cohort Study is a questionnaire-based longitudinal study. We identified 101 625 live non-malformed singleton births, of which 43 673 completed 36 month follow-up. NSAIDs exposure was ascertained by self-report; outcome (internalizing and externalizing behavior) was measured using the Child Behavior Checklist (CBCL); birthweight (BW) and gestational age (GA) were gathered from birth registry linkage. Effect decomposition was used to quantify marginal total (MTE), natural direct (NDE) and natural indirect (NIE) effects of prenatal NSAID exposure on behavior using the SAS macro %mediation, adjusting simultaneously for confounders and allowing for exposure-mediator interaction. Results reported are mean differences in standard deviation units, with 95% confidence intervals (CI) calculated using the delta method.

Results: Of 43 673 pregnancies included, 2907 (6.7%) used NSAIDs during pregnancy. NSAID exposure was associated with an increase in both externalizing (TME: .08, 95% CI .04 to .11) and internalizing (TME: .04, 95% CI .01 to .08) behaviors. These effects were not mediated by BW (NIE for externalizing: -.0009, 95% CI -.0030 to .0020; NIE for internalizing: .0017, 95% CI -.0005 to .0037) or GA (NIE for externalizing: .0017, 95% CI -.0005 to .0039; NIE for internalizing: -.0009, 95% CI -.0011 to .0027).

Conclusions: Prenatal NSAID exposure was associated with increased internalizing and externalizing behaviors in 3-year-old children, and these effects are not attributable to associations between NSAID exposure and BW or GA. The effects are small, but given the frequency of NSAID use, warrant further attention to better understand possible public health implications.

567. Opioid Use Following Discharge After Cesarean Delivery

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Background: Prescription opioid abuse has emerged as a significant public health issue in the U.S., with leftover medications representing a major source of misused or diverted prescription opioids. With over 1.3 million cesarean deliveries (CDs) performed annually in the U.S, it is imperative to align the amount of post-discharge opioids that are prescribed and consumed. Currently, the amount of opioids typically consumed following discharge from CD is not known.

Objectives: To evaluate patterns of oral opioid use after CD.

Methods: We conducted a survey at 6 academic medical centers in the U.S. from 9/2014 to 1/2016. Women undergoing a CD who agreed to participate in the study were contacted by phone two weeks after discharge and answered a standardized interview about their use of oral opioids.

Results: A total of 667 women were enrolled; of these, 576 (86.4%) filled an opioid prescription. Oxycodone

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was the most commonly prescribed opioid (85.4%), followed by hydrocodone (7.4%) and hydromorphone (7.2%). The median number of dispensed tablets was 40 (IQR 30 to 40), the median number of consumed tablets was 20 (IQR 8 to 30), and median number of leftover tablets once the patient finished taking opioid was 15 (IQR 3 to 28). Of those with leftover opioids, 93.2% had not disposed of the excess medication at the time of the interview.

Tertiles were defined corresponding to the number of pills dispensed (≤30, 31 to 40, >40). The median number of pills consumed was higher in the groups with a larger amount dispensed: the median for ≤30 was 15 (IQR 5 to 23), for 31 to 40 was 20 (IQR 10 to 36), and for >40 was 30 (IQR 10 to 50), $p<0.001$. This association was independent of pain scores in the hospital and other clinical characteristics of the patients. The proportion of patients in each group who reported being very satisfied or satisfied with their pain regimen was similar across the 3 groups (86%, 87%, and 86%, respectively; p=0.99).

Conclusions: The amount of opioid prescribed following CD generally exceeds the amount consumed by a significant margin, leading to substantial amounts of leftover medication. Satisfaction with pain regimen was unrelated to the number of pills dispensed.

568. Opioid Use During Pregnancy: A Population-Based Cohort Study

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Background: Opioid use early in pregnancy may contribute to congenital abnormalities and use late in pregnancy has been associated with neonatal abstinence syndrome. Overall use of opioids has been increasing in the Canadian population which may impact opioid use during pregnancy.

Objectives: To assess the level of opioid use before, during and after pregnancy in a population-based cohort.

Methods: A cohort study was conducted in Manitoba, Canada of opioid use from 2000-2014 using the Drug Program Information Network Database. Opioid use was defined by prescriptions for opioids and oral morphine equivalents (MEQ) during the 3 months before pregnancy and each trimester of pregnancy. Chi square and t-test were used to compare opioid use at the beginning and end of the study period. Repeat measures ANOVA and GEE were used to evaluate opioid use across pregnancy trimesters.

Results: Of the 175,174 pregnancies assessed, in the 3 months prior to pregnancy 6.7% of women filled prescriptions for an opioid. This use fell to 4.3% during the first trimester of pregnancy and remained at 3% in the 2nd and 3rd trimesters. The overall average MEQ of use fell from 28mg prior to pregnancy to 21mg, 16mg and 15mg in the 3 trimesters of pregnancy, respectively. For both use and MEQ, all differences were significant ($p<0.02$) except the difference between the 2nd and 3rd trimesters. However, the MEQ among users increased significantly over the study period (281 to 1036mg; $p<0.0001$) with only a modest increase in the number of women who used opioids during pregnancy (4.4% to 4.9%; $p<0.03$). Codeine was used by 96% of all users and accounted for 63% of MEQ.

Conclusions: Many women who use opioids prior to pregnancy discontinue or reduce their use during pregnancy. Use is higher in the critical period of the first trimester than in the second and third trimesters. While the percentage of opioid users in pregnancy is low, the amount of opioid by these users is increasing over time.

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569. Increase in Aberrant Prescription Opioid Use by Pregnant Women in a Nationwide Cohort of Medicaid Beneficiaries

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Background: Opioid abuse during pregnancy is linked to substantial maternal and infant morbidity, but the extent of misuse and abuse during pregnancy has not been well documented in the US population.

Objectives: To describe the prevalence of aberrant prescription opioid use and evaluate geographic and temporal trends in a large, nationwide cohort of Medicaid-enrolled pregnant women.

Methods: Claims data for a cohort of pregnant women were gathered from the Medicaid Analytic eXtract for the years 2000-2010. Data on patterns in opioid dispensing during pregnancy including overlapping prescriptions, use of multiple providers/pharmacies, and excessive dose/supply of opioids were used to identify aberrant opioid use behaviors according to four previously published definitions (the Opioid Misuse Score, Controlled Substance-Patterns of Untilization Requiring Evaluation [CS-PURE], Overutilization Monitoring System, and Cepeda et al algorithms). We examined variations in the prevalence of abberrant use by geographic region and over time, and two-sided Cochran-Armitage tests were conducted to test for time trends.

Results: Of the 1,618,501 pregnant women in the cohort, 20.1% (n = 325,457) received at least one opioid prescription during pregnancy. Prevalence of aberrant use varied by definition, ranging from 0.4 to 3.6 per 1,000 pregnancies. Women who were white, had a chronic pain diagnosis, a mental health disorder, or a substance abuse disorder were more likely display aberrant opioid use behaviors, and there was a more than 6-fold difference in the prevalence of aberrant use between states. Over the ten-year study period, prevalence of aberrant opioid use in pregnancy more than doubled across all definitions ($p < 0.001$ for all algorithms), and the proportion meeting any algorithm increased from 2.4 to 6.2 per thousand pregnancies.

Conclusions: We observed substantial increases in the prevalence of aberrant prescription opioid use among Medicaid-enrolled women between 2000 and 2010. These findings highlight the need for preventative strategies and interventions to safely treat opioid use disorders during pregnancy.

570. Risk Of Preterm Birth Following Late Pregnancy Exposure To Medications Used In The Treatment Of Autoimmune Diseases (AD)

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Background: The number of women of childbearing age with AD has increased over the past decades; women using anti-inflammatory drugs have also been increasing given their potential availability over-the-counter. The modulation of the inflammatory process associated with these diseases during pregnancy leads to high frequency of perinatal complications such as prematurity. However, treatment might change these risks.

Objectives: To quantify the risk of prematurity associated with late pregnancy exposure to anti-inflammatory drugs.

Methods: A cohort study was conducted within the Quebec Pregnancy Cohort (1998-2009). All pregnancies with prescription drug insurance one year before and during pregnancy, ending with a liveborn infant were included. Late pregnancy exposure was defined as having filled at least one prescription for selective or non-selective NSAIDs (excluding: indomethacin and sulindac) or biologic agents in the 3 months prior to delivery. Prematurity was defined as less than 37 weeks of gestation. Crude and adjusted risk ratios (RR) were obtained using Generalized Estimation Equation (GEE) models. Covariates included maternal demographics, maternal autoimmune diseases, pregnancy complications, and other comorbities.

Results: A total of 156,531 pregnancies met inclusion criteria. In the 3 months before delivery, 393 (0.25%) of women used non-selective NSAIDs, 56 (0.036%) used selective NSAIDs, and 13 (0.008%) used biologic agents. Adjusting for potential confounders, selective NSAID use in late pregnancy was associated with a 2.42 fold increased risk of prematurity (OR: 2.42 95%CI 1.24-4.70; 10 exposed cases) as compared to non-use. More specifically, late pregnancy exposure to celecoxib was found to increase the risk of prematurity by more than three-fold (OR: 3.17 95%CI 1.18-8.52; 6 exposed cases). No other statistically significant associations were found.

Conclusions: This study showed that selective NSAIDs, more specifically celecoxib, use during late pregnancy was increasing the risk of prematurity even after taking into account the effect of maternal AD.

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These findings suggest that pregnant women with AD should be closely monitored.

571. Feasibility of Using the Medicaid Statistical Information System (MSIS) to Assess Safety and Effectiveness of 3rd Trimester Vaccination: A Case Study with Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis (Tdap)

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Background: Medicaid claims-based data have rarely been used to evaluate vaccination during pregnancy.

Objectives: To examine the feasibility of using MSIS data to study vaccine safety and effectiveness by evaluating the association of 3rd trimester maternal Tdap vaccination with birth outcomes and infant pertussis.

Methods: This retrospective matched cohort study was conducted among all identifiable MSIS mother-infant pairs with an infant's birth date in 2006-2012 and mother's age between 12 and 55 years at delivery. Mothers and infants were linked using birth/delivery dates and state-specific unique family medical record numbers. Exposure, outcomes, and confounders were identified through ICD-9/CPT/NDC codes. Vaccinated and unvaccinated mother-infant pairs were matched by propensity scores, with exact or Mahalanobis matching on key demographics, comorbidities, and pregnancy conditions. Incidences of preterm birth, low birth-weight and infant pertussis were compared between the two groups using logistic regression or Cox proportional hazards analyses.

Results: Of the 7,694,875 mother-infant pairs identified in MSIS, 5,083,027 (66%) met study eligibility, of which 22,077 (0.4%) were Tdap-vaccinated during the 3rd trimester. Incidence rates (per 10,000 pairs) were 833.0 (preterm birth), 529.6 (low birth-weight), and 3.2 (infant pertussis) for vaccinated pairs, and 1093.6, 548.4, and 5.9 respectively for unvaccinated pairs. The data did not suggest that 3rd trimester Tdap vaccination is associated with increased risk of preterm birth (adjusted OR=0.72, 95% CI: 0.67-0.78) or low birth-weight (adjusted OR=0.96, 95% CI: 0.88-1.05). The risk of infant pertussis appeared to be lower in the vaccinated than unvaccinated pairs (adjusted HR=0.54, 95% CI: 0.22-1.36).

Conclusions: It is feasible to use MSIS data to evaluate the safety and effectiveness of vaccinations during pregnancy. Further information is needed to confirm the safety and effectiveness evaluation of 3rd trimester maternal Tdap vaccination.

572. Prevalence of Maternal and Child Adverse Pregnancy Outcomes Recorded in Primary Care in the United Kingdom

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Background: Diabetes mellitus is one of the commonest chronic conditions affecting pregnancy, with increasing prevalence. Preexisting diabetes in pregnancy is related to adverse events for mother and baby. The St Vincent declaration in 1989 set out to achieve pregnancy outcomes in woman with diabetes that approximate to women without diabetes.

Objectives: Calculate prevalence and trends of maternal and child adverse pregnancy outcomes in women with and without preexisting diabetes.

Methods: Pregnant women permanently registered with a GP aged between 16 and 55 years were identified. Code lists were developed to identify the adverse outcomes: caesarean section, instrumental delivery, perinatal death, preeclampsia and major congenital malformations (MCM). Pregnancies affected by each outcome were identified.

The prevalence of each outcome was calculated by diabetes status (type 1, type 2 and not-diabetic). To investigate trends prevalence was calculated by diabetes status and calendar period: 2000-02, 2003-05, 2006-08 and 2009-12.

Results: A total of 361,806 pregnancies occurred between 2000 and 2012 of which 0.33% and 0.55% were affected by type 1 and type 2 diabetes, respectively. The prevalence of caesarean section, perinatal death and MCM were higher in women with type 1 and type 2 diabetes compared to women without diabetes: 50%, 35% vs 17%, 1%, 1% vs 0.4% and 5%, 3% vs 2%,

respectively. The prevalence of preeclampsia was higher in women with type 1 diabetes compared to women with type 2 and without diabetes: 2% vs 1% and 1%.

For women with type 1 diabetes the prevalence of caesarean section, MCM and preeclampsia increased over the study period. For women with type 2 diabetes only the prevalence of instrumental delivery increased over the study period. For women without diabetes the prevalence of all outcomes, except caesarean section which increased, did not alter over the study period.

Conclusions: Women with preexisting diabetes have higher prevalence of adverse maternal and child outcomes in pregnancy when compared to women without diabetes. Studies examining various drug exposures during pregnancy may need to account for diabetes in their analysis.

573. Pregnancy Studies Assessing Drug Exposure in Populations with Multiple Sclerosis

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Background: Upon making a new treatment option available, particularly to women of childbearing potential, its safety to mother, fetus, and infant is of key interest to regulators, manufacturers, patients and their families, and the public. Different study approaches are available but may differ in their ability to provide this needed information.

Objectives: To evaluate different approaches to pregnancy safety studies among women with multiple sclerosis (MS), provide information on optimal study designs, and evaluate the robustness of reported outcomes.

Methods: A comprehensive literature review was performed using medical literature databases complemented with Internet research and limited to articles published in English from January 1993-October 2015.

Results: A total of 51 studies were identified: 10 industry-sponsored therapy-specific pregnancy exposure registries, 15 studies using three disease-specific pregnancy registries, 8 surveillance programs, 7 miscellaneous prospective cohort studies, 4 retrospective chart reviews, 6 retrospective studies using purpose-built databases, and 1 population-based database study. No meta-analyses were identified. Details of study design were often not reported fully, particularly on planned study size and its justification. Investigated outcomes and their definitions varied across studies. Several studies failed to reach recruitment targets. Most studies had few drug-exposed pregnancies, data on infant health were very scarce, and less than half had internal comparator groups. Regardless of design or source population, even many years after initial marketing authorization, no study was able to produce robust relative risk estimates to reliably inform the use of the investigated drug in pregnancy.

Conclusions: Pregnancy safety studies in MS have produced limited informative outcomes data. Alternatives worth exploring for future studies include larger disease-specific prospective registries that can evaluate pregnancies exposed to specific drugs, retrospective database studies using large population-based or claims data with mother-child linkage, and multidatabase studies that combine data sources using meta-analytic methods for increased precision.

574. Assisted Reproductive Technologies and the Risk of Cryptorchidism and Hypospadias: Population-Based Study

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Background: The use of assisted reproductive technology (ART) for impaired fertility has grown continuously over the last 30 years. Several prior studies have examined the relationship between parental subfertility, as well as ART, and the risk of cryptorchidism or hypospadias, but results have been inconclusive.

Objectives: To assess the risk cryptorchidism and hypospadias, in relation to subfertility and the use of ART.

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Methods: Design: Data were drawn from Maccabi Healthcare Services (MHS), a 2-million member health maintenance organization in Israel. For the present population-based retrospective cohort, we analyzed information on male children born between 1999 and 2008 and their parents.

Exposure: MHS databases were used to retrieve information on parent's subfertility and history of reproductive therapies, including IVF treatment, clomiphene citrate, GnRH analogues, or progestational agents.

Main outcome measures: Boys were followed from birth for a maximum of 12 years to determine the presence of cryptorchidism or hypospadias.

Statistical analysis: Multivariable logistic regression.

Results: A total of 108,548 male children were included in the analysis, including 2706 cases of cryptorchidism (2.5%) and 1736 cases of hypospadias (1.6%). Paternal subfertility was significantly ($P<0.05$) related to cryptorchidism and hypospadias. Maternal infertility and vitro fertilization (IVF) treatment were associated with cryptorchidism, but not with hypospadias.

Conclusions: The results of this large population-based cohort study suggest that parental subfertility and related-procedures may be associated with an increased risk of cryptorchidism.

575. Trends in the Prevalence of Drug Prescribing During Pregnancy in UK Primary Care, 1995-2014

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Background: Drug prescribing in pregnancy is common, however few studies have systematically investigated prescribing in pregnancy in the UK across a broad range of drug types.

Objectives: To investigate the prevalence of drug prescribing during pregnancy in UK primary care over a 20 year period.

Methods: We utilised an established cohort of pregnancies which have been identified in The Health Improvement Network (THIN). Prescriptions issued in this cohort during pregnancy between 1995 and 2014 were extracted and categorised according to the classifications published in the British National Formulary (BNF). The prevalence of prescribing of drugs from each BNF category during pregnancy was calculated as the number of women with a prescription for a drug from a BNF category during pregnancy divided by the total number of pregnancies. Prevalence ratios were calculated to compare the prevalence of drug use in pregnancy to the prevalence in a period of equal length beginning one year before pregnancy.

Results: The study included 516,562 pregnancies in 392,264 women. In 433,755 (84%) of the pregnancies at least one prescription was issued. In 2014, broad spectrum penicillin's were the most commonly prescribed medicine in pregnancy (20.2%). Between 1995 and 2014 prescribing of proton pump inhibitors increased from 0.1% to 4.4%, selective serotonin re-uptake inhibitors from 0.4% to 5.6% and parenteral anticoagulants from 0.1% to 1.2%. Prescribing of drugs to treat vaginal and vulval infections and drugs used to treat nausea and vertigo tripled in pregnancy compared to a similar period one year before (Prevalence Ratio: 3.0 (CI95 2.9-3.2) and 3.2 (CI95 3.0-3.5)) while prescribing of non-steroidal anti-inflammatory drugs and selective serotonin re-uptake inhibitors was considerably lower (Prevalence Ratio: 0.18 (CI95 0.16-0.20) and 0.59 (CI95 0.57-0.62)).

Conclusions: Many women are prescribed medication in primary care during pregnancy and, despite changes in prescribing over the past 20 years, broad spectrum penicillins remain the most commonly prescribed class of medication. For many drug classes, pregnancy is a major determinant of treatment.

576. Drug Utilization Among Pregnant Women: Real-World Findings from a US EMR Database

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Background: The use of prescribed medication during pregnancy are not well characterized.

Objectives: To describe drug utilization among women during the third trimester of pregnancy.

Methods: We utilized Quintiles electronic medical records (Q-EMR) research database which includes patient-level ambulatory medical records from approximately 30 million patients throughout the

United States. We established a retrospective cohort of pregnant women, age 12-55 years with ICD-9-CM code for a delivery from October 1, 2010 until November 1, 2015. Delivery was identified from ≥1 activity claim with the ICD-9-CM 650.xx-679.xx, V30-V39.x. We evaluated the prevalence of several different drug classes in the third trimester (10 weeks before delivery) with ≥1 prescription order identified in the EMR during that time period.

Results: We identified 51,167 women in the pregnancy cohort. 34% of the cohort had information regarding bod mass index (BMI) a year prior to delivery date, with 28% being categorized as normal BMI, 29% overweight, and 41% as obese. 40% of the cohort had ≥1 prescription order for one of the following drug classes: anti-infective agent, ADHD/Anti-narcolepsy/Anti-obesity/anorexiant agent, central nervous system, endocrine and metabolic, or respiratory agents. 16% of the cohort had a prescription for an endocrine and metabolic drugs during the third trimester, with metformin being the most readily utilized drug in this class. 14% of the cohort had a prescription for an anti-infective agent with metronidazole and amoxicillin most commonly used during the third trimester. 12% of the cohort had a prescription for an analgesic and anesthetics with ibuprofen, acetaminophen/oxycodone, and promethazine HCL most readily used. Between 6-8% had a prescription for either a respiratory agent or a central nervous system drug.

Conclusions: Continuous monitoring of medication exposure using secondary data sources will increase our understanding of utilization and associated safety surrounding the use throughout pregnancy. Our findings identify that medications are commonly used during the third trimester emphasizing the need for conclusive evidence regarding teratogenicity and maternal outcomes.

577. Safety Profile of Medication Used in Pregnancy: Results of a Multinational European Study

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Background: Studies have consistently reported the use of potentially harmful medications during pregnancy. However, as medication utilization patterns may change over time there is a continuous need to monitor such use to identify potential harmful practices during pregnancy. Moreover, multinational studies examining the safety profiles of medications used in pregnancy are lacking.

Objectives: To describe the safety profile of self-reported medications used during pregnancy across European countries, and to examine maternal factors associated with use of potentially harmful medications during pregnancy.

Methods: This study is based on a multinational, web-based study conducted in 15 European countries in October 2011-February 2012. Information about maternal demographics, illnesses, and medication use during pregnancy was collected via an electronic questionnaire. Both pregnant women and new mothers with a child <1 year could participate. The Swedish classification system (FASS) was used to classify safety of medications. When a woman used multiple medications, she was assigned to the group with highest risk.

Results: Out of 8363 women who completed the questionnaire, 81% used medication at least once during pregnancy. There were 587 different medications reported by the study participants, and 58% of these could be classified according to FASS. In total, 52% of the women used only medications classified as safe (group A), 16% used one or more medications with undetermined risk (group B1 or B2) and 28% used at least one potentially harmful medication (group B3, C or D) during pregnancy. A higher proportion of women from Northern Europe used potentially harmful medications, compared to women from Eastern and Western Europe. Women with chronic somatic illness or depression were two and three times more likely to use potentially harmful medications than women without these conditions, respectively.

Conclusions: The majority of women use medications that are safe to use in pregnancy. Chronic somatic or mental illness is important drivers for using medications with less safe safety profiles. However, such use may still be appropriate in light of the woman's underlying condition.

578. Improving Safe Use of Medications During Pregnancy: The Roles of Patients, Physicians, and Pharmacists

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Background: Given that data for more than 90% of medications are insufficient to determine fetal risks, women are often faced with making decisions about medication use during pregnancy without adequate safety information.

Objectives: This study explored the roles that women, physicians, and pharmacists play in making decisions about medication use during pregnancy, to identify shared challenges and opportunities.

Methods: Trained moderators conducted six online focus groups (n=48) and in-depth, follow-up interviews (n=12) with women who used commonly prescribed medications to treat chronic or acute conditions either while pregnant or while planning a pregnancy. Interviewers also conducted in-depth interviews with nine physicians and five pharmacists. All focus groups and interviews assessed participants' knowledge, attitudes, practices, and access to information about medication use during pregnancy. Two researchers independently coded the focus group and interview transcripts with NVivo 10.0 software to identify themes and explore patterns across the three groups.

Results: Because of concerns about risks to the developing baby, the women, physicians, and pharmacists interviewed strive to "play it safe" with medication use during pregnancy. All three groups described the need for an engaged patient who can make informed decisions. The groups also described challenges related to communication between physicians and patients, between pharmacists and patients, and between physicians and pharmacists about patients' pregnancy status, as well as a lack of patient-centric resources.

Conclusions: Women, physicians, and pharmacists are highly motivated to protect developing babies from the potential harms of medication use during pregnancy. Strategic message development to help (1) physicians discuss the benefits and risks of medication use during pregnancy with their patients, and (2) pharmacists screen for pregnancy and counsel on medication safety are needed. Improved informational resources for both groups could help maximize the effectiveness of these interactions.

579. Unique Approaches for Conducting Lactation and Placental Transfer Studies

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Background: With issuance of the US Pregnancy and Lactation Labeling Rule and similar EU regulations forthcoming, more post-marketing lactation and placental transfer studies may be required. Barriers to conducting these studies include: identifying rare pregnancy exposures to specific products and daunting study requirements such as repeated breast milk sampling and neonatal blood sample collection immediately postpartum.

Objectives: This study sought to examine the impact of a remote enrollment model employing home health nurses on study recruitment and retention.

Methods: Using descriptive methods, we evaluated data from lactation and placental transfer studies that were conducted in Canada, France, the Netherlands, Switzerland, and US. Where approved by regulatory authorities, remote enrollment was combined with a traditional site-based approach. Investigators had the option to enroll subjects treated at their site (i.e., traditional model) or enroll subjects remotely via phone. For the remote model, recruitment initiatives were targeted to potential subjects and health care providers (HCPs), and subjects contacted the study call center to enroll. The screening interview was via phone and screening assessment was completed by the subject's local HCP. Consent was conducted via phone with signed consent forms transmitted via courier. Home health nurses collected breast milk and blood samples from mothers and neonates. Subjects were monitored remotely throughout the study.

Results: The remote model was accepted by regulatory agencies and ethics committees. However, in the Netherlands and Switzerland some investigators

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rejected the model, and in France, a single investigator served as National Coordinator for multiple sites. Target enrollment was 36 subjects. Thus far, 10 subjects have enrolled through the remote model and 20 through traditional sites. 100% of home visits were completed successfully with 99% completed "in window" and 100% CRF completion.

Conclusions: Employing the remote model boosted enrollment by 50%. However the model was not accepted by all investigators. Home health nurses proved to be highly successful in subject retention and sample and data collection.

580. Utilization of Laboratory Results Data to Enhance Pregnancy Cohort Identification

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Background: Few studies utilize the availability of lab result values to enhance pregnant women cohort identification.

Objectives: We sought to determine the utility of available lab results to enhance cohort identification of pregnant women, including women who may not have delivered a live born infant.

Methods: We conducted a retrospective cohort study in three Mini-Sentinel data partner sites with available lab result values. We defined the first pregnancy (2008 – 2013) as the first indication of pregnancy based on earliest date, whether that date was associated with a positive pregnancy lab result, prenatal care visits or procedures, and/or prenatal pregnancy diagnosis/procedure code (exposure). We assessed the cohort for 1) live born delivery (term, preterm using categories available from diagnosis codes); 2) pregnancy loss (ectopic and other extra-uterine, fetal death, stillborn, miscarriage, and therapeutic/elective abortion); 3) disenrollment, death, end of study timeframe; and 4) no end of pregnancy indicator in electronic data (outcomes). We characterized the population overall and by site based on pregnancy outcome and baseline covariates including availability of pregnancy lab results. For women with live born deliveries we also assessed if the presence of the first pregnancy lab result changed the timing of when a pregnancy was first identified.

Results: We identified 268,219 women with a qualifying pregnancy, including 167,337 (62.4%) with single live birth. Across the cohort, 5.1% (n=13,665) had a positive lab result (exposure) and no pregnancy-related diagnosis/procedure; however, 32.6% (n=6,953) of the abortions and 10.1% (n=3,014) of the miscarriages were included in this subset of women with no pregnancy diagnosis/procedure code. Among women with both a positive lab result and a diagnosis or procedure code, 60.7% had their pregnancy identified earlier using the lab result (up to two weeks).

Conclusions: The availability of lab results can identify additional pregnancies, in particular pregnancies that end in abortion or miscarriage, in studies using electronic healthcare data. Lab results may identify pregnancies earlier than using prenatal diagnosis or procedure codes.

581. Spontaneous Preterm Labor (SPTL) in the Netherlands: Creation Of Linked Mother-Child Cohorts For Epidemiological Studies

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Background: As new tocolytics for spontaneous preterm labor (SPTL) are in development, detailed information is required on epidemiology and outcomes of these women and their children to contextualize trial results.

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Objectives: To establish a cohort that contains healthcare information starting at pregnancy and extending into long-term follow-up and outcomes after birth.

Methods: Two data sources (2000-2010) were used for the study (funding GSK); Netherlands Perinatal Registry (PRN): nationwide registry of perinatal care with maternal and neonatal characteristics, and PHARMO Database Network: population-based network of healthcare databases combining data from various settings e.g. hospitals, pharmacies. Data sources were linked to create study cohorts:

- Mother Cohort: singleton pregnancies of women registered in PRN+PHARMO linked to PHARMO children (live only)
- Mother-Child Cohort: including linked PHARMO children

>Preterm Labor Cohort: pregnancies from Mother-Child Cohort with PTL diagnosis code or preterm birth <37 weeks gestational age (GA) without PTL diagnosis code)>>SPTL Cohort: uncomplicated PTL; excluding those with maternal complications> Full-term Cohort: pregnancies from Mother-Child Cohort without PTL diagnosis, with full-term delivery

- Child GP Cohort: children with additional GP data, enabling long-term follow-up.

Results: From the PHARMO-PRN Mother cohort, 290,133 singleton pregnancies of 212,512 women (mean ± SD age at delivery 30.5 ± 4.6 years, 44% delivering their 1st child) were selected and linked to 134,006 children registered in PHARMO (52% male, mean ± SD birth weight 3,453 ± 573 grams, mean ± SD GA 39.6 ± 1.8 weeks, 94% GA ≥37 weeks). Of pregnancies in the Mother-Child Cohort, 11,112 (8%) were included in the PTL Cohort; 6,599 (59%) were SPTL. The Child GP Cohort comprised 17,903 (13%) children; mean ± SD follow-up was 6.7 ± 3.0 years.

Conclusions: The cohorts developed enable in-depth study of women with SPTL and the possibility to study short- and long-term postnatal outcomes and healthcare utilization in their children, which can be related to medication use and comorbidities of mothers before, during and after pregnancy.

582. What Factors Contribute to Pregnancy Registry Success?

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Background: FDA defines pregnancy registry success as: achieving target enrollment or having registry data referenced in clinical guidelines, published in peer-reviewed journals, or result in a product label change.

Objectives: To build upon previous research examining the association between various factors and registry success.

Methods: For ongoing and closed registries listed on FDA's website, registry characteristics were collected from product labels, publications, clinicaltrials.gov, and other websites. Logistic regression (SAS v 9.2) was used to examine the association between FDA-defined success and the following factors: registry duration, scope, manager, number of products/sponsors, US sales/prescription/patient volume, US disease prevalence for females of child-bearing potential, and registry awareness. As a proxy for awareness, Google searches of the registry name were conducted and the number of hits and whether the search identified registry abstracts, social media sites, or websites for the registry, sponsor(s), CRO, or other organizations (government, medical, or advocacy) were tallied. Whether the label included registry contact information was also assessed.

Results: Of the 14 closed registries, 8 (57%) achieved success. Of the 33 ongoing registries, 10 (30%) achieved success. Factors significantly associated with success included registry duration (OR[years] = 1.3; 95%CI:1.1-1.7) and whether a Google search of registry name produced an advocacy organization website (OR[Y vs. N] = 5.3; 95% CI:1.1-26.9) or abstract (OR[Y vs. N] = 9.1; 95% CI:1.5-54.5). Registries involving multiple drugs (OR[multi vs. single] = 3.1; 95% CI:0.9-11.0) and sponsors (OR[multi vs. single] = 4.3; 95% CI:0.9-20.3) also tended to have higher odds of success.

Conclusions: This study built upon previous research by including both closed and ongoing registries and refining potential factors associated with success. Registry duration and proxies for awareness (advocacy sites and abstracts identified on Google search) were found to be associated with registry success. The study

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was limited in its ability to examine other potentially relevant factors.

583. Validity Of Electronic Health Data For Pregnancy Outcomes

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Background: Electronic data are often used to study medication safety in pregnancy. Little is known about the validity of these data for many pregnancy outcomes.

Objectives: To describe the validity of electronic data for postpartum hemorrhage (PPH), chorioamnionitis, and neonatal intensive care unit (NICU) admission.

Methods: We conducted a two-phase study within two healthcare systems in the US, Group Health (GH) and Kaiser Permanente Southern California (KPSC). Because of the main study's aims, the population included nulliparous women who delivered a live or stillbirth singleton from 2007-2013 and as of 38 weeks gestation lacked medical or obstetrical complications according to electronic data. We oversampled deliveries that appeared to include elective labor induction or certain adverse outcomes. We compared outcomes defined from electronic data (health plan diagnosis and procedure codes and birth certificate data) against the "gold standard" of medical record review. We estimated positive predictive values (PPV) with 95% confidence intervals (CI) using logistic regression that accounted for sampling. We estimated sensitivity and specificity with 95% CI based on these results and outcome prevalence in the electronic data.

Results: Of 43,378 deliveries (37,672 at KPSC; 5,706 at GH), we reviewed 1,752 charts; 1,369 (78%) had available records and met eligibility criteria after review. Estimated PPVs were: for PPH, 81% (95% CI 69–89%) at GH and 75% (65–84%) at KPSC; for chorioamnionitis, 42% (31–54%) at GH and 93% (86–97%) at KPSC; and for NICU, 81% (73–87%) at GH and 91% (85–95%) at KPSC. Specificity was ≥98% for all outcomes except for chorioamnionitis at GH (95% [94–96%]). Estimated sensitivities were: for PPH, 37% (27–49%) at GH and 26% (18–36%) at KPSC; for chorioamnionitis, 99% (90–100%) at GH and 84% (67–93%) at KPSC; and for NICU, 82% (54–95%) at GH and 87% (78–93%) at KPSC.

Conclusions: At two healthcare systems, electronic data had good validity for NICU stay and good PPV for PPH, but PPV for chorioamnionitis varied greatly and sensitivity for PPH was low. Future studies should investigate validity of their outcomes to ensure that using electronic data is appropriate.

584. Using Web-Based Questionnaires to Assess Medication Use During Pregnancy: A Validation Study in Two Prospective Cohort Studies

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Background: Collecting valid self-reported data on medication use during pregnancy is challenging: medication use is often underreported when using paper-based questionnaires or interviews. When carefully designed, Web-based questionnaires may improve maternal recall of medication use, but data on the validity of this relatively new method of data collection are lacking.

Objectives: To validate two comparable Dutch Web-based questionnaires with indication-oriented questions to assess prescription and over-the-counter medication use during pregnancy.

Methods: Participants in the PRegnancy and Infant DEvelopment (PRIDE) Study (n=555) and the Pregnancy Drug Registry pREGnant (n=175) completed a six-week paper-based diary on medication use in

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gestational weeks 19-24 or 26-31. In week 34, they completed a Web-based questionnaire, which included questions on the name of the medication, time period and frequency of use, and quantity taken. To assess the degree of underreporting, the questionnaire's sensitivity (Se) with 95% confidence intervals (CI) was calculated with the medication diary as reference standard.

Results: Among the women who completed a diary, 65.7% used at least one medication in the six-week period. Sensitivity of the questionnaire was high for many medication groups, including topical corticosteroids (Se 0.89; 95% CI 0.74-1.00), levothyroxine (0.76; 0.56-0.97), antiepileptics (0.88; 0.75-1.00), antacids (0.77; 0.69-0.85), and ferrous fumarate (0.77; 0.54-1.00). Sensitivity was lower for medication for short-time use, with sensitivities of 0.50 (95% CI 0.22-0.78) for systemic antibiotics, 0.50 (0.38-0.62) for ear, eye, nose and throat preparations, 0.59 (0.52-0.67) for analgesics, and 0.56 (0.49-0.64) for acetaminophen specifically. No differences in sensitivity were observed between the PRIDE Study and pREGnant questionnaires.

Conclusions: For a large number of medication groups, underreporting in a Web-based questionnaire is limited. For some medications, however, a substantial number of exposures will be missed with this method of data collection, but the degree of underreporting is much lower compared to paper-based questionnaires.

585. Development of a Mother-Baby Linkage Using Integrated Claims and Electronic Health Records (EHR)

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Background: Health insurance claims data offer tremendous potential for the study of drug exposures during pregnancy and their effect on pregnancy outcomes, including major congenital malformations. However, claims data are limited in their capture of certain data elements that might represent exposures, covariates, or outcomes relevant to a particular research question.

Objectives: We sought to enrich a mother-baby claims linkage with EHR data in order to provide information on variables that might address competing hypotheses regarding the effect of maternal exposures to medications.

Methods: This study was conducted using Optum's integrated claims and EHR data. Eligible patients included female members of commercial health plans with medical and pharmacy coverage and a facility claim associated with a diagnosis or procedure code indicating a live birth delivery between January 2008 and March 2015. We characterized the population using pharmacy and medical claims data, and linked structured clinical data and natural language processing (NLP) concepts derived from electronic clinical notes available in the EHR data.

Results: Of the 963,811 women identified via claims (representing 1,023,685 deliveries), 336,502 women were continuously enrolled with medical and pharmacy coverage for the year before and 6 weeks following their index delivery date; 23,047 had an overlap between claims and EHR during the same observation period. Concepts captured via NLP or in structured data fields included: last menstrual period (182,449 mentions) and associated dates; measurements (body mass index, gestational age at birth, birth weight); clinical characteristics (e.g., gestational diabetes, gestational hypertension); smoking/alcohol use; and drug-related mentions (e.g., opioids, prenatal vitamins).

Conclusions: Assessment of drug exposures during pregnancy could be enhanced using a combination of claims data supplemented with EHR data. Increased accuracy with respect to date of conception would be expected, but benefits extend to other aspects of exposure, covariate, or outcome variables that are not well captured in claims data.

586. Validation of Multiple Births in Medicaid Analytic eXtract (MAX) Data

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Background: Previous research established methods using the Medicaid Case ID number, delivery/birth dates to link women to their infants, as an important data source for research on medications in pregnancy. One concern of the methods is that multiple infant beneficiary IDs linked to the same delivery may

represent the same infant. No studies has reported the consequent incorrect linkage and misclassification of multiple births.

Objectives: To examine the validity of multiple births in the Medicaid Case ID-based delivery linkage against Birth Certificates.

Methods: Using Florida MAX in- and outpatient encounter data, we linked women aged 12-55 with a delivery claim to infants born in 1999- 2010 via Medicaid Case ID number, delivery/birth dates. Multiple births were then identified based on the number of infants linked to each unique delivery. Via mothers' social security numbers, we linked mother-infant pairs to Florida Vital Birth Certificates (FVBC). Plurality in FVBC was used as the gold standard to validate multiple births identified in MAX via Case ID.

Results: We identified 710,500 linked deliveries in FVBC and MAX with no missing information on plurality in FVBC. The sensitivity of MAX in identifying multiple births was 88.5%, with a specificity of 99.9% and a PPV of 94.6%. Of note, 496 (5.41%) of all twin deliveries identified in MAX based on the Case ID linkage were single birth in the FVBC. 1083 (11.12%) of all the twin deliveries in FVBC were identified as single birth in MAX. Out of the 496 false positive multiple deliveries, 81.65% had one beneficiary ID assigned to them before their date of birth and the other beneficiaries ID assigned to them after their date of birth, with an average time difference of 373.5 days. The average time from the eligibility start date of the first beneficiary ID to date of birth was 14 days.

Conclusions: Identification of multiple births based on the Case ID-based delivery linkage in MAX showed high sensitivity and specificity. However, caution is required for misclassification of plurality in studies on twins using MAX data. Disjoint enrollment periods could be used to remove duplicate infant records with multiple beneficiary IDs linked to the same delivery.

587. Changes in Prescription Drug Use After Gastric Bypass Surgery: A Nationwide Cohort Study

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Background: Little is known about the prescription drug use before and after Roux-en-Y Gastric Bypass (RYGB) surgery.

Objectives: To evaluate changes over time in drug use among patients undergoing RYGB surgery and a matched population-based comparison cohort.

Methods: A nationwide population-based cohort study, including all 9,908 patients undergoing RYGB in Denmark during 2006–2010 and 99,080 matched general population members. We calculated prevalence ratios (PRs) comparing prescription drug use 36 months after RYGB/index date with use six months prior to this date (baseline).

Results: At baseline, more RYGB patients (median 40 years, 22% men) used a prescription drug (82.0% versus 50.8%) than comparison subjects. After three years, the use had decreased slightly among RYGB patients, PR=0.93; 95% confidence interval (CI)= (0.92, 0.94), but increased in the comparison cohort, PR=1·04; 95% CI=(1·03-1·05). In the RYGB cohort, large sustained decreases occurred for treatment of metabolic syndrome-related conditions [any glucose-lowering drug [PR=0.28; 95% CI=(0·25-0.31)]; lipid-modifying drugs [PR=0·50; 95% CI=(0.46-0.55)]]. Use of inhalants for obstructive airway diseases [PR=0.79; 95% CI=(0.74-0.85)] and glucocorticoid use [PR=0.72; 95% CI=(0.63-0.81)] also decreased. Use of neuropsychiatric drugs was two-fold higher at baseline in the RYGB cohort (22.8% versus 10.9% in comparisons) and increased further after RYGB, [antidepressants [PR=1.13; 95% CI=(1.07-1.19)], antipsychotics [PR=1.39; 95% CI=(1.21-1.60)], and potential treatment of neuropathy [PR= 1.39; 95% CI=(1.28-1.51)]].

Conclusions: Three years after RYGB surgery, we found large reductions in the use of treatment of metabolic syndrome-related conditions, inhalants for obstructive airway diseases, and glucocorticoid use. In contrast, frequent use of neuropsychiatric drugs further increased after RYGB.

588. Impacts of Reimbursement Policy for Targeted Therapies Utilization for Lung Cancer Treatment in Taiwan

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Background: Targeted therapies have been proven to provide clinical benefits to patients with metastatic non-small cell lung cancer (NSCLC). Timely access to such medical innovations is critical for these patients. Gefitinib, a targeted therapy, was initially approved and reimbursed as third-line therapy for advanced NSCLC patients by Taiwan National Health Insurance in 2004; subsequently they became second-line (in 2008) and further first-line (in 2011) therapies for EGFR mutation-positive, advanced NSCLC patients. Another targeted therapy, erlotinib, was initially approved as third-line therapy in 2008, and it became second-line in 2011.

Objectives: This study aims to explore the impacts of above reimbursement policy (broadened indication and eligible patient population, from third-line to second-line then to first-line treatment) on use of targeted therapies.

Methods: We retrieved 2004-2013 claims data with all patients with lung cancer diagnosis from National Health Insurance Research Database. Using an interrupted time series design and segmented regression, we estimated changes in monthly rate of prescribing rate and market shares by costs following each modification in the reimbursement policy for gefitinib and erlotinib for lung cancer treatment.

Results: There was a relative decrease of 5.64% in prescribing rate of targeted therapies at 3 years following the first modification of reimbursement policy (broadened from third-line to second-line treatment); but there was a relative increase of 77.54% in prescribing rate at 3 years following the second modification of reimbursement policy (broadened from second-line to first-line treatment). Market share by costs of targeted therapies reduced 34.93% at 3 years following the first modification of reimbursement policy, but no significant change of market share by cost was found following the second modification of reimbursement policy.

Conclusions: The historical modifications of reimbursement policies for targeted therapies for lung cancer treatment were associated with the increase of their prescribing rate, especially when the gefitinib was broaden the targeted population from second-line to first-line treatment.

589. Reducing Breast Cancer Risk: Why Aren't Providers Screening and Prescribing?

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Background: Breast cancer is the most diagnosed cancer among US women. Breast cancer risk can be predicted using the validated Gail model and high-risk women can take medications to prevent breast cancer. Although the FDA first approved Tamoxifen (1st generation SERM) for breast cancer prevention in 1998, there is no increased uptake for this purpose. SERMs lower the incidence of breast cancer in high-risk women. Evidence-based clinical guidelines exist for use of chemoprevention.

Objectives: We describe primary care provider responses to a survey to study self-assessment of fluency of breast cancer chemoprevention strategies and use of screening and chemoprevention drugs.

Methods: 201 providers completed the survey (40%). Providers answered 8 items related to their knowledge of breast cancer risk screening and treatment using SERM. Outcomes include frequency conducting breast cancer risk assessment, and prescribing breast cancer chemoprevention. Bivariate and logistic regression analyses.

Results: In bivariate analyses providers who agreed they were unaware of evidence-based guidelines were more likely to report never conducted screening (75.2% vs 61.0%) compared to those who were aware of screening recommendations. Providers who agreed that they did not know enough about the chemoprevention drugs were more likely to report past year never prescribing these drugs compared to those who reported knowing about SERMs (81.0% vs. 50.0%). These findings persisted in logistic regression controlling for provider age, sex and practice specialty. Internal medicine providers three times more likely than family practice physicians to report they have not prescribed SERMs.

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Conclusions: According to the USPTF, there is a moderate net benefit from use of tamoxifen and raloxifene to reduce the incidence of invasive breast cancer in women who are at increased risk for the disease. 89% of our respondents reported not prescribing SERMs and 60% reported not screening in the past year. Improved education about screening and indications for prescribing may have a significant impact on breast cancer incidence. Surveys in other settings are indicated to determine whether these findings persist.

590. Prescription Behaviour for Gastroprotective Drugs in New Users as a Result of Communications Regarding Clopidogrel – Proton Pump Inhibitor Interaction

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Background: Safety concerns of concomitant use of clopidogrel and proton pump inhibitors were published in 2009 and 2010 by medicines regulatory agencies, including a direct health-care professional communication.

Objectives: We examined the association between various safety statements and prescription behaviour for gastroprotective drugs in naïve patients in the Netherlands in the years 2008-2011.

Methods: Data from the PHARMO Database Network were analysed with interrupted time series analyses to estimate the impact of each communication on drug prescriptions. Dispensings were used as a proxy variable for prescription behavior.

Results: After the early communication in January 2009 15.5% (95% CI 7.8, 23.4) more patients started concomitantly with (es)omeprazole and 13.8% (95% CI -21.2, -6.5) less with other proton pump inhibitors (PPIs). Directly after the first statement in June 2009 we found an increase in histamine2-receptor antagonists (H2RA) up to ±25%, placing those patients at risk for gastrointestinal events. This effect for H2RA faded away after a few months. In February 2010 when the official advice via an adjusted statement was to avoid (es)omeprazole, we found a decrease of 11.9% (95% CI -18.2, -5.7) for (es) omeprazole and an increase for other proton pump inhibitors (PPIs) of +16.0% (95% CI 10.3, 21.7). Still around 20% of patients started on (es)omeprazole, placing them at risk for cardiovascular events.

Conclusions: Advices of regulatory authorities were followed, however reluctantly and not fully, probably partly because of the existing scientific doubt about the interaction.

591. Changes in Antihypertensive Drug Use After the Implementation of Evidence-Based Drug Formulary in a Private Hospital in South Sumatra, Indonesia

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Background: The ever increasing drug expenditure in the hospital has facilitated the implementation of an evidence-based drug formulary.

Objectives: To evaluate the change in antihypertensive drug prescribing pattern after the implementation of an evidence-based drug formulary in a private hospital in South Sumatra, Indonesia.

Methods: Design: A quasi-experimental study, pre-post test design

Setting: Antihypertensive drug use data in the period before (2010-2011) and after the formulary implementation (2012-2013) were extracted from the private hospital medical records

Exposures or interventions: The implementation of an evidence-based drug formulary in a private hospital

Main outcome measures: Drug use items compared were the average number of antihypertensive drugs prescribed per prescription, the proportion of generic drugs prescribed, average antihypertensive drug cost per prescription, and the proportion of individual antihypertensive drug groups.

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Statistical analysis: The in-hospital prescribing before and after the intervention was compared using t-test, with the significance level of 0.05.

Results: Antihypertensive drugs were prescribed more often after the intervention (5.0% vs 12.9%, $p < 0.05$). The average numbers of antihypertensive drugs prescribed per prescription was slightly increased after the intervention (1.09 vs. 1.13, $p < 0.05$). However, the proportion of antihypertensive generic drugs prescribed was increased significantly (19.7 vs. 70.0%, $p < 0.05$), mostly driven by calcium channel blockers (CCBs) and angiotensin converting enzyme inhibitors (ACEIs). Average antihypertensive drug cost per prescription was 59% lower after the formulary implementation ($p < 0.05$), mostly due to CCBs. CCBs (40.0% vs. 66.1%), ACEIs (28.1% vs. 10.5%) and angiotensin II antagonists (22.6% vs 13.4%).

Conclusions: The implementation of evidence-based hospital drug formulary in a private hospital in South Sumatra, Indonesia significantly increased antihypertensive generic drug use and decreased average antihypertensive drug cost per in-hospital prescription.

592. Are Statin Prescriptions Determined by Social Position?

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Background: During the last 15 years, several statins were made available as generic drugs and therapy became more cost-efficient.

Objectives: The aim was to analyze whether statin prescriptions are associated with the social position in a health care system with universal coverage.

Methods: We used data from the baseline (2000-2003, n=4814, 49.8% male, 45-75 years old) and first follow-up examination (2006-2008, n=4157, 49.4% male) of the population-based Heinz Nixdorf Recall Study, Germany. We only included participants with an indication for statins (n=2305) according to NCEP ATPIII (participants with coronary heart disease (CHD) or CHD risk equivalents, ten year risk for CHD or cardiovascular disease according to Framingham risk scores, LDL-level, number of risk factors). Moreover, we categorized statin prescriptions as generic or brand name. We used education as an indicator of social position (ISCED-97) and set up the three categories low, medium and high education. We applied log regression models to estimate prevalence ratios (PR) with 95% confidence intervals (95% CI). According to a directed acyclic graph, we adjusted for age and stratified by sex.

Results: During the baseline examination, 290 out of 1423 men with an indication for statins took a statin (20.4%). For women we found a prevalence of 21.2%. Among men, the adjusted PR for receiving a statin was 0.70 (95% CI: 0.43-1.15) for men with low education compared to men with high education. For women we found an adjusted PR of 1.03 (95% CI: 0.66-1.61) for participants with low education. Among participants receiving a statin, the adjusted PRs for men receiving a generic drug were 1.38 (95% CI: 1.17-1.63) and 1.25 (1.13-1.39) for low and medium education, respectively, compared to participants with high education. For women the adjusted PRs were 1.05 (95% CI: 0.89-1.23) and 1.09 (95% CI: 0.94-1.26) for low and medium education, respectively.

Conclusions: Men with low education have a lower probability for the prescription of a statin compared to men with high education and are more likely to receive a generic drug. Among women the education level was barely associated with the prescription of statins.

593. Effect of National Drug Utilization Review System on Co-Medication of Statin and Contraindicated Drug in Korea: Time-Series Analysis

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Background: Statins are generally well tolerated, however, the co-medication with CYP3A4 inhibitor and CYP-metabolized statin (Simvastatin, atorvastatin, lovastatin) can increase the risk of adverse events. In Korea, drug utilization review system (DUR system) which is a computerized clinical decision support system has been implemented nationally to reduce contraindicated drug use in December 2010.

Objectives: To evaluate the effect of drug utilization system on contraindicated co-medication with statins.

Methods: We performed an interrupted time series study using Korean National Health Insurance Service National Sample Cohort 2002 to 2013. The medications with a contraindication due to drug-drug interaction were selected on the basis of Notification by Korea Ministry of Health and Welfare Ministry of Food, and Drug Safety. Contraindicated co-medication was defined as overlapping prescription periods of statins and contraindicated drugs at least one day. Quarterly proportion of co-medication of statin user was evaluated by segmented regression.

Results: Among 143,472 CYP-metabolized statin users, 6.7% were co-medicated with contraindicated drug as least one time during 2002 to 2013. The trend in the co-medication proportion of CYP-3A4 metabolized statin user per quarter decreased by 0.01 % ($p < 0.001$) before implication of DUR system, and a statistically significant 0.66% decrease was observed immediately after implication of DUR system. The trend showed not statistically changed after DUR system implication.

Conclusions: The DUR system was related to a statistically significant decrease in co-medication of contraindicated drug in CYP-3A4 Metabolized statin user.

594. Predicting Factors for Reaching Stabilized Maintenance with Once-Monthly Paliperidone Palmitate in Medicaid Patients with Schizophrenia

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Background: With FDA approval of every three month paliperidone palmitate (PP3M), understanding patients stabilized on once-monthly paliperidone palmitate (PP1M) that could be transitioned to PP3M is important.

Objectives: Identify predicting factors associated with reaching stabilized maintenance therapy among schizophrenia patients treated with PP1M.

Methods: A retrospective (07/2008-03/2014) database analysis of Medicaid beneficiaries diagnosed with schizophrenia and initiated on PP1M (index date) was conducted. Baseline characteristics were assessed during the 12-month pre-index period. Reaching stabilized maintenance was defined as ≥3 consecutive PP1M claims with the same dose strength after the first two initiation doses and ≤60 days between claims. A stepwise logistic regression was used to identify the predictors of reaching stabilized maintenance without adjustment for multiplicity.

Results: At baseline, relative to non-stabilized patients (N=2,470), patients reaching stabilized maintenance (N=2,012) were more likely to be adherent to antipsychotics (APs) (Proportion of days covered ≥80%: 46% vs. 27%, $P<0.001$), and were less likely to have dual or capitated coverage (55% vs. 73%, $P<0.001$). Prior use of atypical long-acting injectables (LATs) (odds ratio [OR]=1.38, $P<0.001$), and prior adherence to APs (OR=1.70, $P<0.001$) increased the likelihood of reaching stabilized maintenance. Conversely, hospitalization occuring within 30 days prior to PP1M initiation (OR=0.83, P=0.044) and increasing number of prior APs received (OR=0.94, P=0.035) were factors associated with a lower likelihood of reaching stabilized maintenance.

Conclusions: Patients with prior adherence to AP, prior atypical LAT use, fewer unique APs used, and without hospitalization 30 days prior to PP1M initiation were more likely to reach stabilized maintenance.

595. Up-Scheduling of Alprazolam to a "Controlled Drug": Interrupted Time Series Analysis of Its Impact on Benzodiazepine (BZD) Prescribing, Dispensing and Poisonings in Australia

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Background: Scheduling is used by regulators to control access to prescribed drugs; drugs in the same class are commonly scheduled in the same way. In February 2014, Australia reclassified alprazolam to a "Controlled Drug" increasing the restrictions on its prescribing and dispensing. This provides a unique opportunity to evaluate the consequences of selectively up-scheduling one drug within a class.

Objectives: To quantify the effect of up-scheduling alprazolam on the prescribing and dispensing of BZDs, switching from alprazolam to substitute medicines, and intentional BZD poisonings.

Methods: We performed an interrupted time series analysis using dispensing data for a 10% sample of Australians, and calls to a toxicology service in New South Wales (2010-2015). We used: an autoregressive integrated moving average (ARIMA) model to identify changes in BZD dispensing and prescribing, and switching from alprazolam to another BZD, antidepressant or antipsychotic; and a segmented Poisson regression to identify changes in calls to the toxicology service for intentional BZD poisonings.

Results: During the study period 18 092 people were prescribed alprazolam. After up-scheduling, we observed: a decrease in alprazolam prescribing (14.9/100,000 population/month 95% CI 5.2-24.5); a decrease in alprazolam dispensing (531/month, 95% CI 404-658); and an increase in dispensing of diazepam (491/month, 95% CI 364-619) and oxazepam (274/month, 95% CI 113-435). Switching from alprazolam to another BZD increased by 216% (95% CI 123%-348%) the month of up-scheduling; few switched to a new antidepressant or antipsychotic. Calls to the toxicology service for intentional alprazolam poisonings decreased by 50% (95% CI 31%-68%) over 12 months; there was no change in poisonings involving other BZDs.

Conclusions: Up-scheduling alprazolam was associated with decreased use, increased switching to less harmful BZDs, and a decrease in intentional poisonings. This demonstrates that selectively up-scheduling a commonly abused medicine within a class can be an effective approach for reducing inappropriate use and adverse events.

596. Use of an Automated Database to Characterize Aberrant Opioid Prescribing, Dispensing and Utilization at Local Levels

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Background: Non-medical use of prescription opioids causes substantial morbidity and mortality in the United States. Although local conditions may facilitate opioid overuse, features of the opioid epidemic within small geographic regions remain largely unknown.

Objectives: To characterize an aberrantly high volume of opioid sales observed in a single county in Maryland.

Methods: We used IMS Health's LRx LifeLink data from January 2006 through August 2013, which constitute individual-level, all-payer pharmacy claims. We focused on 13 retail pharmacies linked to 8975 prescribers, 44887 patients and 527178 opioid transactions over the 92-month period. We used Joinpoint™ analysis to analyze trends in opioid volume (assessed by Morphine Milligram Equivalents [MMEs] per transaction, a standardized measure of opioid volume) and investigated the patients, prescribers and pharmacies that accounted for the observed patterns.

Results: On average, prescriptions from the county of interest contained 1.5 to 2 times more MMEs than those from other counties. County-level differences were most pronounced between June 2009 and September 2011 when there was a surge in opioid dispensing in the county of interest. During this period, the mean opioid volume increased 32% from 1586 to 2096 MMEs per transaction, with no significant change in the mean days supply (15 days). The surge was followed a sharp 7-month decline in MMEs per prescription which coincided with local actions designed to address opioid-related injuries and deaths. A small proportion of patients (~10%), prescribers (~1%) and pharmacies (2 of 13) accounted for the majority of the aberrant patterns observed.

Conclusions: We observed a large change in opioid volume in one county accounted for by high risk

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behaviors of a concentrated group of patients, prescribers and pharmacies. These patterns suggest the importance of Prescription Drug Monitoring Programs and other interventions targeted to the needs, and utilization patterns, of local communities.

597. Heterogeneity Among Youth with Serious Mental Illness in Intensive Care Management and Post-Discharge Polypharmacy Use

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Background: Intensive care management (ICM) improves clinical outcomes by targeting behaviors (e.g., aggression) resulting in polypharmacy psychotropic use. Heterogeneity of youth served in an ICM and its association with variability in polypharmacy use over time may confound the intervention effect.

Objectives: To explore heterogeneity of youth in ICM compared with youth served in a traditional outpatient mental health setting on post-discharge polypharmacy exposure.

Methods: A quasi-experimental, time series design using Medicaid medical and pharmacy claims from December 2009-May 2014 involved 814 youth with ≥90 days in ICM and continuous Medicaid enrollment 1 year before through 1 year post-discharge ICM. Non-ICM youth (n= 2,439) in outpatient mental health services were identified. To create a similar non-ICM post-discharge period, enrollment and discharge dates were randomly assigned from ICM youth. Risk differences (RD) in polypharmacy use between ICM and non-ICM youth were adjusted for baseline covariates (demographics, diagnosis, service use, and time-varying psychotropic use) 1-year pre-ICM using propensity score quintiles. Polypharmacy post-discharge was defined as three or more psychotropic classes (i.e., antipsychotics, stimulants, antidepressants, and mood stabilizers) concomitantly for ≥15 days per 30-days. Outcomes were: 1) change in proportion of polypharmacy 1-year post-discharge and 2) RD and 95% confidence intervals in ICM/non-ICM polypharmacy in the first (Q1) and fourth (Q4) quarter post-discharge, overall and by propensity score quintile.

Results: Youth were 14 (±3.1) years old, male (60%), and African-American (63%). The proportion of polypharmacy 1-year post-discharge ICM decreased 19% for ICM and 18% for non-ICM youth. The largest differences in polypharmacy decreases were seen for youth in the third quintile (20% ICM vs. 12.7% non-ICM). Overall RD between ICM and non-ICM youth in polypharmacy in Q1 (-3.1%; 95%CI:-5.2%;-1.0%) and Q4 (-2.5%;95%CI:-4.4%; -0.6%) was significant ($p<0.01$). RD within quintile in Q1 and Q4 was not significant.

Conclusions: Risk differences across strata may be a confounder of the intervention effect.

598. Physician Attitudes and Experiences with Maryland's Prescription Drug Monitoring Program (PDMP)

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Background: Prescription Drug Monitoring Programs (PDMPs) serve an important means of informing prescribers regarding patients' controlled substance utilization, yet physicians' use of these programs varies by state and may depend upon a variety of program features.

Objectives: To evaluate the utility, impact, and perceived barriers of PDMP use among Maryland physicians after PDMP implementation in 2013.

Methods: We conducted a statewide U.S. mail survey of primary care, pain, and emergency medicine physicians. We adopted Dillman's Total Design Method to

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maximize survey response and linked responses to state records of PDMP registration and utilization. Each physician specialty was stratified into three subpopulations: (1) PDMP non-registrants; (2) PDMP registrants who were non-users; and (3) PDMP users. Our primary outcomes were physician views on PDMP accessibility, usefulness, barriers to use, and frequency of use. We used logistic and negative binomial regression to assess the associations between physicians' use of the PDMP and their demographic and clinical characteristics.

Results: Surveys were returned by 405 of 916 eligible physicians (44%). Seventy percent of physicians believe that PDMP access decreased their amount of prescribing and increased their comfort level in prescribing opioids. Commonly reported barriers to PDMP use were lack of knowledge regarding the presence of the PDMP and lack of knowledge regarding how to register. Registered physicians were more likely to access the PDMP if they were pain or substance use specialists (odds ratio [OR]: 3.71, 95% confidence interval [CI]: 1.67-8.24) or were heavier opioid prescribers (OR for every 20 additional patients prescribed opioids per month: 1.13, CI 1.03-1.25). In multivariate analysis after adjusting for key clinical characteristics, practicing at a managed care organization was associated with lower PDMP use (incidence rate ratio 0.19, CI 0.05-0.73).

Conclusions: Increased prescriber education and improvements to the PDMP interface remain essential steps to promote PDMP use. Further research should investigate the effects of PDMP utilization on opioid prescribing, pain management and patient outcomes.

599. Socioeconomic Impacts of Policy on Rx-to-OTC Switch to Prescription of Ethical Drugs in Japan

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Background: Increasing medical expenditure in rapidly aging society of Japan has become a serious problem, exceeding 40 trillion yen in 2014. Policy on the Rx-to-OTC switch is aimed at reducing national healthcare costs. To date, no study has examined the socioeconomic impacts of OTC switch in Japan.

Objectives: To evaluate the impacts of Rx-to-OTC switch on the prescription trends and sales of the OTC-switched ethical drugs in Japan.

Methods: We conducted an interrupted time series study, using a large–scale pharmacy dispencing database from IMS Health, NPA, which covers dispensing at more than 3,000 out–of–hospital pharmacy all over the country. Ethical drugs switched to OTC between April 2009 and October 2013 were analysed for comparison between before and after OTC switch. After eliminating periodical variation by a Seasonal-Trend Decomposition Procedure Based on Loess method, prescription trends in the ethical drugs were fitted to two generalized linear models (GLMs) with or without a trend change term at the point of OTC switch, and a model fitted better was selected based on Akaike Information Criterion (AIC). Changes in sales of OTC–switched ethical drugs after switching were estimated.

Results: Eight ethical drugs were switched to OTC during the study period, including five antiallergic drugs (mequitazine, epinastine, pemirolast potassium, fexofenadine, cetirizine), and one analgesics (loxoprofen), one anti-ulcer drug (troxipide), one dyslipidemia drug (ethyl icosapentate). The models with change in prescription trend were selected for seven drugs. Prescription trends of six ethical drugs were decreased than expected after OTC switch (mequitazine, epinastine, fexofenadine, cetirizine, loxoprofen, ethyl icosapentate). These decreases in prescription of the ethical drugs after OTC switch were resulted in estimated annual reduction of 4.8 billion ($40 million) in total in national healthcare costs.

Conclusions: OTC switch have impacted the prescription trends and sales of the OTC-switched ethical drugs. The OTC switch should be further facilitated to reduce national healthcare costs in Japan.

600. Management of Complications During Pregnancy: A Drug Utilization Study in Western Nepal

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Background: Drugs used during pregnancy can adversely affect the health and life of the mother and unborn child. However, the fact that drugs are needed to mitigate complications during pregnancy cannot be avoided.

Objectives: To identify the common complications during pregnancy and assess the medications that have been used to mitigate those complications in an attempt to promote rational use of drugs.

Methods: A hospital based prospective study was conducted at Manipal Teaching Hospital, Nepal in 275 pregnant women presenting with at least one complication and the use of drugs for management of those complications were analyzed.

Results: Majority of the patients in this study were in the age group 20-24 (44%) and in the third trimester (53.8%). Maximum patients complained pain as primary complication (24.4%) which was followed by nausea/vomiting, upper respiratory tract complications, acid reflux disease and others. Of the total prescriptions eighty six (86) did not have any medicines prescribed to the patients except multivitamins and nutritional supplements. The average drugs prescribed per patient was 2.78 in outpatient setting and 5.41 in inpatients. Iron, calcium and folic acid were the most frequently prescribed medications (47%) followed by ranitidine, hyoscine butylbromide, paracetamol and others. Antimicrobials comprised 12.8% of total drugs used and 18% of total drugs were fixed. dose combinations. Two hundred and thirty four (234) prescriptions out of 275 were prescribed by brand names. Most of the prescribed drugs were from FDA pregnancy category B and C.

Conclusions: The present finding showed that drug use during pregnancy at the study site was Rational in majority of the cases.

601. Longitudinal Trend in Assisted Reproductive Technology and Impacts of The Law in Taiwan

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Background: The problem of low fertility rate has raised concern in Taiwan recently. The enforcement of the Law for assisted reproductive technology (ART) in 2007 regulates general affairs relating to conditions of ART use.

Objectives: This study aims to examine and forecast trends in use of ART. We also evaluated the impacts of 2007 Law for ART on application of ART and rate of newborn babies by ART.

Methods: This study used data from "The annual report on the performance of ART" and the estimations of annual population by Department of Statistics of Minister of the Interior. We used ARIMA models to examine the recent trends (1999-2012) in use of ART and to predict the future trends (2013-2020). An interrupted time series deign and segmented linear regression models were applied to analyze the changes in number of ART treatment cycles and rate of newborn by ART following the Law for ART.

Results: National birth rate decreased from 1.28% in 1999 to 0.98% in 2012, and it was estimated to reach 0.82% until 2020. Number of ART treatment cycles increased from 6,966 in 1999 to 16,041 in 2012, and it was estimated to reach 22,156 until 2020. Rate of newborn babies by ART increased from 0.8% in 1999 to 2.54% in 2012, and it was estimated to reach 3.38% until 2020. There was a relative growth of 130.86% (95%CI: 110.16%, 151.56%) in number of ART treatment cycles at 5 year following the law of ART. Rate of newborn babies by ART relatively increased by 49.94% (95%CI: 19.06%, 80.82%) at 5 year following the law for ART.

Conclusions: The increasing use of ART in Taiwan is apparent and the enforcement of ART law has substantially encouraged use of ART. Additional social and financial incentives by government for individuals in late-marriages may also increase use of ART and increase the fertility rate in Taiwan.

602. Impact of the Black Triangle Label on Prescribing of New Drugs in the United Kingdom

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Background: New drugs in Europe receive black triangle labels to promote more intensive monitoring for 2-3y after approval. The impact of this label on prescribing is unknown.

Objectives: To study whether black triangle labels are associated with more judicious prescribing compared with the post-label period and similar, unlabeled drugs.

Methods: Using data from a 2% sample of The Health Improvement Network (THIN, UK) and an interrupted time-series design, we compared utilization trends for drugs for depression and erectile dysfunction with and without black triangles before and after label removal. We compared new users of labeled drugs with new post-label users with a case-control design. We also compared new users of unlabeled comparator drugs over the same period to account for secular trends.

Results: Escitalopram prescribing increased in the label period (+9 new users (95%CI 3,14)/Million/month) and declined post-label (-4 (95%CI -5,-2)/M/m). Unlabeled comparators (citalopram/fluoxetine) showed opposite trends in the same period (Label: -4 (95%CI -11,-1)/M/m; Post: +1 (95%CI -2,5)/M/m). In contrast, tadalafil and vardenafil prescriptions declined in the label period (-3 (95%CI -7,2)/M/m) and then leveled off post-label (0 (95%CI -2,2)/M/m), paralleling trends for unlabeled sildenafil (Label: -5 (95%CI -9,-2)/M/mo; Post: 0 (95%CI -1,2)/M/m). Compared with new post-label escitalopram users, new users of labeled escitalopram had fewer comorbidities (OR 0.8, 95%CI 0.7,1.01) and less hospitalization (OR 0.4, 95%CI 0.1,0.98). Similar associations were seen in citalopram/fluoxetine users over the same period. Comparisons of new users of labeled and post-label tadalafil/vardenafil, and of new users of unlabeled sildenafil across the same periods, were similar: during the label period, new users were less likely hospitalized.

Conclusions: Black triangle labels were not associated with reduced prescribing at the population level, compared with later trends and comparators. New users of labeled drugs appeared healthier than new users of the same drug after label removal, but this relationship reflected secular trends rather than an effect of labeling. Results from all of THIN are pending.

603. Integration of Medicines Budget Impact with Market Uptake Models in Horizon Scanning Through Use of the C-Tobia Model – A Collaboration Across Europe

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Background: Forecasting of medicines utilization and expenditure is essential to the planning and resource allocation for medicines. Horizon scanning (HS), focused on collecting and assessing evidence on emerging technologies, often does not include early intelligence on budget impact (BI) estimates.

Objectives: To present a new BI model (C-ToBIA) that integrates into the HS phase BI information through an agent-based model, applied initially within the Italian market.

Methods: The analysis relied on a traditional BI model, that compares two scenarios (with and without the new drugs), integrated with (i) an agent-based model (Cellular-Automata) that predicts the uptake of emerging second-line noninsulin antidiabetic drugs (NIADs) and (ii) data from the largest Italian health care database (Arno-Cineca, 11 million inhabitants).

Results: The model predicted future drug market uptake on the basis of the 2000–2014 life-cycle of more than 200 antidiabetic drugs (ATC A10B). It estimated that 104 antidiabetic items will be launched onto the market until April 2018. Target population (4.36% of total population currently receiving second line therapies), unit cost of avoided events (hospitalizations due to severe hypoglycaemia, €2,779) and average duration of therapies (242 days) were derived from the Arno database. Unit price and expected launch date were estimated in line with the NIADs recently marketed. The risk profile for new drugs was considered better, due to less severe hypoglycaemic events. The expected BI in 2015–2017 is €47.8m(+3% vs. the scenario without the new drugs). The increase in drugs expenditure (+€95.4m) is partially compensated by the avoided costs for hospitalisation for hypoglycaemia (-€478m).

To test next stage utility the model will be applied to the NIAD markets in three further countries using routine medicines utilisation databases.

Conclusions: Better use of medicines utilisation data by novel models (C-ToBIA) within HS could provide better intelligence on future market penetration. Such intelligence may provide for a better informed dialogue for market access conditions between payers and suppliers.

604. Varying Patterns of Penetration of New Antidiabetic Medications in Asia and US: A Cross-National Comparison Study

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Background: Dipeptidyl peptidase 4 (DPP-4) inhibitors were approved in the United States (US) in 2006 and thereafter in other countries.Drug utilizations patterns can differ by countries.

Objectives: To examine and compare penetration patterns of DPP-4 inhibitors in Hong Kong (HK), Taiwan (TW), Japan (JP) and US.

Methods: We used Japan Medical Data Center Database (JMDC), the Taiwan's National Health Insurance Research Database (NHIRD), a random sample of the Hong Kong's Clinical Data Analysis and Reporting System (CDARS), and 5% Medicare database converted to the OMOP common data model in the Asian Pharmacoepidemiology Network (AsPEN). We identified users of anti-diabetic drugs and compared prevalence and incidence utilization rates one year after marketing of DPP-4 inhibitors (2009 for HK, 2010 for TW, 2011 for JP and 2008 for US) in those ≥ 65 of age. The rates of drug use were age and gender standardized to those in TW in 2010 for better comparison.

Results: The prevalence (per 1,000) for DPP-4 inhibitors and biguanides were 0.8 and 111.6 in HK, 17.5 and 123.7 in TW, 21.8 and 20.5 in JP and 9.9 and 93.1 in US. The incidence rate (per 1,000 person-years) of new use of DPP-4 inhibitors and biguanides were 1.5 and 19.0 in HK, 15.6 and 14.6 in TW, 26.8 and 7.2 in JP and 7.3 and 18.0 in US. Among new users of DPP-4 inhibitors, the proportion of the single-use and the concurrent use of a biguanide were 4.1 and 77.4% in HK, 7.4 and 53.4% in TW, 36.1 and 23.2% in JP and 23.7 and 42.9% in US. Concurrent hypertension among new users of DPP-4 inhibitors and biguanides were found in 20.1 and 10.7% (difference = 9.4%, 95% CI: 4.1 to 14.8%) in HK, 68.0 and 59.0% (8.9%, 7.1 to 10.7%) in TW, 67.8 and 65.0% (2.8%, -0.3 to 5.9%) in JP and 91.3 and 86.3% (5.0%, 4.6 to 5.4%) in US.

Conclusions: In a country with the low penetration (e.g., HK), the concurrent use of biguanides was common and users of DPP-4 inhibitors had higher comorbidity (e.g., hypertension). These features are not remarkable in a country with the high penetration (e.g., JP). Assessing the patterns of use for new and existing medications is essential to design valid multi-national observational studies.

605. Does Free Medication Impact Drug and Health Services Use by Low-Income Diabetic Patients?

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Background: User fees for medications are known to have negative impact on drug and health services use by low-income diabetic patients. On the contrary, whether the implementation of a free medication policy can increase or decrease drug and health services use by such patients is not well documented.

Objectives: To test the effect of a free medication policy (FMP) on drug and health services use by low-income diabetic patients.

Methods: 1. Design: Interrupted time series; population: low-income elderly and welfare recipients. Monthly data on prescription drug, medical and hospital services use was obtained for each study participant from the Quebec Health Insurance Board for 5 years: three years prior to the FMP and two years after.

2. Setting: The study was conducted in the province of Quebec (Canada) which has a universal health insurance plan that provides free of charge medical and hospital services to all residents. The Quebec public drug plan covers elderly and welfare recipients for prescribed medication. A sample of elderly and welfare recipients diagnosed with diabetes and insured during the whole 5-year study period was randomly selected (n=4487).

3. Main outcome measures: Monthly average number and cost of prescriptions (total and by AHFS class), visits to physicians and hospital admissions.

4. Statistical analysis: General linear models. The independent effect of policy was estimated as the adjusted interaction between policy indicator and calendar time.

Results: Following the implementation of the FMP, the trend for increasing average number of medications over time became statistically significantly stronger overall ($p<0.0001$) and for all drug classes except classes 8 and 68. The trend toward increasing global medication costs became weaker for all drugs combined ($p=0.0002$) and classes 24 and 68 but was reinforced for class 28. The number of medical visits started to increase after FMP in contrast to a decreasing trend before ($p=0.005$), while trend for increasing number of hospital admissions remained unchanged ($p=0.58$).

Conclusions: The FMP had mixed impact on low-income elderly and welfare recipient diabetic patients use of drug and health services in Quebec, Canada.

606. The Use of Nitrofurantoïn in France: Assessment of Compliance with Therapeutic Indication and Guidelines

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Background: Nitrofurantoïn is an oral antibiotic effective for the treatment of urinary tract infection and of particular activity against ESBL-producing E coli. Despite its use for decades there has been low acquired resistance. Since March 2012, given its safety profile, including severe pulmonary and hepatic adverse reactions, the use of nitrofurantoïn is restricted to symptomatic treatment of cystitis for girls 6 years of age and older, adolescent girls and women under the conditions of a microbiological documentation and a lack of oral therapeutic alternatives. An empiric use may nevertheless still be considered under certain conditions.

Objectives: To assess the compliance with therapeutic indication and national guidelines, through the use of a cytobacteriological examination of urine (CBEU).

Methods: A cohort of 7 660 subjects initiating a nitrofurantoïn treatment from March, 1st 2012 to February, 28th 2015 was identified using EGB database, a representative sample of the population protected by the French National Health Insurance. A documented use of nitrofurantoïn was identified if a CBEU had been performed between 7 and 2 days before nitrofurantoïn's dispensing. An empiric use was assumed if a CBEU had been performed within 2 days before nitrofurantoïn's dispensing or prescribed the day of the dispensing and performed the day after nitrofurantoïn's dispensing.

Results: Overall, 15% of the users were men and 45% were women with no CBEU performed prior to nitrofurantoïn initiation, corresponding to non-compliant use of the drug. A documented use in women

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accounted for 26% of treatment courses and an empiric use for 14% of treatment courses. Non-compliant use was significantly less frequent at initiation compared to subsequent treatment courses (55.9% vs. 69.4%, $p<0.0001$). Despite a slight decrease of nitrofurantoïn's dispensing from March 2014, no sizeable modifications in the rates of CBEU was found during the study period.

Conclusions: Despite successive Dear Healthcare Professional Letters in 2012 and 2014, this study shows a persistently low compliance with therapeutic indication and guidelines for nitrofurantoïn use in France.

607. Detection of Trastuzumab Related Cardiotoxicity in Taiwanese Breast Cancer Women

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Background: Current guideline and label information suggest routine cardiac monitoring during trastuzumab (TRA) therapy. The information regarding the impact of cardiac monitoring and associated factors on cardiac risk of TRA in Asian users is limited.

Objectives: To describe the pattern of cardiac monitoring and factors associated with screening during TRA therapy.

Methods: We identified breast cancer patients treated with TRA from the entire Taiwan female breast cancer cohort between 2006 and 2012. We included women who survived at least a year after TRA initiation. Heart failure and/or cardiomyopathy (HF/CM) was defined by ICD9-CM-codes in the datasets. Guideline-adherent screening was defined as having a baseline echocardiogram before TRA and subsequent follow-ups every 4 months during treatment course based on TRA label information.

We applied a multivariate logistic regression to evaluate the factors associated with guide-adherent screening during TRA therapy. We also estimated the impact of screening on the occurrence of TRA-related HF/CM after PS matching. All statistical analyses were performed using SAS software 9.4.

Results: Among 6,407 TRA users, 2,203 (34.38%) women received at least one cardiac monitoring before TRA initiation and only 599 (9.35%) TRA users received cardiac monitoring, adherent to the label information. 132 (2.14%) women had HF/CM within a year after TRA initiation. Patients who received radiotherapy (OR: 1.70, 95% CI: 1.36-2.11) or were prescribed with diuretics (OR: 1.31, 95% CI: 1.01-1.70) or insulin (OR: 1.86, 95% CI: 1.02-5.39) a year prior to TRA treatment were more likely to receive routine cardiac monitoring. However, women that received routine cardiac monitoring were at higher risk of HF (OR: 3.27, 95% CI: 2.00-5.35).

Conclusions: Less than 10% of Taiwanese TRA users received guideline-adherent cardiac monitoring. Elevated HF/CM risks in those receiving guideline-adherent screenings reflected that clinicians arranged cardiac monitoring to confirm the diagnosis of HF/CM, rather than preemptively screened for the purpose of risk mitigation. Further research to optimize guideline-adherent cardiac monitoring is needed to mitigate the cardiac risk of TRA.

608. Compliance to Multiple Sclerosis Disease-Modifying Therapies: A Population-Based Cohort Study In The Lazio Region, Italy

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Background: Compliance to Multiple Sclerosis (MS) Disease-Modifying Therapies (DTMs) is essential to reduce relapse rates and slow disability progression but it is challenging due to parenteral administration and occurrence of side-effects.

Objectives: To evaluate adherence and persistence with intramuscular interferon β1a (IM IFNβ1a), subcutaneous (SC) IFNβ1a, IFNβ1b, glatiramer acetate (GA), and natalizumab (NA), using health administrative databases.

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Methods: The study population included MS patients (18-65 yrs) with at least 1 pharmacy claim for IM IFNβ1a,SC IFNβ1a,IFNβ1b, GA or NA between 01/01/2008 and 12/31/2010. The follow-up period started at the date of the first prescription (index date). Analysis was restricted to naïve patients. Medication Possession Ratio (MPR) was calculated as the proportion of days supply received in 730 days after the index date (adherent if MPR≥80%).Multivariate logistic regression was used to assess covariates affecting adherence probability.Kaplan-Meier analysis was applied to estimate treatment persistence; predictors of treatment discontinuation were evaluated using Cox regression.

Results: The study population included 1823 patients entering 5 treatment cohorts: IM IFNβ1a (N=405,22.2%), SC IFNβ1a (N=524,28.7%), IFNβ1b (N=439,24.1%), GA (345,18.9%), NA (110, 6.0%). Patients (mean age 39 years) were mainly females (68%).Adherence ranged from 51.4% for IM IFNβ1a to 39.9% for IFNβ1b (p= 0.02). SC IFNβ1a and IFNβ1b therapies, age> 55 yrs and previous hospitalizations were associated with a higher probability of non-adherence.At 12 months, among patients treated with IM IFNβ1a a greater proportion of individuals (63%) was still in treatment compared to other DMT cohorts (p <0.0001). Type of medication (IFNβ1b, SC IFNβ1a, NA) and age >55yrs) were strong determinants of treatment discontinuation.

Conclusions: Compliance to DMTs among MS patients in Lazio is far to be optimal. The study identified factors contributing to poor compliance to DMTs that should be considered in MS clinical management. Some limitations due to the use of administrative claims have to be considered in the interpretation of study findings.

609. Effect of a "Pill Mill" Law on Opioid Prescribing and Utilization: The Case of Texas

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Background: States have attempted to reduce prescription opioid abuse through strengthening the regulation of pain management clinics; however, the effect of such measures remains unclear.

Objectives: We quantified the impact of Texas's September 2010 "pill mill" law on opioid prescribing and utilization.

Methods: We used the IMS Health LRx LifeLink database to examine anonymized, patient-level pharmacy claims for a closed cohort of individuals filling prescription opioids in Texas between September 2009 and August 2011. Our primary outcomes were derived at a monthly level and included: (1) average morphine equivalent dose (MED) per transaction; (2) aggregate opioid volume; (3) number of opioid prescriptions; and (4) quantity of opioid pills dispensed. We compared observed values with the counterfactual, which we estimated from pre-intervention levels and trends.

Results: Texas's pill mill law was associated with declines in average MED per transaction (-0.57 mg/month, 95% confidence interval [CI] -1.09, -0.057), monthly opioid volume (-9.99 kg/month, CI -12.86, -7.11), monthly number of opioid prescriptions (-12,200 prescriptions/month, CI -15,300, -9,150) and monthly quantity of opioid pills dispensed (-714,000 pills/month, CI -877,000, -550,000). These reductions reflected decreases of 8.1% to 24.3% across the outcomes at one year compared with the counterfactual, and they were concentrated among prescribers and patients with the highest opioid prescribing and utilization at baseline.

Conclusions: Following the implementation of Texas's 2010 pill mill law, there were clinically significant reductions in opioid dose, volume, prescriptions and pills dispensed within the state, which were limited to individuals with higher levels of baseline opioid prescribing and utilization.

610. Comparison Of Generic-To-Brand Switchback Patterns For Authorized Generic Vs. Independent Generic Drugs

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Background: While brand and generic drugs generally are believed to be equivalent, some ongoing uncertainty exists in terms of whether they produce identical outcomes. Authorized generics, which are chemically identical to a corresponding brand drug but marketed as a generic, provide a unique post-marketing opportunity to study whether utilization patterns are influenced by perceptions of generic drugs as opposed to actual differences in the drug itself.

Objectives: To compare generic-to-brand switchback rates between authorized and independent generics.

Methods: A retrospective cohort study was conducted using claims and electronic health records data from a regional U.S. healthcare system. Ten drugs with authorized and independent generics marketed between 1999 and 2014 were evaluated. Eligible adult patients received a brand drug during the 6 months preceding generic entry, and then switched to a generic. Brand-to-generic switchers were followed for up to 30 months from the index switch date to evaluate occurrence of generic-to-brand switchbacks. Switchback rates were compared between patients on authorized versus independent generics using Kaplan-Meier curves and Cox proportional hazards models, controlling for individual drug effects, age, sex, Charlson comorbidity score, pre-index drug use characteristics, and pre-index healthcare utilization.

Results: Among 4,939 unique patients that switched from brand-to-generic, 235 (4.8%) switched back to the brand drug. Overall switchback rates were similar for authorized generics and independent generics (HR=0.86; 95% CI 0.65-1.15). The likelihood of switchback was higher for alendronate (HR=1.64; 95% CI 1.20-2.23) and simvastatin (HR=1.81; 95% CI 1.30-2.54) and lower for amlodipine (HR=0.27; 95% CI 0.17-0.42) compared with other drugs in the cohort.

Conclusions: Overall switchback rates were similar between authorized and independent generic drug users, indirectly supporting similar efficacy and tolerability profiles for brand and generic drugs. Reasons for differences in switchback rates among specific products need to be further explored.

611. The Recently Introduced System of Generic Substitution and Reference Pricing in Ireland: Generic Dispensing, Savings and Costs to the Health Service, and the Burden of Co-Payment

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Background: Active substance-based generic substitution and reference pricing (GS/RP) was introduced in Ireland on a phased basis from November 2013. Under GS/RP, a fixed drug price is paid by the Health Service Executive (HSE). Where a patient requests a premium priced product, the patient must pay the difference. A prescriber may alternatively request 'Do not substitute' (DNS), in which case the HSE pays the difference.

Objectives: To investigate compliance with the recently introduced (November 2013) system of active substance-based generic substitution and reference pricing (GS/RP) in Ireland. Objectives included monitoring of generic usage, savings released, and characterisation of Irish 'Do Not Substitute' trends and related costs.

Methods: Pharmacy claims data from the 'General Medical Services' scheme, Jan 2013-Oct 2015 inclusive, were analysed using SAS®v9.3. Drugs for which premium-priced products were available were studied where 6 months of follow-up data existed. For each claim the source of payment and price difference were deduced from recorded expenditure. Trends, including costs to the HSE, were examined over time. The impact of time since policy introduction and price difference magnitude on DNS likelihood were explored using multivariate logistic regression.

Results: Overall, generic drug dispensing rose from 79% to 92% at six months following policy introduction. However, within premium-priced products dispensed (8% overall), the proportion of DNS increased from 15% to 39%.Time since policy

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introduction and magnitude of price difference were both positive predictors of DNS (versus patient payment) ($p<0.001$).

Conclusions: GS/RP resulted in predominantly generic dispensing. However, estimated DNS rates increased significantly over time, incurring additional costs to the HSE, and were predicted by higher potential costs to the patient. These trends suggest that the co-payment burden is increasingly passed to the health service. With continual roll-out of GS/RP, interventions may be required to ensure DNS occurrences appropriately reflect medical need.

612. Determinants of Generic Drug Utilization in the United States

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Background: Despite wide-spread availability and favorable costs of generics, their uptake remains incomplete across drug classes. The relative contributions of patient factors and regional influences on generic drug usage are unknown.

Objectives: We sought to identify the determinants of incomplete uptake of generic drugs among commercially-insured beneficiaries in the United States (US).

Methods: We used MarketScan Commercial Claims data, which has pharmacy and medical claims from beneficiaries who are representative of commercially-insured patients in the US. We calculated the generic substitution rates (GSR) for 27 classes of drugs we had systematically prioritized for study. The GSR is days covered by generics divided by total days covered by generic and branded drugs when a generic is available. We calculated the GSR for a 7 day window in November 2013. We pooled drug-specific GSRs within classes. We fit hierarchical generalized linear models with individuals clustered by their metropolitan statistical area (MSA), for seven classes separately. The models included fixed effects for individual- and regional-level covariates and a random intercept.

Results: The GSRs for most classes exceeded 90%; some were lower including thyroid hormones (67%), androgens (31%), estrogens (34%), and adrenal hormones (topical/inhaled -10%). Several determinants were consistent: if the fill was more than a 30-day supply rather than less, it was much more likely to be filled as a generic. If the prescription was a refill rather than a new drug, it was less likely to be filled with a generic product. In four of the seven classes, fill by a mail order pharmacy was associated with a markedly lower likelihood of a generic fill. The impact of patient level determinants (age, sex, prescription burden, and comorbidities) varied by class. The state substitution and consent laws had inconsistent effects on generic use across classes.

Conclusions: Given the high cost of healthcare, it is increasingly important to encourage the use of safe, effective and typically lower cost generic drugs, when available. We identified some, although few, modifiable determinants. Policies directed at mail order pharmacies might impact generic uptake.

613. Disposal of Unused or Expired Medications Among a Mexican Sample

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Background: Unwanted or expired medications are saved for later use, stored or disposed via the sink, toilet or garbage, even though there are some specific containers to destroy them. In Mexico there is no vigilance on medications wastage destruction from households and improper disposal of medications potentially poses environmental and health risks.

Objectives: To assess the disposal and destruction habits of unused or expired medications among a Mexican sample.

Methods: A cross sectional study was conducted in Mexico City during 2015. An anonymous pre-tested electronic survey was administered to a convenience sample in a University, in which the participants were asked how they disposed of a variety of medications. In addition, participants were asked whether they seen or used the specific container to dispose medications.

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Statistical analyses, including X2 tests were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics® version 22.0, USA). All reported p-values were two-sided and a p-value of less than 0.05 was deemed statistically significant.

Results: Of the 245 respondents (mean age of 28.08 years; 55.1% were males; 49.4% were students), 90.2% of the subjects reported have used at least one medication in the last year. 7.3% referred used the ones they already have at home. The most common method for disposal of household medications was dumped medication in the garbage (60.4%), destroyed them (16.7%) or flushed them down the toilet or in the sink (3.26%) and only 10.6% disposed medication appropriately. Regarding if the respondents have seen the specific container 33.5% reported a positive answer and only 23.2% knew what it was for. No differences were found according to age or occupation for any variable.

Conclusions: Little information on the safe disposal of medications was routinely passed on to the public. Public services need to be more proactive about educating people on how to dispose medications, as well as finding a way for implementation on the law on medications wastage destruction in order to guarantee a proper management of them.

614. Pharmacoeconomic Evaluation of Geriatric Diabetics in a Tertiary Care Hospital: A Prospective Study

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Background: Diabetes is a major prevalent chronic disease in the elderly in developing countries like India. The estimated expenditure is approximately 6 billion USD, with a mortality rates of 55% and availability of limited cost economic research studies encouraged to carry out this study in hospitalized elderly.

Objectives: To assess the various costs incurred during the geriatric diabetic treatment (COI model).

Methods: This was a prospective, cross-sectional study conducted from July 2012-July 2014 in the General Medicine Department of Kasturba Medical College Hospital, Manipal, after obtaining ethical clearance. Cost details were obtained from hospital finance and pharmacy. The Descriptive statistical method was applied.

Results: Among 475 enrolled cases, 52.42% had diabetes. In which 27.71% had DM alone, 6.82 % had DM associated renal disease (i.e.: 3.6% were DMAKI, 3.2% were DMCKD), 12.44% had other than renal DM complications (micro vascular), 48.19% had both DMHTN, 4.81% had DMHTN associated complications.

The total cost incurred for the treatment of the disease and its related complications (DM alone, DMAKD, DMCKD, DM neurological complications, DMHTN & DMHTN) did not vary significantly [I.e. Mean+SD (INR): 16044.7 + 37740.06, 15374.51 + 11915.94, 14840.03 + 14124.05, 8395.35 + 16580.11, 27130.28 + 64934.04, 14430.5 + 13113.78) . The cost of treatment (INR) appeared low due to varying factors like free screening or treatment for other symptoms, etc. The cost based on various factors were as listed - Medicine charge > Laboratory/diagnostic charges > Nursing charges > Material charges > Procedure charges > Professional charges > Admission related charges > Miscellaneous charges.

Conclusions: This study clearly indicates that medicine expense is the highest cost factor in DM treatment. The second highest was the laboratory followed by nursing costs. Research on pharmacoeconomic models like cost-effective analysis (CEA), Cost minimization analysis (CMA), and Cost-benefit analysis (CBA) by the pharmacist &the stakeholders is essential to reduce the burden in geriatrics. Lack of availability of direct non-medical cost was the limitation of this study.

615. Selection of Sulfonylureas Over Metformin in Elderly Nursing Home Residents with Diabetes Mellitus

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Background: Diabetes mellitus is common in U.S. nursing homes (NH), yet little is known about the selection of glucose-lowering medications in this setting.

Objectives: To identify predictors of sulfonylurea versus metformin initiation in a nationally-representative cohort of NH residents.

Methods: The study was a retrospective cohort of new users (no dispensing of metformin or sulfonylureas in the 4 months preceding the first eligible dispensing). We analyzed a random 20% national sample of Medicare beneficiaries with Part A and D claims linked to NH facility and Minimum Data Set (MDS) databases in 3,478 U.S. NHs. Resident and facility characteristics were assessed prior to medication initiation using Medicare Part A, NH facility, and MDS data. Medication use was assessed using Part D prescription claims. We included a total of 4,247 long-stay (≥90 days) NH residents ≥65 years old with a prior diagnosis of diabetes who initiated metformin or sulfonylureas between 2008 and 2010. We quantified the association between predictors and sulfonylurea versus metformin initiation using descriptive statistics, univariable logistic regression, and multilevel multivariable logistic regression modeling with a random intercept for NH.

Results: The mean age of the cohort was 81.4 years (SD, 8.5). Approximately 41% were 85 years of age or older, 24.8% had heart failure, 9.1% had severe renal disease, and 1.1% used dialysis. In multivariable analysis, several clinical states were associated with sulfonylurea over metformin use, including heart failure (odds ratio 1.2, 95%CI 1.0-1.4), renal disease (OR 2.2, 95%CI 1.7-2.8), and dialysis (OR 2.8, 95% CI 1.2-6.6). Compared to those aged 65 to <75 years, residents 75 to <85 (OR 1.3, 95%CI 1.1-1.6), 85 to <95 (OR 1.9, 95%CI 1.6-2.3), and ≥95 (OR 3.9, 95%CI 2.6-5.8) years old were more likely to initiate sulfonylureas over metformin.

Conclusions: Age, heart failure, renal disease, and dialysis were significant predictors of selecting sulfonylureas over metformin to treat NH residents with diabetes. These findings suggest that prescribers adhered to FDA labeled warnings and raise questions about the applicability of these warnings to the NH setting.

616. Polypharmacy: Prevalence and Associated Factors in Elderly with Diabetes Mellitus in Minas Gerais, Brazil

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Background: Recent studies in different populations of patients with Diabetes Mellitus (DM) reported the use of a large number of drugs. However, no studies have been observed the association of polypharmacy its associated factors in elderly patients with DM.

Objectives: Measure the prevalence of polypharmacy and to evaluate your associated factors in elderly patients with DM in Minas Gerais, Brazil.

Methods: Cross-sectional study was conducted in 63 municipalities of Minas Gerais in 2014. The dependent variable was polypharmacy defined as the use of 5 or more drugs. The independent variables were gender, marital status, education, race, self-reported health, median time from diagnosis of diabetes, number of comorbidities, frequency of medical visits in the past year, type of health care (public or plan private health), regular physical activity and interruption of routine activities in the last 15 days. Factors associated with polypharmacy were analyzed between two groups: no polypharmacy and polypharmacy. Bivariate analysis was performed using Pearson's chi-square test. Logistic regression was applied in the multivariate analysis of the variables that presented a $p < 0.20$ value during the bivariate analysis.

Results: 1597 elderly people with DM were interviewed. Polypharmacy was observed in 66% of participants. The most frequent therapeutic classes were drugs for DM (92%), agents on the renin-angiotensin system (67%) and diuretics (49%). Presence of five or more comorbidities (OR = 3.33 / 95% CI = 2.66; 4.18), have consulted the physician four times or more in the last year (OR = 1.91 / 1.52;

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2.39), diagnostic time above 10 years (OR = 1.69 / 1.35; 2.11), lack of regular physical activity (OR = 1.56 / 1.24; 1.96) and have private health insurance (OR = 1.35 / 1.06; 1.72) were factors associated with polypharmacy.

Conclusions: Most of the participants had polypharmacy, which increases the risk of adverse reactions and drug interactions. Factors such as disease diagnosis time, comorbidities, physical inactivity and access to health services contributed to increased use of medication.

617. Real-World Risk of Diabetes with Second-Generation Antipsychotics in Older People

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Background: Clinical trials and epidemiological studies have demonstrated that second-generation antipsychotics (SGAs) increase the risk of diabetes in younger populations. Clinical trials have often excluded older people with chronic medical conditions. Multimorbidity, uncontrolled confounding and limited statistical power have confounded associations of SGAs and risk of diabetes in older people.

Objectives: The main objective of this study was to evaluate the risk of diabetes with SGAs in a population-based cohort of older people in New Zealand in a real-world setting.

Methods: In a case crossover study, we identified all individuals aged 65 years and above between 01/01/2006 and 31/12/2014 with diagnoses codes for diabetes using the International Classification of Diseases and Related Health Problems Tenth Revision, Australian Modification from the New Zealand National Minimum Data Set. The day the individual was admitted to the hospital for the first time after 01/01/2006 for an acute event was the index date. For each individual, the case period was defined as the time-interval 1-365 days before the index date, and a control period was defined as the time interval 366-730 days before the index date. The main exposure of interest was SGAs subsidized in New Zealand. We collected information on the type of antipsychotic drug from the pharmaceutical collections. A conditional logistic regression was employed and adjusted odds ratio (OR) and their 95% confidence intervals (CI) are reported.

Results: A total of 81039 individuals hospitalized for an acute event between 01/01/2006 and 31/12/2014 were included, of these 197 of them were prescribed SGAs. The adjusted OR was 1.46 (95%CI: 1.10-1.94) for all SGAs. The adjusted OR for quetiapine was 1.67 (95%CI: 1.03-1.69) and for risperidone was 1.51 (95%CI: 1.01-2.27).

Conclusions: The use of SGAs including quetiapine and risperidone increased the risk of diabetes in older people as compared with nonusers of antipsychotics.

618. Increasing Prevalence Of Anticholinergic Medication Use Over 20 Years In The UK Older Population: Cognitive Function And Ageing Study I and II

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Background: The use of medications with anticholinergic (AC) properties is linked to risks of cognitive decline, dementia, falls and mortality. These medications are prescribed or obtained over-the-counter, so cohort studies offer the best opportunities to understand changing patterns in their use.

Objectives: To determine the prevalence of AC medication use in the UK older population between 1991 and 2011.

Methods: Data were obtained from the first waves of the Cognitive Function and Ageing Studies (CFAS I and II), which are representative of the UK population aged 65 years and older in 1991 and 2011. We estimated the prevalence of medication use with any AC properties (AC =1, 2 or 3) and with potent AC properties (AC=3), rated on the AC Cognitive Burden Scale. Prevalence was calculated using inverse probability weights and standardised to the 2011 UK age and sex distribution. We used multivariable logistic regression to estimate the effect of time, age, sex, education, social class, and relevant morbidities on AC3 use.

Results: 7,639 and 7,762 participants provided medication data in CFAS I and II respectively. In 1991 the prevalence of AC123 and AC3 use was 50% (95%CI 48-51) and 5.7% (CI 5.2-6.3) and in 2011 64% (CI 63- 65) and 9.9% (CI 9.3-10.7). AC3 use increased over 20 years

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(adjusted odds ratio [OR] 2.3; CI 1.9 – 2.7), driven by increased urologicals and antidepressants. AC3 urologicals increased from 0.3 to 2.8% (OR 12.8, CI 7.6-21.5) and AC3 antidepressants from 4.0 to 5.9% (OR 1.8 CI 1.5-2.3). AC3 medications were more commonly used by women, those aged 75 and older, and those reporting depression, anxiety, Parkinsons disease, diabetes, stroke, arthritis or asthma. AC3 use was not independently associated with education or social class.

Conclusions: Potent AC use increased in the UK older population from 1991 to 2011, largely due to rising urological and antidepressant use. This raises concerns as AC medications are associated with a range of side-effects including cognitive decline. This research was supported by funding from Alzheimer's Society (AS-PG-2013-017).

619. Medications with Potent Anticholinergic Activity and Incident Dementia Diagnosis in the UK Older Population

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Background: Evidence is conflicting as to whether the long-term use of medications with anticholinergic (AC) activity increases dementia risk. Many indications for potent ACs are risk factors for or are early symptoms of dementia.

Objectives: To determine if potent AC use is associated with an increased dementia risk.

Methods: We conducted a nested case-control study using the UK Clinical Practice Research Datalink. Up to 7 controls were matched on sex, age, deprivation, and years of data history (minimum 6 years) to each dementia case, aged 65-99 years at diagnosis from April 2006 - July 2015. Index date was defined at first dementia diagnosis or dementia drug prescription. Prescriptions were extracted from 4 to up to 20 years prior to index date. We defined potent ACs as those scoring 3 on the AC Cognitive Burden scale. We used conditional logistic regression to estimate adjusted odds ratios (aOR) and 95% CI for dementia by number of AC prescriptions during the exposure period and within pre-specified drug classes, adjusted for potential confounders.

Results: 14,453 of 40,770 cases (35%) and 86,403 of 283,933 controls (30%) were prescribed potent ACs. The aOR for any potent AC was 1.10 (95%CI 1.08-1.13). However, results were inconsistent across drug classes, with dementia risk increased for potently AC antidepressants, antipsychotics, urologicals and anti-Parkinsonians, but not for antihistamines or antispasmodics. Within antidepressants and urologicals, risks increased with more prescriptions (aOR for 50+ prescriptions of 1.25 [95%CI 1.16-1.34] and 1.22 [95% CI 1.07-1.40] respectively), but not for other classes. However, similar risks were observed for non-AC antidepressants.

Conclusions: In the largest study to date, our analysis suggests that previous observed associations between AC use and dementia risk were attributable to confounding, drug properties unrelated to AC action, study design, or ACs being a marker of early dementia symptoms. However, we are limited by a likely delayed diagnosis of dementia in primary care and potential for survival bias in the case-control design. This research was supported by funding from Alzheimer's Society (AS-PG-2013-017).

620. Antipsychotic Use And The Risk Of Hip Fracture Among Community-Dwelling Persons With Alzheimer's Disease

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Background: Antipsychotic use has been previously associated with an increased risk of hip fracture among older people.

Objectives: To study whether antipsychotic use is associated with risk of hip fracture among community-dwelling persons with Alzheimer's disease (AD) and to compare the risk according to duration of use and between the most frequently used antipsychotics drugs.

Methods: Design: Nationwide register-based MEDALZ cohort study, using data from Prescription Register and Hospital Discharge Register. In this cohort study, 70,718 persons newly diagnosed with AD between 2005 and 2011 were included, with mean age of 79.6 years and 65% were women.

Setting: Community-dwelling residents of Finland.

Exposure: Antipsychotic use recorded in the Prescription register and use modelled with PRE2DUP.

Main outcome measures: Incidence of hip fractures recorded in the Hospital Discharge register.

Statistical analysis: With one year washout period for use, new use of antipsychotics was compared with time without antipsychotics with Cox proportional hazard models. In addition, quetiapine use was compared with risperidone.

Results: During antipsychotic use, hip fracture rate was 2.88 (95% CI=2.86-2.91) per 100 person-years compared with 1.74 (95% CI=1.73-1.74) hip fractures occurring per 100 person-years of nonuse (adjusted HR=1.54, 95% CI=1.39-1.70). The risk of hip fracture was increased from the first days of antipsychotic use and remained increased thereafter. Quetiapine was associated with similar risk of hip fracture as risperidone for the first 2.7 years of use (adjusted HR=0.98, 95% CI=0.79-1.21). Compared with low-dose (≤0.5 mg) risperidone use higher risperidone doses >0.5 mg) were associated with higher risk of hip fracture (adjusted HR=1.72, 95% CI=1.32-2.24).

Conclusions: As the risk of hip fracture was increased from the first days of use, our results confirm the need for having a high threshold for initiating antipsychotic use among community-dwelling persons with AD to avoid serious adverse events. If antipsychotic use is initiated, duration of use should be limited as the risk of hip fracture did not attenuate in long-term use.

621. Atypical Antipsychotics and the Risk of Falls and Fractures Among Older Adults: A Replication Study

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Background: A study by Fraser et al. of claims data from Ontario, Canada reported increased 90 day risks of fractures and falls among patients 65 years and older who initiated atypical antipsychotics, compared to non-users.

Objectives: To investigate the risk of falls and fractures among older adults receiving atypical antipsychotics.

Methods: A replication of the Fraser et al. analysis was performed using the US Truven MarketScan Medicare Supplemental database (MDCR). In addition, we performed modified analyses that: (1) included all covariates used to fit propensity score models in outcome models; and (2) required comparator group patients to have a diagnosis of schizophrenia, bipolar disorder, or major depression and a healthcare visit within 90 days prior to the index date.

Results: The Fraser et al. and the MDCR replication analyses yielded very similar results. Respectively for Fraser et al. and our replication, the results were: non-vertebral osteoporotic fractures OR=1.51 95%CI (1.41–1.60) and OR=1.49 95%CI(1.37–1.63); hip fractures OR=1.67 95%CI(1.53–1.81) and OR=1.59 95%CI(1.43–1.77); any fracture OR=1.29 95%CI (1.24–1.34) and OR=1.32 95%CI(1.23–1.41), and falls OR=1.54 95%CI(1.47–1.61) and OR=1.45 95% CI(1.11–1.89). However, in modified analyses, no associations were significant: non-vertebral osteoporotic fractures OR=1.09 95%CI(0.95–1.27); hip fractures OR=1.04 95%CI(0.87–1.24); any fracture OR=0.90 95%CI(0.81–1.01); and falls OR=1.14 95%CI(0.74–1.76). The primary change that resulted in the attenuation of associations was the modification to the comparator group.

Conclusions: Replicating the methodology of Fraser et al., the MDCR analysis yielded very similar results; however, in modified analyses, the associations between fractures and falls and atypical antipsychotics were no longer significant. The contrast of results between the replication and modified analyses may be due to the analytic approach used to compare patients (and potential confounding by indication). Further research is warranted to further evaluate these

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associations, while also examining methods to account for differences in older adult patients who use and don't use these medications.

622. Risk of Mortality Associated with Antipsychotic Monotherapy and Polypharmacy Among Community-Dwelling Persons with Alzheimer's Disease

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Background: Little is known about safety of long-term use of antipsychotics, and antipsychotic polypharmacy (ie. use of two or more antipsychotics concomitantly) among persons with Alzheimer's disease (AD).

Objectives: To analyze the risk of non-cancer mortality according to duration of antipsychotic use and to compare the risk associated with polypharmacy and monotherapy among community-dwellers with AD. The risk of mortality between most frequently used antipsychotic drugs was compared.

Methods: Design: Retrospective cohort study based on health care register data.

Setting: Nationwide register-based MEDALZ study including all 70,718 community-dwellers newly diagnosed with AD during 2005-2011 in Finland.

Exposure: Antipsychotic use recorded in the Prescription register data and drug use periods modelled with PRE2DUP.

Main outcome measures: Deaths were extracted from Cause of Death Register. Deaths due to cancer were not considered.

Statistical analysis: Incident antipsychotic use was compared with time without antipsychotics with Cox proportional hazard models. Quetiapine and haloperidol use were compared with risperidone use.

Results: Antipsychotic use was associated with an increased risk of mortality (adjusted hazard ratio [aHR] 1.62; 95% Confidence Interval [CI] 1.53-1.71). The risk of mortality was increased from the first days of use and attenuated gradually but remained increased even after two years of use (aHR 1.31; 95% CI 1.17-1.47). Compared with nonuse, antipsychotic polypharmacy (aHR 2.83; 95% CI 2.33-3.42) was associated with a higher risk of mortality than monotherapy (aHR 1.55; 95% CI 1.46-1.63). Haloperidol was associated with higher risk of mortality (aHR 1.51; 95% CI 1.14-2.02) and quetiapine with lower risk (aHR 0.84; 95% CI 0.75-0.94) compared with risperidone.

Conclusions: The findings support current treatment guidelines on having a high threshold for antipsychotic initiation among persons with AD. Antipsychotic polypharmacy and long-term use should be avoided and drug choice should be weighed against risk/benefit evidence.

623. Resident and Facility Level Predictors of Antipsychotic Use in Assisted Living

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Background: Although initiatives have been introduced to reduce antipsychotic use in long-term care (LTC), the use of these agents in assisted living (AL) has attracted considerably less attention. This is potentially troubling given the high prevalence of dementia in AL and relatively lower levels of staffing and clinical oversight.

Objectives: To examine the prevalence and predictors (resident and facility level) of antipsychotic use among a large cohort of AL residents in a Canadian setting.

Methods: Cross-sectional study of 1,089 residents (mean age 85; 77% female; 57% with dementia) from 59 AL facilities in Alberta, Canada. Research nurses completed comprehensive resident assessments at baseline (2006-07). Facility-level factors were assessed

using standardized administrator interviews. Resident and facility level variables significantly associated with prevalent antipsychotic use in bivariate analyses (and/or identified in the literature) were examined in multivariable logistic regression models (with considerations of collinearity).

Results: The prevalence of antipsychotic use was 26% (94% atypical). In adjusted analyses, resident characteristics significantly associated with antipsychotic use included: older age (≥90 years) [OR (95% CI) 0.56 (0.36-0.86)]; dementia diagnosis [OR 2.75 (1.93-3.92)]; psychiatric diagnoses (schizophrenia, bipolar disorder and/or anxiety) [OR 2.32 (1.62-3.31)]; presence of delusions and/or hallucinations [OR 1.84 (1.14-2.97)]; higher levels of aggressive behaviours [OR 2.36 (1.53-3.64)], and frailty status [OR 1.86 (1.24-2.79)]. Resident factors not associated with use included sex, medication number and depression. Adjusting for resident factors, facility factors significantly associated with a higher likelihood of antipsychotic use included: presence of designated dementia beds, urban setting, absence of chain affiliation and for-profit status.

Conclusions: Antipsychotic use in AL was common and similar to recent estimates reported for LTC. We found a mix of resident and facility factors associated with antipsychotic use highlighting a need for further work to evaluate antipsychotic appropriateness in this setting.

Correction added on 7 September 2016, after first online publication. Abstract **623. Resident and Facility Level Predictors of Antipsychotic Use in Assisted Living** has been added. Author index has been updated.

624. Co-Prescription of Antipsychotic and Antiparkinson Medication Regimens Containing Levodopa: Adherence to Guidelines and the STOPP (Screening Tool of Older Persons' Potentially Inappropriate Prescriptions) Criteria in Beneficiaries of the Nova Scotia Seniors' Pharmacare Program

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Background: Patients with Parkinson disease are at increased risk for dementia. Optimal prescribing is critical to minimize adverse effects.

Objectives: To study the co-prescription of antipsychotic and antiparkinson medication regimens for older persons and to determine adherence to STOPP criteria and guidelines.

Methods: We determined the dispensing of antipsychotic and antiparkinson drug regimens for the Nova Scotia Seniors' Pharmacare Program (NSSPP) beneficiaries aged 66 years and older from April 1, 2009 to March 31, 2014. We determined the number of unique NSSPP beneficiaries who received >= 30 days supply of both antipsychotic and antiparkinson drugs concomitantly. Individual drugs, identified by ATC, and concomitant use were determined. The STOPP criteria (D6) and the US National Parkinson Foundation guideline which categorized antipsychotics based on their safety and effectiveness were used to determine potentially inappropriate prescribing. Multivariate analysis determined predictors of first choice antipsychotic therapy.

Results: 3838 beneficiaries claimed any antiparkinson drug, with 554 also dispensed an antipsychotic medication. For the 294 beneficiaries dispensed an antiparkinson medication regimen containing levodopa, 59.8% of antipsychotic prescriptions were considered first line (quetiapine and clozapine), 27.5% were considered second line (aripiprazole, olanzapine and aripiprazole) and 12.5% were considered inappropriate. Females 80 years and over had an OR .240 (.105-.547) of receiving a first line drug compared to men 80 and over.

Conclusions: About 87% of patients dispensed an antiparkinson regimen containing levodopa received an antipsychotic drug considered first or second line. Determining the reasons for the gap between the guidelines and prescribing and strategies to facilitate improvement are needed.

625. Frequent Use Of Psychotropic Drugs Among Persons with Alzheimer's Disease Aged 90 Years Or More In Finland

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Background: Drug use among persons aged 90 years or more has been rarely investigated.

Objectives: To compare central nervous system (CNS) drug use among persons with AD aged ≥90 years to younger persons with AD, and to matched comparison persons without AD.

Methods: Design: Register-based data was from the MEDALZ cohort including all community-dwelling persons diagnosed with AD 2005-2011 in Finland. One comparison person without AD was matched with age-, gender- and region or residence.

Setting: Community-dwelling persons aged 90 years and older in Finland. Mean age 92.3 years and 78.2% were women.

Exposure: Psychotropic drugs including antipsychotics, antidepressants and benzodiazepines and related drugs (BZDR), and anti-dementia drugs including acetylcholinesterase inhibitors (AChEIs) and memantine. Drug use periods were modelled with PRE2DUP method.

Main outcome measures: Prevalence of drug use during six months after the diagnoses (corresponding index date for matched cases).

Statistical analysis: Persons with AD were divided to those aged ≥90 years (N=3,319) and <90 years (N=63,896) at the time of AD diagnoses. Logistic regression models were constructed to compare prevalence of drug use among persons with and without AD aged 90 years or more, and persons with AD aged ≥90 years compared to younger persons.

Results: Compared to younger persons with AD, those aged ≥90 years were more likely to use psychotropic drugs (55.6% vs. 48.4%, comorbidity adjusted OR [aOR] 1.30, 95% CI 1.21-1.39), including antipsychotics (21.5% vs. 16.1%, aOR 1.40, 95% CI 1.28-1.52) and BZDRs (34.3% vs. 27.6%, aOR 1.34, 95% CI 1.25-1.45). However, persons aged ≥90 years were less likely to use anti-dementia drugs (63.3% vs. 72.4%, aOR 0.68, 95% CI 0.63-0.73), except that memantine use was more frequent (19.9% vs. 13.7%, aOR 1.56, 95% CI 1.42-1.70, respectively). Compared to comparison persons without AD aged ≥90 years, persons with AD were more likely to used antipsychotics (aOR 4.84, 95% CI 4.07-5.75) and antidepressants (OR 2.45, 95% CI 2.14-2.80).

Conclusions: The oldest persons with AD receive high burden of psychotropic drugs.

626. Benzodiazepine and z-Substance Use and Risk of Dementia – A German Claims Data Analysis

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Background: Benzodiazepines (BDZ) and the related z-substances (jointly now referred to as BDZR) are often prescribed for the treatment of sleep disorders and anxiety, particularly in the elderly. Acute detrimental effects of BDZR use on cognition and memory are known. However, the association of BDZR use and risk of dementia in the elderly is controversially discussed. For Germany, analyses on large population-based data sets are missing.

Objectives: To evaluate the association between BDZR prescription and incident any dementia in a large German claims data set.

Methods: We conducted a matched case-control analysis using longitudinal German public health insurance data from 2004 to 2011 and evaluated the association between long-term and regular BDZR prescription (at least 12 months) and incident dementia. We examined patient samples aged ≥60 years that were free of dementia at baseline. To address potential protopathic bias we introduced a lag time between BDZR prescription and dementia diagnosis. Odds ratios were calculated applying conditional logistic regression, adjusted for potential confounding factors

such as comorbidities (stroke, depression, ischemic heart disease, diabetes, epilepsy, anxiety, insomnia, schizophrenia, and hypertension) and polypharmacy.

Results: BDZR prescription was associated with an increased risk of incident dementia for patients aged ≥60 years (adjusted odds ratio [OR] 1.21, 95% confidence interval [CI] 1.13-1.29). The association of BDZR use with dementia was slightly stronger for long acting substances (OR 1.26, 95% CI 1.15-1.39) than for short acting ones (OR 1.13, 95% CI 1.04-1.23). A trend for increased risk for dementia with higher exposure was observed.

Conclusions: The restricted use of BDZRs may contribute to dementia prevention in the elderly.

627. Trends in Prescribing of Antipsychotics in Dementia: A Population-Based Study

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Background: Evidence that typical and atypical antipsychotics (APS) increase all-cause mortality and stroke in patients with dementia is growing.

Objectives: To examine the trends in co-prescribing of antipsychotics in community dwelling individuals aged ≥ 70 years receiving anti-dementia drugs (ADD).

Methods: Design: Retrospective cohort study in community dwellers aged ≥ 70 years prescribed > 1ADD during the period 2009- 2014. The population-based cohort derived from a pharmacy claims database to identify co-prescription of typical and atypical APS.

Statistical analysis: Generalised estimating equations were used to examine trends in percentage use of APS over time (interactions time by gender, age, typical/atypical APS). Predictors of APS use in new initiators of anti-dementia medicines, including age, gender and year of initiation, were determined using logistic regression. Adjusted odds ratios (OR) and 95% confidence intervals (CI) are presented.

Results: There was an increase in the overall prevalence of co-prescribed APS in patients receiving ADD from 2009-2014. The percentage of APS use in males on ADDs increased slightly from 31.5% (Jan 2009) to 33.4% (Dec 2014) but remained static in females (interaction, $p<0.001$). Patients aged ≥85 years had the highest APS use (34.2%), followed by 70-79 (30.6%) and 80-84 years(30.5%; $p<0.001$). There was a trend of increasing use of atypical antipsychotics ($p<0.0001$). Overall, quetiapine was the most frequently prescribed, significantly increasing over time ($p=0.008$). However, decreasing rates of prescribing for haloperidol ($p=0.002$) and prochlorperazine ($p<0.001$) were found with no change for olanzapine. The likelihood of initiating APS in newly treated dementia patients significantly decreased over time (2013 vs 2010; OR=0.82, 95%CI 0.77, 0.89).

Conclusions: Increased prescribing of APS, particular in males and the older aged population, suggests that clear guidance, particularly in these groups, may be required.

628. Psychotropic Medication Use and Alzheimer's Disease: A Story of Sex Differences in Two Countries

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Background: Current evidence suggests high prevalence of psychotropic medication use among people with dementia. To date, no study has compared the role of sex on psychotropic prescribing practices in older people with Alzheimer's Disease (AD) living in different regions.

Objectives: Our study aimed to examine the role of sex to predict psychotropic medication use in older adults with AD living in the US and Finland.

Methods: We used data collected between 2005 and 2011 as part of the National Alzheimer's Coordinating Center (NACC) in the US, and Medication use and Alzheimer's disease (MEDALZ) cohort in Finland. We evaluated psychotropic medication use (defined as the use of an antidepressant, antipsychotic, or anxiolytic, sedative or hypnotic) at diagnosis during cohort

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follow-up (NACC) or within 6-months following an AD diagnosis (MEDALZ), and investigated whether sex was a significant predictor of use. Multivariable logistic regression adjusted for demographic characteristics, comorbidities, and other medications to estimate the magnitude of the association (odds ratio [OR] with 95% confidence intervals [CI]) were performed.

Results: From NACC, we included 1099 enrollees ≥65 years (502 men, 597 women) diagnosed with AD. From MEDALZ, 67,049 individuals (22,961 men, 44,088 women) were ≥65 years and alive at 6-months after the AD diagnosis when medication use was assessed. Compared to men, women were more likely to use psychotropic medications: US- 46.2% vs 33.1%, p<0.0001, Finland- 45.3% vs 36.1%, p<0.0001.The adjusted OR was 2.08 (95% CI: 1.58 – 2.70) in the US and 1.38 (95% CI: 1.33-1.43) in Finland. Similarly, when evaluating different psychotropic medication classes, in both countries, women were more likely to use antidepressants (US-adjusted OR: 1.76 [1.34 – 2.3]; Finland adjusted OR: 1.52 [1.46 - 1.59]) and anxiolytics (US-adjusted OR: 2.43 [1.49 – 3.98]; Finland adjusted OR: 1.18 [1.13 - 1.23]), as compared to men.

Conclusions: As older women with AD are more likely to use psychotropic medications than older men, regardless of country, prescribers should be aware of potential bias when treating older adults with AD.

629. Risk of Pneumonia Associated with Incident Benzodiazepine Use Among Community-Dwelling Persons with Alzheimer's Disease

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Background: There is a lack of knowledge if benzodiazepine and related drug (BZDR) use is associated with an increased risk of pneumonia among older persons.

Objectives: To investigate the risk of pneumonia associated with BZDR use among community-dwelling persons with Alzheimer's disease (AD).

Methods: Design: Retrospective cohort study based on nationwide register-based MEDALZ (Medication use and Alzheimer's disease) cohort including all community-dwelling persons newly diagnosed with AD 2005-2011 in Finland. The final sample included 49,471 persons with AD (63% women, mean age 80 years).

Setting: Community-dwelling persons with AD. Data from Prescription, Hospital Discharge and Causes of Death registers.

Exposure: Use of benzodiazepines and related drugs (Z-drugs, including zopiclone, zolpidem) modelled with PRE2DUP method. New users identified with one year washout period.

Main outcome measure: Hospitalization or death due to pneumonia.

Statistical analysis: BZDR use was compared with time without BZDR use with Cox proportional hazard models. In addition, benzodiazepine use was compared with Z-drug use.

Results: BZDR use was common among persons with AD as 21% (N=10,276) started using these drugs during the follow-up (median follow-up time 2.2 years, interquartile range 1.3-3.7 years). BZDR use was associated with an increased risk of pneumonia (adjusted HR 1.61 [95% CI 1.48-1.74]). The risk was higher in the beginning of BZDR use (adjusted HR 2.37 [95% CI 1.92-2.93]), and although the risk decreased gradually it was elevated even 1-3 years after the initiation. In comparison to Z-drug use, benzodiazepine use was associated with an increased risk of pneumonia (adjusted HR 1.28 [95% CI 1.07-1.54]).

Conclusions: BZDR use was associated with an increased risk of pneumonia among persons with AD. Benefits and risks of BZDR use should be carefully considered among older persons also in terms of pneumonia risk.

630. Risk Of Stroke Associated With Benzodiazepine And Related Drug Use Among Persons With And Without Alzheimer's Disease

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Background: There are no previous studies on risk of stroke associated with benzodiazepine use among persons with Alzheimer's disease although they frequently use these drugs.

Objectives: To investigate the risk of any, ischemic and hemorrhagic stroke associated with benzodiazepine and related drug (BZDR) use among community-dwelling persons with and without Alzheimer's disease (AD).

Methods: Design: Retrospective cohort study based on data from Finnish health care registers.

Setting: Data from the MEDALZ (Medication use and Alzheimer's disease) cohort including all community-dwelling persons diagnosed with AD between 2005 and 2011 in Finland was utilized. Two age- and sex-matched comparison persons without AD were identified for each AD case. The final study sample included 45,050 persons with incident AD and 90,100 persons without AD.

Exposure: New use of benzodiazepines and related drugs (Z-drugs, including zopiclone and zolpidem) was compared with nonuse of these drugs. Drug use periods were modelled with PRE2DUP method.

Main outcome measures: Stroke defined as hospitalization or cause of death from nationwide registers. Strokes were further classified as ischemic, hemorrhagic and unspecified strokes.

Statistical analysis: The risk of stroke between BZDR use and nonuse was compared with Cox proportional hazard models with BZDR use as time-dependent variable. In addition, benzodiazepine use was compared with Z-drug use.

Results: During the follow-up, 21.9% (N=9,879) of persons with AD and 13.3% (N=11,992) of persons without AD started BZDR use. BZDR use was associated with any stroke among persons with AD (adjusted HR [aHR] 1.21 [95% CI 1.04-1.40]) and among persons without AD (aHR 1.39 [95% CI 1.20-1.61]). Similarly, BZDR use was associated with ischemic stroke among both persons with (aHR 1.21 [95% CI 1.02-1.44]) and without AD (aHR 1.30 [95% CI 1.10-1.54]) but the association between BZDR use and hemorrhagic stroke was found only among persons without AD. Benzodiazepine use was associated with similar risk as Z-drug use.

Conclusions: BZDR use was associated with slightly increased risk of stroke among older persons with and without AD.

631. Comparative Risk Of All-Cause Mortality In Older Patients Prescribed Codeine Or Tramadol For Non-Malignant Pain: Retrospective Cohort Study

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Background: Opioids are increasingly used to treat non-malignant pain, despite risks of poor tolerance and dependence. A US study in patients without cancer showed a greater risk of all-cause mortality for codeine, but not tramadol, relative to hydrocodone (Solomon et al 2010). This result was counterintuitive given tramadol is more potent and used to treat more severe pain. Confounding by indication would be expected to bias the result in the other direction.

Objectives: To compare the risk of all-cause mortality in adults aged 65+ years prescribed codeine or tramadol for non-malignant pain in UK primary care.

Methods: Data on patients newly prescribed codeine or tramadol 1990-2012 were extracted from the Clinical Practice Research Datalink. Exclusion criteria included; previous opioid or NSAID prescription, malignancy, opioid dependence or illicit drug use in the year prior to the index date. Follow-up was censored upon transfer out of the GP practice, last data

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collection, date of switch to different opioid, 90+ day treatment gap, 365 days after the final opioid prescription, death or 31/12/2012 whichever was earliest. Hazard ratios were estimated using the Cox model using codeine as the baseline.

Results: 66,061 patients were prescribed codeine (mean age 75.8 yrs, 38% male) and 73,874 tramadol (74.6 yrs $p<0.0001$, 39% male $p<0.001$). The crude mortality rate for codeine was 84.4/1,000 person years (95% CI 82.2-86.7) and for tramadol was 72.4/1,000 person years (70.5-74.3). The unadjusted mortality hazard ratio for tramadol vs. codeine was 0.88 (95% CI 0.85-0.91). Gender, age and calendar year adj. HR was 1.01 (0.97-1.05). After further adjustment for medical history, opioid treatment indication, concomitant medication and lifestyle factors, the HR was 1.04 (0.99-1.08).

Conclusions: Our unadjusted HR suggesting a reduced risk of all-cause mortality with tramadol compared to codeine is consistent with the US study, albeit with a different comparator. However, we found no association after adjusting potential confounders. This could suggest residual confounding in the earlier study and provides reassuring data on the safety of tramadol.

632. Long-Term Use of Opioids Among Community-Dwelling Persons with and without Alzheimer's Disease

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Background: There is insufficient evidence to support long-term opioid use, but adverse effects may be serious in older persons, especially with cognitive impairment.

Objectives: To find out whether opioid use of ≥6 months is more common in community-dwelling persons with Alzheimer's disease (AD) than in comparison persons, and what other factors are associated with it.

Methods: Design: Retrospective cohort study. Altogether, 63 415 persons with AD and one comparison person for each case were included in this study.

Setting: Data from register based MEDALZ (Medication use and Alzheimer's disease) cohort consisting of all community-dwelling persons diagnosed with AD during 2005–2011 in Finland. Drug use data were collected from the Prescription Register and comorbidities from Special Reimbursement and Hospital Discharge Registers. Follow up started from the diagnosis of the case and ended to long-term hospitalization ≥90 days), death or end of the study period (December 31. 2012), whichever came first.

Exposures: Opioid use compared between persons with and without AD, modelled with PRE2DUP method.

Main outcome measures: Prevalence of long-term use of opioids ≥6 months).

Statistical analyses: Factors associated with long-term use were analyzed with logistic regression models. Long-term use was compared with short-term use of opioids.

Results: Proportion of opioid users during the study period was 21.0% and 27.3% in persons with and without AD, respectively. Proportion of long-term users was 26.1% vs. 23.1% among opioid users with and without AD, respectively. Long-term opioid use was associated with AD (OR 1.14, 95% CI 1.08-1.21), female gender (OR 1.25, 1.17-1.34) and age of ≥80 years (OR 1.27, 1.20-1.34). Long-term transdermal opioid use was more common among person with AD compared to person without AD (35.2% vs. 13.7%).

Conclusions: Although the proportion of opioid use was lower among persons with AD, they were more likely to be long-term users, especially of transdermal opioids than those without AD. Due to high proportion of long-term opioid use in older patients efficacy and risks of the treatment should be closely monitored.

633. Hospice Use and Pain Management in Nursing Home Residents with Cancer

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Background: The prevalence of untreated pain in nursing home residents with cancer is unacceptably high. While the benefits of hospice for treating pain

in the community are well established, less is known about hospice care in the nursing home.

Objectives: To estimate the extent to which receipt of hospice in nursing homes increases the use of pain management for residents with cancer at the end of life.

Methods: We conducted a cross-sectional study of a national United States sample of Medicare decedents who had cancer and were nursing home residents during the last 90 days of life in 2011–2012. We used the last Minimum Data Set (MDS) 3.0 assessment before death and the Medicare Beneficiary Summary File to measure hospice use, pain, and pain management. We matched residents with cancer and in pain who received hospice care to residents in pain not receiving hospice care on nursing home facility and time from last MDS assessment to death. The primary outcomes were receipt of pharmacologic pain management including scheduled and PRN analgesics and non-pharmacologic pain management. Conditional logistic models were used to estimate the association between hospice use and pain management.

Results: In matched analyses, untreated pain was uncommon (2.9% in hospice users and 5.6% in non-hospice users), though there was an absolute difference of 15.4% in scheduled analgesic use between hospice and non-hospice users (71.5% vs. 56.1%, respectively). Hospice use was associated with receipt of scheduled analgesics (adjusted Odds Ratio (aOR): 1.85, 95% Confidence Interval(CI): 1.73–1.97), PRN medication (aOR: 1.31, 95% CI: 1.20–1.43), and non-pharmacologic pain management (aOR: 1.18, 95% CI: 1.11–1.26).

Conclusions: Untreated pain at the end of life among nursing home residents with cancer was uncommon. Hospice use in nursing homes was associated with increased pain management in residents with documented pain. Further work to examine the type and effectiveness of pain management strategies used for nursing home residents at the end of life are warranted.

634. Antidepressant Use And Associated Risk Of Head And Brain Injuries Among Persons With And Without Alzheimer's Disease

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Background: Antidepressant use has been associated with an increased risk of falls and fractures among older persons. However, risk of head and brain injuries has not been investigated.

Objectives: To investigate the risk of head injuries and traumatic brain injuries (TBI) associated with antidepressant use among persons with and without Alzheimer's disease (AD).

Methods: Design: Register-based retrospective cohort study. Data from Finnish health care registers was utilized.

Setting: MEDALZ cohort included all community-dwelling persons newly diagnosed with AD during 2005-2011 in Finland. Two comparison persons without AD were matched for each person with AD after exclusions based on antidepressant use during one year washout period and previous head injury. In this study, 48,962 persons with AD and 97,924 persons without AD were included.

Exposure: Antidepressant use time compared with nonuse. Duration of use was modelled with PRE2DUP method.

Main outcome measures: Any head injury or TBI recorded in the Hospital Discharge register.

Statistical analysis: Incident antidepressant use (with one year washout period) was compared with time without antidepressant use separately among persons with and without AD. Separate analyses were performed for head injury and TBI. Analyses were conducted with Cox proportional hazard models.

Results: Among 48,962 persons with AD, 22% (10,973) initiated antidepressant use and 10% (9,569/97,924) among persons without AD. Antidepressant use was associated with an increased risk of head injury among persons with AD (adjusted HR 1.40, 95% CI 1.25-1.55) and among persons without AD (aHR 2.50, 95% CI 2.17-2.87). Similarly,

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antidepressant use was associated with an increased risk of TBI among persons with AD (aHR 1.36, 95% CI 1.17-1.58) and among persons without AD (aHR 2.75, 95% CI 2.30-3.28). The risk of head and brain injuries were highest in the beginning of use but the elevated risk was observed even after 1-2 years of use.

Conclusions: When risks and benefits of antidepressant use among older persons with and without AD are evaluated also the risk of head and brain injuries should be considered.

635. Antidepressant Use And Associated Risk Of Hip Fractures Among Community-Dwelling Older Persons With And Without Alzheimer's Disease In Finland

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Background: Hip fractures are significant health concern among older persons. Antidepressant use has previously been associated with an increased risk of hip fracture among older people. However, the association with antidepressant use and hip fractures has not previously studied among persons with clinically verified diagnosis of Alzheimer's disease (AD).

Objectives: To study whether antidepressant use is associated with an increased risk of hip fracture among community-dwelling persons with and without AD, and to compare the risk according to duration of use.

Methods: Design: Retrospective cohort study, including 50,491 persons with AD (mean age 80) and 100,982 age- and sex-matched comparison persons without AD.

Setting: Nationwide register-based MEDALZ cohort which includes all community-dwelling persons newly diagnosed with AD during 2005-2011 in Finland. The follow-up until December 31, 2012.

Exposures or interventions: Antidepressant use was compared with nonuse. A one year washout period was utilized for antidepressant use. Drug use was modelled with PRE2DUP method from Prescription register data.

Main Outcome measures: Incident hip fractures according to Hospital Discharge register.

Statistical analysis: Cox proportional hazard models were used and adjusted for confounders.

Results: During antidepressant use, the age-adjusted rate of hip fractures per 100 person-years was 3.01 (95% CI 2.75-3.34) among persons with AD and 2.28 (1.94-2.61) among persons without AD. Antidepressant use was associated with an increased risk of hip fracture among persons with and without AD (adjusted HR 1.66, 95% CI 1.49-1.85; HR 2.76, 2.39-3.93, respectively) compared with nonuse. The risk was most prominent in the beginning of use and was elevated even 2-4 years after the initiation. The risk was increased with all of the most frequently used antidepressants.

Conclusions: Antidepressants should be used with caution among older persons with and without Alzheimer's disease. If the antidepressant treatment is necessary for severe depression, treatment should be regularly monitored.

636. Factors Influencing the Quality of Antidepressant Prescribing for Older, Community-Dwelling Adults, and the Risk of Emergency Outcomes

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Background: Various antidepressants are considered potentially inappropriate for older adults by Beers 2012 criteria. The identification of factors associated with the choice of antidepressants will guide interventions to support appropriate prescribing.

Objectives: (i) To identify determinants of inappropriate antidepressant prescribing for older, community-dwelling adults; and (ii) to evaluate the risk of emergency referrals among users.

Methods: Office visits by older adults >64y) who received antidepressants, were extracted from the National Ambulatory Medical Care Survey 2010. Visits were classified as 'Avoid' for tertiary tricyclic antidepressant (TCAs) use, 'Caution-Avoid' for serotonin inhibitors, secondary TCAs and bupropion, or 'Unrestricted'. Associations between various factors, and the choice of antidepressant were measured using multivariate logistic regression. Bivariate regression measured the risk of emergency referral for patients receiving Avoid antidepressants.

Results: Over 23 million older adults (92%) received potentially inappropriate antidepressants mostly Caution-Avoid antidepressants (82%). Tertiary TCA prescribing was less likely with increasing age (ARR=0.93, 0.890-0.971), asthma (ARR=0.114, 0.018-0.70), consultation time (ARR=0.928, 0.869-0.991) and electronic medical records (EMR) use (ARR=0.355, 0.141-0.893). Prescribing of Caution-Avoid antidepressants was less likely with physician assistant involvement (ARR=0.218, 0.072-0.663) and EMR use (ARR=0.226, 0.094-0.545), but more likely with depression (ARR=2.526, 1.068-5.978), income $40,627-52,387 (ARR=3.529, 1.171-10.639) and cardiology visits (ARR=7.106, 1.417-35.652). Emergency referrals were more likely among tertiary TCA users (RR=28.637, 3.793-216.216).

Conclusions: Older antidepressant users primarily receive antidepressants to be used with caution or to avoid in selected conditions. EMRs, longer consultations and physician assistants may minimize prescribing of potentially inappropriate antidepressants. Patients receiving tertiary TCAs should be monitored during and after office visits due to the increased risk of emergency outcomes.

637. Incidence Of Antidepressant Use In Community-Dwelling Persons With And Without Alzheimer's Disease – 13-Year Follow-Up

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Background: Prevalence of antidepressant use is high among older persons with dementia but no studies on the incidence of antidepressant use has been published.

Objectives: To investigate the incidence of antidepressant use in persons with and without Alzheimer's disease (AD) from 9 years before to 4 years after AD diagnosis, and to examine the incidence of different antidepressant groups.

Methods: Design: Register-based data from the Medication use and Alzheimer's disease (MEDALZ) cohort including all Finnish persons diagnosed with AD in 2005–2011 with their age- and gender matched comparison persons without AD. In this study, 62,104 persons with AD and 62,104 comparison persons were included after exclusions based on one year washout period.

Setting: Community-dwelling older persons of Finland.

Exposure: Any antidepressant, and categorized as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine and other antidepressants, from Prescription register data.

Main outcome measures: The incidence of antidepressant use after a one year washout period 9-10 years before the diagnoses. The follow-up time for the incidence started 9 years before and ended 4 years after AD diagnoses.

Statistical analysis: The incidence rate between persons with and without AD was compared with Poisson regression.

Results: The incidence of antidepressant use in persons with AD was higher during the whole study period compared with persons without AD. The incidence rate was highest at six months after AD diagnosis (Incidence Rate Ratio IRR=5.22, 95% confidence interval 4.77–5.72). Selective serotonin reuptake inhibitors was the most frequently initiated group (61.3% of initiations in persons with AD).

Conclusions: The incidence of antidepressant use was higher in persons with AD than in comparison persons and it was not explained by history of hospital-treated psychiatric disorders. Widespread use of antidepressants in persons with AD is concerning as their efficacy is controversial and their use is associated with adverse events.

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638. Comorbidity in Vascular Neurocognitive Disorders: A Matched Case–Control Study

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Background: Patients with vascular dementia may present more medical illnesses than generally thought, but that these diseases remain undetected. A few series of autopsies have confirmed this hypothesis, showing that demented patients often have a number of comorbid conditions that are frequently underestimated by clinicians.

Objectives: The objective of the study was to compare the presence of comorbid medical conditions between patients with Vascular Neurocognitive Disorders (also called vascular dementia) and a control group, from the Integrated Healthcare Information Services (IHCIS) database.

Methods: Vascular Neurocognitive Disorders (VNCD) was defined by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 290.40, 290.4, 290.41, 290.42, and, 290.43. An individual matching method was used to select the controls, which were matched to cases on a 15:1 ratio by age, gender, type of health plan, and pharmacy benefits. Alzheimer's disease, any other dementia or cognitive deficits associated were considered exclusion criteria.

Results: Among the IHCIS patients with 60 years of age or older and full year of eligibility during 2010, there were 898 VNCD patients, from which 63.6% were women. Cerebrovascular disease, atherosclerosis, heart failure, and atrial fibrillation were found at 12.6, 4.6, 2.8, and 1.7 times higher in VNCD patients, respectively. Compared to controls, VNCD patients had more septicemia, injuries, lung diseases, and urinary diseases (all at $p < 0.0001$).

Conclusions: The present study confirms that these four medical comorbidities are frequent complications of VNCD and physicians should be alert to the presence of them in patients with VNCD.

639. Outcomes After Induction Agent Use In Older Kidney Transplant Recipients

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Background: Induction agents are commonly used as an initial intensive immunosuppression after kidney transplantation (KT) to prevent acute organ rejection; this practice is mostly off label. Clinical trials of induction agents typically exclude older recipients.

Objectives: To study the outcomes after induction agent use in older KT recipients.

Methods: We used data from the Scientific Registry of Transplant Recipients (a national registry of all solid organ transplants) to study 10,777 older deceased donor KT recipients (2005-2013). Induction agents were classified as ATG or IL-2. The risk of delayed graft function (DGF) and 1-year acute rejection by induction agent use was estimated using adjusted logistic regression. Mortality and death-censored graft loss risks were estimated using an adjusted Cox Proportional Hazards model. All models were weighted by the IPTW estimated from a multi-level model for ATG or IL-2 use which included recipient, donor, transplant and center-level factors.

Results: Among older KT recipients, 36% received IL-2. Center characteristics were more strongly associated with the choice of induction agent than recipient factors. IL-2 induction agent use was associated with a lower odds of DGF (OR=0.82, 95%CI:0.71-0.94, P=0.01), but greater odds of one year acute rejection (OR=1.35, 95%CI:1.07-1.71, P=0.01) compared to those who received ATG induction. There was no association between induction agent use and mortality (HR=1.02, 95%CI:0.90-1.16, P=0.76), or death-censored graft loss (HR=1.08, 95%CI:0.88-1.32, P=0.48).

Conclusions: Induction agent use is mainly influenced transplant center rather the patient factors in both older and younger KT recipients. We developed IPTW to account for center-level factors in addition to recipient level factors to reduce confounding and address channeling bias. While we noted no differences in long-term outcomes (mortality and graft loss) by induction agent use, we did note differences in delayed graft function and 1 year acute rejection. We cautiously interpret these results as they may still reflect channeling bias of IL-2 to reduce acute rejection.

640. Time Trends of Vitamin B12 Deficiency in Older Adults: A Population-Based Cohort Study

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Background: Vitamin B12 deficiency has serious consequences such as neurologic damages. Prevalence is the highest in older adults (5-15%). These rates may have increased over years due to the growing use of drugs known to alter vitamin B12 absorption (eg, metformin, proton pump inhibitors). However, time trends in the epidemiology of vitamin B12 deficiency and incidence rates at the population level remain unknown.

Objectives: To assess time trends in incidence and prevalence rates of diagnosed vitamin B12 deficiency in older adults from 1995 to 2010.

Methods: The cohort includes a random sample of 367,500 residents of Quebec, Canada, aged >65 years between 1995 and 2010, and registered to the Public Drug Insurance Plan for ≥1 year. Medico-administrative data related to drug claims, medical services and hospitalisations, including diagnoses recorded as ICD-9 or 10 codes, were used. Individuals with one of the following were deemed having been diagnosed with vitamin B12 deficiency: prescribed vitamin B12 therapy, diagnosis of vitamin B12 deficiency anemia, or diagnosis of B vitamin deficiency without evidence of vitamin B9, B6, or B2 deficiency within ±6 months of the record date. Crude prevalence and incidence rates were calculated by sex and age groups for each calendar year. Age- and sex-adjusted rates were computed using the 2009 Quebec population data. Poisson regression was used to estimate incidence rate ratios (IRRs) for sex, age, and calendar year.

Results: In total, 21,635 incident cases of vitamin B12 deficiency were identified. The overall adjusted incidence rate was 0.87/100 person-years. Incidence rates increased sharply with age, from 0.42-0.47 in men and women aged 66-69 years to 1.9-2.1 in those aged ≥85 years (IRR 4.5, CI:4.3-4.8). Adjusted annual incidence rates varied from 0.66 to 1.00 with no consistent time trend over years. Adjusted prevalence rates increased steadily from 2.3% in 1995 to 5.6% in 2010.

Conclusions: The high incidence and the increasing prevalence suggest vitamin B12 deficiency as a public health issue in older adults, especially in the oldest-olds. Research is needed to define the role of drug exposure in the epidemiology of vitamin B12 deficiency.

641. Patterns and Predictors of Potentially Inappropriate Medication Use in Older Colon Cancer Patients

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Background: Potentially inappropriate medications (PIMs) are those with an unfavorable risk-benefit balance in older adults. PIMs increase the risk of drug-drug interactions, side effects, and adverse clinical outcomes; yet, little is known about PIM use in older cancer patients.

Objectives: Describe longitudinal patterns and predictors of PIM use in adults aged 66+ years diagnosed with stage II/III colon cancer using 2012 Beer's drug and disease-drug interactions lists.

Methods: We used the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, a linkage of cancer registry and Medicare data, to identify older adults diagnosed with stage II/III colon cancer (2007-11) and enrolled in Medicare part D with ≥1 prescription dispensed in the month of diagnosis and Medicare parts A/B in the prior 12 months. We estimated the monthly point prevalence of ≥1 PIM from 6 months pre- to 24 months post-diagnosis. To identify predictors of PIM use, we used binomial regression to estimate adjusted prevalence ratios (aPR) and robust 95% confidence intervals.

Results: Among 7,283 older colon cancer patients, mean age was 78 and most were living with 1+ comorbidity (53%). PIM point prevalence was stable before cancer diagnosis (37-39%), but increased in the 6 months post-diagnosis (initial treatment period) to

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43%, returning to pre-diagnosis levels in months 12-24 post-diagnosis (35-39%). A higher comorbidity score (2+ vs. 0, aPR=1.2 (1.2, 1.3)), number of prescriptions >10 vs. 0-2 drugs, aPR=2.1 (2.0, 2.2)), and claims-based functional dependence (high vs. low, aPR=1.6 (1.5, 1.7)) predicted PIM use. Digoxin (doses>0.125 mg/d, 7%), glyburide (3%), and spironolactone (doses>25 mg/d, 2%) were the most common PIMs. During initial treatment, PIMs for supportive cancer care, promethazine (3%), megesterol (2%), and belladonna alkaloids (2%), were common.

Conclusions: PIM prevalence was high during the initial cancer treatment period due to PIMs used for supportive care. Alternative supportive agents with more favorable benefit-risk profiles should be considered. As the majority of PIMs were unrelated to supportive cancer care, continued efforts to reduce overall PIM are needed.

642. Prevalence and Predictors of Inappropriate Medications According to START/STOPP Criteria Version-2 in Indian Elderly

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Background: Balanced and safe prescribing is difficult to achieve in older adults with multiple comorbidities. The avoidance of medications that are considered to be inappropriate is a valuable intervention to improve the safety and appropriateness of prescriptions in this vulnerable population.

Objectives: To determine the prevalence and predictors of Inappropriate Medications according to the Screening Tool of Older Person's Prescription (STOPP) and screening Tool to Alert doctors to Right Treatment (START) criteria version 2 in elderly patients.

Methods: Design: This is a prospective observational study.

Setting: 614 elderly patients (≥60 years) admitted to medicine wards of 4 private tertiary care hospitals of Warangal (India) were recruited in this study after the ethics committee approval. These patients were followed from admission to discharge.

Main outcome measures: 1) Detecting potentially inappropriate medications (PIMs) and potentially prescribing omissions (PPOs) as per START/STOPP Version-2 by reviewing medical records 2) To determine the predictors for PIMs and PPOs.

Statistical analysis: Bivariate and Multivariate Logistic Regression Analysis was used to determine various predictors for PIMs and PPOs.

Results: Out of 614 patients, 211 patients (34.4%) and 178 patients (29%) were found to have at least one PIM and PPO respectively. Multi logistic regression showed that: i) 6-10 days Hospital stay (OR: 2.918, 95% CI: 2.005-4.247, $p<0.0001$); ii) 5-6 Diseases (OR: 1.736, 95% CI: 1.017-2.965, $p<0.043$); iii) ≥5 Medications during hospital stay (OR: 5.077, 95% CI: 1.778-14.496, $p<0.002$) are the strongest predictors for PIMs. The Predictors for PPOs were i) Diseases >3 (OR: 3.197, 95% CI: 2.102-4.822, $p<0.0001$), ii) ≥6 days Hospital stay (OR: 2.115, 95% CI: 1.444-3.098, $p<0.0001$).

Conclusions: A higher prevalence of PIMs & PPOs compared to previous Indian studies was observed. Clinicians should carefully monitor Elderly patients with multiple diseases and polypharmacy as these are found to be the influential predictors for both PIMs & PPOs.

643. Effectiveness of the STOPP/START (Screening Tool of Older Persons' Potentially Inappropriate Prescriptions/ Screening Tool To Alert Doctors To The Right Treatment) Criteria: Systematic Review And Meta-Analysis Of Randomized Controlled Studies

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Background: STOPP/START are explicit screening tools that identify potentially inappropriate prescribing

in older adults. A systematic review published in 2013 found limited evidence of the tools' efficacy.

Objectives: To synthesize all available evidence from published randomized controlled trials (RCTs) that assessed the effectiveness of STOPP/START tools on prescribing quality, and clinical, humanistic and economic outcomes in adults aged 65 years and older.

Methods: We performed an updated search of PubMed, EMBASE, CINAHL, ISI Web of Science and grey literature to retrieve RCTs published in English from January 2012 through June 2014. The Cochrane Risk of Bias Tool was used to assess internal validity. We performed a random-effects meta-analysis of the effect of STOPP/START on potentially inappropriate medication (PIM) rates and a narrative synthesis on other clinical, humanistic and economic outcomes.

Results: A total of 228 records were identified afterduplicate removal. Four RCTs (n=1,925 patients) from four countries were included. Settings of studies included acute care (n=2) and long-term care facilities (n=2). The studies differed in implementation of the tools. Two studies were judged to have a low risk of bias in key domains, and two were judged to have moderate-to-high risk of bias. PIM rates in intervention arms were reduced across all trials (range, 12.2%-39.5%), but considerable statistical heterogeneity (I^2=86.7%) prevented calculation of a pooled statistical summary. Across the trials, we found evidence that use of STOPP/START reduced falls, episodes of delirium, hospital length-of-stay, and primary and emergency care visits. Medication costs were found to be reduced in two studies. There was no evidence of improved quality-of-life or mortality.

Conclusions: Application of STOPP/START may be efficacious in improving prescribing quality, clinical, humanistic and economic outcomes. More research investigating these tools is required, especially in frail elderly and community-living patients receiving primary care.

644. Potentially Inappropriate Prescribing Measured by STOPP and START and Functional Decline and Quality of Life in Older People: A Cohort Study

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Background: Potentially inappropriate prescribing (PIP), including over- and under-prescribing, is prevalent in older people. Although PIP has been shown to be associated with adverse drug events, the relationship with patient-centred outcomes is less clear.

Objectives: To determine if PIP is associated with functional decline and reduced quality of life (QoL) in a cohort of older people.

Methods: This prospective cohort study included community-dwellers aged ≥65 years from The Irish Longitudinal Study on Ageing (TILDA) with linked administrative pharmacy claims data who were followed up after two years. PIP was determined using the Screening Tool for Older Persons Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START). The association with functional decline (increased difficulties with Activities of Daily Living between baseline and follow-up) and QoL measured by CASPR12 were analysed using multivariate logistic and linear regression respectively, adjusting for demographics, medication use and chronic conditions. Marginal structural models investigated the impact of time-dependent confounding.

Results: Of participants followed up (n=1,753), PIP was detected in 57% by STOPP and 41.8% by START, and 8.3% of all participants had functional decline at follow-up. Having a START prescribing omission was significantly associated with functional decline (adjusted OR 1.55, 95% CI 1.07, 2.24), however, no evidence of an effect due to STOPP was found. CASPR12 scores at follow-up ranged from 5 to 36 (mean 26.2, SD 5.2). Neither presence of any STOPP nor any START criterion was significantly associated with CASPR12 score, but considering number of PIP criteria, having ≥2 START criteria was associated with a small but statistically significant reduction in QoL (adjusted β -1.05, 95% CI -1.83, -0.26). Accounting for time-varying confounding did not significantly alter these results.

Conclusions: Exposure to START was related to functional decline and reduced QoL, however, effect sizes were modest. Optimising prescribing to reduce PIP may provide an improvement in patient outcomes.

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645. STOPP 2 versus EU(7)-PIM: Comparing Prevalence and Impact of Inappropriate Prescribing on Mortality and Hospitalisation

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Background: Inappropriate prescribing in older adults is linked to adverse drug events. Explicit criteria were developed to identify medication misuse.

Objectives: Comparing prevalence and associations with outcomes in a cohort of community-dwelling oldest old (≥80 years) of a subset of clinically-oriented STOPP 2 criteria and the medication-only EU(7)-PIM.

Methods: Explicit criteria were cross-referenced and linked to medications and clinical problems of the Belfrail-Med cohort (n=503). Survival analysis was performed at 18 months after inclusion using Kaplan-Meier, with Cox regression to control for covariates.

Results: Mean age was 84.4 years (range 80 – 102). Mean medication use was 5 (range 0 – 16).

Prevalence of misuse was 72.8% and 56.1%, predominantly benzodiazepines and lorazepam for STOPP and EU(7)-PIM respectively.

STOPP and EU(7)-PIM were strongly correlated (rs=.61, p<.001).

Mortality and hospitalisation rate were 8.9%, and 31.0% respectively. In univariate analysis, neither STOPP (HR 1.16, 95%CI 0.92 – 1.47), nor EU(7)-PIM (HR 1.15, 95%CI 0.93 – 1.42) were associated with mortality. For hospitalisation, STOPP showed a significant association (HR 1.20, 95%CI 1.06 – 1.36), but EU(7)-PIM did not (HR 1.11, 95%CI 0.99 – 1.25).

After adjusting for the number of medications, both misuse measures showed no associations with mortality (STOPP, HR 0.93, 95%CI 0.69 – 1.24; EU(7)-PIM, HR 0.99, 95%CI 0.76 – 1.29), nor hospitalisation (STOPP, HR 0.98, 95%CI 0.84 – 1.14; EU(7)-PIM HR 0.92, 95%CI 0.80 – 1.0).

Conclusions: Misuse was highly prevalent in community-dwelling oldest old, but no association with outcomes was found, whether misuse was operationalised by the clinically-oriented STOPP 2 or by the medication-only EU(7)-PIM.

646. Drug Burden in Aging Adults with Intellectual Disabilities Living in Residential Facilities: A Cross-Sectional Study

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Background: Use of drugs with sedative and/or anticholinergic effects have been associated with adverse outcomes such as falls and daytime sedation. Older people with intellectual disabilities (ID) are at increased risk of exposure to these medicines owing to higher prevalence of multimorbidity, particularly psychiatric morbidities.

Objectives: The aims of this study were to determine individuals with ID who live in residential instititution's exposure to anticholinergic and/or sedative medication through use of the evidence-based prescribing tool; the Drug Burden Index (DBI), to identify therapeutic classes contributing to burden and to examine associations between higher burden and functional adverse effects.

Methods: Cross-sectional (self-report/proxy report) medication data were drawn from those living in residential institutions from Wave2 of the Intellectual Disability Supplement to the Irish Longitudinal

Study on Ageing, a study on aging of 708 nationally representative people with ID aged over 44 years living in a variety of settings randomly selected from the National Intellectual Disability Database. Medication data were available for 275 participants living in residential institutions.

Each individual's exposure to anticholinergic and/or sedative medicines was calculated using the DBI. Bivariate analysis examined associations between functional adverse effects and DBI scores 1-2 and >2.

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Results: In the eligible population of 275 participants (59.3% female, 51.3% aged 50-64 years), 92.4%(243) were exposed to a DBI medicine, a mean (±SD) score of 1.86 (±1.31), 45.4% (114) a DBI score of >2.0. Antiepileptics accounted for 26.3% of the cumulative DBI score in the cohort, followed by antipsychotics (21.9%) and anxiolytics (14.5%). Higher DBI score >2) was not significantly associated with daytime dozing (p=0.99), falls (p=0.80) or constipation (p=0.70).

Conclusions: Use of medications with anticholinergic and/or sedative properties in older adults with ID is high. Utilisation of the DBI tool may be useful in predicting effects of medication on function in older people with ID and informing development of interventions to improve appropriate prescribing.

647. The Effect of Pharmacist-Led Interventions in Optimising Prescribing in Older Adults in Primary Care: A Systematic Review

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Background: Medication-related problems are common in older people and place a significant burden on health care resources. Pharmacists can play a key role in gate-keeping medication appropriateness by enhancing the quality and safety of prescribing.

Objectives: To evaluate published studies of pharmacist-led interventions addressing potentially inappropriate prescribing (PIP) among community-dwelling older adults receiving primary care in order to identify components of a successful intervention.

Methods: An electronic search of the literature was conducted using 12 databases from inception to December 2015. Studies were included if they were randomised controlled trials (RCTs) or quasi-randomised studies that evaluated a pharmacist-led intervention to reduce PIP among older adults in primary care compared to usual/routine practice. Study selection was conducted by two independent researchers. Methodological quality of the included studies was independently assessed by two researchers using objective risk of bias criteria e.g. The Cochrane Risk of Bias Tool. In any case of disagreement consensus was reached with a third researcher.

Results: Two thousand one hundred and ninety three relevant studies were identified of which 5 met the inclusion criteria. Four studies involved a pharmacist conducting a medication review and providing feedback to patients or their family physician. One RCT evaluated the effect of a computerised tool that alerted pharmacists when older patients were newly prescribed potentially inappropriate medications. Four studies were associated with an improvement in prescribing appropriateness. Overall, four of the five studies were considered to be at high risk of bias.

Conclusions: This review demonstrates that pharmacist-led interventions may improve prescribing appropriateness in community-dwelling older adults. However the quality of evidence is low. Further high-quality research should be conducted to explore the generalizability of these interventions. Finally, the role of a pharmacist working as part of a multidisciplinary primary care team requires further investigation to optimise prescribing in this group of patients.

648. Medication Regimen Complexity and Clinical Outcomes in Older People: A Systematic Review

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Background: Additional to the number of medications that a patient takes, the dose form, dosing frequency, and additional directions for medication use

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increase the complexity of medication regimens. Especially for older people these factors may be important.

Objectives: To systematically review clinical outcomes associated with medication regimen complexity in older people.

Methods: A systematic review of EMBASE, MEDLINE, International Pharmaceutical Abstracts, Cumulative Index to Nursing and Allied Health Literature, and the Cochrane library was conducted using medical subject headings, Emtree and key search terms. Inclusion criteria comprised 1) primary peer-reviewed research articles in English published January 2000-June 2015, 2) quantification of medication regimen complexity taking into account the number of medications plus at least one other parameter, 3) medication regimen complexity was calculated for participants' overall regimen, 4) at least 80% of participants were aged ≥60 years, and (4) the study investigated a clinical outcome associated with medication regimen complexity.

Results: Eleven observational studies met the inclusion criteria. Complex medication regimens were associated with medication non-adherence (n=2 of 4 studies), and higher rates of hospitalisation (n=2 of 3 studies). One study each identified an association between regimen complexity and higher medication management capacity, medication self-administration errors, Family Caregiver Medication Administration Hassles, hospital discharge destination, post-discharge potential adverse drug events and all-cause mortality. Regimen complexity had no association with post-discharge medication modification, change in medication- and health-related problems, and emergency department visits.

Conclusions: Moderate quality evidence suggests an association between medication regimen complexity and non-adherence and there is mixed evidence regarding an association with higher rates of hospitalization. High quality prospective intervention studies are needed to determine whether reducing medication regimen complexity improves clinical outcomes in older people.

649. An Educational Intervention to Reduce Acute Health Care Consumption in Elderly Patients with Inappropriate Drugs - A Cluster Randomised Trial in Primary Care

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Background: Inappropriate drug use may cause 5-15% of unplanned hospitalizations in the elderly. As a possible measure to reduce inappropriate prescribing, drug utilization reviews (DURs) have been proposed.

Objectives: To evaluate an educational intervention towards general practitioners and nurses working in primary care, with the aim to reduce acute healthcare consumption and inappropriate drug use in elderly patients.

Methods: Cluster randomized trial performed among 69 primary healthcare centers (PHCs) in Stockholm, Sweden. One PHC dropped out after randomization, leaving 33 in the intervention and 35 in the control group. The tutors, two pharmacists, gave two lectures within 4 months at intervention PHCs, including theoretical knowledge on inappropriate drug use, feedback on prescribing and interprofessional discussions of how to implement DURs. Follow-up was 9 months.

Outcomes were assessed in all individuals aged ≥65 listed with the participating PHCs (n=118 210) using healthcare register data. The combined primary outcome was emergency department visit or unplanned hospitalization. Among secondary outcomes were major polypharmacy (≥10 drugs ATC 5th level) and DURs/no of patients.

We estimated risk differences (RD) of outcomes between intervention and control PHCs using generalized linear models (binomial family, identity link), taking into account clustering within PHCs. The difference in DURs was evaluated at PHC level using a t-test.

Results: During follow-up, 22.9 % of patients in the intervention and 21.9 % in the control group experienced an emergency department visit or unplanned hospitalization (RD 1.0%, 95% CI -0.58 to 2.56). The prevalence of major polypharmacy was 11.3% in the intervention and 10.8% in the control group (RD 0.5%, 95% CI -0.44 to 1.4). In intervention PHCs, 13.5 DURs/100 patients had been performed, in control PHCs 15.5

DURs/100 patients ($p>0.05$). There were no differences regarding the remaining secondary outcomes.

Conclusions: The intervention had no influence on the selected outcome measures. Possible reasons for the lack of effect are discussed.

650. Risk Factors For Unplanned Readmissions In French Older People Discharged From Acute Geriatric Units

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Background: Some studies have assessed risk factors for readmission in older people, but none have considered drug-related variables except polymedication. Moreover, causes for readmissions are not usually described.

Objectives: To identify the risk factors associated with 6 month- unplanned readmissions among older people discharged from acute geriatrics units (AGU), with a focus on drug-related variables.

To examine causes for readmissions in subgroups at risk.

Methods: Design: A 6-month prospective multi-centre cohort study (ancillary study of a randomized controlled trial).

Setting: 6 French acute geriatric units

Subjects: Three hundred and forty eight consecutive individuals aged 70 and older admitted in emergency to an acute medical care or surgical from April 2007 to October 2008

Main outcomes measures and statistical analysis: Factors associated with 6-month unplanned rehospitalisation were identified by use of Cox model, taking into account socio-demographic data, functional abilities, comorbidities and drug-related variables. Cause for readmissions was assessed in the subgroups found at risk for readmission.

Results: Unplanned readmissions occurred in 133 (38.2%) participants within the 6 months after discharge from acute geriatric units. Chronic severe renal failure (HR at 2.18 (95% CI 1.29-3.69)), chronic pulmonary insufficiency (with HR 1.65 (95% CI 1.06–2.58), and polypathology, defined as the co-existence of at least 4 chronic diseases among a list of 20 pre-specified diseases (HR at 1.62 (95%CI 1.15–2.29)), were found to be associated with the risk for 6-month readmissions. No drug-related variables was associated to the risk for readmissions. However,drug-related problems were the first cause for readmission in people with polypathology or with chronic severe renal failure and the second cause in people with chronic pulmonary insufficiency.

Conclusions: Risk for 6-month readmissions among older people discharged from acute geriatric units are associated with specific severe chronic diseases and comorbidities. The main cause for these readmissions is drug-related (avoidable) medication.

651. Pro Re Nata (as Needed) Medications in Nursing Homes: The Longer You Stay, the More You Get?

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Background: On average, nursing home residents take five to nine different medications daily. Next to regularly administered long-term medication, this often includes ‘as needed’ or ‘pro re nata’ drugs, which are prescribed by the treating physician and administered by nurses according to the need of the patient. Injudicious pro re nata prescribing can lead to polypharmacy, potentially harmful drug interactions and total drug doses exceeding the maximum recommended.

Objectives: To examine characteristics of pro re nata drug use and potential predictors in nursing homes.

Methods: The multi-center cross-sectional study included a heterogeneous sample of 21 nursing homes in Northwestern Germany. From each nursing home resident, the medication schedule, socio-demographic data and underlying diseases were included. Descriptive statistics and adjusted multivariable regression models were used to analyse the data.

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Results: Overall, the study population comprised 852 residents. Mean age was 83.5 ± 10.5 years. About three quarters of the study population were female (76.5%). Of all residents, 638 (74.9%) were treated with at least one pro re nata medication (2.5 ± 2.3 per resident). Most commonly used pro re nata drug was acetaminophen prescribed to 289 (33.9%) residents, followed by metamizole (30.4%) and ibuprofen (14.3%). Length of stay above the median (2.1 years) was associated with a higher number of pro re nata drugs yielding an adjusted odds ratio of 2.38 (95% CI 1.77, 3.20). Adjusted odds ratio for treatment with five or more long-term medications was 2.10 (95% CI 1.51, 2.93).

Conclusions: The high prevalence of pro re nata medication should be taken into account when considering polypharmacy and inappropriate drug use in nursing homes and highlights the importance of an accurate documentation. Since number of pro re nata drugs was associated with length of stay, physicians should regularly reconsider the need of each drug on the medication schedule. Further studies are needed to assess how often such medication is really administered and to examine the impact on health outcomes.

652. Assessment of Frequency and Effects of Potentially Inappropriate Medications in Elderly Persons: An Italian Population-Based Study

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Background: Potentially inappropriate medications (PIMs) are commonly used in elderly increasing the risk of severe adverse drug reactions (ADR) in this frail population.

Objectives: This population-based study was aimed at measuring frequency of PIMs and their association with the risk of hospitalization and emergency department visits (EDV) in an elderly population of Southern Italy.

Methods: We measured the frequency of elderly receiving PIMs, as listed in the Updated Beers Criteria, using Caserta Local Health Unit database during the years 2010-2014. Thereafter, a cohort study was conducted matching new PIM users to PIM-free patients by sex, age, and number of prescribed drugs within one month prior to the index date (ID), defined as the first PIM prescription for users. Propensity score adjusted COX-regression examined the association between PIM use and the risk of all-cause hospitalization and EDV within 30 and 90 days after ID.

Results: Overall, 13,669 (11% of the total elderly) new PIM users were matched to as many non-users. PIM users received more frequently ketorolac (13.6%) and doxazosin (10.5%). Within 30 days after ID, 1,553 (11.4%) PIM users received >1 PIM. The most frequent comorbidities were hypertension (83.9%) or lipid metabolism disorders (32.2%).

For PIM users, a statistically significant increase of all-cause hospitalization risk was observed within 30 days (RR: 1.26; IC95%: 1.10-1.44) and 90 days (RR: 1.12; IC95%: 1.02-1.24) after ID, as well as observed for the EDV risk within 30 days (RR: 2.03; IC95%: 1.65-2.50) and 90 days (RR: 1.72; IC95%: 1.50-1.98) after ID. Considering subjects receiving >1 PIM, a higher risk of hospitalizations was observed within 30 days (RR: 1.64; IC95%: 1.16-2.33) and 90 days (RR: 1.62; IC95%: 1.26-2.07) after ID, as well as a 2-fold increased risk of EDV within 30 days and 90 days after ID (RR: 2.22; IC95%: 1.34-3.68 and RR: 2.04; IC95%: 1.43-2.91, respectively).

Conclusions: PIM use was associated with an increased risk of all-cause hospitalization and EDV within 30 and 90 days after ID. Identification of alternative medications may help in decreasing PIM use, in order to prevent ADRs.

653. Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs. 2011

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Background: Prescription and over-the-counter medicines and dietary supplements are commonly used, alone and together, among older adults. The impact of recent regulatory forces on these patterns, however, is not known.

Objectives: (1) To characterize changes in the prevalence of medication use, including concurrent use of prescription and over-the-counter medications and dietary supplements; and (2) to quantify the frequency and types of potential major drug-drug interactions.

Methods: Descriptive analyses of a longitudinal, nationally-representative sample of community-dwelling older adults aged 62 through 85 years. In-home interviews with direct medication inspection were conducted in 2005-2006 (N=2,351) and again in 2010-2011 (N=2,206). We defined medication use as the use of at least one prescription or over-the-counter medication or dietary supplement at least daily or weekly and concurrent use as the regular use of at least two medications.

Results: Use of at least 1 prescription medication slightly increased from 84.1% in 2005-2006 to 87.7% in 2010-2011 ($p<0.05$). The concurrent use of at least 5 prescription medications increased from 30.6% to 35.8% ($p<0.001$). While the use of over-the-counter medications declined from 44.4% to 37.9%, the use of dietary supplements increased from 51.8% to 63.7% (all $p<0.001$). There were clinically significant increases in the use of statins (33.8% to 46.2%), anti-platelets (32.8% to 43.0%), and omega-3 fish oils (4.7% to 18.6%) (all $p<0.05$). In 2010-2011, 15.1% of older adults were at risk of a potential major drug-drug interaction, compared to 8.4% in 2005-2006 ($p<0.001$). The vast majority of these interacting regimens involved medications and dietary supplements increasingly used in 2011.

Conclusions: Use of prescription medications and dietary supplements, and the concurrent use of interacting medications, has increased since 2005, with nearly 1 in 6 older adults potentially at risk for a major drug-drug interaction. Improving safety when using multiple medications has the potential to reduce preventable adverse drug events associated with medications commonly used among older adults.

654. Feasibility of Using Real-World Databases to Assist Discovery of Unknown Associations Between Genetic Diseases and Other Health Conditions --A Testing Case of Gaucher's Disease and Parkinson's Disease

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Background: Few studies have explored the feasibility of using real-world databases (RWD) to discover unknown associations between genetic diseases and other health conditions. General RWD may help to substantiate genetic links between Mendelian and common, complex diseases at the level of a large health-care population.

Objectives: Use Gaucher's disease (GD), a rare lysosomal storage disorder caused by mutations in the GBA gene, as a test case to examine whether the known association between GBA mutations and Parkinson's disease (PD) can be detected under a setting of screening in a general-purpose claims database.

Methods: We identified GD subjects who had at least one HCPCS (Healthcare Common Procedure Coding System) code for enzyme replacement therapy (ERT) in a US claims database with data up to 9/30/2014. Ten controls without GD were randomly selected matched by age and gender for each GD. We used Clinical Classifications Software (CCS) to automatically pre-classify all health conditions claims for both GD and controls as single-level CCS diagnoses. The associations between GD and every pre-classified CCS category were measured by Odds ratio (OR) and 95% CI, standardized proportion differences (SPD) and posterior probabilities through Bayesian screening.

Results: 894 GD subjects were identified from the database. 68% of them had GD related diagnoses and 30% had other treatment supporting claims when they had ERT claims (both non-mutually exclusive). All three association measures indicated a probable association between GD and PD: 1) OR 4.9 (95% CI 2.4-9.7); 2) SPD is 0.12; and 3) posterior probabilities by various levels of observed "true" ORs ($\leq$3, 4, 5, 6, 7 and 8) assuming critical OR=4 in Bayesian screening are: 0.000, 0.002, 0.004, 0.006, 0.009 and 0.017.

Conclusions: The known association between GD and PD can be detected as a signal in non-hypothesis testing settings in our testing database. RWD warrants further studies as a valuable resource in discovery of potential novel associations.

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655. Meta-Analysis of the Genome Wide Association Studies (GWAS) on the Intolerance of Angiotensin Converting Enzyme Inhibitors (ACEIs)

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Background: ACEIs are frequently used to treat hypertension and heart failure. Cough and angioedema are the two main adverse drug reactions (ADRs) associated with ACEI use that occur in up to 20% of the patients and are the main reason of therapy discontinuation.

Objectives: To identify single nucleotide polymorphisms (SNPs) associated with switching of an ACEI to an angiotensin receptor blocker (ARB) as a marker for ADRs.

Methods: A cohort of patients starting ACEIs was identified within the Rotterdam Study in the Netherlands and the GoDARTS study in Scotland. Cases were subjects that switched from an ACEI to an ARB while controls were subjects who used ACEIs for at least 2 years and did not switch. The validity of using switching as a marker for ACEI-induced adverse drug reaction (ADR) was investigated in a subset of users that had the primary care records available. A GWAS using an additive model was performed and results were meta-analyzed using METAL.

Results: In total 5109 ACEI starters were included in the study of which 959 were cases. The validation of switch as marker for ACEI-induced ADRs showed the positive predictive value of 90.5% for at least possible ADRs within a subset of 1132 patients. Ten SNPs within four genes reached the GWAS significance level in the meta-analysis. The strongest associated SNP was located on chromosome 17q25 (MAF=0.16, OR=1.52 [95%CI: 1.32-1.76], p=6.2x10-9).

Conclusions: These results indicate a substantial contribution of genetic variation in determining the risk of ACEI-induced ADRs, and warrant further studies in larger populations.

656. Long-Term Survival After Myocardial Infarction: Impact of Patient Non-Compliance to the EOLE Study Protocol

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Background: Non-compliance to secondary prevention is difficult to measure. Adherence to an observational study protocol may be a proxy for global non-compliance.

Objectives: To study the impact of patient non-compliance with study questionnaires on overall mortality.

Methods: EOLE is a cohort of post-MI patients followed yearly using patient questionnaires. Vital status at end of study was reconciled with the national death registry. Statistical analyses used Cox models with time-dependent variables.

Results: Of 5525 patients followed 6 years, 2715 provided data at all possible time-points during the study or before death (compliants (C)); for 2810 at least one time-point was missing (non-compliants, (NC)). At inclusion, C were older (63.0±12.3 vs 61.2±14.2 years), more often male (78.7 vs. 75.8%) and retired (58.9 vs 49.0%), with lower BMI (18.4 vs 19.3% above 30) than NC. Fewer C smoked (5.9 vs 12.6%), were diabetic (14.7 vs 18.9%) or had previous MI (12.1 vs 13.9%). There was no difference in hypercholesterolemia, excess triglycerides, hypertension, or in the inclusion MI. C were more often enrolled in a physical rehabilitation program (43.6 vs 38.8%); Post MI treatment was beta-blockers 90.7 vs. 88.5%, antiplatelet agents 99.6 vs.99.5%, statins 97.6 vs. 95.6% and ACEI/ARB 83.2 vs. 82.0%.

Overall mortality was 16.9‰ person-years (PY) in C vs 30.6 in NC. Coronary mortality in C was 3.9 vs

4.5‰ PY in NC. Coronary morbi-mortality was 37.9‰ in C vs 45.5‰ in NC.

In the fully-adjusted Cox model, non-compliants had higher all-cause deaths (HR 2.70; 95%CI [2.33-3.22]); Age (1.65 [1.06-2.56] for 50-59 to 17.9 [11.6-27.6] for ≥ 80, vs. <50), diabetes (1.36 [1.11-1.63], and smoking (1.76[1.22-2.53]) were associated with higher mortality. Statins (0.63 [0.50-0.79]) and ACEI (0.75 [0.62-0.91] were associated with lower death rates.

Conclusions: Non-compliance with the protocol was the strongest predictor of all-cause death post-MI perhaps because of non-compliance to secondary prevention. Compliance to follow-up is easy to monitor and should be included in analytical models of survival or outcomes studies.

657. In Silico Integration of Epidemiologic and Genetic Evidence on Sex/Race-Related Modifying Effects on Hip Arthroplasty Outcomes

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Background: Translational epidemiology and precision medicine applications are key prerequisites for enabling CDRH's vision to provide access to safe and effective medical devices.

Objectives: As part of DEPI/CDRH's regulatory research program, which is aimed at integrating epidemiologic and genetic evidence for more predictive evaluation of real-world device performance, the current project is focused on new evidentiary approaches to evaluating safety of hip arthroplasty.

Methods: Study design was based on a retrospective analysis of pre-existing data pertaining to hip arthroplasty. Using the Nationwide Inpatient Sample, Agency for Healthcare Research & Quality (NIS/AHRQ), the hip arthroplasty related procedures and adverse events (AE) were identified by corresponding ICD9 codes. AE frequencies and AE odds ratios stratified by sex/ethnicity were obtained using STATA14. Using the available genetic data on White patients with hip arthroplasty (Personalized Medicine Research Project, PMRP/MCRF), the frequencies of hip arthroplasty related AEs were also analyzed in juxtaposition to the allele distribution of some disease-related SNPs.

Results: NIS/AHRQ-derived epidemiologic evidence revealed a presence of intricate sex/race-related modifying effects on the occurrence of main AE in hip arthroplasty (V43.64). Among other trends, White Females showed higher frequency of Dislocation (996.42; OR=1.16 [1.12-1.20]), but lower frequency of Osteolysis (996.45; OR=0.54 [0.50, 0.58]. PMRP/MCRF-derived evidence showed that some of the trends were associated with SNP linkage disequilibrium. For instance, a higher frequency of Osteolysis in White Males vs. White Females was accompanied by a 2-fold increased C(T) Minor Allele Frequency in rs7121.

Conclusions: In silico analysis of pre-existing epidemiologic and genetic data can enable more precise evaluation of implant-related outcomes in sex/ethnicity-stratified patient subgroups as well as more efficient identification of implant-related genetic markers, thus facilitating precision medicine applications to medical devices.

658. Multi-Variant Genetic Panel for Genetic Risk of Opioid Addiction

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Background: Over 116 million people worldwide have chronic pain and prescription drug dependence. In the US, opioid abuse accounts for the majority of overdose deaths. Genetic factors which may play a key role in opioid prescription addiction are generally not evaluated in clinical practice. We believe a subset of patients with chronic pain are genetically predisposed to opioid dependency.

Objectives: Develop and evaluate a model to determine risk of prescription opioid addiction with a multi-variant NeuR panel.

Methods: We genotyped samples for 16 SNPs involved in the brain reward pathways from 37 patients diagnosed with prescription opioid/heroin addiction and 30 normal control patients with a multiplexed

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film-based microarray technology (AutoGenomics, Vista, CA). The NeuR panel targets 16 mutations: 5-HTR2A (rs7997012), 5-HTTLPR (rS25531), COMT (rs4680), DRD2 (rs1800497), DRD1 (rs4532), DRD4 (rs3758653), DAT1 (rS6347), DBH (rs1611115), MTHFR (rs1801133), OPRK1 (rs1051660), GABA (rs211014), OPRM1 (rs1799971), MUOR (rs9479757), GAL (rs948854), DOR (rs2236861) and ATP-BCT (rs1045642). Data were modeled with TreeNet 10-fold cross validation (Salford Systems, San Diego, CA), and generates a weighted score.

Results: Observed data: ROC statistic=0.92, sensitivity=82%(95% CI: 66-90), specificity=75%(95% CI: 56-87), positive predictive value=78%(95% CI: 61-89), and negative predictive value=80%(61-92). TreeNet "learn" data: ROC statistic=0.92, sensitivity=92%, specificity=90%, precision=92%, and overall correct=91%. TreeNet "test" data: ROC statistic=0.80, sensitivity=72%, specificity=80%, precision=82%, and overall correct=77%. Variable ranking showed important SNPs associated with opioid drug/heroin addiction include: OPRM1 (rs1799971), 5-HTR2A (rs7997012) and DRD2 (rs1800497).

Conclusions: The prediction algorithm with the NeuR panel can be used for the prescription opioid addiction risk assessment. By identifying patients with high risk to prescription opioid addiction along with mutations status of cytochrome p450 genes involved in therapeutics, it may provide information to physicians to improve therapeutic decisions in pain management, guide to medical detoxification and reduce adverse events for patients.

659. KRAS Testing Status in Patients with Metastatic Colorectal Cancer – A Danish Population-Based Study

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Background: Mutant KRAS predicts absence of response to treatment with epidermal growth-factor receptor (EGFR) monoclonal antibodies, but little is known about the prevalence of specific KRAS mutations in real-world populations of patients with primary or distant metastatic colorectal cancer (mCRC) at recurrence.

Objectives: Using data from Danish population registries, we examined prevalence of KRAS testing and distribution of KRAS mutations in patients with primary mCRC and in mCRC patients with distant metastasis at recurrence.

Methods: Between 2009 and 2013, we identified newly diagnosed patients with primary mCRC in the Danish Cancer Registry or patients with distant metastasis at recurrence in the Danish National Patient Registry, covering all Danish hospitals. We identified KRAS testing status and mutation types by linkage to the Danish National Pathology Register (DNPR). We included all KRAS test results recorded through 2014 and described the distribution of specific KRAS mutations according the mCRC type.

Results: We identified 4,538 patients with primary mCRC and 2,707 mCRC patients with distant metastasis at recurrence.

Among the patients with primary mCRC, 1,591 (35%) had KRAS test results in the DNPR, of whom 695 (44%) tested positive for a KRAS mutation, including 463 patients with a specific mutation identified. Among these 463 patients, 383 (83%) and 76 (16%) had exon 2 mutations in codon 12 and 13, respectively.Among the mCRC patients with distant metastasis at recurrence, 880 (32%) had KRAS test results in the DNPR, of whom 387 (44%) tested positive for a KRAS mutation, including 232 patients with a specific mutation identified. Among these 232 patients, 184 (79%) and 45 (19%) had exon 2 mutations in codon 12 and 13, respectively.

Conclusions: In our data from routine clinical practice, the prevalence of KRAS mutations was similar to that seen in data from clinical trials. The prevalence of KRAS testing and the distributions of specific mutations were similar among Danish patients with primary mCRC and distant mCRC at recurrence diagnosed with mCRC between 2009 and 2013.

660. Comorbidity Among Patients with Metastatic Colorectal Cancer According to KRAS-Mutation Testing Status – A Danish Nationwide Prevalence Study

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Background: Mutant KRAS predicts absence of response to treatment with epidermal growth factor receptor (EGFR) monoclonal antibodies. Treatment with anti-EGFR therapies in patients with metastatic colorectal cancer (mCRC) may also be contraindicated due to comorbidities.

Objectives: Using data from Danish population registries, we examined the prevalence of comorbidity in patients with mCRC and prevalence of KRAS testing at different levels of comorbidity, defined by the Charlson Comorbidity Index (CCI).

Methods: We used the Danish Cancer Registry and the Danish National Patient Registry (DNPR), covering all Danish hospitals, to identify mCRC patients diagnosed in 2009-2013. We included patients with primary mCRC (metastatic cancer at first cancer diagnosis) and mCRC patients with distant metastasis at recurrence (recurrent mCRC). Via linkage to the National Pathology Register, we identified the patients' KRAS testing status, recorded through 2014. From the DNPR, we obtained data on all hospital-diagnosed comorbidities included in the CCI before the date of mCRC diagnosis. We computed prevalence of KRAS testing by level of the CCI-based comorbidity score.

Results: There were 7,245 patients with mCRC (4,538 with primary mCRC and 2,707 with recurrent mCRC). Overall, 2,258 (31%) patients had CCI score 1-2 and 531 (7.3%) had a CCI score ≥3. Patients with primary mCRC were more likely to be free of comorbidities than patients with recurrent mCRC (65% vs. 56%). Among patients with primary mCRC and recurrent mCRC, the proportions of patients with a CCI score of 1-2 were 29% and 35%, respectively. The proportions of patients with a CCI score of ≥3 were 6.2% and 9.2%, respectively. Proportions of the mCRC patients tested for KRAS mutation were 1,684/4,456 (38%) among those with CCI score 0; 672/2,258 (30%) among patients with CCI score 1-2; and 115/531 (22%) among patients with CCI score ≥3.

Conclusions: In Denmark, patients with recurrent mCRC have a higher level of comorbidity than patients with primary mCRC. The proportion of patients tested for KRAS mutations decreased with increasing comorbidity level.

661. The Prevalence RAS and BRAF Mutations Among Patients in the Middle East and Northern Africa with Metastatic Colorectal Cancer

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Background: Anti-EGFR therapies are recommended for metastatic colorectal cancer (mCRC) patients with confirmed wild-type RAS (exons 2, 3, 4 of KRAS and NRAS) status. There is limited published information on the prevalence of RAS mutations using real world data.

Objectives: The objective of this study was estimate the prevalence of RAS and BRAF mutations among patients with mCRC in the Middle East and Northern Africa (MENA) in an effort to inform the rationale for biomarker testing and treatment choice.

Methods: The study included 1,669 patients from August 2013 to July 2015 with mCRC from Algeria, Bahrain, Egypt, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Qatar, Saudi Arabia, and the United Arab Emeritus. Information on RAS mutation status was obtained from one pathology lab using High Resolution Melting Analysis. Extended RAS analysis was conducted in a subset of patients, including: overall RAS (exon 2, 3, 4 of KRAS and NRAS; n=750), KRAS exon 2 (n=750), KRAS exon 3 and 4 (n=507), NRAS exon 2, 3, and 4 (n=507), and BRAF exon 15 (n=78). The proportion of patients with each mutation was summarized.

Results: The overall RAS mutation in the full sample was 35.3% (n=589/1669). The observed mutation for KRAS exon 2 in a subset of patients with extended RAS analysis (n=750) was 32.4% (243/750). Out of the subjects with wild-type exon 2 (n=507), the observed mutations rates were as follows: KRAS exon 4 (20/507=3.9%), KRAS exon 3 (13/507=2.6%), NRAS exon 2 (7/507=1.4%), NRAS exon 3 (6/507=1.2%), and NRAS exon 4 (0%). The prevalence of BRAF exon 15 was 3.8% (3/78). The most robust data on specific RAS mutations was obtained from

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Algeria, Egypt, and Saudi Arabia. The prevalence of KRAS exon 2 mutations in these countries was as follows: Algeria (n=33/86=38.4%), Egypt (n=83/303=27.4%), Saudi Arabia (n=85/245=34.7%).

Conclusions: To our knowledge, this is the first study to evaluate the prevalence of RAS and BRAF mutations in the Middle East using real world data. The results of this descriptive study illustrate that there is variation in the prevalence of RAS and BRAF mutations in MENA.

662. An Estimation of RAS Mutation Prevalence Amongst Patients With mCRC Using A Meta-Analytical Approach

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Background: Guidelines for prescribing anti-EGFR therapy for metastatic colorectal cancer (mCRC) require prior testing to confirm RAS (exons 2, 3, 4 of KRAS and NRAS) wild-type status in Europe and the USA. There is limited published evidence reporting the prevalence of RAS mutations in patients with mCRC in a real-world setting.

Objectives: The aim of this study was to use data from a range of real-world sources to obtain RAS mutation prevalence estimates for different geographic regions.

Methods: Aggregated RAS mutation prevalence data were collected from 13 sources, including individual pathology centers (n=7), mCRC registries (n=3), and Amgen-sponsored studies (n=3). Data sources included in this study originated in Europe (n=10), the Middle East (n=2), and South America (n=1). A meta-analysis of all collected data was carried out to investigate the effect of heterogeneity amongst the data sources and obtain pooled RAS prevalence estimates for each, using a mixed regression model.

Results: Aggregate data from 4322 patients with mCRC were included in the pooled meta-analysis. The overall RAS mutation prevalence across all data sources was estimated to be 43.5% (95% CI: 41.5–45.5%). RAS mutation prevalence varied between data sources, ranging from low estimates of 33.7% (95% CI: 28.4–39.3%) for a Middle Eastern pathology dataset, and 34.6% (95% CI: 27.7–42.1%) for a Middle Eastern mCRC registry, to the highest estimates of 53.6% (95% CI: 43.2–63.8%) and 54.1% (95% CI: 51.7–56.5%) in two European pathology centers, in the Czech Republic and Poland, respectively.

Conclusions: This is one of the first studies to carry out a large pooled analysis of RAS mutation prevalence, based on real-world data. There was a high degree of heterogeneity between the sources included, which could be due to the type of data source, patient selection criteria, geographic location, or differences in laboratory testing methods. The estimated RAS mutation prevalence reported here is lower than that in a recent pooled analysis of past clinical trials, which reported an overall prevalence of 55.5%. Further investigations are required to explain the disparity in these findings.

663. A Comparative Effectiveness Review of Benefits and Harms of PCSK9 Inhibitors

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Background: PCSK9 inhibitors, a new class of cholesterol-lowering drugs with 2 drugs currently available, cause significant reductions in lipids, but are costly. Comparative effectiveness can improve informed decision-making.

Objectives: To conduct a systematic review of alirocumab and evolocumab.

Methods: We searched for trials of PCSK9 inhibitors reporting deaths, adjudicated cardiovascular (CV) events, LDL-C, HDL-C, and harms in Medline, the Cochrane Library, SCOPUS and ClinicalTrials.gov in September 2015. We also requested information from manufacturers. Study selection, assessment, and synthesis were carried out according to standard review methods, including random-effects models for meta-analyses.

Results: We found 17 trials, none directly comparing the drugs or reporting mortality or CV outcomes as primary outcomes. Alirocumab (75 mg-150 mg subcutaneously every 2 weeks) significantly reduced LDL-C (-8% to -67%) at 12 to 24 weeks, in patients with heterozygous familial hypercholesterolemia and with high or mixed CV risk not at LDL-C goals on statins. The strongest evidence was for high CV risk patients not at LDL-C goals. Alirocumab increased HDL-C 6% to 12%. For adjudicated CV events at 52 to 78 weeks no benefit was found. There were also no differences in adverse events. Evolocumab (120 mg subcutaneously every 2 weeks to 420 mg every 4 weeks) significantly reduced LDL-C (-32% to -71%) at 12 to 52 weeks in patients with heterozygous or homozygous familial hypercholesterolemia, patients intolerant to statins and those not at LDL-C goal on statins. Evolocumab increased HDL-C (4.5% to 6.8%). There was no statistical difference in adverse event outcomes, but more overall adverse events were with evolocumab. For evolocumab, evidence on adjudicated CV outcomes is insufficient to draw conclusions.

Conclusions: While both drugs result in large improvements in lipids, evidence is stronger for alirocumab in high CV risk not at LDL-C target. Evidence for evolocumab is stronger for those with heterogeneous familial hypercholesterolemia and patients with mixed CV risk not at LDL-C target. Evidence on adjudicated CV outcomes is unable to show clear benefit for either drug at this time.

664. Systematic Evaluation of Interventions to Reduce Overprescribing of Antibiotics for Acute Respiratory Tract Infections

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Background: Overuse of antibiotics contributes to increasing resistance. Acute respiratory tract infections (aRTI) often do not require antibiotics.

Objectives: To systematically review evidence on interventions to reduce antibiotic use for aRTI.

Methods: We searched for studies of interventions designed to improve antibiotic use in aRTIs reporting antibiotic resistance, improved appropriate and overall prescribing and not causing adverse consequences in Medline and the Cochrane Library through February 2015 and requested information from rapid diagnostic test makers. Study selection, assessment, and synthesis were carried out according to standard review methods, including random-effects models for meta-analyses.

Results: 133 studies were included; resistance couldn't be assessed and definition/ascertainment of appropriate prescribing varied, so overall use of antibiotics was the main outcome. Moderate-strength evidence found improved/reduced antibiotic prescribing and low-strength evidence of not causing adverse consequences for: clinic-based parent education (21% overall reduction), public patient education with clinician education (7% reduction overall and better appropriateness), procalcitonin for adults (12%-72% overall reduction), and electronic decision support (5%-9% reduction overall and improved appropriateness). Public parent education alone was low-strength overall. Other interventions improved or reduced prescribing but had lacking/insufficient (e.g. rapid step tests and education plus audit/feedback) or mixed (e.g. delayed prescribing, CRP tests) evidence on adverse consequences.

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Education for parents of young children with AOM, point-of-care influenza, tympanometry in children, and clinician education with audit/feedback had no benefit and using adult procalcitonin algorithms in children results in increased prescribing.

Conclusions: Specific education interventions for patients/parents and clinicians, procalcitonin in adults, and electronic decision support to reduce overall antibiotic prescribing (and in some cases improve appropriate prescribing) without causing adverse consequences, although the reduction in prescribing varied widely.

665. The Association Between Diabetic Complications and Androgen Deprivation Therapy Used for Clinically Localized Prostate Cancer

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Background: Androgen deprivation therapy (ADT) has become increasingly used for localized prostate cancer and has been associated with an increased risk of diabetes onset. However, the risk of diabetic complications among patients with existing diabetes has not been investigated.

Objectives: To examine the association between ADT use and diabetic complications in diabetic prostate cancer patients.

Methods: We assembled a retrospective cohort study of men with newly diagnosed clinically localized prostate cancer enrolled in three integrated healthcare delivery systems based in California and Michigan. The sample included men who were diagnosed between 1995 and 2008, treated with curative intent therapy, and had existing diabetes at prostate cancer diagnosis (n=5,336). Men were followed through the date of first complication, health plan disenrollment, or study's end, December 2010, whichever occurred first. Cox proportional hazards models, adjusted for potential confounders,were used to examine the associations between ADT use (versus non-use) and diabetic complications (any complication), and individual complications (diabetic neuropathy, diabetic retinopathy, diabetic amputation or diabetic cataract). ADT use was modelled as a binary time-dependent variable. We also examined person-year rates of the complication given that men had varying follow-up lengths.

Results: ADT use was associated with an increased risk of any complication (first incidence post diagnosis) adjusted hazard ratio (HR), 1.15 [95% CI 1.04-1.27] and a 36% increased risk of diabetic retinopathy HR 1.36 [95% CIs 1.03-1.80].A statistically significant two-fold increase in diabetic amputations (HR 2.23 95%CIs 1.27-3.92), as well as increased risk of diabetic neuropathies (HR 1.21 95% CIs 1.05-1.39) and cataracts (HR 1.13 95% CIs 1.01-1.26) were observed.

Conclusions: Compared to non-ADT users, ADT use was associated with an increased risk of diabetic complications. As diabetes is a common comorbidity in men with localized prostate cancer new information on the adverse consequences of ADT may more fully inform treatment decisions and appropriate use of adjuvant or salvage ADT.

666. Temperature, Real-Time, On-Site, Potency Monitoring Studies of Three Brands of Amoxicillin Dispersible Tablets Stored in Hospital and Community Pharmacies in Different Part of Kerala

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Background: Quality is of vital importance for patient safety. The loss of potency may influence the efficacy and safety of pharmaceuticals. Improper storage of the pharmaceutical products is one of the fundamental concerns in patient care.

Objectives: The current study scientifically capture the variations observed in the temperature and humidity levels in various pharmacy outlets in different part of Kerala and to study the real time effect of storage on

the stability of amoxicillin tablet stored in these outlets.

Methods: Adequate quantities of different brands of Amoxicillin tablets were selected from hospital and community pharmacies located in different regions of Kerala. Samples collected from different time intervals were suitably coded and analyzed for all the listed parameters.

Results: Study was observed that, Mean Maximum Temperature was recorded more in Kannur (33.350C) and Kozhikode (32.440C) city as compare to Cochin (31.450C). The Mean Relative Humidity was recorded more at Cochin (86.75%) as compared to Kannur (84.5%) and Kozhikode (84.58%). The study data show that percentage strength was least in samples collected from Cochin compared with those collected from Kozhikode and Kannur. Mean kinetic humidity was more in coastal area, which may have accelerated the degradation of samples from Cochin. A significant statistical difference (p= 0.0000) was observed across brands. Microbiological data showed significant reduction in zone of inhibition for samples collected from Cochin in comparison with other regions.

Conclusions: The study identifies the importance of storage conditions of antibiotics in pharmacies for the better pharmaceutical care.

667. Cohort Study Examining the Contribution of Antiepileptic Drugs to Poisoning Deaths in Epilepsy

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Background: People with epilepsy are known to have an increased risk of unnatural death, but the extent to which antiepileptic drugs (AEDs) contribute to elevated risks of fatal accidental and suicidal medicines poisonings in this population is unknown.

Objectives: To determine the risks of accidental and suicidal poisoning deaths and the extent to which AEDs are implicated according to cause of death coding, in a primary care cohort of people diagnosed with epilepsy versus those without this condition.

Methods: We conducted a cohort study using the Clinical Practice Research Datalink (CPRD) linked with Office of National Statistics (ONS) mortality data. People with epilepsy diagnosed between 01/01/1998-31/03/2014 were each matched with up to twenty people without epilepsy by age, gender and registered general practice. Individuals were followed to the earliest of these dates: death, transfer out of the practice, last data collection or end of study. Medicine poisoning deaths were ascertained from ICD-10 codes X40-44 (accident) or X60-64, Y10-14 (suicide). Cox regression was used to estimate the relative risk of poisoning deaths in people with epilepsy versus people without a history of epilepsy. The specific involvement of medication groups was identified using ICD-10 codes T36-50 among the contributory causes of death.

Results: A total of 47 poisoning deaths occurred in 42,657 people with epilepsy and 139 in 820,494 people in the unaffected comparison cohort. People with epilepsy were at an elevated risk of suicidal (HR, 6.81; 95%CI 4.14-11.19) and accidental (HR, 5.92; 95%CI 3.56-9.83) medicine poisoning, when adjusted for age, gender and area-level deprivation. In both cohorts, psychotropic drugs and opioids were the most commonly implicated medications. The involvement of AEDs in poisoning deaths was low in both cohorts, but more common in people with epilepsy (11% vs 3%). In all deaths which involved AEDs, the person had been prescribed AEDs within 30 days of their death.

Conclusions: Epilepsy is associated with an increased risk of death by accidental or suicidal medicine poisoning. AEDs are rarely implicated in these events.

668. Level of Evidence for Labeled Dosing Recommendations in Renal Impairment

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Background: Medications that are renally excreted frequently require dose adjustment in patients with kidney impairment. While drug development and approval in the US are typically based on multiple Phase I and II studies and one or more larger Phase III randomized trials, the basis for labeled dosing

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recommendations for patients with renal impairment is less well known.

Objectives: To quantify the level of evidence used to recommend labeled dosing adjustments for newly approved drugs in patients with renal impairment.

Methods: We reviewed publicly available drug labels and approval packages for new molecular entities (NMEs) approved in the US between 2012 and 2014. The sample was restricted to 62 renally-excreted NMEs that were not granted orphan drug status. We extracted data regarding approved indications; normal dosing; dosing adjustments for patients with mild (eGFR >60 mL/min/1.73m2), moderate (eGFR 30 to <60 mL/min/1.73m2), and severe (eGFR <30 mL/min/1.73m2) renal impairment; characteristics of studies used to justify dosing adjustments; and numbers of subjects in each study. We used descriptive statistics to analyze our data.

Results: Eighteen of 62 (29%) NMEs had labels that recommended dosing adjustments for patients with mild, moderate, and/or severe renal impairment. Among these 18 NMEs, 5 (28%) used only pharmacokinetic studies to justify the recommendations, with no examination of clinical outcomes for patients with renal impairment. Of the 44 NMEs with no recommended dosing adjustments for renally impaired patients, 11 (25%) did not report assessing the effects of renal impairment. Across the 51 NMEs that reported assessing the effects of renal impairment, the median number of patients with renal impairment evaluated was 32 (range 4 to 5,976).

Conclusions: More than a quarter of newly approved drugs included dosing adjustments for renal impairment in the label, but the recommendations were usually based on very small numbers of patients and often based on pharmacokinetic studies alone. More research is needed to understand the benefits and risks of new drugs in patients with renal impairment.

669. The DIFFuse Algorithm: A Practical Method for Data Source Identification, Feasibility, and Follow-Up for Use in Real-World Research Around the Globe

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Background: The growing demand for real-world data has created a parallel demand for an efficient means of identifying these sources of data globally. Sources include: existing healthcare (claims or EHR) databases, patient/population surveys, cohort studies and registries. Some excellent healthcare database compendia exist, but may not capture disease-specific (DS) data sources and/or contain updated profiles. Moreover, sponsors may be interested in identifying individual patients for further study so that the clinical data in the patient's electronic health record can be supplemented with patient-reported outcomes (PRO) from an electronic survey.

Objectives: We sought to devise an algorithm that would identify and vet real-world data sources in selected countries (n=8) throughout NA/EU. We employed a tiered approach wherein we prioritized DS registries over non-disease-specific (NDS) commercial database vendors. Our objectives included identifying: 1) potential sources of registry and commercial vendor data in the initial data-mining (identification) exercise, and 2) the most promising sources in terms of willingness to share data, patient mix and volume, density of clinical data (feasibility), and potential to collect PRO data (follow-up).

Methods: We identified potential NDS data sources through various healthcare database compendia (Bridge to Data, ISPOR's Digest, etc.), whereas DS data sources were identified via Embase, PubMed, and Google Scholar. Each potential data source was assigned a Y/N feasibility and follow-up designation based on various characteristics. Those designated for feasibility assessment and possible further follow-up were surveyed via an emailed web link or a telephone call.

Results: A total of 33 unique registries in 8 countries were identified initially; 18 (55%) of these were selected for feasibility inquiry and follow-up. Among 176 (non-unique) commercial vendors identified via database compendia; 63 (36%) were chosen for feasibility and follow-up.

Conclusions: Summary results of the feasibility and follow-up inquires (along with response and engagement data) will be available in Q2 2016.

670. Worldwide Mapping of Generic Sources of Real-World Data: A Systematic Review

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Background: The use of real-world data to assess epidemiology, effectiveness and safety of various interventions, patient characteristics and treatment patterns in the management of diseases, has become an important source of valuable evidence for decision making among different stakeholders of the health care system.

Objectives: This study aimed to identify non-disease specific real-world patient-level data sources on health indicators, variables and markers which can inform future research and real-world evidence generation.

Methods: Medline and EMBASE via OvidSP interface were systematically searched from January 2010 to September 2015 for English and non-English publications using real-world evidence from generic databases worldwide. Article inclusion was determined through title and abstract screening; where unclear, full text was reviewed and/or an internet search was conducted. A list of unique sources of non-disease specific patient-level real-world data was compiled.

Results: The review of 10,069 publications yielded a list of 2,658 unique data sources categorised as administrative databases (n=1,669), medical records/health information systems (n=397), health surveys (n=256), claim databases (n=152), surveillance databases (n=82), observational cohorts (n=58), drug registries (n=34) and others (n=10). The highest number of data sources were found in Europe (n=1,180), of which 825 have national coverage; followed by 590 in the US and 366 in the Asia-pacific region. In Latin America, 262 data sources were identified, of which 133 only contain regional data. In China most data sources are medical records/health information systems. In addition to country-specific data sources, 101 multi-country databases were identified, with international and/or continental coverage.

Conclusions: There is a wealth of real world, cost-effective and reliable sources of information on general health outcomes globally albeit unevenly distributed. The identified data sources are being critically evaluated based on its completeness, health-related variables, linkage and accessibility.

671. Dynamic Real World Data Platform Integrating Automated Claims and Registry Data for Pharmacoepidemiologic Studies

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Background: Real world data (RWD) are used for pharmacoepidemiologic studies. While RWD have advantages, single data sources have limitations, e.g. level of detail, and lack of clinical (disease severity)/ laboratory data. There is a need for comprehensive, real-time data that support a wide variety of research objectives across the lifecycle of a drug.

Objectives: Create a dynamic RWD platform in rheumatoid arthritis (RA) that integrates claims and registry data to monitor drug use and patient outcomes for a US drug launch and use the platform to conduct pharmacoepidemiologic studies.

Methods: The REAL Platform includes data from PharMetrics Plus® (adjudicated medical claims), Longitudinal Pharmacy Claims (Rx; data covering about 70% of prescription claims in the United States), Longitudinal Medical Claims (Dx; professional fee claims), and the Corrona RA registry. Platform data are updated quarterly and a rolling 36 months of data are available. By applying encryption/linking technology, patients in >1 data source are linked in a Health Insurance Portability and Accountability Act-compliant manner.

The REAL Platform includes analytical services/ reporting in a technology suite that uses the Observational Medical Outcomes Partnership data model,

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provides standard reports (persistence, adherence, line of therapy), custom reports (integrated views of clinical and economic data), and user-defined queries. These tools enable development of targeted study protocols and timely execution of protocol-driven scientific studies.

Results: Over 10 million patients are included in the platform: 10.8 million in PharMetrics Plus, 160,000 in Dx, 1.1 million in LRx, and >40,000 in the Corrona RA registry (10,000 with personally identifiable information (PII)). About 80% of the registry patients with PII linked with the LRx, 30% of which (2,995) had the equivalent of 12 months of continuous enrollment.

Conclusions: Registry data linked with claims provides comprehensive data that can be used to efficiently address a wide array of study objectives. Regular data updates and on-demand reporting enable scientific monitoring of drug use and patient outcomes before/during/after launch.

672. Time Trends Of Studies Accounting For Immortal-Time Bias – A Review

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Background: "Immortal time refers to a period of follow-up during which, by design, death or the study outcome cannot occur" which systematically overestimates the outcome rate in the unexposed group and at times also underestimates the rate in the exposed group in database studies. The illustrations of immortal-time bias (IMTB) in pharmacoepidemiological observation studies using computerized databases were published during the year 2003-08 [2-5]. Therefore, this review will explore its awareness/impact on the observational studies published since that period and the methods used for adjusting for IMTB.

Objectives: The main objective of this review is to present the time-trends of studies accounting for immortal-time bias.

Methods: PubMed and Embase were searched up to 10/Jan/2016 using the keyword 'Immortal time bias'. Studies in English language that accounted for IMTB in the design/analysis were included in the review. The studies were segregated by year of publication and the method used to account for IMTB. Letters/editorials and methodological studies were excluded.

Results: A total of 254 studies were identified and after removing duplicates, there were 162 studies. Out of a total of 162 studies, 68 studies (30/68 conference abstracts) were included in the review which accounted for IMTB in the design/analyses and started to appear from 2003. Of the 68 studies, 2 (2003), 3 (2004-05), 2 (2006-2007), 2 (2008-09), 5 (2010-11), 14 (2012-13), and 40 studies (2014-15), respectively, accounted for IMTB. Most of the included studies used time-varying/time-dependent analysis to account for IMTB. Six studies used landmark analyses to adjust for IMTB.

Conclusions: This review reflects the increasing trend of awareness and accounting for IMTB in the design/analysis which was expected since it was first introduced and discussed in database studies. As more and more pharmacoepidemiological observational studies are being conducted using computerized databases, it becomes important to take such a misclassification of person-time in to account to prevent spurious results and avoid potential detrimental impact on clinical practice and health policies.

673. Quality of Cancer Records in the Information System for the Development of Primary Care Research (SIDIAP)

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Background: The Information System for the Development of Primary Care Research (SIDIAP) is a potential data source to investigate adverse drug reactions related to cancer. The number of cancer records in SIDIAP was previously validated with data from the Hospital del Mar tumour registry (RTHMar) as the gold standard which found a high sensitivity, but moderate positive predictive value (PPV).

Objectives: To identify possible inaccuracies in the cancer diagnoses assessment in a primary care

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database (SIDIAP) compared with data from the RTHMar in Barcelona which could explain the PPV previously found.

Methods: Patients with a cancer diagnosis (cervix/colon/breast/prostate/lung) recorded in SIDIAP between 2006 and 2012, which were not included in the RTHMar, from the closest (C1) and farthest (C2) primary care centres belonging to the catchment area of the hospital were included. We asked GPs to validate cancer diagnosis of their assigned patients by checking the patients' clinical records from their workstations (including both primary care records and hospital data). Anonymised and aggregated data were used and only GPs had access to patients' identification. Descriptive analyses of GPs replies were performed by centre and cancer site.

Results: In this study, 467 cases were included. The 89% (n=414) of cases diagnoses were confirmed by GPs (cervix=55%, colon=86%, breast=96%, prostate=93%, lung=75%), 3% (n=16) had a cancer diagnosis in a different site, 2% (n=11) were in situ or benign neoplasms, and 2% (n=8) had no cancer diagnosis in their clinical history. From the confirmed cases, 73% (C1=57%, C2=80%) were not visited at the hospital of the RTHMar, while 10% (C1=19%, C2=6%) were visited at the hospital during the study period, and 6% (C1=11%, C2=4%) before 2006.

Conclusions: The majority of absent cancer cases in the hospital registry that are recorded in SIDIAP were confirmed as cancer cases by GPs, and most were treated in a different hospital, which could explain the previous findings of moderate PPV for RTHMar confirmed cases. These findings insure the quality of cancer records in SIDIAP for future research studies.

674. The Danish Centre for Strategic Research in Type 2 Diabetes (DD2) Study Cohort: Presentation of 5,870 Patients with New Type 2 Diabetes Enrolled from 2010 Through 2014

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Background: The Danish Centre for Strategic Research in Type 2 Diabetes (DD2) database is a new nationwide prospective cohort of newly diagnosed type 2 diabetes. The DD2 database and biobank contain detailed interview data, clinical examination data and biomarker data, collected from general practitioners and hospital outpatient clinics in all of Denmark.

Objectives: To present baseline data for the first 5,870 patients with new type 2 diabetes prospectively enrolled during 2010-2014.

Methods: We linked primarily collected DD2 data for each participant with data from a nationwide clinical quality database (the Danish Diabetes Database for Adults) and with routine registry data on comorbidities, mortality, and drug-use. Detailed individual-level information on all reimbursable drugs dispensed at all pharmacies in Denmark can be linked to each DD2-participant.

Results: Median age was 62 years (quartiles 53-68), and 58% were men. A family history of diabetes was reported in 53%, 61% did no sports during leisure time, 34% were overweight and another 53% obese. Tobacco smoking (19%) and alcohol overuse (7%) was not increased compared to the general population. Within the last year prior to enrolment, 84% had used a glucose-lowering drug; 77% received oral antidiabetics only, and 7% received insulin, with 83% having HbA1c $<7.5\%$ at baseline. The most frequently used oral antidiabetic drug was metformin (used by 80%) followed by DPP-4 inhibitors (9%), sulfonylureas (7%), GLP-1 analogues (5%), and SGLT-2 inhibitors (0.4%). Use of glitazones, meglitinides and alpha-glucosidase inhibitors was negligible. Within the last year prior to enrolment, 73% received antihypertensive and 70% hypolipidemic treatment. At enrolment, 22% and 14% already had a hospital history of macrovascular and microvascular complications, respectively. The mortality rate was 1.06 per 100 person-years (131 deaths); 1.32 in men and 0.72 in women.

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Conclusions: In the future, the DD2 database represents a very valuable source for pharmocoepidemiological and outcome studies in type 2 diabetes.

675. The Surveillance of HealthCare in Asian Network (SCAN): Infrastructure Development for Multinational Pharmacoepidemiologic Studies (MPES)

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Background: The Asian Pharmacoepidemiology Network (AsPEN) aims to assess safety/effectiveness of medications in Asia using large databases. However, an optimal infrastructure to support such MPES is still being developed. The SCAN aimed to implement a distributed network approach and apply a common data model (CDM).

Objectives: To convert four Asian databases (Japan, Taiwan, Hong Kong, and Korea) and US Medicare data to a CDM and assess the quality of conversion.

Methods: We converted the Japan Medical Data Center Database (JMDC), a 4% random sample of the Taiwan's National Health Insurance Research Database (NHIRD), a 1% random sample of the Hong Kong's Clinical Data Analysis and Reporting System (CDARS), Korea's hospital electronic health records and 5% Medicare database to the OMOP CDM ver.4. We generated descriptive statistics from publicly available OSCAR program to examine the quality of conversion. All participating sites recorded the processes of conversion and reviewed mutually.

Results: It took 30 months to complete the conversion, including converting standard terminology codes and the refinements of the conversion. Mapping of domestic drug codes to standard terminology codes was the biggest challenge. Examining % of distinct codes observed in the source data, we mapped 97 %, 87%, 93% and 81% of domestic drug code of US, Taiwan, Hong Kong and Korea to RxNorm, respectively. The mapping rate from Japanese domestic drug to RxNorm was relatively lower than other countries (71%), but we mapped the rest to ATC code. We mapped approximately 83%, 99%, 98 %, 93% and 98% of diagnosis codes in Medicare, JMDC, NHIRD, CDARS and Korean databases respectively to SNOMED-CT.

Conclusions: The SCAN successfully converted four Asian databases and Medicare data to a CDM, which will reinforce more MPES within the AsPEN. Mapping domestic terminology codes was the biggest challenge. Further studies are underway to examine and understand possible cross-national differences in healthcare and drug utilizations and their potential impacts on multinational safety and effectiveness studies.

676. A Study to Assess the Capture of Sublingual Immunotherapy Within an Electronic Health Record (EHR) System

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Background: Sublingual immunotherapies (SLITs) including Ragwitek (Short Ragweed Pollen Allergen Extract) were approved for marketed use in the US in April 2014. Because of the potential for serious allergic reaction, the first dose should be administered under physician supervision. SLIT initiation is likely to be missed in claims data as there are no relevant procedure codes, and the first dose may be provided as part of a sample pack. However, SLIT initiation may be observable in EHR data.

Objectives: To develop operational definitions to identify the initiation of Ragwitek within a large US EHR data system.

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Methods: To identify potential Ragwitek users, we used natural language processing (NLP) to identify mentions of Ragwitek in the electronic clinical notes of the Humedica Research Database. De-identified clinical notes were then sought and reviewed for a sample of patients to classify Ragwitek use (initiation, prevalent use, non-use/insufficient information). Linking the note review results to the information extracted via NLP, we looked for patterns (NLP concept of Ragwitek in combination with NLP modifiers) that may indicate in-office Ragwitek initiation.

Results: We identified 201 NLP concepts of Ragwitek from 133 unique notes among 95 patients in 2014. Of these, we requested 20 notes (among 19 patients); 19 notes (for 18 patients) were received and reviewed. The notes documented that 9 had initiated Ragwitek, 4 were prevalent users (i.e., initiation not captured by the note reviewed), and 5 were non-users. Among the 9 initiators, 5 (56%) had an NLP concept of Ragwitek with a modifier of "administer" or "self-administer". Including mentions of an NLP concept of Ragwitek with a modifier of "start" and a recorded date corresponding to the date of the note increased the capture of Ragwitek initiators to 67%.

Conclusions: We identified 3 NLP concept algorithms that jointly captured 67% of the patients who initiated Ragwitek. Confirmation that these algorithms are generalizable to a broader sample of mentions of SLIT will be needed. Further refinement of the NLP patterns may also be needed.

677. Pitfalls and Value of Clinical and Laboratory Values in Electronic Health Record Data

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Background: In type 2 diabetes (T2D) studies, electronic health record (EHR) systems contain clinical measures and laboratory results that are useful for evaluating drug effectiveness and safety. However, collection is part of routine patient care, and is not uniformly obtained across patients or time. Further, different instruments and recorders add heterogeneity and potential error to the data.

Objectives: We applied data cleaning, including restriction and outlier removal (marginal and within patient) and missing data methods to conduct a study evaluating changes in these measures across consistent intervals of time.

Methods: Clinical measures (weight, BMI, blood pressure), and laboratory values (HbA1c, Creatinine, Albumin-Creatinine Ratio, Lipids, Liver Profiles, CBC) were extracted from EHR data for T2D patients initiating a new diabetes drug. We restricted measures to values having the same units, and within ranges of plausible values. We further removed within patient outliers. Pre-treatment values were the last measure in baseline. Values were summarized quarterly or biannually in the first year of follow-up, using the interval mean when measures were available, or an imputed value if no measure was observed.

Results: A cohort of 370,382 patients yielded 393,109 ALTs and over 6 million CBCs. Trimming removed approximately 3% of observations outside valid ranges and 2% that were extreme within an individual. Baseline clinical measures were available for blood pressure (97%) and BMI (93%). Higher proportions were missing in the follow-up; 35% and 51% of patients were missing weight or BMI in the first and last quarter of follow-up. Measures important to T2D treatment had low missingness in baseline: HbA1c (21%) and creatinine (24%); there was greater missingness in follow-up. Other measures had greater missingness ranging from 40% to 90%.

Conclusions: The availability of clinical and laboratory data in EHR offers advantages and efficiencies to observational studies. Their use requires an understanding of their limitations, and application of methods to clean and standardize data. Imputation methods may further enhance the use of these data.

678. The Role of Poison Data in Regulatory Decision-Making

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Background: Data from the poison databases such as the National Poison Data System (NPDS) in the U.S., and the TOXBASE in the U.K. are used by national medicine regulatory agencies, researchers, and the pharmaceutical industry to assess the safety of medical products in the postmarketing phase of their lifecycle.

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NPDS is the poisoning surveillance database of the American Poison Control Centers. TOXBASE is the primary clinical toxicology database of the National Poisons Information Service in the U.K.

Objectives: To describe the NPDS in the U.S.

To evaluate the utility of NPDS for identifying, assessing postmarketing drug safety signals, and assessing the impact of regulatory decisions.

Methods: A review of the literature and a search in the U.S. Food and Drug Administration (FDA)'s website was made to identify case examples where NPDS database was used in regulatory decision-making process; and to study the impact of regulatory decisions.

Results: There are a number of case examples that involved acetaminophen/paracetamol; cough and cold preparations; where data from the NPDS was used to inform regulatory decision-making. The FDA's experience and approach with NPDS data will be presented with examples of successful use of data to assist in licensing decision. Salient features of case examples where NPDS was used will be presented.

Conclusions: NPDS data has been used to study poisoning patterns of several commonly used therapeutic products. Regulatory agencies may use evidence from various data streams and data from the NPDS is an important data source that is commonly used by the FDA to help inform regulatory decision-making. Poison data serves as a tool in the assessment of postmarketing safety of therapeutic drugs and to study the impact of regulatory decisions.

679. Determining the Citation Impact of the Canadian Network for Observational Drug Effect Studies (CNODES) Publications: Methods and Outcomes

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Background: The Canadian Network for Observational Drug Effect Studies (CNODES) conducts research on drug safety and effectiveness. As one measure of success of the knowledge translation of its findings through publications, we applied citation metrics, nearly all of which are based on citation counts (the number of times a publication is cited).

Objectives: To determine the uptake of publications from CNODES as measured by the quantity and characteristics of their citing articles and to compare citation tools with respect to accuracy, comprehensiveness, and timeliness.

Methods: For five CNODES articles (2012-2014), we searched citation tools Web of Science (WoS), Scopus and Google Scholar (GS) through June 2015. To create a comprehensive list, citations from all sources were collected and duplicates removed. We used Fleiss' Kappa to measure agreement between all three tools and Cohen's Kappa for the three pairwise comparisons. Counts and proportions were calculated and presented for summarizing the articles returned, both by article and by publisher. Logistic regression was used to compare tools between publishers.

Results: We observed discrepancies in the number of citing articles found by each source. WoS and Scopus provided useful analysis tools for tracking citations according to variables such as the discipline and country of citing authors, with the United States (22%), Canada (19%) and the United Kingdom (10%) ranking in the top 3 of 33 countries. Scopus provided a higher number of citations (102) than WoS (79), though the latter did contribute a few unique citations. GS provided the highest citation count (155) but included duplicates and missed some listed by the others.

Conclusions: The most accurate, comprehensive and current citation count requires careful use of multiple sources. We determined the frequency of CNODES publication citation uptake through Scopus, WoS, and GS tools and identified strengths and limitations. Knowledge of the publication metrics can help inform publication decisions to reach desired audiences and assist in planning further knowledge translation activities.

680. Impact of the EU Orphan Drug Regulation on the Development of Orphan Drug: A 15-Year Analysis

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Background: The European Union (EU) Orphan Drug Regulation was adopted on December 16, 1999 and became effective on April 27, 2000, to encourage the research, development, and marketing of orphan drugs. It was estimated that the global orphan drug market totalled nearly $123 billion in 2014 and may reach nearly $191 billion by 2019.

Objectives: To summarise and highlight what the EU Orphan Drug Regulation has accomplished since its inception.

Methods: The European Medicines Agency's (EMA) website was searched to collect all rare disease (orphan) designations evaluated. The European Public Assessment Reports (EPAR) for human medicines published by the EMA was also searched to obtain the number of approvals and refusals of orphan drug applications since 2000. The results of the two searches were cross-reviewed and then combined.

Results: Since 2000, 1,563 compounds applied for orphan drug designation; 1,244 (79.6%) received positive opinion. However, in the past 15 years, only 97 (7.8%, 97/1,244) applied for central market authorisation in Europe, of these, 85 approvals were granted (87.6%, 85/97) and 10 were refused (9.7%, 10/97). Of the 10 refusals, 7 received comments on at least one aspect of inadequate trial design, which disallowed proper evaluation of the clinical benefits of the investigative drug.

Conclusions: The provision of market exclusivity, protocol assistance, and fee reductions through the EU Orphan Drug Regulation have led to increased overall product availability for rare diseases in the past 15 years, year-over-year, as demonstrated by the high approval rate of market authorisation of orphan drugs. Of the few that had failed to receive a positive recommendation from the EMA, a common shortfall seemed to be the lack of fundamental trial design rigour. This may indicate the lack of knowledge on the sponsors' part to fully utilise the resources offered by the EMA on protocol assistance, to minimise the probability of rejection on grounds of mere deficiencies in research methodology. Therefore, the promotion of these incentives through the Regulation remains critical in increasing the success of future and ongoing development of orphan drugs for rare diseases.

681. Weighted Multiple Imputation of Ethnicity Data That Are Mising Not at Random in Primary Care Databases

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Background: Ethnicity is an important factor to be considered in health research because of its association with inequality in disease prevalence and the utilisation of healthcare. Ethnicity recording has been incorporated in primary care electronic health records, and hence is available in large UK primary care databases such as The Health Improvement Network (THIN). However, since primary care data are routinely collected for clinical purposes, a large amount of data that are relevant for research including ethnicity is often missing. A popular approach for missing data is multiple imputation (MI). However, the conventional MI method assuming data are missing at random does not give plausible estimates of the ethnicity distribution in THIN compared to the general UK population. This might be due the fact that ethnicity data in primary care are likely to be missing not at random.

Objectives: I propose a new MI method, termed 'weighted multiple imputation', to deal with data that are missing not at random in categorical variables.

Methods: Weighted MI combines MI and probability weights which are calculated using external data sources. Census summary statistics for ethnicity can be used to form weights in weighted MI such that the correct marginal ethnic breakdown is recovered in THIN. I conducted a simulation study to examine weighted MI when ethnicity data are missing not at random. In this simulation study which resembled a THIN dataset, ethnicity was an independent variable in a survival model alongside other covariates. Weighted MI was compared to the conventional MI and other traditional missing data methods including complete case analysis and single imputation.

Results: While a small bias was still present in ethnicity coefficient estimates under weighted MI, it was less severe compared to MI assuming missing at random. Complete case analysis and single imputation were inadequate to handle data that are missing not at random in ethnicity.

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Conclusions: Although not a total cure, weighted MI represents a pragmatic approach that has potential applications not only in ethnicity but also in other incomplete categorical health indicators in electronic health records.

682. The Joint Action Of Patient, Physician And Pharmacist In Order To Improve Adherence To Medication

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Background: Medication adherence usually refers to whether patients take their medications as prescribed and whether they continue to take a prescribed medication. The impact of poor adherence grows as the burden of chronic disease grows worldwide. Adherence to long-term therapy for chronic illnesses in developed countries averages 50%.

Objectives: Objective is improve adherence to medication, especially among patients with multimorbidity.

Methods: Design: The cross-sectional survey was conducted at 106 Zagreb, Croatia pharmacies and the questionnaire was filled out by the study subjects; we used a 33-item self-administered questionnaire.

Setting: A convenience sample of 635 individuals who were buying drugs for the treatment of chronic diseases.

Main outcome measures: Study subjects were divided into two groups, with adherent defined as a "yes" response to the statement that they "never fail to take their medication on time."

Statistical analysis: Student's t-test and Chi-square test with a significance level of $p<=0.05$ were used when appropriate for the evaluation of the results.

Results: In our study population (n=635), non-adherent subjects prevailed over adherent subjects (n=370; 58.3% vs. n=265; 41.7%). The most common diagnoses were diseases of the circulatory system (n=500; 36.8%) and endocrine, nutritional and metabolic diseases (n=285; 21.0%). The great majority of study subjects reported forgetfulness ("I just forgot") as the main reason for skipping drug doses, followed by being away from home and shortage of the drug (having consumed it all).

Conclusions: Nonadherence to medication is a growing concern to patients, physicians, healthcare systems, and other stakeholders because that it is prevalent and associated with adverse outcomes and higher costs of care. There is usually no single reason for medication nonadherence, and therefore must be a comprehensive approach to improve adherence. Research on adherence has typically focused on the barriers patients face in taking their medications. Common barriers to adherence are under the patient's control, so that attention to them is a necessary and important step in improving adherence.

683. Counselling In Community Pharmacies In The Nelson Mandela Metropole, South Africa: Codeine-Containing Analgesics

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Background: The rational use of codeine-containing analgesics will ensure positive health outcomes. Interventions aimed at effectively counselling clients play an important role in ensuring the rational use of these analgesics.

Objectives: The aim of the study was to evaluate the counselling content provided to clients receiving these analgesics and how this information compare to the requirements in pharmacy-specific legal documents.

Methods: Two questionnaires were administered to pharmacists who dispensed codeine-containing analgesics. The first questionnaire determined the content of information on these agents provided to clients by pharmacists. The second questionnaire evaluated the information pharmacists perceive as important regarding the counselling of these agents. Counselling information perceived as important were compared to the legal requirements in the Pharmacy Act 53 of 1974, as amended. Ten community pharmacies in the Nelson Mandela Metropole were randomly selected to participate in the survey. Fieldworkers administered the questionnaires to two randomly selected pharmacists in each of the participating pharmacies.

Results: Of the 20 respondents, 85% (n=17) were of the opinion that counselling clients on the use of codeine-containing analgesics form an integral part of the responsibilities of community pharmacists,

especially due to the side-effect and addiction profile thereof. However, 85% (n=17) of the respondents believed that clients are not effectively counselled on the rational use of these analgesics. Pharmacy-specific legal documents in South Africa also lack guidelines in supporting pharmacists in counselling clients using these analgesics effectively.

Conclusions: Community pharmacists play a valuable role in ensuring the rational use of codeine-containing analgesics, and also can provide an important educational role in informing clients against the risk of abuse of these agents.

684. The EpiChron Cohort Proven Useful for Pharmacoepidemiological Studies

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Background: New sources of reliable data for pharmacoepidemiologic research are needed. In Aragon (Spain), The EpiChron Research Group on Chronic Diseases has developed the EpiChron Cohort linking clinical, services utilization and administrative information contained in Aragon's health registries.

Objectives: To describe the EpiChron Cohort in the context of an European regulatory multidatabase study of characteristics of new users of cilostazol.

Methods: We identified and described a subcohort of new users of cilostazol between 2009 and 2012.

Results: The EpiChron Cohort covers all individuals enrolled in the public health system of the region of Aragon in Northern Spain with approximately 1.3 population from 2010 onwards. The database is based on information from the health registries of primary and secondary care, and it contains detailed data on all prescription medicines dispensed in the community pharmacies.

The following data are linked at patient level: administrative data, clinical information from primary care, emergency departments and hospital discharges, hospital procedures, health services use (primary, specialised, hospital and emergency care), pharmacy expenditure and health outcomes as mortality.

Studies are to be conducted in collaboration with the Institute of Public Health and Health Services Research. Access to medical records by EpiChron researchers to validate potential cases or to complete additional clinical information is possible is stated by the research protocol and approuved by the Research Ethical Committee.

A total of 4,024 subjects had a recorded prescription for cilostazol, 72% were men, the median age was 70.0 years, and 74.5% had a history of cardiovascular diseases other than peripheral arterial disease. Hypertension was the most frequent cardiovascular condition (54.9% of users). About 82% of users were concurrently treated with CYP3A4 or CYP2C19 interacting medications, and 10% with potent CYP3A4 or CYP2C19 inhibitors.

Conclusions: The EpiChron Cohort is useful for population-based pharmacoepidemiological studies, contains primary and secondary care data and detailed information on prescriptions dispensed, and it allows acces to medical records for case validation.

685. Training Pharmacy Students and Disseminating Information on Appropriate Use of Medicines: The Weblog as a Tool

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Background: The provision of high-quality information on medicine use is determinant for decision making in health. Thus, the training of students aiming at adequate interpretation of scientific evidence on health is crucial.

Objectives: Describe the four-year experience of a Drug Information Centre in training pharmacy students for the provision of information on appropriate use of medicines.

Methods: Descriptive analysis of a set of educational activities of pharmacy students using the weblog (Cemed-Blog - https://cemedmg.wordpress.com/) for disseminating information on medicines use performed at the Cemed - "Centro de Estudos do Medicamento" of the Federal University of Minas Gerais, Brazil. Two/three-page articles are produced by students summarizing the interpretation of health

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evidences translated into an easy and accessible language. This includes different steps within the training process: identification of sources of information, selection and collection of information, writing, review by the Cemed-group, and dissemination through the weblog. Two professors, one pharmacist and one host researcher supervise all activities.

Results: Eighteen pharmacy students participated in the activities of the Cemed from 2012 to 2015. Altogether 196 articles were published in the Cemed-Blog. The top ten read articles included different issues regarding the drugs/substances - omeprazole, diarrhea agents, phosphoethanolamine, non-steroidal anti-inflammatories, alcohol and concomitant use with drugs, generic vs. brand drugs, acetaminophen, clonazepam, methotrexate and warfarin. Cemed-Blog reached more than 250,000 entries during the period, coming from 120 countries. Most visits came from Brazil (92%), United States (4%) and Portugal (2%). Besides, 327 commentaries - including the answers, accompanied the visits to the Cemed-Blog.

Conclusions: The weblog registered an intense consultation and has motivated pharmacy students to strengthen their formation on evidence-based health for disseminating adequate drug information. We believe that the bilingual publication - portuguese/english - could expand access to information and further encourage the training of students.

686. Description of 2014-2015 ICPE Abstract Submissions

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Background: The annual program of the International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE) is developed "organically" from submissions of members of the International Society of Pharmacoepidemiology (ISPE) rather than through solicitation around a particular theme.

Objectives: To assess ICPE Taipei (2014) and ICPE Boston (2015) abstract submissions by overall category, population, exposure, outcome, significant interest group (SIG), and country of submission.

Methods: Submitted abstracts were reviewed by ISPE members and graded 1 (best) to 10 (worst). Mean, and distribution (range and inter-quartile range [IQR]) were calculated overall and by category.

Results: There were 973 abstracts submitted in 2014 with mean score 4.5 (range 2.3-9.1; IQR 1.2) and podium presentation cut-point ~3.65. There were 1166 abstracts submitted in 2015 with mean score 4.3 (range 2.0-9.2; IQR 1.2) and podium cut-point ~3.50. More than 50 of the 2014 podium presentations would not have met the 2015 cut-point. Across both years, the largest numbers of abstracts were seen for categories of drug utilization research/health services research (DUR) and methods, outcomes of cancer and cardiovascular, exposures of nervous system and cardiovascular, DUR and Database SIGs, and from the United States.

In addition, across both years, a larger proportion of pharmacovigilance and pharmacoeconomics/outcomes research categories had slightly higher (worse) scores compared with the overall distribution. Slightly larger proportions of abstracts with high scores were also noted in both years for outcomes of respiratory disorders, skin disorders, and treatment failure; exposures of antiinfectives, antineoplastic/immunomodulating agents, and dermatologicals; and countries in Asia. Slightly larger proportions of abstracts with low (better) scores were noted in both years for population of pregnant women and for abstracts submitted from the United States, Denmark, and Australia.

Conclusions: No grouping had a substantially better distribution of scores or proportion of podium presentations. The ICPE program is generated from a diverse set of abstracts representing the broad scientific interests and activities of the ISPE membership.

687. Lost in Translation: No Effect of a High-Profile Publication on the Co-Prescribing of Interacting Drugs

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Background: Drug-drug interactions (DDIs) are an important clinical and public health problem. It is unknown whether high-profile publications identifying serious consequences of DDIs influence future concomitant use of those medications.

Objectives: To assess whether a high-profile publication by Juurlink et al. (2003), which demonstrated serious consequences of specific DDIs, reduced the concomitant use of those drugs.

Methods: We conducted a quasi-experimental study using prescription claims from a large commercial health insurer. We examined trends in the prescription of the object-precipitant drug pairs reported by Juurlink et al. (2003): glyburide+cotrimoxazole, digoxin+clarithromycin, and ACE inhibitors (ACEIs) +potassium-sparing diuretics. As a comparison group, we examined trends in prescription of non-interacting object-control drug pairs: glyburide+amoxicillin, digoxin+cefuroxime, and, ACEI+indapamide. The pre- and post- publication periods were 5/2000-3/2003 and 10/2003-12/2008, respectively. We used Poisson regression to assess the pre-post change in slope for the target pairs vs. the control pairs, both overall and individually.

Results: There was no overall difference in the post- vs. pre-publication trends for targeted vs. control drug pairs ($p=0.24$). When each individual targeted pair was compared to its control, publication was not associated with a change in slope for ACEI+potassium-sparing diuretic ($p=0.11$). Publication was associated with a reduction in the co-dispensing of digoxin +clarithromycin vs. its control ($p<0.001$; relative rate=0.9996: CI 0.9993, 0.9998), although this reduction was small in magnitude. Publication was associated with an increase in co-dispensing of glyburide +cotrimoxazole vs its control ($p<0.001$; relative rate=1.0220: CI 1.0187, 1.0254).

Conclusions: We found that a high-profile DDI publication had little to no measurable effect in reducing the co-prescription of the interacting drugs studied. Through use of a large, representative database and a long study period, we demonstrated the need for strategies to improve the translation of knowledge into clinical practice.

688. Development, Applications, and Methodological Challenges to the Use of Propensity Score Matching Approaches in FDA's Sentinel Program

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Background: Propensity scores (PSs) are an important tool for active post-approval medical product safety surveillance systems, such as the US Food and Drug Administration's Sentinel program. By reducing a vector of covariates into a single number, PSs facilitate adjustment for a large number of potential confounding variables without limitation by the number of outcome events. PSs also help protect patient privacy by minimizing data sharing in distributed data settings. For these reasons, PSs were incorporated into the Sentinel routine querying framework in 2013 in the form of a PS matching (PSM) tool.

Objectives: To describe the development, application, and performance of PS-based approaches used in Sentinel, with a focus on early challenges and successes within Sentinel's distributed database.

Methods: We summarized six applications of the PSM tool in Sentinel including four retrospective assessments (dabigatran, apixaban, and niacin on strokes/bleeds, levetiracetam on agranulocytosis) and two prospective assessments (rivaroxaban on stroke/bleeds, mirabegron on stroke/myocardial infarction).

Results: In these assessments, the number of included patients ranged from 28,809 to 581,455, the number of Data Partners (DPs) ranged from 4 to 10, and the outcome event rates ranged from 0.04 to 49 per 1000 person-years. Unconditional analyses were determined to be more statistically efficient than analyses conditional on the matched set when 1:1 matching. It was discovered that PS matched sets shifted between monitoring periods due to the dynamic nature of the data when performing prospective analyses. A lack of new users caused model convergence issues at smaller DPs in some assessments and precluded sequential analysis in one prospective assessment.

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Conclusions: The PSM tool has been successfully applied to multiple one-time and prospective safety assessments. Future investigations into the use of PS matching methods in distributed databases should seek to address challenges related to loss of precision in conditional analyses, the dynamic nature of the underlying data for prospective analyses, and confounding adjustment in smaller DPs.

689. Effect of Lawyer-Submitted Reports on Safety Signals in the FDA Adverse Event Reporting System (FAERS)

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Background: Lawyers have reported adverse events (AEs) related to prescription drugs to FAERS as part of ongoing litigation; this practice can inflate measures of disproportionality. However, the extent to which lawyer reporting of one AE obscures the ability to detect a safety signal for another AE is unknown.

Objectives: To assess the effect of lawyer-submitted AE reports on the ability to detect safety signals in FAERS using three known drug-AE associations (isotretinoin/birth defects; atorvastatin/rhabdomyolysis; rosuvastatin/rhabdomyolysis) in which the drug of interest was the subject of litigation for different AEs.

Methods: Publicly available FAERS data from Jan 2004 to Sept 2015 were used to estimate yearly cumulative proportional reporting ratios (PRRs) and 95% confidence intervals (CIs) for the drug-AE pairs of interest with and without lawyer-submitted reports, where PRR is the AE prevalence for a drug divided by the corresponding AE prevalence for all other drugs. A signal was defined as a lower bound of the 95% CI $\geq$1 and $\geq$3 individual reports. We determined if the inclusion of lawyer-submitted reports delayed time-to-signaling for the pairs of interest.

Results: Cumulative PRRs met signaling criteria for each pair in each year, with and without inclusion of lawyer reports. For isotretinoin, early lawyer reports for birth defects slightly increased PRRs for birth defects before 2008, with the largest increase in 2006 (2.9 [95% CI: 2.4, 3.5] to 3.3 [2.8, 3.9]); later reports for inflammatory bowel disease decreased PRRs for birth defects after 2011, with the largest difference in 2013 (2.2 [2.0, 2.5] to 1.9 [1.7, 2.1]). In the atorvastatin analysis, lawyer reports for diabetes reduced PRRs for rhabdomyolysis in 2014 (16.4 [15.5, 17.4] to 14.8 [13.9, 15.6]) and 2015 (18.0 [17.1, 19.1] to 15.4 [14.5, 16.2]). Lawyer reporting had no impact on PRRs for rosuvastatin and rhabdomyolysis.

Conclusions: While lawyer reports of an AE can inflate a signal for that AE, it can also modestly reduce signal strength for other AEs of interest. Despite this, lawyer reports did not qualitatively affect signaling in three examples with prominent lawyer reporting for other AEs.

690. Comparing Spontaneous Report Disproportionality Measures to Estimates of Adverse Events from Cochrane Systematic Reviews

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Background: Although spontaneous report measures are used regularly by health authorities to update product labels, it is commonly accepted that these measures should only be used to detect positive signals and that disproportionality estimates are not thought to be directly associated with real adverse event relative risk.

Objectives: We aimed to compare disproportionality measures from the FDA Adverse Event reporting system (FAERS) database to adverse event estimates extracted from Cochrane reviews as a reference standard.

Methods: 30 drugs were randomly selected from the FAERS database and corresponding updated Cochrane systematic reviews were screened to extract data on adverse event risk estimates of medications. Drug combinations were excluded. Reviews presenting groups of drugs, comparing the drug of interest to another drug or not presenting appropriate estimates of adverse event relative measures were excluded from the study. Adverse event terms extracted from the reviews were mapped to MEDDRA terms by experienced MEDDRA coders blinded to any relative measure estimates. Corresponding disproportionality measures and 95% CIs were then calculated for these

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groups of terms and compared with estimates extracted from the Cochrane reviews. Correlation coefficients and difference between the estimates were calculated. Analyses were additionally stratified to investigate patterns in the relationship between the two estimates with regards to the number of events used to calculate the estimate, the quality of the Cochrane reviews involved, and the seriousness of the adverse event reported.

Results: Although we found 140 Cochrane systematic reviews related to the randomly selected drugs, only 3 of them met our inclusion criteria and included appropriate reports of adverse event relative risk estimates. We extracted 86 drug-adverse-event estimates from the reviews and compared them with corresponding estimates extracted from the FAERS database. Detailed results will be given in the final presentation.

Conclusions: This is the first study comparing measures from FAERS to adverse event estimates obtained from Cochrane systematic reviews.

691. An Educational Intervention to Improve Nurses Reporting of Adverse Drug Reactions

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Background: Drug safety data before commercialization is limited and incomplete which is why spontaneous reporting system of ADR is fundamental to the safety surveillance of market medicines.

Nurses can have an important role in adverse drug reactions (ADR) reporting due to their daily activities of drugs administration, however among these professionals there is a high rate of underreporting which according to previous studies is due to indifference (the belief that a single case can not contribute to medical knowledge) and lack of knowledge about the pharmacovigilance system.

Objectives: The aim of this study is to evaluate the quantitative and qualitative increase of ADR reports by nurses after an educational intervention.

Methods: A quasi- experimental study was performed in nurses working in primary care in Braga district, Portugal. 113 individuals were placed in the intervention group while the control group included 590 individuals. Two educational interventions were performed to nurses working in primary care in ACES Cávado II (intervention group) that focused on the problem of adverse drug reaction, the impact on public health and spontaneous reporting. Statistical analysis was based on absolute and relative frequencies.

Results: Between January 2013 and September 2014 the Northern Pharmacovigilance Unit received 9 reports per 100 nurses from the intervention group and 5 reports per 100 nurses from the control group. 37 % of the intervention group reports and 43% of control group reports corresponded to serious ADR (p=1.000). 87% the intervention group reports and 83% of control group reports corresponded to described ADR (p=1.000).

Conclusions: The educational intervention increased 1.8 times the number of reports during the study period. The 2nd intervention had more impact than the 1st one.

There was no significant increase in the quality of ADR reports in the intervention group. In the 2nd intervention the number of reports increased only at the intervention day.

692. One Size Does Not Fit All - Right-Sized Signal Detection Systems That Are Appropriate for Your Portfolio Benefit-Risk Management Strategy

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Background: The requirement to properly plan, track and manage signals from all sources has never been greater. This poster describes flexible approaches to fit-for-purpose signal management strategies in different-sized biopharmaceutical companies with differing benefit-risk management needs.

Objectives: Whether a company holds one or more authorizations, a cost-effective, compliant signal management system is central to any PV program. We describe the use of tailor-made signaling strategies in small and large companies, with a focus on quality management across the lifecycle of the signal.

Methods: Regulatory expectations for signal management are becoming more stringent and a quality framework with good scientific decision making and prioritization must be demonstrated by all stakeholders.

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Over half the signals managed by the European Medicine Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) in its first year of operation, resulted in changes to the product information* and we are seeing an increasing focus by inspectors on signaling strategies. The second most common critical finding and the number one major inspection finding made by the MHRA related to signaling strategies**.

In the EU, transparency, compliance and quality are critical elements of the pharmacovigilance legislation. Regulators and PRAC are making increased use of EudraVigilance with detected signals currently published each month and available to the EU QPPV and general public. FDA continues to expect strong and swift signal detection and analysis throughout a product's lifecycle. We describe the correct application of the signal management process including the importance of terminology, strategy setting, tracking, timely decision making and escalation processes.

We will also summarize the current signal management regulatory landscape in a number of major jurisdictions before moving on to highlight compliant signaling strategies in different types of companies.

*Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8-11 September 2014, accessed 12 Sep 2014

** MHRA GPvP Symposium Nov 2015.

693. Withdrawn by Author

694. PRR Computations Over Time Continue to Reveal Serious Safety Signals Aoon After Drug Approval

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Background: In the past we have written on the use of PRR over time methodologies to detect signals of previously unknown adverse events. Furthermore, we have shows that most times,non-serious adverse events should be discarded when performing any disproportionality analysis as differential reporting of non-serious events introduces differential biases against finding a signal for new drugs. We update our previous results with reviews from new drugs such as SGLTs inhibitors, Benicar (olmesetran), Xarelto (rivoraxaban), and isotretinoin.

Objectives: To show how the use of PRR over time methodology provides graphical views of safety data that allow for more reobust signal detection. To evaluate signals soon after launch of drugs.

Methods: Data from the FDA AERS system was selected for use. This data was extensively prepared to allow for PRR calculations. Last best cases were determined for reports with multiple versions. Dates of first report were computed for each adverse event term in each report. For each event, the percentage of event reports to total reports for the drug was computed. These calculations were computed for each quarter. Because of differential reporting, nonserious reports were excluded.

Results: There were various safety signal findings for the subject drugs. Viewing how these signals evolved over time provided a more intuitive view of the possible significance of the signal. For the study drugs, we find strong evidence soon after launch for Coeliac disease (Benicar), bleeding (Xarelto), diabetic ketoacidosis (SGLT2's), and systemic reactions (isotretinoin).

Conclusions: PRR over time reveals signals that might not be otherwise obvious looking at a single point in time. Eliminating non-serious events further clarifies the signals and more importantly allows for signals to be seen in newer drugs which may report a large number of non-serious events soon after launch.

695. Utilising Electronic Healthcare Data To Support Early Phases Of Safety Signal Assessment

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Background: Electronic healthcare record (EHR) databases are commonly used to conduct pharmacoepidemiological studies to confirm or refute signals arising from spontaneous adverse event (AE) reports. However, there has been limited routine use of this data earlier in the signal assessment process.

Objectives: To pilot the use of the Longitudinal Data Explorer (LODEX) software, which is based on

methods described by Noren et al. 2010 and is designed to provide rapid access to summary EHR data on prescriptions at drug substance level and clinical diagnoses, with the UK Clinical Practice Research Datalink (CPRD) primary care database and explore its value in strengthening signal assessment within a regulatory environment.

Methods: A review of all signals arising from spontaneous AE reports and other sources raised at the MHRA weekly signal management review meeting, at which they are validated and prioritised for assessment, 07/2014-06/2015 was conducted using LODEX and the CPRD.

Results: 83 unique drug-event combinations were discussed as signals during the study period. Of these, 14 were already listed in product information and a further 20 were for drugs prescribed mainly in secondary care or available without prescription. A further 17 were excluded because they were brand, formulation, or dose specific issues, the outcome was death, they were relevant only to a subgroup of patients, or they related to drug interactions. For the remaining 32 (39%) signals, summaries of patient exposure and incidence of the relevant AE could be accessed using LODEX. Three case studies where exposure and event could be clearly identified were used to further explore the scientific value of the data within signal assessment. These showed that the data provided useful support in increasing the body of evidence, confirming the assessment, and deciding upon the need for further action.

Conclusions: EHR data can provide useful insights into the clinical context when assessing the strength of safety signals arising from different sources on a routine basis provided that suitable flexibility is available when defining exposure and limitations related to the use of different event coding systems are overcome.

696. Identification of Generic Drugs in the FDA Adverse Event Reporting System

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Background: Generic drugs represent 88% of drugs prescribed in the US. The FDA's Adverse Events Reporting System (FAERS) may provide a source for evaluation of the adverse events associated with generic drugs. However, there are few reliable and valid methods that identify generic drugs in FAERS.

Objectives: To evaluate the reliability and validity of a novel algorithm developed to identify reports about generic drugs in FAERS.

Methods: Publically available FAERS data from 2011 to 2013 was used for analysis. We extracted case reports with complete information on age, sex, suspected drug name and adverse event where levothyroxine, amphetamine/dextroamphetamine or tamsulosin were the primary suspect drug. We developed an algorithm to classify the suspected drug as definitely generic, probably generic, brand or unclassifiable using name of manufacturer, new drug approval (NDA/ANDA) number and presence of the word "generic" mentioned verbatim in the variable listing drug name. Two authors reviewed the case reports independently and a third author adjudicated any disagreements. Kappa statistic was calculated to assess concordance. Validation of the grading scheme is ongoing using source narratives obtained from the FDA via the Freedom of Information Act.

Results: A total of 1237 unique case reports had either levothyroxine, amphetamine/dextroamphetamine or tamsulosin as a primary suspect drug. On applying the algorithm, the suspected drug was classified as a generic product [definite or probable] in 9%, 16.7% and 15.8% of case reports for levothyroxine, amphetamine/dextroamphetamine and tamsulosin, respectively. Overall 37% of the reports did not have sufficient information to be classified. Unweighted kappa statistic was 0.96, 0.79 and 0.86 for levothyroxine, amphetamine/ dextroamphetamine and tamsulosin respectively.

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Conclusions: The algorithm developed for identifying generic drugs in the FAERS database had strong inter-rater reliability when complete data were available. However, the data in FAERS is often insufficient to classify the suspected drug for a large proportion of reports. Efforts at increasing the completeness of reporting will help in identification of ADRs associated with generic drugs.

697. The Landscape of Active Surveillance Systems for Postmarketing Drug Safety Monitoring

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Background: Postmarketing surveillance is important for identifying new adverse drug events (ADE) that are potentially unidentified in premarketing studies. Spontaneous reporting systems (SRS) have been routinely used as an important source for postmarketing ADE monitoring. However, limitations like reporting bias & lack of denominator data are common in SRS. Active surveillance (AS) systems have been developed worldwide to supplement SRS by monitoring the safety of drugs in population-based healthcare databases.

Objectives: This review presents the landscape of AS systems & the methods used in AS systems for postmarketing monitoring of ADE using healthcare databases.

Methods: An assessment of the current AS systems was performed through literature search & online review. The characteristics of AS systems & the methodologies commonly applied in signal detection are described.

Results: We report the characteristics of 7 AS systems. In the US, the FDA Mini-Sentinel Initiative & the Observational Medical Outcomes Partnership (OMOP) were initially formed. These were transitioned to the FDA Sentinel Initiative & the Innovation in Medical Evidence Development and Surveillance (IMEDS), respectively. This was followed by the Observational Health Data Sciences & Informatics (OHDSI) project. In Europe, the Exploring & Understanding Adverse Drug Reactions (EU-ADR) & the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) programs were established. In Canada, the Canadian Network for Observational Drug Effect Studies (CNODES) was formed; & the Asian Pharmacoepidemiology Network (AsPEN) was formed as a cross-country network. Differences in scope (targeted vs. untargeted events), design (cohort vs. self-controlled), & methodology (propensity score adjustment, comparison groups, & visualization of results) were observed across systems.

Conclusions: Many approaches are in use worldwide for AS, with no consensus on analytic methods. Further development of various designs will continue to improve the capacity for early safety evidence gathering & AS, including optimization of designs based on high-dimensional propensity score algorithm & self-controlled cohorts.

698. Web-Based Query Log Reaction Score Methods to Detect Safety Signals for Pharmaceutical Drugs

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Background: Rare drug adverse events (AEs) which may develop after long-term exposure to a drug may be missed in spontaneous adverse reporting databases. It has been proposed by the FDA, that web-based data could be mined as a resource to detect latent signals associated with adverse drug reactions. A query log reaction score (QLRS) was developed to detect if AEs associated with certain drugs could be found from search engine query data.

Objectives: To test if other signal detection algorithms (SDAs) for internet search engine query data would find similar adverse event signals compared to traditional disproportionality testing in the FDA Adverse Event Reporting system (FAERS) database.

Methods: We extracted all English language queries submitted to the Microsoft Bing search engine by users in the U.S. for the period from 3/1/2013 to 9/31/2013 and identified drug-health event pairs for 10 common prescription medications. Adverse events for the same drugs were identified in FAERS (January 1/1/1969 to 9/31/2013). Two algorithms' (PQR, PQRR) and the QLRS's performance in web query

data was compared to traditional SDAs used in disproportionality analysis, EGBM and PPR, applied to the FAERS. Various refinements to the query based SDAs were tested to see if they enhanced performance.

Results: 898 drug-event pairs found in the overlapping time periods for FAERS and the search query log database were used for comparison. The PQRR metric had the lowest false positive rate (32.23%) and the QLRS had the highest false positive rate (51.28%) compared with the traditional PRR gold standard. The PQRR test also had the highest AUC score for an individual metric (AUC=0.65) when compared to the gold standard SDA of EBGM ≥4, and the composite model of all the metrics had the strongest agreement with EBGM≥4 overall (AUC= 0.82).

Conclusions: The web query SDAs were as sensitive to detecting the signals as the gold standard SDA, however, the web query SDAs generate more signals than were found with the traditional SDAs in the FAERS database. Future research is needed to find better refinements of query data and SDAs to reduce the false positive rate of these algorithms.

699. Can Facebook and Twitter Monitoring Yield Earlier Detection of Safety Signals for Medical Products?

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Background: The rapid expansion of the Internet and computing power in recent years has opened up the possibility of using social media for pharmacovigilance. While this general concept has been proposed by many, central questions remain as to whether social media can provide earlier warnings for rare and serious events than traditional signal detection from spontaneous report data.

Objectives: To determine if analysis of social media data mined from public Facebook and Twitter posts could lead to earlier detection of rare and serious adverse events.

Methods: A retrospective analysis of public Facebook and Twitter data was conducted for 10 recent FDA MedWatch post-marketing safety signals, at the drug-event pair level, with 6 negative controls. Social media data corresponding to two years prior to signal detection of each product-event pair were compiled. Automated classifiers were used to identify each Post with Resemblance to an Adverse Event (Proto-AE), among English language posts. A custom dictionary was used to translate Internet vernacular into MedDRA preferred terms. Manual review by drug safety physicians was conducted to determine causality using WHO-UMC assessment criteria. Comparison with cases reported in FAERS was also undertaken.

Results: A total of 935,246 posts were harvested from Facebook and Twitter, from March 2009 through October 2014. The automated classifier identified 98,252 Proto-AEs (15%). Of these, 13 posts were selected for causality assessment of product-event pairs. Clinical assessment revealed that posts had sufficient information to warrant further investigation for two possible product-event associations, dronedarone-vasculitis and skin burns from Banana Boat Sunscreen. No product-event associations were found among the negative controls. In both positive cases, Internet posts occurred prior to signal detection from FAERS.

Conclusions: An efficient semi-automated approach to social media monitoring may provide earlier insights into certain adverse events. More work is needed to elaborate additional uses for social media data in pharmacovigilance and to determine how they can be applied by regulatory agencies.

700. Risk Management and Specialist Cohort-Event Monitoring – Responding to Change

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Background: It is recognised that there is a paucity of data sources to conduct studies in the EU on hospitalised patients (pts) and those seeing specialists.SCEM is a method which has been used to meet the requirements of Post-Authorisation Safety Studies

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(PASS) to address this need for systematic large scale safety surveillance of new medicines mostly initiated by hospital specialists in a hospital or other secondary care settings (e.g. outpatient clinics). To date, four SCEM studies have been included with Risk Management Plans (RMP) of recently marketed drugs.

Objectives: To discuss design considerations of SCEM.

Methods: A description of design of SCEM, incl. pt identification, specialist research frameworks, study size, data collection and study duration.

Results: SCEM assembles new user cohorts on the basis of a common exposure (study drug). The sampling frame comprises all secondary care settings likely to use the study drug in clinical practice. Specialists register within a research network established with collaborative support from the UK NIHR Clinical Research Network.Pt inclusion criteria are minimal and eligible pts are those for whom the clinical decision to treat has been made by a specialist, prior to pt consent. NHS ethics approval is required. The desired pt sample size is powered to examine primary safety issues identified in the RMP, and study duration planned to maximise cohort accrual. Longitudinal data collection (min 3 mths per pt) is supported via specialist completed questionnaires (secondary use pt medical charts). Inclusion of a comparator cohort is possible, dependent on the availability of an ideal counterfactual treatment.

Conclusions: Since the adoption of a new medicine into clinical practice in the UK is often initially facilitated by specialists, there is a need for data capture across all clinical settings to ensure that exposed populations are characterised and monitored. SCEM studies attempt to overcome some limitations of PASS (such as potential selection bias and under-reporting) conducted exclusively in the primary care setting, or using primary care based data sources with partial information on pts health experience since specialist initiation.

701. Knowledge and Attitude Towards Adverse Drug Reactions Among Healthcare Professionals

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Background: Healthcare professionals are the primary reporter of the adverse drug reaction (ADR). Knowledge and attitudes towards ADR has great impacts on ADR reporting.

Objectives: To investigate the knowledge and attitudes towards ADR among healthcare professionals in a single tertiary hospital.

Methods: A cross-sectional survey was carried out by using a self-administered questionnaire. A total of 514 healthcare professionals completed the survey. We compared the results between skilled professionals who have been working at hospital and beginner professionals who are attending an orientation program for new employees just after university.

Results: A total of 359 were skilled professionals (doctors 15.6% and nurses 84.4%), the mean professional experience was 8.8 years. One hundred and fifty five were beginners (doctors 18.1% and nurses 81.9%). The rate of respondents who know pharmacovigilance and ADR reporting system was significantly lower in beginner professionals than skilled professionals (41.3% vs 78.9%, $P<0.001$). However, majority of them in each group agreed that ADR reporting is necessary and their own obligation. Reporting of which cases of ADR is different between two groups; ADR of new drugs, rare ADR, and new ADR to existing drugs is more common in skilled professionals, while previously known ADR is more common in beginner professionals. Concern that the report may be wrong is the most common cause of hesitate to report ADR, much more beginner professionals worried about ADR reporting causes disadvantage to themselves (45.5% vs 2.2%).

Conclusions: Healthcare professionals have knowledge and attitude towards ADR with great difference. Regular training and education may improve the ADR reporting.

702. Implementation of Pharmacovigilance Practices by Clinical Pharmacists in an Oncology Hospital--A Step to Improve Patient Safety Monitoring During Cancer Care

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Background: Adverse drug reactions (ADRs) are highly predicted and expected following to the use of anti-cancer drugs. Early detection and management of these reactions is essential to avoid treatment delay and additional health care expenditure. The role of clinical pharmacists in detecting and monitoring ADRs to anti-cancer drugs was explored.

Objectives: This study was conducted to detect and monitor ADRs through spontaneous reporting and intensive monitoring system in patients receiving anti-cancer drugs.

Methods: Clinical pharmacists prospectively followed the patients admitted to different wards and ambulatory care unit of an oncology hospital for the period of two years. Medical records of the patients were reviewed and patients and their care givers were interviewed to identify ADR(s). Identified ADRs were discussed with concerned oncologists and nurses, documented electronically and assessed further.

Results: A total of 960 ADRs were reported in 784 patients from 844 patients followed during two years of period. Vomiting (25%), blood and bone marrow toxicities (19.5%), alopecia (7%), diarrhoea (6.14%), myalgia (4.82%) and peripheral neuropathies (4.82%) were common ADRs reported. Anaphylaxis (3.5%), hyperpigmentation (3.2%) opportunistic infections (2.63%), muscle cramps (2.4%), hands foot syndrome (1.7%) were found less commonly. Cisplatin (27%), Paclitaxel (14.9%), Cyclophosphamide (7%) and Doxorubicin (4.82%) were drugs found to be commonly associated with ADRs. Clinical Pharmacists' assessment attributed ADRs to Inappropriate frequency and regimen of anti-emetics (22%), poor or lack of supportive care (18%), administration errors (16%), poor patient education system (14%), use of specific brand products of certain drugs (10%) and inappropriate dosing (5%).

Conclusions: There is a need to implement quality drug distribution system and patient monitoring & education policies in order to avoid many preventable ADRs to anti-cancer drugs. Role of clinical pharmacist is crucial in strengthening pharmacovigilance practices in hospital settings to improve patient safety.

703. Assessing Studies of Patients Spontaneously Reported Adverse Drug Reactions (ADR's): A Review Study

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Background: Adverse drug reactions (ADRs) are an important health issue with significant impact on patient safety. Most ADRs are submitted by health professionals (HCP) however there is increasing interest in patient reporting of ADRs. Reports submitted by patients is considered limited majorly due to lack of knowledge on the reporting process.

Objectives: To review spontaneous reporting of ADRs by patients with a focus on the methods used for reporting.

Methods: MEDLINE and EMBASE databases were searched for studies in English published any year. Main keywords used were patient self-reporting, ADR, spontaneous reporting, patient safety, and patient ADR reporting. Studies that evaluated ADRs reported by HCP were excluded. Two independent reviewers were responsible for assessing studies eligibility and data extraction. A third reviewer resolved any disagreement regarding.

Results: Thirteen studies were included in this review. The studies were mainly from Europe (53.8%) and the majority of patients who completed ADR reports were female (69.2%). The most commonly used method by patients for spontaneous reporting were paper based (n=6) and web-based forms (n=4). Studies investigated any ADRs had a slightly higher prevalence rate compared to reports of ADRs secondary to a specific pharmacological class or medical condition. Patient ADR reporting using pre-specified forms yielded higher response rate than general reporting forms. In addition, patients tended to take

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longer time to complete an ADR report compared with health professionals and in some cases there was considerable difference in content between health professional and patient reported ADRs.

Conclusions: Encouraging patients to report encountered ADRs can add to the patient safety profile, capturing different aspects of ADRs than that reported by health professionals. Using a specific designed questionnaire for a certain drug class or medical condition may help in increasing the number of reports submitted by patients, however patient education is needed to ensure that patients are aware of and able to complete such forms.

704. Performance of Disproportionality Analysis for Statistical Signal Detection in Social Media Data

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Background: Social media have emerged as a potentially useful complementary pharmacovigilance data source. While disproportionality analysis (DA) is the state of the art for statistical signal detection in spontaneous reporting data, its performance in social media data has not been systematically evaluated.

Objectives: To evaluate the performance of DA for statistical signal detection in social media data, and to compare that to spontaneous reporting data.

Methods: 62 time-stamped US FDA label changes (positive controls) and 75 drug-event pairs without known association (negative controls) were used as reference. About 2,025,000 posts dated between March 2012 and February 2015 (23% Facebook; 77% Twitter) on the 44 drugs from the reference set were combined with 3,710,000 background posts on other drugs. A trained classifier algorithm identified posts suggestive of adverse events, at varying classification thresholds. For each threshold, monthly retrospective DA was performed, using IC_{025} (the lower IC 95% credibility limit) and three standard PRR variations. An analogous analysis was performed in VigiBase®. Receiver operating characteristics (ROC) with respect to the reference set were computed as of December 2012, when all positive controls were yet unlabelled. Also, the retrospective time points at which the positive controls were statistically highlighted were computed and compared to the time-stamped label changes.

Results: For the social media data, the maximum area under the ROC curve (AUC) was 0.56. For VigiBase, AUC ranged between 0.70 and 0.75. Using the recommended classification threshold, five positive controls were present in the social media data, one of which was statistically detected prior to its label change. Using IC_{025} on VigiBase, 25 positive controls were detected pre-labelling.

Conclusions: Disproportionality analysis on Facebook and Twitter data performed considerably worse than on global spontaneous reporting data, when benchmarked against historical label changes. This is likely due to limited prevalence or retrieval of the labelled events from social media, rather than the disproportionality methods themselves.

705. Assessment of Reported Medication Errors in General Medicine Wards in a Tertiary Care Hospital

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Background: Iatrogenesis is an injury or illness that occurs because of medical care, which is an inevitable reality in health care system. Medication errors (ME) are the part of iatrogenic incidents that jeopardizes patient safety and IOM reported 98,000 annual deaths costing $2 billion. However, in the developing countries frequency, etiologies, and outcomes of MEs evaluated rarely. It is important to understand how often and why these errors are occurring to develop interventions and to prevent their occurrence.

Objectives: To determine the etiologies, patterns, and outcomes of MEs in general medicine wards.

Methods: A prospective cohort study was conducted among patients aged ≥ 18 years hospitalized on a general medicine ward from October 1, 2014 - March 31, 2015 in a south Indian hospital. On a daily basis, patients, patient's care givers, and health care professionals (HCPs) were interviewed regarding the

medication usage process and patients' notes were reviewed for identifying and evaluating outcomes of ME using the National Coordinating Council for Medication Error Reporting and Prevention standards. Root cause analysis was performed to understand the reasons and discussed with the relevant HCP to minimise the likelihood of recurrence of the ME.

Results: A total of 256 medication errors were reported among 4787 patients hospitalized on the general medicine ward. The common aetiologies of these MEs were administration errors (27.7%), and procurement errors (26.9%). Root cause analyses determined that these MEs were due to excessive work-load (28.1%), incoherent communications (25.4%), and patient -related factors, i.e. delayed procuring and procuring fewer quantities of medicines than prescribed quantities. Majority of reported medication errors had an outcome of Category A (54.2%).

Conclusions: The incidence of MEs at study site was 5.3%. Reasons included excessive work load and incoherent communications. MEs did not result in adverse outcomes. Providing continuous education on MEs to HCPs and patients will improve in minimising the scope of the inevitable factors contributing towards the medication misadventures and improves the patient safety.

706. Barriers and Facilitators to Using a Mobile App for Two-Way Risk Communication: A Qualitative Study

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Background: A mobile app may improve two-way risk communication (i.e. reporting adverse drug reactions and communicating safety information). Barriers and facilitators of using such an app need to be considered at the development stage.

Objectives: To determine the barriers and facilitators of healthcare professionals (HCPs) and patients of using an app on two-way risk communication.

Methods: A qualitative study using focus groups and face-to-face (F2F) interviews was conducted in the Netherlands, Spain and the UK. Patients with type 2 diabetes, a rare disease or their caregivers, and adolescents were included. Pharmacists, professionals caring for patients with a rare disease, paediatricians, general practitioners, internists and practice nurses were included as HCPs. Participants were asked about the barriers and facilitators to using an app on two-way risk communication. The study was conducted until theoretical saturation was reached at an overall level. The video- or audio-recorded data were transcribed verbatim, analysed using thematic analysis and arranged according to the themes in the Unified Theory of Acceptance and Use of Technology (i.e. performance expectancy, effort expectancy, social influence and facilitating conditions).

Results: Seven focus groups and 13 F2F interviews were conducted in which a total 21 HCPs and 50 patients participated. The identified factors related to performance expectancy were the interaction between a patient and the regulatory authorities; between a patient and a HCP; and app functionality. In relation to effort expectancy, the security, ease of use and language in the app were identified as influencing factors. Potential factors related to social influence were the source of drug information in the app and the possibility for comparison. Layout, operating system and costs were identified as factors related to facilitating conditions.

Conclusions: This study identified barriers and facilitators that may influence the use of an app on two-way risk communication. These exploratory influencing factors are of interest to regulatory agencies, app researchers and developers and can be systematically assessed in future quantitative studies.

707. Improving the Yield of Relevant Data for Pharmacovigilance Analysis by Reducing Search Term Complexity – A Study on Reddit Data

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Background: Retrieving data from social media for pharmacovigilance analysis involves matching its content with a list of pharmaceutical products containing the substances of interest in a first step. However, some products have ambiguous meaning (e.g. the product 'today') which should not be used since it would result in huge amounts of non-relevant posts.

Objectives: To develop and evaluate a method capable of identifying a list of products to be used as search terms for the purpose of retrieving data from social media so that the amount of non-relevant posts is minimized.

Methods: WHODrug™ was used to create a lookup dictionary for levetiracetam, methylphenidate, terbinafine, zolpidem and insulin glargine. Our previously developed medication name entity recognition algorithm for social media was applied to predict the likelihood that a product name would refer to an actual medication in a social media post. This allowed us to predict the total number of useful posts for product names when used as search terms for social media post retrieval. A gold standard annotation of medication names present in Reddit posts was produced by two expert pharmacists and used for evaluation.

Results: Of 7.3M total posts, 7,151 mentions of 85 product names for the five substances were identified. 28 names had a predicted probability above 0.5 and was therefore selected as search terms. The effect of this reduction was evaluated on the gold standard annotated data set containing 1.069 dictionary lookup matches. The proportion of relevant posts increased: from 7% to 98% for levetiracetam; 90% to 100% for methylphenidate; 3% to 100% for terbinafine; 6% to 92% for zolpidem; and no change for insulin glargine, 100%. Overall, the proportion of relevant hits increased from 21.4% to 98.6%, at the cost of losing only 0.9% of relevant mentions of medications.

Conclusions: It is possible to substantially increase the yield of relevant posts by carefully selecting a reduced list of medication names used as search terms when retrieving social media data with only a small loss of relevant posts.

708. What are Patients Asking Social Media About Drug Products and Treatments?

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Background: Social media is increasing in popularity and use as a communication tool. Much research is ongoing and still needed to define the potential contribution of social media within the broader context of pharmacovigilance.

Objectives: To describe the types of drug product-related questions patients are asking in social media.

Methods: Publicly available social media posts naming 16 GSK drug products on social media sites were collected by a third party vendor and de-identified. Posts were then manually reviewed by healthcare professionals. The information-seeking posts were further classified by types of information sought.

Results: Of a total of 27,521 posts reviewed, 1,725 (6%) were information-seeking (where the author was asking a direct question of the social media audience). Of these, 915 (53%) were seeking treatment recommendations, including novel or additive treatment options, experience of other users with a product, or treatment regimens of other users; 421 (24%) were safety-related questions, including experiences of other users with particular side effects, dosing questions, drug interactions, and storage concerns; 171 (10%) of posts queried product properties such as availability, indication, cost, mechanism of action, ingredients/identification, and product/formulation complaints; 69 (4%) sought more information about either an established diagnosis or what a possible diagnosis might be; and 34 (2%) sought advice about drug product use in pregnancy. There were 19 posts (1%) seeking opportunity for drug diversion such as borrowing, buying, or selling, and the remaining 96 (6%) were seeking advice unrelated to medical treatment.

Conclusions: Over half of the patients who asked a drug product related question were seeking advice about which products to use and another 24% were asking directly safety-related questions. Social media listening may be a way of understanding from a first-

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hand perspective what product-related questions patients or their caregivers may have, including questions relevant for drug safety. More research is needed to fully understand the capability of this tool and ways that it may complement existing pharmacovigilance practices.

709. Web-Based Signal Detection Using Medical Forums Data in France from 2005-2015

Marie-Laure Kürzinger[1], Nathalie Texier[2], Stéphane Schuck[2], Carole Faviez[2], Thierry Deliens[3], Ling Zhang[4], Stéphanie Tcherny-Lessenot[1], Juhaeri Juhaeri[4] and Susan Welsh[4]

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Background: While traditional signal detection methods in pharmacovigilance are based on individual case safety reports, the use of web-based data (such as social media) is emerging among regulators, industry and academia. The strength of web-based data relies on their real time availability allowing early signal detection.

Objectives: This study aims at assessing the ability of identifying early signals from web-based patient's medical forums in France on 3 products over the last 10 years. Signals detected from this web-based source will be compared with those from standard data sources (adverse events reporting system and labels) using traditional signal detection methods.

Methods: This is a retrospective study. The data sources are patient's medical forums in France, the WHO adverse events reporting system (VigiBase®) and the labels of the selected drugs. Data will be extracted from the Detec't database, composed of messages posted on patient's forums between 2005 and 2015. All drug-event pairs from the selected forums will be included. Several metrics will be used to define signal of disproportional reporting (PRR, ROR, EBGM, IC, RFET). Comparison of signals detected from the forums to signals detected in VigiBase® and adverse events from the labels will be done by describing the sensitivity, specificity, positive predictive value, negative predictive value and ROC curves. For expected signals, time difference in months between the detection date of signals from the patient's forums and date of signals from Vigibase will be done.

Results: The number of posts from the patient's forums containing teriflunomide, insuline glargine, zolpidem and with the mention of intake were respectively: 102, 3326, 4579. The comparison analysis is still ongoing.

Conclusions: At this stage of the project, we cannot conclude on the ability to identify early signals from the patient's medical forums as the analysis is still ongoing (analysis will be terminated end of March).

710. Medication Name Entity Recognition in Tweets Using Global Dictionary Lookup and Word Sense Disambiguation

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Background: Analyzing social media postings such as Twitter for pharmacovigilance purposes requires the identification of key components of information in a first step. Medication Name Entity Recognition (NER) invariably relies on matching the text with a dictionary of medication names. However, a number of names have ambiguous meanings which necessitates the use of disambiguation before the final annotation is done.

Objectives: The objective of this study was to develop and evaluate a Named Entity Recognition algorithm for medications in Tweets.

Methods: A convenience sample of around 70,000 Tweets were included. They were previously gold standard classified with regard to medication names by coding experts. Evaluation was performed on Tweets containing 16,268 verbatim matches of medication names. A dictionary with medication names was created from WHODrug™. A component for word sense disambiguation was developed based on a logistic regression model using the following features: Number of reports containing the medication name in the WHO international database of suspected adverse drug reactions, VigiBase®; Whether the annotated term is a substance or product name; and Word Frequency of the annotated term in ordinary Tweets.

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Results: By combining a drug dictionary with global scope for dictionary lookup with a method for word sense disambiguation, it was possible to correctly detect 81% (13,154/14,773) of mentioned medicines while maintaining an acceptable precision equal to 0.85. Without disambiguation, 83% (13,477/14,773) of all names could have been detected but the precision would then be as low as 0.41.

Conclusions: Effective identification of medication names in Twitter with a global dictionary requires sophisticated disambiguation to maintain acceptable precision.

711. Impact of the 2012 European Pharmacovigilance Legislation on Required Additional Risk Minimisation Measures

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Background: Additional risk minimisation measures (aRMM) can be requested to improve the benefit-risk balance of a medicinal product. Previous research has shown an increase over time in the proportion of centrally authorised products (CAPs) in Europe with aRMM up to 2010.

Objectives: To determine the impact of the new pharmacovigilance legislation (implemented July 2012) on the proportion of new medicinal products for which aRMM are requested.

Methods: In this cross-sectional study, the European Public Assessment Reports (EPAR) of all new chemical entities licensed through the centralised procedure approved between January 1st 2010 and December 31st 2015 that were still authorised as of January 1st 2016 were analysed. Information extracted from Annex II of the EPARs encompassed the active substance, Anatomical Therapeutic Chemical classification (ATC), authorisation date, aRMM (categorised as educational material for the healthcare professional (HCP), for the patient or other measures). A $\chi 2$-test was performed to test the difference between the study period prior to implementation of the new legislation and after.

Results: aRMM were in place for 72 of the 232 (31%) new CAPs authorised during the study period. The proportion of products with aRMM authorised before the new legislation was 39% as compared to 27% after the new pharmacovigilance legislation (p=0.03). During the study period, aRMM were most often assigned to products in ATC group Antineoplastic and immunomodulating agents (28%) and Blood products (13%). No analysis was performed to test for difference before and after implementation of the new legislation due to low numbers. The provision of educational material to HCPs was requested in 90% of CAPs with aRMM and to patients in 53%. Other aRMM were identified for 6 products, all approved after implementation of the new legislation. These included 3 CAPs with pregnancy prevention programs and controlled access or distribution schemes for 4 products.

Conclusions: There has been a significant decrease in the proportion of CAPs for which aRMM are requested after the implementation of the new pharmacovigilance legislation.

712. An Analysis of Characteristics of Post-Authorisation Safety Studies Registered on ENCePP

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Background: European legislation issued in 2010 obliges all Post-Authorisation Safety Studies (PASS) that are imposed as a condition of granting marketing authorisation to be published in a publicly available register. In Europe, the main register for PASS studies is that held by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

Objectives: This study aims to investigate the characteristics of European Medicine Agency (EMA) imposed PASS registered on ENCePP.

Methods: The electronic register of studies was searched on 16th March 2016 for all observational studies requested by the EMA. Data on study status (finalised, ongoing or planned), study timelines, medical condition to be studied, source of data, study scope and presence of ENCePP seal (given to studies following ENCePP's principles of standards, transparency and independence) were collected.

Results: Data from 213 PASS studies were analysed (45 were listed finalised, 110 ongoing, and 58 planned).

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12 (5.6%) studies had an ENCePP study seal. 65.7% of studies included safety in their scope, 43.6% drug utilisation, and 26.3% of studies effectiveness.

79 (37.1%) studies used established data sources. The most frequent established data sources used were the United Kingdom's (UK) Clinical Practice Research Datalink (CPRD, 32.9%); National Registries from the Nordic countries (29.1%), the Health Improvement Network (THIN, (also from the UK), 13.9%) and the PHARMO database network from the Netherlands (12.6%).

For studies not using established data sources, the majority (62.7%) used prospective data collection methods.

The proportion of finalised studies using an established data source was much higher than planned (62.2% vs 24.1%). No PASS in the area of oncology used an established data source, instead usingprospective data collection.

Conclusions: The results show the reliance on a few key data sources in Europe and the need for data collection where necessary data are lacking.

713. Studies Evaluating Effectiveness of Risk Minimisation Measures

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Background: Monitoring the effectiveness of risk minimisation measures is mandatory since the European pharmacovigilance legislation that was implemented in 2012. There is currently limited knowledge on which studies are proposed in new medicinal products that have additional risk minimisation measures (aRMM) at the time of approval in the EU.

Objectives: To describe the studies proposed to assess the effectiveness of aRMM for new medicinal products authorised in the European Union.

Methods: The European Public Assessment Report (EPAR) published at time of initial marketing authorisation of all new medicinal products authorised through the centralised procedure between July 1st 2012 and December 31st 2015 were reviewed. The risk management plan (RMP) section published in the EPAR was used to identify products with aRMM and to obtain information on planned post-marketing studies for those products with aRMM Information on study objectives was then reviewed to identify those studies evaluating effectiveness of aRMM. Data on study type, study category (imposed/non-imposed) and time to submit study results were collected.

Results: Of the new medicinal products licensed during the study period, 26% (44/170) had aRMM at the time of approval. In the majority (86%, 38/44 products) post-marketing studies were included in the RMP. For 18 products with aRMM (41%, 18/44) the studies clearly aimed to evaluate the effectiveness of the aRMM. This percentage was stable over the study period. Of the in total 19 studies, 7 were described as post-authorisation safety study or non-interventional study, 5 as drug utilisation study, 2 as registry study, 1 survey for healthcare professional, 1 survey for patients, 1 chart review and 2 as unknown. Two of the 19 studies were imposed studies. Final study reports were planned to be completed between 1,5 and 11 years after marketing authorisation, with a median of 3.5 years. For 7 products this was unknown.

Conclusions: Although measuring the effectiveness of aRMM is mandatory, at time of initial marketing authorisation less than half of the products with aRMM has planned studies in the RMP with clear objectives to assess their effectiveness.

714. Development of Patient Reporting Systems - A Worldwide View

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Background: Voluntary adverse drug reactions (ADR) reporting is one of the most versatile and useful pharmacovigilance methods. Recently, the introduction of voluntary reporting systems specially designed for patients have improved the spontaneous reporting for general public, however, patient reporting systems (PRS) continue to have different levels of development worldwide.

Objectives: To describe the level of development of PRS worldwide.

Methods: A descriptive-correlational study was conducted during November and December of 2015 looking for the characteristics of the PRS worldwide.

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A web-based questionnaire was constructed based on qualitative interviews, and distributed through SurveyMonkey® platform to all countries listed on WHO Programme for international drug monitoring (n=178). Data were analyzed using descriptive statistics and chi-square ($\chi 2$) test.

Results: A total of 141 countries (79,2%) answered the survey. From 194 answers received, 143 were selected for analysis. A general reporting system used by both healthcare professionals and patients is present in 41,1% (n=58) countries. Official PRS to report ADR directly is implemented in 31,2% (n=44) countries. Patients are not allowed to report in 34 countries (24,1%). The reasons for not have an official PRS are mainly due to lack of resources/budget (56,5%) or lack of information/education for patients (56,5%). Reports are collected mainly through paper reporting form (84,3%), electronic reporting form (53,7%) email (63,9%) or telephone (63,9%). ADR's are collected on prescribed medicines (92,6%), over-the-counter medication (80,6%), vaccines (74,1%) and medication errors (66,7%). Patient reports are used in signal detection (64,5%) and insight and knowledge about the impact of the ADR on daily life (52,3%).

Conclusions: There is a wide range of maturity of the reporting systems. Most of the countries accept ADR reports from patients by an official reporting system designed for patients or through the existing system for healthcare professionals. Patient reports are useful in signal detection and to gain insight and knowledge about the impact of ADR on daily life, however, some countries don't use them actively.

715. Assessment of Impact of Structured Educational Intervention on Adverse Drug Reaction Reporting Behaviour of Community Pharmacists in South India

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Background: Community pharmacists are in better position to detect, monitor and report adverse drug reaction (ADRs) due to direct access to the patients. Lack of awareness and motivation are the prime reasons for under reporting of ADRs by the community pharmacists in developing countries.

Objectives: To assess the impact of structured educational intervention on ADR reporting behaviour of the community pharmacists in selected practice settings of south India.

Methods: A cross sectional study was conducted after educational program to assess impact of intervention on knowledge, attitude and practice of community pharmacists towards ADR reporting. A series of training programs were conducted to improve the awareness and to provide education to community pharmacists on ADR detection and reporting. Training program included basic concepts of ADRs, importance and application of ADR reporting, safety reporting methods, ADR reporting and documentation process as per national requirements, management of common ADRs, possible barriers in reporting. The impact of educational intervention was measured by reviewing number and quality of ADRs reported. Quality of ADR was assessed using prepared checklist. Barrier Assessment Questionnaire (BAQ) was administered to assess the barriers if any in ADR reporting.

Results: About 68 community pharmacists with mean age of 39.69 ± 8.65 years, with a practicing experience of 15± 2.5 years had participated in this study. During the 6 month regular follow–up, 82 ADR reports received from 23 (28%) trained pharmacists. Quality of ADRs were satisfactorily only for 68% of reports. However, remaining reports were not of satisfactory quality. Major barriers identified for under reporting were lack of time (83%), forgetfulness (68%), and shortage of time from patients (46%).

Conclusions: The study findings suggest that educational intervention improved the ADR reporting culture among community pharmacists. However, quality of reported cases should be routinely reviewed to further strengthen reporting culture.

716. Development and Validity Testing of a Clinical Documentation-Tool to Assess Individual Case Safety Reports in an International Setting

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Background: A good clinical documentation of Individual Case Safety Reports (ICSRs) is important for

signal detection. To our knowledge, there is no tool available to express the clinical documentation of an ICSR.

Objectives: To develop and test a Clinical Documentation-tool (ClinDoc) to assess the clinical documentation of ICSRs in pharmacovigilance in an international setting as part of the WEB-RADR project.

Methods: Development of ClinDoc by an expert panel with 4 pharmacovigilance experts. Face validity testing by 8 assessors from 4 countries (Croatia, Sweden, UK and the Netherlands), followed by validity and reliability testing by the same assessors in 2 rounds with 14 ICSRs selected which covers the whole spectrum of clinical documentation by the expert panel.

Agreement between each country and expert panel (validity) and 2 assessors in 1 country (reliability) was calculated using Cohen's kappa coefficient.

Results: We developed a clinical Documentation-tool for ICSRs, ClinDoc. This tool gives insight in the clinical documentation by scoring four domains that are important regarding clinical documentation namely information about: adverse drug reaction, chronology, drug and patient characteristics. Each domain contains multiple subdomains. The assessor indicates which items are relevant for the specific ICSR, after which he indicates if this information is present or not in the report. The score given to each domain is the proportion of information present in relation to the information deemed relevant. The final score consists of the average of the percentages scored per domain with the following cut offs: poor (≤45%), moderate (from 46- 74%) and well (≥75%).

Validity testing showed an overall 'substantial' agreement (k range 0.49 - 0.76, mean 0.55 SD 0.10) and reliability testing a 'moderate' agreement (k range 0.35 - 0.69, mean 0.63 SD 0.10).

Conclusions: ClinDoc is the first tool that provides a measurement of the clinical documentation of an ICSR. Per item it can be decided if this is relevant to assess the clinical documentation of a specific report. Testing shows that the tool can be used in an international setting.

717. Evaluation of a Newly Developed Intelligent Drug Alert System for Enforcing Medication Safety

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Background: The design and development of an intelligent drug alert system for enforcing medication safety brings to focus the major role of artificial intelligence in health care to intercept medication errors before they happen. Medication safety is one of the fundamental areas of patient safety as medication errors are the most common single preventable cause of adverse events in patient management.

Objectives: To evaluate a newly developed intelligent drug alert system for enforcing medication safety.

Methods: A newly designed intelligent drug alert system was evaluated using previously generated e-Prescriptions over a three year period from the database of the hospital information system of a tertiary healthcare institution in South-South Nigeria for Prescription error detection with special focus on some target dangerous Drug-Drug Interactions (DDIs).

Results: Medication safety audit of 9859 e-prescriptions against a limited pharmacological knowledge base yielded 1343 (13.6%) prescriptions with errors which in turn generated a total of 2753 drug alerts. While there was a decline in the number of e-Prescriptions with errors from 18.3%, 14.6% to 7.5% over the three year period, the change in Prescription /Alert Ratio from 47.8%, 52.6% to 47.3% in the prescriptions with errors over the same period were not statistically significant.

Conclusions: This study suggests that an e-based decision support system appears feasible as a method to enhance patient safety and outcomes in drug therapy. Drug drug interactions and other forms of medication errors can result in harmful outcomes thus alert messages in the designed clinical software may help clinicians decide on the safe use of medicines for their patients.

718. The Documentation of Clinical Information of Adverse Drug Reaction Reports: A Paired Comparison of 'Duplicate' Reports of Patients and Healthcare Professionals

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Background: The value of patients reporting adverse drug reactions (ADRs) to pharmacovigilance centres has been widely acknowledged in recent years. However, little is known about differences in documenting clinical information, for example the description of the ADR and the course of the reaction, between reports of patients and healthcare professionals (HCPs).

Objectives: To determine the differences in documenting clinical information between paired ADR reports of patients and HCPs.

Methods: All ADRs that were reported in duplicate, i.e. a report on the same case by the patient and the patient's HCP, so called 'paired reports', were selected from the database of the Dutch pharmacovigilance centre Lareb until October 1st, 2015. The ClinDoc-tool, a validated measure, was used to assess the grade of clinical documentation. ClinDoc includes the following domains: 'ADR'; (description of the ADR and additional information), 'chronology', 'drug' and 'patient characteristics' (physical factors, risk factors). Each domain had several subdomains. The score given to each domain was defined as the proportion of information present in relation to the information deemed relevant. An overall clinical documentation score was calculated based on the average score of each domain.

All included ADR reports were scored independently by two assessors. In case of discrepancies, consensus was reached after discussion. Data were analysed using a paired sample t-test and Wilcoxon rank tests, statistical significance based on $p<0.05$.

Results: This study included 197 paired ADR reports. HCP scored statistically significant better for the domain patient characteristics (HCP 66% vs patients 57%, p=0.003) and the overall score (HCP 78% vs patients 75%, p=0.039). Similar scores were found for the domains ADR (HCP 80% vs patients 79%, p=0.57), drug (HCP 77% vs patients 46%, p=0.10) and chronology (HCPs 89% versus patients 89%, p=0.8).

Conclusions: This unique study of cases reported by HCPs and patients showed that clinical information is well documented, but HCPs achieve higher scores than patients.

719. National Prevalence and Trends in Drug Allergies Among Admissions in the Veterans Affairs Health System from 2000-2014

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Background: Drug allergies are a common obstacle in patient care which often necessitate use of less effective and/or more toxic alternatives. An allergy history is commonly completed for VA healthcare inpatient admissions. Understanding commonly documented drug allergies can help inform subsequent research.

Objectives: Our primary objective was to determine the most common documented drug allergies among VA inpatients and how these have changed over time.

Methods: This study is a retrospective cohort of all inpatients in the VA health system from 2000-2014 extracted from the VA Corporate Data Warehouse. Allergy histories documented prior to or on admission were linked with inpatient records. All drug allergies documented, regardless of reaction type or severity, were aggregated and reported as percent of admissions in a given year (i.e. sample may contain non-allergic adverse drug reactions). To understand secular trends among commonly allergies, drug treatment-related diagnoses were identified from ICD-9 codes present during admission.

Results: We included 2,948,548 patients with 10,858,433 admissions in 127 VA facilities across 48 states, D.C. and Puerto Rico. Overall patients were 95% male, with a mean age of 63 ± 14 years. The most common documented allergies on admission were penicillin (11.7%, n=1,265,799), lisinopril (4.5%, n=493,079), simvastatin (2.8%, n=302,553), codeine (4.5%, n=487,064) and sulfonamide or "sulfa" (3.9%, n=428,640). Patients' mean age increased over time from 62 to 64 years. Penicillin, codeine, and sulfonamide allergy prevalence remained steady over

time while lisinopril increased substantially from 0.8 to 8.6% of admissions. From 2000 to 2014, the prevalence of admissions with a diagnosis of diabetes (22 to 31%), hypertension (38 to 57%), and congestive heart failure (10 to 14%) increased.

Conclusions: From 2000 to 2014, penicillin allergies have remained steady at ~12% of admissions while lisinopril allergies increased. This increase coincides with an increasing elderly Veteran population and related diagnoses such as hypertension, diabetes, and congestive heart failure.

720. Prevalence and Predictors of Adverse Drug Reactions in Hospitalized Elderly Patients of India

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Background: Elderly are at a higher risk of developing Adverse drug reactions (ADRs) due to various reasons like Polypharmacy, Inappropriate drug prescribing, multiple co-morbid conditions, age related pharmacokinetic and pharmacodynamic changes of the drug. ADRs in older people are currently a challenging and growing public health problem.

Objectives: To determine the prevalence and strength of various predictive factors associated with ADRs.

Methods: Design: This is a prospective observational study.

Setting: 614 elderly patients (≥60 years) admitted to medicine wards of 4 private tertiary care hospitals of Warangal (India) were recruited in the study after the ethics committee approval. These patients were followed from admission to discharge.

Main outcome measures: 1) To determine the prevalence and various predictors associated with ADRs in the hospitalized elderly patients .2) To assess all the ADRs.

Statistical analysis: Bivariate and Multivariate Logistic Regression Analysis were used to determine the strength of various predictive factors associated with ADRs.

Results: At least one ADR occurred in 186 patients (30.3%) out of 614 patients recruited in the study. Multi logistic regression showed that:(i) PIMs as per Screening Tool of Older Person's prescription (STOPP) version-2 (OR= 3.465, 95% CI: 2.353-5.103, $p<0.0001$); (ii) ≥3 Diseases (OR= 1.750, 95% CI: 1.169-2.619, p-0.007); (iii) Increased duration of Hospital stay (≥6 days) (OR: 3.067, 95% CI: 2.059-4.567, $p<0.0001$) are the strongest predictors for ADRs.

Conclusions: Prevalence of ADRs in Indian elderly is alarmingly high.Preventing inappropriate medications; careful monitoring of elderly patients with multiple diseases and longer duration of hospital stays may help to reduce the prevalence rates of ADRs.

721. [NEWCOMER TRACK] A Hospital-Based Prospective Cohort for Adverse Herbal Drug Reactions

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Background: Despite the social suspicions regarding the safety of herbal drugs have been raised, a large portion of the herbal drugs used in South Korea is out of the boundary of current pharmacovigilance system.

Objectives: This study was aimed to estimate the prevalence of adverse herbal drug reactions (h-ADRs) and build up a groundwork for the surveilance system for herbal drugs.

Methods: This is a prospective cohort study based on a registry of the patients who had been prescribed herbal drugs in a Korean Medicine hospital. The authors monitored the patients by phone calls and the medical record review to check if anyone among them had ever experienced adverse events (AEs) since herbal-drug taking. We assessed the causality between a herbal drug and an AE using WHO-Uppsala Monitoring Center Causality Scale. When the relationship between them was categorized to 'possible', 'probable', or 'certain', the event was considered to be a h-ADR. WHO-Adverse Reaction Terminology (WHO-ART, version 092) and Severity Categories of Adverse Drug Reactions (Ministry of Food and Drug Safety, Republic of Korea) were used to categorize the type and severity of the h-ADRs. Odds ratio (OR) and its

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95% confidence intervals (CI) were calculated to find out any risk factors for h-ADRs.

Results: A total of 341 patients signed the informed consent form, and the authors could get the follow-up record from 235 participants. The number of people who had experienced any AEs since herbal-drug administration was 28, and we could draw 22 cases of h-ADRs from their records. The prevalence of h-ADR was 9.36%. The most frequently reported type of h-ADR was dyspepsia (20.7%), followed by nausea and diarrhea (17.2%, each). Gastrointestinal system disease (75.9%) was the most commonly referred type of system-organ class. The severity of h-ADRs was mostly mild (89.7%), and no serious h-ADR was detected. Old age (over 65 years) was a risk factor for h-ADRs (OR 4.4, CI from 1.76 to 11.0).

Conclusions: This study can be a basis for the establishment of pharmacovigilance system as well as further studies on the safety for herbal drugs.

722. Rate of Off-Label Prescriptions in Adverse Drug Reactions in Crimean Children

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Background: Adverse drug reactions (ADR) in children is important health problem, which is studied significantly worse in comparison with ADR in adult patients. There are many reasons predisposing ADR in pediatrics: specifics of pharmacokinetics, lack of drug forms for children, insufficient amount of clinical trials, etc. One of the most important factors is off-label (OL) use of drugs.

Objectives: Our goal was to characterize the pediatric cases of ADR reported to Crimean regional office of pharmacovigilance (PV) and define rate of OL prescriptions in these cases.

Methods: We analyzed records in local PV database ARCADe (Adverse reactions in Crimea Autonomy database), which contains data from "yellow cards" sent by Crimean doctors. We started from records received in 1.1.2011 and finished with ones obtained in 12.31.2014.

Results: We found 4313 records in defined period, from which 359 (8.3%) described ADR in infants and 610 (14.1%) in children from 12 months till 17 years. Therefore, rate of ADR in children was 22.5%. Incidence of ADR in males was 54.9% in infants and 55.2% in older children, while in adults it was only 33.3%. Most of ADR in infants (59%) but only 49% of ADR in older patients were registered in hospital. In both groups hospital doctors were main sources of information. The leading groups of drugs caused ADR in children were antibacterials (513 reports), NSAIDs (104) and drugs influencing on respiratory system (100). The top drugs caused ADR in each leading group were Cefotaxime (117 ADR) and Ceftriaxone (96 reports), Ibuprofene and Fenspiride (71 and 17 records). Ignoring of indications/contraindications was the most frequent type of OL use (30% of all pediatric records). Ignoring of requirements for dosing (22.8%) or regimen of use (19.5%), breach of age restrictions (17.9%) and incorrect choice of route of introduction (12.8%) was associated with ADR too. In 58.7% of ADR a few types of OL prescriptions occurred, therefore only 41.3% (400) of ADR were not associated with OL use.

Conclusions: Pediatric ADR represents about 22.5% of the reports received by Crimean PV office. Every third pediatric ADR is the case in infant. Most ADR is associated with OL prescriptions.

723. Patient Relevant Outcomes Associated with Generic Drugs in FDA's Adverse Event Reporting System

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Background: While almost 88% of prescriptions in the US are for generics, questions about their efficacy and safety persist. There has been an increasing interest in patient relevant concerns with drugs. However there is limited understanding of patient relevant concerns associated with generic drugs.

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Objectives: To determine the distribution of patient-relevant outcomes reported in FDA's Adverse Event Reporting System (FAERS) across the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) domains (global, physical, mental and social health) for three representative generic drugs (levothyroxine, amphetamine/dextroamphetamine and tamsulosin).

Methods: Adverse events (AEs) for these representative generic drugs were identified in the publically available FAERS data from 2011 to 2013 using an algorithm developed by the authors. Two authors independently assigned the reported AEs to the NIH PROMIS domains and disagreement was adjudicated by discussion. Each AE could be classified into one or more domains. Evaluation of reports that did not map into any of the above domains is ongoing using case narratives received from the FDA via the Freedom of Information Act.

Results: After screening 1237 case reports, we identified 381 AEs reported with use of generic drugs (144 for levothyroxine; 160 for amphetamine/dextroamphetamine; 77 for tamsulosin), from 148 unique case reports. Majority of AEs associated with all three drugs mapped to the physical health domain: levothyroxine (physical: 63.9%; mental: 11.1%; social: 1.4%), amphetamine/dextroamphetamine (physical: 51.9%; mental 23.8%; social: 1.3%) and tamsulosin (physical: 68.8%; mental: 10.4%; social: 1.3%) respectively. Around one-fourth of reports could not be classified because either they did not present patient relevant concerns around generics, or complete information was unavailable.

Conclusions: Majority of AEs associated with generic drugs in FAERS can be mapped to the three health domains of PROMIS framework to identify a spectrum of patient-relevant outcomes. Further investigations will allow better understanding of patient-relevant outcomes associated with other classes of generic drugs.

724. Current State of Pharmacovigilance in the Arab and Eastern Mediterranean Region: Results of a 2015 Survey

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Background: Although the urgency of strengthening pharmacovigilance programs in developing countries is increasingly being recognized, little is known about the state of pharmacovigilance in Arab and Eastern Mediterranean countries.

Objectives: This study sought to describe the current state of pharmacovigilance systems in Arab and Eastern Mediterranean countries.

Methods: A descriptive cross-sectional study between May and September 2015 was conducted. Data was gathered from two complementary sources: a standardized online questionnaire and data provided from the Uppsala Monitoring Centre (UMC). Total scores were assigned to structural, process and impact pharmacovigilance indicators and countries were compared depending on their final performance score.

Results: Responses were received from 21 countries, representing an 87.5% response rate. From a total possible score of 19 for structural indicator performance, the mean score for all 21 countries in the survey was 12.28 (SD: 5.9) and the scores ranged from 0 to 19. From a total possible score of 17 for process indicator performance, the mean score for all 21 countries in the survey was 8.7 (SD: 5.5) and the scores ranged from 0 to 17.From a total possible score of 12, the mean score for the impact indicators was 6.38 (SD: 3.9) and scores ranged from 0 to 12. From a total possible score of 48 across the three primary PV performance domains, the mean score in the 21 countries in the survey was 27.28 (SD: 14.6) with a range from 0 to 47.

Conclusions: This study is the first study to comprehensively evaluate and benchmark the current landscape of pharmacovigilance in Arab and Eastern Mediterranean countries. The findings suggest wide disparities in PV systems development in the region, underscoring the need for a multi-stakeholder effort in bolstering PV programs and the necessity to build collaboration regionally and internationally to build capacity and assist the development of PV systems still in their nascent stage.

725. Prescribing Errors Incidence in Four Hospitals in Saudi Arabia

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Background: In-hospital prescribing errors research is still in its early stages and has not been given due priority in Saudi Arabia.

Objectives: To determine the incidence of prescribing errors and assess their severity.

Methods: Design: An outcome-based prospective chart review study.

Setting: The study involved 12 years or older patients admitted to medical, surgical and intensive care units (ICUs) of four hospitals during four month.

Main outcome measures: The study outcomes were the incidence of prescribing errors; their types and severity. The severity of prescribing errors was determined by two independent reviewers using the National Coordination Council for Medication Errors Reporting and Prevention (NCC MERP) index.

Statistical analysis: Descriptive statistics was used to analyze the study data.

Results: Medical charts of 3,985 patients were reviewed by pharmacists. The total length of hospital stay for the patients was 30,996 days. The study included 977 patients from a teaching hospital, 2033 patients from a private hospital; 683 patients from a large government hospital; and 292 patients from a small government hospital. Patients were admitted to three different services (Medicine; 1352 patients, surgery; 1771 patients and ICU; 862 patients). A total of 1205 prescribing errors were identified in all hospitals. The total incidence of prescribing error was 30.2 (95% CI, 28.5 -31.9) per 100 admissions. The incidence in the teaching government hospital was 17.5 (95% CI, 15.0 – 20.2) per 100 admissions. The incidence of prescribing errors in the large government hospital was 54.7 (95% CI, 46.7 -63.8) per 100 admission. The most commonly identified prescribing error type was dosing errors 243 (20.2%) with 140 overdoses and 103 under doses. Antibiotic 362 (30%) was the most common drug class involved with prescribing errors. Out of the 1205 prescribing errors identified 74 (6.1%) errors were judged to have caused harm to the patients. Of these 1 (1.4%) was fatal, 9 (12.1%) were life-threatening, 34 (46%) were serious and 30 (40.5%) were significant.

Conclusions: The study has identified important prescribing errors and based on these findings strategies to prevent future errors should be developed.

726. Knowledge, Attitude and Concept of Pharmacovigilance Among Community Health-Care Professionals in Saudi Arabia

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Background: Drug safety is an important issue in healthcare. However, this concept is still considered new to healthcare professionals.

Objectives: To determine the knowledge, attitude and concept of pharmacovigilance among the healthcare professionals in different community settings in Saudi Arabia.

Methods: This was a cross-sectional study conducted in the period between November 2015 and January 2016. The survey was conducted in community settings including community hospitals, polyclinics, community pharmacies and dental centres throughout two cities (Riyadh, and Hail) Saudi Arabia. The subjects of the study were physicians, pharmacists, nurses and dentists within 60 locations. The questionnaire consists of 24 questions assessing the knowledge, attitude and concept of pharmacovigilance among the healthcare professionals (HCPs). The data were analyzed using Statistical Analysis Software (SAS® 9.3).

Results: Five hundred and fourteen healthcare professionals completed the survey with a response rate of 79%. Around half (54%) of the healthcare professionals were nurses followed by physicians (24%), pharmacists (15%), and dentists (7%). Majority (55%) of the participants were working in polyclinics.Almost 53% didn't know the correct definition of pharmacovigilance. Furthermore, 57% of the HCPs had no knowledge about the aim of post-marketing surveillance. However, 76% percent of the HCPs were well aware that reporting ADRs is the responsibility of all HCPs. Fifty three percent of the HCPs believed that they should be paid for ADRs reporting.While, 54% of HCPs did not believe that lack of time was a major factor to discourage ADRs reporting. In addition, only (43%) were aware that the National Pharmacovigilance and Drug Safety Centre is the

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official regulatory body for ADRs reporting in Saudi Arabia. However, 35% of the HCPs didn't know if they have specific unit for medication safety in their institutions.

Conclusions: There was poor knowledge about pharmacovigilance among community HCPs, which ultimately affects reporting of ADRs. There is an urgent need of having educational and training programs in pharmacovigilance from regulatory and health agencies.

727. First Characterization Of Adverse Drug Reactions in the Dominican Republic

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Background: Pharmacovigilance (PV) remains a Public Health challenge in low- and middle-income countries. In 2013, a pilot PV program was started in a semi-public hospital (350 beds) in Santo Domingo, Dominican Republic. Twenty-seven months of passive and active collection of adverse events across all hospital departments allowed the construction of a PV database.

Objectives: To characterize the patterns of adverse drug reactions (ADRs) in the hospital PV database.

Methods: ADRs reported between July 2013 and October 2015 to the PV unit of the hospital were analyzed by reaction characteristics (including seriousness, and causality according to the Naranjo scale), drug class (ATC classification 2nd level), and outcome of the ADR categorized according to the system organ classes of the WHO Adverse Reaction Terminology.

Results: A total of 234 reports were collected, corresponding to 32,300 hospitalizations and 86,400 visits to the emergency room. Spontaneous reports represented 43.5% of reports. More than half of reports were from physicians (53%), followed by nurses (34%), and residents (13%). Fifty reports were for serious ADRs, including 31 life-threatening cases. Causality of ADRs was most often rated as possible (61%) and probable (33%). Systemic antibacterial agents were the most commonly involved (19%), followed by anti-inflammatory drugs (13%), analgesics (11%), and contrast media (11%). Dexketoprofen (5%), metoclopramide (3.6%), and ketorolac (3.6%) were the individual drugs most frequently reported. Dermatological disorders were the most commonly reported ADRs (46%), including pruritus (17%) and rash (15%). Respiratory disorders were the second most reported ADRs (13%), including dyspnea (8% of all reports).

Conclusions: This is the first time that patterns of ADRs in Dominican Republic have been reported. They constitute an important basis for the improvement of hospitals care protocols and safer drug use. The extension of the PV program to other hospitals in the Dominican Republic would refine these patterns but would call for investment from public health authorities.

728. Development of a New Trigger Tool for Adverse Drug Reaction Detection at a Large Teaching Hospital, Thailand

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Background: Adverse drug reaction (ADR) monitoring system at Ramathibodi Hospital is composed of spontaneous reporting system and ward pharmacist surveillance (conventional method). Underreport is common, while the latter method is labor-intensive. ADR Thai trigger tool has recently been proposed for general hospitals.

Objectives: To modify ADR Thai trigger tool for a large teaching hospital.

Methods: The data of ADR occurring at 4 medicine wards during the year of 2013 were retrieved and were intensively chart reviewed to detect all ADR occurring. ADR Thai trigger tool composed of 27 types of

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triggers was matched with those ADR events and modify to make a new trigger tool.

Results: Total of 149 events among 88 patients were found after intensive chart review. The conventional method was able to detect 119 events, while 141 (94.6%) events were detected by ADR Thai trigger tool. Thirteen types of triggers with 364 detections were traced back in 141 ADR events. The type and number of trigger found were presented as follows provision diagnosis 132 times (37.4%), abrupt medication stop 73 times (20.1%) and using chlorpheniramine 35 times (9.6%). The common laboratory tests related with ADR were serum creatinine rising plus nephrotoxic drug 27 times (7.4%), white blood cell count less than 3000 cell^3/μl in cancer patient 27 times (7.4%) and abnormal liver function test $>$ 2 UNL plus hepatotoxic drug 17 times (4.7%). Specific serum drug level found vancomycin and gentamicin which drug level was related with acute renal failure.

Conclusions: Four triggers were added which were hypokalemia plus drug induced, using statin plus creatinine kinase $>$ 5 ULN, voriconazole level and pharmacogenetics test of drug allergy. This new Ramathibodi medical trigger tool should be further validated.

729. Testing of ADR Thai Trigger in Surgical Patients at a Large Teaching Hospital, Thailand

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Background: Testing of ADR Thai Trigger in Surgical Patients at a Large Teaching Hospital, Thailand.

Objectives: To test ADR Thai trigger tool in surgical patients.

Methods: The data of ADR occurring at 4 surgery wards during the year 2013 period were retrieved and intensively chart reviewed in order to detect all ADR occurring. ADR Thai trigger tool composed of 27 types of triggers was matched with those ADR events. The type and number of trigger found was assessed.

Results: Total of 51 events among 44 patients were found after intensive chart review. Forty-eight events (94.1%) were able to detect by Thai trigger tool method. Total of 9 types of triggers with 134 detections were traced back to 48 ADR events. The type and number of trigger found were presented as follows provision diagnosis 48 times (35.8%), chlorpheniramine oral/injection 33 times (24.7%) and abrupt medication stop 28 times (20.9%), respectively. Laboratory test trigger found abnormal liver function test $>$ 2 UNL plus hepatotoxic drug 10 times (7.5%), rising serum creatinine plus drug induced nephrotoxicity 3 times (2.2%) and white blood cell counts less than 3000 cell^3/μl in cancer patient 1 times (0.7%). Specific serum drug level found 1 event from high level of vancomycin related serum creatinine rising.

Conclusions: Although ADR Thai trigger tool was proposed for medical patients, it seems to be effective for ADR detection in surgical patients with less time consume and labor-saving. However, ADR Trigger tool for surgical patients should be modified.

730. Adverse Drug Reactions in Medicine Wards at a Large Teaching Hospital, Thailand

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Background: Adverse drug reaction (ADR) monitoring composing of multidisciplinary team at Ramathibodi Hospital, a large teaching hospital has been established for a decade. The characteristics of these events have not been explored.

Objectives: To determine the occurrence rate and ADR characteristics of hospitalized patients at Medicine department.

Methods: ADR monitoring were performed by spontaneous reporting and ward pharmacist surveillance, then were evaluated by the team and recorded in the

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clinical pharmacy unit database. We recruited the database from January to December 2013 from four Medicine wards and determined the rate and characteristics of ADR occurring. Only ADR with significant harms were selected. The occurrence rate was calculated by number of ADR divided by the number of patient admission and their length of hospital stay.

Results: Total of 149 ADR events from 88 patients and 98 admissions were retrieved. The ADR occurrence rate was 2.77% and 4.39 per 1,000 patient-days. Eighteen admissions (18.4%) were caused by drug. Common organ disorders were skin, white cell and urinary system disorder in 30 (20.1%), 27 (18.1%) and 24 events (16.1%), respectively. The most common manifestation of skin disorders was maculopapular rash (25 events; 83.3%): 6 from phenytoin, 5 from piperacillin-tazobactam, 5 from vancomycin and 9 from others. For white cell disorder, febrile neutropenia was the most common presentation (25 events; 92.5%), particularly in hematologic patients suffered from chemotherapy. The most common disorders of urinary system were acute renal failure (19 events; 79.1%): 9 from amphotericin B, 6 from colistin, and 4 from vancomycin.

Conclusions: Although the ADR occurrence rate seems to be low due to selection of high severity, their characteristics suggests how to prevent their occurring in the future.

731. Drug Therapy Related Problems Among Critical Care Patients in A Tertiary Care Hospital in Nepal

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Background: Drug therapy related problems are the major concern that affects success of pharmacotherapy. Adverse Drug Reactions (ADRs), Medication errors and Drug- Drug Interaction are the major one.

Objectives: To study the pattern and nature of ADRs, Medication Errors and Potential drug Interactions (PDIs) in critical care patients.

Methods: Prospective study was conducted in critical care inpatients between September 2015 to November 2015 at Manipal Teaching Hospital Pokhara, Nepal. Data from patients and their medication record was collected in predesigned data collection form. Naranjo Algorithm, modified Hartwig & Siegel and modified Shumock & Thornton Scales were used for causality, severity and preventability respectively for ADR. Patients' file record and patient interview on medication were used as source of data medication error. The medications of patients were analyzed for potential drug interactions (PDIs) using Micromedex 2.0.

Results: Among 316 patients, 27 have experienced ADRs. Rashes (22.22%), Edema (11.11%), Fever (7.40%) were common ADRs. ADRs incident were higher with Antibiotics (51.85%) and cardiovascular drugs (25.92%). Dermatological (22.22%), Gastrointestinal (18.52%) and Cardiovascular (18.52%) systems were more affected. About 77.78% drugs were continued, 14.81% were stopped and 48.15% needed medical treatment. Antipruritic (17.65%), antihistamine (11.76%) and corticosteroids (11.76%) were used to treat ADRs. Forty two medication errors were noticed consisting 19 prescription errors, 7 Administration errors, 14 transcription errors and 2 documentation errors. 61.90% of medication errors are Category B i.e. medication did not reach to the patients and more than 2/3rd of errors were clinically significant. PDIs was found in 21.2% of prescriptions. Altogether 92 interactions were found. Majority of PDIs were Moderate severity (59.78%).

Conclusions: Study finding suggest the existence of drug therapy related problem even at critical care setting which need to be addressed. Hence, a careful monitoring is required. Providing education and awareness regarding drug therapy related problem are very much essentials for its minimization.

732. Pharmacovigilance in Pakistan - Hospital Pharmacists' Views

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Background: Knowledge about pharmacovigilance among hospital pharmacists (HPs) is essential for better pharmaceutical care planning of the patients.

Objectives: This project was designed to assess hospital pharmacists' knowledge, perceptions and practices towards pharmacovigilance in Punjab, Pakistan.

Methods: A cross-sectional, questionnaire-based study was performed among registered HPs in Pakistan. A pre-tested and pre-validated research tool was used to collect data. The research tool was divided into three sections. Descriptive and inferential statistics were applied at a significant value of $p \leq 0.05$. Data were statistically analyzed using SPSS version 22.

Results: A total of 97 HPs participated in the study (79% males with 21% females) and the response rate was 47%. Around 22% felt that only registered medical practitioners are responsible for ADRs and their reporting in Pakistan. Knowledge score about overall pharmacovigilance concept was relatively low among old graduates. Around 31% agreed they were not very well familiar with the pharmacovigilance concept, and around 69% knew that pharmacists are the key players in pharmacovigilance. Majority of them (89%) agreed that knowledge and awareness of pharmacovigilance is crucial for HPs in order to provide better pharmaceutical care to the patients. Foremost reason for non-awareness of pharmacovigilance concept was the misconception that it is the duty of medical doctors not the HPs.

Conclusions: Based on the results of the study, specific and targeted educational interventions with some hands-on activities are crucial for HPs regarding pharmacovigilance advancements in Pakistan. This study indicated that HPs were aware about the importance and benefits of pharmacovigilance. The majority of HPs in Punjab, Pakistan have appropriate knowledge and positive perception towards pharmacovigilance concept and its benefits in patient care.

733. A Survey to Evaluate Electronic Healthcare Databases for Potential Post-Marketing Drug Safety Surveillance in China

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Background: Electronic healthcare databases (EHDs) provide real world data of clinical practice with broader patient populations and have been increasingly used for post marketing drug safety surveillance over past decade. However, few studies have examined the potentials of these data sources in China.

Objectives: To evaluate the availability and characteristics of EHDs for post-marketing drug safety surveillance in China.

Methods: Three major types of EHDs in China, including two regional community based databases, one annual sample of national claims database, and one electronic medical records (EMR) database covering 40 hospitals, were selected for the evaluation. A questionnaire was designed to understand data accessibility, basic database characteristics, and core variables in the databases for post-marketing drug safety surveillance (i.e. 39 key variables derived from US Mini-Sentinel common data model etc.). The survey questionnaire was sent to the owners of each database on June 15, 2015 and the respondents were contacted by email, telephone, or face-face interview if retuned responses were ambiguous.

Results: All database owners responded all questions on the survey. Three database owners confirmed their willingness to share the databases with academic institutions. However, access to national claims data required a special approval procedure. Two regional databases contain 3.6 and 1.2 million patients with 90% and 82% of core variables available respectively. The claims data were resampled annually from the entire country (6.6 million people in 2013) and had 64% of core variables. The EMR database consists of 3 million inpatient data with 87% core variables. Lab data are available in 3 databases except for claims data. Diagnosis data are available in all 4 databases while the clinical symptom data can only be found in one regional database. Inconsistent drug and diagnosis coding systems are seen across 4 databases.

Conclusions: The survey provided valuable data on 3 major types of EHDs for potential post-marketing drug safety surveillance in China. Future research is warranted to assess the quality and completeness of these data sources.

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734. Adverse Drug Reactions Among Hospitalised Children in South Africa

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Background: There is scant paediatric pharmacovigilance data, especially from developing countries. South Africa's high HIV and tuberculosis (TB) burden and massive antiretroviral therapy (ART) program may contribute to the local risk for drug-related harm.

Objectives: To describe the adverse drug reaction (ADR) burden among hospitalised children at two South African hospitals.

Methods: We assessed 30 days' paediatric (age 1m to 18y) ward admissions (except oncology). We used a trigger tool to help identify adverse drug events (ADEs). A multidisciplinary panel assessed causality (using the WHO-UMC system), seriousness, and preventability.

Results: 922 patients had 972 admissions. 519/922 (56%) were male and 421/922 (46%) were ≤1y of age. There were 28 HIV-infected children, of which 21 were on antiretroviral (ARV) therapy, and 80 HIV-exposed children, of which 34 were on ARVs to prevent mother-to-child HIV transmission.

We identified 205 ADEs in 134 children. We classified 132 as ADRs (18 certain, 33 probable, and 81 possible), 31 as unlikely, and 9 as unassessable. 33 ADEs are unclassified, still requiring panel review. 40 ADRs were present on admission; ADRs caused 14/972 (1.4%) admissions. 92 ADRs occurred during admission, of which 13 were serious, and three near-fatal: anaphylaxis after vancomycin, respiratory depression after midazolam, and hyperkalaemia with enalapril. The most common ADRs were diarrhoea (n=24, mostly due to antibiotics), hypokalaemia (n=16, mostly due to diuretics), and tachycardia (n=14, mostly due to β-agonists.) 21/132 (16%) ADRs were preventable. ARVs, anti-TB therapy, and/or cotrimoxazole were implicated in 13/132 (9.8%) ADRs. 8/28 (29%) HIV-infected children had ADRs.

Conclusions: ADRs caused only 1.4% of admissions in our survey, lower than a previous meta-analysis (2.9%, 95% CI 2.6% to 3.1%). ADRs occurred during 9.5% of admissions, within a previous systematic review's range of 0.6% to 16.8%. A serious ADR occurred during 1.3% of admissions. ART and anti-TB therapy contributed little to the ADR burden compared with drugs used in common paediatric conditions such as infections and asthma, but HIV-infected children had a high incidence of ADRs.

735. Attitudes of Community Pharmacy Professionals Towards Consumers Reporting in Portugal

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Background: An Adverse Drug Reaction (ADR) is a harmful and unintentional response to drugs. The National Pharmacovigilance System (NPS) receives reports from healthcare professionals and consumers and analyzes them in order to prevent, eliminate or minimize the risks of drugs to the consumers' health.

The community pharmacy professionals (CPP) have privileged access to consumers and throughout their pharmacotherapeutic follow-up, they can have the real perception of a possible ADR and encourage the consumer to report.

Objectives: To evaluate CPPs' role as active agents for improving consumers' involvement in pharmacovigilance and to describe their attitudes related to ADR report and consumers' reporting.

Methods: An observational study will be performed in a large group of CPPs contacted through e-mail. A web-based survey was created and sent through Google Docs platform questionnaire. Data will be

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collected between February and April 2016 and will be analyzed using Descriptive Statistics, $\chi 2$ tests, Spearman's correlation coefficients and statistical analysis, with software SPSS v. 20.

Results: As far as authors know, this is the first study conducted in Portugal to evaluate the role of CPPs in improving consumers' involvement in Pharmacovigilance. Other studies conducted in Portugal in pharmacy professionals, concluded that just a small part of professionals reported suspected ADRs. The main reasons for ADR under-reporting are pointed as low knowledge in pharmacovigilance as well as the indifference and lack of time of the professionals in this field. Reports could be improved by NPS disclosure and educational programs.

Conclusions: In this study it is expected to understand why there are such low report values and what factors should be changed to increase the number of reports.

Reporting of ADRs is fundamental to pharmacovigilance and consumer reporting is important to construct useful information on drug safety. Therefore, the lack of reports is a concern to the NPS. it In community pharmacies, CPPs can play an important role in pharmacovigilance, encouraging consumers to report and to promote an active pharmacovigilance.

736. Withdrawn by Author

737. Risk of Hemorrhagic Stroke Associated with Non-Insulin Blood Glucose Lowering Drugs. Results from the SAFEGUARD Project

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Background: The SAFEGUARD project aims to assess the cardio/cerebrovascular and pancreatic safety of non-insulin blood glucose lowering drugs (NIGBLDs) in type 2 diabetes mellitus patients (T2DM). To date, no studies addressing the risk of Hemorrhagic stroke (HS) in patients exposed to NIGBLDs have been published.

Objectives: To estimate the risk of HS associated with individual NIBGLDs in the multi-database network of the SAFEGUARD project.

Methods: A case-control design, nested in a cohort of new NIBGLD users was performed. Incident HS cases (intracerebral/subarachnoid hemorrhage) were matched with up to 5 controls on database (DB), sex, cohort entry (±3 months) and date of birth (±1 year) using risk set sampling. Data were retrieved from 9 electronic healthcare data sources (PHARMO, IPCI (Netherlands); BIFAP (Spain); GePaRD (Germany); Health Search, Regional DBs of Lombardy and Puglia (Italy); CPRD (United Kingdom); Medicare (US)). DB-specific adjusted odds ratios (ORs) and corresponding 95% confidence intervals (95%CI) were estimated by comparing current use of metformin in combination with sulfonylureas (SUs) (reference) with each NIGBLD monotherapy, dual therapy of metformin plus another NIGBLD (not SUs) and other NIGBLD combinations. Meta-analyses of data source specific estimates (ORmeta with 95% CI) and conditional logistic regression based on the individual pooled data (adjOR pool with 95% CI) were performed.

Results: A total of 3,817 cases of HS were matched to 18,656 controls T2DM. As compared with users of metformin in combination with SUs, current use of repaglinide monotherapy (adjOR pool=1.68 (1.28-2.20); ORmeta=2.12 (1.11-4.05)). The meta-analysis also showed an increased risk of HS in current users of metformin in combination with rosiglitazone (ORmeta=1.85 (1.04-3.29)).

Conclusions: Our findings suggest that the risk of HS is higher in current users of repaglinide monotherapy and in those using the combination of metformin and rosiglitazone as compared with current users of metformin and SUs.

738. Development of a Detection Algorithm for Prednisolone-Induced Diabetes Mellitus Using a Medical Information Database

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Background: Recently, medical information databases (MIDs) have been used to conduct post-marketing surveillance studies to identify adverse events and improve medication and regulatory implementation. Development of high-accurate detection methods of adverse reactions using MIDs is very important for medical research. Prednisolone is a commonly prescribed drug for the management of a various diseases, including inflammatory conditions and hematological malignancies but are known as a main causative drug for drug-induced hyperglycemia.

Objectives: We conducted pharmacoepidemiological study to develop a novel detection algorithm for prednisolone-induced diabetes mellitus (PIDM) using a MID.

Methods: We collected data on prescriptions, laboratory tests, diagnoses from a MID of Hamamatsu University Hospital in Japan. The 1812 patients were newly prescribed prednisolone from Jan 1st, 2008 to Dec 31st, 2014. The patients who had been diagnosed as DM before prednisolone administration were excluded. 349 patients who were available to be evaluated based on the current DM criteria by the Japan Diabetes Society (JDS). Definite diagnosis of PIDM were made from medical record review by a diabetologist. Lastly, we compared the patients who were diagnosed as PIDM to non-PIDM and assessed the developed algorithms using receiver operating characteristic curves.

Results: The 63 patients were identified by the current JDS criteria. Of these, 35 patients were definitely diagnosed as PIDM after medical record review by the diabetologist (positive predictive value=55.6%). We found that the patients with PIDM had significant higher maximum increased rates of FBG and HbA1c levels than those with non-PIDM. Therefore, we applied the maximum increased rate as the second screening to the algorithm for PIDM. Moreover, usage of the maximum increased rate of HbA1c as the second screening factor showed much higher sensitivity and specificity than those of FBG (HbA1c: Area under the curve (AUC) =0.93 vs. FBG: AUC=0.64, $P<0.05$).

Conclusions: The algorithm for PIDM composed of the maximum increased rate of HbA1c in screening was superior to the current criteria by the JDS alone.

739. FDA AERS Data Shows a Strong Signal for SGLT2 Inhibitors and Diabetic Ketoacidosis

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Background: In May, 2015 there was significant interest in the possible association between SGLT2 Inhibitors (Invokana, Farxiga, Jardiance) and diabetic ketoacidosis (DKA) which is an uncommon event in type 2 diabetes. FDA AERS data is publicly available at little or no cost and can be used as a part of routine pharmacovigilance. PRR like analyses were performed looking for signals in the FDA AERS data.

Objectives: To review FDA AERS data for the presence of signals concerning DKA and various antidiabetic medications by calculating proportional reporting rates (PRR) over time. To further see if there are previously unrecognized signals.

Methods: Data from the FDA AERS system was selected for use. This data was extensively prepared to allow for PRR calculations. Last best cases were determined for reports with multiple versions. Dates of first report were computed for each adverse event term in each report. For each event, the percentage of event reports to total reports for the drug was computed. These calculations were computed for each quarter. Because of differential reporting, nonserious reports were excluded. Several antidiabetic drugs were compared over time to see if there were any notable differences.

Results: There is a clear signal for SGLT2's and DKA no later than 2014Q2. This predates FDA's alert by 9 months. Surprisingly, there is also a very strong signal

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for serious fungal infections which suggests the label is inadequate at this time.

Conclusions: Calculating PRR over time is an effective method of detecting signals. Furthermore, seeing how the signals develop over time provides more information than a simple disproportionality score at a given point in time. In the current study, the signals for DKA with SGLT2's is very strong and apparent almost immediately after launch. Seeing a signal for multiple drugs within the same class provides further reinforcement of the signal. Lastly, the method has also detected a signal for serious fungal infections which suggests the current label may need to be enhanced.

740. Adverse Drug Reactions Related to DPP-4 Inhibitors - A Review

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Background: The DPP-4 inhibitors used in the treatment of type 2 diabetes mellitus increase insulin secretion and reduce the secretion of glucagon, preventing the inactivation of GLP- 1, thereby decreasing glucose levels. As these drugs reduce the secretion of glucagon, they can cause adverse effects in gastrointestinal tract, such as nausea, vomiting and pancreatitis. Recent studies also suggest that DPP-4 inhibitors could contribute to the reduction of cardiovascular risk.

Objectives: To review the prevalence of adverse effects of the DPP-4 inhibitors.

Methods: A bibliographic review was performed through an online search in National and International Authorities - INFARMED, IP, European Medicines Agency and EudraVigilance about adverse drug reactions (ADR's) related to DPP-4 inhibitors as monotherapy or in combination with metformin. All SPC (summary of product characteristics) were analyzed. Articles found in Google Scholar and PubMed databases were also taken into account for analysis of ADR's related to DPP-4 inhibitors.

Results: According to the European Database of Suspected Adverse Drug Reaction Reports, 21831 suspected ADR's were reported to DPP-4 inhibitors until January 2016. Prevalence is higher in men, and in the 65-85 years class. Sitagliptin (61,1%) and vildagliptin (23,3%) are the DPP-4 inhibitors with more ADR reports. Most common ADR's according to MedDRA system were gastrointestinal disorders, general disorders and administration site conditions, metabolism and nutrition disorders and skin and subcutaneous tissue disorders.

Conclusions: DPP- 4 inhibitors' ADR's are more frequent in the gastrointestinal tract and the most common are nausea and vomiting, but most may be reversible through an adjustment in dosage. Other studies also suggest that DPP-4 inhibitors could contribute to the reduction of cardiovascular risk; however, 9,2% of the individual cases identified in EudraVigilance were cardiac disorders.

741. A Population-Based Cohort Study Suggests No Elevated Risk of Severe Joint Pain in Association with Dipeptidyl Peptidase-4 Inhibitors Use in Patients with Type 2 Diabetes

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Background: The US Food and Drug Administration (FDA) warned of a strong temporal association between use of dipeptidyl peptidase-4 inhibitors (DPP4i) and severe arthralgia on the basis of 33 case reports of severe joint pain (SJP) in August, 2015. However, the current evidences were limited to case reports and lack of the information regarding the incidence of SJP after the use of DPP4i from population-based studies with longer follow-up periods.

Objectives: To investigate the putative association of SJP with the use of DPP4i in patients with type 2 diabetes (T2D).

Methods: A propensity score matched population-based cohort study was performed between 2009 and 2013 in a group of T2D who were stable metformin users. Totally 4,743 T2D were later added with DPP4i (i.e., DPP4i users) and the same number of matched non-DPP4i users were selected. The two study groups were followed to the occurrence of SJP diagnosis (ICD-9-CM code: 719.4), termination of health insurance policy, or end of 2013. Incidence rate of SJP was estimated under the Poisson assumption. Cox proportional hazard model was used to estimate the covariate adjusted hazard ratio (HR) and 95% confidence interval (CI) of SJP in association with DPP4i use.

Results: Over a maximum of 5-year follow-up, 679 DPP4i users and 767 non-DPP4i users were newly diagnosed with SJP, representing an incidence rate of 47.20 and 50.66 per 1,000 person-years. The Cox model analysis indicated a slightly but insignificantly reduced risk of SJP in association with DPP4i use (adjusted HR: 0.92 [95% CI: 0.83-1.02]). Such null results were also observed in patients with all age and sex stratifications, as well as in a sensitivity analysis using all nonspecific arthropathies as the study end-point.

Conclusions: This study provides no support for the putative risk of SJP in relation to DPP4i use in T2D during up to 5 years of follow-up.

742. Changes in Health Parameters Over 12 Months in Users of Once Weekly Exenatide (Bydureon®)

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Background: Bydureon®, licensed in 2011, is indicated for treatment of type 2 diabetes mellitus (T2DM). Favourable changes in health parameters in T2DM patients (pts) can help reduce cardiovascular disease risk and improve glucose homeostasis. A post-marketing safety study is underway as part of the EU Risk Management Plan.

Objectives: To quantify mean changes at group level in health parameters (weight, body mass index (BMI), systolic blood pressure (SBP) and HbA1c) in Bydureon® users at interim.

Methods: An observational, population-based cohort study in primary care in UK. Pts were identified from dispensed prescriptions (Rx) issued by GPs Sep 2011-Sep 2015 (interim datalock). GPs were sent questionnaires 12 months after each pts' 1st Rx for exposure, outcome and risk factor information from medical charts. For pts continuing treatment to the end of 12 months, changes in each pts' health parameters were calculated from index (1st Rx) to 12 months post-index (12m) to estimate mean change (Δ) at group level. Denominators are pts with both index and 12m data provided.

Results: Interim evaluable cohort=2538 pts; 55.6% (n=1410) males; median age 57 yrs (IQR 50;65). At end of the 12 months 1752/2538 (69.0%) pts remained on treatment. Of these pts, 1384/1495 (92.6%) were obese and 521/1129 (46.1%) had HbA1c>9% at index. Mean weight Δ=-3.0kg [SD 6.7] (index 109.4kg [22.0]; 12m 106.4kg [21.7]; N=1395). Mean BMI Δ=-0.9kg/m2 [2.5] (index 38.0kg/m2 [6.7]; 12m 37.0kg/m2 [6.6]; N=1292). Mean SBP Δ=-2.1mmHg [16.2] (index 133.8mmHg [14.2]; 12m 131.6mmHg [14.2]; N=1509). Mean HbA1c Δ=-7.6mmol/mol [18.9] (index 75.9mmol/mol [19.3]; 12m 68.3mmol/mol [19.5]; N=1057).

Conclusions: Overall at aggregate level, Bydureon® use appears to be associated with favourable changes in health parameters over 12 months in this single group study in primary care setting. However the clinical significance of such changes is unclear. Limitations are lack of adjustment for concurrent medications and potential regression towards the mean as pts prescribed Bydureon® may be extreme relative to the T2DM population (obese and/or poor diabetes control). This analysis will be superseded once final cohort accrual and analysis are complete.

743. Identification of Potential Signals of Serious Risks for Sitagliptin: Analysis of Spontaneous Adverse Event Reports in VigiBase®

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Background: Sitagliptin was the first dipeptidyl peptidase 4 inhibitor approved for the treatment of type 2 diabetes in 2006. It is one of the most commonly prescribed oral hypoglycemic agents (OHAs) as monotherapy or in combination with other OHAs.

Objectives: To analyse spontaneous adverse event reports (SAERs) associated with the use of sitagliptin for potential signals of serious risks.

Methods: VigiBase®, the World Health Organization/Uppsala Monitoring Centre global individual case safety reports database were used to examine all reports of adverse events associated with sitagliptin through the end of January 2016. Disproportionality analysis was conducted for the quantitative detection of signals. A signal is detected if the count of co-occurrences ≥3 and the Proportional Reporting Ratio (PRR) ≥2.0 with an associated $\chi 2$ value of ≥4.0.

Results: There were a total of 12,565,490 SAERs found in VigiBase®, among these 19,438 (0.15%) were associated with sitagliptin. Around 78% of SAERs related to sitagliptin reported from USA; and gastrointestinal disorders (30.9%) were the most commonly reported adverse events. Of these, pancreatic disorders accounted for 42.4%. The most important signals for risks identified in the database were pancreatic neoplasm (PRR 62.41, $\chi 2$ 1513.11), Hepatic metastasis (PRR 51.51, $\chi 2$ 14244.91), pancreatitis (PRR 32.13, $\chi 2$ 65533.42), prostatic hyperplasia (PRR 18.67, $\chi 2$ 1610.03) and thyroid neoplasm (PRR 12.98, $\chi 2$ 780.86).

Conclusions: A large proportion of adverse events were associated with the use of sitagliptin. As pancreatic and hepatic disorders are the important signals identified, clinicians must be vigilant in identifying early signs and symptoms of these disorders and discontinue sitagliptin.

744. Managing the Risk of Medication Errors - Where to Start?

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Background: Medication errors are a major public-health burden representing 18.7–56% of all adverse drug events among hospital patients. However, the concept of medication error is not limited to those that harm the patient (preventable ADEs) but includes those intercepted during the medication process (prescribing, storing, dispensing, preparation for administration or administration of a medicinal product). In the process of obtaining a marketing authorisation (MA), companies are expected to evaluate the safe use of their medicinal product and describe in the risk management plan that accompanies the MA application the potential for medication errors and preventive measures. In October 2015, EMA published several good practice guides to assist companies in doing so and has a dedicated webpage on this and related documentation.

Objectives: Per the new guides, a medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. Proposed MA holders (MAHs) should consider their product design, packaging, labelling and any other applicable measures to prevent errors associated with use of the product. Looking at the drug treatment process, all steps where a failure could occur, take place when the product has left the companies factory. To know in how far the risk minimisation strategies are working, their effectiveness needs to be assessed at the level of the actors in the medication process.

A specific dedicated guide was created for high-strength insulin products and published in its final form also in October 2015. The objective of this study is to identify in how far the recommendations of the EMA as outlined in this guide have been followed by MAHs manufacturing such products.

Methods: The study will include a review of available SmPC data and educational material and what the initial effects are on the reporting rate of medication errors since October 2015.

Results: The results presented at the ICPE 2016 meeting will include the data available up to 1 July 2016 for high strength insulin (degludec/lispro/glargine) products as retrieved from EMA/national websites.

745. Postmarketing Safety Profile of Ledipasvir/Sofosbuvir Chronic HCV Infection Therapy

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Background: Hepatitis C virus (HCV) is a blood-borne infection with acute & chronic presentations. About 85% of patients develop chronic infection, with estimated 3.5 million people in the US have chronic disease. There are many biologic therapies for chronic HCV infection, including the latest ledipasvir/sofosbuvir (LS) single-tablet combination therapy.

Objectives: To describe the safety profile of LS.

Methods: Adverse event (AE) reports voluntarily sent to FDA Adverse Event Reporting System through June 30, 2015 were retrieved & analyzed. Reports for LS were identified by generic name, & events were defined by the Preferred Term (PT) of the Medical Dictionary for Regulatory Authorities, & described by System Organ Classes (SOC).

Results: Overall, 9123 AE reports were submitted for LS. Gastrointestinal disorders accounted for 23% of reported events (n=2067), with nausea being the most frequently reported event (n=126). The distribution of reports by SOC & corresponding most frequently reported PT was the following: 12% (n=1056) General disorders (fatigue, n=330); 10% (n=905) nervous system disorders (headache, n=359); 9% (n=817) hepatobiliary disorders (cirrhosis, n=19); 7% (607) psychiatric disorders (insomnia, n=113); 6% (574) blood disorders (anemia, n=29); 5% (n=418) investigations (liver-related tests, n=79); 4% (n=341) cardiac disorders (arrhythmias, n=30); 3% (n=271) infections (nasopharyngitis, n=28); 3% (n=255) musculoskeletal disorders (arthralgia, n=40); 3% (n=237) skin disorders (rash, n=55); 2% (n=224) vascular disorders (hypertension, n=90); 2% (n=223) respiratory disorders (dyspnea, n=51); 2% (n=206) injuries (drug dose omission, n=23); 2% (n=205) neoplasms (hepatocellular carcinoma, n=5); 2% (n=201) metabolism disorders (hyperglycemia, n=37); 2% (n=176) renal disorders (acute kidney injury, n=31); and 1% ear (n=113) & eye (n=107) disorders (tinnitus, n=18; blurred vision, n=15, respectively).

Conclusions: Treatment with LS appears to be well tolerated; however, an epidemiologic study is recommended to characterize the natural & treated history of the disease in order to understand if treatment-emergent hepatobiliary outcomes are due to the underlying hepatitis.

746. Effect of Antibiotic Exposure on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Background: Antibiotics are commonly implicated in Stevens-Johnson syndrome (SJS), overlap syndrome (SJS-TEN), and toxic epidermal necrolysis (TEN), rare disorders of the skin and mucosal membranes most often the result of adverse drug reactions.

Objectives: Examine the association between SJS, SJS-TEN, and TEN and antibiotic exposure, using varying degrees of exposure (i.e. overlapping with diagnosis date, and within 3, 6, and 12 months prior to diagnosis).

Methods: A case-control study was conducted using data from the PharMetrics LifeLink® Health Plan Claims Database (2001-2013). Cases included patients with ≥1 diagnoses of SJS/TEN identified using International Classification of Diseases, Ninth Revision (ICD-9) codes, and at least 1 year of continuous health plan enrollment prior to their earliest diagnosis. Controls were randomly selected from patients with no diagnoses of SJS/TEN, and were matched to cases 4:1 on age, gender, and amount of continuous health plan enrollment. Multivariate logistic regression was used to estimate odds ratios for varying antibiotic exposures.

Results: 192 cases and 768 controls were included. The odds of having an antibiotic fill overlap the diagnosis was ten times higher for cases than controls (OR=10.4 [95% CI 5.1,21.1]). The most common antibiotics overlapping diagnosis were aminopenicillins (n=8) and cephalosporins (n=8), however associations between specific antibiotics and SJS/TEN were not significant (OR=1.03 [95% CI 0.6, 1.9]). The unadjusted ORs for 3 months (OR=1.05 [95% CI 1.03-1.07]), 6 months (OR=1.03 [95% CI 1.02, 1.04]), and 12 months (OR=1.02 [95% CI 1.01, 1.02]) prior to diagnosis show that the farther back the exposure, the less association there is between antibiotic exposure and disease.

Conclusions: A significant association was found between overlapping antibiotic exposure and SJS/TEN; significant associations were also found when exposures were extended to 3, 6, and 12 months prior to diagnosis. Likely due to small sample sizes, associations between specific antibiotic classes and SJS/TEN were not found to be significant; further studies should be pursued to examine specific antibiotics.

747. Neuropsychiatric Events Associated with the Use of Helicobacter Pylori Eradication Therapy Containing-Clarithromycin: Self-Controlled Case Series

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Background: There have been concerns that clarithromycin might be associated with neuropsychiatric events in many case reports and spontaneous reports from the World Health Organization and the Food and Drug Administration. Nevertheless, no observational study has been conducted to examine this association.

Objectives: To investigate the association between the use of Helicobacter pylori therapy containing-clarithromycin and acute neuropsychiatric events.

Methods: Using the Clinical Data Analysis and Reporting System database in Hong Kong, we identified patients who had both exposure of at least one out-patient H. pylori therapy containing-clarithromycin and outcomes of interest during the study period from 2003-2012 in a self-controlled case series study. The primary outcome was composite neuropsychiatric events while secondary outcomes were psychotic events and cognitive impairment. The observation period started from one year after patients entered the database and was censored at the earliest of end of study, death, date of receiving clarithromycin script or in-patient H. pylori therapy containing-clarithromycin. Several risk periods were defined as 14 day pre-exposure, day 1-14 and day 15-30 since prescription start date. Age adjusted incidence rate ratios were estimated using the conditional Poisson regression.

Results: The preliminary findings showed that 1824, 354 and 726 patients were identified with a first recorded composite neuropsychiatric event, psychotic event and cognitive impairment respectively within the study period. The increased incidence rate ratios of 4.12 (95% confidence interval 2.94 to 5.76), 5.42 (2.77-10.60) and 2.63 (1.36-5.09) were found during current use for outcomes of composite neuropsychiatric events, psychotic events and cognitive impairment respectively. However, no increased risk was found during all other risk periods for all outcomes.

Conclusions: This study showed a short-term increased risk of neuropsychiatric events associated with H. pylori therapy containing-clarithromycin among Hong Kong population. There was no evidence of a long-term increased risk of neuropsychiatric events.

748. A Prospective Observational Pharmacovigilance Study to Evaluate Incidence, Onset and Severity of Adverse Effects During Anti-Tubercular Therapy

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Background: Adverse drug reactions (ADRs) leads to non-adherence in tuberculosis (TB) treatment contributing to regimen failure, morbidity, loss in quality of life and death.

Objectives: To evaluate incidence, onset and severity of ADR profile of first line anti-TB drugs. To evaluate causality of ADRs and determine association of ADRs with demography, socio-economic status & smoking.

Methods: This prospective study included 60 cases of newly diagnosed patients on first line anti-TB therapy in outpatients of poor socio-economic background (tertiary care hospital). Patients of either sex aged 18 - 70 years were included. Clinical, biochemical and physical examination was done at start, 2nd month and after treatment. ADR severity and causality were assessed using Hartwig Severity assessment scale and Narango Algorithm respectively. The statistical analysis was done using ANOVA test.

Results: Patients older than 40 years had higher proportion of ADRs (60% versus 40%). The proportion of ADRs was more common in women (55% versus 45%) than men. The incidence of organ systems most affected by ADRs were the gastrointestinal tract [GIT] (50%) followed by skin (10%), hepatobiliary system (6%), hematologic system (1.5%), ototoxicity (2.5%) and renal system (4%).The earliest onset of ADRs was GIT (15 days) followed by skin, hepatobiliary system, renal system, hematologic system and ototoxicity. The onset of ADR was earlier in older than 40 years age group by a mean of 5 days. All ADRs were mild in severity except (10 % of GIT) ADRs which were moderate but no severe reactions. On evaluation of causality of all ADRs reported, majority (90%) of them were in 'probable' category. The frequency of

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smokers was 20 % reporting a higher incidence of ADR (58% versus 42%) than non-smokers.

Conclusions: Incidence of ADRs due to anti-TB therapy was 56.4% with majority of GI symptoms highlighting the importance of developing strategies to ameliorate ADRs both to improve the quality of patient care and to control TB safely. Age, gender and smoking are independent risk factors which significantly affect the incidence, onset and severity of drug induced ADRs.

749. Use of an Automated Short Message Service to Monitor Adverse Events Following Immunization with a Quadrivalent Influenza Vaccine in Mexico

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Background: Inactivated quadrivalent influenza vaccine (QIV) is recommended for the prevention of influenza disease caused by influenza A and B viruses contained in the vaccine (4 strains). Post-market surveillance ensures that the safety profile of the vaccine is still acceptable when used in routine care. Active surveillance using an automated short message service (SMS) text messaging system is a contemporary method used to rapidly collect information on adverse events following immunization (AEFI).

Objectives: To estimate reporting rates of serious and non-serious AEFI with QIV using an automated SMS text messaging system.

Methods: In this prospective observational surveillance study, all individuals over the age of 6 months who were vaccinated with QIV in Mexico were eligible to participate. Participants (or their parent/guardian in the case of a pediatric participant) were required to own a cellular phone to be reachable by SMS. Participants received 4 automatically generated SMS text messages asking if they experienced an adverse event (AE) at day 1, 7, 28 and 42 following immunization. All SMS responses were classified as either "no AE", "AE present" or "non-respondent". Those who reported an AE were contacted by telephone to obtain additional details. Non-respondents were followed-up with a reminder SMS.

Results: Between 29 January 2015 and 12 February 2016, a total of 1236 participants (mean age 26 years) were enrolled from 11 sites in Mexico. 862/1236 (70%) participants responded to the SMS text messages, with 122/1236 (10%) participants reporting non-serious AEs. No serious AEs were reported and all participants who reported a non-serious AE recovered.

Conclusions: The interim results are consistent with the current safety profile of QIV and that of other influenza vaccines. The results demonstrate that an automated SMS text messaging system is an effective way to monitor AEFI in real-time.

750. Comparing Systolic and Diastolic Blood Pressure by Initial ART Regimen

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Background: HIV infection is associated with increased risk of cardiovascular disease (CVD) events.

Objectives: To test if antiretroviral therapy (ART) is associated with increased blood pressure (BP), as a possible pathway for increased CVD events.

Methods: This observational study was conducted in the CNICS cohort of 8 clinical care sites across the United States and included CNICS participants who initiated their first ART regimen during CNICS care in 2006 or later. Linear mixed models were used to compare the systolic or diastolic BP over the duration of the initial ART regimen for the 9 most common regimens. Models were adjusted for age, sex, race/ethnicity, BP at ART initiation, site, HIV transmission

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risk factor, Hepatitis C status, diabetes, time on ART, year of ART initiation, CD4 nadir, maximum HIV viral load, kidney function (eGFR), body mass index, and current statin and anti-hypertensive medication use.

Results: 2693 patients were included: 87% were male, 59% were <40 years old, and 47% were white. The most commonly initiated ART regimen with 49% of patients was Efavirenz/Tenofovir/Lamivudine (EFV/TDF/3TC). Compared to EFV/TDF/3TC, we found that Darunavir/Ritonavir/TDF/3TC: -1.9 mmHg 95% CI (-3.1,-0.7) and Elvitegravir/TDF/3TC: -1.7 (-3.4,-0.1)) had significantly lower systolic BP while EFV/Abacavir/TDF had significantly higher systolic BP 3.0 mmHg (0.1,6.0). Three regimens had significantly lower diastolic BP: Darunavir/Ritonavir/TDF/3TC: -1.1 mmHg (-1.9,-0.2), Atazanavir/Ritonavir/TDF/3TC: -0.8 mmHg (-1.4,-0.2), and Lopinavir/Ritonavir/TDF/3TC: -2.1 mmHg (-3.7,-0.4).

Conclusions: Though there were statistically significant differences in BP by ART regimen with several protease inhibitor regimens having lower diastolic or systolic BP than EFV/TDF/3TC, and regimens with abacavir having higher systolic BP than similar regimens with tenofovir, the differences were all ≤3 mmHg, which is not clinically meaningful. ART regimens may affect cardiovascular disease risk through other pathways but this study does not support a large role for differences in BP as a likely important mediating pathway.

751. Pharmacovigilance of Capecitabine: Hepatic Function Alterations in Mexican Women with Breast Cancer

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Background: Capecitabine is an oral chemotherapy drug used for the treatment of breast cancer. Common adverse drug reactions by Capecitabine are hand-foot syndrome, fatigue, abdominal and gastrointestinal pain. Previous studies have shown that some chemotherapic drugs are related to hepatic injury.

Objectives: To determine if the Capecitabine therapy modifies the levels of hepatic enzymes as an indicator of liver injury in Mexican women with breast cancer.

Methods: We realized a descriptive retrolective study. The inclusion criteria were Mexican women that had breast cancer in stages II and III with 3 to 7 cycles of oral chemotherapy with Capecitabine and complete the laboratory analysis. All clinical histories with 2 or less cycles of treatment, incomplete records or ilegibles were excluded. Descriptive parameters were collected: weight, age, breast cancer initiation, type of neoplasia, comorbilities, other treatments and the hepatic profile including: LDH, AST, ALT, GGT and ALP. Changes in the profile were compared with the intervals: LDH 105-333 U/L, AST 5-35 U/L, ALT 10-50 U/L GGT 30-50 U/L and ALP 68 U/L. The information was analyzed using SPSS v.22, statistic test included: τ-test, X2, and McNemar test considering $p<0.05$.

Results: 124 records were reviewed and 82 of them were included in the study (66%). Patients received doses of Capecitabine between 2000 and 3000 mg as single treatment or combined with other drugs.

GGT levels decreased during treatment (121.667 U/L to 44.758 U/L) (n=33; τ= 1.967; p= 0.058). In contrast, ALP increased from 306.176 to 334.235 U/L (n=34; τ= -6.74; p= 0.505).

The changes in the hepatic profile at the end of the 7-cycle showed that AST and ALT were similar during treatment. All the women that were analyzed started the chemotherapy with fatty liver, statistics presented for LDH 73%, AST 30%, ALT 21% and GGT 28% (n=33-34). The exception was the ALP, because in all the cycles appeared in a higher level than the literature range proposed.

Conclusions: Our results showed that the changes in the hepatic profile are not associated with the Capecitabine therapy, as the patients presented fatty liver before start the treatment.

752. Study Update for a Postmarketing Case Series Study of Adult Osteosarcoma and Teriparatide in the US

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Background: The Osteosarcoma Surveillance Study, a 15-year safety surveillance study, was initiated in 2003 to monitor for a possible association between teriparatide treatment and osteosarcoma, a rare bone cancer occurring at a rate of approximately 2.5 cases per million per year in the US in adults aged 40 years or older.

Objectives: To provide a study update for this ongoing study, including descriptive characteristics of US osteosarcoma patients aged 40 years and older.

Methods: Incident cases of osteosarcoma diagnosed on or after January 1, 2003, and tumor information are identified through cancer registries in the US. After consent, information including demographics, prior medications, and exposure to possible risk factors is ascertained via telephone interview. Medical record review is performed for a random sample each year to validate self-reported information.

Results: As of September 30, 2015, 939 patients diagnosed with osteosarcoma between 2003 and 2013 had been interviewed, and one reported use of teriparatide prior to diagnosis. Taking into account the age- and sex-adjusted background incidence rate, the estimated person-years at risk following first exposure to teriparatide, and the proportion of osteosarcoma cases that have been interviewed, three cases would be expected to have been reported at this time. Demographic characteristics were similar for interviewed and noninterviewed patients. Mean age of interviewed patients was 61 years, 52% were male, 85% were white, and 10% were African American. Osteosarcoma, NOS (71%) and chondroblastic osteosarcoma (12%) were the most common morphologic types; leg bones (31%), pelvis/sacrum (15%), and skull/face/mandible (15%) were the most common anatomical tumor sites. Reported prevalence of known risk factors was 19% for history of radiation and 5% for history of Paget's disease of bone.

Conclusions: Data from this ongoing study continue to contribute to knowledge about the long-term safety of teriparatide.

753. Completeness of Reporting of Basal Cell Carcinoma and Squamous Cell Carcinoma to a Pharmacovigilance Register and the Health and Social Care Information Centre

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Background: The British Association of Dermatologists Biologic Interventions Register (BADBIR) is a prospective, longitudinal, observational pharmacovigilance register of psoriasis patients, which aims to explore the long-term safety of biologic agents compared to conventional systemic agents. Patients are currently recruited from 152 dermatology centres in the UK and Republic of Ireland. Patients are flagged with the Health and Social Care Information Centre (HSCIC) for cancer reporting in England and Wales to maximise the capture of these events.

Objectives: To investigate the overlap in reporting of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) to BADBIR and the HSCIC.

Methods: Data up to 1st December 2014 including 8413 patients receiving biological and/or systemic therapy from England and Wales were included in this analysis. SCCs and BCCs were pre-specified as an event of special interest in BADBIR. SCCs and BCCs with an event date prior to the start date of the BADBIR registration therapy were recorded as previous cancers; incident SCCs and BCCs were classified as serious adverse events (SAEs) that were identified during follow-up following registration. In situ SCCs (Bowen's disease) were excluded.

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Results: 142 SAEs (63 SCCs and 79 BCCs) for 86 patients were recorded with BADBIR and 32 SAEs (17 SCCs and 15 BCCs) for 29 patients recorded with the HSCIC. In total, 152 SAEs (69 SCCs and 83 BCCs) were recorded for 94 patients. 318 previous cancers (141 SCCs and 177 BCCs) for 150 patients were recorded with BADBIR, and 105 previous cancers (36 SCCs and 69 BCCs) for 94 patients recorded with the HSCIC. Overall, 342 previous cancers (150 SCCs and 194 BCCs) were recorded for 172 patients. 91 patients were recorded in both databases, but only 24 of 68 SAEs and 81 of 204 previous cancers were matched for these patients.

Conclusions: The findings suggest that the reporting of SCCs and BCCs is more complete in BADBIR than HSCIC. Each data source missed a substantial proportion and failure to use linked sources may lead to biased estimates of the incidence of SCCs and BCCs.

754. Role of Clinical Pharmacists in Monitoring Radiation Related Adverse Events in Patients on Radiation or Chemo-Radiation Therapy

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Background: Radiation therapy is an important modality of treatment for cancer patients. However, it is associated with various adverse events following treatment which influence quality of life of the cancer patients.

Objectives: This study was conducted to detect and monitor radiation related adverse events and its management in patients who are on radiation therapy or chemo-radiation therapy.

Methods: This was a prospective observational study conducted at private cancer hospital for a period of six months. Patients on radiation therapy or hemo-radiation therapy were enrolled and followed by clinical pharmacists on daily basis to identify adverse event(s) if any. Upon identification, adverse events were discussed with concerned radiation oncologists for authentication and graded as per defined by Radiation Therapy Oncology Group (RTOG).

Results: A total of 226 radiation related adverse events were found during study period. Among the study subjects, majority of them received chemo-radiation (56%) than radiotherapy (44%) alone. Majority of events observed were Fatigue (17.2%), followed by Mucositis (12.8%), Pain (10.17%), Diarrhea (10.17%) and Gastritis (9.7%). Less common events were Proctalgia (8.8%), Vomiting (7.9%), Burning micturition (3%), Dermatitis (3%) and Pyrexia (2.6%). Majority of the vomiting (55%), dehydration (80%), proctalgia (65%), pyrexia (67%) and burning micturition (57%) were categorized as grade 1 and grade 2. Grade 3 and 4 events were observed as vomiting (17%), diarrhea (13%), fatigue (5%), gastritis (4.5%), proctalgia (5%) and mucositis (14%). Most of the grade 3 events or grade 4 events were reported in patients who received external radiation therapy and was on chemo-radiation therapy compare to patients who received other types of radiation therapy and was on radiation therapy alone.

Conclusions: Adverse events were found more in patients who received external radiation therapy than other types of radiation therapy. Clinical Pharmacists initiated adverse events monitoring in our study setting was found to be helpful for early detection and management of adverse events in patients on chemo-radiation therapy.

755. Adverse Drug Reactions (ADRs) of Tumour Necrosis Factor Inhibitors (Adalimumab, Infliximab, Etanercept) in a Paediatric Population: An Analysis of Individual Case Safety Reports from VigiBase

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Background: Tumor necrosis factor-alpha (TNF-α) inhibitors are being increasingly used in children despite limited evidence and safety concerns.

Objectives: The objective of the study was to review in a paediatric population adverse drug reactions (ADRs) to infliximab (IFX), etanercept (ETA) and

adalimumab (ADA) recorded in the World Health Organization (WHO) database, VigiBase.

Methods: Reports of ADRs associated to IFX, ETA, and ADA in a paediatric population (aged 2-17 years) were extracted from Vigibase between January 2007 and December 2014. Reports involving more than one TNF-α inhibitor were excluded. Characteristics of patients (age, gender, medical history), type of ADR (system organ class [SOC] and preferred term according to MedDRA international classification), and ADR seriousness were described.

Results: A total of 1,486 case safety reports were included in the study [IFX n=366 (24.6%), n= ETA n=812 (54.6%), ADA n=308 (20.7%)], corresponding to 3,206 ADRs. Mean age was 12.2 ± 4.0 years. ADRs were more frequently reported in adolescents (12- 17 years, n= 929, 62.5%) and in girls (n=946, 63.7%). Anti-TNF were mainly used in rheumatic diseases (848 reports, 57.1%). Overall, 46.5% of the reports (n=691) were "serious". For ADA, 87 (28.2%) ADR reports were "serious", 332 (40.9%) for ETA and 272 (74.3%) for IFX. The most frequently ADRs were general disorders and injection site reactions (n=615, 41.4%), infections (n=255, 17.2%), cutaneous ADRs (n=222, 14.9%), gastrointestinal disorders (n=211, 14.2%) and nervous system disorders (n=155, 10.4%). A different safety profile was found for each anti-TNF.

Conclusions: This study shows that anti-TNF ADRs were mainly reported in adolescents and in girls. Moreover, these preliminary results suggest a difference in safety profile of these 3 TNF-α inhibitors.

756. Intravenous Immune Globulin and Thromboembolic Adverse Events: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: Prior case reports and observational studies indicate that intravenous immune globulin (IVIg) products may cause thromboembolic events (TEEs), leading the FDA to require a boxed warning in 2013.

Objectives: To assess the effect of IVIg treatment on the risk of serious TEEs (acute myocardial infarction, ischemic stroke or venous thromboembolism) using adverse event data reported in randomized controlled trials (RCTs) of IVIg.

Methods: We identified RCTs of IVIg in adult patients published in 1995-2015 from Pubmed, Embase, ClinicalTrials.Gov and two large prior reviews of IVIg's therapeutic applications. Trials at high risk of detection or reporting bias for serious adverse events were excluded. Two abstractors independently reviewed each study to extract relevant information and assess risk of bias.

Results: We identified 31 RCTs with a total of 4129 participants (2318 IVIg-treated, 1811 control) that were eligible for quantitative synthesis. We found no evidence of increased TEE risk among IVIg-treated patients compared to control patients (odds ratio = 1.10, 95% CI: 0.44, 2.88; risk difference = 0.0%, 95% CI: -0.7%, 0.7%, I^2= 0%). No significant increase in risk was found when arterial and venous TEEs were analyzed as separate endpoints.

Conclusions: We did not find evidence of elevated TEE risk attributable to IVIg in our meta-analysis. However, care should be taken in extrapolating our results to patients with higher baseline risks of TEE. Trial publications provided little specific information concerning the methods used to ascertain potential adverse events. In addition, the low incidence of serious TEEs limited the precision of our risk estimates.

757. Evaluation of New Oral Anticoagulants (NOACs) Bleeding Adverse Reaction Reports in the FDA Adverse Events Reporting System (FAERS)

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Background: New oral anticoagulants (NOACs) have shown similar safety profiles in pre-marketing studies, however a little is known about their potential safety from post marketing data and spontaneous reporting systems.

Objectives: To describe and evaluate the bleeding related spontaneous adverse event reports associated with NOACs compared to warfarin.

Methods: We identified adverse events reports listing warfarin, apixaban, rivaroxaban or dabigatran in the FDA Adverse Events Reporting System (FARES) from the first quarter of 2014 to third quarter of 2015. Bleeding events were identified as adverse events described with the terms haemorrhage, haemorrhagic, bleed, bleeding. Fatal bleeding events were identified as bleeding cases with reported outcome described as death (data with duplicate case ID were excluded).

Results: We identified 28,862 adverse reports associated with oral anticoagulants. Of these, 3262 (11%) were associated with warfarin, 1394 (5%) were associated with apixaban, 21800 (76%) were associated with rivaroxaban and 2406 (9%) were associated with dabigatran. 6131 (21%) of the identified adverse reports were bleeding events and 789 (3%) were fatal bleeding events. Dabigatran was the most commonly reported anticoagulant exposure among bleeding events (826, 34.3%) and warfarin was the least common (584, 18%). Dabigatran was also the most commonly reported among fatal bleeding events (215, 26%) and warfarin was the least common (43, 7.4%).

Conclusions: Among the NOACs, dabigatran exposure was associated with the highest frequency of reported bleeding and fatal bleeding events. Though FAERS is subject to significant limitations, the results suggest that dabigatran associated bleeding evets are higher in clinical practice than they were in pre-marketing studies.

758. Risks of Bleeding Among New Oral Anticoagulants Compared to Warfarin: Analysis of Post Marketing FDA Adverse Event Reporting System (FAERS) Database, 2010-2015

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Background: Following using warfarin as an anticoagulant for years, several new oral anticoagulants (NOACs) drugs were introduced to the market. However, risk of bleeding is yet a major adverse effect of NOACs that concerns prescribers given that an antidote is not available for some of them.

Objectives: To compare risk of bleeding between NOACs and warfarin using the FDA Adverse Event Reporting System (FAERS) database.

Methods: Reports of bleeding and related terms events submitted to FAERS between October 2010 and September 2015 were retrieved and analyzed by the reporting odds ratio (ROR) along with its 95% confidence interval. The ROR of case/non-case reports of bleeding and its related terms associated with NOACs were compared with warfarin as standard therapy using FAERS database. Only reports with code of primary suspected drug "PS" were included in the analyses. All statistical analyses were conducted using Statistical Analysis Software (SAS 9.3).

Results: The total number of reports included in FAERS during the study period and met the inclusion criteria were 7,433,769 reports. Among all dabigatran reports received (n=64,894), 1,541 reports linked dabigatran to bleeding representing a proportion of bleeding reports with dabigatran of 2.3% while there were 94 reports linked rivaroxaban to bleeding out of 2,161 reports received. Furthermore, the risk of bleeding was 3.4% for warfarin with 656 reports out of 19,259 connected to bleeding. The ROR showed a statistically significant association between bleeding and its related terms with the use of these three anticoagulants dabigatran (ROR=11.8 [95% CI 11.2- 12.5]), rivaroxaban (20.4 [95% CI 16.5- 25.1]) and warfarin (16.3 [95% CI 15.1- 17.7]) consequently.All patients characteristics for each drug will be presented during the conference.

Conclusions: Based on FAERS analysis using updated period of reports, the risk of bleeding was high for all anticoagulants. Yet, the risk is higher with rivaroxaban and it double the risk with dabigatran. Healthcare professional should consider

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the risk of bleeding when making decision about the selection of the anticoagulant.

759. The Effect of Race, Age, and Sex on the Risk of Angioedema Among Heart Failure (HF) Patients Initiating Angiotensin Converting Enzyme Inhibitors (ACEIs)

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Background: Data on the effect of race, age, and sex on the incidence of angioedema specifically for HF patients initiating ACEIs are not available. Such data may inform patient care, since studies suggest that HF is a risk factor for angioedema.

Objectives: To estimate incidence rates (IRs) and incidence rate ratios (IRRs) for angioedema among HF patients without prior angioedema initiating ACEIs, stratified by race, age, and sex.

Methods: We conducted a cohort study of adult HF patients using the PharMetrics Plus database linked to consumer health data (for race data) from 1 Jan 2007 to 31 Mar 2015. Follow-up began on the index ACEI initiation date (no ACEI pharmacy fill in the prior 12 months) after being diagnosed with HF (i.e., the earliest of either a hospitalization or the first of ≥2 outpatient visits with a HF diagnosis). Follow-up ended on the earliest occurrence of an angioedema event (identified by an out- or inpatient ICD-9 code 995.1), ACEI discontinuation, loss to follow-up, or after 12 months. We estimated unadjusted IRRs with 95% confidence intervals (CI) for angioedema separately for race (Black vs. non-Black), age (≥65 years vs. <65), and sex (female vs. male).

Results: We identified 2,479 Black (median age 56 years, 45% females, 6.3 months mean follow-up) and 19,160 non-Black (median age 59 years, 34% females, 6.9 months mean follow-up) patients. Black patients had a higher angioedema risk than non-Black patients (IRR=2.1, 95% CI 0.9-4.7; IR for Black=6.2/1,000 patient-years [PYs]) as did females compared to males (IRR=2.2, 95% CI 1.1-4.4; IR for females=5.2/1,000 PYs). Patients ≥65 years of age had comparable angioedema risk than younger patients (IRR=1.2, 95% CI 0.5-2.5; IR for patients ≥65 years=3.8/1,000 PYs).

Conclusions: Our results suggest that Black patients and females are at increased risk of angioedema among HF patients without prior angioedema initiating ACEIs, similar to what is known for a non-HF specific population initiating ACEIs. Further research is needed to identify other important risk factors and interactions between risk factors in a larger data source.

760. Withdrawn by Author

761. Signal Detection Using Temporal Pattern Discovery (TPD) in Electronic Health Records (EHRs) - Lessons from Statins and Rhabdomyolysis

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Background: EHRs are valuable sources for drug safety signal detection. Novel visualization tools allow rapid insight into relationships of health outcomes and drug treatments in longitudinal observational data (LOD). Designated medical events (DMEs) may be underrepresented in general practice databases (GPD) versus those more reflective of specialty/hospital care.

Objectives: Use a well-known DME to investigate issues in the interpretation of temporal patterns between drug prescriptions and health outcomes for signal detection in a GPD.

Methods: Rhabdomyolysis with statin exposure was studied in the UK Health Improvement Network (THIN). Two TPD methods developed for safety surveillance in LOD were used: 1. A normalized metric IC delta representing outcomes occurring more often after exposure than prior. 2. Chronograph, a statistical graphical representation of observed and expected counts of medical events recorded in 30-day time window before and after drug therapy starts. IC delta and chronographs for the associations between statins and rhabdomyolysis, and myalgia-myositis are examined.

Results: Rhabdomyolysis was not highlighted for any of the statins prescribed in THIN. When myalgia-

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myositis was investigated, IC delta scores of 1.662 and 1.39 were seen for Simvastatin and Cerivastatin but negative scores of -1.907, -0.848, -1.233 and -1.668 were seen for Pravastatin, Fluvastatin, Atorvastatin and Rosuvastatin.

Conclusions: Statins and the term rhabdomyolysis were not highlighted with TPD. Low counts could reflect a rare and/or serious outcome not captured frequently in UK GPD. The more frequently recorded term myalgia-myositis was highlighted for some, but not all, statins, possibly reflecting complex statin switching patterns accentuated by NICE guidelines, but this is to be confirmed. Hypothesis-free signal detection in EMRs is no panacea; more work is needed to determine optimal granularity level for signal detection and whether data sets more reflective of specialist/hospital care are preferred for some DME surveillance.

762. The Impact of Age and Gender on Reporting of Cough and Angioedema with RAS Inhibitors: A Case/Non-Case in VigiBase

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Background: Little is known about the effect of age and gender on reporting of cough/ angioedema with renin angiotensin system (RAS) inhibitors (angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and aliskiren, a direct renin inhibitor (DRI).

Objectives: To assess the impact of age and sex on the occurrence of cough/angioedema with RAS inhibitors using information reported to the World Health Organization (WHO) global individual case safety report database (VigiBase).

Methods: A case/non-case study was performed in VigiBase. Cases were defined as reports of cough/angioedema and non-cases were all reports of other adverse events. Age was divided into 6 categories: infant and childhood (0-11 years), adolescence (12-19 years), young adulthood (20-39 years), middle adulthood (40-59 years), elderly (60-79 years) and late elderly (≥80 years). Logistic regression analysis was used to assess the association between reporting of cough/ angioedema with each class of RAS inhibitors stratified by age/ sex and to control for confounding.

Results: The reporting of cough with ACE inhibitors was significantly higher in women than in men (adjusted reporting odds ratio (ROR): 29.2, 95%CI (28.5-29.9) for men versus 44, 95%CI (43.2-44.8) for women). There was no difference in reporting of cough with ARBs and DRI between men and women. In contrast, the reporting of angioedema with ACE inhibitors and ARBs was significantly higher in men than women but for DRI (aliskiren), women had significantly higher ROR than men. For the effect of age, the reporting of cough with ACE inhibitors was significantly increased with age until reaching a plateau at 60 years and the reporting of angioedema with ACE inhibitors was significantly increased with age until 80 years. Age had only a slight effect on reporting of cough/angioedema with ARBs and DRI.

Conclusions: Age and sex have substantial effects on reporting of cough/angioedema with RAS inhibitors especially with ACE inhibitors. Further studies are needed to study both factors on occurrence of cough/ angioedema with RAS inhibitors and to elucidate the underlying mechanism involved.

763. A Novel Approach to Study the Impact of Ethnicity on Reporting of Cough/Angioedema with RAS Inhibitors in VigiBase

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Background: Cough and angioedema are adverse events associated with especially angiotensin-converting enzyme (ACE) inhibitors but also reported with angiotensin receptor blockers (ARBs) and aliskiren, a direct renin inhibitor (DRI). Susceptibility of developing cough/angioedema with ACE inhibitors depends on ethnicity, which is not documented in spontaneous reporting systems of drug safety.

Objectives: To assess the impact of ethnicity on the occurrence of cough/angioedema with renin angiotensin system (RAS) inhibitors using information

reported to the the World Health Organization database(VigiBase).

Methods: A case/non-case study was performed in VigiBase. Cases were defined as reports of cough/angioedema and non-cases were all reports of other adverse events. The reporting countries were divided into three categories: black African countries, East Asian countries and other countries. Logistic regression analysis was used to assess the association between reporting of cough/angioedema with each class of RAS inhibitors stratified by country group and to control for confounding.

Results: The reporting of cough with ACE inhibitors was significantly higher in East Asian countries than black African countries and other countries (adjusted reporting odds ratios (RORs): 256, 95%CI (236-278), 48.9, 95%CI (42.7-56.1) and 35.4, 95%CI (34.8-35.9), respectively. The reporting of angioedema with ACE inhibitors was significantly higher in black African countries than East Asian countries and other countries (adjusted RORs: 55.3, 95%CI (45.5-67.2), 5.29, 95%CI(3.89-7.21) and 16.5, 95%CI (16.1-16.8), respectively. There was no difference in reporting of cough/angioedema with ARBs and DRI between black African countries, East Asian countries and other countries.

Conclusions: Our results by grouping countries according to ethnicity in VigiBase are consistent with previous results in the literature suggesting that the occurrence of cough with ACE inhibitors is higher in East Asian patients and the occurrence of angioedema with ACE inhibitors is higher in black patients. These findings indicate that ethnicity should be included as scientific parameter in pharmacovigilance.

764. Cardiovascular and Gastrointestinal Safety of Paracetamol in French Population: A Self-Controlled Cohort Study

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Background: Though paracetamol is one of the most commonly used drugs worldwide, very little is known of its cardiovascular (CV) and gastrointestinal (GI) safety.

Objectives: To evaluate the risk of acute coronary syndromes (ACS), stroke and GI bleeding events associated with the use of paracetamol.

Methods: A self-controlled cohort study in EGB, the permanent 1/97 representative sample from the French national healthcare insurance database that covers 84% of paracetamol sales. All exclusive episodes of paracetamol use in patients aged ≥15 years between 2009 and 2012 were identified. Main outcomes were ACS, stroke and GI bleeding. Risk periods were the periods from the first day of exposure (t0) to the next episode of NSAIDs/paracetamol use, or 3 months after t0. Control periods were the non-exposure time right before t0. Risks of outcome occurrence were estimated by comparing hazard rates in risk periods to their control periods by COX proportional hazard models.

Results: 1 026 041 paracetamol exclusive episodes in 342 561 users (mean age 47.2 years; 55.8% female) were included. We identified in total 685 and 843 ACS events (event rate 3.2 and 3.2 per 10,000 episode-months); 340 and 378 stroke events (event rate 1.6 and 1.4); 132 and 227 GI bleeding events (event rate 0.6 and 0.9) during control and risk periods respectively. CV risk did not increase overall (ACS hazard ratio 0.99, 95% CI 0.90 to 1.10; stroke HR 0.90, 0.78 to 1.04). However, if we exclude episodes with co-dispensed low-dose aspirin, ACS risk increased significantly (HR 1.37, 1.21 to 1.55). GI bleeding risk also increased significantly (1.39, 1.12 to 1.73). Episodes with low baseline CV risk were associated with significant increase of stroke risk (1.45, 1.09 to 1.92). Patients aged ≥60 years had significant increases of ACS and GI bleeding risk (1.38, 1.18 to 1.60 and 1.49, 1.11 to 2.00).

Conclusions: Our study contributes data on safety of paracetamol. We found a 37% increase of ACS risk associated with paracetamol without co-dispensed aspirin. Use of paracetamol in the elderly should be reconsidered because of poor CV and GI safety.

765. Cardiovascular and Gastrointestinal Safety of OTC and Prescription-Only Ibuprofen versus Paracetamol in French Population

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Background: Ibuprofen and paracetamol are the two most widely used analgesics, yet few studies have compared the cardiovascular (CV) and gastrointestinal (GI) safety of OTC and prescription-only (POM) ibuprofen to paracetamol.

Objectives: To evaluate the CV and GI bleeding risk associated with OTC and POM ibuprofen versus paracetamol.

Methods: A cohort study in EGB, the permanent 1/97 representative sample from the French national healthcare insurance database, which accounts for 70% of OTC ibuprofen sales (81% of ibuprofen use was at OTC doses) and 84% of paracetamol sales. All exclusive episodes of paracetamol or ibuprofen use in patients aged ≥18 years between 2009 and 2012 were identified. We used propensity scores to match paracetamol episodes with OTC and POM ibuprofen episodes. Patients were followed-up to the end of exposure +60 days, or to the next treatment episode. Main outcomes were acute coronary syndromes (ACS), stroke and GI bleeding. Risks of all outcome occurrence, as well as ACS only were estimated by COX proportional hazards models.

Results: 835 313 paracetamol, 200 379 OTC ibuprofen and 73 888 POM ibuprofen episodes were included (mean age 50.2, 42.4 and 42.3 year-old respectively). OTC matched sample included 197 267 ibuprofen and 197 267 paracetamol episodes (age 42.3). POM matched sample included 72 091 ibuprofen and 144 032 paracetamol episodes (age 42.2). There was no significant increase of any outcome occurrence risk associated with ibuprofen, either OTC (hazard ratio 0.98, 95% CI 0.69-1.40; event rate 2.1 vs. 2.1 per 10,000 episode-months), or POM (HR 1.16, 0.68-1.98; event rate 2.1 vs 2.0). ACS risk associated with OTC ibuprofen did not increase overall (HR 1.11, 0.71-1.72), but did in the first 15 days (3.21, 1.45-7.09; event rate 2.8 vs. 0.9). No significant increase of ACS risk associated with POM ibuprofen was found (15 days: 1.32, 0.47-3.70; overall: 1.14, 0.57-2.29).

Conclusions: Regarding all safety outcomes, there was no significant difference between OTC/POM ibuprofen and paracetamol. However, there was a significant increase of ACS risk associated with OTC but not POM ibuprofen in the first 15 days.

766. Cardiovascular and Gastrointestinal Safety of and Prescription-Only NSAIDs versus Paracetamol in French Population

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Background: Few studies have compared the cardiovascular (CV) and gastrointestinal (GI) safety of prescription nonsteroidal anti-inflammatory drugs (POM NSAIDs) to paracetamol.

Objectives: To evaluate the CV and GI bleeding risks associated with some frequently used POM NSAIDs in France versus paracetamol.

Methods: A cohort study in EGB, the permanent 1/97 representative sample from the French national healthcare insurance database, which accounts for all POM NSAIDs and 84% of paracetamol sales. All exclusive episodes of paracetamol and POM NSAIDs use in patients aged ≥30 years between 2009 and 2012 were identified. Paracetamol episodes were matched with episodes of individual POM NSAIDs by age and propensity scores. Patients were followed-up to the end of exposure +60 days, or to the next episode. Main outcomes were acute coronary syndromes (ACS), stroke and GI bleeding. Risks of all outcome occurrence, as well as CV outcomes were estimated by COX proportional hazard models.

Results: 706 095 paracetamol (mean age 55.3, 60% female) and 527 755 POM NSAID episodes (mean age 51.7, 58% female) were identified. Ketoprofen was the most frequently used (n=117 837, age 49.8), following by diclofenac (n=105 876, age 54.7) and naproxen (n=37 131, age 51.1). The three matched samples included 222 916 paracetamol and 111 824 ketoprofen (mean age 49.6); 191 856 paracetamol and 96 339 diclofenac (mean age 53.6); 37 018 paractamol and 37 018 naproxen (mean age 51.1). No increase of CV risk associated with ketoprofen, diclofenac and naproxen was found in comparison to paracetamol (ketoprofen: hazard ratio 0.93, 95% CI 0.65-1.32, event rate 2.3 vs. 2.5 per 10,000 episode-months; diclofenac: HR 0.94, 0.68-1.28, event rate 3.0 vs. 3.3; naproxen HR 0.85, 0.41-1.79, event rate 1.9 vs. 2.1). Regarding all safety outcomes, we also found no increase of risk associated with either

ketoprofen (HR 0.89, 0.64-1.24), or diclofenac (0.95, 0.71-1.26), or naproxen (HR 1.02, 0.53-1.99).

Conclusions: CV and GI safety of the most frequently used POM NSAIDs (ketoprofen, diclofenac and naproxen) were not significantly different from paracetamol.

767. Gastrointestinal Toxicity Among Patients Taking Selective Cox-2 Inhibitors or Conventional NSAIDs Alone or Combined with Proton Pump Inhibitors: A Case Control Study

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Background: Conventional NSAIDs increase the risk of gastrointestinal (GI) toxicity. This risk can be reduced by combining with a proton pump inhibitor (PPI) or by replacing with a selective COX-2 inhibitor. In daily practice a selective COX-2 inhibitor is sometimes combined with a PPI but only a few studies evaluated the added value of this combination.

Objectives: We assessed the risk of GI perforation, ulcers or bleeding (PUB) associated with use of selective COX-2 inhibitors with or without PPIs, and conventional NSAIDs with PPIs, all compared to conventional NSAIDs alone.

Methods: A nested case control study was performed in a cohort of users of conventional NSAIDs and/or selective COX-2 inhibitors within the Dutch PHARMO Record Linkage System from 1998-2012. Cases were patients aged ≥18 years with a first hospital admission for PUB. Only current users of conventional NSAIDs and selective COX-2 inhibitors with or without PPIs were analyzed. For each case, up to 4 controls without PUB were matched on age and sex at the date each case patient was hospitalized. Logistic regression was used to calculate adjusted odd ratios (aORs) and 95% confidence intervals (95% CIs) of PUB.

Results: Among 15,962 cases and 62,683 controls, 2,634 cases and 5,074 controls were current users of conventional NSAIDs or selective COX-2 inhibitors. Compared to conventional NSAIDs alone, use of selective COX-2 inhibitors with PPIs had the lowest risk of PUB (aOR, 0.51: 95%CI, 0.35-0.73), followed by selective COX-2 inhibitors alone (aOR, 0.66: 95%CI, 0.48-0.89) and conventional NSAID with PPIs (aOR, 0.79: 95%CI, 0.68-0.92). Compared to patients aged 18-74 years, those aged ≥75 years taking conventional NSAIDs with PPIs, the risk of PUB was lower (aOR, 0.79: 95%CI, 0.64-0.99), while for those taking selective COX-2 inhibitors the risk was higher (aOR, 1.22: 95%CI, 1.01-1.47) compared to conventional NSAIDs alone.

Conclusions: Use of selective COX-2 inhibitors with or without PPIs and conventional NSAIDs with PPIs were associated with lower risks of PUB compared to conventional NSAIDs alone and this effect was modified by age.

768. Safety Of Non-Prescription NSAIDs

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Background: Regulation of NSAIDS is an area of ongoing controversy, with lower dose preparations and smaller pack sizes available as non-prescription items in many countries. Multiple studies have identified harms associated with the use of NSAIDs, however these studies have focused on prescribed medications, and it is unknown to what extent such harms are evident with non-prescription NSAIDs.

Objectives: The aim of this study was to quantify the risk of adverse gastrointestinal, cardiac and renal outcomes associated with the use of non-prescription NSAIDs.

Methods: Disproportionality analyses using national voluntary reporting data from Australia and Canada were used to detect potential signals of gastrointestinal bleed, cardiovascular and renal adverse effects associated with the use of non-prescription NSAIDs. Outcomes were classified using the Medical Dictionary for Regulatory Activities (MedDRA) terminology and medications were classified using the Anatomical Therapeutic Chemical Classification System (ATC). Non-prescription NSAIDs were identified using relevant brand names in each dataset. Sensitivity analysis

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was conducted in the ADRS dataset to confirm the robustness of identification of non-prescription NSAIDs. Exposure variables were adjusted for age, gender and relevant confounding risk factors.

Results: Non-prescription NSAIDS were associated with a 100% increase in the risk of GI bleed in both datasets (Australia: Relative Odds Ratio (ROR) =2.847 (95% CI: 2.432 - 3.332), Canada: ROR=2.322 (95% CI: 2.141 – 2.519)). A small but significant increased risk of adverse renal outcomes was observed in both datasets (Australia: ROR=1.240 (95% CI 1.039 – 1.481), Canada: ROR=1.333, (95% CI 1.224 – 1.452)). A small increased risk of adverse cardiovascular outcomes was observed in the Canadian dataset (ROR=1.343 (95% CI: 1.288 – 1.401)), however no increased risk was found in the Australian data.

Conclusions: Considerable risks were associated with the use of non-prescription NSAIDs, despite the availability of lower dose formulations and smaller pack sizes in many markets. These results have implications for both the use and the regulation of NSAIDs, demonstrating that considerable harms may be associated with non-prescription products.

769. Codeine Use in Children with Common Cold in Taiwan: Data from National Health Insurance Research Database (NHIRD) and National Adverse Drug Reaction (ADR) Reporting System

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Background: The use of codeine for the treatment of cough and common cold in children is restricted in developed countries due to the safety concern of potential opioid-associated toxicity.

Objectives: To examine the prescription pattern of codeine products and associated codeine toxicity in children with common cold in Taiwan.

Methods: Two data sources were used in this study. We retrieved outpatient codeine prescriptions in Taiwan's NHIRD (year 2010) to examine the prescription pattern of codeine for children with common cold (defined as patients aged ≤18 having a primary diagnosis of acute respiratory infection [ARI]). We also reviewed all codeine-associated reports in the Taiwan National ADR Reporting System Database to analyze the characteristics of children who received codeine (year 2003-2015).

Results: From the NHIRD, we identified a total of 164,670 children diagnosed with a common cold, and 10.7% of them received codeine prescription in year 2010. It could be estimated that a total of over 400,000 children nationwide, annually, were prescribed codeine for common cold. Approximately one-seventh (14.5%) and one-eighth (12.8%) of children aged 2-5 and 6-12 received codeine prescriptions. In addition, we found that codeine was prescribed for 3.6% of the ARI episodes for children who received their care in clinics, followed by 2.4% in local hospitals, 0.5% in regional hospitals, and 0.3% in medical centers, respectively. In the ADR database, 216 codeine-associated reports were reviewed. Of them, 38 received codeine for respiratory disorders. Two cases (one dyspnea and one skin rash) were identified in patients aged under 18, but neither of them was severe.

Conclusions: A considerable number of children with common cold in Taiwan were exposed to codeine. Although no serious case of codeine-associated reports has been reported in children with respiratory disorders, codeine-induced ADRs in such population might have been underestimated as codeine was prescribed for a common cold mostly in clinics, whereas ADRs in Taiwan were mainly reported by medical centers and hospitals.

770. Automating Opioid Overdose Surveillance Using Natural Language Processing

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Background: The epidemic of opioid-related overdoses demands new methods for public health surveillance.

Objectives: Develop an automated method to identify and classify types of opioid overdoses using electronic health record (EHR) text clinical notes.

Methods: We developed a natural language processing (NLP) application for identifying events related to overdose in text notes of the EHR. We first defined events related to overdose, as documented in care records. These were used to build a NLP application based on terms, concepts, and combinations of concepts (including rule-out concepts) that indicate overdose and intention. We began with established overdose cases from Kaiser Permanente Northwest (2008-2013) identified using ICD diagnosis codes and chart-reviewed (n=1053). We selected 505 cases, of which 69% had indicators of opioid-related abuse and 95% were confirmed opioid overdoses according to chart audit. Text clinical notes for encounters up to 7 days following the event date were extracted and, after dropping cases that had no EHR encounters available, the final dataset included 493 cases for 467 patients with 6,442 encounters. Cases were re-abstracted for a set of 25 criteria to ascertain outcomes, substances involved, and patient intentions and behaviors related to putative overdose events. For each case, all encounters in the 7-day window beginning on the event date were processed by the NLP application to identify overdoses, and whether or not the overdose included a suicide attempt. Any indication of intent to commit suicide by overdose resulted in an Inten-OD classification. Otherwise, indications of overdose yielded the classification Uninten-OD. These classifications were compared to chart review. All false positives and false negatives were investigated to understand discordance, and iterative changes were made in the NLP application to reduce discordance.

Results: Uninten-OD/Inten-OD.79(.74,.84)/.97 (.81,.92) Sensitivity.85(.79,.89)/.94(.91,.96) Specificity.86(.81,.90)/.87(.81,.92) Pos Pred Value.

Conclusions: Results indicate that statements attributing overdose and intent of overdose can be identified in text clinical notes from the EHR with relatively high degree of accuracy.

771. Antiepileptic Drugs, Risk Of Suicide Attempts And The Impact Of Underlying Medical Conditions: Results From The PGRX Information System

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Background: In 2008, the Food and Drug Administration issued an alert after finding an increased risk for suicidality in 199 clinical trials of 11 antiepileptic drugs (AED) used across different indications. Following this, several cohort studies were performed using electronic healthcare databases (eHCD), which may be inadequate to explore fully confounding by indication.

Objectives: To explore the association between AED use and risk of suicide attempt (SA) in adults, taking account of psychiatric and neurological condition.

Methods: A case-control study was performed in France nationwide between June 2008 and September 2012. Cases were adults patients with 1 incident episode of suicide attempt requiring hospitalization for at least 12 hours and occurring within the previous month and with no other episode in the 12-month preceding recruitment (n=506). Controls were patients without history of suicide attempt, seen by a general practitioner (n=2829), and matched to SA cases on age and sex. Information on AED use, socioeconomics, lifestyle and personal medical history was collected by the psychiatrist for cases or by the physician for controls. Data on drug exposure was self-reported by participants through standardized patient telephone interviews. The association between AED use (all AEDs) and risk of suicide attempt was explored using logistic conditional regression and adjusted analyses after stratification on depression and neurologic status.

Results: There was a crude association between AED use in the 12 months preceding the index date and risk of suicide attempt (Odds Ratio [OR], 3.1; 95% confidence interval [CI], 2.1 to 4.5). In patients with current and/or past depression, AED use was associated with risk of suicide attempt, but this was no longer the case when clonazepam was excluded from the group of AEDs (OR, 0.9; 95% CI, 0.5-1.7). In patients with epilepsy, migraine or chronic neuropathic pain, no significant association was found between AED use and risk of suicide attempt (OR, 1.3; 95% CI, 0.6-2.8).

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Conclusions: The association observed between AEDs and SA is explained by underlying psychiatric or neurological conditions.

772. Social Media Mining to Investigate Multiple Sclerosis Treatment Patterns and Adverse Effects

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Background: Multiple sclerosis (MS) is a common complex disorder, with new treatment options emerging each year. Social media is being increasingly used to investigate patient opinions about diseases.

Objectives: To investigate whether social media can be used to provide information on MS treatment patterns and treatment related adverse effects.

Methods: The Twitter resource Topsy was searched for tweets mentioning the following MS treatments: Aubagio, Avonex, Betaferon or Betaseron, Copaxone, Extavia, Gilenya, Lemtrada, Novantrone, Rebif, Tysabri and Tecfidera between 1 Jan 2006 to 31 Jul 2014. These tweets were curated manually, with tweets being classified into groups relating to 1) adverse effects, 2) switching or discontinuing MS treatment or 3) both. This dataset acted as the training dataset for machine learning approaches to automate the identification of similar tweets in Twitter data from 2015-2016.

Results: In total, in the manually curated training dataset there were 58196 unique tweets mentioning an MS treatment; 3510 of which contained words related to adverse effects (n=2282) , switching or discontinuing an MS treatment (n=837) or both (n=391). The drugs with the highest frequency of tweets mentioning switching and/or discontinuing were Copaxone (27.0%), Tysabri (19.7%), Rebif (18.8%) and Avonex (17.7%). The most frequent switch mentioned was between Avonex and Copaxone (22.2%). Of the 2282 tweets associated with adverse effects, aches and/or pains (15.7%), discomfort at the injection site (13.8%), being fatigued (7.9%), having flu-like symptoms (7.4%) and headaches (7.01%) were the most frequently mentioned.

Conclusions: Social media is a potentially rich data source that can be used to investigate MS treatment patterns and drug-related adverse effects; however appropriate methods are required to separate signal from noise. The lack of a denominator needs to be considered when trying to quantify the impact of these findings in the overall MS population.

773. Lymphopenia in Multiple Sclerosis Patients Treated with Delayed-Release Dimethyl Fumarate: Analysis of 2 Electronic Health Record Databases in the US

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Background: In clinical trials, delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) significantly reduced clinical and neuroradiological disease activity and exhibited a favorable benefit–risk profile in patients with relapsing-remitting multiple sclerosis (RRMS). DMF treatment was also associated with severe (Grade 3) lymphopenia (absolute lymphocyte counts [ALC] <500 cells/μL) in 6% of patients. More data on a large cohort is needed to understand the effects of DMF on ALCs in the real-world setting.

Objectives: Evaluate ALCs in patients with MS treated with DMF using data from two US electronic health record (EHR) databases.

Methods: Using 2 US EHR databases (Geisinger Health System and Humedica), we identified patients with a diagnosis of MS (ICD-9: 340). Patients included in the analyses received ≥1 prescriptions for DMF and had ALC values available at baseline (within 6 months prior to DMF initiation) and at one or more times during DMF treatment. ALC ≥1000 cells/μL was considered normal.

Results: A total of 1014 patients (201 Geisinger and 813 Humedica) met the inclusion criteria; demographic characteristics of patients were similar (71% and 77% female, respectively; mean age: 44 and 47 years, respectively). Among patients who had both baseline and 12-month ALC values, mean ALCs decreased from 1881 to 1272 cells/μL (32% decrease) in Geisinger and from 1858 to 1339 cells/μL (28% decrease) in Humedica. Among patients who had a normal ALC at baseline, 6% (Geisinger) and 5% (Humedica) developed severe lymphopenia (≥1 ALC <500 cells/μL) during DMF treatment. Mean time from DMF initiation to severe lymphopenia was approximately 9 months.

Conclusions: ALC profiles in DMF-treated patients were generally stable throughout time in the real-world setting. Findings in terms of percentage reduction in ALCs at 12 months, proportion of patients who developed severe lymphopenia, and time to severe lymphopenia were similar to observations in clinical trials. Additional analyses are being conducted to examine ALC recovery in severely lymphopenic patients.

774. Rapidly Increasing Atypical Antipsychotic Use in Middle Age Australians

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Background: There has been a significant increase in the prescribing of atypical antipsychotics in preference to typical antipsychotic agents for the treatment of schizophrenia and bipolar disorder due to fewer extrapyramidal side effects. Patterns of antipsychotic use vary with age, gender and indication. Although the harms associated with antipsychotics are well documented there has been a significant increase in the off-label prescribing of these medicines to treat less well evidence-based conditions.

Objectives: To assess changes in drug utilization of atypical antipsychotics subsidised by the Australian Government Pharmaceutical Benefit Scheme (PBS) by age.

Methods: The Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee reviewed de-identified pharmacy dispensed claims for R/PBS-subsidised atypical antipsychotics from 1 December 2011 to 31 December 2012. Data elements extracted for each de-identified record were age at date of supply, gender, medicine form and strength, and prescriber type.

Results: An estimated 155,630 Australians aged between 20-60 years received a subsidised antipsychotic in 2012 - an increase of 70% over the last 5 years.

The most rapidly increasing atypical antipsychotic in 2011/12 was quetiapine. Of people aged 20-59 years dispensed an atypical antipsychotic 37.6% received quetiapine. Overall, 23.2% of patients taking quetiapine were taking only the 25mg strength tablet.

The analysis suggests that quetiapine 25mg is being used once daily for indications other than schizophrenia, bipolar disorder or other psychoses. Quetiapine 25mg is increasingly used for its sedative properties although there is only limited trial evidence for this 'off-label' indication.

Conclusions: The increasing prevalence of use of quetiapine 25mg once daily requires clinicians to be vigilant for potential harm and long-term consequences at an individual and societal level.

775. Metabolic Syndrome Among Clients On Atypical Antipsychotics In Jos, Plateau State

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Background: Psychosis is a serious mental disorder characterized by defective or lost of contact with reality often with hallucination or delusions. It is managed non- pharmacologically and pharmacologically using antipsychotics (typical and atypical) Metabolic syndrome is a name given to a group of risk factors that raises one's risk for heart disease and other health problems, such as diabetes and stroke caused by atypical antipsychotics. Metabolic risk factors include; a high triglyceride, low HDL cholesterol level, High blood pressure, High fasting blood sugar, Obesity.

Objectives: The aim was to assess the metabolic syndrome induced by atypical antipsychotics in patient with psychosis in Jos, Plateau State.

Methods: It was a prospective study design for a period of 6 months and multistage sampling method was used, data was collected using a pretested profoma and analysed using SPSS version 17. A total of 122 respondents both male and female on atypical antipsychotic in Jos, Plateau state were used.

Results: The age range was between 15 to 70 years. About 62% of the subjects had increased fasting blood sugar levels when compared with the baseline values, 21% of participant had increased triglyceride, 34.5%

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had body mass index value increased making them overweight and obese, while 39% had increase in their blood pressure value.

Conclusions: At the end of the study, the prevalence of metabolic syndrome was 70.5%. The study shows that atypical antipsychotics cause metabolic syndrome and there is need for continuous monitoring of the patients in order to reduce their effects and manage the complications.

776. Safety of Brotizolam in Hospitalized Patients in Internal Medicine Departments

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Background: The balance between the benefits of sleep improvement during hospitalization and the downside of sleep medications is delicate. Brotizolam is a benzodiazepine medication used commonly for sleep induction; data regarding its safety in hospitalized patients is limited.

Objectives: To evaluate the safety of Brotizolam in hospitalized patients.

Methods: A single center, comparative historic cohort analysis of patients hospitalized in internal medicine departments during the year 2012. Patients treated with Brotizolam were compared to patients not treated with any benzodiazepines during hospitalization. Data was collected from the computerized medical records and subjected to rigorous statistical analysis including descriptive and multivariate logistic regression analysis with propensity score. Primary outcome was any of the following safety events: mechanical ventilation, delirium, and falls.

Results: 600 records were included after exclusion in the final analysis; 300 treated with Brotizolam (treatment) and 300 not treated with any benzodiazepines (comparator). There were statistically significant differences between the groups in regard to the epidemiological characteristics; Age, Charlson Comorbidity Index, and psychotropic drug use. After adjustment the primary outcomes occurred at significantly higher rates in treated patients than in untreated patients (17 vs. 2 events; OR=7.33; 95%CI[1.66-32.4]; p=0.008). Any psychotropic medication administered during hospitalization was found by logistic regression to be the main independent risk factor for the studied safety outcomes (OR=3.66; 95%CI[1.35-9.9]; p=0.011) while age, comorbidities and the cause of hospitalization were not.

Conclusions: Treatment with Brotizolam during hospitalization in internal medicine departments was linked to a higher risk of respiratory deterioration, delirium and falls. Use of psychotropic medications during hospitalization in internal medicine departments was the main independent risk factor of safety outcomes in the studied cohort.

777. Associations Between Anticholinergic Burden and Adverse Health Outcomes in Parkinson Disease

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Background: Medications used in the treatment of cardiovascular, genitourinary, and psychiatric conditions have anticholinergic effects in the brain. Individuals with Parkinson disease (PD) may be vulnerable to adverse effects of anticholinergic medications due to disease-related disruption of central cholinergic pathways. Pharmacoepidemiology data in PD are limited.

Objectives: The primary objectives of our study were to determine if anticholinergic burden in PD was associated with the diagnosis of fracture and delirium. Secondary objectives were to examine whether anticholinergic burden increased the risk of emergency department (ED) visit and inpatient readmission within 30-days of discharge.

Methods: We examined dispensed medications, diagnoses, and readmission in a cohort of 16,302 PD inpatients admitted to hospitals in the United States subscribed to Cerner Health Facts, an electronic medical record platform, between 2000 and 2011. Anticholinergic burden was assessed using the Anticholinergic Risk Scale (ARS). Unconditional logistic regression was used to compute the odds of fracture and delirium compared to ARS score = 0 for categories of anticholinergic burden. Cox proportional hazard models were used to estimate the 30-day ED visit and inpatient readmission risk associated with increasing anticholinergic burden.

Results: Use of non-PD medications with moderate to very strong anticholinergic potential was common (57.8%). Individuals with the highest ARS score (≥4) had an increased odds of fracture (adjusted odds ratio (AOR): 1.56, 95% CI: 1.29-1.88) and delirium (AOR: 1.61, 95% CI: 1.08-2.40) compared to those with no anticholinergic burden. Similarly, individuals with the highest ARS score were at increased risk of ED visit (adjusted hazard ratio (AHR): 1.32, 95% CI: 1.10-1.58) and inpatient readmission (AHR: 1.16, 95% CI: 1.01-1.33) within 30-days of discharge.

Conclusions: We found a positive association between increased anticholinergic burden and adverse health outcomes among individuals with PD. Additional studies are needed to better understand the risks of anticholinergic medications in PD.

778. Eosinophilic Pneumonia and NSAIDs: Contribution of Spontaneous Reports Database

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Background: The majority of adverse drug reactions (ADR) induced by non-steroidal anti-inflammatory drugs (NSAIDs) are well-known such as bleeding or renal failure. Spontaneous reporting system is essential for signal detection. Rare events are not detected in national database.

Objectives: The aim was to describe eosinophilic pneumoniae associated with NSAIDs in French Pharmacovigilance Database (FPVD) and highlight potential signals of pneumotoxicity through combined literature evaluation.

Methods: All cases of ADR involving eosinophilic pneumonia and NSAID reported to the FPVD from January 1985 to December 2015 were reviewed. We analyzed the database using the MedDRA terms (PT) : "eosinophilic pneumonia", "eosinophilic pneumonia acute", "eosinophilic pneumonia chronic" and "pulmonary eosinophilia". We performed a literature search in the Medline and Cochrane library database, using the following terms : "eosinophilic pneumoniae", "eosinophilic pneumoniae acute", "eosinophilic pneumonia chronic", "pulmonary eosinophilia" and NSAID until December 2015.

Results: Five reports were recorded in the FPVD (2 with naproxen, 2 with ibuprofen and 1 with niclofenac). In two cases, NSAID was the only suspected drug, and one had a positive rechallenge. In the literature, 26 cases of eosinophilic pneumonia with NSAIDs were published. Most commonly involved drug were naproxen (n=8), followed by nenbufen (n=4), ibuprofen (n=3) and diclofenac (n=2). All the patients were hospitalised and recovered. In 12 cases corticosteroid therapy was needed in addition with the NSAID discontinuation.

Conclusions: Naproxen is the only one NSAID with eosinophilic pneumonia mentioned in the Summary of Product Characteristics. Our study highlights that other NSAID are involved in this side effect. Spontaneous reports database are a value added in signal detection. Prescribers should be informed and aware of this ADR.

779. Withdrawn by Author

780. Varenicline and Risk of Self-Harm: A Nested Case-Control Study

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Background: Smoking remains a serious public health concern. Pharmacotherapy for smoking cessation, including bupropion and varenicline, are proven means to increase quit rates. Post-marketing reports describing suicidal behaviours have raised concerns about the safety of varenicline. However, whether varenicline imparts a higher risk of suicide relative to bupropion remains uncertain.

Objectives: To examine the risk of self-harm associated with varenicline compared to bupropion.

Methods: A nested case-control study in Ontario, Canada, from April 1, 2011 to March 31, 2015 was conducted. Subjects were residents of Ontario aged 18 years and older with publicly funded drug coverage receiving either bupropion or varenicline for smoking cessation. Cases were defined as those with a hospitalization or emergency department visit for suicide or non-fatal self-harm within 90 days of treatment. For each case, we identified up to fifty controls from the same cohort matched on age, sex, history of self-harm, use of selected psychotropic medications, alcohol abuse and prior admission to a mental health unit. Conditional logistic regression was used to estimate odds ratios for self-harm or suicide following exposure to varenicline relative to bupropion.

Results: We identified 331 cases and 5,346 matched-controls. Following adjustment for potential confounders, we found that varenicline was not associated with an increased risk of suicide/self-harm relative to bupropion (adjusted odds ratio 1.15; 95% confidence interval 0.71 to 1.87).

Conclusions: Treatment with varenicline does not appear to significantly increase the risk of suicide or self-harm relative to bupropion.

781. Adverse Drug Reaction Monitoring at a Regional Pharmacovigilance Centre (B.P.K.I.H.S.)

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Background: Adverse drug reactions (ADR) are unintended drug consequences which are often preventable. ADR monitoring is the cornerstone of Pharmacovigilance. Pharmacovigilance plays an important role in rational use of drugs. This study was to observe the pattern of ADRs at Eastern Regional Pharmacovigilance Centre of Nepal, (B.P.Koirala Institute Health Sciences).

Objectives: to observe the pattern of ADRs at Eastern Regional Pharmacovigilance Centre of Nepal.

Methods: It was a cross-sectional study of clinician-diagnosed ADR among patients presented to BPKIHS between July 2012 to July 2015. 150 ADRs from different departments of the Institute were collected and analyzed in the department of clinical pharmacology and Therapeutics, Regional Pharmacovigilance Centre.

Results: There were total 150 ADRs reported among patients during 3 years monitoring period. Highest percentage of ADR was collected from Department of Psychiatry (60.67%). Maximum number of ADRs observed were due to CNS drugs (64.66%) followed by endocrinal drugs (17.33%) and antimicrobial drugs (12.00%). ADR due to steroid (16.67%), i.e., Headache, Insomnia, puffiness of face, acid peptic disorder, oral candidiasis etc. and diverse CNS drugs related ADRs (14.66%) e.g. dryness of mouth, sexual dysfunctions etc. were the most common ADRs seen.

Conclusions: CNS drugs related ADRs were most commonly observed. Careful monitoring, better reporting and dedicated follow up of the patients might lead to more and better ADR detection.

Keywords: Pharmacovigilance, ADRs, BPKIHS.

782. Daily Limit of Acetaminophen More Likely to be Exceeded in Cold/Flu Season

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Background: Excessive intake of acetaminophen is associated with risk of liver injury.

Objectives: To estimate variations in consumption of acetaminophen doses exceeding the 4 gram daily limit, based on seasonal variations in cold and flu illnesses.

Methods: Adults recruited from online research panels completed diaries detailing Rx and OTC acetaminophen use over 7 days, including products combining acetaminophen with other ingredients, some of which are labeled to treat upper respiratory conditions such as colds and flu ("UR" medications). Seasons were defined based on Google trends data on relevant search terms. Analyses were based on 11,184 acetaminophen users and 45,705 acetaminophen usage days from 3 years of data, 2011-2014, and focused on comparing cold/flu season (CFS) to off-season.

Results: As expected, days with cold/flu symptoms increased during CFS, as did use of acetaminophen medications – especially UR medications – to treat them. More usage days exceeded the 4 gram limit in CFS (3.9% vs 2.9%, OR =1.3 [1.0-1.7]), and more users exceeded the limit on at least 1 day (6.5% vs 5.4%, OR =1.2 [1.0-1.5]). The rise in daily rates of exceeding 4 grams was especially high in the particularly severe CFS of 2012-2013, increasing over the previous year from 5.7% to 7.0% of users (OR=1.2 [1.0-1.6]). The increased overdosing was not attributable to seasonal changes in the characteristics of users, but to the increased use of UR medications, both on their own and with other acetaminophen medications: Without UR medications, there was no difference between CFS and off-season in the probability of overdosing.

Conclusions: The probability of overdosing with acetaminophen increases in CFS, due to increased use of UR medications. Warning the public not to overtreat cold/flu symptoms, and concentrating public education in cold/flu season may help reduce the probability of overdose of acetaminophen.

783. Evaluation of Impact of a Japanese Regulatory Action Against Denosumab-Induced Hypocalcemia Using the Japanese Adverse Reaction Reporting Database

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Background: Denosumab (DEN), an anti-RANKL antibody, has been approved in Apr. 2012 in Japan, but a Dear Healthcare Professional Letter of Rapid Safety Communication was released by the regulatory authority due to the risk of severe hypocalcemia in Sept. 2012. Until now, the impacts of this regulatory action have not yet been evaluated.

Objectives: The impact of the regulatory action against hypocalcemia for DEN was assessed using the Japanese Adverse Drug Event Report database (JADER).

Methods: We collected the case reports from Apr. 2012 to Sept. 2014 in the JADER, in which a total of 151,746 adverse events for the primary suspected drugs were included. Reporting odds ratio (ROR) adjusted by age and sex was analyzed for hypocalcemia, a target of the regulatory action for DEN. Changes in RORs for DEN and zoledronic acid (ZOL: a reference drug) after the regulatory action were evaluated comparing between the periods before (Pre: Apr. 2012 to Sept. 2012) and after the regulatory action (Post1: Oct. 2012 to Sept. 2013, Post2: Oct. 2013 to Sept. 2014).

Results: A significant and higher ROR of hypocalcemia was detected for DEN [1718.5 (95% CI: 381.7 - 1238.5)] compared with that of ZOL [36.4 (15.0 - 88.5)] in Pre period. A decreasing trend in ROR of hypocalcemia was observed for DEN in periods of Post1 [1104.1 (658.4 - 1851.4)] and Post2 [789.2 (415.7 - 1498.3)] comparing with Pre. Contrary, the ROR of hypocalcemia for ZOL was slightly increased in Post1 [47.4 (22.8 - 98.5)] and decreased afterward in Post2 [27.7 (10.8 - 71.3)]. Multiple logistic regression analysis showed a significant decrease of hypocalcemia report in Post2 ($p<0.039$. vs. Pre), although this decrease was not specific for DEN.

Conclusions: This study revealed that the regulatory action against hypocalcemia for DEN had a impact on decreasing of severe hypocalcemia reports. Further study using medical information databases will be performed to confirm this result.

784. Effectiveness of Trigger Tools to Detect Adverse Drug Events from Discharge Summaries

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Background: Adverse events constitute a potentially avoidable component that may contribute to patient's morbidity and mortality. Trigger tool methodology was found to be an effective way of identifying adverse drug events (ADE).

Objectives: The present study was aimed to identify adverse drug events by using the triggers from the discharge summaries.

Methods: The hospital ethics committee approval was obtained prior to the study. A list of triggers were developed from previous studies and validated. This list was used to screen the discharge summaries, for the presence of triggers. The positive trigger records were further verified for the presence of actual adverse drug event. Adverse events were classified according to the NCCMERP index.

Results: A total of 751 discharge summaries were screened with trigger tool and 2251 triggers were present in these records. Out of which 519 (69%) were males and remaining 232 (31%) were females. Most of the patients were of the age group > 60 (41.5%). These triggers were successfully able to identify 355 adverse drug events. According to the NCCMERP index, the ADE were categorised into E, F and H.

Conclusions: The present study reviewed discharge summaries with the help of trigger tools to identify the adverse drug events. The discharge summaries identified with actual ADE had more than two triggers. This trigger tool system was found to be an effective, practical and relevant approach for ensuring appropriate monitoring of ADEs in medication safety audits in health care settings.

785. Psychosocial Predictors of Acetaminophen Use Exceeding the Daily Limit

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Background: Excessive intake of acetaminophen is associated with risk of liver injury. Previous analyses have identified demographic and medically-related characteristics of users who exceeded the 4 gram daily limit.

Objectives: To explore factors indicative of psychosocial marginalization as predictors of overdosing.

Methods: US adults recruited from online research panels completed online diaries detailing acetaminophen use over 7 days, and then completed self-reports including psychiatric and smoking history, and a measure of psychological functioning from the SF-12. We constructed a 0-3 index of psychosocial marginalization that assigned one point for an SF-12 Mental Component Score ≥1 SD below the mean, any current smoking, and any other indicator of psychological dysfunction (history of alcoholism, depression, or other mental illness, or long-term disability). Analyses based on 11,337 acetaminophen users evaluated the index in relation to the likelihood of exceeding the 4-gram daily limit on one or more days of diary-keeping.

Results: Most acetaminophen users had no indicators of psychosocial marginalization (55% scored 0), and only 3.1% had all three indicators (score 3). Higher scores on the index were associated with greater likelihood of exceeding 4 grams, with odds ratios comparing those scoring of 1, 2, and 3 to those at 0 rising from 2.0 [1.7-2.4] to 5.0 [3.7-6.8]. Adjusting for other known predictors of exceeding 4 grams reduced but did not eliminate prediction from the index (ORs 1.4 to 2.2).

Conclusions: Individuals with indicators of psychosocial marginalization are more likely to exceed 4 grams acetaminophen per day. This association may not be specific to acetaminophen, but may apply to other medications as well, or to compliance with directions in general. Research to better understand the processes underlying this link, and interventions targeted to this population, are needed.

786. Safety Profile of H1-Antihistamines In Children: An Analysis Based On Data From VigiBase

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Background: H1-antihistamines are commonly used in infants and children for the relief of several conditions, including allergic rhinitis and conjunctivitis, but also used against coughs, colds and insomnia. Despite being marketed for many years, little is known about the safety profile of these drugs in young children and literature suggests a widespread use starting from the first weeks of life although several products lack full pediatric approval.

Objectives: To investigate the safety profiles of H1-antihistamines through a comparative analysis using data from the WHO database (VigiBase).

Methods: Only reports on H1-antihistamines in paediatric patients (0-17 y) up to June 2014 from VigiBase were selected considering the Medical Dictionary for Regulatory Activities terminology for Adverse Drug Reactions (ADRs). The analysis was performed for drug-reaction pairs calculating Reporting Odds Ratio (ROR) with 95% confidence interval and p value $< .05$).

Results: We identified 8918 reports corresponding to 19503 drug-reaction pairs and to 68 different substances. Fifty-three percent of reports involved males, 42% females. This information was missing in 5% of the reports. Twenty-three percent of the cases were serious and 400 were fatal: most were infants (45.3%) and child (32.5%). Most of the serious ADRs are not listed in the Summary of Product Characteristics (SPCs). We found a significant disproportionality for several drug-reaction pairs: "delirium" and promethazine (ROR = 3.13; CI 95% 1.29 - 7.59), "hypoxia" and "coma" and diphenhydramine (6.23; 2.01 - 19.32 and 2.47; 1.4 - 4.33), "chocking" and cetirizine (6.17; 1.47 - 25.81), "cardio respiratory arrest" and chlorphenamine (5.58; 2.81 – 11.1) and "electrocardiogram QT prolonged" and fexofenadine (3.95; 1.21 - 12.92).

Conclusions: Although our findings suggests a limited risk for serious ADRs, data from VigiBase highlight potential associations with serious or unexpected ADRs occurring in age groups where use of some product is unlicensed or adequate supporting evidence are still lacking. SPCs should be revised on indication and risk of ADRs, in order to maximizes the benefits and reduce the risk of negative effects.

787. Drug Causality in Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis in Europe: Analysis of 10 Years RegiSCAR-Study

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Background: Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN) is a rare, but severe and life-threatening adverse reaction with a high mortality of up to 50% in TEN. Good evaluation of risk factors is essential for efficient pharmacovigilance.

Objectives: To investigate evolution of drug causality in SJS/TEN over time.

Methods: From January 2003 to December 2012 the international Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) included 1096 cases of SJS/TEN collected in seven countries (France, Germany, Israel, Italy, Netherlands, Spain, United Kingdom). Diagnoses and dates of onset were validated by an expert group blinded for any information on exposures. Causality was established based on ALDEN, the specific algorithm for causality assessment in SJS/TEN, which had previously shown good correlation with the results of a case-control study.

Results: At least one medication was evaluated as the "probable" or "very probable" cause in 744/1096 cases (68 %). A medication cause was determined as "possible" in 209 cases (19%), as "unlikely" in 68 cases (6.2%) and "very unlikely" in 57 cases (5.2%). 18

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patients (1.6%) denied any exposure to medications. The 5 medications most often incriminated ("probable" or "very probable" causality) were allopurinol (n = 187; 17%), sulfamethoxazole (n = 80), lamotrigine (n = 76), carbamazepine (n = 51), phenytoin (n = 42). We observed substantial differences between reactions developing in the community and in the hospital, e.g. older age, exposure to a far higher number of drugs and a noticeable role of metamizole. In both groups we saw a signal for proton pump inhibitors.

Conclusions: Despite prior warnings in medical journals and towards regulatory agencies, allopurinol is still the principal cause of SJS/TEN in Europe. Sulfamethoxazole and other anti-infective sulfonamides are still frequent inducers of SJS/TEN. Lamotrigine is now the third cause and the first one among antiepileptic drugs, independent of the indication of use. Finally, it is important to realize that at least 13% of SJS/TEN-cases have no drug cause. Therefore, investigation of other possible causes, e.g. infections, should be a priority.

788. Use of Sildenafil or Other Phosphodiesterase Inhibitors and Risk of Melanoma

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Background: Two recent studies reported an increased risk of melanoma associated with use of phosphodiesterase 5A-inhibitors (PDEIs), which are a common treatment for erectile dysfunction. This putative association is supported by established pharmacological effects of PDEIs. A carcinogenic effect of these extensively used drugs would have major public health implications.

Objectives: To examine the association between use of PDEIs and the risk of melanoma.

Methods: We conducted two parallel case-control studies, one using the Danish nationwide health registries (DNHR) and one using the Kaiser Permanente Northern California (KPNC) electronic health records. We identified men with histologically verified melanoma (cases) and 10 cancer-free controls, matched to each case by birth year. We estimated the odds ratio (OR) for melanoma associated with high use of PDEIs (≥100 tablets), adjusting for available confounders.

Results: Among 7,045 (DNHR) and 2,972 (KPNC) invasive melanoma cases, 1.6% and 4.5% had high use of PDEIs. Corresponding values among controls were 1.2% and 4.6%. The adjusted OR for invasive melanoma, comparing high PDEI use with non-use, was 1.22 (95%CI, 0.99–1.49) in DNHR and 0.95 (95%CI, 0.78–1.14) in KPNC. ORs were highest for localized invasive melanoma in DNHR (OR, 1.21) and melanoma in situ in KPNC (OR, 1.15), and lowest for non-localized disease in both populations (ORs 0.75 and 0.61, respectively). The increased ORs were attenuated upon adjustment for markers of health-seeking behavior (education and number of ambulatory visits).

Conclusions: We found no convincing evidence supporting a causal relationship between PDEI use and risk of melanoma. The marginally increased risk of early-stage disease likely results from more frequent healthcare contacts among PDEI users.

789. Androgen-Deprivation Therapy and Cardiovascular Risk (ADTCR): A Nationwide Population-Based Cohort Study

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Background: Androgen deprivation therapy (ADT) is a cornerstone treatment of prostate cancer (PCa). The cardiovascular (CV) risk profile of the different ADT modalities is under scrutiny.

Objectives: To assess the hypothesis that the CV risk profile of the different ADT modalities (antiandrogens, GnRH antagonist, GnRH agonist (including intermittent ADT and combined androgen blockade) and orchiectomy) is heterogeneous.

Methods: - Design: It was a prospective cohort on 4 years thanks to the French Health Reimbursement Agency database (SNIIRAM) and French hospital discharge database (PMSI). We identified men with PCa who had at least one dispensation of an ADT or a hospitalization for orchiectomy (OT) between the 1st July 2010 and the 31st December 2011 and followed them up until the onset of myocardial infarction (MI) or ischemic stroke or until the 31st December 2013.

- Setting: French nationwide population-based study.

- Exposures or interventions: We focused on new users of GnRH agonist (in monotherapy or associated with long-term AA (≥ 6 months) for combined androgen blockade [CAB]) or GnRH antagonist. AA and OT were also analyzed.

- Main outcome measures: myocardial infarction (MI) or ischemic stroke whichever came first, occurring after initiation of ADT or bilateral orchiectomy, identified through main diagnosis code (ICD-10) in PMSI database.

- Statistical analysis: We used Cox regression analysis including time-varying covariates to estimate hazard ratios (HRs) while controlling for age and comorbidities assessed at baseline.

Results: We identified 133,032 men: 40,613 were new GnRH agonist users and 5,709 new GnRH antagonist users; 96 % were ≥ 60 years-old; 1476 have been diagnosed with cerebral infarction and 1742 with MI after ADT initiation. Data analysis is on-going.

Conclusions: Results could modify prescribing habits of practitioners.

790. Liver Enzyme Elevations Associated With Two-Month Rifampicin, Isoniazid, Pyrazinamide, And Ethambutol Anti-Tubercular Therapy In Indonesia

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Background: Drug therapy for tuberculosis (TB) may cause drug-induced liver injury (DILI), which can lead to major morbidity and acute liver failure. The incidence of acute liver injury associated with rifampicin, isoniazid, pyrazinamide, and ethambutol (RHZE) combination anti-tubercular therapy has not been studied among Indonesian pulmonary TB patients.

Objectives: To determine the incidence of liver transaminase elevations among pulmonary TB patients after two months of anti-tubercular treatment with RHZE.

Methods: We performed a cohort study of acid-fact bacilli smear-positive adults with uncomplicated, pulmonary TB treated with two months of RHZE between 2012-2013 in Lampung and Yogyakarta, Indonesia. The main study outcomes were grade 2 (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >2.5-5 times upper limit of normal) and grade 3 (ALT or AST >5-10 times upper limit of normal) liver enzyme elevations after two months of RHZE.

Results: Among 262 recruited patients (mean age, 39 years; 64% male; 55% current smokers), 20 (8%) developed a higher grade of ALT elevation and 27 (13%) developed a higher grade of AST elevation after two months of treatment. Some (15%) developed a higher grade of liver transaminase elevation after two months of RHZE treatment. Several subjects developed grade-3 (severe) ALT (n = 3) and AST (n = 1) elevation. According to the widely used ATS criteria, 2.18% of the subjects developed DILI.

Conclusions: Among pulmonary TB patients undergoing RHZE treatment, liver enzyme elevations occurred frequently (15%). Clinicians should ensure that liver aminotransferases are regularly monitored. Referral to liver specialists should be considered if hepatic dysfunction ensues.

791. Effect of Concomitant Use of Tamoxifen and Selective Serotonin Reuptake Inhibitors on Mortality

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Background: Tamoxifen, which reduces breast cancer recurrence, is a pro-drug that requires activation by cytochrome-P450 (CYP) enzymes. Concern has been raised that CYP2D6 inhibitors, including certain selective serotonin reuptake inhibitors (SSRIs), might reduce tamoxifen effectiveness.

Objectives: To compare differences in mortality between women concomitantly treated with tamoxifen and SSRIs that are potent inhibitors of CYP2D6 vs. tamoxifen plus SSRIs that are not potent inhibitors.

Methods: We assembled 2 cohorts of female tamoxifen initiators using data from 5 US electronic healthcare databases covering >100 million individuals between 1996 and 2013. In Cohort 1, patients initiated an SSRI during tamoxifen treatment. In Cohort 2, patients were exposed to an SSRI at the time of tamoxifen initiation. We compared all-cause mortality between patients exposed to SSRIs that are potent inhibitors of CYP2D6 (paroxetine, fluoxetine) vs. SSRIs that are not potent inhibitors. We used propensity scores to match exposure groups at a variable ratio, 1: up to 10. Follow-up started on the first day of concomitant tamoxifen and SSRI exposure and continued until patients died or until the end of available data. We examined results separately for each cohort and combined the hazard ratios (HR) from Cox regression models across the 2 cohorts using random effects meta-analysis.

Results: There were 5,835 and 7,918 matched tamoxifen new users in Cohorts 1 and 2, respectively. Mean age was 55 years. A total of 1,003 and 1,024 deaths occurred in Cohorts 1 and 2, respectively, during mean follow-up of 2.7 (SD, 2.5) and 2.3 (SD, 2.1) years, respectively. Overall HRs comparing potent vs. non-potent CYP2D6-inhibiting SSRIs were 0.90 (95% CI, 0.79 to 1.02) in Cohort 1 and 0.98 (0.86 to 1.11) in Cohort 2. The pooled HR was 0.95 (0.86 to 1.04). Results were consistent across sensitivity analyses, including analyses censoring follow-up when patients discontinued one or both treatments.

Conclusions: Concomitant use of tamoxifen and potent CYP2D6-inhibiting SSRIs did not increase the risk of all cause death. SSRI inhibition of CYP2D6 does not appear to reduce the effectiveness of tamoxifen.

792. The Effect of BMI on Unintended Pregnancy Rates Amongst Users of Combined Oral Contraceptives

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Background: Obesity rates around the world are increasing. The effect of BMI on the Pearl index (PI) of COC is unknown.

Objectives: To determine if the PI of COC differs with BMI.

Methods: Design: Meta-analysis of five prospective, observational cohort studies with primary endpoints of venous thromboembolism in women using COCs (IOC, TASC, ISCO, IFOC, LASS) were included. All studies were conducted between 2007 and 2016 using a similar methodology. ISCO and IFOC are ongoing prospective cohorts with study end dates of 2015 and 2016. 246,209 women with an observation time of 382,789 women-years were included. All women were followed for 3-5 years. Inclusion criteria for all studies was prescription of a new COC, with no specific exclusion criteria. Studies were conducted across Europe and the United States.

Main outcome measures: Results were analysed within four age cohorts <25 years, 25-29, 30-39, and >=40 years. BMI was defined dichotomously as <35 kg/m^2 and >=35 kg/m^2 (US) and <30 kg/m^2 and >=30 kg/m^2 (EU).

Statistical analysis: The PI was calculated within each age and BMI category stratified by region of origin (Europe or United Sates). Significance of both factors was tested in a stratified Cox regression model, age and BMI were included as continuous variables.

Results: The contraceptive failure rate was increased in women with a higher BMI across all age strata. The PI decreased with advancing age. European data showed sample PI ranges from 0.06 (age 40+, BMI<30) to 0.80 (age <25, BMI>=30). Cox

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regression show independent effects of age ($p<0.0001$) and BMI ($p=0.0003$) on the occurrence of unintended pregnancies.

Pooled data from US showed PI ranges from 0.15 (age 40+, BMI<35) to 4.12 (age <25, BMI>=35) with consistently higher values observed in women with BMI >=35 kg/m^2. The difference in contraceptive failure rates between BMI groups was largest for women <25 years (PI=2.60 versus PI=4.12) and smallest in women >40 years (PI=0.15 versus PI=0.18). Significance ($p<0.0001$) was obtained for both factors simultaneously included in a Cox regression model.

Conclusions: BMI has a significant effect on the PI of COC. Increasing BMI decreases the efficacy of COC in EU and US.

793. Unwanted Pregnancies in Women Using Intrauterine Devices: Final Results from the EURAS-IUD 5-Years Study

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Background: Intrauterine devices (IUDs) are a well accepted and widely-used method of contraception and have shown high contraceptive efficacy in clinical trials. Complications associated with unintended pregnancies during IUD use have previously been poorly described.

Objectives: The primary objective of the analysis is to determine the rate of unwanted pregnancies in women using IUDs and to describe associated complications.

Methods: Large, comparative, multinational, prospective, non-interventional cohort study with new users of different types of IUDs: LNG-IUDs and copper IUDs. The combined cohort included more than 60,000 women in six European countries (Germany, Austria, UK, Finland, Poland and Sweden). The study was conducted from 2006 to 2015. The women received a follow-up questionnaire 12 months and 5 years after enrolment. All patient-reported outcomes of interest were validated by the women's treating physicians. A multifaceted 4-level follow-up procedure ensured low loss to follow-up rates. The analysis was based on Cox regression models comparing the cohorts.

Results: In September 2015, 58,324 women (70% LNG-IUDs, 30% copper IUDs) had provided 133,015 WYs of exposure. Women in the LNG-IUD cohort were slightly older (37.4 yrs vs 33.3 yrs). A total of 175 contraceptive failures have been reported (41 LNG-IUS, 134 copper IUD), giving a pearl index (PI) of 0.04 for LNG-IUS and a PI of 0.4 for copper IUD. The hazard ratio adjusted for age, BMI and parity for LNG-IUS vs. copper IUD was 0.16 (95% CI: 0.11-0.23). The risk for contraceptive failure in LNG-IUS users compared to copper IUD users remained substantially and statistically significantly lower in all age groups. 33 pregnancies (13 LNG-IUS, 20 copper IUD) were ectopic pregnancies, giving an adjusted hazard ratio of 0.28 (95% CI: 0.14-0.58). Final results will be shown at the ISPE meeting.

Conclusions: The contraceptive failure rate for both cohorts was low, with LNG-IUD having a significantly lower contraceptive failure rate compared with copper-IUD. Physicians should have a high index of suspicion for extra-uterine gravida if they suspect a pregnancy under IUD use.

794. Intrauterine Devices and the Risk of Uterine Perforations: Final Results from the EURAS-IUD 5-Years Study

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Background: Uterine perforation is a potentially serious complication of intrauterine device (IUD) use. The absolute risk of uterine perforation associated with levonorgestrel-releasing IUDs (LNG-IUD) over the entire treatment period is unknown. It is also unknown whether the perforation rate is higher with this IUD than with copper IUDs.

Objectives: Aim of the study is to determine the uterine perforation rate in women using intrauterine devices (IUD).

Methods: Large, comparative, multinational, prospective, non-interventional cohort study with new users of different types of IUDs: LNG-IUDs and copper IUDs. The combined cohort in the 5-year follow-up included almost 38,000 women in six European countries (Germany, Austria, UK, Finland, Poland and Sweden). The study was conducted from 2006 to 2015. Both the women and their treating physicians received a

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follow-up questionnaire 12 months after enrolment. In addition, women were contacted again after 5 years. All patient-reported outcomes of interest were validated by the treating physicians. A multifaceted follow-up procedure ensured low loss to follow-up rates. The analysis was based on logistic regression models.

Results: In September 2015, 37,890 women were included in the 5 year analysis (71% LNG-IUDs, 29% copper IUDs). In total, 49 perforations with LNG-IUD (1.8 per 1,000 insertions (95% CI: 1.4-2.4)) and 16 with copper IUD (1.5 per 1,000 insertions (95% CI: 0.8-2.4)) occurred. The odds ratio (OR) adjusted for age, BMI, breastfeeding and parity was 1.6 (95% CI: 0.9 – 2.8). When adjusted for age, BMI, time since last delivery and experience of the inserting HCP, the OR did not change. None of the perforations led to serious illness or injury to intra-abdominal or pelvic structures.

Conclusions: Perforation rates for intrauterine devices are low. The adjusted RR for perforation comparing LNG-IUD and copper IUDs was 1.6. An association of this magnitude identified in observational research is too low to discriminate among bias, confounding, causation, and chance as alternative explanations. Perforation rates were significantly higher among women breastfeeding at the time of insertion.

795. Comparative Risk of Serious Infections During Pregnancy in Patients Treated with Immunomodulatory Agents

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Background: Treatment with immunomodulatory agents is common during pregnancy for active autoimmune conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), spondyloarthritis (SpA), and inflammatory bowel disease (IBD); yet the comparative risk of serious infections (SI) after treatment with these agents is not well-studied.

Objectives: To compare the risk of SI after treatment with steroids, non-biologic agents, or tumor-necrosis factor- inhibitors (TNF-I) in pregnancy.

Methods: A cohort of pregnant women with SLE, RA, SpA, or IBD was identified from Medicaid (2001-2010) or UnitedHealth Care (2004-2012). SLE patients were classified into steroid or non-biologic users; RA, SpA, and IBD patients were classified into steroid, non-biologic, or TNF-I users based on the first filled prescription in pregnancy. The outcome of hospitalization for bacterial or opportunistic infections was assessed throughout pregnancy. Hazard ratios (HR) were derived using cox-proportional hazard regression models after confounding adjustment with propensity score stratification separately in patients with SLE and with other conditions in each data source. HRs were pooled for each comparison across populations using inverse variance meta-analytic methods.

Results: Among 1,627 patients with SLE and 5,024 patients with RA, SpA, or IBD using immunomodulatory medications during pregnancy, the incidence rate (IR)/100 person-years (95% CI) for SI was 2.9 (1.9-4.2) and 2.2 (1.7-2.8), respectively. In the adjusted analyses, users of non-biologics had a 46% lower risk of SI compared with steroid users (pooled HR, 95% CI 0.54,0.29-0.99). No differences were noted in the risk of SI between users of TNF-I and steroids or non-biologics (pooled HR, 95% CI 0.92,0.38-2.18 & 0.89,0.37-2.12, respectively).

Conclusions: Use of non-biologics in pregnancy may be associated with a lower risk of SI compared with steroids. No suggestion of higher SI risk with TNF-I was noted. Future studies with larger sample sizes should be considered to confirm our findings.

796. Venous Thromboembolism Risk Following New Use of NSAIDs in U.S. Women

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Background: Epidemiologic studies have suggested that non-steroidal anti-inflammatory (NSAID) use increases risk of venous thromboembolism (VTE), however biologic mechanisms for a causal association are unclear.

Objectives: To evaluate risk of VTE following new use of NSAIDs in a cohort of U.S. women.

Methods: We identified new use of NSAIDs (Cox-2 selective and non-selective excluding aspirin) and incident VTE (deep vein thrombosis or pulmonary embolism) among 39,876 enrolled in the Women's Health Study (WHS) from 1993-95 to 2011. The WHS randomized women without chronic >1 day per week) NSAID use to low dose aspirin and vitamin E. Annual questionnaires included number of days NSAIDs were used in the past month and incident VTE. We defined NSAID initiation as the first reported use for ≥4 days of the past month and counted only VTE events confirmed by an endpoint committee. We estimated the hazard ratio (HR) with 95% confidence intervals (CI) for initiation v. non-initiation using aggregated Cox proportional hazard models with robust variance estimation whereby each women contributed to non-initiation cohorts until initiation. Propensity scores (PS) were estimated using separate models for 2-calendar year periods and implemented by standardized morbidity ratio weighting. The PS incorporated age, BMI, and relevant medical, behavioral, and socioeconomic variables updated over time. We designed as-treated (AT) and intention to treat (ITT) analyses restricted to 0-5 years after each eligible index date; at-risk periods began on the questionnaire date. For AT, follow-up was censored on the date of first reported treatment change.

Results: Women contributed 284,779 and 287,389 observations in the AT and ITT analyses, respectively. The AT HR (95% CI) for VTE was 1.43 (1.11, 1.83) for any NSAID, 1.22 (0.93, 1.60) for non-selective NSAIDs, and 2.27 (1.35, 3.80) for coxibs; the ITT HR was 1.17 (1.02, 1.35) for any NSAID, 1.12 (0.97, 1.30) for non-selective NSAIDs, and 1.49 (1.04, 2.21) for coxibs.

Conclusions: New use of NSAIDs was associated with modestly increased VTE risk in this cohort of initially healthy cancer-free women. Increased risk appears driven by coxibs, which might reflect different indications.

797. Relationship Between Glycaemic Burden and Micro- and Macrovascular Complications in Patients with Type 2 Diabetes Mellitus

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Background: Results from clinical trials among patients with type 2 diabetes mellitus (T2DM) showed that glycaemic control is related to decreased risk of microvascular complications, while the relationship with macrovascular complications remains unclear. Observational studies using glycaemic burden to investigate these relationships are scarce.

Objectives: To investigate the relationship between glycaemic burden and micro- and macrovascular complications among T2DM patients using real-world data.

Methods: T2DM patients receiving antihyperglycaemic agents (AHAs) during 2004-2013 were selected from the PHARMO Database Network. All HbA1c measurements between the first AHA prescription (index date) recorded and end of follow-up were used to assess glycaemic burden. Glycaemic burden was defined based on the extent and duration that HbA1c values exceeded a threshold of 7% (53 mmol/mol) and was expressed as glycaemic burden years (GBY). The relationship between GBY and microvascular (including retinopathy, diabetic foot, nephropathy) and macrovascular (including coronary artery disease [CAD], cerebrovascular disease) complications were analysed using a time-dependent Cox proportional hazards model, with glycaemic burden entered in each regression as a categorical variable with four levels.

Results: A total of 34,153 T2DM patients were included; mean (±standard deviation) age at index date was 66 (±11) years and 53% were male. As compared to patients with no GBY, patients with GBY ($0<GBY\leq1$, $1<GBY\leq3$, $3<GBY$) had a significantly higher risk of developing retinopathy (hazard ratio

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[HR]: 1.38, 1.76, and 2.22, respectively), diabetic foot (HR: 1.08, 1.24, and 1.55, respectively), nephropathy (HR: 1.11, 1.16, and 1.14, respectively), and cerebrovascular disease (HR: 1.16, 1.28, and 1.36, respectively). For CAD, a significantly higher risk was found only for patients with 1<GBY≤3 and 3<GBY (HR: 1.12 and 1.32, respectively) as compared to patients without GBY.

Conclusions: Results of this study show that GBY is an important predictor of micro- and macrovascular complications and thus may be important to consider in T2DM management.

798. Comparative Effects of Second Line Antidiabetic Agents Added to Metformin on Patient Centered Outcomes: A Retrospective Cohort Study

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Background: There is no consensus on the optimal choice of second-line antidiabetic agent (ADA) in patients with type 2 diabetes who require treatment beyond metformin monotherapy.

Objectives: The aim of this study was to compare time to further treatment intensification, hypoglycemia, and major adverse cardiovascular events for all commonly-used second-line ADAs.

Methods: Observational cohort study using claims data from the OptumLabs data warehouse, covering privately insured and Medicare Advantage enrollees aged > 18 years with baseline continuous metformin use, no prior exposure to other ADAs, and initiation of a sulfonylurea, DPP-4 inhibitor, GLP-1 RA, SGLT-2 inhibitor, thiazolidinedione, or basal insulin at the index date. Propensity score adjusted Cox multivariate models were used to assess hazard ratio (HR) for progression to use of any third ADA, use of insulin, MACE (composite of acute MI and acute stroke), and hypoglycemia.

Results: Sulfonylureas were associated with the least progression to a third ADA (including insulin therapy), but not with reduced progression to insulin therapy alone. Sulfonylureas were associated with significantly increased risk of MACE compared to DPP-4 inhibitors (HR 0.75, 95% CI 0.60-0.94) and GLP-1 RA's (HR 0.51, 95% CI 0.29-0.90). Compared to sulfonylureas, the risk of hypoglycemia was significantly lower for DPP-4, GLP-1 RA, and thiazolidinediones.

Conclusions: Sulfonylurea initiators are less likely than other ADA users to progress to a third ADA, but no less likely to progress to insulin use. Sulfonylureas are associated with higher rates of hypoglycemia and MACE than most other second-line ADAs. Thus, choice of second line ADA appears to have significant effects on patient-centered outcomes. Patients who can accept increased cost may benefit more from DPP-4 or GLP-1-based therapy over sulfonylurea.

799. Abstract Withdrawn

800. Magnitude of HbA1c Reduction and Attainment of Early Glycemic Control Predict Cardiovascular Outcomes and Mortality: A Population-Based Cohort Study of 24,752 People with Type 2 Diabetes Initiating First Metformin Therapy

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Background: The association between stringent glycemic control early in diabetes and risk of later cardiovascular events remains debated.

Objectives: To investigate the association of early glycemic control with subsequent cardiovascular complications or death in an unselected population-based cohort of first metformin initiators.

Methods: We used medical databases to assemble a population-based cohort of 24,752 incident patients with type 2 diabetes and first metformin initiation.in Northern Denmark, 2000-2012.

We examined early glycemic control achieved within the first 180 days, grouped by attainment of HbA1c <6.5%, 6.5-6.9%, 7-7.4%, 7.5-7.9%, ≥8%,

and assessed HbA1c change from baseline to 180 days (HbA1c (%) groups: -4,-3,-2, -1, 0, +1, + ≥2). Patients were followed until acute myocardial infarction, stroke, death, emigration, or end of follow-up in 2012, using Cox regression analysis for confounder adjustment.

Results: The risk of a combined outcome event increased with increasing levels of early HbA1c control, compared to achievement of HbA1c <6.5%; adjusted hazard ratio (HR) = 1.18 (95% confidence interval (CI) 1.07-1.30) for 6.5%-6.9%, HR = 1.24 (1.09-1.40) for 7.0%-7.4%, HR = 1.34 (1-14-1.57) for 7.5%-7.9%, and HR = 1.60 (1.38-1.85) for ≥8%. Results were consistent for individual outcome events, and when stratified on age, gender, cardiovascular history, calendar year of follow-up, and baseline HbA1c. The magnitude of early HbA1c reduction predicted outcome; adjusted HR = 0.73 (0.59-0.91) for = -4, HR = 0.80 (0.65-0.99) for = -3, HR = 0.91 (0.78-1.07) for = -2, HR 1.01 (0.91-1.12) for = -1, compared to no HbA1c change (= 0), while a substantially increased risk was seen in patients with increasing HbA1c despite metformin initiation; HR 1.29 (0.99-1.67) for = +1, and HR = 2.59 (1.65-4.10) for = + ≥2.

Conclusions: A large initial HbA1c reduction and attainment of early glycemic control levels are associated with lower risk of cardiovascular complications and death among first-time metformin initiators.

801. Risk of Acute Myocardial Infarction Associated with Non-Insulin Blood Glucose Lowering Drugs. Results from the SAFEGUARD Project

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Background: Increased risk of acute myocardial infarction (AMI) associated with some non-insulin blood glucose lowering drugs (NIBGLD) has caused restriction in their use or withdrawal of some marketed products. The complex patterns of NIBGLD use, the underlying conditions in type 2 diabetes mellitus (T2DM) patients, the relatively short time some of these drugs have been available hamper the assessment of the AMI risk associated with NIBGLD.

Objectives: To estimate the risk of AMI associated with NIBGLDs in the SAFEGUARD project.

Methods: A case-control design, nested in a cohort of new NIBGLD users was performed. AMI cases were matched with up to 5 controls on database (DB), sex, cohort entry (±3 months) and date of birth (±1 year) using risk set sampling. Data were retrieved from 8 European electronic healthcare databases (Netherlands: PHARMO, IPCI; Spain: BIFAP; Germany: GePaRD; Italy: Health Search, Regional DBs of Lombardy and Puglia; United Kingdom: CPRD) and 1 US DB (Medicare) participating in SAFEGUARD. DB-specific adjusted odds ratios (ORs) and corresponding 95% confidence intervals (95%CI) were estimated by comparing current use of metformin in combination with sulfonylureas (reference) and each monotherapy, dual therapy of metformin/no sulfonylurea or other combinations. One (ORpool) and two stages (ORmeta) approaches were applied to combine the DB specific results.

Results: A total of 25,979 cases of AMI were matched to 127,570 controls. We observed a decreased risk of AMI in users of metformin monotherapy (adj. ORpool = 0.82, 95%CI: 0.78-0.87 and ORmeta = 0.83, 95%CI 0.77-0.90,) metformin/pioglitazone (ORpool = 0.81, 0.70-0.94 and ORmeta = 0.85, 0.72-0.99) and metformin/rosiglitazone (ORpool = 0.73, 0.63-0.85 and ORmeta = 0.82, 0.69-0.99,). Instead current use of rosiglitazone as monotherapy was associated with an increased risk of AMI by 32% and 29% (95%CI 1.07-1.63 and 1.01-1.64).

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Conclusions: Our findings suggest an increased risk of AMI in current users of rosiglitazone alone and decreased in users of metformin (alone or in combination with pioglitazone and rosiglitazone) as compared with the AMI risk in users of metformin and sulfonylureas.

802. Risk of Congestive Heart Failure (CHF) Associated with Vildagliptin: Pan-European Non-Interventional Safety Study

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Background: Vildagliptin (vilda) is a DPP-4 inhibitor for type 2 diabetes treatment, available as a single agent and in fixed-dose combination with metformin. In response to an EMA request, vilda safety outcomes including CHF were assessed under real-world conditions.

Objectives: Assess if vilda is associated with an increased risk of incident CHF compared to other non-insulin antidiabetic drugs (NIADs).

Methods: Data from 5 European healthcare databases (DBs) from the UK (CPRD), Germany and France (IMS), Denmark (OPED) and Sweden (National Registers) were used. Patients with type 2 diabetes aged ≥18 with a NIAD prescription from Jan 2005 were included. Index date was the date of first prescription in the study period. Time-dependent exposure (vilda vs. other NIADs) was assigned. Patients with cancer, HIV/AIDS or insulin prescription prior to index date were excluded. Patients were followed until earliest of DB coverage end, transfer out of the DB, death, insulin prescription or outcome. Incidence rates (IRs) and 95% confidence intervals (CIs) were calculated and negative binomial regression used to estimate incidence rate ratios (IRRs) and 95% CIs, adjusting for age, sex and other confounders.

Results: 738,054 patients were included, of which 20,973 (2.8%) were exposed to vilda. Total vilda exposure was 28,330 person-years (PYs), 1.4 years on average. Mean age at index date ranged from 63 to 65 across DBs, with vilda patients being younger (mean age 59-63). Over half of patients were male (56%). 24,790 patients experienced incident CHF, 521 of which during vilda exposure. IRs for CHF during vilda exposure ranged from 2.3 (Sweden) to 30.4 (Germany) per 1,000 PYs. No increased IRRs of CHF associated with vilda were observed. Adjusted IRRs were close to or <1, with upper bound of the 95% CI <1, favoring vilda, in UK, German and French analyses (IRR 0.51, 95% CI 0.27-0.95; 0.72 (0.64-0.81); and 0.49 (0.28-0.85) respectively).

Conclusions: Analyses from 5 European DBs didn't suggest an increased risk of incident CHF associated with vilda compared to other NIADs. Due to the range of observed IRs and limited confounder adjustment, residual confounding may remain.

803. Risk of Erectile Dysfunction Associated with Use of 5-Alpha Reductase Inhibitors for Benign Prostatic Hyperplasia or Alopecia

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Background: 5-alpha reductase inhibitors (5ARIs) have been reported to increase the risk of erectile dysfunction (ED). One indication for 5ARI use, benign prostatic hyperplasia (BPH), is an ED risk factor.

Objectives: To estimate the risk of ED in men who used 5ARIs to treat BPH or alopecia.

Methods: We conducted cohort studies with nested case-control analyses using the UK Clinical Practice Research Datalink. We identified two populations of men who were free from ED risk factors and evidence of sexual dysfunction or treatment: 1) BPH population, comprised of men (40+ year)s with BPH who received 5ARI Only (finasteride or dutasteride), 5ARI + alpha blocker (AB), or AB Only, and 2) Alopecia population, comprised of men (18-59 years) with alopecia who received finasteride 1 mg or no treatment. Cases were men who had an ED diagnosis or treatment (surgery or phosphodiesterase type-5 inhibitor prescription) during follow-up. We calculated incidence rates (IRs) and adjusted incidence rate ratios (IRRs) with 95% confidence intervals (CIs). We also conducted nested case-control analyses to control for major confounders and calculated adjusted odds ratios (ORs) with 95%CIs.

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Results: For the BPH population, IRs were 15.3 (95% CI 14.3-16.5), 19.2 (95%CI 17.4-21.1), and 20.1 (95% CI 19.6-20.7) per 1000 person-years (PY) for users of 5ARI Only, 5ARI + AB, and AB Only, respectively. The risk of ED was not elevated with use of 5ARI Only (IRR = 0.92, 95%CI 0.85-0.99) or 5ARI + AB (IRR = 1.09, 95%CI 0.99-1.21) in comparison with AB Only. ORs were 0.94 (95%CI 0.85-1.03) for 5ARI Only and 0.92 (95%CI 0.80-1.06) for 5ARI + AB, compared to AB Only, and remained null regardless of number of prescriptions or exposure timing. The risk of ED increased with longer duration of BPH, regardless of exposure. For the alopecia population, the IRs of ED were 10.1 (95%CI 7.0-13.9) and 9.8 (95%CI 8.9-10.7) per 1000 PY for finasteride and unexposed men, respectively (IRR = 1.03, 95%CI 0.73-1.44). The OR for ED was 0.95 (95%CI 0.64-1.41) for users of finasteride compared to unexposed men.

Conclusions: 5ARIs do not significantly increase the risk of incident ED, regardless of indication for use.

804. Risk of Breast Cancer in Risperidone Users: A Nationwide Cohort Study

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Background: Several antipsychotics, especially risperidone, are known to increase serum prolactin. Hyperprolactinemia has been associated with an increased incidence of mammary gland tumors in animal studies.

Objectives: To investigate the association between risperidone use and the risk of breast cancer in a nationwide cohort of patients.

Methods: All women aged 18 years or older who initiated treatment with risperidone or any other antipsychotic between 2006 and 2012 were identified in the Swedish nationwide registers. Patients with two recorded consecutive dispensations of the same antipsychotic drug within 3 months, no previous cancer diagnosis, and no recorded dispensations of paliperidone were included in the study. The final cohort consisted of 22 908 women exposed to risperidone, 24 524 women exposed to other atypical antipsychotics, and 8 544 women exposed to typical antipsychotics. A Cox regression model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the association between exposure to risperidone and breast cancer.

Results: Women exposed to risperidone were markedly older than women exposed to other antipsychotics. Mean follow-up time ranged 2.4 to 2.8 years for different exposed groups. Compared with patients exposed to other atypical antipsychotics, there was no statistically significant increased risk for breast cancer among users of risperidone (age adjusted HR = 0.94, 95% CI 0.72-1.22) or typical antipsychotics (age adjusted HR = 1.25, 95% CI 0.94-1.66). Analyses stratified by stage of tumor, using active treatment follow-up time or restricting the data to treatment naïve patients did not reveal any noteworthy change in the results.

Conclusions: Risperidone use does not confer a short-term increased risk of breast cancer compared with other antipsychotic agents.

805. Prescription Opioid Use and Infection-Related Hospitalization in Hemodialysis Patients

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Background: Opioid analgesics are commonly prescribed for severe pain in US hemodialysis (HD) patients, but are known to have immunosuppressive effects and may increase infection risk.

Objectives: To examine the comparative short-term risk of infection-related hospitalization among HD patients initiating a prescription opioid versus a non-steroidal anti-inflammatory drug (NSAID).

Methods: We conducted a retrospective cohort study of opioids and NSAIDs initiators using clinical data from a large dialysis provider linked with data from the US Renal Data System (2006-2010). Initiators were HD patients with Medicare D eligibility initiating an opioid or NSAID with at least 30 days of supply.

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Patients were excluded if they initiated multiple opioids or had a history of cancer or hospice use in the baseline period. We assessed treatment effects on infection-related hospitalization risk using inverse probability of treatment weighted Kaplan-Meier methods, in which the propensity score contained a wide range of clinical, demographic, and health utilization variables. From cumulative survival curves, we estimated 45-day risk differences (RDs) and their 95% confidence intervals (CI) comparing opioid to NSAID initiators.

Results: Of 5,113 new users who met study entry requirements, 67.3% received an opioid. Compared to new NSAID users, new opioid users had similar baseline laboratory values, but had a higher prevalence of comorbidities including recent infections, cardiovascular diseases, and chronic obstructive pulmonary disease. We observed an increased 45-day risk of infection-related hospitalization (RD: 1.7%, 95% CI: 0.8-2.7%). In subgroup analyses, infection-related hospitalization risks were elevated among patients with a dialysis catheter (RD: 5.9%, 95% CI: 1.5-10.3%), history of serious infections (RD: 5.5%, 95% CI: 1.1-9.5%) and low nutrition marker (RD: 5.0%, 95% CI: 1.7-8.4%).

Conclusions: Use of opioids, compared to NSAIDs, increased the short-term risk of infection-related hospitalization in HD patients, particularly among those with a dialysis catheter, a history of serious infections and poor nutritional status.

806. Seasonality of Guillain-Barré Syndrome in the United Kingdom from April 2005 to March 2015

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Background: Background incidence rates (IR) are key to assess suspected adverse events (AEs). For interventions that occur on a seasonal basis such as influenza vaccination, it is equally important to understand seasonal patterns of such AEs. Seasonality of Guillain-Barré syndrome (GBS) is not well understood. Large epidemiological databases are a potential resource to define the expected incidence rates and seasonal patterns of GBS.

Objectives: To determine the IR and describe the seasonal patterns of GBS in the UK.

Methods: Cohort study based on the number of incident cases of GBS and total person-time at risk from April 2005 to March 2015 in the UK Clinical Practice Research Datalink (CPRD). Incidence rates with 95% CIs were calculated, by age group, gender and calendar month. A model with seasonal time dependence for monthly number of incident cases was fit using Poisson regression with an offset for person-time (log), and sine function to capture yearly seasonality (amplitude and phase). Model extensions were explored to account for overdispersion, linear time trend and second-order harmonic. ISAC 15_189R.

Results: A study population of 7.98 million accrued 42.66 million person-years of follow-up. 749 GBS cases were identified, 56.34% male and mean age 48.58 years old. Overall GBS IR was 1.76 per 100000 person-years (95%CI: 1.63-1.89) with higher IR in males (1.99; 1.80-2.19) and subjects 60 years or older (3.14; 2.81-3.50). The seasonal model provided a good fit ($p = 0.47$), except for the year 2014. The sinusoidal term in the model was significant ($p < 0.001$). The overall (geometric) mean IR was 1.74 per 100000 person-years [1.62-1.87]. Peak-to-trough IRR was 1.48 [1.21-1.82] with peak location end March (Day 89; 61-117) and the trough end September (Day 271; 244-299). Model extensions were rejected.

Conclusions: A regular seasonal pattern of GBS incidence was identified with highest incidence around end March about 1.5 times higher than the lowest IR end September. Although the peak GBS incidence is commonly reported to occur during the colder winter months, we found a seasonal peak around end March. The departure from the model prediction in 2014 warrants further investigation.

807. Trends in Specialty Drug Spending and Use in Commercial Health Plans in the United States: 2003-2014

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Background: Recently there has been considerable interest in drug pricing in the United States, particularly for so-called "Specialty" medications – those used to treat complex conditions and priced at over $600 per month.

Objectives: To (1) evaluate trends in commercial insurance spending on prescription medications across specialty and non-specialty drugs from 2003-2014, (2) to estimate trends in patient out-of-pocket payments over that same period, and (3) to summarize the top 25 products that are driving commercial health plan spending in 2014.

Methods: Secondary analysis of a 1% random sample of MarketScan Commercial Claims and Encounters outpatient prescription drug claims from 2003-2014 (N = 28,879,517 claims). Outcomes included (1) the proportion of unique products with a median price of $600 or more per fill year; (2) the proportion of all fills that are >$600; (3) the total reimbursed for specialty and non-specialty medications; and (4) patient out-of-pocket spending for specialty and non-specialty medications. All dollars were inflation adjusted to 2014 USD.

Results: Between 2003 and 2014 the proportion of products priced at $600 or more increased from 3.2% to 12.1%. Specialty medications represented slightly less than one percent of fills in 2003, increasing to 2.7% of fills in 2014. Over the same period, these drugs grew from 13.5% of total prescription medication spending to approximately 49.1% in 2014. Median patient out-of-pocket spending on specialty medications increased from $29.20 to $50.00 from 2003 to 2014 while spending on non-specialty medications decreased from $14.60 to $7.00.

Conclusions: Prescription drug spending, particularly for specialty medications, has increased significantly over the last decade. Products for infectious diseases, immunosuppression, multiple sclerosis, and cancer are among the highest cost products per use and contribute significantly to total commercial health plan spending, although the number of users is small relative to the number of insured individuals. Prescription drug spending in the United States will likely continue to increase as payers grapple with providing coverage for important and expensive therapies.

808. Identifying Incident Uterine Fibroids Using Electronic Medical Record Data

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Background: Uterine fibroids are the most common benign tumors of the uterus and are associated with considerable morbidity in women. Studies often rely on self-report to identify incident cases. Diagnosis codes such as the International Classification of Diseases, 9th revision (ICD-9) also have been used to identify fibroid cases but their accuracy, especially for incident cases, is uncertain.

Objectives: To assess the accuracy of ICD-9 diagnosis codes to identify incident uterine fibroid cases.

To develop algorithms using additional electronic data to improve incident fibroid case-finding.

Methods: Women aged 18-65 who received a uterine fibroid diagnosis code during 2012-2014 were identified from electronic databases at Group Health Cooperative, an integrated healthcare system in Washington State. Women with a fibroid history or hysterectomy were excluded. Medical records were reviewed on a random sample of 617 women to confirm incident fibroid status. Additional electronic data on demographics, symptoms, treatment, imaging, healthcare utilization, comorbidities and medication were collected. Classification and regression tree analysis incorporated these additional data to develop algorithms to identify incident fibroid. Algorithm performance was assessed by calculating sensitivity, specificity, and positive and negative predictive values (PPV, NPV).

Results: Mean age at diagnosis was 48 years. Medical record review confirmed 583 (95%) fibroid cases, and 482 incident cases, a 78% PPV of a fibroid diagnosis code for incident cases. Using additional electronic data, the algorithm classified 395 cases who had a pelvic ultrasound on the diagnosis date and in the 3 prior years as incident fibroid. Of these, 344 were correctly classified, yielding an 87% PPV. Sensitivity was 71%, specificity 62%, and NPV 38%. A second algorithm further classified women based on a fibroid code of 218.9 in

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the 2 years post-diagnosis and BMI, yielding a 93% PPV, 53% sensitivity, 85% specificity, and 34% NPV.

Conclusions: Algorithms using uterine fibroid diagnosis codes and additional electronic data can identify incident cases with high PPV and can increase either sensitivity or specificity to meet study aims.

809. The Association Between Lansoprazole and Tuberculosis Disease; a Primary Care Based Cohort Study

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Background: Laboratory screening for drugs with anti-tuberculosis (TB) activity found the proton pump inhibitor (PPI) lansoprazole has strong activity against drug-resistant TB, whilst omeprazole and pantoprazole do not. Given the widespread use of PPIs over many years, a direct comparison of the rate of TB disease could be made between lansoprazole users and users of omeprazole or pantoprazole.

Objectives: To estimate the hazard ratio (HR) for TB disease comparing people prescribed lansoprazole with people prescribed omeprazole or pantoprazole.

Methods: We used electronic healthcare records from the United Kingdom Clinical Practice Research Datalink (CPRD). New users of lansoprazole were identified along with new users of omeprazole or pantoprazole, with neither group having been exposed to a PPI previously. Subsequent time was divided into periods exposed to 1) omeprazole or pantoprazole, 2) lansoprazole, or 3) no PPI. The outcome was first clinical record of TB. Since the median time from TB infection to clinical presentation is 1.26 years, TB onset was assumed to be 12 months earlier in the primary analysis. Sensitivity analyses varied this period from 0 to 5 years. Multiple covariates were examined for confounding potential, and a Cox model compared the hazard of TB amongst lansoprazole users with omeprazole or pantoprazole users. Myocardial infarction (MI) was analysed separately as a negative control outcome.

Results: 528,438 lansoprazole users and 925,142 omeprazole or pantoprazole users were identified. Median age was 55 years and 55% were female. The fully adjusted HR for TB comparing person-time currently on lansoprazole vs currently on pantoprazole or omeprazole was 0.67 (95% CI: 0.52-0.85). Comparing past use of lansoprazole against past use of pantoprazole and omeprazole the HR for TB was 0.94 (0.75-1.17). Results were similar in sensitivity analyses. The HR for MI comparing current use of lansoprazole against pantoprazole and omeprazole was 1.01 (0.98-1.05).

Conclusions: Current use of lansoprazole is associated with a reduced risk of TB disease compared with other PPIs, raising the possibility that reported in vitro anti-TB activity may be clinically relevant.

810. Do Proton Pump Inhibitors Impact Clinical Outcomes in Staphylococcus Aureus Bacteremia?

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Background: Proton pump inhibitors (PPIs) are commonly used in clinical practice for gastric acid suppression. These agents have been associated with negative clinical outcomes, including C. difficile infection, pneumonia, and infectious gastroenteritis. Older data suggest acid suppression allows for increased intestinal bacteria resulting in infections and in vitro studies suggest possible immunosuppressive effects.

Objectives: To examine the effects of incident PPI use on clinical outcomes in patients with S. aureus bacteremia.

Methods: This retrospective cohort study included patients admitted to Veterans Affairs hospitals with positive S. aureus blood cultures collected between 2002 and 2013 receiving appropriate antibiotics within 48 hours of culture collection. Incident PPI use was defined as PPI initiation on the day or day after culture and continued use for more than 7 days. Non-users

included patients without PPI use in the year prior to culture through discharge. Propensity score matched Cox proportional hazards regression models quantified the effect of PPIs on clinical outcomes.

Results: We included 531 propensity matched pairs from 809 PPI users and 12,402 non-users. The propensity score controlled for antibiotic treatment, concomitant medications, as well as comorbid conditions, and medical history. We observed a significantly lower mortality rate among PPI users, including time to 14-day mortality (hazard ratio [HR] 0.48, 95% confidence interval [CI] 0.30-0.78; number needed to treat [NNT] 23) and inpatient mortality (HR 0.58, 95% CI 0.36-0.94; NNT 66). No difference in mortality was observed at 30 days (HR 0.96, 95% CI 0.69-1.33). Length of stay was also significantly shorter in PPI users (HR 0.70; 95% CI 0.58-0.84; NNT 30).

Conclusions: In our large, national cohort study, PPIs were associated with significantly lower mortality rates and length of stay among patients with S. aureus bacteremia, including a 52% lower 14-day mortality rate among PPI users compared to non-users.

811. Opioid Analgesic Use as a Risk Factor for Laboratory-Confirmed Invasive Pneumococcal Diseases: A Nested Case-Control Study

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Background: Prescription opioid sales have almost quadrupled in the U.S. since 1999. Animal and in vitro studies suggest that certain opioids have immunosuppressive effects and their use may increase the risk of serious infections. However, the association between opioids and infections remains understudied in humans.

Objectives: To determine if opioid analgesic use is associated with an increased risk of laboratory-confirmed invasive pneumococcal diseases (IPD).

Methods: Our nested case-control study used data from the Tennessee (TN) Medicaid health insurance program to identify enrollees, demographics, and co-morbidities, and the TN Active Bacterial Core surveillance system (1995-2013) to identify laboratory-confirmed IPD. Among a cohort ≥5 years of age who had used opioids, we identified IPD cases and 20 controls per each case matched to their case on their index identification date, age and county of residency, using incidence density sampling. Current opioid users (excluding antitussive formulations) were compared with remote users (no use in 6 months), and further classified based on new use, duration of action, and immunosuppressive properties of the opioid. Conditional logistic regression estimated adjusted odds ratios (aOR) and 95% confidence intervals (CI) that accounted for the matched design and relevant covariates including gender, race, alcohol or substance abuse, smoking, cardiovascular disease, chronic liver and lung disease, hemodialysis, HIV, cancer, immune disorders, nursing home residency and numbers of healthcare encounters, among others.

Results: 1,425 IPD cases were identified. The median age was 50 years. Current opioid users had a higher risk of IPD compared with remote users [aOR:1.42 (95% CI:1.21-1.67)]. The associations were strongest for new users of opioids [aOR:1.94 (95% CI:1.18-3.22)], long-acting opioid users [aOR:2.41 (95% CI:1.75-3.30)], and those using potentially immunosuppressive opioids [aOR:1.80 (95% CI:1.33-2.43)] compared with remote use.

Conclusions: These preliminary findings indicate that opioid use is associated with an increased risk of IPD, and could represent a novel risk factor for these conditions.

812. Hepatitis C Virus Infection Increases Risk of Developing Chronic Kidney Disease

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Background: An estimated 4 million Americans have been exposed to the hepatitis C virus (HCV) in the U. S. Increasing evidence suggests an association between HCV and extrahepatic complications. However, it is not clear whether and to what extent HCV infection affects the development and progression of chronic kidney disease (CKD) at a population level.

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Previous studies have reported conflicting results regarding HCV infection and the risk of CKD.

Objectives: The objective of this study was to examine the association of HCV infection with incidence of CKD.

Methods: A retrospective cohort analysis of the Truven Health MarketScan Database (2008 - 2013) was conducted. Patients aged >=18 years with newly diagnosed HCV infection (ICD-9: 070.44, 070.54, V02.62, 070.70, 070.71) using one inpatient or two outpatient claims were included (HCV cohort). Patients were excluded if they had CKD during 1 year prior to the first diagnosis of HCV. A matched comparison cohort of patients without HCV (non-HCV cohort) were established at a ratio of 1:3 using propensity score matching based on age, gender, year and comorbidities (e.g., diabetes, hypertension, and HIV/AIDS). Follow-up continued until CKD (ICD-9: 585.3-585.5), end of enrollment, or 31 December 2013. Cox proportional hazards models were used to compare the risk of developing CKD between HCV and non-HCV groups. Additional covariates adjusted in the model included renal-modifying therapies (i.e., ACE inhibitors or ARBs), alcohol/drug abuse disorders, hepatitis B virus, and cirrhosis.

Results: 49,358 patients with HCV (HCV cohort) and 148,074 matched patients without HCV (non-HCV cohort) were identified. The mean follow-up were 2.20 years for the HCV cohort and 2.21 years for the non-HCV cohort. The overall incidence rates of CKD were 124 and 55 per 10,000 person-years in the HCV and the non-HCV groups. Adjusted risk of CKD remained significantly higher in the HCV group than in the non-HCV group (adjusted hazard ratio (HR)=1.97; 95% CI=1.81-2.13).

Conclusions: The analysis of a large US administrative claim database suggested that patients with HCV infection were at greater risk of developing CKD than individuals without HCV infection.

813. Risk of Hepatic Decompensation with Cumulative Mitochondrial Toxic Nucleoside Analogue Use in HIV/Hepatitis C Coinfection

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Background: Among HIV/hepatitis C virus (HCV)-coinfected patients, antiretroviral therapy (ART) regimens containing mitochondrial toxic nucleoside reverse transcriptase inhibitors (mtNRTIs) might induce chronic liver injury that accelerates progression of liver disease.

Objectives: To determine if mtNRTI use (didanosine, stavudine, zalcitabine, zidovudine) increases risk of hepatic decompensation (HD) in HIV/HCV patients.

Methods: We conducted a retrospective cohort study of HIV/HCV patients newly initiating an NRTI-containing ART regimen in the Veterans Aging Cohort Study from 1997-2011. HD was defined as the first occurrence of 1 hospital discharge diagnosis or 2 outpatient diagnoses of ascites, spontaneous bacterial peritonitis, or variceal hemorrhage. Follow-up began on ART initiation and continued until HD, death, initiation of HCV therapy, or last visit. To account for time-dependent confounding by indication, marginal structural models were used to estimate hazard ratios (HR) with 95% CIs of HD and death associated with cumulative mtNRTI use compared to non-use.

Results: Among 4,945 HIV/HCV patients, 303 HD events occurred over a median 4.2 years of follow-up (incidence rate, 11.5/1,000 person-years). The initial month of mtNRTI use was associated with an increased risk of HD (HR, 1.59 [1.03-2.46]), but this association became non-significant with greater cumulative use (2-11 months: HR, 0.83 [0.44-1.56]; 12-35 months: HR, 0.87 [0.50-1.50]; 36-71 months:

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HR, 0.93 [0.48-1.78]; >71 months: HR, 0.52 [95% CI, 0.26-1.06]). The initial month of mtNRTI use was not associated with risk of death (HR, 0.84 [0.60-1.19]), but very long-term use was >71 months; HR, 2.35 [1.14-4.85]).

Conclusions: Among HIV/HCV patients, the initial month of mtNRTI use was associated with an increased risk of HD. However, for patients who survive through the initial month of mtNRTI use without HD, increasing cumulative use did not increase risk of this outcome, possibly because of the beneficial effects of HIV suppression and immune restoration. Future analyses should evaluate the risk of HD with use of other antiretroviral drugs and classes in HIV/viral hepatitis patients.

814. Slow Efavirenz Metabolism Alleles Are Associated with Antiretroviral Failure in Botswana

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Background: A polymorphism in cytochrome p450 2B6 (rs3745274) is well-known to result in higher plasma efavirenz concentrations and greater early central nervous system symptoms in HIV infected individuals, but the effect on treatment outcome has been debated.

Objectives: To determine whether slow metabolism alleles are associated with better or worse efavirenz treatment outcomes.

Methods: HIV infected adults initiating efavirenz-based regimens in Botswana were followed for 6 months for the primary outcome of treatment failure, defined as death, loss to care, or HIV RNA>25 copies/ml. If participants did not show at month 6, a tracking algorithm included multiple phone calls, review of clinic records for follow-up visits or death, and review of computerized laboratory records. Genotyping of rs3745274 was done with the Taqman Open Array platform. Individuals were categorized as having 0, 1, or 2 slow metabolism (variant) alleles and included in logistic regression models of composite failure with homozygous native as the base case. In multivariable models, we controlled for sex, age, baseline viral load and CD4 count, and alcohol use. 95% confidence intervals determined statistical significance.

Results: The 928 individuals included 478 (51%) males, median age 38 years, median baseline CD4 count 194 cells/mm^3, and plasma HIV RNA 4.9 $\log_{10}$ copies/ml. Failures in 339 (37%) included 40 (4%) deaths, 181 (20%) lost to care, and 105 (11%) with plasma HIV RNA>25 copies/ml. One variant allele was present in 395 (43%) and 2 alleles in 127 (14%). Heterozygotes were 1.2 (0.91, 1.7) and homozyous variants 1.7 (1.1, 2.6) times as likely as homozygous natives to have failure. The component of failure most strongly associated with metabolism alleles was virologic failure, with heterozygotes 1.6 (1.0, 2.7) and homozygous variants 2.2 (1.2, 4.2) times as likely as homozygous natives to have virologic failure. There was no evidence of confounding.

Conclusions: Slow metabolism alleles were associated with composite failure with evidence of a dose-response relation. Screening for this polymorphism may be warranted to allow for lowering of efavirenz doses or choosing an alternate drug in this setting.

815. Narcolepsy Incidence Rates in the SOMNIA (Systematic Observational Method for Narcolepsy and Influenza Immunization) Study

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Background: Risk of narcolepsy following AS03-adjuvanted H1N1 influenza vaccine has been observed, especially in children and adolescents. To assess this possible risk, it is important to understand it in the context of influenza virus circulation, vaccination, and media attention about the possibility of narcolepsy as an adverse reaction.

Objectives: To assess incidence rates (IRs) of narcolepsy and the changes in incidence of narcolepsy before, during, and after the pandemic influenza (A) H1N1 pandemic.

Methods: A retrospective cohort study was conducted in nine sites (Sweden, Denmark, UK, Canada (2), Taiwan, Netherlands, Spain (2)) using electronic health care data spanning 2003-2013. We calculated IRs by age, sex, year and month. For pooled analyses, we excluded sites where signals for narcolepsy had been detected. Sweden was excluded as the signal was raised there in 2010. To compare patterns over time, we plotted cumulative age standardized IRs for each site against time. We also conducted Joinpoint analyses to investigate time-related changes.

We calculated IRs for periods defined by influenza circulation, vaccination campaigns, and public awareness, and estimated incidence rate ratios (IRRs) using Poisson regression with control for age and sex. We also calculated the positive predictive value (PPV) of narcolepsy diagnosis codes.

Results: The IR of narcolepsy increased between the pre-pandemic period and the period beginning at the peak of immunization (IRR 1.64, 95%CI 1.55,1.76). Excluding Sweden (IRR 2.02, 95%CI 1.82,2.24), the IRR reduced to 1.50 (95%CI 1.38,1.62). Joinpoint analyses showed that incidence increased with an annual percent change of 8.6% over the study period, which was primarily in the 5-19 age group who experienced a 21% annual percent change in incidence over the same period. PPVs were approximately 5-10%.

Conclusions: Changes in narcolepsy IRs in the H1N1 pandemic period may be due to changes in diagnostic practices, awareness, a true association with influenza disease or vaccination, or some combination. The results should be viewed in the context of the case-control study currently in progress within SOMNIA.

816. Assessing Quadrivalent HPV Vaccine Safety Using the Self-Controlled Tree-Temporal Scan Statistic

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Background: HPV vaccine coverage in the U.S. is lower than that of other adolescent vaccines. One reason cited by parents for refusing or delaying HPV vaccination for their children has been concern about its safety.

Objectives: To study the safety of quadrivalent HPV vaccine (HPV4) with respect to thousands of medically attended potential adverse events occurring within 6 weeks of vaccination, using claims data.

Methods: We used the conditional self-controlled tree-temporal scan statistic, which simultaneously evaluates several thousand potential adverse events and a large number of potential risk windows, while adjusting for multiple testing. Members of five Sentinel System Data Partners who received HPV4 Dose 1 at 9-26.99 years of age during 6/1/2006-12/31/2014 were included. Electronic health insurance claims data from emergency department and inpatient encounters of these Dose 1 vaccinees were analyzed.

Results: 1,903,697 first doses of HPV4 were included in analysis. Two statistically significant alerts were

detected, both with multiple-testing-adjusted $p < 0.00001$: 1) 31 cases of "cellulitis and abscess of the upper arm and forearm" (attributable risk (AR) = 1.3/100,000 first-dose vaccinees), and 2) 36 cases of "other complications of surgical and medical procedures," including "other serum reaction due to vaccination" (AR = 0.6/100,000 first-dose vaccinees).

Conclusions: We found two statistical alerts, one for cellulitis/abscess, a known adverse reaction listed in the HPV4 package insert, and the other for complications of surgical/medical procedures, a catch-all group of codes typically used for minor adverse reactions such as local reactions; local reactions are also currently listed in the product label. The statistical power was sufficient to detect adverse reactions with ARs of less than 5 per million. Thus, HPV4 vaccine appears safe with respect to a wide range of medically attended potential adverse events that could have occurred in the first 6 weeks after vaccination. The conditional self-controlled tree-temporal scan statistic promises to be a useful method for assessing the safety of other vaccines as well.

817. Human Papillomavirus Vaccination and Risk of Autoimmune Diseases: A Large Cohort Study of Over 2 Million Young Girls in France

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Background: Whether human papillomavirus (HPV) vaccination could induce or trigger autoimmunity diseases (AID) is often questioned, leading to low immunization coverage.

Objectives: To evaluate the association between HPV vaccination and the risk of AID.

Methods: All girls aged 13 to 16 years between 2008 and 2012, covered by the French general health insurance scheme and without history of HPV vaccination or AID, were included and followed using French nationwide databases. Fourteen neurological, rheumatological, haematological, gastrointestinal or endocrine AID, were identified from hospital stays, long-term illnesses and marker drugs. Their incidence was compared between girls exposed and non-exposed to HPV vaccination, using a time-dependent Cox model with age as time scale, adjusted for inclusion year, geographic area, socio-economic indicators, healthcare use level and other immunizations.

Results: Among 2,252,716 girls, 37% received HPV vaccine (mean age at vaccination, 15.0 years ±0.84) and 4,096 AID occurred during a mean follow-up of 33 months. Exposure to HPV vaccination was not associated with the occurrence of twelve AID. A significant 18% increase in the risk of inflammatory bowel disease was found, which however became non-significant after censoring the first three months following vaccination (HR: 1.14 [0.97 to 1.35]). The risk of Guillain-Barré syndrome (GBS) was significantly increased (HR: 4.00 [1.84 to 8.69]) after vaccination (19 cases among the exposed [1.36 per 100 000 PY] vs. 21 cases among the unexposed [0.37 per 100 000 PY]; $p<0.001$). This association, particularly marked in the first months following vaccination, persisted regardless of the specialty of the HPV vaccine, concurrent vaccinations, history of recent infection or even season. Under the hypothesis of a causal relationship, this would result in 1.8 GBS cases attributable to HPV vaccine per 100,000 girls vaccinated.

Conclusions: Our study provides reassuring results regarding the risk of AID after HPV vaccination. An increased risk of GBS after HPV vaccination seems likely; nevertheless, this increased risk, if confirmed, would have a limited public health impact.

818. Effectiveness of the Quadrivalent Human Papillomavirus Vaccine (QHPV) Against Anogenital Warts (AGWs) in Manitoba, Canada: A Population-Based Study

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Background: QHPV became available in Manitoba in 2006, and was introduced into the publicly-funded school-based program in 2008. AGWs are one of the earliest clinical outcomes of HPV infection. They tend to occur at a younger age than other HPV-related disease, and can therefore provide an early indication of the success of school-based vaccination programs. To date, few studies have assessed the effectiveness of these programs in preventing AGWs using population-based, individual-level data.

Objectives: We used a historical matched cohort study to assess the effectiveness of the QHPV program in Manitoba, in reducing the incidence of medically-attended AGWs and, whether effectiveness depends on age at vaccination, and evidence of prior sexual activity.

Methods: Using Manitoba's population-based vaccine registry, females > 9 years old who received QHPV between September 2006 and March 2013 (n = 31,464) were matched, with replacement, on age and area of residence to three unvaccinated females (n = 94,327). Information on incident AGWs was obtained from hospital, physician and drug prescription databases using validated algorithms. Evidence of prior sexual activity was determined using codes for pregnancy, sexually transmitted infection, or contraceptive drug use. We used Cox regression models, stratified to account for matching, to determine hazard ratios for AGW among the vaccinated, compared to the unvaccinated.

Results: We identified 500 cases of incident AGWs. QHPV was associated with 40% reduction in AGW risk (HR 0.6, 95% CI 0.4-0.8) among females vaccinated before they turned 18. Among Females vaccinated at >18 years of age, QHPV was associated with increased AGW risk, especially among those who were sexually active (HR 2.8, 95% CI 2.1-3.7), likely because of increased QHPV use among high-risk women. Adjustment for socioeconomic and medical history covariates did not alter these estimates.

Conclusions: In order to optimize our current publicly-funded QHPV vaccination program in Manitoba, further efforts should be targeted at increasing vaccine uptake in young adolescents, prior to the initiation of sexual activity.

819. Long Term Effectiveness of Herpes Zoster Vaccine Among Patients with Autoimmune and Inflammatory Diseases

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Background: Recent results from long-term follow-up of healthy older participants of the Shingles Prevention Study (SPS) demonstrated that the herpes zoster (HZ) vaccination lost most of its benefit after approximately 10 years. However, the duration of protection among patients with autoimmune or inflammatory (AI) diseases is unclear.

Objectives: Current study aimed to evaluate the duration of HZ vaccine effectiveness in preventing HZ among older patients with autoimmune diseases.

Methods: Using Medicare data from 2006-2013 for patients with AI diseases, this retrospective cohort study identified patients who had HZ vaccination. To control for confounding, patients without HZ vaccination were matched 2:1 to vaccinated patients on year of vaccination, age, gender, race, type of AI diseases, and use of biologics, DMARDs and glucocorticoids. Follow up began one month after vaccination and ended at: HZ, death, loss of coverage or 12/31/2013. We calculated HZ incidence rates for each year and used Poisson regression to calculate the adjusted risk ratio of HZ for each year.

Results: Of 59,627 vaccinated patients with AIs matched to 119,254 unvaccinated AI patients, we identified 1,242 and 3,183 HZ events during follow-up respectively. Incidence rates among vaccinated increased from 0.75 per 100 person years (PY) during the first year post vaccination to 1.36 during the 6th year post. After multivariable adjustment, vaccinated patients had a significantly lower risk of HZ compared to unvaccinated patients through 5 years but not beyond.

Conclusions: Among patients with autoimmune diseases, the effectiveness of HZ vaccination waned over time, and a significant benefit to reduce HZ risk

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compared to non-vaccinated patients was found only through 5 years post vaccination.

820. New Methods to Estimate Vaccination Coverage from Health Care Databases

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Background: The evaluation of vaccination programs and especially the introduction of new vaccines requires tools to closely monitor the vaccination coverage. Health care databases allow monitoring vaccination coverage at a relatively low cost and for a large geographical area. However, incomplete follow-up hamper the accurate estimation of vaccination coverage.

Objectives: We developed new methods to estimate vaccination coverage accounting for incomplete follow up and assess their performance through simulation.

Methods: We explore inverse probability weighting techniques. When vaccination is recommended at a specific age (or time period, e.g. influenza vaccination), we derive weights from the estimated cumulative distribution function for the age (or time period) at vaccination (cdf-method). Alternatively, we derive weights from a comparison of the observed strata-specific follow-up time to the theoretical follow-up time in case all subjects would have been completely followed-up (fu-method). We run several simulation studies for varying coverages with age at vaccination generated from a distribution with median age of 3 months and varying levels of incompleteness. For each simulation setting, 1000 simulations of a birth cohort of 10.000 subjects are generated. Each time we estimate the coverage at 12-months. We calculate bias and mean squared error (MSE) to assess the performance of the different methods.

Results: Given a vaccination coverage of 30% and when 30% of the subjects have incomplete follow-up, the bias is 0.01% for the cdf-method and -0.2% for the fu-method compared to -8.5% when ignoring incomplete follow-up. The $\sqrt{\text{MSE}}$ is 5% and 6%, respectively compared to 8.5%. Similar trends in results hold for the different vaccination coverages and levels of incompleteness.

Conclusions: We developed new methods to estimate vaccination coverage in case of incomplete follow-up. Both methods perform very well, even if 80% of the subjects have incomplete follow-up. In this simulation setting, the cdf-method slightly outperforms the fu-method. However, the cdf-method cannot be used when vaccination is not recommended to be given at a specific age (or time period).

821. Multi-State Models – A Complimentary Approach to Group Based Trajectory Models

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Background: There have been recent analytic approaches proposed to better account for the dynamic nature of adherence using group based trajectory models (GBTM). GBTM analyses cannot deal with informative censoring, are typically restricted to relatively short follow-up due to concerns about continuous enrollment, only allow adherence trajectories to take a polynomial shape, and are known to suffer from convergence issues. Multi-state models (MSM) can address these limitations and provide unique insights in future adherence. MSM estimate the probability of being in different states over time while GBTM shows the probability of being assigned to a specific adherence trajectory. Additionally, MSM can be extended to incorporate the dynamic relationship between adherence and outcomes.

Objectives: To compare MSM and GBTM for estimating adherence to endocrine therapy (ET) for women with breast cancer.

Methods: We examined monthly adherence to ET using the proportion of days covered (PDC) during one year post-initiation for women with breast cancer between 2007-2010 using SEER-Medicare data. We compared the performance of the models measuring monthly adherence as a binary variable (PDC>80) and by breaking adherence into quintiles (PDC = 100-80, 79-60, etc). We used the model

output to simulate adherence and compared the model performance using root mean squared error and c-statistic.

Results: The models performed similarly when breaking up PDC into quintiles. The RMSE was 0.33 (CI = 0.30-0.37) and 0.31 (CI = 0.31-0.33) and the C-statistic was 0.754 (CI = 0.753-0.755) and 0.725 (CI = 0.723-0.725) for the MSM and GBTM, respectively. We find the MSM slightly outperforms the GBTM when treating PDC as a binary variable; RMSE was 0.375 (CI = 0.33-0.43) and 0.471 (CI = 0.44-0.51) and the c-statistic was 0.786 (CI = 0.785-0.787) and 0.743 (CI = 0.740-0.745). Also, MSM would allow the sample to increase by up to 30%.

Conclusions: Generally, MSM and GBTM perform similarly when predicting adherence. MSM may be more appropriate when there are high rates of informative censoring or when wanting to predict the probability of different adherence states overtime.

822. Covariate Adjustment of Cumulative Incidence Functions for Competing Risks Data Using Inverse Probability of Treatment Weighting

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Background: In time to event analysis, competing risks may be a concern. They arise if only the earliest of several times to event, corresponding to different event types, is observed or is of interest.

Objectives: Our objective was to describe a simple method to perform covariate adjustment with competing risks data and to develop a SAS macro to make the method readily usable.

Methods: Competing risks data may be characterized by the cumulative incidence functions (CIFs), one for each event type. We propose the use of inverse probability of treatment weighting (IPTW) to calculate adjusted CIFs. Confidence intervals can be estimated by bootstrap.

Results: We developed a SAS macro implementing this method. We illustrate its use by analyzing the Hodgkin's disease example data from Pintilie's book on competing risks. The considered event types are relapse, second malignancy, and death. Patients are treated either with radiation only or with radiation and chemotherapy. For radiation, the crude cumulative incidence at 15 years from diagnosis was 37%, 2%, and 10% for relapse, second malignancy, and death, respectively (e.g., 37% is the estimated probability that relapse occurs within 15 years and this before second malignancy or death). For radiation and chemotherapy, the corresponding values were 23%, 8%, and 7%, respectively. Covariate adjustment reduced the difference in cumulative incidence of death between both treatments, but increased the difference in cumulative incidence of relapse. We explored the distribution of the weights and we performed balance diagnostics in the weighted population: there was no indication of non-positivity or misspecification of the weight model.

Conclusions: IPTW can be used to adjust for measured confounders when studying associations between treatment and different types of event, while focusing on the earliest event only. The presented approach requires no assumption about the form of the CIF. When the weight model is saturated, the method is equivalent to direct standardization. Interpretation of the estimated CIFs is therefore simple and intuitively appealing.

823. Propensity Score Methods for Subgroup Analyses: Investigating Covariate Balance

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Background: Prior studies have shown that propensity scores (PS) using the full cohort can be used to control measured confounding in subgroup analyses. However, misspecification of the PS model could lead to residual confounding through imbalance of important confounders within subgroups.

Objectives: To describe the balance of measured confounders in subgroups using alternative PS modeling

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approaches. We used an empirical example of the effect of adjuvant chemotherapy on adverse functional outcomes in older breast cancer women, stratified by age at diagnosis <75 and 75+ years).

Methods: Using the Surveillance, Epidemiology, and End Results program (SEER)-Medicare data 2004-2011, we identified a cohort of women ≥66 years old, diagnosed with stage I-II incident breast cancer, who underwent surgery ≤90 days from diagnosis. Adjuvant chemotherapy was identified ≤90 days from surgery and all women were followed for: an adverse functional outcome (e.g., durable medical equipment claims, home health and skilled nursing facility visits), death, end of continuous enrollment, or end of the 2-year period. PS models were estimated using logistic regression including demographic, tumor, socioeconomic, and healthcare use factors in: (1) the full cohort, (2) women <75 years, (3) women 75+ years, and (4) the full cohort with age interactions <75 vs. 75+ years).

Results: The full cohort PS balanced measured confounders reasonably well with an average absolute standardized mean difference (SMD): 0.017 in <75 and 0.030 in 75+ year old women. Cancer stage, an important confounder, was imbalanced with an absolute SMD of 0.039 in <75 and 0.077 in 75+ year old women. The average absolute SMD was improved in the full cohort PS model with age interactions: 0.010 in <75 and 0.014 in 75+ year old women, but it was best with subgroup-specific PS models: 0.009 in <75 and 0.007 in 75+ year old women.

Conclusions: Subgroup-specific PSs balanced measured covariates the best. Researchers studying subgroup effects should evaluate covariate balance within subgroups and consider subgroup-specific models or interaction terms in the overall PS. This is important in network studies when PSs are shared to protect patients' privacy.

824. Adjustment for Unobserved Confounders in Health Administrative Databases

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Background: In health administrative databases, information on potential confounders such as tobacco or alcohol consumption can be missing. Often, this information is readily available in cohort data. Multivariate imputation by chained equations (MICE) and 2-stage calibration (TSC) using the propensity score may be applied to adjust for unobserved confounders (UC) in administrative databases using cohort data.

Objectives: We aimed at comparing by simulation the performances of MICE and TSC to adjust for UC in an administrative database using a cohort data. These methods are then be applied to study the association between benzodiazepine consumption and fracture.

Methods: We generated large samples of incomplete data with a binary exposure, a binary response and two observed confounders (OC) and small samples of complete data including also the measures of two additional confounders (UC). The impact of the distributions of OC and UC, the strength of confounding effects, the misspecification of the propensity score model, and the lack of representativeness of the cohort where investigated. MICE was applied by imputing the UC or the propensity score while TSC was applied with linear or spline estimation. Comparisons were based on bias, mean square error and confidence interval coverage of the true exposure effect.

Results: When the cohort data is a representative sample with Gaussian confounders and the propensity score model is well-specified, both methods gives no bias, nominal coverage rate with smaller variance from TSC. The coverage rates of TSC slightly decrease when the propensity score model is misspecified or in cases with strong confounding effect of UC and nonstandard distributions for the confounders; TSC with spline is slightly more robust. TSC may be biased when inclusion of subjects in the cohort depends on an interaction between the exposure and the outcome. Both methods are severely biased when inclusion depends on an interaction between UC and exposure or response.

Conclusions: Our results give guidance for using MICE and TSC to adjust on unobserved confounders in an administrative database.

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825. The Impact of Censoring on Discontinuation When Modeling the Disease Risk Score

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Background: Disease risk scores (DRSs) are used frequently in pharmacoepidemiology. While both intention-to-treat (ITT) and as-treated (AT) follow-up models can be used for effect estimation, the proper choice for DRS development is not widely discussed. Since AT approaches may reduce the number of outcome events and thus the maximum dimensionality of the DRS model, it is possible that, in some settings, bias could be reduced by utilizing a DRS estimated under ITT, even if subsequent effect estimation is done under AT.

Objectives: To compare the ability of DRSs estimated under varying follow-up models to control confounding.

Methods: We defined a cohort (N = 7,034) of rivaroxaban and warfarin initiators in the Optum Research Database between 2011 and 2014, and a historical cohort (N = 41,206) of warfarin initiators from 2004 to 2011. We defined composite safety and effectiveness endpoints in both cohorts, and used the historical cohort to develop DRSs using both follow-up models. We assessed the correlation of DRSs estimated under each approach and compared DRS-adjusted treatment effects. We used the "dry-run analysis" proposed by Hansen to estimate "pseudo-bias" on the log hazard ratio (HR) scale remaining after control for each DRS.

Results: Use of the AT approach resulted in a 70%-79% reduction in events. Rivaroxaban patients were on average younger and healthier than warfarin patients, resulting in downward bias of the HR. For both outcomes, adjustment with the ITT and AT DRSs yielded similar HRs. For the combined bleeding outcome, the AT-DRS was highly correlated with the ITT-DRS (r2 = 0.78), while the correlation for the combined embolic outcome was modest (r2 = 0.39). For the combined bleeding outcome, the pseudo-bias was -0.19 for both the ITT and AT DRSs. For the combined embolic outcome, the pseudo bias was -0.02 for the ITT DRS and -0.12 for the AT DRS.

Conclusions: There may be situations in which it desirable to estimate DRSs under ITT principles, even if the final analysis uses an AT principle. Under the assumption that the outcome risk factors are the same in patients on and off therapy, efficiency may be gained and bias reduced by estimating the DRS under an ITT principle.

826. Survival Bias in Exposure Crossover Studies

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Background: In an exposure cross-over study, treatment effect is estimated by comparing observed event frequency in a treated cohort during a post-treatment period with the frequency observed in the same cohort during a pre-treatment period. In recent years, this design has been used to study effects of new medications on recurring adverse events associated with survival (e.g., heart attacks or strokes); these studies attempted to control survival bias by restricting analysis to subjects surviving to the end of the post-treatment period.

Objectives: We show that such restriction does not eliminate survival bias in exposure cross-over studies.

Methods: Survival bias is illustrated analytically, in simulations, and using a real cohort of patients diagnosed with localized prostate cancer (PC) in the US SEER database in the years 2000-2007, with "treatment" defined as 3 years from PC diagnosis (no active treatment), and outcome defined as any new cancer diagnosed during a 1-year post-"treatment" period versus a 1-year pre-"treatment" period.

Results: The analytic argument makes use of the fact that in the unrestricted analysis, pre-treatment events must be sufficiently mild to allow for survival to treatment, while the post-treatment events may represent the entire severity spectrum of the disease. Similarly, in the restricted analysis, pre-treatment events must be sufficiently mild to allow for survival to the end of the combined length of the pre-treatment and the post-treatment periods, while the post-treatment events must only allow for survival to the end of the post-treatment period. Based on these considerations alone, we expect to see more post-treatment than pre-treatment events, even if treatment effect is absent. In the SEER cohort of 60,261 PC patients surviving to "treatment", there were 512 pre-"treatment" and 767 post-

"treatment" events. Age-adjusted rate ratio for "treatment" in a log-linear GEE model was 1.49 (95% CI: 1.34-1.68) in the unrestricted analysis and 1.30 (95% CI: 1.13-1.49) in the restricted analysis.

Conclusions: Restricting analysis to patients surviving the post-treatment period does not eliminate survival bias in exposure-crossover studies.

827. Pattern Discovery in Observational Health Data - What We Did Not Know to Look For

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Background: The detection and exploration of adverse drug reactions require an open mind and an alertness to the unexpected. Statistical methods have become part of many approaches to screen large observational health databases for unanticipated effects of medicines, but their routine use is often limited to the search for pairwise associations between single drugs and single adverse events. In contrast, complex medical conditions may be described by a combination of signs and symptoms, laboratory test results, and/or diagnoses. The failure to detect more sophisticated patterns may lead to signal fragmentation and delayed detection of emerging adverse drug reactions. Similarly, the risk of adverse drug reactions may vary between patients and over time after exposure in ways which are not well understood. The discovery of such patterns may help uncover signals that would remain hidden in overall analyses and may guide subsequent research to better evaluate and describe potential adverse drug reactions.

Objectives: To raise awareness of the potential for more effective analysis of observational health data through pattern discovery, to illustrate these opportunities by case studies in different data sets, and to discuss some of the associated challenges.

Description: This symposium will introduce the concept of formal pattern discovery and detection. It will present four case studies with different approaches to pattern discovery and detection in different databases: the U.S. Food and Drug Administration and Centers for Disease Control and Prevention Vaccine Adverse Event Reporting System (VAERS), the FDA Sentinel System, the World Health Organisation's international database of suspected adverse drug reactions (VigiBase), and the Humedica longitudinal observational health data. The panelists will specifically discuss the need for effective human-computer interaction and associated challenges related to transparency and reproducibility.

828. Clinical And Analytic Considerations In The Selection And Evaluation Of Comparators In Observational Database Studies

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Background: In observational database studies, neither the hypothetical ideal of a counterfactual nor the practical advantage of placebo-control in a randomized trial is available, so study designs must define a comparator group to serve as the proxy for the counterfactual and baseline from which to estimate relative risks. Currently, there is no consensus for how researchers should make this comparator selection.

Objectives: To review multi-disciplinary considerations for comparator selection in pharmacoepidemiology study designs, and examine empirical diagnostics for evaluating the suitability of the comparison group.

This symposium is aimed at researchers designing observational studies or reviewing comparative analyses that have already been conducted.

Description: This symposium will provide a forum for multi-stakeholder discussion around current perspectives and evolving best practices for comparator selection in pharmacoepidemiology studies.

Dr. Shakir will discuss clinical and pharmacological considerations that must be evaluated in comparator selection. He will illustrate through topical examples surrounding drug safety surveillance of antidiabetic agents and novel oral anticoagulants.

Dr. Madigan will provide context for the statistical interpretation of observational analysis model using comparators. In particular, he will discuss

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exchangeability assumptions and the role of confounding as it relates to inter-person comparisons made within cohort study designs and intra-person comparions made within self-controlled methods.

Dr. Ryan will highlight empirical approaches that can be used to identify candidate comparators for new user cohort designs, and highlight analytical diagnostics that can be performed to evaluate the appropriateness of a comparator group as part of a feasibility assessment prior to study execution.

The panel will debate whether comparator selection should be considered 'art vs. science' and the degree to which standard principles for comparator selection can be systematically applied to improve the reproducibility and reliability of observational studies.

829. Pharmacoepidemiology and Risk Management Planning: Essential Enablers for Development of Innovative Medicines

Peter R. Arlett[1], June Munro Raine[2], Almath Spooner[3], Sebastian Schneeweiss[4] and Eva Flahavan[5]

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Background: The regulation of medicines needs to balance the gatekeeper role of protecting patients with the facilitator role supporting the development of innovative medicines to fulfil the unmet needs of patients. Pharmacoepidemiology and risk management planning have traditionally been associated with evaluation of drug safety issues and minimising harm from known risks. This seminar will make the case for the critical role of pharmacoepidemiology and risk management in supporting innovation.

Objectives: The symposium will outline the business case for investment in pharmacoepidemiology and risk management in supporting innovation. The symposium will explore how pharmacoepidemiology and risk management planning can support the development of medicinal products from early drug development through to non-prescription use of medicines. The symposium will emphasize the role of planned collection of data throughout development and will look to the opportunities presented by new technologies including e- and m-health. Of interest to all those colleagues working in medicines R&D, in risk management, in pharmacoepidemiology and in regulation.

Description: The session will be chaired by Dr Arlett (EMA) who will provide a brief introduction on the critical link between pharmacoepidemiology, risk management and innovation. The first speaker, Dr Raine (Chair of the PRAC) will outline key EU initiatives to support the development of innovative medicines and will explain how risk management planning and use of real-world evidence can play a central role. Dr Spooner (HPRAr) will explore the role of pharmacoepidemiology and real-world evidence for efficacy studies and draw on the new EMA guidance on post-authorisation efficacy studies. She will also highlight some of the opportunities that new technologies present. Eva Flahavan (Lilly) will give industry examples in pre-authorisation medicines development. The session will then move to an extended panel discussion including Sebastian Schneeweiss and questions and interventions from the audience on how pharmacoepidemiology and risk management should be fostered to meet their promise as key enablers.

830. Transitioning to ICD-10: International Lessons Learned and Strategies for Moving Forward

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Background: The United States (US) introduced ICD-10 on October 1, 2015 and ICD-10 codes have just begun accruing in US data systems. The transition from ICD-9 to ICD-10 will have profound research and regulatory implications for pharmacoepidemiology studies conducted in US databases. While crosswalks to map ICD-9 to ICD-10 codes are available, there is no guarantee that outcomes and covariates defined using mapped ICD-10 codes will have the same performance characteristics as their validated ICD-9 counterparts. Moreover, the validity of ICD-10 codes may change over time as and physicians and coders gain experience with the new system. Other countries have already

transitioned to ICD-10 coding. For example, Denmark began using ICD-10 in 1994, Canada in 2001, and Korea in 2008. ICPE provides an ideal forum to bring together stakeholders with different perspectives and different levels of experience with this transition to discuss lessons learned and strategies for affected entities to move forward.

Objectives: To provide a forum for discussion of challenges, solutions, and best practices for managing the transition to ICD-10 as it relates to the practice of pharmacoepidemiology. Researchers using data affected by the US transition to ICD-10 or with experience in using ICD-10 codes would benefit by attending.

Description: The transition to ICD-10 in the US represents a major change that is affecting many research organizations. This workshop will bring together panelists from countries that have already implemented ICD-10 and panelists from regulatory and research organizations within the US who are currently preparing for the transition. Panelists will share international experience and insights, as well as discuss optimal strategies for approaching this fundamental change affecting commonly used data sources. A brief presentation from panelists will be followed by discussion and brainstorming regarding the most pressing needs with respect to outcome validation for the field of pharmacoepidemiology. Participants should leave the session feeling better equipped to handle this transition in their respective.

831. Who to Ask and How? Preference-Based Methods for Benefit-Risk Assessment

Kevin Marsh[1], Hans L. Hillege[2,3], Quazi Ataher[4] and Tommi Tervonen[1]

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Background: Preference-based methods for incorporating patient, physician, and other expert opinion into drug benefit-risk assessments (BRA) have received increasing attention from regulatory bodies, academics, and the pharmaceutical industry. Various methodologies offer powerful tools for preference-based BRA, but their use imposes methodological, organizational and practical challenges.

Objectives:

1. To review and critically contrast two prominent methodologies available for BRA: multi-criteria decision analysis (MCDA) and discrete choice experiments (DCE)
2. To convey regulator view on these methods
3. To present industry experience and practical challenges in implementing such methods
4. To discuss audience views on BRA with preference-based methods

The symposium is targeted at a wide audience and the contents will be accessible with little background knowledge on the topic.

Description: This symposium brings together regulatory, academic and industry experts to share experience and knowledge on how preference-based methods can and should support BRA. We will start with a brief introduction to topic and symposium presenters. (10 min, Marsh)

In the first part of the symposium, we review the techniques of DCE and MCDA in BRA, including relevant ISPOR task force guidance, to illustrate the differences and similarities between the two methodologies. (20 min, Tervonen)

The second part presents a regulator view. We will describe results from an EMA pilot in which patients and experts participated in different BRA procedures, and discuss recent EMA exploration of methodologies for systematically collecting quantitative information about patient preferences by combining face to face meetings and online questionnaires. (20 min, Hillege)

The third part presents the industry perspective. We discuss how adoption of preference based methods in routine BRA will require a paradigm shift that will come with further familiarity with the methods, in-house technical capacity building, and regulatory agency interest and guidance. Real life examples will be presented. (20 min, Ataher)

Symposium finishes with a panel discussion where audience is encouraged to participate. (20 min).

832. The Agony and the Ecstasy: The Creation of the Revised ICH M4E Benefit-Risk Assessment Guideline and Practical Implications for Patients, Industry and Regulators

Meredith Y. Smith[1], Tarek Hammad[2], Rebecca Noel[3], Paul Huckle[4], Francesco Pignatti[5] and Declan Noone[6]

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Background: An Expert Working Group recently revised the International Conference on Harmonisation (ICH)'s Benefit-Risk Guideline in order to harmonize the presentation of benefit-risk information in medicinal product regulatory submissions. The revised Guideline provides a structured process for sponsors to use in presenting the benefit-risk assessment of new medicines in the Common Technical Document. The Product Development Rationale (Sect. 2.5.2), and Benefits and Risks Conclusions (Sect.2.5.6) have both been revised to include greater detail regarding the content and structure of benefit-risk information, and to include patient preference data. The Guideline is expected to be finalized by June 2016.

Objectives: The objectives are: 1) to present the newly revised ICH M4E(R2) Guideline with comments from Expert Working Group members regarding the issues considered during the development process; and 2) to discuss the practical implications of the revised Guideline for patients, industry and regulators.

Description: The symposium will start with a brief web-based audience engagement exercise followed by 4 presentations (10 minutes per) from Expert Working Group members:

- "Overview of changes: the new ICH-M4E(R2) Guideline for benefit and risk assessment in the CTD" (Rebecca Noel, Eli Lilly)
- "Key methodological challenges in conducting benefit-risk assessment in drug development" (Tarek Hammad, Merck- formerly of FDA)
- "The evolving role of benefit-risk assessment in informing regulatory decision-making" (Francesco Pignatti, EMA)
- "An industry perspective on the changes in the CTD section 2.5.6 on benefit-risk" (Paul Huckle, GSK)
- A patient's perspective: patient input into product benefit-risk assessment (Declan Noone, Patient advocate, Irish Hemophilia Society)

A 25 minute panel discussion will follow (moderated by M. Smith, Amgen) on the practical implications of the revised Guideline for patients, industry and regulators. Panelists will include F. Pignatti, EMA (regulator), D. Noone, Irish Haemophila Society (patient representative), and R. Noel, Eli Lilly (industry).

833. Validity of a Web-Based Questionnaire to Assess Perinatal Outcome

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Background: Previous validation studies showed that maternal recall of perinatal outcomes, including infant birth weight and gestational age, is generally excellent when using interviews or paper-based questionnaires. However, knowledge on the validity of data on perinatal outcome collected with Web-based questionnaires is limited.

Objectives: To validate a Web-based questionnaire used in a prospective cohort study to assess perinatal outcome.

Methods: For 1,124 women with an estimated date of delivery between February 2012 and February 2015 participating in the PRegnancy and Infant DEvelopment (PRIDE) Study in the Netherlands, we compared data on pregnancy outcome, including mode of delivery, plurality, gestational age, birth weight and length, head circumference, birth defects, and infant sex from Web-based questionnaires with data from obstetrical records. For the continuous outcome variables, intraclass correlation coefficients (ICC) with 95% confidence intervals (CI) were calculated, while sensitivity and specificity were determined for categorical variables.

Results: We observed only very small differences between the two methods of data collection for gestational age (ICC 0.85; 95% CI 0.83-0.88), birth weight (ICC 0.98; 95% CI 0.98-0.98), birth length (ICC 0.89; 95% CI 0.86-0.92), and head circumference (ICC 0.85; 95% CI 0.73-0.95). Agreement between the Web-based questionnaire and obstetrical records was high as well, with sensitivity ranging between 0.90 (post-term birth) and 1.00 (multiple outcomes) and specificity between 0.95 (emergency caesarean section) and 1.00 (multiple outcomes).

Conclusions: The validity of the Web-based questionnaire for perinatal outcomes was similar or even higher compared to the traditional modes of data collection.

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Therefore, Web-based questionnaires should be considered as a complimentary or alternative method of data collection in reproductive pharmacoepidemiology.

834. Consistency of Measures of Asthma Symptom Control Collected During Pregnancy vs. Retrospectively at 6 Months Post-Partum

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Background: Assessment of asthma symptom control is essential in both prospective cohort and retrospective case-control studies of asthma drug safety in pregnancy, as suboptimal asthma control is associated with adverse pregnancy outcomes.

Objectives: To determine how maternal report of asthma symptom control obtained in pregnancy corresponds with post-partum recollection.

Methods: Women were recruited through the MotherToBaby/Vaccines and Medications in Pregnancy Surveillance System into a prospective cohort study. Asthmatic women in the U.S. or Canada who were pregnant and <20 weeks' gestation were eligible. Women were assessed in each trimester by telephone using the Asthma Symptom Control Test (ACT). Those who delivered live born infants responded to the ACT questions again at 6 months post-partum, recalling each trimester of pregnancy. Possible scores ranged from 5-25; higher scores indicated better control. Scores were categorized as poorly/moderately controlled (5-19) or well controlled (20-25). Pearson correlation coefficients, 95% confidence intervals (CIs) and chi-square tests were computed comparing ACT scores in pregnancy to post-partum. In addition, the same comparisons were performed among women who had an adverse outcome of pregnancy.

Results: 196 asthmatic mothers were enrolled 2009-2014 and delivered live born infants. Overall 63-87% of women reported good symptom control in pregnancy. The correlation coefficients and 95% CIs for each trimester were 0.67(0.58,0.74); 0.61(0.52,0.70); 0.65(0.56,0.72) respectively. Categorically, the distribution of scores differed by time collected ($p<0.0001$); scores in each trimester were generally attenuated at post-partum recall compared to the corresponding in-pregnancy report. There was little evidence that the strength of correlations differed among women who had an adverse outcome.

Conclusions: There was differential report of asthma symptom control in pregnancy vs. post-partum recall. These data suggest that attenuation of scores could be addressed in the analysis of case-control studies that involve retrospective measures of asthma control.

835. Comparison of Electronic Healthcare Data and Prospective Face-to-Face Studies for Evaluating Neurodevelopmental Disorders Following In-Utero Medication Exposures

Rachel Charlton[1], Anita McGrogan[1], Julia Snowball[1], Laura Yates[2], Amanda Wood[3], Jill Clayton-Smith[4], Henry Smithson[5], Jonathan Richardson[2], Neil McHugh[1], Simon Thomas[6], Gus Baker[7] and Rebecca Bromley[7]

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Background: Investigating neurodevelopmental effects by face-to-face assessment is time intensive and financially costly. This has led to an increase in research using electronic healthcare data, however the accuracy of this data compared to face-to-face review is unknown.

Objectives: To determine whether data from the UK Clinical Practice Research Datalink (CPRD) produces similar risk estimates to a prospective study in relation to the risk of neurodevelopmental disorders (NDDs) following prenatal exposure to antiepileptic drugs (AEDs).

Methods: A cohort of mother-child pairs of women with epilepsy (WWE) was identified in the CPRD, along with a matched cohort without epilepsy. Children needed to be born between 01-01-2000 and 31-03-2007 and be in the CPRD at age 6 years. AED

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exposure during pregnancy was determined from prescription data and children with a diagnosis of autistic spectrum disorder, attention deficit hyperactivity disorder or dyspraxia by 6 years were identified from Read codes. The prevalence and risk of NDDs was determined for mother-child pairs in WWE stratified by AED treatment and for those without epilepsy. Comparisons were made to the results of a prospective study by the Liverpool and Manchester Neurodevelopmental Group which recruited 201 WWE and 214 without epilepsy.

Results: 1,018 mother-child pairs to WWE and 6,048 to women without epilepsy were identified in the CPRD. The CPRD identified a lower prevalence of NDDs compared to the prospective study, although small numbers limited comparisons between the two. In both studies, NDDs were more frequently reported in children of WWE than women without epilepsy (2.16% v 0.96% p = 0.001 and 7.46% v 1.87%). The prevalence of NDDs differed between AED exposure groups but the CPRD data (ORadj 2.02 CI95 0.52-7.86) did not replicate the significantly higher risk of NDDs in children exposed in-utero to valproate that was observed in the prospective study (ORadj 6.05 CI95 1.65-24.53).

Conclusions: It was possible to identify NDDs in the CPRD, however the CPRD appears to under-record these outcomes. Larger studies are required to investigate further.

836. Bias from Restricting to Live Births in a Study of Prescription Drug Use and Pregnancy Complications: A Simulation

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Background: Administrative claims data are frequently used to study effects of prenatal exposure to prescription medications but are typically missing data on spontaneous abortions and stillbirths. When using these data sources, we are forced to condition on live birth through restriction. This has been shown to be potentially problematic when fetal death is a competing risk for a postnatal outcome. Conditioning on live birth may also induce selection bias when the outcome of interest occurs in pregnancy and is a cause of fetal death, such as a birth defect or a pregnancy complication. The combination of these potential sources of bias when restricting to live births has not been explored with realistic values.

Objectives: To examine the potential for bias when studying a pregnancy complication in a data source restricted to live births, where fetal death is both a competing risk and caused by the complication.

Methods: We simulated the association of exposure to antidepressant medication and the outcome of preeclampsia, assuming a risk ratio (RR) of 1.25 or 1.5. The prevalence of spontaneous abortion and stillbirth were set at 10% and 1%, respectively, and the prevalence of antidepressant use and preeclampsia were both set at 4%. We simulated 500 cohorts, each with a sample size of 100,000, for scenarios varying the strength of relationships between antidepressant use, preeclampsia, and fetal death (RR = 2 to 4). We estimated the RR for the relationship between antidepressant use and preeclampsia restricted to live births only.

Results: Conditioning on live birth resulted in a consistent downward bias. Given a true RR = 1.25, the biased RR ranged from 1.07 (95% CI: 0.88, 1.25) to 1.20 (1.03, 1.37). Given a true RR = 1.5, the biased RR ranged from 1.27 (1.08, 1.46) to 1.43 (1.25, 1.61).

Conclusions: Restricting studies of pregnancy complications to live births may underestimate the effect of exposure to a degree that would obscure a modest but real effect, even when assuming realistic relationships between the exposure, outcome, and fetal death.

837. Utilization Patterns of Drugs or Biologics with Pregnancy Exposure Registries in Pregnant and Matched Non-Pregnant Women in the Sentinel Database

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Background: Pregnancy Exposure Registries (PER) are typically conducted when a medical product may be used in pregnant women but has a concerning or unknown safety profile during pregnancy.

Objectives: Among 37 products with PERs, we sought to examine relative rates of utilization among primarily commercially insured pregnant and non-pregnant women.

Methods: We identified 1.9 million live birth pregnancies, using a previously validated algorithm, and 1.9 million non-pregnant women, matched on age, calendar year, and data partner, in the Sentinel Distributed Database between 2001 and 2013. The date of conception was estimated as 270 days prior to hospital admission for delivery, adjusted for preterm and postterm birth identified by procedure and diagnosis codes, when applicable. Relative rates of utilization in pregnant versus non-pregnant women were calculated for 37 products with PERs.

Results: Among 37 products with PERs, the most common pregnancy exposures were bupropion (1.09% of pregnancies), sumatriptan (0.44%), lamotrigine (0.33%), letrozole (0.29%), duloxetine (0.25%), and aripiprazole (0.13%). The median (interquartile range, IQR) relative differential use between pregnant versus non-pregnant women for these products was RR 0.23 (IQR: 0.23-0.31). Only one product, letrozole, had a RR >1 (RR = 2.63; 5,413 exposed pregnancies, 99.0% were during the first trimester). Use of letrozole during pregnancy increased from 0.0% in 2001, 0.3% in 2004, 0.15% in 2007, 0.34% in 2010, and 0.53% of all pregnancies in 2013.

Conclusions: Lower utilization rates during pregnancy for almost all study drugs suggest that efforts to minimize unnecessary or potentially harmful use of drug therapy during pregnancy were largely successful. The high utilization of letrozole in pregnant women was unexpected and may be an artifact of its off label use as a fertility drug. Because its intended use occurs just before the beginning of pregnancy, but not during pregnancy, slight inaccuracy for defining the date of conception in Sentinel data may have contributed to our findings. Effort is ongoing to further characterize this finding.

838. Oral Contraceptive Induced Hypertension and Subsequent Pre-Eclampsia: A Retrospective Cohort Study

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Background: Pre-eclampsia occurs in 2-8% of pregnancies, leading to severe maternal morbidity and rarely, maternal death. Pre-eclampsia is also associated with adverse neonatal outcomes, principally related to preterm delivery.

Objectives: A dataset validation exercise in which known associations were tested in an Irish perinatal epidemiology dataset indicated that a history of oral contraceptive induced hypertension (OC-HTN) may be associated with pre-eclampsia. This hypothesis generating study aimed to examine the association between OC-HTN and subsequent pre-eclampsia.

Methods: Retrospective cohort study of all births at an Irish tertiary referral maternity hospital between 2000 and 2007. Self-reported maternal sociodemographic, medical and obstetric history was recorded as part of the booking interview carried out by a midwife. Pre-eclampsia, defined as onset of hypertension and proteinuria after 20 weeks' gestation, was ascertained from Labour Ward records. Multivariable logistic regression analyses were used to examine the association between OC-HTN and subsequent pre-eclampsia with adjustment for known risk factors.

Results: Of 61,213 deliveries, 3669 (6.0%) had a diagnosis of pre-eclampsia. 65 (20.4%) of 319 women with a history of OC-HTN developed pre-eclampsia. Maternal characteristics associated with pre-eclampsia included history of hypertension (aOR 6.12, 95% CI 5.38-6.95), kidney disease (aOR 3.24, 95% CI 1.68-6.22), OC-HTN (aOR 2.86 2.12-3.86), multiple pregnancy (aOR 2.60, 95% CI 2.13-3.17), diabetes (aOR 2.36, 95% CI 1.86-2.98), nulliparity (aOR 2.04, 95% CI 1.90-2.19) and smoking during pregnancy (aOR 0.63, 95% CI 0.57-0.69). Results were not altered if the analysis was restricted to women booking below 20 weeks' gestation.

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Conclusions: The potential association between a history of oral contraceptive induced hypertension and pre-eclampsia warrants investigation with independent data as it may help identify women at risk of pre-eclampsia and confer etiological clues. Furthermore, identification of at-risk patients prior to or in early pregnancy could facilitate more intensive monitoring combined with risk reduction and disease modifying interventions.

839. Time Trends Of Idiopathic Pulmonary Fibrosis (IPF) in the United Kingdom (UK) from 1999 to 2013 Using the Clinical Practice Research Datalink (CPRD)

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Background: Epidemiologic data on the incidence and prevalence of IPF in Europe remains scarce and inconsistent. Better understanding of the epidemiology is required to quantify and address the unmet medical need of this patient population.

Objectives: To estimate prevalence and incidence ranges of IPF in the UK from 1999 to 2013 using an electronic medical records database.

Methods: Using the CPRD, IPF case definitions were developed using READ codes. Idiopathic fibrosing alveolitis (IFA), IFA not otherwise specified (NOS), cryptogenic fibrosing alveolitis (CFA), Hamman-Rich syndrome, IPF, diffuse pulmonary fibrosis (PF), and PF codes were used for "broad". "Narrow" included IFA, IFA NOS, CFA, and IPF. Patients with connective tissue disease, extrinsic allergic alveolitis, sarcoidosis, pneumoconiosis, and asbestosis at any time in the medical record were excluded. Counts and incidence and prevalence rates (per 100,000) with 95% confidence intervals (CI) overall and by age, gender, and case definition were calculated by year from 1999 to 2013.

Results: A total of 7,989 patients were identified as "broad" from 1999 to 2013, with 62% male and 96% aged 50 years or older. The "narrow" algorithm identified 1,714 patients with similar gender and age distributions. "Broad" definition showed a gradual increase in prevalence from 22.4 (CI: 20.8, 24.1) in 1999 to 51.0 (CI: 48.9, 53.1) in 2013 with incidence increasing from 5.8 (CI: 5.0, 6.7) in 1999 to 11.0 (CI: 10.0, 12.2) in 2004 and remaining at that rate through 2013. "Narrow" definition showed an increase in prevalence from 1999 to 2002, but a decrease from 2005 through 2013 resulting in a net decrease in IPF from 1999 to 2013 [11.3 (CI: 10.2, 12.4) in 1999 to 7.8 (CI: 7.0, 8.6) in 2013]. Incidence for "narrow" mirrored the "narrow" prevalence trend [3.4 (CI: 2.8, 4.1) in 1999 to 0.9 (CI: 0.6, 1.2) in 2013].

Conclusions: Incidence and prevalence trends of IPF using the CPRD vary according to case definition, which showed opposite time trends. Clinical validation of IPF case definitions in the CPRD would greatly enhance the accuracy of these estimates.

840. The Impact and Longevity of Measles-Associated Immune Suppression

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Background: Measles infection is known to cause immune suppression, resulting in susceptibility to infections. Recent studies have indicated that these effects could last longer than two years.

Objectives: To assess whether children who have a had measles experience more clinical events potentially related to reduced immune response than non-diseased children.

Methods: Measles-diseased children between the ages of 1 and 15 years were matched by age, sex, and practice to up to 10 children without a measles diagnosis code who also had a code for measles mumps rubella (MMR) vaccination in The Health Information Network (THIN) database. Subjects with a history of immune-compromising conditions were excluded. Cohort entry for diseased and matched non-diseased subjects was the date of the diseased subject's measles diagnosis. Outcomes were infections, anti-infective

prescriptions, and hospitalizations. Incidence rate ratios (IRRs) of the outcomes in diseased vs. non-diseased subjects in the first month, 1 month to 1 year, 1 year to 2.5 years, and 2.5 years to 5 years following measles diagnosis were analyzed with Poisson regression with adjustment for sex, age in years, history of chronic cardiovascular or respiratory conditions, and exposure to other childhood vaccines .

Results: 2,301 measles-diseased subjects were matched to 22,507 non-diseased subjects. Exposure to childhood vaccines other than MMR was lower among diseased subjects (97.5% vs. 99.0, $p < 0.0001$). The IRR of infections was significantly elevated in the first month (1.46, 95%CI 1.26-1.69) and from the first month to first year following infection (1.16, 95%CI 1.08-1.24), but not beyond. Diseased subjects received more anti-infective prescriptions over all periods [IRR (95% CI): 3.62 (3.36, 3.92), 1.21 (1.14, 1.28), 1.20 (1.13, 1.28), and 1.17 (1.09, 1.26)]. The analysis on hospitalizations showed inconclusive results with increased significant IRRs in the first and last period only.

Conclusions: Immune suppression as measured by rates of diagnosed infections and anti-infective prescriptions is elevated following measles infection when compared to non-diseased children. This period of increased susceptibility could be as long as five years.

841. Beta-Thalassemia Treatment and Complications in Two Large US Insured Population Databases

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Background: No ongoing nationwide surveillance efforts exist to monitor the prevalence or changes in outcomes among individuals with beta( )-thalassemia in the US. Administrative health data have been uninformative owing to lack of specific diagnosis codes, but in 2011, new ICD9 codes for thalassemia subtypes were introduced, allowing analyses of -thalassemia in the US using insurance claims data.

Objectives: To describe the prevalence of -thalassemia diagnoses, treatments and outcomes among pediatric and adult patients in two administrative databases covering broad US geographic areas.

Methods: We analyzed data from two large insurance claims databases: OptumInsight Life Sciences Inc. Clinformatics™ DataMart MultiPlan and Truven Health MarketScan® Research commercial insurance database. Patients with -thalassemia were defined as those with ≥3 diagnosis codes for -thalassemia (ICD9 282.44) or HbE/ -thalassemia (ICD9 282.47). For comparison to general population, 5 controls were selected per case, matched on age, sex, and follow-up time.

Results: 1,044 patients (866 adults, 178 patients under age 18 y) with -thalassemia were observed from 2011-2014, of which 304 were from the Clinformatics™ database and 740 were from the MarketScan® database. Iron overload was diagnosed in 20-21% of all cases and upwards of 74% of transfusion-dependent cases. The most common oral chelating agent was deferasirox (62% of transfusion-dependent patients); deferoxamine claims occurred in 19% and deferiprone in 12% of transfusion-dependent patients. Narcotic analgesics were used by 23-25% of -thalassemia patients in the outpatient setting, and anti-anxiety or antidepressants medications were used by 16-17% of patients. Cases had significantly higher occurrence of numerous diagnoses, including viral and bacterial infections, mood and anxiety disorders and diseases of the heart or liver, compared to controls.

Conclusions: Using extensive data from relatively large samples of -thalassemia patients, we observed significant comorbidities that may be overlooked in small clinical studies in which such broad data collection is not feasible.

842. Epidemiological Assessment of Real-World Treatment Patterns in Advanced Pancreatic Neuroendocrine Tumors in the Era of Targeted Therapy: Perspectives from an Academic Tertiary Center and Community Oncology Practices

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Background: Pancreatic neuroendocrine tumors (PanNETs) are rare, slow-growing cancers. Optimal

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treatment of advanced PanNETs is unclear. For unresectable disease, somatostatin analogs (SSAs), targeted agents, chemotherapy, and liver-directed therapy are routinely administered.

Objectives: We aim to evaluate treatment patterns in the era of targeted therapy among patients with newly-diagnosed advanced PanNETs in both academic and community practice settings.

Methods: Retrospective chart review identified patients at an academic cancer center (University of California, San Francisco, UCSF) and a large network of community oncology practices in the US (Altos Solutions' OncoEMR database; ALTOS). Eligible patients were ≥18 years and newly-diagnosed between 2010-2013 with advanced and well- to moderately-differentiated PanNET. Patients were followed for ≥6 months after diagnosis date, with ≥2 visits in 12 months.

Results: Fifty-four out of 159 patients (UCSF = 23; ALTOS = 31) were identified as eligible. Mean age at diagnosis was 61 years (ALTOS patients were non-significantly older than UCSF, p = 0.11); 61.1% were male; median time to treatment initiation was 1.1 months; median follow-up time was 22.9 months. UCSF patients underwent more lines of therapy than ALTOS patients despite similar median follow-up times. The most common first-line treatments were SSA, everolimus, or chemotherapy at ALTOS and surgery, SSA, or chemotherapy at UCSF. The median time to treatment discontinuation for 1st/2nd-line was statistically significantly shorter for patients on chemotherapy than targeted therapy (chemotherapy = 2.2 months vs. targeted = 18.6 months, $p<0.01$).

Conclusions: Treatment patterns and duration for newly-diagnosed advanced PanNETs vary widely both within and between different practice settings. Limitations related to study methodology (e.g., incomplete information in the EMRs [type of PanNET was unknown in 84% of ALTOS medical charts]) preclude making definitive conclusions. Prospective studies are needed to more completely examine factors affecting choice of therapy.

843. 10-Year Landmark Survival and Characteristics of Advanced Non-Small Cell Lung Cancer (aNSCLC) Long-Term Survivors

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Background: Potential for long-term survival (LTS) is a compelling attribute of new therapies for aNSCLC such as immunotherapy. Real-world data (RWD) analyses to describe landmark survival and characteristics associated with LTS can provide meaningful benchmarks for evaluation of survival benefits observed in clinical studies.

Objectives: To describe 10-year landmark survival for aNSCLC and characteristics associated with LTS >2 years after aNSCLC diagnosis) among treated aNSCLC patients in a population-based observational data source.

Methods: Patients aged >66 years with stage IIIb or IV NSCLC at diagnosis between 1 Jan 1999 and 31 Dec 2001 were identified in the US SEER-Medicare linked database. Comorbid conditions were defined with the Deyo-modified Charlson Comorbidity Index. Treatment was defined as chemotherapy and/or radiotherapy within 4 months after aNSCLC diagnosis. Kaplan-Meier survival analysis was used to describe landmark survival up to 10 years after diagnosis. Logistic regression analyses were used to calculate odds ratios (OR) for characteristics associated with LTS among treated aNSCLC patients.

Results: In 14,524 aNSCLC patients, 35% received chemotherapy within 4 months after diagnosis. Year 1 landmark survival was 31.2% (95% CI 29.9-32.5) for treated vs. 13.2% (95% CI 12.6-13.9) for untreated; survival differences decreased by Year 5 with 2.2% of treated (95% CI 1.9-2.7) vs. 1.6% (95% CI 1.4-1.9) of untreated patients surviving. Among treated patients, 12% survived >2 years after diagnosis (LTS). In multivariate logistic regression analysis, odds of LTS were significantly higher for females (OR 1.5, 95% CI 1.3-1.8), patients aged <75 years (OR 1.38, 95% CI 1.1-1.7), with stage IIIb tumors at time of aNSCLC diagnosis (OR 2.6, 95% CI 2.2-3.1), and treated only with chemotherapy (OR 1.4, 95% CI 1.1-1.6).

Conclusions: Population-based RWD demonstrate poor long-term survival for Medicare-eligible aNSCLC patients in the pre-immunotherapy era. Patient and clinical characteristics associated with higher odds of LTS will be important to recognize as survival improves with new treatments.

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844. Reoperation Due to Surgical Bleeding in Breast Cancer Patients and Breast Cancer Recurrence: A Danish Population-Based Cohort Study

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Background: Breast cancer patients who develop postsurgical bleeding requiring reoperation may be at increased risk of breast cancer recurrence, since bleeding activates platelets that can bind to tumor cells, potentially promoting metastatic growth.

Objectives: To investigate the association between postsurgical bleeding requiring reoperation and the rate of breast cancer recurrence.

Methods: Using the Danish Breast Cancer Group (DBCG) registry and the Danish National Patient Registry (DNPR), we identified women with incident stage I-III breast cancer, who underwent breast-conserving surgery or mastectomy during 1996-2008. We retrieved information on reoperation due to bleeding within 14 days of primary surgery from the DNPR. Follow-up began 14 days after primary surgery and continued to the first of recurrence, death, emigration, ten years of follow-up, or 01/01/2013. We computed incidence rates (IRs) of recurrence, and 5- and 10-year cumulative incidence accounting for death as a competing risk. Cox regression models were used to quantify the association between reoperation and recurrence, adjusting for potential confounders (age, menopausal status, stage, grade, surgery type, estrogen receptor status, cancer treatment, comorbidity, and co-medications). Simvastatin and aspirin use, which reportedly can modify breast cancer prognosis, were modelled as time-varying covariates lagged by one year. Furthermore, we computed crude and adjusted hazard ratio according to site of recurrence.

Results: Among the included 30,711 patients (205,926 person-years (PY) of follow-up), 767 patients had at least one reoperation within 14 days of primary surgery, and 4,769 patients developed breast cancer recurrence. The incidence rate of recurrence was 24/1000 PY for reoperated patients and 23/1000 PY for non-reoperated patients. The corresponding adjusted hazard ratio was 1.07 (95% CI, 0.89-1.28). The estimates did not vary by site of breast cancer recurrence.

Conclusions: In this large cohort study, we found no evidence of an association between reoperation due to bleeding and breast cancer recurrence.

845. Opioid Use Prior to Incident Myocardial Infarction and Subsequent Risk of Ischemic Stroke, Venous Thromboembolism, and Death

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Background: Opioid use is associated with risk of myocardial infarction (MI), but its prognostic impact is unclear.

Objectives: To examine the impact of pre-admission opioid use on MI prognosis.

Methods: Using Danish nationwide registries, this cohort study included all patients admitted for an incident MI between 2006 and 2012. Patient were categorized according to timing of last redeemed opioid prescription prior to admission into either: current (0-30 days prior), recent (31-365 days prior), former (365+ days prior), or non-user. The primary outcome was all-cause mortality at 30-days and 31-365-days following admission. Secondary outcomes included ischemic stroke and venous thromboembolism. Mortality risk was estimated using Kaplan-Meier method and hazard ratios (HR) with 95% confidence intervals (CI) were computed based on Cox-regression. Adjusted models included age, gender, civil status, co-medication, surgery, and comorbidity.

Results: The study included 53,466 MI patients (8% current, 10% recent, 13% former, and 70% non users). The 30-day mortality was 23% for current users, 15% for recent users, 12% for former

users and 11% for non-users. After multivariable analysis, only current users compared with non-users remained at an elevated risk of dying within 30 days following admission, HR 1.30 (1.20-1.40). A similar pattern was evident for 31-365-day all-cause mortality, with an adjusted HR of 1.46 (1.33-1.61) for current users. Secondary outcome analysis showed a possible increased risk of 30-day-VTE for current (adjusted HR 1.51 (0.87-2.64)) and recent users (adjusted HR 1.50 (0.87-2.64)) compared with non-users. This was also observed for 31-365-day VTE (current users adjusted HR 1.58 (104-2.39) and recent users adjusted HR 1.26 (0.83-1.92)). Preadmission opioid use was not associated with ischemic stroke following MI.

Conclusions: Use of opioids at time of incident MI was associated with increased mortality rate within a year.

846. Long Acting Bronchodilators and Risk of Myocardial Infarction in Patients with Chronic Obstructive Pulmonary Disease and Who Are at High Risk for Cardiovascular Disease: A Quasi-Cohort Approach

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Background: Long-acting bronchodilators are the mainstay of pharmacologic therapy for moderate to severe chronic obstructive pulmonary disease (COPD), yet the concern regarding their cardiovascular safety remains.

Objectives: This study aimed to evaluate whether use of long-acting bronchodilators increases the risk of acute myocardial infarction (MI) in patients with COPD who are at high risk for cardiovascular disease.

Methods: A new-user cohort of patients 55 years of age or greater who were prescribed at least one long-acting bronchodilator from September 2003 to August 2011 was identified using the Clinical Practice Research Datalink (CPRD) and followed from the first prescription up to a maximum of two years. The study cohort was further restricted to patients at high risk for cardiovascular disease at cohort entry. All cases of acute MI occurring during follow-up were identified and up to 5 quasi-cohort person-moments were selected at random. The association between current long-acting bronchodilator use and acute MI was estimated using a quasi-cohort approach, focusing on users of long-acting 2-agonists (LABA) and long-acting muscarinic antagonist (LAMA) together, LABA alone and LAMA alone.

Results: The cohort included 76,965 subjects, with 1,462 who had the outcome event of acute MI during more than 49.6 million person-days of follow-up (rate of acute MI: 10.8 per 1,000 person-years). The adjusted quasi-rate ratios of LABA and LAMA together, LABA alone and LAMA alone were 1.06 (95 % confidence interval [CI]: 0.82 to 1.37), 1.04 (95% CI: 0.85 to 1.27) and 0.91 (95% CI: 0.74 to 1.11), respectively, relative to no current use. The adjusted quasi-rate differences were 0.65 (95% CI: -2.15 to 3.37), 0.37 (95% CI: -1.88 to 2.45) and -0.99 (95% CI: -3.13 to 0.98) per 1,000 person-years for LABA and LAMA together, LABA alone and LAMA alone, respectively.

Conclusions: The use of LABA and LAMA, given alone or together, do not appear to increase the risk of acute MI in patients with COPD at high risk for cardiovascular disease.

847. Association of Proton Pump Inhibitor Use and Acute Myocardial Infarction Among Privately Insured Adults, 2001-2014

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Background: Proton pump inhibitors (PPIs) are a frequently prescribed medication in the United States. While PPIs provide benefit for conditions like gastroesophageal reflux disease, recent studies detected an increased risk of acute myocardial infarction (AMI) associated with PPI use.

Objectives: To estimate the association of PPIs and AMI among privately insured U.S. adults.

Methods: Using the Truven Health Analytics Marketscan database random one-percent sample, we performed an as-treated analysis in a new user, active comparator study to evaluate the effect of PPIs versus histamine-2 receptor antagonists (H2RAs) on AMI risk. We included adults aged >17 who were continuously enrolled for ≥12 months prior to first prescription for a PPI or H2RA in employer-based insurance or supplemental Medicare plans from 2001-14. To control measured confounding, we estimated the propensity of PPI use based on age, sex, region, obesity and type 2 diabetes diagnoses, and prior prescription use of antihypertensives, antidiabetics, statins, or NSAIDs. We used Cox proportional hazards regression with stabilized standardized mortality ratio (SMR) weighting to estimate adjusted hazard ratios for AMI and 95% confidence intervals using robust variance. Censoring occurred at drug switching, discontinuation, or end of enrollment.

Results: We identified 59,309 new users of PPIs or H2RAs. The majority initiated a PPI (81.5%). Average follow-up time was 201.3 days for PPI users and 118.7 days for H2RA users. Mean age was 50.1 for H2RA users and 52.3 for PPI users. Overall incidence of AMI in our cohort was 2.2%, higher in adults ≥65 (5.8%). PPI users were more likely to have a prescription for an antihypertensive (44.3 vs 40.9%) or statin (25.1 vs 21.6%). PPI use was not associated with an increased risk of AMI when compared to H2RA use before (HR = 0.99, 95% CI 0.76-1.29) or after SMR-weighting (HR = 0.84, 95% CI 0.64-1.10).

Conclusions: There was no increased risk of AMI associated with PPI use when compared to H2RA use, providing reassuring evidence for the safety of PPI use relative to a clinical alternative.

848. Incidence of Cardiovascular Events in New Users of Overactive Bladder Medications in Denmark

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Background: A higher prevalence of cardiovascular comorbidities has been reported in users of antimuscarinic overactive bladder (OAB) medications.

Objectives: We investigated whether the incidence rate of acute myocardial infarction (AMI), stroke, cardiovascular mortality, and all-cause mortality differed comparing users of six different OAB drugs. A composite endpoint, major adverse cardiac events (MACE)—nonfatal AMI, nonfatal stroke, or cardiovascular mortality—was also examined.

Methods: Using the Danish national registries, we identified a cohort of new users of oxybutynin, tolterodine, solifenacin, fesoterodine, trospium, or darifenacin, aged ≥18 years, 2004-2012. Follow-up ended with event diagnosis, death, disenrollment, or end of study period. Exposure to OAB drugs was ascertained from the Danish National Prescription Registry; outcomes were ascertained from the Danish National Registry of Patients. We calculated crude and age-sex–standardized incidence rates (SIR). Regression models were used to estimate multivariable adjusted incidence rate ratios (IRR) and 95% confidence intervals for cardiovascular endpoints with reference to current exposure to other OAB drugs. In addition, 12 different propensity score models were constructed representing exposure propensity at cohort entry (six different sets of comparators, for both current and recent use).

Results: The study population included 72,917 patients; 60% female; mean age at cohort entry, 66 years. For current use of any OAB drug, the SIR per 1,000 person-years was 2.7 (2.5-2.9) for AMI, 1.3 (1.2-1.5) for stroke, 15.2 (14.8-15.6) for all-cause mortality, and 7.8 (7.5-8.1) for MACE. We did not observe differences in risk between any of the cardiovascular endpoints for any of the individual OAB drugs with the age-sex-adjusted IRRs or in the multivariate analyses: IRRs comparing each individual drug with the other OAB drugs pooled were generally around 1. The same pattern was observed when adjustment was performed with propensity scores.

Conclusions: The risk of the targeted cardiovascular endpoints was similar among individual OAB medications studied.

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849. Cardiovascular Risk in Users of Antimuscarinic Drugs for Overactive Bladder: A Cohort Study in the Swedish National Registers

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Background: It has been noted that patients with overactive bladder (OAB) may have increased cardiovascular (CV) risks, but we lack information on risks in users of individual OAB drugs.

Objectives: In preparation for a postauthorization safety study for mirabegron, a drug with a novel mechanism of action to treat OAB, we assessed the risk of acute myocardial infarction (AMI), stroke, CV mortality and all-cause mortality in users of individual antimuscarinic OAB drugs.

Methods: We identified new users of tolterodine, solifenacin, fesoterodine, darifenacin, and oxybutynin aged ≥18 years without cancer or HIV from the Swedish National Registers in years 2006-2012. We estimated age-sex-standardized incidence rates per 1,000 person-years (IRs) and incidence rate ratios (IRRs). For the latter, we used propensity scores with a large number of variables, we trimmed the distribution tails, estimated IRRs in deciles of scores, and pooled IRRs using Mantel-Haenzel methods. We report point estimates and 95% confidence intervals.

Results: The cohort of 130,944 patients had a mean age of 66 years; 60% were women. The most commonly used OAB drugs were tolterodine, solifenacin and fesoterodine. During follow-up, 4% had an AMI, 5% had a stroke, 3% died of CV causes and 8% died of any cause.

For current use of the three most commonly used OAB drugs, the standardized IR (95% CI) for AMI was lowest for fesoterodine, 8.2 (6.6-9.8), and greatest for tolterodine, 13.3 (12.3-14.3). For stroke, it was lowest for solifenacin, 16.9 (15.6-18.1), and greatest for tolterodine, 21.0 (19.7-22.3). For CV mortality, it was lowest for fesoterodine, 4.2 (3.0-5.4), and greatest for tolterodine, 7.8 (7.0-8.5). For all-cause mortality, it was lowest for fesoterodine, 12.4 (10.4-14.4), and greatest for tolterodine, 21.4 (20.1-22.6).

With reference to current use of tolterodine, IRRs for current use of solifenacin and fesoterodine for all endpoints were lower than one, between 0.69 (95% CI, 0.48-0.99) and 0.88 (0.79-0.98). Other point estimates were close to one, generally below.

Conclusions: We observed higher CV risks with tolterodine than with solifenacin and fesoterodine.

850. Development of a Predictive Model for Drug-Induced QT Prolongation in the Inpatient Setting Using Electronic Health Record Data

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Background: Several medications have been found to cause cardiac arrhythmias even at therapeutic doses. One of the most common drug-induced alterations to the electrical activity of the heart is prolongation of the QT interval. Displayed in electrocardiograms, this interval represents the electrical depolarization and repolarization of ventricles. Focus on prevention of QT prolongation in clinical practice is imperative as it is a precursor of Torsades de Pointes, a life threatening polymorphic tachycardia that can easily degenerate into ventricular fibrillation and sudden cardiac death.

Objectives: We aimed to construct a dynamic predictive risk model for severe QT prolongation in hospitalized patients at risk for this arrhythmia for purposes of real-time use in inpatient electronic health records (EHR).

Methods: We established a retrospective cohort from the two largest University of Florida affiliated

hospitals including all admissions aged ≥ 18 years between 1/2012 – 10/2013. We operationalized 27 risk factors for automated EHR retrieval, and upon univariate analyses, retained 20 for model inclusion. Severe QT prolongation was defined as the Bazett's formula-corrected QT value (QTc) interval ≥ 500 ms or an increase in QTc interval of ≥ 60 ms from baseline. For each of the first 5 hospital days with exposure to pro-QT meds we predicted QT prolongation at the following hospital day using multivariate logistic regression.

Results: A total of 1,672 QT prolongation events occurred in 165,847 risk days during the study period. C-statistics varied between 0.78 and 0.82 depending on the hospital day. The C-statistic model for the combined 5 days of hospitalization was 0.79. Strongly predictive risk factors ($p < 0.01$) included age, BMI, history of heart failure, acute myocardial infarction, cardiomyopathy, hypocalcemia, bradycardia, number of high risk pro-QT meds, history of an abnormal QTc, and increase in the QTc interval on the previous hospital day.

Conclusions: Risk models achieved good predictive validity. All risk factors were operationalized from discrete EHR fields and allow for full automation for real-time prediction of high-risk patients.

851. Trends in Oral Glucocorticoid Utilization Among Older Adults with Respiratory Disease

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Background: Oral glucocorticoids (GC) are critical anti-inflammatory agents, yet they increase the risk for osteoporosis, myopathy, hyperglycemia, and hypertension. The management of respiratory disease (asthma and chronic obstructive pulmonary disease) with oral GCs has changed over time, with an aim to reduce oral GC exposure and preference for inhaled GCs and bronchodilators.

Objectives: To describe changes in prescribing patterns of chronic oral GCs over time among older adults with respiratory disease.

Methods: We identified community-dwelling adults (aged 66+ years) with respiratory disease initiating chronic oral GC therapy in Ontario using healthcare claims data, 1998/01-2012/12. Chronic oral GC use was defined as ≥450 mg prednisone equivalent and ≥ 2 prescriptions over a 6-month period. Oral GC duration and cumulative dose, dispensing of inhaled GCs and bronchodilators, and prescriber specialties were described by calendar year. Spline regressions were used to describe quarterly trends in oral GC utilization.

Results: We identified 80,770 chronic oral GC users with respiratory disease (45% men, mean age = 75.0 years, SD = 6.6). Age and sex were similar over time. We observed a downward linear trend over time, representing a reduction of 93% in the median days of GC exposure from 1998 to 2012 (58 days [IQR:93] in 1998 to 30 days [IQR:63] in 2012), yet only 17% (linear trend) reduction in the GC cumulative dose (median 1080 mg [IQR:1250] to 925 mg [IQR:1110]). The concomitant use of bronchodilators showed a convex curve with an initial decrease, followed by increase after 2007. Oral GC prescriber specialty changed little over time (overall: 11% respirologists, 6% rheumatologists, and 69% general practitioners).

Conclusions: Duration of oral GC use among older adults with respiratory disease decreased over time, yet the cumulative dose remained similar. These results suggest that patients are receiving higher GC doses for shorter duration despite recent efforts to reduce the total exposure.

852. Use of Glucocorticoids and Risk of Community-Acquired Staphylococcus aureus Bacteraemia: A Population-Based Case-Control Study

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Background: Glucocorticoids exert multiple regulatory effects on the immune system, which may

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increase the risk of Staphylococcus aureus bacteraemia (SAB) among users. However, existing clinical data are sparse and conflicting.

Objectives: We investigated the risk of community-acquired (CA) SAB in users and non-users of systemic glucocorticoids.

Methods: We utilized population-based medical registries to conduct a case-control study including all adults with first-time CA-SAB and population controls matched by age, gender, and residence. The study setting was Northern Denmark between 2000 and 2011. Glucocorticoid users were categorized as current users (new or long-term use), former users, and non-users. Using conditional logistic regression, we computed odds ratios (ORs) of CA-SAB according to glucocorticoid exposure, overall and by 90-day prednisolone-equivalent cumulative dose. We adjusted for marital status, coexisting morbidity, and recent use of antibiotics and immunomodulating agents.

Results: We identified 2,638 patients with first-time CA-SAB and 26,379 matched population controls. Current glucocorticoid users experienced considerably increased risk of CA-SAB compared to non-users (adjusted OR = 2.48 (95% confidence interval (CI), 2.12-2.90). The adjusted OR was 2.73 (95% CI, 2.17-3.45) among new users, 2.31 (95% CI, 1.90-2.82) among long-term users, and much lower at 1.33 (95% CI, 0.98-1.81) among former users of glucocorticoids, as compared to non-users. The risk of CA-SAB increased with higher 90-day cumulative doses. Compared with non-users of glucocorticoids, the adjusted OR was 1.32 (95% CI, 1.01-1.72) for persons with a cumulative dose ≤150 mg, 2.42 (95% CI, 1.76-3.33) for persons whose cumulative dose was >500-1000 mg, and as high as 6.25 (95% CI, 4.74-8.23) for persons with a cumulative dose >1000 mg.

Conclusions: Glucocorticoid use was associated with substantially increased risk of CA-SAB. The risk increased with higher cumulative dose, revealing a distinct dose-response relation.

853. Use of Glucocorticoids and the Risk of Osteoporotic Fracture in Patients with Sarcoidosis

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Background: Sarcoidosis is a chronic inflammatory multisystem disorder that manifests in every organ, including the bone. Glucocorticosteroids (GCs) are key to disease management, but are associated with decreased bone density and an increased risk of fractures.

Objectives: To examine the risk of osteoporotic fractures in sarcoidosis patients receiving GCs.

Methods: A population-based case-control study was performed using the Danish National Database. Cases were those who sustained a fracture and controls (matched on age and gender) were those without a fracture during the study period (1 Jan 1996 – 31 Dec 2011), all aged 18 years or older. Index date was the date of the initial fracture (controls received the same date as their matched case). GC use was defined prior to index-date, and patients were classified as current users (1-91days prior to index), recent (92-182 days), past (183-264days) and distant >364 days). All analyses were stratified by sarcoidosis diagnosis (yes/no). Conditional logistic regression estimated odds ratios (OR) for the risk of fracture in individuals with and without sarcoidosis using GC and compared to individuals without GC use. Analyses were adjusted for comorbidities and recent medications.

Results: Among cases (n = 376,858) there were 493 (0.13%) with sarcoidosis and 14,751 (3.9%) with current GC use. Similarly, among controls (n = 376,858) 402 (0.1%) had sarcoidosis and 9,789 (2.6%) had current exposure to GCs. In the adjusted analysis, current GC exposure was associated with a significant increased osteoporotic fracture risk in sarcoidosis (ORadj = 1.74, 95% CI 1.17-2.58) and non-sarcoidosis (ORadj = 1.38, 95% CI 1.32-1.40) patients. The noted risk was not significantly different between sarcoidosis and non-sarcoidosis patients. There was also no significant fracture risk for recent, past or distant GC use, as compared to non-users.

Conclusions: In a population-based case-control study we identified increased osteoporotic fracture risk with current GC use. This risk was not different between patients with and without sarcoidosis, suggesting the disease itself may not increase osteoporotic fracture risk.

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854. Risk of Lymphoma in Users of Topical Tacrolimus, Pimecrolimus and Corticosteroids (JOELLE Study)

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Background: Topical tacrolimus (TAC) is indicated for the treatment of moderate to severe atopic dermatitis (AD), and topical pimecrolimus (PIM) for the treatment of mild to moderate AD. Data on the risk of lymphoma associated with use of these medications are inconclusive.

Objectives: To estimate the incidence rate ratio (IRR) of lymphoma, including cutaneous T-cell lymphoma (CTCL), in children and adults comparing new users of TAC and PIM with users of moderate- to high-potency topical corticosteroids (TCS), and users of TCS with general population untreated subjects.

Methods: Cohort study in the PHARMO Database Network (Netherlands), the Danish and Swedish national registers, and the Clinical Practice Research Datalink (United Kingdom), with RTI-HS acting as coordinating/pooled analysis center. New users of TAC and PIM were frequency matched to users of TCS on twentiles of propensity scores; users of TCS were individually matched to untreated subjects on age, sex, region, and calendar year. We estimated IRRs and 95% confidence intervals (CI) using Mantel-Haenszel methods.

Results: We included (a) 19,948 children and 66,127 adults treated with TAC matched with 79,700 children and 264,482 adults treated with TCS; (b) 23,840 children and 37,417 adults treated with PIM matched with 90,268 children and 149,671 adults treated with TCS; and (c) 79,040 children and 257,074 adults untreated with any study medication. For use of TAC vs. TCS, the adjusted IRR (95% CI) for any lymphoma was 3.74 (1.00-14.06) in children and 1.27 (0.94-1.71) in adults; by lymphoma type, the highest IRR was 1.76 (0.81-3.79) for CTCL in adults. For PIM vs. TCS, the IRR for any lymphoma was 1.07 (0.25-4.60) in children and 1.03 (0.71-1.51) in adults; by lymphoma type, the highest IRR was 1.31 (0.33-5.14) for CTCL in adults. The IRR for adults treated with TCS vs. untreated subjects was 1.49 (1.19-1.87) for any lymphoma and 10.66 (2.60-43.75) for CTCL.

Conclusions: These results suggest an association between TAC and PIM and the risk of lymphoma. Residual confounding by AD severity, reverse causation (particularly for CTCL), and surveillance bias cannot be ruled out.

855. Pharmacological Treatments Preceding Diagnosis Of Progressive Multifocal Leukencephalopathy

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Background: Progressive multifocal leukencephalopathy (PML) is a rare, often fatal viral disease, which affects the white matter of the brain. It is caused by John Cunningham (JC) polyomavirus, which is present in most people and is usually harmless. For immunocompromised persons, such as those who are taking immunosuppressive treatments, the risk of JC virus causing PML is increased, although still rare. As PML diagnosis is not always accurate, epidemiology of PML, including the true incidence and patient characteristics, is incompletely described.

Objectives: To identify pharmacological treatments preceding diagnosis of definitive, probable and

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possible PML, after excluding incorrect PML diagnoses by medical record review.

Methods: Patients with a PML diagnosis in Sweden between 1988 and 2013 were identified through the Patient register using ICD 9 code 046D and ICD 10 code A81.2 (n=281). Medical records were reviewed and information on clinical characteristics and pharmacological treatments were collected. Each of the diagnoses was determined as definite PML, possible PML, probable PML or non-PML based on the consensus statement for the AAN neuroinfectious disease section published in 2013. (PMCID: 3662270).

Results: Medical records for 251 patients (89%) were available and examined. In total, 84 (33%) of the 251 PML diagnoses were confirmed. For those with a record of being exposed to immunosuppressant drugs, 60 (65%) of the 92 records were confirmed as being definite PML. Among 12 patients exposed to rituximab 11 (92%) had definite and 1 (8%) had probable PML. For the 9 natalizumab users, 8 (89%) had definite PML and 1 (11%) was diagnosed incorrectly.

Conclusions: A substantial proportion of PML diagnoses recorded in Sweden are incorrect, however amongst those exposed to immunosuppressants such as rituximab and natalizumab the majority of diagnoses are correct. Assessing immunosuppressive drug history could be an important part of the diagnostic processes for PML.

856. Association Between Breast Cancer Recurrence With Immunosuppression In Rheumatoid Arthritis And Inflammatory Bowel Disease: A Cohort Study

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Background: Breast cancer recurrence may be promoted by immunosuppression due to decreased immune surveillance.

Objectives: Among patients with immune-mediated disease and previously treated breast cancer, we examined rates of breast cancer recurrence with use of methotrexate, thiopurines, and anti-TNF therapy.

Methods: Three retrospective cohort studies within Medicare (2000-2012) included women with rheumatoid arthritis or inflammatory bowel disease who completed surgery for primary breast cancer. Recurrent or second primary breast cancers beyond 365 days from initial surgery were identified. Separate Cox regression models examined risk of cancer recurrence with use of methotrexate, thiopurines, and anti-TNF therapy after surgery, each compared to no use. Analyses were matched on type of breast surgery, and receipt and type of adjuvant therapy.

Results: Across all medication groups, 107 women developed breast cancer recurrence during 5,196 person-years. Incidence rates were 20.3 and 19.6 per 1,000 person-years in methotrexate users and nonusers, 32.3 and 17.6 in thiopurine users and nonusers, and 22.3 and 19.5 in anti-TNF users and nonusers, respectively. There was no significantly increased risk of breast cancer recurrence with use of methotrexate (adjusted hazard ratio [HR] 1.07, 95% CI 0.67-1.69), anti-TNF therapy (HR 1.13, 95% CI 0.65-1.97), or thiopurines (HR 2.10, 95% CI 0.62-7.14).

Conclusions: Among women with immune-mediated disease and treated breast cancer, there was no significantly increased risk of breast cancer recurrence with methotrexate, thiopurine, or anti-TNF therapy, although we cannot rule out a 2-fold or greater increased risk with thiopurines. These data may help clinicians to better assess the risk-benefit relationship when choosing between common immunosuppressants for patients with a history of cancer.

857. Safety and Effectiveness of Dabigatran Relative to Warfarin in Routine Clinical Practice–Interim Results of a Long-Term Study Program

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Background: Dabigatran etexilate is a newer oral anticoagulant developed as an alternative to warfarin for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). Although the efficacy and safety of dabigatran were established in a randomized trial, evaluation of its effects in routine clinical practice is ongoing.

Objectives: Quantification of the comparative safety and effectiveness of dabigatran in routine care within two large US commercial health insurance databases, Truven MarketScan (MS) and Optum Clinformatics (OC).

Methods: Cohort design with propensity score (PS) matching to compare new initiators of dabigatran with warfarin between Oct 2010 and Jun 2013. Primary outcomes were stroke and major bleeding. Proportional hazards regression of time to outcome was conducted separately within each data source and results were pooled.

Results: There were 22,336 PS matched dabigatran and warfarin initiators with NVAF pooled across data sources (MS = 18,276; OC = 4,060). The matching resulted in well balanced cohorts with no individual characteristic having an absolute standardized difference >0.1. The average follow-up for the as-treated analyses was 5 months for dabigatran and 4 months for warfarin. There were 65 strokes amongst dabigatran initiators and 78 strokes amongst warfarin initiators for a pooled HR of 0.72 (95% CI 0.52 – 1.00) (MS; HR = 0.64, 95% CI = 0.44-0.93, OC; HR = 1.11, 95% CI = 0.54-2.31). For the outcome of major hemorrhage, there were 395 events amongst dabigatran initiators and 459 events amongst warfarin initiators for a pooled HR of 0.74, 95% CI = 0.64 – 0.84) (MS; HR = 0.77, 95% CI = 0.67 - 0.89, OC; HR = 0.51, 95% CI = 0.34 - 0.76). Pooled results in the full cohort were fairly consistent across numerous subgroup and sensitivity analyses, however, comparative conclusions within some subgroups are limited by small numbers and limited follow-up time.

Conclusions: Analyses from this ongoing long-term study program suggest a reduced risk of both stroke and major hemorrhage for dabigatran relative to warfarin. Continued follow-up will increase the sample size, permitting greater precision in effect estimates.

858. Comparative Effectiveness and Safety of New Oral Anticoagulants (NOACs) and Warfarin in Patients with Atrial Fibrillation: A Multi-Database Study in the US and UK

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Background: Potential bias due to channelling of patients to newly approved medications due to patient, physician, and system-related factors as well as rapid changes in the characteristics of the user population during the early phase after launch pose major methodological challenges.

Objectives: To compare characteristics of patients starting on different oral anticoagulant(OAC) medications and the risk of ischaemic stroke (IS), acute myocardial infarction(AMI) as well as major bleeds (MB) over time since launch.

Methods: Using the US MarketScan commercial claims and the UK CPRD database, we included atrial fibrillation/flutter patients who started OAC if they were enrolled at least 6 months and not using oral OAC medications during the six months prior to start of OAC(index date), were 18 years or older. Hazard ratios(HR) for IS, AMI, and MB were estimated in users of new oral anticoagulants (NOACs, dabigatran and rivaroxaban) versus warfarin at different time periods after launch using multivariable Cox regression and propensity scores(PS) methods. Confounder distributions among the groups were summarized as PS and time trends since launch were assessed.

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Results: In general, the US MarketScan population was at lower risk for stroke compared to the UK population(younger and had lower mean CHA2DS2-VASc score) although the trend over time was similar between different OAC medications. There was substantial overlap in PS distributions between the treatment groups in both datasets. The risk of IS for NOACs was lower in MarketScan [HR 0.74, 95%CI: 0.61; 0.90] but higher in CPRD [HR: 1.31, 95%CI: 1.04; 1.65]. The risk for AMI was similar for NOACs and warfarin whereas the risk of MB was higher in NOACs compared to warfarin [HR: 1.34, 95%CI: 1.11; 1.62 in MarketScan and 1.41, 95%CI: 1.06; 1.87 in CPRD]. HRs were similar from PS methods.

Conclusions: Differences between characteristics for NOAC users compared to warfarin users were small with no noticeable change over the years suggesting minimal channelling bias after launch. Treatment with NOACs seems to be have lower risk IS for US patients compared to UK patients.

859. Clinical Events Preceding Changes During Treatment With Non-VKA Oral Anticoagulants In Patients With Atrial Fibrillation

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Background: Switching between oral anticoagulants and treatment discontinuation are common events during therapy with non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation. However, knowledge on the reasons leading to these treatment changes is scarce.

Objectives: To identify potential reasons for treatment changes during NOAC therapy in patients with atrial fibrillation through exploration of clinical events preceding these changes.

Methods: We performed a nationwide register-based study including all registered Danish atrial fibrillation patients initiating a NOAC in the period August 2011 to October 2015 (n = 43,500). We explored reasons leading to changes in NOAC treatment by identifying clinical events preceding switches from vitamin K antagonists (VKA) to NOAC, switches from NOAC to VKA, and discontinuations of NOACs.

Results: Among 22,764 NOAC users experiencing ≥1 treatment changes during the study period, 14,206 switched from VKA to NOAC, 4,670 switched from NOAC to VKA, and 8,151 discontinued NOAC. Approximately half of treatment changes were preceded by a hospitalization and in 1 in 5 treatment changes, a relevant preceding clinical event was identified. Switches from VKA to NOAC were most often preceded by a thromboembolic event (7.3%), whereas cardioversion was the most common event prior to a switch from NOAC to VKA (10.7%). Discontinuations were most often preceded by bleeding events (7.3%).

Conclusions: Treatment changes during NOAC treatment in atrial fibrillation are rarely preceded by a clinical event related to the use of anticoagulants. Potential reasons for treatment changes can be identified by considering preceding clinical events using health registries. Detailed information on reasons for treatment changes requires data acquired directly from the patient or physician.

860. Hospitalization and Length of Stay Among Patients with Non-Valvular Atrial Fibrillation Taking Dabigatran or Warfarin: A Population-Based Cohort Study

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Background: Previous studies showed that dabigatran use was associated with reduced hospital resources utilization when compared to warfarin in clinical trial settings. However, this has not been well studied in the general population, especially among Asians.

Objectives: To compare the rate of hospitalization and length of stay (LOS) associated with the use of dabigatran and warfarin in the real-life setting.

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Methods: This study utilized the population-wide database managed by the Hong Kong Hospital Authority. Patients newly diagnosed with NVAF during 2010-2014 and received dabigatran or warfarin were identified and followed up until September 2015. Rates of hospitalization and total LOS related to ischemic stroke, intracranial hemorrhage(ICH), and all causes were assessed by zero-inflated negative binomial regression with 1:1 propensity-score matching.

Results: Preliminary results indicated that among 51,946 patients with AF, 6192 eligible users of dabigatran or warfarin were matched by propensity-score. Dabigatran users had a lower rate of all-cause hospitalization(1.1 vs. 1.3 hospitalizations per patient-year[py];incidence rate ratio[IRR] = 0.78;95% confidence interval[CI] = 0.72-0.84) and shorter LOS (6.8 vs. 9.5 days per py;IRR = 0.69;95%CI = 0.62-0.77) when compared to warfarin. For ischemic stroke, dabigatran and warfarin users had comparable rate of hospitalization(1.9 vs. 1.7 hospitalizations per 100 py;IRR = 1.22;95%CI = 0.79-1.87) and LOS (37.4 vs. 39.8 days per 100 py;IRR = 1.30;95%CI = 0.70-2.41). The rate of hospitalization with ICH was lower with dabigatran versus warfarin (0.5 vs. 1.4 hospitalizations per 100py;IRR = 0.29;95%CI = 0.15-0.55), with no significant difference in LOS(13.6 vs. 25.2 days per 100 py;IRR = 1.28;95%CI = 0.62-2.61).

Conclusions: This study showed that dabigatran use was associated with a lower rate of all-cause hospitalization and shorter LOS versus warfarin. Specifically, dabigatran users had a lower rate of hospitalization with ICH and a comparable rate of hospitalization with ischemic stroke. There were no significant differences in the LOS with respect to hospitalizations with ischemic stroke and ICH.

861. The Safety and Effectiveness of New Oral Anticoagulants versus Vitamin K Antagonists - Pilot Implementation of a Real-Time Monitoring Program in Italy

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Background: Electronic healthcare data are a valuable resource to assess post-approval safety of medical products in Italy. The regional government of Lazio (Italy) ordered the implementation of a real-time monitoring program for all patients prescribed with New Oral Anticoagulants (NOACs) in Lazio. This pilot phase will lay the foundation for the development of a nationwide distributed monitoring system.

Objectives: To evaluate effectiveness and safety of NOACs vs. Vitamin K antagonists (VKAs) in patients with atrial fibrillation as treated in routine care.

Methods: We conducted a cohort study using a sequential propensity-score (PS) matched design for 5 monitoring periods between July 2013 and December 2014. In each period, we 1:1 matched NOAC and VKA initiators with the nearest PS value. We calculated Hazard Ratios (HRs) and 95% confidence intervals (CI) for total mortality (ICD-9 codes 001-999), cardiovascular mortality (ICD-9 codes 390-459) and myocardial infarction (ICD-9 codes 410-414 and ICD-9-CM codes 410.x0, 410.x1) Patients were followed-up from the first prescription until the occurrence of a study outcome, death, health care disenrollment, switching, treatment discontinuation, whichever came first. For each monitoring period, sequential analyses and group sequential test were performed for each outcome.

Results: During the overall study period, 11894 anticoagulant users were enrolled, 32% of whom used NOACs. After PS matching 6282 patients contributed to the analyses. Adjusted HR for total mortality moved from 0.28 (CI 0.10-0.75) in the first monitoring period to 0.92 (CI 0.65-1.29) in the last period. HRs for cardiovascular mortality and myocardial infarction were 0.26 (CI 0.05-1.21) and 0.25 (CI 0.03-2.26) in the first period and 0.99 (CI 0.63-1.58) and 0.76 (CI 0.41-1.43) in the fifth period.

Conclusions: Results from the early stage of this monitoring program indicate no significant differences between NOACs and VKAs for study outcomes. Further data accrual is warranted to obtain more precise results and to explore additional safety and effectiveness outcomes.

862. Stroke, Bleeding, and Mortality Risks in Older Patients Treated with Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation

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Background: Dabigatran and rivaroxaban are non-vitamin K oral anticoagulants approved for stroke prevention in patients with nonvalvular atrial fibrillation. There are no randomized head-to-head comparisons of these drugs.

Objectives: To compare stroke, bleeding, and mortality risks in patients initiating treatment with standard doses of dabigatran or rivaroxaban for nonvalvular atrial fibrillation.

Methods: Cohorts of treatment-naive patients with nonvalvular atrial fibrillation who initiated treatment with standard doses of dabigatran (150 mg twice-daily) or rivaroxaban (20 mg once-daily) were created using national Medicare data. Differences in baseline characteristics were adjusted using stabilized inverse probability of treatment weights based on propensity scores. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for thromboembolic stroke, intracranial hemorrhage, major extracranial bleeding including major gastrointestinal bleeding, and mortality, with rivaroxaban as the reference.

Results: A total of 52,240 dabigatran and 66,651 rivaroxaban patients contributed 15,524 and 20,199 person-years of on-treatment follow-up, respectively, during which 2537 primary outcome events were observed. Dabigatran was associated with a non-statistically significant increase in the HR for thromboembolic stroke (HR = 1.24, 95% CI 0.99-1.55, p = 0.066), statistically significant reductions in intracranial hemorrhage (HR = 0.61, 95% CI 0.44-0.83, p = 0.002), major extracranial bleeding (HR = 0.67, 95% CI 0.60-0.76, p<0.001), and major gastrointestinal bleeding (HR = 0.71, 95% CI 0.63-0.81, p<0.001), and with a non-statistically significant reduction in the HR for mortality (HR = 0.87, 95% CI 0.76-1.00, p = 0.051).

Conclusions: In patients with nonvalvular atrial fibrillation, treatment with standard dose dabigatran was associated with significant reductions in intracranial hemorrhage, major extracranial bleeding, and major gastrointestinal bleeding compared with standard dose rivaroxaban.

863. Are Natural Language Processing Models For Pneumonia Surveillance Valid For Benchmarking Event Rates Across Healthcare Institutions?

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Background: Natural language processing (NLP) models are increasingly used for pneumonia surveillance in acute care hospitals, but limited information is available on their generalizability, which is important for valid benchmarking.

Objectives: To determine the generalizability of a statistical NLP model using electronic health record (EHR) data to identify pneumonia; an adverse event associated with significant morbidity, mortality and cost.

Methods: We randomly sampled 4,000 narrative reports of chest radiological examinations performed at a university health network (UHN) in Quebec (Canada) between 2010 and 2014. We manually identified pneumonia within each report, which served as our reference standard. We used a nested cross-validation approach to train and validate a support vector machine (SVM) model predicting pneumonia. This model was then applied to a random sample of 2,281 narrative radiology reports from another UHN in Ontario (Canada), and accuracy was measured. The accuracy of the Quebec model, as applied to Ontario data, was compared to that of two alternative models: 1) a model recalibrated on Ontario data and; 2) a model trained and validated using all available data (pooled Quebec-Ontario model).

Results: On manual review 640 (16.0%) and 303 (13.3%) reports were pneumonia-positive in Quebec and Ontario data, respectively. The SVM model predicting pneumonia on Quebec data achieved 83% sensitivity (95%CI: 78% - 88%), 98% specificity

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(95%CI: 97%-99%) and 88% PPV (95%CI: 83%-94%). When applied to Ontario data, this model achieved 57% sensitivity (95%CI: 51%-63%), 99% specificity (95%CI: 98%-99%) and 86% PPV (95% CI: 80%-90%). In comparison, the model retrained on Ontario data achieved 76% sensitivity (95%CI: 70%-82%), 98% specificity (95%CI: 97%-99%) and 86% PPV (95%CI: 82%-91%), while the pooled Quebec-Ontario model performed worse than the Quebec model, but better that the Ontario one.

Conclusions: A statistical NLP model predicting pneumonia has limited generalizability when it is directly applied to EHR data from another institution, but good prediction performances can be achieved with model recalibration on local data.

864. Analysis of Patient Narratives in Disease Blogs: Enhancing Pharmacovigilance Using Real-World Health Data on the Internet

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Background: While several reports have suggested that real world data from Internet sources (e.g. Twitter and Facebook) could produce beneficial outputs to improve pharmacovigilance, few studies have identified such data sources in Japan. Here, we introduce a unique Japanese data source: tōbyōki, which translates literally as "an account of a struggle with disease". In these diary-like accounts, patients record observations about their lives and diseases, and some patients share their tōbyōki as blogs on the Internet. The epidemiologic data contained in these blogs could be an important resource for pharmacovigilance.

Objectives: To describe the basic characteristics of tōbyōki blogs, and to evaluate their potential application for pharmacovigilance.

Methods: We analyzed data from TOBYO, a growing online collection of health-related blogs. Because the original content of the blogs was unstructured text-based data, we used natural language processing techniques to extract necessary elements (e.g. gender, diseases, and drugs). Then the structured data were summarized using descriptive statistics. We also used data-mining software (d2) to create word co-occurrence networks and other visualizations.

Results: As of 5 February 2016, the website comprised 52029 blogs representing 1393 diseases. Overall, more entries on TOBYO were written by women (69%) than by men (31%). Among disease distributions, the most frequently observed diseases were breast cancer (4273 blogs), depression (2869), infertility (2198), rheumatoid arthritis (1009), and panic disorder (829). Restricting data to the patients with gastric cancer, as an example, showed that the drugs appearing in the most blogs in this disease category were TS-1 (a combination of tegafur, gimeracil, oteracil potassium; 173), Taxol (paclitaxel; 88), and Loxonin (Loxoprofen sodium hydrate; 65). It was also shown that the symptoms appearing in the most blogs in this category were pain, nausea, and diarrhea.

Conclusions: This study describes the fundamental characteristics of tōbyōki blog data and insights into considering the use of such data for pharmacovigilance.

865. Prediction Model Based Algorithm for a Computer-Assisted Database Screening Tool

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Background: The Netherlands Pharmacovigilance Centre Lareb uses two different methods for signal detection. A case-by-case method, where all reports are individually assessed, and a computer-assisted database screening tool. After evaluation of the current screening tool [1], an alternative is warranted.

Objectives: To develop a new algorithm for the screening tool based on a prediction model in order to improve statistical signal detection.

Methods: A logistic regression based prediction model was made for drug – ADR associations in the Lareb database. Associations were categorized using the ATC code of the suspect drug and the MedDRA preferred term of the reported ADR. Cases were defined as ADRs described in the Summary of Product Characteristics (SmPC) of the suspect drug, which was used as the gold standard. We used a backward selection procedure with the following variables: number of reports (NUM), lower limit of the 95% CI of the reporting odds ratio (LLROR), Naranjo score and the proportion reports of healthcare professionals (HCP) and Marketing Authorization Holders (MAH). Area under the ROC curves (AUC) for individual

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variables and the final model were used to evaluate discrimination. For internal validation bootstrapping was performed.

Results: A total 23815 associations were used for modeling. After the backward selection procedure no variables were eliminated from the model. The most discriminative individual predictive variable was the Naranjo score (AUC = 0.724; 95%CI, 0.717 – 0.730), followed by MAH, HCP, NUM and LLROR. The AUC for the full model was 0.824 (95%CI, 0.818 – 0.829) and the model showed good calibration. After bootstrapping the optimism-corrected AUC was 0.823.

Conclusions: The developed prediction model showed a good performance and can be a useful screening tool for signal detection in pharmacovigilance. The yield of this model compared to our already existing screening tool remains to be investigated.

[1] van Hunsel F, Ekhart C. Experiences With a Computer-Assisted Database Screening Tool at the Netherlands Pharmacovigilance Centre Lareb. Pharmacoepidem Drug Saf 2015; 24(S1):442.

866. Assessment of the US Food and Drug Administration's Sentinel Analysis Tools: Angiotensin-Converting Enzyme Inhibitors And Angioedema

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Background: The US Food and Drug Administration's Sentinel system has developed the capability to conduct active safety surveillance of marketed medical products in a large network of electronic healthcare databases.

Objectives: To assess the extent to which the newly developed, semi-automated Sentinel Propensity Score Matching (PSM) tool could produce the same results as a more traditional customized protocol-driven assessment, which found a hazard ratio (HR) of 3.04 (95% confidence interval [CI], 2.81 to 3.27) comparing angioedema in patients initiating angiotensin-converting enzyme (ACE) inhibitors versus beta-blockers.

Methods: We implemented Sentinel's PSM tool to compare rates of angioedema (ICD-9-CM code 995.1) between initiators of ACE inhibitors and beta-blockers in data from 13 Sentinel Data Partners covering the years 2008 to 2013. The propensity score model included demographic characteristics, measures of health service utilization, and whether patients had prior claims for allergic reactions, diabetes, heart failure, ischemic heart disease, and prior prescription nonsteroidal anti-inflammatory drug use. Matching was performed without replacement in a 1:1 ratio using a nearest-neighbor algorithm. Patients were followed until the end of continuous exposure to the index medication, death, outcome, or the end of the study period. A Cox proportional hazard model was used to estimate a HR and 95% CI in the matched cohort.

Results: Among 2,211,215 eligible ACE inhibitor and 1,673,682 eligible beta-blocker initiators, we observed 5,158 and 1,292 angioedema events during a total of 1.1 million and 0.7 million person-years of follow-up, respectively. The crude HR was 2.55 (95% CI, 2.40 to 2.71). The PSM tool yielded 1,309,104 matched pairs that were well balanced on baseline characteristics. The HR in the propensity score-matched cohort was 3.14 (95% CI, 2.86 to 3.44).

Conclusions: Despite some differences in data analyzed and design and analysis specifications, the Sentinel PSM tool was able to produce an estimate that was very consistent with that produced by a highly customized protocol-driven assessment.

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867. An Automatized Model for Sequential Monitoring of Effectiveness of New Drugs Using Dronedarone as Example

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Background: Although the randomized controlled clinical trial is the most reliable design for causal inference, it is usually conducted in selected populations different from most patients treated with the drug in clinical practice. It is therefore important to optimize real-time post-market evaluation of effectiveness, safety, and cost of new drugs.

Objectives: The aim of this study was to build and evaluate a generic automatized model for real-time sequential monitoring of the effectiveness of newly marketed drugs.

Methods: Using data from electronic health records and administrative health databases in Stockholm, Sweden, we built a model for post-marketing monitoring of drugs. The antiarrhythmic agent dronedarone was selected as study drug example and flecainide as comparator drug. To emulate real-time monitoring the model was built as if dronedarone was marketed today. Time-at-risk started on May 26, 2010 and the model was divided into monitoring periods, sequentially updated every 6th month until June 15, 2014. In each period, new users of dronedarone and flecainide were selected and a propensity score (PS) of receiving dronedarone over flecainide was estimated. Using an as-treated approach, new users of dronedarone and flecainide were followed until first recurrence of atrial fibrillation (RAF). Using two PS approaches (PS-adjusted and PS-matched), RAF were analyzed every 6th month using Cox regression.

Results: During a total of 9 monitoring periods, we identified 1282 and 826 initiators of dronedarone and flecainide respectively. Over the 9 periods, the PS-adjusted model produced a more stable HR-pattern compared to the PS-matched. In the last period, hazard ratios comparing dronedarone with flecainide for RAF was 1.68 (1.40-2.00) and 1.64 (1.30-2.06) for the PS-adjusted and PS-matched respectively. RAF was experienced after a mean of 193 and 256 days for dronedarone and flecainide, respectively.

Conclusions: Automatized real-time sequential monitoring of new drugs is possible. In order to bridge the gap between efficacy and effectiveness in clinical practice, we propose that real-time models are considered at introduction of every new drug.

868. Which Variables Influence Signal Detection in Well-Established Products?

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Background: Spontaneous reports databases are regularly monitored to detect signals. Currently all medicines are monitored with a comparable frequency in the Eudravigilance (European spontaneous reports) database. A more risk proportionate approach would be preferable.

Objectives: To test which variables are associated with higher odds of signals occurrence.

Methods: 52 well-established drugs were monitored for safety signals from 1-10-2012 to 30-11- 2014 in EudraVigilance. Number of signals was the outcome. Variables investigated as predictors included: time since marketing authorization (MAtime), patient exposure, number of spontaneous cases at baseline, and recent regulatory/media attention (RA attention). We adjusted for ATC class. RA attention was defined as any communication of a safety issue to patients or healthcare professionals in the past 2 years before study start or during follow up time. Poisson regression was used as a model. After univariate analysis variables significantly associated with the outcome were retained in a multivariate model.

Results: Over the study period, 124 potential signals for 37 drugs were identified. After an initial peak in the first 6 months of monitoring, the number of detected signals gradually decreased. MAtime was non-

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significantly lower for drugs with signals compared to those without (median time: 18 vs. 24 years, p=0.286). Patient exposure was significantly higher for drugs with signals (median: 370,000 vs 7,000 patients, p=0.04) as was the number of cases (3,212 vs. 317, p<0.001). Drugs with signals were more likely to have recent RA attention (53% vs. 6.7%, p=0.04). In the univariate Poisson analysis, RA attention and number of spontaneous cases were associated with the number of signals (P<0.05, Wald test). In the multivariate model (ATC class, RA attention and number of spontaneous cases at baseline) none of the association remained significant.

Conclusions: Recent RA attention and number of spontaneous cases at baseline influenced the number of detected signals, highlighting the tendency of over-reporting for drugs with a safety issue or media attention.

869. Autoimmune Disorders Following HPV Vaccination in Young Women: Is the Risk Real?

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Background: Cases of onset or exacerbation of autoimmune diseases (ADs) following vaccination against HPV in patients at high risk for the onset of ADs have triggered concerns about the vaccine's safety.

Objectives: To assess the risk of ADs associated to HPV vaccines among adolescent/young female adults in France.

Methods: A systematic prospective case-control study to assess risks associated with real-life use of HPV vaccines. Cases were female 11-25 years old with incident ADs (central demyelination/multiple sclerosis (CD/MS), connective tissue diseases (CTD), Guillain-Barre syndrome (GBS), type-1-diabetes (T1D), autoimmune thyroiditis (AT), idiopathic thrombocytopenic purpura (ITP)]. Cases consecutively identified through specialised centres across France over 6 years, were matched on age and place of residence to controls recruited in general practice. Risk was computed using multivariate conditional logistic regression models adjusted for family history of ADs, north/south origin, comedication/covaccination.

Results: 478 definite cases were matched to 1869 controls. Cases were less likely to be born to parents from Northern Europe or North America (56.7% vs 76.8%, p<0.05) and more likely to have a first-degree relative history of AD (13.3% vs 7.4%, p<0.05). ADs were negatively associated to HPV vaccine exposure with adjusted OR 0.58 (95% CI: 0.41-0.83) for all ADs combined. Stratifying this result by AD risk factors did not show a different tendency in the subgroups. Similar results were obtained for CD/MS, AT, CT and T1D (the last two did not reach statistical significance). No association was found for ITP and GBS. Sensitivity analyses combining definite and possible cases or secondary time window showed similar results.

Conclusions: No increased risk of ADs was observable following HPV vaccination. The apparent lower risk observed with the occurrence of MS and AT has to be further explored as it could be due to remaining unmeasured confounding factors, chance, or protection conferred by the vaccination itself. Results were robust to case definitions and time windows of exposure. Continued active surveillance is needed to confirm this finding with individual ADs.

870. Rotavirus Vaccine Schedules and Vaccine Response Among Infants in Low- and Middle-Income Countries: A Systematic Review

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Background: Little is known about factors contributing to low rotavirus vaccine efficacy in low- and middle-income countries (LMIC). The number and timing of vaccine doses may influence vaccine response due to immune development and maternally acquired antibodies.

Objectives: To systematically review the literature evaluating the effects of rotavirus vaccine schedules on vaccine response in LMIC.

Methods: We searched PubMed, Web of Science, Embase, and ClinicalTrials.gov for eligible trials that were conducted in LMIC, compared ≥2 vaccine schedules of the monovalent or pentavalent rotavirus vaccines, and reported immunologic response or incident rotavirus gastroenteritis. We reviewed all entries identified by search criteria and abstracted data from all eligible trials. We present the range of estimated rates of seroconversion difference (schedule 1–schedule 2) and 95% confidence intervals (CI).

Results: We reviewed 639 abstracts, 58 full texts, and 183 registered trials. We abstracted data from 8 eligible trials of the monovalent vaccine. Immunologic response was assessed in all. Seroconversion was defined as 1mo post-vaccination IgA antibody titers of >20 U/ml. Seroconversion difference between those vaccinated at 6/10 weeks versus 10/14 weeks ranged from -0.25 (-0.41, -0.09) to -0.09 (-0.19, 0.02). There was little difference in seroconversion comparing 3 doses administered at 6/10/14 weeks versus 2 doses at 10/14 weeks (seroconversion difference ranged from -0.02 (-0.12, 0.09) to 0.10 (-0.08, 0.28)). Only one trial reported 1-yr efficacy (95% CI) on incident rotavirus gastroenteritis. In Malawi, efficacy was 49.7% (11.3, 72.2) and 49.2% (11.1, 71.7) for the 6/10/14 and 10/14 schedule, respectively. In South Africa, efficacy was 81.5% (55.1, 93.7) and 72.2% (40.4, 88.3) for the 6/10/14 and 10/14 schedules.

Conclusions: There was lower seroconversion comparing the 6/10 week schedule versus 10/14 week. In addition, there was little or no increase in seroconversion for an additional dose at 6 weeks in the 6/10/14 week schedule versus 10/14 week only. Further research is needed using rotavirus gastroenteritis as the outcome and on the pentavalent vaccine.

871. Cluster Analysis of HPV Vaccine Reports in a Global Database of Suspected Adverse Events

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Background: A number of safety signals (complex regional pain syndrome, postural orthostatic tachycardia syndrome, chronic fatigue) have emerged with human papilloma virus vaccines and share a similar pattern of symptoms. Previous signal evaluations and epidemiological studies have been restricted to specific diagnoses, and the signals considered in isolation.

Objectives: To identify HPV reports with similar symptoms as earlier signals and evaluate their impact and geographic spread.

Methods: We used probabilistic cluster analysis to identify natural groupings of reports based on AE profiles of 39,953 HPV vaccine reports with two or more co-reported AE in VigiBase as of Jan 1 2015. We assumed a latent class model with independent binomial distributions for AE, conditional on report class. So-called expectation-maximization was used to optimize the allocation of reports to classes while determining the AE profiles for each class. This was repeated 100 times and the individual solutions rank ordered by penalized likelihood. Consensus clustering based on the best 50 individual solutions yielded a wisdom-of-the-crowd partitioning. Clinical assessment of the clusters was performed.

Results: 54 clusters containing at least 5 reports resulted. The four largest clusters included 71% of the HPV reports and described AEs which are included in the product label. Four smaller clusters (694 reports) were identified which included cases reporting a combination of the AE of headache, dizziness, and fatigue or syncope. The cases in these clusters were further characterized by their serious nature and impact on quality of life. Although 3 of the 4 clusters contained cases reporting POTS, CRPS and CF, the majority of cases in the clusters did not report a unifying diagnosis. The cases in the clusters originated from multiple countries.

Conclusions: Cluster analysis reveals a pattern of co-reported AEs which is consistent between signals for HPV vaccines; this pattern is more extensive than specific diagnoses and more widespread than certain countries. More advanced analyses of spontaneous reports such as clustering can identify a relevant case series for thorough signal evaluation.

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872. Safety of TDaP Vaccination in Pregnancy

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Background: In 2012, the US recommended TDaP vaccination for all pregnant women during the third trimester of each pregnancy to directly convey passive pertussis immunity to newborns, superseding prior recommendations to vaccinate mothers and caregivers immediately after delivery. Altered immune states may result in different risk profiles for vaccination during pregnancy, and the safety of widespread vaccination during pregnancy needs to be established.

Objectives: To determine the impact of prenatal TDaP vaccination in pregnant women on adverse birth outcomes. To compare adverse vaccine reactions in women vaccinated during pregnancy to those vaccinated immediately postpartum ('cocooning').

Methods: Pregnancies were identified at live- or stillbirth delivery in the Truven MarketScan® database (2010-2013). TDaP vaccination was identified and categorized as early prenatal, prenatal, postnatal in the 7 days post-delivery, or none. Adverse vaccine reactions (anaphylaxis, fever, Guillian-Barre syndrome, etc.) and adverse birth outcomes were identified with claims. Propensity score-matched log-binomial regression models were used to estimate risk ratios (RR) for adverse birth outcomes, comparing women with early prenatal vs. prenatal TDaP. Cox models were used to determine differences in adverse vaccine reactions, comparing women with early or prenatal TDaP vs. postnatal.

Results: We identified 957,759 pregnancies; 7.9% prenatally vaccinated, 5.6% postnatally. There was no evidence of increased risk of pre-eclampsia, postpartum hemorrhage, premature rupture of membranes, placental abruption, or cesarean section with prenatal TDaP vaccination vs. none in pregnancy. Cases of chorioamnionitis were rare (prenatal = 45, early = 14, none = 556), so precision was limited, but our RR was consistent with previously-published estimates showing increased risk (prenatal TDaP vs. none: RR = 1.29, 95% CI: 0.56-2.95, early prenatal TDaP vs. none: RR = 2.33, 95% CI 0.62-8.82). Adverse vaccine reactions were very rare, and were not increased during pregnancy vs. postnatal vaccination.

Conclusions: TDaP vaccination during pregnancy appears not to increase risk of adverse birth events or vaccine reactions, with the potential exception of chorioamnionitis.

873. Methodological Approaches to Enhanced Safety Surveillance for Seasonal Flu Vaccines: Early Experience in the UK

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Background: In 2014, the European Medicines Agency issued draft guidance for enhanced safety surveillance (ESS) on seasonal influenza (flu) vaccines. In the UK, conventional vaccine surveillance is through spontaneous reporting which is limited by underreporting and lack of denominator data. We have therefore developed and implemented new methods for ESS.

Objectives: To describe pilot experience of ESS in the UK.

Methods: In 2014/5, an 'active' surveillance study was conducted on an intranasal flu vaccine used in children (Q-LAIV: quadrivalent live attenuated influenza vaccine). Vaccinees were invited to participate after routine vaccination at participating GP practices and schools. Postal or electronic questionnaires solicited data on adverse events (AE) of interest 14 days after vaccination. Incidence rates were calculated for reported AEs.

In contrast, for 2015/6, a 'passive' ESS programme was conducted on the same vaccine. Vaccinees were handed a Safety Report Card (SRC) after vaccination and asked to report any suspected adverse drug reactions (sADRs) directly to the vaccine manufacturer. Reporting rates for sADRs were calculated using concurrent denominator data provided by immunisation sites.

Both pilots were collaborations between DSRU and AstraZeneca, were supported by the UK Clinical Research Network and received Ethics Committee approvals.

Results: In the 'active' design, 385 (64%) of 600 recruited vaccinees responded (46 immunisation sites), of which 237 experienced AEs. In the 'passive' ESS, 165 vaccinees reported sADRs (1.9% of 8,753 SRCs issued; 67 sites). In both years, the most frequently reported symptoms were pyrexia, malaise, rhinorrhoea, cough and headache. One serious event was reported in the passive phase (flu-like symptoms requiring hospitalisation).

Conclusions: Both active and passive ESS are feasible methods to collect patient-reported safety outcomes that may otherwise go unrecorded. Whilst both methods can capture denominator data, larger samples are needed to detect rare events. Reporting rates in the passive model were low. Promotion of safety surveillance, however, requires caution so as not to affect vaccine uptake.

874. Passive Enhanced Safety Surveillance In Children Receiving Fluenz® Tetra Vaccination In England During The Early 2015/2016 Influenza Season

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Background: Fluenz® Tetra is a quadrivalent, live attenuated, intranasal, influenza vaccine recommended for use in children vaccinated as part of the seasonal influenza immunisation programme in the UK. We report results from a pilot safety surveillance programme in England consistent with regulatory guidance for all influenza vaccines.

Objectives: To measure and assess the frequencies of suspected adverse drug reactions (sADRs) in children receiving Fluenz® Tetra during the early 2015/2016 influenza season in England.

Methods: Passive enhanced safety surveillance was conducted through stimulated spontaneous reporting of sADRs. Vaccinees or parents/guardians received a Safety Report Card (SRC) to return if children experienced sADRs after vaccination with Fluenz® Tetra; no time limit for reporting was specified. At participating sites, 42 general practices and 25 primary schools in England, immunisation teams provided numbers of SRCs distributed. The study was approved by an NHS Research Ethics Committee (North West - Liverpool East).

Results: Between 8th October 2015 and 10th January 2016, 8,753 SRCs were issued for 4,134 children (47.2%) aged 2 to 4 years, 4,078 (46.6%) aged 5 to 10 years and 541 (6.2%) aged 11 to 17 years. Of 323 SRCs returned during this period, 165 reported at least one sADR. The most frequently reported sADRs were rhinorrhoea (n = 54), cough (35), and pyrexia (31). One serious and unexpected sADR involved a child with flu-like symptoms requiring a hospital visit 2 days after vaccination. The child recovered from the sADR.

Conclusions: These data are broadly comparable with the frequency of adverse events reported for Fluenz® Tetra in clinical trial and post-marketing data, despite differences in methods. No evidence from the limited data available suggests an increased frequency of minor expected events or other safety signals.

Study co-sponsored by DSRU and AstraZeneca.

875. Rates of Therapy Switching Is Higher Among Initiators Insulin Glargine versus of Insulin NPH in a Population-Based Type 1 Diabetes Mellitus Cohort

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Background: Insulin analogues (eg. insulin glargine) may produce better glucose control than NPH insulin in type 1 diabetes mellitus (T1DM) in randomized trials, but benefits in the general population are not clear. As patients with poor control are more likely to switch agents, rates of switching therapies may indirectly assess effectiveness.

Objectives: To compare rates of therapy switch among T1DM patients initiating either NPH insulin or insulin glargine.

Methods: Retrospective cohort study using the MarketScan database. We selected individuals <24

years who were newly dispensed either insulin NPH (basal insulin or mixtures containing NPH insulin) or insulin glargine, between 2011-2013. Cohort entry was defined by date of first prescription of the agent, and a 6-month pre-period was used to exclude prior users. Therapy switching was defined as the interruption of the initial therapy followed by a dispensation of a different insulin type within 90 days after interruption. We performed adjusted Cox regression models using time to switching as outcome. Patients were censored at time of death, transfer out of the health plan, or end of study period. Models were adjusted for baseline variables: age, sex, year of cohort entry, comorbidities, and prior hypoglycemia or diabetic ketoacidosis.

Results: We studied 10,809 individuals, most (92%) were glargine initiators. The NPH group included more women (61.4% versus 45.0% on glargine), and tended to be younger at cohort entry (16.9 ± 6.5 versus 14.8 ± 5.9 years), and have less prior diabetic ketoacidosis (20.1% versus 27.3%). The rate of switching was higher in the glargine group (33.8%) than the NPH group (25.8%; 95% confidence interval [CI] for the difference = 4.9%-11.1%). In multivariable analysis, switching during follow-up was significantly lower for patients starting on NPH insulin (hazard ratio, HR = 0.78; 95%CI 0.68-0.90).

Conclusions: Our study suggests that T1DM patients initiating glargine are quicker to switch therapies, versus NPH insulin users. This potentially suggests poorer control with glargine versus NPH insulin, in the general population.

876. The Science and Art of Evaluating Heterogeneity in Treatment Effects

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Background: Research typically focuses on average effect of treatment in a population. Clinical practice emphasizes that patient comorbidities influence treatment response. Both researchers and clinicians want to understand individual treatment effectiveness in order to guide decision-making.

Objectives: To compare 3 strategies for investigation of heterogeneity in treatment effects in an applied example. We focus specifically on rate differences for time to event outcomes and methods that consider joint influence of multiple patient characteristics on treatment effectiveness.

Methods: We identified new initiators of dabigatran (n = 59,125) or warfarin (n = 109,822) in Medicare (2010-2012). The outcome of interest was ischemic stroke (n = 723). We evaluated 3 strategies for creating groups of patients: 1) lasso selected interactions between risk factors and exposure in additive survival models; 2) subgroups based on tertiles of a disease risk score (DRS), e.g. CHA2DS2-VASc or a DRS estimated in warfarin initiators; 3) subgroups based on tertiles of a predicted individual treatment effect (PITE) score. We used stabilized inverse-probability of treatment weights to adjust for confounding and split data 100 times for repeated training and validation.

Results: The adjusted difference in rate of stroke for dabigatran versus warfarin in the whole cohort was -2.8 (-5.2, -0.5) per 1000 patient years. Lasso modifiers of exposure effect were inconsistently selected in repeated training splits. Patterns of treatment effect within Lasso and PITE subgroups identified in training data were not seen in validation data. In contrast, DRS based subgroups were highly concordant in training and validation data. No statistically significant subgroup differences were found.

Conclusions: We implemented strategies for identifying subgroups based on multiple patient characteristics and observed a consistent modest absolute benefit of dabigatran over warfarin at preventing stroke. Creating subgroups based on joint influence of patient comorbidities requires both statistical modeling and artful decisions about which patients to group together – these decisions affect robustness of findings in external data.

877. Empirical Identification of Treatment Regimens for Studies of Long-Term Exposure

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Background: Lack of information on treatment regimens has been a challenge for evaluating long-term

exposure to treatments in pharmacoepidemiologic research. Commonly used measures, including cumulative exposure and average exposure over a time period, are susceptible to residual confounding bias and selection bias and not reflective of clinical decisions in practice.

Objectives: To empirically identify treatment regimens of intravenous (IV) iron among hemodialysis (HD) patients.

Methods: We used clinical data from a large US dialysis provider linked to healthcare utilization data from US Renal Data System (2004-2011). Our cohort included patients aged ≥65 who were receiving HD for >3 months and had Medicare as their primary payer. With a longitudinal treatment decision study design, we discretized the follow up of patients into intervals anchored by transferrin saturation, a parameter of iron status used to make treatment decisions. We used clinical knowledge and results from complex data visualization of patient treatment trajectories to construct IV iron treatment regimens. Treatment regimens consisted of anemia management parameter levels and corresponding iron dosage levels and frequencies. After treatment regimens were identified, we assigned to each interval treatment regimens consistent with treatment pattern in the first 2-week period of the interval.

Results: We identified 42,094 patients who met the inclusion criteria (median age 75 (IQR 70-81), 51.7% male, 23.5% black), with a total of 794,375 treatment intervals. Seven IV iron treatment regimens were constructed. Of the index interval for each patient, 58.7% were consistent with ≥2 regimens while 26.3% were not consistent with any of the 7 regimens considered. The most frequently initiated regimen was among 47.9% of patients while 45.4% initiated the second most common regimen. Similar trend was observed across the calendar years under study.

Conclusions: Identification of treatment regimens may make possible comparative effectiveness study of long-term treatment effects. Data visualization can be a useful tool to facilitate insights into the data structure and aid the identification process.

878. Comparative Incidence of Cardiovascular Events in Older Adults Initiating DPP-4 Inhibitors versus Other Antidiabetic Drugs

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Background: Randomized trials have examined cardiovascular (CV) effects after adding dipeptidyl peptidase-4 inhibitors (DPP) versus placebo to existing therapy, but limited data exist on CV effects relative to therapeutic alternatives in real world settings.

Objectives: We compared the relative and absolute risks of CV events with DPP relative to sulfonylureas (SU) and thiazolidinediones (TZD).

Methods: We implemented an active-comparator new-user cohort study using Medicare claims data 2007-2013. Patients >65 years with no prescriptions for DPP, SU or TZD during 6 month washout were included if they had at least two claims for the same drug within 180 days. As TZD are contraindicated in patients with existing heart failure (HF), for the DPP vs TZD comparison we excluded patients with HF diagnoses or related conditions. We used an as-treated approach and propensity score weighting and accounted for death as a competing risk. We estimated hazard ratios (HR) using Cox models, risk differences (RD) using weighted cumulative survival curves, and their 95% confidence intervals for myocardial infarction (MI), stroke, HF hospitalization and all-cause mortality in the entire population and subgroups based on prior CV disease.

Results: In the DPP vs SU comparison, 725 DPP initiators had an MI, 593 had a stroke and 3770 died over ~1 year median treatment duration. The HR for the composite outcome was 0.83 (0.80, 0.86), mainly driven by death. The RDs for MI and stroke were -1 to 0 per 100 patients. In the DPP vs TZD comparison, the HR for the composite outcome was 0.94 (0.88, 1.01) with the RDs for MI and stroke -1 to 0. As expected, absolute risks of MI and stroke were higher in the group with prior CVD (5-year risk MI:~6%; stroke:~5%) than the subgroup without CVD (5-year risk MI:~3.5%; stroke:~3%) for all treatments. RDs were similar in subgroups based on prior CVD, however. The risk of HF hospitalization was slightly lower with DPP than with SU and TZD.

Conclusions: Though limited by the real world duration of treatment in the US, our well-controlled population based study suggests no increased short-term risk of CV events with DPP relative to SU or TZD.

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879. Discrete Event Simulation for Facilitating Between-Study Comparisons

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Background: In the presence of heterogeneity of treatment effect (HTE), the average treatment effect from a randomized controlled trial (RCT) may not generalize to other patients, such as those included in observational studies.

Objectives: To propose an approach that uses individual-level simulation to expand RCT results to external populations in the presence of HTE.

Methods: We compared the results of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial and two observational studies (Graham 2014 and Larsen 2013) that compared the benefits and risks of dabigatran and warfarin in atrial fibrillation. We developed a discrete event simulation that replicates the rates of ischemic stroke, intracranial hemorrhage, and major bleeding observed in RE-LY using published outcome risk models and participants' baseline characteristics. We used the model to predict the results of the RCT had it been conducted in populations similar to those in the observational studies.

Results: The model successfully replicated the overall RE-LY results. For a population similar to Graham 2014, the model predicted rates of ischemic stroke of 1.13 and 1.45 (HR, 0.78; 95% CI, 0.61-1.02) and rates of major bleeding of 3.85 and 3.92 (HR, 0.98; 95% CI, 0.83-1.15) in dabigatran and warfarin groups, respectively. Corresponding HRs from Graham 2014 were 0.80 (95% CI, 0.67-0.96) and 0.97 (95% CI, 0.88-1.07), respectively, suggesting that differences between trial and observational results are attributable to HTE. Predicted rates of ischemic stroke were 0.66 and 0.91 (HR, 0.72; 95% CI, 0.50-1.04) for a population similar to Larsen 2013, which differed from the observed rates of 3.5 and 3.0 (HR, 1.18; 95% CI, 0.85-1.64), suggesting differences between the RCT and observational study results are due to factors other than HTE.

Conclusions: We propose a method that uses a simulation model based on RCT data to adjust for population differences across studies. This method can be used to provide counterfactual outcomes of an RCT in a target population and to determine if differences between studies are more likely due to HTE or other factors, such as confounding, misclassification of outcomes, and other biases.

880. Comparing the Safety Profile of Two Formulations of Tiotropium (Handihaler® vs Respimat®): A Population Based Cohort Study

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Background: Long-acting anticholinergics represent a therapeutic option for the treatment of chronic obstructive pulmonary disease according to clinical guidelines. Tiotropium is the most widely used drug in the class of anticholinergics and two different formulations are available in Italy (Handihaler® and Respimat®). Doubts were raised about the safety profile of Respimat® formulation as well as the generalizability of findings from trials.

Objectives: To estimate the risk of myocardial infarction and arrhythmic disorder in the incident users of tiotropium Respimat® compared with Handihaler® one.

Methods: The study population included all patients aged ≥ 45 years, resident in the Lombardy and Umbria regions who received at least one prescription of tiotropium (ATC code R03BB04) between 1 July 2011 - 30 November 2013. Only subjects who received the first prescription of tiotropium were included. The study cohort was identified through the drug prescriptions. Comorbidities and outcomes were obtained from hospital discharges. The primary

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outcome was hospitalization for myocardial infarction and/or arrhythmic disorders during the current exposure (defined through DDDs from the date of the first prescription). Each subject was followed from the first tiotropium prescription up to: end of the exposure; change from a formulation of tiotropium; hospitalization for one of the study events; end of the study (31 December 2013). Hazard ratio was estimated in the two propensity score-matched groups through Cox regression.

Results: Overall, 120,434 patients with incident prescription of tiotropium were identified, with a mean age of 73 years. The two groups point out different percentages for co-morbidities and drug use. We observed 645 events during 159,589 months of exposure to Handihaler® (incidence: 4.0 per 1000 person-months) and 152 events during 42,965 months of Respimat® (incidence: 6.5 per 1000 person-months). The hazard ratio for the primary outcome (Respimat® vs Handihaler®) was 0.86 (95% CI: 0.72 to 1.02).

Conclusions: This cohort study on a large population showed a comparable cardiovascular safety profile among the two tiotropium formulations.

881. Inclusion of Elderly Patients in Randomized Controlled Trials on Targeted Agents in the Treatment of Metastatic Colorectal Cancer: A Systematic Review

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Background: Since 2005, survival in metastatic colorectal cancer (mCRC) was improved by targeted agents. As mCRC is frequent in elderly patients (median age >73 years), the issue of their representation in randomized controlled trials (RCT) is crucial.

Objectives: This study aimed to describe the inclusion of elderly patients in RCT on targeted agents in mCRC.

Methods: A systematic review in Medline, Scopus, Cochrane Database and ISI Web of Science was performed to identify phase II or III RCT on bevacizumab, cetuximab, panitumumab, regorafenib and aflibercept in mCRC. Two reviewers performed independently the study selection and data extraction on eligibility criteria and characteristics of included patients.

Results: Over 1369 retrieved references, 54 RCT were included; two-third (65%) studied these agents as 1st-line therapy in mCRC. Progression-free survival was the main outcome in 46% of included RCT. Targeted agents evaluated in these RCT were most often bevacizumab (57%) and cetuximab (41%). Eight RCT (15%) excluded elderly patients (maximum age for inclusion between 70 and 80 years); median age of the included population was ≥65 years in 5 RCT (9%). Twenty-one RCT (39%) excluded frail patients (according to ECOG/Karnofsky performance status); 5 RCT (9%) included >10% of frail patients (missing data: 33%). Most RCT excluded patients with brain metastases (n = 42; 78%), patients with at least one cardiovascular disease (n = 47; 87%) [mainly hypertension (44%), heart failure (41%) or stroke (31%)], and patients treated with specific medications (n = 39; 72%) [mainly anticoagulants (37%)]. Most RCT (n = 45; 83%) included only patients with adequate creatinine clearance.

Conclusions: Even if elderly patients were not systematically excluded from RCT, they are still underrepresented. Moreover, elderly patients included in RCT do not reflect the general elderly population with mCRC because of exclusion criteria such as comorbidities and/or medications. RCT results on targeted agents can only be extrapolated to relatively healthy elderly subjects, which reinforce the need for observational data in the elderly population with mCRC.

882. The Long-Term Use of Biologics in Hong Kong

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Background: Biologic agents initially introduced as treatment for rheumatoid arthritis (RA) but have also been used for several other conditions. As the growing

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availability of new biologics in regiments, it is important to understand the utilization of biologics agents. However, little was known in Asian countries.

Objectives: To investigate the drug utilization of biologics rheumatology specialist clinic in Hong Kong.

Methods: We identified patients from the Clinical Data Analysis and Reporting System (CDARS) from year 2001-2014. Patients who have visited rheumatology specialist clinic were identified from CDARS. The corresponding demographics, clinical and drug prescription records were retrieved from the database. The yearly prevalence (per 1,000 persons) of rheumatology specialist clinic visit and the prevalence of biologics prescribing in this group of patients were evaluated.

Results: In total, 54,577 patients from CDARS with rheumatology specialist clinic visit, 27.5% were male. The mean age on first visit is 50.2 for male and 49.9 for female. The yearly prevalence increased by 2.4 times from 1.5 in 2001 to 3.6 in 2014. Increasing trend was found in both gender. Among patients with specialist care, 2,811 received biologics treatment. The prevalence of biologic agents prescribing was increasing dramatically throughout the study period by 118 times from 0.6 in 2001 to 72.3 in 2014. The prescribing prevalence in male (95.3) is higher than female (57.6). Etanercept was the most common treatment during the study period which were prescribed to 1,012 patients (36%), followed by infliximab (616 patients, 21.9%) and adalimumab (587 patients, 20.9%). RA (42.4%), ankylosing spondylitis (23.0%), psoriatic arthropathy (9.2%) and psoriasis (6.0%) are the most common potential indication in treated patients. Hypertension is one of the most common comorbidity which affected 15.7% of the treated patients. The most common adverse event was upper respiratory tract infection (12.6%) and anemia (10.8%).

Conclusions: With an increasing prevalence in rheumatology patients and biologics treatment prescribing, it is important for health care professionals to maintain awareness of the effectiveness as well as the safety of biologic treatments.

883. Assessment of Biosimilar Somatropin Use in Italian Routine Care: A 6-Year, Multicenter, Retrospective Study Using a Database Network

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Background: Somatropin (recombinant growth hormone, rGH) is a biological product approved for growth disturbances due to GH deficiency/Turner or Prader-Willi syndrome/chronic kidney disease or in children born small for gestational age. From 2006, biosimilar rGH is available in Italy, but population-based data about its prescribing pattern in Italian routine care are lacking.

Objectives: To explore the prescribing pattern of biosimilar/originator rGH in five Italian geographic areas, where various healthcare policies promoting biosimilar use were taken.

Methods: This drug utilization study was conducted using administrative databases of Tuscany and Umbria Region and Caserta, Treviso and Palermo Local Health Units in the years 2009-2014 ("Assessment of short and long term risk-benefit profile of biologics through healthcare database network in Italy" project, funded by the Italian Ministry of Health). Characterization of naïve rGH users and prevalence of biosimilar and originator use over time and across centers were assessed.

Results: In the study years, 4,103 (0.1% of the total residents in the catchment areas) patients used rGH. Of these, naïve users were 2,707 (66.0%), most of

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whom were 6-11 years old (N = 1,075, 39.7%). The main indication for use was growth disturbance due to GH deficiency (N = 942, 34.8%). The overall prevalence of rGH use was rather stable across years (0.2-0.3 per 1,000 inhabitants). The proportion of biosimilar users increased from 5.7% (2009) to 11.1% (2014), but heterogeneity across different areas was reported, with greater increase in Tuscany (from 5.2% to 16.9%) and lower in Umbria (from 5.6 to 7.5%).

Conclusions: In comparison to other biosimilars (e.g. filgrastim and epoetin alpha), the proportion of biosimilar rGH users was low in recent years, despite a slight increase. Notably, relevant heterogeneity in the biosimilar rGH use across centers was documented. Differences may be due to different policies across centers, which may be specific per type of biosimilar drug. Since somatropin accounts for most of the pharmaceutical expenditure in hormonal preparations in Italy, these data warrant more research.

884. Safety, Efficacy and Pharmacokinetic Bioequivalence of Biosimilar Tumor Necrosis Factor-alpha (TNF-a) Inhibitors Compared with Their Reference Biologics: A Systematic Review

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Background: Biosimilars are of growing regulatory and commercial importance, yet there is uncertainty about their safety and efficacy relative to their reference products.

Objectives: The objective of this review was to summarize the evidence comparing biosimilar and reference tumor necrosis factor-alpha (TNF-) inhibitors.

Methods: We searched PubMed, EMBASE, Cochrane Collaboration Clinical Trials and LILACS through September 15, 2015 for English-language trials and observational studies comparing the safety, efficacy or pharmacokinetic profiles of biosimilar and reference TNF- inhibitors. No restrictions were applied regarding study population, size or design. Two reviewers assessed abstracts and a third resolved discordances. A single reviewer completed the full text review and data extraction. We narratively synthesized included studies. Strength of trial evidence was assessed using the Cochrane Collaboration instrument. Public registries of clinical trials were searched for unpublished trials. Our registration number on PROSPERO is #CRD42015025262.

Results: Of 3,365 publications identified, 15 were included: 8 randomized controlled trials (RCTs), 4 abstracts describing trial extensions, 2 retrospective case series and 1 cross-sectional study. Of the RCTs, two Phase 1 crossover trials were in healthy volunteers, one Phase 1 parallel-group study was in patients with ankylosing spondylitis, one Phase 1 parallel-group study was in patients with rheumatoid arthritis (RA), and four Phase 3 studies were in patients with RA. In the Phase 1 trials, biosimilars and reference biologics were equivalent in pharmacokinetic parameters. In Phase 3 trials, treatment-emergent adverse events and serious adverse events were comparable across arms. For all Phase 3 trials, patients receiving biosimilars and reference biologics showed similar American College of Rheumatology Remission Criteria responses. The risk of bias was generally low for all trials; incomplete follow-up was the most common bias.

Conclusions: The existing published studies support the biosimilarity and interchangeability of these products.

885. Real-World Comparative Risks of Herpes Virus Infections in Tofacitinib and Biologic-Treated Rheumatoid Arthritis Patients

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Background: While placebo-controlled clinical trials have suggested an increased rate of herpes zoster (shingles) with tofacitinib, the real-world risks of herpes zoster and herpes simplex associated with tofacitinib compared to other biologics for rheumatoid arthritis are largely unknown.

Objectives: To evaluate the risks of herpes zoster (HZ) and herpes simplex virus infection (HSV) associated with tofacitinib compared to biologic agents among patients with rheumatoid arthritis (RA).

Methods: Using health plan data, we identified RA patients without a history of HZ or HSV who initiated tofacitinib or biologics from 2010-2013. Among this cohort, new cases of HZ or HSV were found and incidence rates calculatedby drug. We used Cox proportional hazards models evaluated the adjusted association between tofacitinib and either HZ, and a composite outcome of HZ or HSV.

Results: A total of N = 1,746 patients initiating tofacitinib were compared with initiations of other biologics including anti-TNF (n = 38,871), abatacept (n = 11,434), rituximab (n = 4,785), and tocilizumab (n = 6,266). Tofacitinib patients were somewhat younger (mean age 57 years) versus those on other biologics, and somewhat less likely to use concomitant MTX (39% vs. 44-56%, depending on drug).

Crude incidence of HZ associated with tofacitinib was 4.33/100py and after multivariable adjustment, was significantly elevated (hazard ratio, HR = 2.09, 95% CI 1.33-3.26) compared to abatacept (referent). Rates and adjusted HRs for all other RA biologics were comparable to each other and abatacept. Older age, female sex, prednisone >7.5 mg/day, prior outpatient infection, and greater number of hospitalizations were also associated with increased HZ risk Incidence rates for the combined outcome were greatest for tofacitinib (9.33/100py) and also significantly elevated after adjustment (HR = 1.65, 95%CI 1.21-2.23).

Conclusions: Zoster infections were relatively common among RA patients. The risk for zoster associated with tofacitinib was approximately double that observed in patients using biologics.

886. Use of Systemic Antibacterials Before and After Start of Topical, Non-Biologic Systemic or Biologic Therapy for Psoriasis. A Nation-Wide Cohort Cross-Over Study

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Background: An increased risk of in- or out-patient care for infections following start with biologic regimens have been established.

Objectives: To examine the risk of infections as identified by **dispensed systemic antibacterials** (ATC-code J01) in patients who are prescribed a new treatment for psoriasis.

Methods: A cohort cross-over study of patients with psoriasis, who between July 2007 and December 2011 started treatment with i) biologics, ii) non-biologic systemics, or iii) topicals (calcipotriol preparations) for the first time since July 2005.

Rates of subjects that filled prescriptions of systemic antibacterials one year before treatment start was used as reference when comparing (in an intent-to treat analysis) such rates, yearly, up to three years thereafter, giving Rate Ratios (RR) with 95% confidence intervals.

Results: A total of 3,618 patients started a biologic regimen, with a total of 10,785 years of follow-up; 15,855 started non.-biologic systemic (43,399 years of follow-up); and 54,678 started topical treatment (154,338 years of follow-up).

Comparing the rate of antibacterial users in year 1 through 3 after start, with the rate in the year proceeding start yielded, for biologics, an RR of 1.14 (1.06-1.23) in year 1, RR 1.06 (0.98-1.14) in year 2 and RR 1.04 (0.96-1.12) in year 3. For non-biologic systemics, the RR's observed were: 0.91 (0.88-0.94) in year 1; 0.84 (0.81-0.87) in year 2; 0.81 (0.78-0.84) in year 3; and for topicals, year 1: 1.03 (1.01-1.05); year2: 0.90 (0.88-0.92); and year 3: 0.87 (0.86-0.89).

Conclusions: For patients with psoriasis starting a new treatment with a biologic agent, the risk of receiving systemic antibacterials during the first year after start of treatment was increased by 14% as compared with the rate before treatment, but that risk disappeared in year 2 and 3. Except a very slight increase during year 1 in topically treated, no such patterns were observed in those with non-biological or topical treatment.

887. Real-World Effectiveness of Omalizumab for the Treatment of Severe Asthma

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Background: Omalizumab is indicated for the treatment of moderate to severe persistent asthma. There is limited observational evidence of the real-world effectiveness of omalizumab.

Objectives: To examine the effectiveness of omalizumab for treatment of severe asthma, including changes in healthcare costs and patient outcomes, relative to non-users of omalizumab.

Methods: We conducted an individual-level, matched repeated measures cohort study using administrative claims data in Ontario, Canada from April 1, 2012 to March 31, 2014. Subjects were residents of Ontario aged 18 years and older with publicly-funded drug coverage and severe asthma. We matched each new, continuous users of omalizumab with up to 4 non-users according to age, sex, recent specialist visits, oral corticosteroid use, asthma severity based on medication use, and Charlson comorbidity score. The primary outcome was total direct healthcare costs. Secondary outcomes were asthma-related hospitalizations or emergency department visits, short-acting beta agonist use, oral corticosteroid use and number of physician visits. Analyses were adjusted for potential confounders.

Results: We identified 95 omalizumab users and 352 matched non-user controls. Among omalizumab users, there was a significant increase in total healthcare utilization costs of approximately $1,800 per quarter per person due to the cost of the medication following treatment initiation ($p<0.0001$). There was no significant change in the total healthcare utilization trajectory among omalizumab users after drug initiation ($p=0.59$) or compared to non- users ($p=0.43$). We found no significant difference in any of the secondary outcomes studied between users and non-users.

Conclusions: Our results suggest that omalizumab may have limited effectiveness in real- world use. These findings may be due to small effect sizes that may require a larger sample size, which would also allow for examining subsets of patients that may benefit.

888. Determining the Optimal Position For Vedolizumab In The Current Treatment Paradigm For Ulcerative Colitis: A Markov Model

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Background: Vedolizumab (VDZ), an 4 7 integrin monoclonal antibody inhibiting lymphocyte trafficking to the gut, is approved for the treatment of ulcerative colitis (UC).

Objectives: To determine the ideal position of VDZ in the current treatment paradigm.

Methods: Using Markov modeling, we assessed the ideal position for VDZ use, with the primary outcomes of greatest benefit in clinical outcomes and quality adjusted life years (QALYs). The base case was a 35-year old male with moderate to severely active UC who had not previously used immunomodulators or biologic therapies. The time horizon was 1 year. The model included VDZ in 5 different positions in a step-up treatment algorithm, prior to: (A1) initiating an immunomodulator, (A2) infliximab monotherapy, (A3) combination therapy with an anti-TNF and thiopurine, (A4) combination therapy with a second anti-TNF and thiopurine, and (A5) colectomy. With each medication, individuals could enter clinical remission or response, or develop medication-related complications requiring cessation. Transition probabilities and QALY estimates were derived from published literature. Primary analyses included first order Monte Carlo simulation of 100 trials of cohorts of 100,000 individuals. Additional analyses employed

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longer time horizons, simulated the clinical course of 100,000 individuals, and included one-way sensitivity analyses with 25% variation for all variables.

Results: VDZ use prior to all other therapies (A1) was the preferred strategy at 1 year, resulting in 11,294 additional individuals in remission, 12 fewer cases of lymphoma, and 817 fewer serious infections per 100,000 patients compared to last-line use (A5). VDZ use prior to immunomodulators or anti-TNFs (A1) resulted in 0.0215 to 0.0282 greater QALYs as compared to any other strategy. This benefit increased with longer time horizons. Early VDZ use remained the preferred strategy in all one-way sensitivity analyses.

Conclusions: This model suggests that incorporating VDZ early in the treatment paradigm results in the greatest potential benefit for individuals with moderate to severe UC who require steroid-sparing therapy.

889. Risk of Serious Infections During Use of Biologic Therapies for Psoriasis: A Systematic Review

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Background: The risk of infections leading to significant morbidity and/or mortality in association with biologic therapies for psoriasis is a key concern.

Objectives: We have performed a systematic review and meta-analysis of serious infection in people taking any licensed biologic therapy for psoriasis compared to those taking placebo or non-biologic therapy.

Methods: We searched PubMed, Medline, Embase and Cochrane databases up to the 29th of September 2015 for randomised clinical trials (RCTs) or prospective cohort studies involving etanercept, infliximab, adalimumab, ustekinumab or secukinumab for the treatment of psoriasis. The results were meta-analysed using RevMan 5.3 and study quality and risk of bias assessed using National Institute for Health and Care Excellence (NICE) checklists and GRADE. Heterogeneity was assessed using the I^2 statistic.

Results: Data from 32 RCTs (13359 participants) and one cohort study (4993 participants) were included. No significant heterogeneity was found amongst the pooled analyses. The individual studies ranged from having a low to a very high risk of bias. In adults, low to very low quality RCT data showed no significant difference between any biologic therapy and placebo at weeks 12-16 (24 RCTs, overall pooled Peto odds ratio [OR] 0.71, 95% confidence interval [CI]: 0.36,1.41) and weeks 20-30 (4 RCTs, Peto OR 2.27, 95%CI 0.45,11.49). Prospective cohort study data of low quality suggests only adalimumab (adjusted hazard ratio 2.52, 95%CI 1.47,4.32) was associated with a significantly higher risk of serious infection compared with retinoid and/or phototherapy in adults.

Conclusions: No association was found between biologic therapies and serious infections in patient with psoriasis who were eligible for RCTs. Observational data from one study suggests that adalimumab is associated with a higher risk of serious infections as compared to acitretin and/or phototherapy in adults. Adequately powered, well-designed observational studies are needed to inform the uncertainty about the risk of serious infection when biologic therapies

are used in patients with psoriasis in the real-world rather than in clinical trials.

890. Quality of Life Outcomes of a 12-Month-Follow-Up Brazilian Cohort of Patients with Rheumatic Diseases Using Biological Agents

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Background: Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis are rheumatic chronic inflammatory diseases, once not properly treated, can lead to great impairment of quality of life (QOL).

Objectives: We aimed to evaluate QOL in a cohort of rheumatic patients using biological agents.

Methods: This study examines an open prospective cohort of patients treated by the Brazilian Public Health System. The study included RA, AS and PsA patients who had approved applications for biological drugs (adalimumab, etanercept, infliximab, rituximab, golimumab, abatacept, tocilizumab and certolizumab pegol). The data were collected from March 2011 to December 2014. All patients signed an informed consent form. The inclusion criteria were: being over 18 years old and meet the respective specific qualifying criteria for each disease. We used a convenience sample. A standard form was used to collect sociodemographic and Clinical variables. QOL of participants was assessed using EuroQol-5 dimensions (EQ-5D). Continuous and categorical variables were compared using analysis of variance, t-student test and Pearson's chi-square test. QOL measurements by the EQ-5D was performed at the baseline and after 6 and 12 months of treatment by means of paired t test. The significance level was set at 5% in all analyses.

Results: At baseline, 544 patients were included in the study. Of them, 373 (68.6%) patients were with RA, 105 (19.3%) with AS and 66 (12.1%) with PsA. Mean disease duration (SD) was 10,33 (9.39) years. In addition, 292 patients completed the 12-month-follow-up with a significant improvement on QOL ($p = 0.000$). After 6 and 12 month, respectively, 181 (62.0%) and 185 (63.4%) patients reached the EQ-5D Minimal Clinically Important Difference (MCID). Poorer baseline QOL and functionality were related to better quality of life response following 12 month use of biological drugs ($p = 0.000$ and $p = 0.037$ for EQ-5D and Health Assessment Questionnaire Disability Index (HAQ-DI), respectively).

Conclusions: Our study showed that the use of biological drugs promoted considerable improvement in the participants' QOL.

891. Identifying Anti-TNF Use for Crohn's Disease and Ulcerative Colitis in Primary Care

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Background: The use of anti-TNF therapy (infliximab "IFX", adalimumab "ADA") to treat Crohn's disease "CD" and ulcerative colitis "UC" is not readily identifiable in UK primary care medical databases such as CPRD/THIN. Nonetheless, primary care physicians are informed of IFX/ADA use through specialist letters which are now often scanned into free-text comment fields.

Objectives: To elucidate the usefulness of free-text comments to identify IFX and ADA use in CD/UC and create, for the first time, a cohort of such patients from the general population.

Methods: Patients with either CD or UC records in the UK primary care database called The Health Improvement Network "THIN" (11 million patients), were selected and a word search was performed to identify comments mentioning IFX or ADA at any time in their records. Anonymised free-text comments for 2092 patients were provided. We read the free-text comments to confirm if the IFX/ADA mention implied that the patient was using either anti-TNF to treat IBD (confirmation rate) following initial feasibility (93 patients). We then compared the results with the recent UK IBD Audit to gauge the validity of this approach.

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Results: Initial feasibility revealed that patients can be identified as IFX or ADA users but that dose, timing of administration, and treatment effectiveness were not routinely recorded. In addition, automating extraction was not possible and we found patients had received IFX or ADA for other indications. The confirmation rate in all 2092 IFX or ADA recipients was 72%. Among confirmed patients, most (81%) received IFX only, 9% ADA only and 10% received both. Median age at first mention of IFX/ADA was 26 years and 54% were female. Among patients using IFX or ADA the proportion with a diagnosis of CD was 80% (UK IBD Audit = 83%). Also, among these patients with CD there was similarity with the audit in terms of median age at initiation of IFX or ADA (THIN: 33.6; Audit: 32.1) and male gender (THIN: 45%; Audit: 49%).

Conclusions: The use of free-text comments provides a means to create a cohort of patients who have received ADA or IFX to treat IBD without having to resort to field studies. It is representative of UK IBD patients.

892. Incidence of Bowel Surgery in a Cohort of Crohn's Disease Patients Treated with Infliximab or Adalimumab in Lazio, Italy

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Background: Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract which can lead, in more severe cases, to surgical treatment. Evidence on head-to-head comparative effectiveness of biologic medication is scarce, therefore, it is important to evaluate these drugs in clinical practice to see if differences in outcome exist.

Objectives: To compare the incidence of bowel surgery in CD patients newly treated with Infliximab or Adalimumab.

Methods: We performed a population based cohort study among CD patients resident in Lazio Region enrolled from 2000 to 2009. We retrieved data from linked hospitalization, drug prescription, mortality and population archives. We selected all new user patients that had a prescription of Adalimumab or Infliximab (ATC codes: L04AB04, L04AB02 respectively) from 2008 to 2010 and have not received a dispensing of biologic medications under study during the 12 months preceding the date of their first medication (index date). We classified the exposure as the drug prescribed at the index date. We followed up patients for the two years after the index date, outcome was the first CD related bowel surgery. Comorbidities (including autoimmune diseases) and drugs utilization (Antimetabolites , Immunosuppressants, Corticosteroids, Aminosalicylic acids) were retrieved respectively within 5 and 1 years before the index date.

Results: 104 Adalimumab and 201 Infliximab new drug users were included in the analysis, median age was 36 years. Differences among Adalimumab and Infliximab users arose for percentage of, female patients (respectively 46.1% vs 53.2%), patients aged more than 44 years (46.1% vs 53.2%), past use of corticosteroids (34.6% vs 51.7%) and immunosuppressants (23.1% vs 30.3%). Incidence rate for 100 person-years of bowel surgery resulted in 10.6 among Infliximab users and 7.0 among Adalimumab users.

Conclusions: In the biologic era, risk for bowel surgery in CD patients is still evident. Further analysis will evaluate the comparative effectiveness of the two drugs taking into account the role of potential confounders / effect modifiers.

893. Top-Down versus Step-Up Strategy of Tumor Necrosis Factor Alpha Inhibitors in Children and Young Adults with Inflammatory Bowel Disease

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Background: Patterns of medication use and especially early initiation of tumor necrosis factor-alpha inhibitor (TNFI) therapy for children and young adults with inflammatory bowel disease (IBD) are not well described.

Objectives: We aimed to examine the use of the top-down approach for children and young adults with IBD and more specifically to compare medication utilization between the step-up and top-down strategies.

Methods: We conducted a retrospective cohort study of children and young adults (≤24 years) newly diagnosed with IBD using health insurance claims from 2009 to 2013. Conventional "step-up" treatment was defined as TNFI use after use of immunomodulators, whereas "top-down" treatment involved early TNFI initiation. Switching rates, time to discontinuation, and adherence to TNFIs were compared between the two strategies.

Results: A total of 11,962 patients with incident IBD were identified. Among 3,300 TNFI users, 1,405 (42.6%) were treated with the top-down approach, while 1,895 (57.4%) were treated with the step-up approach. Employment of the top-down approach increased from 35.2% to 50.5% during the 5-year period, and under this approach, most patients (75.4%) were treated with TNFIs alone. Time to TNFI initiation was shorter for patients diagnosed in more recent years (hazard ratio and 95% confidence interval: 1.18 [1.05-1.32], 1.35 [1.20-1.52], 1.76 [1.56-1.99], and 2.01 [1.72-2.35] for year 2010 to 2013, respectively, compared to 2009). Compared to step-up treatment, patients treated with the top-down strategy had lower rates of corticosteroid use (39.4% vs 92.6%, $p<0.0001$) and switching (5.3% vs 7.8%, $p=0.006$) but a higher rate of TNFI discontinuation (log-rank test $p=0.0056$). The adherence to TNFIs was high (proportion of days covered: 83.1% to 95.4%) and no differences were found between the two strategies.

Conclusions: Early TNFI initiation increased over time for children and young adults with IBD and was related to lower rates of corticosteroid use and switching compared to the conventional approach. However, the higher rate of TNFI discontinuation under the top-down approach requires further examination.

894. Effectiveness and Safety of Cetuximab in First-Line Therapy of Metastatic Colorectal Cancer According to Frailty in the EREBUS Study

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Background: Besides old age, frailty considering also performance status (PS) or comorbidities is useful to help treatment decisions in cancer patients.

Objectives: As part of the EREBUS study, cetuximab use, safety and effectiveness were compared according to frailty of included patients.

Methods: EREBUS is a French multicenter observational cohort study of 389 patients initiating cetuximab 1st-line therapy for wild-type KRAS unresectable metastatic colorectal cancer in 2009-2010 followed 2 years for progression-free survival (PFS) and 3 years for overall survival (OS). Three groups of frailty were defined: not frail (G1), moderately frail (G2) and very frail (G3) using baseline age, BMI, number of comorbidities, ECOG PS and hemoglobin.

Results: At baseline, 77 patients (20%) were classified as not frail (G1), 196 (50%) moderately frail (G2) and 116 (30%) very frail (G3). Gender was comparable between groups (65% male in G1 vs 69% in G2, $p=0.53$ and 66% in G3, $p=0.84$). Median duration of cetuximab use was similar in G1 and G2 (5.5 vs 5.3 months, $p=0.91$) but significantly shorter in G3 (3.5 months, $p<0.01$). Incidence of grade ≥3 adverse events (AE) was similar between groups (57% in G1 vs 56% in G2 and G3, $p=0.88$). Cutaneous AE (any grade) were more frequent in G1 than G2 and G3 (84% in G1 vs 71% in G2, $p=0.02$ and 67% in G3, $p<0.01$). AE (any grade) more frequently observed in G2 than G1 were respiratory (27% vs 10%, $p<0.01$) and hematological (93% vs 83%, $p<0.01$). AE (any grade) more frequently observed in G3 than G1 were respiratory (28% vs 10%, $p<0.01$) and metabolic (63% vs

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48%, p=0.04). Median PFS [95%CI] in G1 was longer than in G2 with a non-significant difference: 10.7 months [8.7;11.5] vs 9.0 [7.9;9.7] (p=0.24) but much longer than in G3: 5.8 months [4.7;7.2] (p=0.002). Median OS in G1 was significantly longer than in G2 and G3: 34.5 months [21.3;-] vs 24.3 [20.3;28.4] (p=0.04) and 17.6 [12.8;20.1] (p<10-3).

Conclusions: While old age was not previously found to affect effectiveness and safety in the EREBUS study, these results indicate that frailty should be taken into account in clinical practice and anticancer medication evaluation.

895. Tracking Trastuzumab (H) Therapy in Early Through Late Stage HER2-Positive Breast Cancer (HER2BC) in Australia: A National, Retrospective Cohort Study

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Background: Clinical trials established the efficacy of H in the metastatic setting (MBC) in H-naïve patients. Little is known about patients initiating H in the adjuvant setting (EBC) and subsequently receiving H for MBC. Observational studies provide a unique opportunity to examine the treatment and outcomes of this patient cohort.

Objectives: To characterise patterns of treatment and outcomes for patients treated with H for EBC and MBC. We estimate time from EBC treatment initiation to MBC therapy and overall survival (OS).

Methods: We identified a cohort of patients initiating H for EBC in Pharmaceutical Benefits Scheme (PBS) dispensing claims and persons commencing MBC therapy from the Herceptin Program (HP) claims. We calculated duration of EBC treatment as date of first H dispensing until 21 days after the last PBS dispensing for H or observation of an H dispensing record in HP claims, whichever came first. We used Kaplan-Meier methods to estimate time-to-MBC treatment and OS.

Results: Of 11,477 H-treated patients for EBC, 637 were also treated for MBC. Median age at EBC treatment initiation was 53 (range 17 – 87). 94% of EBC patients received taxane, anthracycline, cyclophosphamide and/or carboplatin as part of their treatment protocol. 61% of MBC patients received H with a taxane, 18% as monotherapy and 7% with capecitabine. Median duration of H therapy in EBC and MBC was 11.3 (95% CI 10.7-11.6) and 9.3 (8.6-10.4) months, respectively. Median time-to-MBC therapy was 27.3 (25.5-28.2) months. Median OS from initiation of EBC and MBC treatment initiation was 58.1 (52.9-65.7) and 23.2 (20.5-25.4) months, respectively.

Conclusions: HER2BC patients initiating EBC therapy and progressing to MBC treatment are little examined in the clinical trial and observational literature. We showed: most EBC patients are treated according to guideline recommendations; that this patient cohort receive approximately 20 months of H therapy across both settings; and median OS from initiation of MBC therapy is approximately 2 months shorter than in the pivotal clinical trial (25.1 months).

896. Risk of Type 1 Diabetes Mellitus Associated with Vaccination During Childhood and Adolescence

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Background: To date, studies reporting on a potential link between childhood vaccination and the occurrence of Type 1 Diabetes (T1D) have found discordant results and the topic remains controversial.

Objectives: To evaluate the incidence of T1D following either exposure to overall vaccination or to specific vaccine types, including influenza, MMR, DTPP, HBV, pneumococcal and meningococcal vaccines, in children and adolescents aged 0 to 25 years.

Methods: Prospective case-control study conducted on 281 incident T1D cases aged 0-25 years and recruited by a network of endocrinology centres across France and Quebec between April 2008 and May 2013. A network of general practitioners from similar regions to the cases recruited 1170 controls matched to cases on age, sex, country and date of consultation. Vaccination and other potential risk factors for T1D were collected using a standardised telephone interview. Cases and controls were compared for vaccination at 24, 12 and 6 months before the index date (date of first symptom presented by the case), using Odds ratios (OR) from conditional logistic regression.

Results: 281 cases and 1170 controls were included of which 130 (46.3%) and 436 (37.3%), respectively, had been vaccinated at least once in the 24 months prior to the index date. No increase in T1D was shown following vaccination at 24, 12 or 6 months (adjusted OR for the previous 24 months = 1.1; 95% confidence interval, 0.8-1.5) before the index date. Equally, no increase on the risk of T1D associated with any of the studied vaccines (influenza, MMR, DTPP, HBV, pneumococcal and meningococcal vaccines) was found.

Conclusions: The results of this population-based case-control study showed that exposure to vaccines pertaining to regular immunisation schedules among people aged 0-25 years is not associated with any observable risk of developing T1D.

897. Social Determinants of Zoster Vaccine Uptake in England: Use of Electronic Health Records for Ascertainment of Inequity Parameters

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Background: Vaccination-related inequities remain a challenge for public health. Identification of subgroups with lower vaccine uptake is thus an essential step towards minimising health inequities.

Objectives: To ascertain the quality and extent of recording of social factors in electronic health records and to investigate the social determinants of zoster vaccine uptake among older UK individuals.

Methods: Data sources comprised anonymised UK primary care electronic health records from Clinical Practice Research Datalink (CPRD), linked to hospitalisation and social deprivation data. We first conducted a cross-sectional study to ascertain the completeness and timeliness of recording of social determinants (deprivation, ethnicity, religion, country of birth, residence, living arrangement and marital status) and their representativeness compared to census data, amongst individuals aged ≥65 years. The association of these potential determinants with zoster vaccine uptake (2013-2015) was then examined amongst individuals aged ≥70 years. For this analysis we used a cohort study design and multivariable random effects Poisson regression to examine the independent effects of these factors on zoster uptake and their interrelationships.

Results: Amongst 781,402 individuals, completeness of recording of social determinants in CPRD varied from 2% (religion) to 67.5% (ethnicity). Recorded ethnicity and care home residence were comparable to the census data, in contrast to religion and living arrangement data that were not comparable. For time-varying variables such as living arrangements and residence, only 8% and 6.5% individuals respectively had recordings in last 5 years. Detailed results from the cohort study will be presented.

Conclusions: This work provides methods to identify social determinants in electronic health records and clarifies their utility. Application of these methods to vaccine uptake data allows identification of social determinants linked to low uptake and hence guide

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targeting of public health interventions to decrease inequity in vaccine uptake.

898. Is Mortality Associated with Combination DTPa Vaccines? A Linkage Study Among Australian Children Using 12 Years of Data

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Background: Mortality risk has been a concern among infants administered multivalent vaccines (multiple antigens in a single injection).The timing of infant 3-dose primary immunisation course at 2 months which includes diphtheria-tetanus-acellular pertussis (DTPa)–containing vaccines, coincides with peak incidence of infant mortality.This occurrence highlights the importance of establishing mortality risk as a disease or vaccine issue.

Objectives: To compare all-cause one-year mortality rates between 4 DTPa types, using whole-of-population linked data containing child immunisation and death information.

Methods: Children were included if aged ≤12 months, administered at least 1 dose of trivalent DTPa, quadrivalent DTPa with Hepatitis B (QVHepB), DTPa with Haemophilus influenzae type b (QVHib) or hexavalent DTPa with HepB, Hib and polio between 1999-2010. Separate cohorts were established for the 3 doses at 2, 4 and 6 months of age and followed for 12 months post-vaccination. Kaplan-Meier survival curves for mortality compared DTPa types for each cohort by calendar year, and all years combined. Cox models estimated hazard ratios (HR) for up to 81 vaccine schedule variants representing antigens administered concurrently with different DTPa types.

Results: There were 2.8, 2.2, & 1.6 million children in the 2, 4 and 6 month cohorts. Overall mortality was low and declined with age (0.064% at 2 m to 0.038% at 6 m). A difference in mortality between DTPa types was observed in the combined 2 m cohort (Log-rank test p = 0.0188). Cox regression by calendar year identified an increased mortality risk in 2003 with a QVHepB vaccine schedule variant compared to the standard schedule at that time (HR = 3.2 95% CI 1.5-7.0). In 2003, this variant included the pneumococcal vaccine, targeted at children medically-at-risk of pneumococcal disease. By 2005 when the QVHepB variant was recommended for all children, a protective effect became apparent (HR = 0.7 95% CI 0.4-1.5).

Conclusions: While a difference in mortality between DTPa types was observed, this effect is most likely due to confounding by indication, with vaccine schedule variants received by children with impaired health.

899. Uptake and Predictors of TDaP Immunization During Pregnancy in Privately-Insured US Women, 2010-2013

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Background: In October 2012, the Advisory Committee on Immunization Practices (ACIP) issued a recommendation for pregnant women to receive tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (TDaP) immunization during every pregnancy, between 27 weeks and 36 weeks, 6 days gestation. Little is known about the national uptake of the recommendation in practice.

Objectives: To examine uptake and to identify individual, provider, and ecological predictors of compliance with the ACIP recommendation for prenatal TDaP immunization.

Methods: Using the MarketScan® Commercial Claims and Encounters database (2010-2013), we conducted a retrospective cohort study of pregnant women with deliveries (live births or stillbirths) that occurred at ≥20 weeks gestational age. TDaP immunization was identified using CPT procedure codes. Per the 2012 ACIP recommendation, guideline-concordance was defined as TDaP receipt between 27 weeks and 36 weeks, 6 days gestation. We calculated the monthly proportion of pregnancies to receive guideline-concordant TDaP. To identify predictors of guideline-concordant TDaP immunization since the ACIP recommendation (11/2012 – 12/2013), we used multivariable Cox proportional hazards regression analyses

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to estimate hazard ratios (HRs) and confidence intervals (CIs).

Results: We identified 956,445 eligible pregnancies. After the October 2012 recommendation, guideline-concordant TDaP immunization in pregnancy increased from 6% to 27% by December 2013. In multivariable analyses, strong predictors of guideline-concordant TDaP included maternal age (14-19 years: HR = 0.71 (95% CI: 0.67-0.75); 20-24 years: HR = 0.83 (0.80-0.85); 25-29 years: HR = 0.96 (0.93-0.98); vs. ≥30 years), nulliparity (0 previous children: HR = 1.09, 95% CI: 1.06-1.12; vs. ≥1 previous child), geographical region (north central: HR = 1.60 (95% CI: 1.56-1.64); west: HR = 1.31 (1.27-1.34); northeast: HR = 1.09 (1.06-1.13); vs. south), and residence in a metropolitan area (HR = 1.22, 95% CI: 1.18-1.26).

Conclusions: Timely TDaP immunization during pregnancy remains low. Implementation and dissemination strategies are needed to increase TDaP coverage among pregnant women.

900. Measles, Mumps, and Rubella (MMR) Vaccines Differ Considerably with Regards to Immediate Injection Pain: A Systematic Literature Review

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Background: Injection site pain associated with immunization is a significant source of anxiety and distress for vaccine recipients and parents. Pain at injection site may lead to vaccine hesitancy putting the individual and public at risk. A recent WHO position paper provides recommendations to mitigate pain and anxiety during immunization and calls for future research in this field. Some studies have compared the immediate pain associated with the administration of various formulations of MMR vaccines.

Objectives: We present here the results of a systematic literature review aiming at comparing the intensity of immediate pain at injection site experienced by children during and after vaccination with different MMR vaccines.

Methods: A systematic literature search was conducted in Pubmed, Embase and Cochrane to identify publications studying pain at injection site after immunization with widely used MMR vaccines. Immediate pain (acute pain as per Brighton Collaboration case definition) was defined as pain occurring at the time of injection or within 5 minutes thereafter.

Results: Four studies comparing the intensity of immediate pain at injection site experienced by children after immunization with MMR vaccines were identified. Various pain assessment tools and methods were used to quantify the intensity of pain. For instance, median difference in Visual Analog Scale scores were computed and compared between vaccine groups. All 4 studies showed significantly less immediate pain caused by one MMR vaccine (Priorix™, GSK Vaccines) compared to another one (MMR™-II, Merck & Co., Inc.).

Conclusions: To our knowledge, this review summarizes for the first time the available scientific evidence on the intensity of pain following different MMR vaccines. It highlights that MMR vaccines can differ in terms of immediate pain. Among the different parameters that may influence level of pain, vaccine diluent type and/or formulation may play an important role in generating immediate pain at the time of injection or in the minutes that follow.

901. Increased Incidence of Narcolepsy After the 2009 H1N1 Pandemic and Vaccination Campaign in Taiwan

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Background: In 2010–2011, several European countries and Canada observed an association between narcolepsy and H1N1 vaccines containing AS03® adjuvant, mostly in children and adolescents. Studies in China suggested that H1N1 infection could have played a role in triggering narcolepsy in children. In Taiwan, a nationwide campaign administered H1N1 vaccines without adjuvant or with MF59® adjuvant during November 2009–February 2010, covering 67% and 12% of persons aged 0–18 and ≥19 years.

Objectives: To compare incidence of narcolepsy before, during, and after the H1N1 2009 pandemic and vaccination in Taiwan.

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Methods: The study population included all individuals registered in the National Health Insurance databases during 2000–2012. Patients with narcolepsy were defined as those with a referral record for multiple sleep latency test (MSLT) and three or more ICD-9-CM codes 347* after an MSLT referral. We compared age-stratified (0–4, 5–18, 19–59, and ≥60 years) number of first-ever MSLT referral per 100,000 person-years (PY) for the prepandemic (January 2000–June 2009), pandemic/prevaccination (July–October 2009), and vaccination/postpandemic (November 2009–December 2012).

Results: Overall, 444 patients were newly diagnosed with narcolepsy over the 183.87 million PY of observation time (0.24 per 100,000 PY, 95% confidence interval [CI] 0.22–0.27). The highest incidence of narcolepsy was observed in the age group 5–18 years (0.70 per 100,000 PY, 95% CI 0.61–0.80). A significant increase in referrals for MSLT was observed in the pandemic/prevaccination and vaccination/postpandemic periods in the age groups 5–18 (incidence rate ratio [IRR] 3.39, 95% CI 2.11–5.44 and IRR 1.40, 95% CI 1.05–1.86) and 19–59 (IRR 2.90, 95% CI 1.67–5.02 and IRR 2.01, 95% CI 1.52–2.66) years, but not in other age groups.

Conclusions: H1N1 infection is more likely than H1N1 vaccination to contribute to this increase in incidence of narcolepsy. Controlled studies are being conducted to verify these ecological findings.

902. Comparison Of Different Collection Methods For Reported Adverse Events Following Pandemic And Seasonal Influenza Vaccination

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Background: During the 2009/2010 season, information on adverse events after administration of seasonal and pandemic influenza vaccines was collected by different active surveys in the Netherlands.

Objectives: To compare data from a paper-based questionnaire with data from a web-based questionnaire with respect to outcomes and target population, in order to guide future influenza vaccine safety monitoring.

Methods: The paper-based survey collected data from patients who attended primary care practices in the province of Utrecht for influenza vaccination. The web-based survey recruited participants from the general population all provinces of the Netherlands. To analyze the association between study approach and the reported local and systemic adverse events, a generalized linear mixed model was applied. We adjusted for age, gender, comorbidity, previous vaccination and socio-economic status score.

Results: In the web-based survey, systemic adverse events were significantly more often reported compared with the paper-based survey (OR: 1.15, 95% CI 1.01-1.30). There were important differences in the age groups that responded. The elderly were more represented in the paper-based survey where participants were recruited via GPs (79% ≥ 60 years) compared to 37% in the web-based survey where participants were recruited via internet.

Conclusions: The paper-based survey with recruitment of participants through GPs is more representative for the target group of influenza vaccination compared to the web-based survey with recruitment of participants via internet. A web-based approach with recruitment of participants via internet seems more suitable for situations where national representative information about adverse events is desirable. We recommend to use a combination of both approaches for future pandemic vaccine safety monitoring to comply with the recommendations of the European Medicines Agency.

903. Comparison Of The Tolerability Of Newly Introduced Childhood Vaccines In The Netherlands

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Background: In the Netherlands, the 7-valent conjugated Pneumococcal vaccine (PCV7) was replaced by the 10-valent vaccine (PCV10) and universal Hepatitis B vaccination has been introduced in 2011.

Objectives: To compare the tolerability of these different vaccine combinations to enable reliable information to parents.

Methods: A questionnaire study was conducted to assess the (differences in) tolerability of DTaP-IPV-Hib + PCV7 (PCV7-cohort), DTaP-IPV-Hib + PCV10 (PCV10-cohort) and DTaP-IPV-Hib-HepB + PCV10 (HepB-cohort). Parents were asked to report in questionnaires local and systemic adverse events (AEs) that developed in the week prior and in the week after vaccination of their infant at 2, 3, 4, and 11 months of age.

Results: For 29.0% and 29.4% infants of the PCV7-cohort, at least one local reaction was reported in the week after the first dose of DTaP-IPV (left leg) and PCV-7 vaccination (right leg). Significant more infants from the PCV10- (45.1%; $p=0.000$ and 44.6%; $p=0.000$) and HepB-cohort (42.6%; $p=0.000$ and 41.9%; $p=0.000$) reported at least one local reaction. This effect was less pronounced after the successive doses. Most of the infants experienced at least one systemic AE. After dose 4 this was higher for infants in the PCV10- (65.9%; $p=0.047$) and HepB-cohort (70.6%; $p=0.000$) compared to the PCV7-cohort (62.3).

Conclusions: Addition of antigens to a vaccine, i.e. 3 PCV types and Hepatitis B, resulted in a higher reactogenicity but the AEs were in general mild and transient. These results are useful for information purposes and for monitoring variations in rates of AEs over time.

904. Disease and Exposure Misclassification in Studies of Vaccine Effectiveness: A Simulation Tool

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Background: Studies of vaccine effectiveness (VE) rely on accurate identification of cases of vaccine-preventable disease and vaccination. In practice, diagnostic tests and clinical case definitions will not be perfect. Vaccination records or determination of vaccine exposure will present inaccuracies. Disease and exposure statuses may reciprocally affect each other's ascertainment (i.e. differential misclassification) and lead to bias in estimation of the true VE.

Objectives: We present a simulation tool to assess the impact of disease and exposure misclassification on VE estimates by different study designs, with examples a) Influenza, b) Pertussis VE estimation.

Methods: For each example, 1,000 simulations of a population of 50,000 were generated. Assumed VE's were 70% for Influenza and 80% for Pertussis; and for vaccination coverage, 10% and 95% respectively. Risk of disease due to vaccine preventable pathogens (attack rate) in non-vaccinees was assumed 15% for Influenza vs 30% risk of similar disease from non-vaccine pathogens. For Pertussis, 15% vs 10.5% risks applied. Sensitivities and specificities of disease and exposure classification were allowed to vary. For each simulation, VE estimates based on case-control, cohort, test-negative and case-coverage (screening) designs were made and assessed graphically alongside bias and mean squared error.

Results: The sensitivity and specificity parameters had differing impacts, more noticeable than between study designs. Decreased specificity of exposure classification (poorer identification of non-vaccinees) had greatest impact for Influenza VE estimation. Conversely decreased sensitivity of exposure classification (poorer identification of vaccinees) had greatest impact for Pertussis. The simulations of non-differential misclassification gave rise to underestimation of VE, whereas certain configurations of differential misclassification led to overestimation.

Conclusions: As seen here, the impact of misclassification depends on study scenario. We hope the simulation tool can be used by researchers to guide better design, conduct and interpretation of future VE studies.

905. Systematic Review and Quantitative Synthesis of Evidence to Support Regulatory Review of Oncaspar for Treatment of Acute Lymphoblastic Leukemia (ALL)

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Background: An EU marketing authorization application (MAA) was submitted for Oncaspar (pegaspargase) for treatment of patients with ALL, the most common pediatric cancer. During MAA review the EMA requested evidence to support the comparability of Oncaspar with native E. coli asparaginase (native ASP), an older asparaginase product.

Objectives: To assess the relative benefit of Oncaspar vs native ASP in newly diagnosed pediatric ALL pts in terms of event free survival (EFS) and overall survival (OS).

Methods: A systematic approach was taken to identify all available evidence for newly diagnosed pts treated in pediatric ALL protocols using Oncaspar or native ASP. Randomized and observational studies were included. Outcomes were EFS and OS. Safety/immunogenicity was also examined. Feasibility was explored in this order for: Direct comparison meta-analysis (MA) if ≥ 2 head to head trials were found, indirect comparison (network MA) if a common comparator could be identified or separate product MAs (pooled estimates) of Oncaspar and native ASP using a random effects model.

Results: There were 39 studies that met criteria for abstraction; 13 used Oncaspar and 27 used native ASP. Direct MA was not feasible as one head to head study was identified. Also, no common comparator made indirect MA infeasible. The individual product MA was done for standard (S) and high (H) risk pt categories. In S risk pts treated with native ASP (n = 537), 5-yr EFS was 82% (95% CI 75-88) vs. 89% (95% CI 85-93) for Oncaspar (n = 7,067). OS was 81% (95% CI 67-96) for native ASP and 85% (95% CI 64-100) for Oncaspar. For H risk pts. treated with native ASP (n = 3,367), 5 yr EFS was 71% (95% CI 67-76) vs 80% (95% CI 75-86) for Oncaspar (n = 6,843) and OS was 73% (95% CI 59-86) vs 80% (95% CI 73-87), respectively.

Conclusions: This SLR and MA was undertaken to synthesize existing evidence in support of the Oncaspar marketing authorization. The results support a favorable effectiveness profile of Oncaspar vs native ASP in the treatment of newly diagnosed ALL pts with a less frequent administration. Oncaspar is now approved for treatment of ALL pts in the EU.

906. Treatment Regimens and Duration of Lines of Therapy in Medicare-Enrolled Patients with Multiple Myeloma

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Background: Multiple myeloma (MM) patients are often treated with multiple lines of therapy (LOT).

Objectives: To describe the use of drug regimens by LOT and the duration of LOT in Medicare MM patients.

Methods: Using a validated algorithm, adult MM patients (2008-2011) were identified from the 100% Medicare hematologic cancer file. Patients receiving treatments were identified for LOT from 1 to 4 lines. Drug regimens were based on National Comprehensive Cancer Network MM treatment guidelines and were identified using National Drug Code and Health Care Procedure Coding System codes. Drug regimens included proteasome inhibitor (PI): bortezomib; immunomodulatory agents (IMiD): lenalidomide, thalidomide; PI/IMiD combinations; and other chemotherapies. Duration of LOT was defined from first drug prescription or administration to the start of the subsequent LOT, death, disenrollment, or end of data (12/31/2012).

Results: 15474, 8308, 3878, and 1608 MM patients initiated 1st, 2nd, 3rd, and 4th LOTs, respectively. Mean (SD) age at start of first regimen was 75.1 (8.8) years; 54.4% were female and 77.5% were white. Regimen distributions by LOT were similar for lines 1-4 with 24-30%, 28-30%, 10-12%, and 31-37% of patients treated with PI, IMiD, PI/IMiD, and other chemotherapies, respectively. The mean (median) duration of LOT 1, 2, 3, and 4 was 386 (284), 329 (241), 268 (199), and 232 (177) days, respectively.

Conclusions: In the Medicare MM population, the distribution of treatment regimens including PI, IMiD drugs, and other chemotherapies were similar across lines 1 through 4. The duration of LOT decreased from line 1 to 4. These data provide insights into real world use of MM treatments.

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907. Transitions Across Different Lines of Therapy in Medicare-Enrolled Patient Populations with Multiple Myeloma

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Background: Multiple myeloma (MM) patients are often treated with multiple lines of therapy (LOT). However, transition rates and reasons for not transitioning across LOT have not been well characterized.

Objectives: To characterize LOT transition rates and reasons for advancing or not advancing across LOT in an United States MM patient population.

Methods: Using a validated algorithm, adult MM patients (2008-2011) were identified from the 100% Medicare hematologic cancer file. Patients receiving treatments were identified for LOT up to 5 lines. Patients advanced LOT after a 90 day gap in all treatments (break) or when a drug was added to a regimen after 90 days (direct switch). Claims-based transition across LOT was determined using a previously published algorithm. LOT transition rates, reasons for advancing to the next line and disposition of those who did not advance were determined.

Results: 15474, 8308, 3878, 1608 and 604 MM patients initiated LOT 1, 2, 3, 4 and 5, respectively; accounting for transition rates of 54%, 47%, 42% and 38% from lines 1 - 4. Of those who initiated a 1st line treatment and advanced to 2nd line treatment (n = 8308), 4293 (52%) had a break in current treatment before line advancement while 4015(48%) switched directly. Similar patterns of advancement were observed for the other LOTs: 48% (of 3878 patients) had a break before 3rd LOT and 52% switched directly; 51% (of 827 patients) had a break before 4th LOT and 49% switched directly; approximately half each of 605 patients had a break before 5th LOT or switched directly. The reasons for not advancing LOT were death (52%-35%, with increasing LOT), censoring due to study end (41%-63%), and cessation of Medicare coverage (7%-2%).

Conclusions: Transition rates across LOT decreased with increasing LOT as expected. While half of the patients advance LOT directly, the other half experience a break in treatment between LOTs.

908. Risk of Skin Cancer in Users of Topical Tacrolimus, Pimecrolimus and Corticosteroids. JOint European Longitudinal Lymphoma and Skin Cancer Evaluation (JOELLE) Study

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Background: Topical tacrolimus is indicated for the treatment of moderate to severe atopic dermatitis, and topical pimecrolimus for the treatment of mild to moderate atopic dermatitis. Data on the risk of skin cancer associated with use of these medications are scarce.

Objectives: To estimate incidence rate ratios (IRRs) of malignant melanoma (MM) and non-melanoma skin cancer (NMSC) comparing new users of tacrolimus and pimecrolimus with current users of moderate- to high-potency topical corticosteroids (TCS), and users of TCS with general population untreated subjects.

Methods: Cohort study in the PHARMO Database Network (Netherlands), the Danish and Swedish national registers, and the Clinical Practice Research Datalink (United Kingdom), with RTI Health Solutions acting as coordinating/pooled analysis center. New users of tacrolimus and pimecrolimus were frequency matched to users of TCS on twentiles of propensity scores; users of TCS were individually

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matched to untreated subjects on age, sex, region, and calendar year. We estimated IRRs and 95% confidence intervals (CI) using Mantel-Haenszel methods.

Results: We included (a) 19,948 children and 66,127 adults treated with tacrolimus matched with 79,700 children and 264,482 adults treated with TCS; (b) 23,840 children and 37,417 adults treated with pimecrolimus matched with 90,268 children and 149,671 adults treated with TCS; and (c) 79,040 children and 257,074 adults untreated with any study medication. In adults, the adjusted IRR (95% CI) for tacrolimus vs. TCS was 0.90 (0.66-1.22) for MM and 1.08 (0.98-1.19) for NMSC. The IRR for pimecrolimus vs. TCS was 1.16 (0.87-1.56) for MM and 1.20 (1.07-1.35) for NMSC. IRRs for TCS vs. untreated were 0.87 (0.74-1.03) for MM and 1.19 (1.11-1.27) for NMSC. In children, the number of events was too small to draw conclusions.

Conclusions: These results suggest little or no effect of tacrolimus and pimecrolimus on the risk of skin cancer. Estimates were close to the null, and residual confounding by severity of atopic dermatitis and surveillance bias cannot be ruled out.

909. Phosphodiesterase Type 5 Inhibitors And Risk Of Malignant Melanoma: Matched Cohort Study Using Primary Care Data From The UK Clinical Practice Research Datalink

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Background: Laboratory evidence suggests that the use phosphodiesterase type 5 (PDE5) inhibitors could affect melanoma risk. Two major epidemiological studies have investigated this and come to differing conclusions.

Objectives: We aimed to investigate whether PDE5 inhibitor use is associated with an increased risk of malignant melanoma, and whether any increase in risk represents a causal relationship.

Methods: We conducted a matched cohort study using primary care data from the UK Clinical Practice Research Datalink. All men initiating a PDE5 inhibitor and with no prior cancer diagnosis were matched on age, diabetes status, and general practice, to up to four unexposed controls. Ever use of a PDE5 inhibitor was investigated as the exposure, and the primary outcome was malignant melanoma. Basal cell carcinoma, solar keratosis, and colorectal cancer were investigated as negative control outcomes to exclude bias. Hazard ratios were estimated from Cox models, stratified by matched set, and adjusted for potential confounders.

Results: 145,104 men with ≥1 PDE5 inhibitor prescription, and 560,933 unexposed matched controls were included. 1,315 incident malignant melanoma diagnoses were observed during 3.44 million person-years of follow-up (mean 4.9 years per person). After adjusting for potential confounders, there was weak evidence of a small positive association between PDE5 inhibitor use and melanoma risk (HR = 1.14, 95% CI 1.01-1.29). A similar increase in risk was seen for the two sun-related negative control outcomes (HR = 1.15, 1.11-1.19 for basal cell carcinoma, and HR = 1.21, 1.17-1.25 for solar keratosis), but there was no increased risk for colorectal cancer (HR = 0.91, 0.85-0.98). In a post-hoc analysis, there was strong evidence that solar keratosis was associated with future use of PDE5 inhibitor (OR = 1.28, 1.23-1.34), suggesting that men with high sun exposure were more likely to become PDE5 users.

Conclusions: Our results were not consistent with PDE5 inhibitors causally increasing melanoma risk, and strongly suggest that observed risk increases are driven by greater sun exposure among exposed patients.

910. 'Real World' Ipilimumab Survival Data in Ireland

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Background: Ipilimumab is licensed for the treatment of adults with advanced (unresectable or metastatic) malignant melanoma. In Ireland, the Oncology Drug Management System (ODMS) was in July 2012; it allows direct hospital reimbursement for approved high cost anti-cancer drugs for

individual patients. Ipilimumab is reimbursed through this scheme.

Objectives: The objective of this study was to analyse Irish real life ODMS patient level data for ipilimumab and to estimate mean overall survival.

Methods: Anonymised data on all patients who had received ≥1 dose of ipilimumab (June 2012 - May 2015) through the ODMS was extracted. Patient demographics were examined. The Kaplan-Meier survival curve for the cohort was constructed. Here, it was assumed that the reimbursement claim date was reflective of the date of administration. Patients who had not received a full course of ipilimumab (4 doses) were censored at the time of the last dose. The Kaplan-Meier curve was extrapolated with a range of parametric models. The best fit curve was chosen using AIC/BIC statistics. Mean overall survival was estimated. Analyses were performed in Excel 2010 and R 2.10.1.

Results: A total of 202 individuals who had received ≥1 dose ipilimumab over the defined period were identified. Mean age was 59.1 years (SD ±14.0); 58.9% were male. All 4 doses had been received by 59.4% of patients. The Exponential extrapolation was the best fit for the Kaplan-Meier curve. The estimated mean overall survival with this extrapolation is 13.6 months (95%CI 11.3, 16.5).

Conclusions: The mean overall survival in our cohort if lower than that which has been estimated previously using pivotal trial data.

911. Cardiovascular Risks of Exogenous Testosterone Use Among Men: A Systematic Review and Meta-Analysis

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Background: Exogenous testosterone products are widely used for symptoms of age-related hypogonadism. However, their cardiovascular safety remains uncertain.

Objectives: We evaluated whether exogenous testosterone therapy is associated with an increased risk of serious cardiovascular events, as compared to other treatments or placebo.

Methods: We searched Pubmed, MEDLINE, EMBASE, Cochrane Collaboration Clinical Trials, clinicaltrials.gov, and the US Food and Drug Administration website, through August 28, 2015. Randomized controlled trials (RCTs) and observational studies which enrolled men > 18 years receiving testosterone for > 3 days were included. Two reviewers independently conducted all stages of review, with adjudication by a third reviewer when necessary. The primary outcomes were death due to all causes, myocardial infarction, and stroke. Secondary outcomes included heart failure, arrhythmia, and cardiac procedures. The risk of bias of RCTs and observational studies was evaluated using the Cochrane Collaboration tool and the Newcastle and Ottawa scale, respectively. The Peto odds ratio was used for meta-analysis. PROSPERO (#CRD42015019259).

Results: A total of 39 RCTs and 10 observational studies were included. Meta-analysis was conducted on 30 RCTs. Compared to placebo, exogenous testosterone treatment did not show any statistically significant increase in risk of myocardial infarction (odds ratio [OR] 0.87, 95% confidence interval [CI] 0.39-1.93, 16 RCTs), stroke (OR 2.17, CI 0.63-7.54, 9 RCTs) or mortality (OR 0.88, CI 0.55-1.41, 20 RCTs). Sensitivity analysis showed similar results. The design and methodology of the studies were poorly reported. Observational studies showed conflicting results with marked clinical and methodological heterogeneity.

Conclusions: We did not find any significant association between exogenous testosterone treatment and myocardial infarction, stroke or mortality, although the evidence was imprecise. Our results may differ from previous reviews because of choice of outcomes and analytic approaches used. The low quality of the evidence precludes definitive conclusion.

912. Association Between Exogenous Testosterone and Cardiovascular Events: An Overview of Systematic Reviews

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Background: Evidence remains conflicting about whether exogenous testosterone increases cardiovascular events.

Objectives: We systematically evaluated evidence of the direction and magnitude of association between exogenous testosterone and cardiovascular events; exploring discordance between existing systematic review findings.

Methods: Two independent reviewers screened 950 full texts of 21,903 initial abstracts, and identified all published systematic reviews or meta-analyses evaluating cardiovascular effects of exogenous testosterone on males aged 18 years or older from January 1966 through November 2015. We extracted data on study characteristics; analytic methods; key findings; and applied a checklist for assessing the methodological quality of systematic reviews (AMSTAR).

Results: We identified seven systematic reviews that included six meta-analyses. The number of included trials ranged from 3 to 75 and study participants ranged from 308 to 5464. Four meta-analyses reported no significant association between exogenous testosterone and cardiovascular events (odds ratio [OR] 1.14, 95% confidence intervals [CI] 0.59-2.20 by Calof et al; OR 1.82, CI 0.78-4.23 by Haddad et al; relative risk [RR] 1.12, CI 0.70- 1.81 by Fernandez-Balsells et al; Mantel-Haenszel OR 1.07, CI 0.69-1.65 by Corona et al. A qualitative review by Carson et al also reported that testosterone does not increase cardiovascular risk. Conversely, two meta-analyses reported a significant association between testosterone and cardiovascular risk (OR 1.54, CI 1.09-2.18 by Xu et al; and RR 2.20, CI 1.45-3.55 by Borst et al). Four reviews examined disaggregated cardiovascular outcomes while three examined composite events. We observed significant clinical heterogeneity, differing statistical methods, and variable methodological quality. AMSTAR scores ranged from 1 to 9 out of 11.

Conclusions: Different outcomes, analytic methods and study quality may explain the discordant systematic reviews. Given the challenge of adequately powering clinical trials for these rare outcomes, rigorous observational studies examining major cardiovascular outcomes are needed to help clarify this association.

913. Risk of Gynecomastia with Use of 5-Alpha Reductase Inhibitors for Benign Prostatic Hyperplasia

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Background: Case reports and clinical trials suggest that gynecomastia occurs in excess among men who use 5-alpha reductase inhibitors (5ARIs).

Objectives: To estimate the risk of gynecomastia with use of 5ARIs to treat benign prostatic hyperplasia (BPH).

Methods: We conducted a cohort study with a nested case-control analysis using the United Kingdom Clinical Practice Research Datalink. We identified men with BPH who were free from gynecomastia and its risk factors (e.g. pituitary or adrenal cancer, liver disease, renal failure or hypogonadism) prior to cohort entry. Patients entered the cohort at age 40 years or older and at least 3 years after the start of their electronic medical record. We calculated person-days of exposure in the following categories: 5ARIs (alone or in combination with alpha blockers (ABs)), AB Only, or unexposed to 5ARIs and ABs. Cases were men who had a first-time diagnosis of gynecomastia recorded during follow-up. We calculated crude incidence rates (IRs) and adjusted incidence rate ratios (IRRs) with 95% confidence intervals (CIs). We also conducted a nested case-control analysis to control for major confounders and calculated adjusted odds ratios (ORs) with 95% CIs.

Results: The IR of gynecomastia was 40.2 per 10,000 person-years (PY) (95% CI 35.6-45.2) for 5ARI users, 12.2 per 10,000 PY (95% CI 10.7-13.9) for AB Only users, and 7.2 per 10,000 PY (95% CI 6.7-7.8) for unexposed men. Compared to unexposed men, the risk of gynecomastia was elevated for 5ARI users (IRR = 3.55, 95%CI 3.05-4.14), whereas the IRR was 1.15 (95%CI 0.98-1.34) for AB Only users. In the

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case-control analysis, the adjusted OR was 3.31 (95% CI 2.66-4.10) for 5ARI users in comparison to unexposed men and there was no elevation in risk for ABs Only users. The increased risk for gynecomastia with use of 5ARIs persisted regardless of the number of prescriptions, exposure timing, and with or without concomitant prescriptions for drugs known to be associated with gynecomastia.

Conclusions: In men with BPH, there was a greater than 3-fold elevation in risk of gynecomastia for users of 5ARI compared to unexposed men and users of ABs only.

914. Population-Based Comparison of the Risks of Serious Adverse Events from Intermittent versus Continuous Androgen Deprivation Therapy in Advanced Prostate Cancer Patients

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Background: Randomized trials have reported that intermittent androgen deprivation therapy (IADT) for the treatment of advanced prostate cancer (PCa) improves quality of life more than conventional continuous administration of ADT (CADT) while providing a similar survival benefit. It is unknown whether IADT lowers the risk of ADT-related adverse events associated with CADT use.

Objectives: To compare risk of ADT-associated serious adverse events in IADT versus CADT.

Methods: We conducted a retrospective cohort study of 9,772 advanced PCa patients aged 66 or older, diagnosed during 2002- 2011 who received ADT as primary treatment for their PCa. We identified incidence of serious adverse events, including acute myocardial infarction, stroke, heart failure, type-2-diabetes, and fracture, using inpatient and outpatient claims. We used the cox-proportional hazard model to assess hazard ratios (HRs) of ADT-associated serious adverse events in IADT and CADT users.

Results: The cohort included 5,026 and 4,746 men with metastatic and non-metastatic PCa at diagnosis. A total of 1,709 (17%), 678 (7%), and 945 (10%) men were newly diagnosed with a serious cardiovascular event, diabetes, or fracture, respectively, during the first 5 years after ADT initiation. We found IADT to be associated with a lower risk of heart failure than CADT in the metastatic group (HR = 0.58, 95%C.I. = 0.36- 0.92, p = 0.02). We did not find differences in risk of other serious cardiovascular events, diabetes, or fracture between IADT and CADT.

Conclusions: This large population-based study showed that compared to CADT, IADT may not alter the risk of serious ADT-associated adverse events in advanced PCa. IADT may have the potential to lower heart failure risk among metastatic PCa patients with ADT. Physicians should consider the potential risks and benefits when initiating ADT among elder men with advanced PCa.

915. Oral Contraceptives and VTE Across the Sentinel Data Network – An IMEDS Evaluation Pilot Assessment

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Background: The risk of venous thromboembolism (VTE) with oral contraceptives (OCs) is well documented. Recently, questions have been raised about an increased risk of VTE of 4th generation OCs (containing drospirenone) compared to 2nd generation (containing levonorgestrel).

Objectives: This IMEDS Evaluation pilot used a distributed network of FDA Sentinel data partners to examine the rate of VTE in new users of 2nd and 4th generation OCs using the standardised data analytics capabilities of the IMEDS Evaluation pilot.

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Methods: The analytic cohort consisted of women aged 15-44 who were new OC users (2nd or 4th generation). Patients with VTE risk factors were excluded.

Dispensings were defined by National Drug Code in outpatient pharmacy claims. VTE was defined by ICD9 codes 415.1 or 453.xx, occurring in the inpatient or emergency department setting.

Nine Sentinel data partners participated. Publicly available Sentinel modular programs were used. Feasibility data were reviewed to inform use of the more complex modular analyses. Consistent with typical FDA use of these programs, the analysis did not include a direct comparison or statistical testing; rather, the results include rates of VTE stratified by age, sex, and year.

Results: Between January 1, 2008 and April 30, 2015 there were 350572 new users of 4th generation OCs and 317363 new users of 2nd generation OCs. There were 158 new VTE events for 4th generation OCs, and 121 for 2nd generation OCs. The rate of VTE events per 10000 person-years was 8.56 for 4th generation and 6.58 for 2nd generation OCs (interquartile range from 5.86 to 9.23 for 4th generation OCs, and from 0 to 7.07 for 2nd generation OCs across the data partners).

Conclusions: In line with the literature, rates of VTE were greater for 4th generation than 2nd generation OCs. Limited variation was seen across data partners, although some partners had few events. Limitations include lack of confounding control, no direct comparisons or matching, and VTE defined only by diagnosis code. The pilot shows the value of the large distributed data network in exploring safety issues by a pharmaceutical sponsor.

916. Testosterone Replacement Therapy (TRT) and Risk of Acute Myocardial Infarction (AMI): An Administrative Healthcare Claims Study

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Background: Conflicting and inconsistent data surrounding the benefit and risk of TRT use justifies the need for further investigating the potential risk of AMI for patients undergoing TRT.

Objectives: To investigate whether an association exists between TRT use and the risk of AMI.

Methods: This retrospective cohort study used the Truven Marketscan database to compare the crude incidence rate of AMI and adjusted hazard ratio (HR) among adult patients treated with any testosterone product versus two propensity score (PS) matched comparator cohorts: (1) untreated hypogonadal and (2) PDE5i-treated patients.

Results: A total of 207,176 patients were identified for the treated and untreated cohorts (mean age, 51.8 ± 11.4 vs. 51.8 ± 12.6 years respectively) after PS matching and balanced baseline risk factors. Using a Cox regression model, no statistically significant association was found among TRT treated patients overall (HR: 0.99; 95% CI: 0.90, 1.09), by age groups, or by prior cardiovascular disease (CVD). When stratified by different routes of administration, the association between injectable TRT and AMI was statistically significant (HR: 1.55; 95% CI: 1.24, 1.93) but was not for gel, patch, or other non-specified routes. A total of 198,528 patients were identified for the TRT and PDE5i treated cohorts after PS matching (mean age, 52.4 ± 11.4, 52.3 ± 11.5 years). TRT use was not statistically significantly associated with AMI (HR: 1.00; 95% CI: 0.95, 1.07); however, the association reached statistical significance among patients older than 65 years (HR: 1.16; 95% CI: 1.03, 1.31) and those with prior CVD (HR: 1.12; 95% CI: 1.02, 1.23).

Conclusions: When compared to untreated hypogonadal patients, no statistically significant association was found between AMI and overall TRT use. Analysis stratified by route of administration was statistically significant only for injectable TRT. Inconsistent findings were seen in the subgroup analyses (elderly, prior CVD) using different comparators (TRT treated vs PDE5i treated; TRT treated vs untreated hypogonadal).

917. Effects of Supplemental Intravenous Agents to Mitigate Peri-Operative Complications Arising from Inhaled Anesthetics

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Background: Inhaled anesthetics have several known complications in the peri-operative period, including post-operative nausea and vomiting (PONV),

delirium, hyperalgesia, triggering of malignant hyperthermia and other side effects. The use of intravenous (IV) agents (e.g. propofol, remifentanil, fentanyl, etc.) has been suggested as means to mitigate these risks by decreasing or eliminating patient's exposure to inhaled anesthetics.

Objectives: The objective of this study was to assess the difference in post-op side effects and post-anesthesia care unit (PACU) times in patients receiving inhalational only versus inhalational and IV anesthesia, specifically Remifentanil.

Methods: Using structured EMR data, we identified a cohort of anesthetized surgical patients within the University of Utah hospital system. Post-surgical recovery times, amount of exposure to inhaled anesthetics, incidence of PONV and other post-op morbidities were assessed. Multivariable models controlled for age, sex, BMI, surgical category, length of surgery, and anesthesia type.

Results: Percentages of inhaled anesthetics were decreased when used concomitantly with remifentanil. The relative decrease in end-tidal anesthetic was: Nitrous oxide 29.1%, Isoflourane 7.9%, Desflourane 21.4% and Sevoflourane 17.4%; all with $p<0.001$. We conjecture that this decrease in inhaled anesthetic will also lead to decreased side-effect of inhaled anesthetics such as post-op recovery and PONV. Indeed, PACU recovery times were significantly lower in patients receiving IV remifentanil compared to those who did not. The adjusted difference in PACU time was -5.0 min for patients receiving Remifentanil (955 CI -8.6, -1.4). PONV was also reduced in patients with IV remifentanil.

Conclusions: The use of IV anesthetics, specifically remifentanil, was associated with shorter post-op recovery times and reduced patient exposure to inhaled anesthetics, independent of surgery type and duration. These findings suggest that the use of IV anesthetics decreases the amount of inhaled anesthetics patients are exposed to and leads to a decrease in peri-op morbidity and side-effects of inhaled anesthetics.

918. Elevated Bladder and Prostate Cancer Rates Following Initiation of OAB Medication: Findings from a Danish Registry

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Background: Symptoms reported by patients with undiagnosed genitourinary cancers may be confused with those of overactive bladder (OAB) syndrome.

Objectives: We studied incidence rates (IRs) of genitourinary cancers and other common cancers in initiators of antimuscarinic OAB drugs in the Danish national registries, overall and stratified by time since first prescription.

Methods: The study cohort comprised new users of oxybutynin, tolterodine, solifenacin, fesoterodine, trospium, or darifenacin (2004-2012), aged $\geq$ 18 years, with no history of cancer before entry. Follow-up ended with cancer diagnosis, death, disenrollment, or end of study. Drug exposure was ascertained from the Danish National Prescription Registry, and cancer outcomes, from the Danish National Registry of Patients and the Danish Cancer Registry. IRs per 1,000 person-years and 95% confidence intervals (CIs) were estimated overall and by categories of months since cohort entry (MSCE) for each study cancer (bladder, breast, colorectal, lung, melanoma, non-Hodgkin lymphoma [NHL], pancreas, prostate, renal, and uterine).

Results: The study cohort included 72,917 patients (60% women, mean age at entry 66 years); 3,475 patients (1,832 men; 1,643 women) developed study cancers during 259,072 person-years. The most frequent study cancers were prostate (881; 25.4% of study cancers), breast (658; 18.9%), lung (534; 15.4%), colorectal (434; 12.5%), and bladder (369; 10.6%). The overall study cancer crude IR was 13.4 (95% CI, 13.0-13.9). Cancer IRs did not vary by OAB drug used. Bladder cancer IR (95% CI) was highest for $<$ 6 MSCE (4.2; 3.6–5.0), lower for 6 to $<$ 12 MSCE (1.3; 0.9–1.7) and thereafter. Prostate cancer IR was also highest for $<$ 6 MSCE (23.3;

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20.8–26.0), lower for 6 to < 12 MSCE (8.8; 7.3–10.6), and lower thereafter. Other cancer IRs did not show this effect of time since cohort entry.

Conclusions: Protopathic and/or detection bias are plausible explanations for higher IRs of bladder and prostate cancers in the first 6 months after starting OAB drug treatment. These findings are in line with results from other studies and must be considered in etiologic studies of OAB drugs and cancer risk.

919. Cancer Risk in Users of Antimuscarinic Drugs for Overactive Bladder: A Cohort Study in the Swedish National Registers

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Background: Cancer risks associated with the use of individual drugs to treat overactive bladder (OAB) are not known.

Objectives: In preparation for a postauthorization safety study for mirabegron, a drug with a novel mechanism of action to treat OAB, we assessed the risk for 10 common cancers in users of antimuscarinic OAB drugs.

Methods: We identified new users of tolterodine, solifenacin, fesoterodine, darifenacin and oxybutynin ≥18 years old without cancer or HIV from the Swedish National Registers in years 2006-2012. We assessed two sex-specific composite cancer endpoints and the 10 individual cancers (lung/bronchus, colon/rectum, skin melanoma, bladder, non-Hodgkin lymphoma, kidney, pancreas, prostate, female breast, and uterus). We estimated age-sex-standardized incidence rates (IRs) per 1,000 person-years and 95% confidence intervals (CIs) for ever exposure to the study drugs overall and in strata of time since start of treatment.

Results: The cohort of 130,944 patients had a mean age of 66 years; 60% were women. The most commonly used OAB drugs were tolterodine, solifenacin and fesoterodine. During follow-up (mean 3.2 years), 5,653 patients (4.3%) were diagnosed with any of the study cancers, most frequently prostate (1,530; 27%), breast (961; 17%), or colorectal (888; 16%) cancer.

For all study drugs combined, the IR (95% CI) for the composite endpoints was 10.0 (9.6-10.4) in women and 19.4 (18.7-20.1) in men. For each type of cancer, IRs were similar across individual drugs: prostate cancer, IRs ranged from 8.6 (6.2-11.0) for oxybutynin to 10.2 (9.4-11.1) for solifenacin; female breast cancer, 3.4 (2.7-4.1) for fesoterodine to 4.0 (3.3-4.7) for darifenacin; colorectal cancer, 1.6 (1.2-2.0) for fesoterodine to 2.4 (1.7-3.1) for oxybutynin. Some less common cancers had larger variations by individual drugs. IRs for bladder and prostate cancer were highest in the first 6 months after treatment start.

Conclusions: Based on age-sex standardized IRs, no antimuscarinic OAB drug seemed to carry increased cancer risks. IRs were higher during early treatment, driven by prostate and bladder cancer, which is consistent with protopathic bias or surveillance bias.

920. Do Individual Antimuscarinic Drugs to Treat Overactive Bladder Have Different Cardiovascular Risks? A UK CPRD Cohort Study

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Background: Users of drugs to treat overactive bladder (OAB) have been reported to have a higher prevalence of cardiovascular (CV) comorbidities.

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Objectives: We investigated whether the risk of acute myocardial infarction (AMI), stroke, major adverse cardiovascular events (MACE), CV mortality, and all-cause mortality differed by antimuscarinic OAB drug.

Methods: The study cohort consisted of new users of oxybutynin, tolterodine, solifenacin, fesoterodine, trospium, or darifenacin ≥18 years old in the Clinical Practice Research Datalink (CPRD), 2004-2012. Follow-up ended with a study endpoint, cancer, HIV, death, disenrollment, or end of study. Exposure was ascertained from general practitioner (GP) prescriptions, and outcomes and covariates from GOLD, HES, ONS, and questionnaires completed by GPs. We estimated age-sex–standardized incidence rates (IRs) per 1,000 person-years and adjusted incidence rate ratios (IRRs) compared with current use of any other OAB drug. We first estimated propensity scores for drug use at baseline, stratified on deciles of propensity score among the exposed, and pooled the stratified IRRs using the Mantel-Haenszel approach.

Results: The study cohort included 119,912 new users of OAB drugs: mean age at cohort entry, 62 years; 70% female; mean follow-up, 3.3 years (range, 1 day to 9 years). Of all index therapy episodes, 33% were for oxybutynin, 31% for tolterodine and 27% for solifenacin.

For current use of any OAB drug, the standardized IR (95% confidence interval [CI]) was 4.9 (4.5-5.3) for AMI, 6.0 (5.6-6.4) for stroke, 4.5 (4.2-4.9) for CV mortality, 12.2 (11.6-12.8) for MACE, 19.9 (19.1-20.6) for all-cause mortality.

IRRs for CV endpoints were generally ~1 for individual antimuscarinic OAB drugs except for oxybutynin and solifenacin. The IRR (95% CI) for current use of oxybutynin was 1.3 (1.1-1.4) for MACE and 1.4 (1.3-1.5) for all-cause mortality; for current use of solifenacin, 0.7 (0.6-0.8) for MACE, 0.7 (0.6-0.7) for all-cause mortality.

Conclusions: Compared to current use of other study drugs combined, the risk for MACE and all-cause mortality was increased in users of oxybutynin and decreased in users of solifenacin.

921. Withdrawn by Author

922. Risk of Major Adverse Cardiovascular Events Associated with Biologic Therapies in Patients with Plaque Psoriasis: Systematic Review and Meta-Analysis of Randomised Controlled Trials

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Background: Concerns about anti-interleukin (IL)-12/23 therapies increasing risk of major adverse cardiovascular events (MACE: myocardial infarction, cerebrovascular accident, or cardiovascular death) in patients with psoriasis have been raised. However, the potential association between biologic therapies and MACE in patients with plaque psoriasis is still unclear.

Objectives: To perform a meta-analysis of randomised controlled trials (RCTs) evaluating risk of MACE in adults with plaque psoriasis treated with biologic therapies.

Methods: Systematic searches for RCTs reporting adverse events in adults with plaque psoriasis receiving at least 1 licensed dose of biologic therapy, including tumour necrosis factor inhibitors (TNFi; adalimumab, etanercept, or infliximab), anti-IL-12/23 (ustekinumab), or anti-IL-17A (secukinumab) therapy. Extracted data were meta-analysed (RevMan 5.3) and the Peto odds ratio (OR) with 95% confidence interval (CI) was calculated. I^2 statistics were used to assess heterogeneity.

Results: Overall, 35 RCTs involving 15,079 patients were included. MACE were not observed in 26 RCTs, while 9 RCTs reported 10 MACE in patients receiving biologics or placebo during the randomised controlled phase. Exposure to biologic therapy was not associated with MACE (OR 1.62; 95% CI, 0.39–6.65). No associations with MACE were observed with TNFi (OR 0.67; 95% CI, 0.10–4.63), anti-IL-12/23 therapy (OR 4.48; 95% CI 0.24-84.77) and anti-IL-17A therapy (OR 4.52, 95% CI 0.24 – 86.22). Using Mantel-Haenszel fixed-effects model with absolute risk differences as sensitivity analysis also generated

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similar results. No heterogeneity was found among these comparisons.

Conclusions: In this meta-analysis of RCT data, biologic therapies were not associated with MACE. Current evidence is limited and the results can only be generalizable to RCT population. Thus, adequately powered, population-based studies are needed to assess the long-term impact of biologic therapies on MACE in patients with plaque psoriasis.

923. Development of a Prospective, Non-Interventional, Longitudinal, Multicenter Registry Study of Patients Initiating a New Course of Drug Therapy for Overactive Bladder (OAB)– PERSPECTIVE

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Background: Management of overactive bladder (OAB) often involves antimuscarinics, though newer therapies for OAB including mirabegron (a beta-3 agonist) have been approved worldwide. Current evidence on the real-world use of OAB pharmacotherapies is limited.

Objectives: To identify demographic and clinical factors, treatment patterns and patient reported outcomes (PROs) utilizing a new international registry of OAB patients. Outcomes will include differences in OAB treatment patterns (e.g., persistence, switching, reasons for discontinuation), comorbidities, adjunctive non-pharmacologic therapy and PROs in patients on mirabegron vs. antimuscarinics.

Methods: PERSPECTIVE is a prospective, longitudinal observational registry of patients initiating a new course of OAB treatment with either mirabegron or an antimuscarinic. Based on sample size calculations, target enrollment is 1500 patients (600 mirabegron and 900 antimuscarinic) from 100-120 centers in the US (85%) and Canada (15%). PROs using OAB-validated scales (OAB Questionnaire Short-Form, Patient Perception of Bladder Condition, EuroQol-5D, OAB Treatment Satisfaction Questionnaire) are collected at baseline, months 1, 3, 6, and 12, and ad-hoc points when patients have switched/discontinued their current OAB medication. If physician visits occur after baseline, clinical data are prospectively recorded by the investigator and are collected from patients' medical records. The recruitment period is 16 months, targeting gynecology, urology, and primary care sites. Each patient is followed for up to 12 months.

Results: With 1095 patients enrolled as of January 15, 2016 (73% of target sample), the study is on target to close recruitment by early 2016.

Conclusions: To date, PERSPECTIVE is the first observational study across two countries with over 1000 patients enrolled that provides data on clinical and patient perspectives on management of OAB. The study has recruited sites reflective of the centers where patients are treated for OAB to maximize the generalizability of study results to the real-world population seeking care for OAB.

924. Risk of Urinary Adverse Events Associated with Inhaled Anticholinergics in Adult Men

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Background: Medications with anticholinergic properties can result in a urinary adverse event, acute urinary retention (AUR), likely due to parasympathetic innervation on the bladder.

Objectives: To determine if the risk for urinary adverse events is associated with the use of inhaled anticholinergics (tiotropium and ipratropium) compared to inhaled corticosteroid or long-acting beta agonists

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(non-anticholinergics) in adult men aged 45 to 64 years coded for chronic lung disease.

Methods: We identified new-users of inhaled anticholinergics and non-anticholinergics in the Truven MarketScan databases from 2006-2012. Subjects were excluded if AUR, medication for urinary symptoms (alpha blocker or 5-alpha reductase inhibitor (5-ARI)), prostate or bladder cancer, or benign prostatic hyperplasia (BPH) was present prior to the date of first inhaled prescription (index date). Subjects were censored at the end of insurance enrollment, death, medication discontinuation or ≥50% non-adherence. Cox regression was used to examine the association between inhaled medications and urinary adverse events; 1) AUR and 2) medications for urinary symptoms (alpha blocker or 5-ARI), as a surrogate for the AUR causal pathway.

Results: Of the 65,625 new-users of inhaled anticholinergics, 727 (1.1%) were coded for AUR and 2,609 (4.0%) received medication for urinary symptoms. In comparison, of the 56,694 new-users of inhaled non-anticholinergics, 353 (0.6%) were coded for AUR and 1,501 (2.6%) received medication for urinary symptoms. After controlling for age, region, non-BPH urology symptoms, oral medications with anticholinergic activity, and Elixhauser comorbidities, inhaled anticholinergics users were more likely to be coded for AUR (HR 1.33, 95% CI 1.17-1.51) and more likely to have received medication for urinary symptoms (HR 1.17, 95% CI 1.09-1.24), compared to inhaled non-anticholinergic users.

Conclusions: Among middle-aged men, this research suggests a higher risk for urinary adverse events in inhaled anticholinergic users compared to non-anticholinergic users. These results may impact future prescribing of inhaled medications in this population.

925. Survival In Kidney Transplantation In Patients Who Used Cyclosporine Or Tacrolimus

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Background: In Brazil, the Unified Health System (SUS) is responsible for 95% of all kidney transplantations and it ensures access to immunosuppressive medicines. The Clinical Protocols of the Ministry of Health of Brazil recommend the use of cyclosporine or tacrolimus as pillars of immunosuppression in renal transplantation. Moreover, the cost of treatment with tacrolimus is about three times higher than that of cyclosporine in Brazil.

Objectives: To analyze 10 years graft survival of renal transplant patients according to the base drug of the maintenance therapy: cyclosporine or tacrolimus.

Methods: We analyzed a nationwide cohort of kidney transplant recipients from January 2000 to December 2010 developed through deterministic-probabilistic linkage of SUS administrative databases: Hospital Information System (SIH/SUS); Subsystem for High Complexity Procedures (SIA/SUS) and the Mortality Information System (SIM). To be included, patients must have used either cyclosporine or tacrolimus. Graft loss was defined as death or dialysis for more than three months. We used the Kaplan-Meier method to estimate the cumulative probability of survival.

Results: In total, 13,489 patients were included (54.7% living donor); 5,803 used cyclosporine as regime base, and 7,686 used tacrolimus. Most patients were male with a median age of 41 years. The overall 10-year graft survival was 72.2%. In five years the survival rate of patients treated with cyclosporine was 88.6% and tacrolimus was 86.6% In ten years the survival rate of patients treated with cyclosporine and tacrolimus was 73.2% and 69.6%, respectively ($p<0.001$).

Conclusions: In Brazil tacrolimus showed worst graft survival than cyclosporine. Various factors may be involved in this difference. The study, assessed the graft survival in ten years more than 13,000 kidney transplant patients at SUS. The choice of immunosuppressive agents is one of the key factors that have direct influence in the survival of renal graft amenable to intervention by the prescriber. In addition, the results provide subsidies to Governmen to renegotiate tacrolimus prices and reorganization of the supply of medicinal products.

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926. Risk of Venous Thromboembolism Amongst Users of Different Anti-Osteoporosis Drugs: A Multinational Population-Based Cohort Study

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Background: Most adverse drug reactions for anti-osteoporosis medicines (AO) users have been described comparing AO users to AO-naïve patients.

Objectives: We aimed to compare the risk of venous thromboembolism (VTE) amongst incident users of different AO –and in particular Strontium Ranelate (SR)- in the UK (CPRD) and Spain (SIDIAP and BIFAP).

Methods: Three cohort studies were performed separately using primary care records data from CPRD, SIDIAP and BIFAP. All patients aged ≥50 years, >1 year of data available and a new AO prescription (therapy initiation) in 2001-2013 (BIFAP), 2007-2014 (SIDIAP), or 2000-2014 (CPRD) were included. AO included: 1.alendronate (AL), 2.other (oral) biphosphonates (OB), 3.SR, 4.denosumab (DE), or 5. teriparatide (TE). SERM users were excluded since VTE was a contraindication, as were TE and DE users in CPRD due to low numbers. Patients were followed to the earliest of: VTE (diagnosis combined with anticoagulant use), AO cessation, switching, drop-out, death, or end of study. Incidence rate (IR) of VTE and Hazard ratios (HR) for VTE were estimated for each cohort versus AL adjusted for NICE risk factors for VTE.

Results: Overall, 2,035/159,209 (1.28%) in CPRD, 386/148,564 (0.26%) in SIDIAP, and 401/83,334 (0.48%) in BIFAP had VTE. Crude IR per 1,000 py were 4.84, 2.47 and 2.36 for AL; 5.08, 2.43 and 2.21 for OB; and 5.06, 1.60 and 2.89 for SR in CPRD, SIDIAP and BIFAP respectively; 5.08 and 5.16 for DE; and 2.38 and 4.67 for TE in SIDIAP and BIFAP.

Adjusted HRs of VTE were 1.05 (0.94-1.18), 1.48 (1.17-1.85) and 0.96 (0.78-1.18) for OB; and 0.90 (0.61-1.34), 1.12 (0.67-1.88) and 1.19 (0.82-1.74) for SR in CPRD, SIDIAP and BIFAP respectively; and 1.11 (0.55-2.23) and 1.77 (0.25-12.66) for DE; and 1.00 (0.37-2.72) and 1.27 (0.59-2.71) for TE in SIDIAP and BIFAP.

Conclusions: VTE risk during AO therapy did not differ by drugs, except OB showing higher risk in SIDIAP only. Our data does not support an increased risk of VTE associated with SR in the UK or Spain.

927. Preadmission Use of Prescription Drugs and Risk of Red Blood Cell Transfusion in Elderly Patients Undergoing Hip Fracture Surgery

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Background: Increasing number of hip fracture patients presents with several comorbidities such as inflammatory, cardiovascular or pulmonary diseases, and therefore often uses prescription medication. Still, little is known about the impact of these drugs on the risk of blood loss during hip fracture surgery.

Objectives: To examine whether pre-surgery use of non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, statins, corticosteroids or oral anticoagulants is associated with the risk of red blood cell transfusion (RBCT) (as an indirect measure of blood loss) within 7 day of surgery.

Methods: Using prospectively collected data from population-based registries, we included 44,049 patients older than 65 years who underwent surgery for hip fracture during 2005-2013. We defined use of NSAIDs, antidepressants, statins, corticosteroids and oral anticoagulants as at least 1 prescription redeemed <90 days before admission for hip fracture. We used Cox regression to compute 7-day risk of RBCT with 95% CIs, controlling for age, gender, Charlson

Comorbidity index score, body mass index, type of surgery, time from admission to surgery, and year of surgery comparing users with non-users for each class of prescription drug.

Results: The proportion of patients who received NSAIDs, antidepressants, statins, corticosteroids and oral anticoagulants was 39%, 20%, 17%, 9% and 2%, respectively.

Risks of RBCT were 52% and 45% in NSAIDs users and non-users, 53% and 46% in antidepressants users and non-users, 49% and 47% in statin users and non-users, and 46% and 48% in corticosteroids users and non-users. Compared with non-users, the adjusted risk of RBCT was 1.12 (CI: 1.09-1.16) for users of NSAIDs, 1.10 (CI: 1.08-1.13) for antidepressants users, 1.00 (CI: 0.98-1.02) for statin users, 0.93 (CI: 0.91-0.98) for corticosteroid users, and 1.08 (CI: 1.00-1.16) for oral anticoagulants users.

Conclusions: Use of NSAIDs, antidepressants and oral anticoagulants was associated with increased 7-day risk of RBCT among older patients with hip fracture surgery.

928. Fracture-Preventing Benefit of Bisphosphonates by Compliance and Its Timing Following Therapy Start: A Register-Based Study of Postmenopausal Women in Sweden

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Background: Therapy breaks are common among bisphosphonate users. It is unclear how the timing of breaks, or rather a function of these – compliance, is associated with the fracture-preventing benefit of bisphosphonates.

Objectives: To study the association between bisphosphonate therapy and osteoporotic fracture by compliance and its timing in postmenopausal women.

Methods: Using the Swedish Prescribed Drug Register, we identified a cohort of new bisphosphonate users among women aged ≥55 years in 2010-2014. Compliance with therapy, measured as the medication possession ratio (MPR; low: ≤50%, intermediate: >50-<80%, high: ≥80%), was handled as a time-dependent variable to accommodate changes in exposure within and across on- and off-therapy episodes. We used Cox proportional hazards models to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between compliance and incident osteoporotic fracture, defined as closed, non-traumatic fracture of the spine, rib, forearm, upper arm, hip/femur or pelvis as ascertained in the National Patient Register using ICD-10 codes. HRs were estimated over the entire follow-up period (max. 5 years), and over <1.5 years and ≥1.5 years of available follow-up to indicate the importance of timing of compliance.

Results: The study cohort included 36,108 women at baseline. During an average 2.5 years of follow-up, we identified 1,810 incident fractures. Compared with low MPR, age-adjusted HRs for the association of intermediate and high MPR with osteoporotic fracture were 0.44 (0.38-0.50) and 0.88 (0.81-0.97), respectively, for the entire follow-up period. Results are pending from analyses of the association between timing of compliance, i.e., MPR during early and late follow-up, and fracture.

Conclusions: Preliminary results showed that intermediate compliance with bisphosphonate therapy was associated with lower osteoporotic fracture risk than high compliance. Further analyses will examine the robustness of these results and the importance of timing of compliance for fracture risk.

929. Clinical Effectiveness and Safety of Analogue Glargine in Type 1 Diabetes: Systematic Review and Meta-Analysis

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Background: The use of insulin analogues for the treatment of type 1 diabetes mellitus (T1DM) is widespread, but the therapeutic benefits still require further evaluation given the higher costs of the analogues in Brazil and other countries.

Objectives: To evaluate the effectiveness and safety of the insulin analogue Glargine (AG) compared to

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recombinant DNA insulin (rDNA) in patients with DM1 among published observational studies and grey literature, building on previous reviews of RCTs assessing the relative efficacy and safety of NPH insulin versus the analogues.

Methods: A systematic review (SR) with meta-analysis. The SR included cohort studies and registries available on CENTRAL, LILACS and PUBMED, LILACS and including manual and gray literature searches. Only prospective and retrospective cohort studies and database records of T1DM patients, as well as studies evaluating AG preparations in comparison with rDNA insulin were included.The meta-analysis was conducted in Review Manager ® 5.2 software. Primary outcomes were: glycohemoglobin (Hb1Ac), weight gain and occurrence of hypoglycemia. Methodological quality was assessed using the Newcastle-Ottowa scale.

Results: From a total of 796 publications, 11 studies were finally included. There were differences in findings between studies with conflicts of interest compared to without. The overall meta-analysis favored AG in Hb1Ac outcomes (adult patients) and hypoglycemic episodes ($p < 0.05$), but without reaching glycemic control (Hb1Ac to around 7%). The methodological quality of the studies was moderate, noting that 45% of studies were funded by pharmaceutical companies.

Conclusions: It is difficult to support recommending analogues first line given the high heterogeneity of the studies, the discrete value presented by the estimated effect on the effectiveness and safety outcomes, potential conflicts of interest of the included studies and the additional cost of the analogues. The future role of analogues in the treatment DM1 should be better determined by instigating studies with good methodological quality that assess their long-term safety, effectiveness and cost-effectiveness.

930. Incretin-Based Treatments and the Risk of Pancreatic Cancer in Patients with Type 2 Diabetes

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Background: The risk of pancreatic cancer associated with incretin-based treatments (gliptins and GLP-1analogues), a recently introduced class of antidiabetic drugs, is controversial.

Objectives: The objective of this study was to investigate the pancreatic cancer risk associated withincretin-based drugsusing French medico-administrative databases.

Methods: The study was based on national health insurance database linked with hospitalisation database. All general health insurance scheme beneficiaries aged 40 to 80 years with type 2 diabetes in 2010 were included and followed-up until 31/12/2013. The risk of pancreatic cancer associated with gliptins, other oral antidiabetic treatments (OADs) and GLP-1analogues was measured using Cox models adjusted forage, sex, other diabetes treatments and risk factors ofpancreatic cancer.

Results: Among the 1,346,055 people included (54% men, mean age 63.8 years), 41.1% were exposed to gliptins and 7.2% to GLP-1during a mean follow-up time of 3.7 years; 3,113 cases of pancreatic cancer occurred.

The risk of pancreatic cancer was significantly higher among people ever vs. never exposed to gliptins (adjusted Hazard Ratio [aHR]: 1.30; 95% CI: [1.20-1.40]). The risk of pancreatic cancer decreased with time since first exposure to gliptins (≤18 months: aHR 1.58 [1.42-1.75]; >30 months: aHR1.13 [0.89-1.42]) and with gliptins doses (≤540 ddd: aHR 1.45 [1.31-1.60]; >900ddd: aHR0.83 [0.63-1.10]).

Exposure to other OADs (metformin/sulphonamides/others) was also associated with an increased risk of pancreatic cancer (aHR 1.23 to 1.37).

Exposure to GLP-1 analogues was not associated with pancreatic cancer risk (aHR: 0.98 [0.83-1.16]).

Conclusions: The risk of pancreatic cancer is increased in people treated with gliptins with recently initiated treatment or low level of exposure, but not in those with long-lasting or high level of exposureto gliptins nor in those exposed to GLP-1. These results do not support a causal association between incretin-based treatments and pancreatic cancer.

931. The Association of Metformin Exposure and Specific Types of Digestive Cancers Among Diabetic Patients: Real-World Findings from a US EMR Database

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Background: Several epidemiological studies have noted a reduction of cancer among patients taking metformin. The majority of studies lack adequate sample size to investigate the associations within sub-types of cancers.

Objectives: To describe the association between metformin and cancers of the digestive organs among diabetic patients in a US ambulatory medical care setting.

Methods: We utilized Quintiles electronic medical records (Q-EMR) research database which includes patient-level ambulatory medical records from approximately 30 million patients throughout the United States. All patients were required to have activity (i.e. ≥ 1 visit) with their healthcare provider during the time period 1/1/2014 – 9/30/2015. Diseases were defined using ICD-9 codes: Diabetes (250.xx) and malignant neoplasms of digestive organs (150.xx-157.xx) and metformin was identified in the prescription records, which also included combination therapies with metformin. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated for each sub-type of cancer.

Results: We identified 1,397,070 diabetic patients with 647,149 (46%) having at least one prescription of metformin. 49% of the population were at least 65 years old and 51% were female. The odds of most cancers studied were significantly lower among patients exposed to metformin compared to those without metformin [OR (95% CI)]: esophagus: 0.78 (0.69, 0.89); stomach: 0.84 (0.73, 0.97); colon: 0.92 (0.89, 0.96); liver: 0.72 (0.65, 0.79); pancreas: 0.91 (0.85, 0.98). No significant associations were identified for cancers of the small intestine, rectum, and gallbladder.

Conclusions: Our findings suggest that the strength of association between metformin and cancer varies across sub-types of digestive cancers, with liver and esophagus appearing to have the strongest association.

932. Cardiovascular Risks Associated with Dipeptidyl-Peptidase 4 Inhibitor Compared to Other Diabetes Drugs: A Cohort Study

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Background: There are few studies to compare Cardiovascular (CV) risks between dipeptidyl-peptidase 4 (DPP–IV) inhibitors and other diabetes drugs in Japanese patients.

Objectives: To compare the CV risks of between DPP–IV inhibitors and other diabetes drugs by use of Japanese claims data.

Methods: Design: A cohort study using Japanese claims data (2010–2014) provided from Japan Medical Data Center including about 1.9 million patients.

Setting: The patients with a first prescription of any diabetes drugs were identified as cohort.

Exposures: Exposure group was defined as monotherapy users of DPP–IV inhibitors. Control groups were defined as monotherapy users of biguanides (BGs), sulfonylureas (SUs), or –glucosidase inhibitors (–GIs), respectively.

Main outcome measures: The CV events was defined as diagnosis of cardiovascular diseases (CVDs) coded by ICD–10.

Statistical analysis: Propensity score (PS) adjustment for confounding (matching or standardization) and cox proportional hazard regression model were used to estimate the CV risks with DPP–IV inhibitors in comparison with BGs, SUs, or –GIs.

Results: DPP–IV inhibitors, BGs, SUs, and –GIs were prescribed as a first-line drug to 5,468, 2,187, 1,045, and 1,152 patients, respectively. PS model included the covariates such as age, sex, drugs, and concomitant diseases. According to PS matching analysis, the use of DPP–IV inhibitors had neither significant association with the occurrence of CVDs relative to BGs (hazard ratio 1.15 [95%CI; 0.85, 1.54]), SUs (hazard ratio 0.81 [95%CI; 0.54, 1.21]), nor –GIs (hazard ratio 0.94 [95%CI; 0.64, 1.41]). PS standardized analysis showed similar result.

Conclusions: Monotherapy with DPP–IV inhibitor as a first-line drug for diabetes show no significant association with CVDs in comparison with other diabetes drugs. Further studies using definition of CV events in combination with diagnosis, prescription, and medical practice may be required.

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933. Evaluation of Three HbA1c Metrics in Relation to Heart Failure in 94,332 UK Type II Diabetes Mellitus Subjects

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Background: In patients with type 2 diabetes mellitus (T2DM) heart failure (HF) is one of the most common causes of excess death and impaired glycemic control, hemoglobin A1c (HbA1c) is the most frequently used risk factor in relation to cardiovascular disease (CVD). Metrics of HbA1c include baseline and the updated mean HbA1c but it remains unclear which one is most appropriate when evaluating repeated measures of HbA1c in relation to HF. In this study, we propose a third metric, the updated latest HbA1c.

Objectives: To evaluate the risk of HF and impaired glycemic control in a cohort of T2DM patients.

Methods: The Clinical Practice Research Data Link was used to identify a representative T2DM population (01/01/1998 to 31/12/2014). Index date was first recorded at T2DM diagnosis. Patients ≥18 yrs were included. Potential confounders between repeated measures of HbA1c and incident HF were: gender, age, blood pressure, smoking status, CV drug use, and prior history of CVD. Follow-up was time from diagnosis to incident HF, death, lost to follow-up, or end of study 30/06/2015. Proportional hazard models compared the association between 3 HbA1c variables and HF. Baseline HbA1c was recorded 90 days before to 30 days after diagnosis. Updated latest HbA1c and updated mean HbA1c are time-varying variables which are recalculated each time a new HbA1c measurement is recorded.

Results: Median follow-up was 6.4 yrs, men comprised 53% of the cohort, mean age was 62 yrs at T2DM diagnosis, mean BP was 141 mmHg, 60% were on statins, 39% were on ACEi and 51% were ever smokers at baseline. There was a significant association between HbA1c and HF. The estimated overall risk increase per 1% (10 mmol/mol) increase in HbA1c ranged from 6% for baseline HbA1c to 15% for the updated mean HbA1c. In addition when categorized by HbA1c, the latest variable showed a J-shaped increased risk for the lowest HbA1c category of <6% (42 mmol/mol) 1.16 (1.07-1.25) compared to the referent category (ref = 6%-7%).

Conclusions: The updated mean HbA1c variable showed the strongest relation with HF. Our results show that diabetic risk estimates are dependent on HbA1c metric type.

934. Pharmacoepidemiological Profiles of Glucose-Lowering Drug Use in Patients with Diabetes and Its Impact on Mortality from All-Cause and Cardiovascular Disease in the U.S. Adults

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Background: Little evidence is available to identify the effectiveness of glucose-lowering treatment on mortality from all-cause and cardiovascular disease (CVD) using data from large-scale population surveys.

Objectives: To describe the patterns of glucose-lowering drug use in DM patients and its impact on all-causes and CVD mortality.

Methods: Of 272,147 subjects aged ≥18 participating in the U.S. 2000-2009 National Health Interview Surveys and MEPS were analyzed with a prospective cohort design to examine the impact of glucose-lowering drug use on the outcomes. Glucose-lowering drugs were classified on patients' medication records. Vital statues were followed by December 31, 2011 and causes of death were recorded using ICD-9. Cox proportional hazard regression was conducted to estimate hazard ratios (HR) of glucose-lowering drug use for outcomes, with adjusting age, sex and survey years.

Results: Of the study, 22,305 (8.20%) had DM (M: 9,892, and F: 12,413). In males, 10.0% did not use any glucose-lowering drug, 38.1% used only one drug (metformin, sulphonylureas (SU), insulin or the other), and 51.89% combination drugs (≥2), respectively. In females, these values were 10.3%, 40.45% and 49.4%. Within an average 7.39 years follow-up, 4728 (21.2%) died of all-cause, and 1295 (5.81%) died of CVD.

Multivariate Cox model analyses show that HR (95% CI) of metformin, SU or insulin for all-cause mortality were 0.53 (0.36-0.77, p=0.001), 0.89 (0.66-1.21, p=0.46), and 1.65 (1.26-2.16, p<0.001), respectively. The corresponding HRs (95%CI) for CVD mortality were 0.82 (0.42-1.61, p=0.56), 1.10 (0.66-1.83, p=0.72), and 1.51 (0.86-2.66, p=0.15), respectively. Similar results in patients with combination drugs were observed.

Conclusions: Metformin, SU, and insulin were the top three glucose-lowering medications. Patients who receive metformin or a combination of metformin with other drugs, except with insulin, had significantly lower risk of mortality from all-cause and had a protective effect on CVD mortality. The effect of metformin on mortality risk reduction should be addressed in primary healthcare.

935. Bile Duct and Gallbladder Diseases and the Use of Incretin-Based Drugs in Patients with Type 2 Diabetes

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Background: The use of dipeptidylpeptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogs may be associated with an increased risk of bile duct and gallbladder disease. No observational study has yet assessed this possible association.

Objectives: To determine whether the use of DPP-4 inhibitors and GLP-1 analogs are associated with an increased risk of incident bile duct and gallbladder disease in patients with type 2 diabetes.

Methods: Design: Population-based cohort study.

Setting: The UK Clinical Practice Research Datalink linked with the Hospital Episodes Statistics database.

Participants: A cohort of 71,369 patients initiating antidiabetic drugs between 2007 and 2014.

Exposure: Current use of DPP-4 inhibitors and GLP-1 analogs compared with current use of at least two oral antidiabetic drugs.

Main Outcome and Measures: Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) of incident hospitalized bile duct or gallbladder events (cholelithiasis, cholecystitis, cholangitis), comparing current use of DPP-4 inhibitors and GLP-1 analogs with current use of at least two oral antidiabetic drugs.

Results: During 227,994 person-years of follow-up, 853 patients were hospitalized for bile duct and gallbladder disease (crude incidence rate: 3.7 [3.5-4.0] per 1000 person-years). Current use of DPP-4 inhibitors users was not associated with an increased risk of bile duct and gallbladder disease compared with current use of at least two oral antidiabetic drugs (3.6 vs. 3.3 per 1000 person-years; adjusted HR: 0.99, 95% CI: 0.75-1.32). In contrast, the use of GLP-1 analogs was associated with an increased risk (6.1 vs. 3.3 per 1000 person-years; adjusted HR: 1.79, 95% CI: 1.21-2.67). GLP-1 analogs were also associated with an increased risk of cholecystectomy (adjusted HR: 2.08, 95% CI: 1.08-4.02).

Conclusions: The use of GLP-1 analogs was associated with an increased risk of bile duct and gallbladder disease. Physicians should be aware of this potential adverse event when prescribing these drugs, especially to patients who are at higher risk of bile duct and gallbladder disease.

936. Metformin and Other Glucose-Lowering Drug Initiation and Rates of Community-Based Antibiotic Use and Hospital-Treated Infections in Patients with Type 2 Diabetes: A Danish Nationwide Population-Based Cohort Study

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Background: Data on early infection risk in first-treated patients with type 2 diabetes are limited.

Objectives: To examine the rates of community-based antibiotic use and hospital-treated infection in initiators of metformin and other glucose-lowering drugs (GLDs).

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Methods: This is a population-based study based on Danish national cohort of 131 949 patients with type 2 diabetes who initiated pharmacotherapy with a GLD between 2005 and 2012. We estimated rates and adjusted hazard ratios (HRs) of community-based antibiotic use and hospital-treated infection according to choice of first GLD. We performed intention-to-treat analysis using Cox regression method.

Results: The rate of community-based antibiotic use was 362 per 1000 patient-years at risk [PYAR] and that for hospital-treated infection was 51/1000 PYAR. Compared to metformin, the risk of hospital-treated infection was slightly higher in sulfonylurea initiators (HR 1.12, 95% confidence interval [CI] 1.08 to 1.16) and substantially higher in insulin initiators (HR 1.63, 95% CI 1.54 to 1.72) initiators after adjustment for comorbid conditions, comedications, and other confounding factors. In contrast, virtually no difference was observed for overall community-based antibiotic use (HR 1.02, 95% CI 1.01 to 1.04, for sulfonylurea initiators; and 1.04, 95% CI 1.01 to 1.07, for insulin initiators). Compared with metformin initiators, sulfonylurea and insulin initiators experienced higher hospitalisation rates for viral and fungal infections, intra-abdominal infections, pneumonia, septicaemia, and urinary tract infections, and had higher rates of redeeming broad-spectrum antibiotics such as quinolones and cephalosporins.

Conclusions: Rates of community antibiotic treatment and infection hospitalization are high in first-treated patients with type 2 diabetes. Pharmacotherapy initiation with metformin was associated with lower infection risk compared with sulfonylurea or insulin initiation.

937. Treatment Discontinuation And Rates Of Hypoglycemia In Type 2 Diabetes Patients Treated With Dipeptidyl Peptidase-4 (DDP-4) Inhibitors or NPH Insulin As Third-Line Therapy

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Background: Clinical studies suggest that DPP-4 inhibitors are effective as third-line therapy for type 2 diabetes (T2D) patients. However, a direct comparison of DPP-4 inhibitors with NPH insulin in the general population is lacking.

Objectives: To compare therapy discontinuation and hypoglycemia hospitalization rates among T2DM patients initiating either DPP-4 inhibitors or NPH insulin.

Methods: Retrospective cohort study using the MarketScan database (2011-2014). We selected T2DM individuals who were newly dispensed either DPP-4 inhibitors or insulin NPH (basal insulin or mixtures containing NPH insulin) as third-line therapy, after metformin and sulphonylurea in combination. Cohort entry was defined by date of first prescription of the agent, and a 6-month pre-period was used to exclude prior users. Time to therapy discontinuation (prescription gap >90 days) and to first hospitalization for hypoglycemia were compared using Cox regression models. Patients were censored at time of death, transfer out of the health plan, or end of study period. Models were adjusted for baseline variables: age, sex, year of cohort entry, comorbidities, hypertension, and prior history of hypoglycemia or diabetic ketoacidosis.

Results: We studied 54,318 individuals, most (92.7%) were DPP-4 initiators. The NPH group included more women (47.2% versus 40.5% on DPP-4), and more had prior history of hypoglycemia at baseline (21.0% versus 4.1%). In multivariable analysis, treatment discontinuation during follow-up was higher for patients initiating NPH insulin compared with DDP-4 inhibitors (hazard ratio, HR = 1.48; 95%CI = 1.42-1.54). Risk of hypoglycemia was also higher in NPH insulin initiators (HR = 2.82; 95%CI = 2.57-3.10).

Conclusions: Our study suggests that T2D patients initiating third-line therapy with NPH insulin had higher risk of discontinuation and hypoglycemia when compared to DPP-4 inhibitors initiators. This real-world analysis suggests poorer control with NPH insulin versus DPP-4 inhibitors in T2DM patients in need of a third line agent although residual confounding may partially explain results.

938. Risk of Hypoglycaemia in Users of Sulphonylureas with Renal Impairment: A Population-Based Cohort Study

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Background: Sulphonylureas (SUs) are a primary treatment option for patients with type 2 diabetes mellitus. Hypoglycaemia is a well-known severe side-effect that occurs more often in patients with renal impairment. However, data about the incidence of hypoglycaemia in patients with renal function is conflicting.

Objectives: To determine whether treatment with SUs only in patients with renal impairment is associated with a higher risk of hypoglycaemia compared to metformin-only users.

Methods: We conducted a retrospective cohort study using data from the Clinical Practice Research Datalink (CPRD) database (2004–2012). New users (N = 120,803) with at least one prescription for a non-insulin antidiabetic agent (NIAA) and aged 18+ were included. The first NIAA prescription defined start of follow-up. Patients were followed until the end of data collection or a record for hypoglycaemia or a blood glucose serum level < 3.0 mmol/l. The associations between the SU dose, renal impairment, different SUs used, and the risk of hypoglycaemia were determined using Cox proportional hazard models. Adjustments were made for age, sex, life style, comorbidity and drug use.

Results: The risk of hypoglycaemia in current SU-only users was significantly increased compared with current metformin-only users (adjusted Hazard Ratio [HR] 2.50 [95% Confidence Interval [CI] 2.23–2.82]). The higher risk in current SU-only users was further increased in patients with an eGFR < 30 mL/min/1.73 m2 (adjusted HR 4.96 [95% CI 3.76–6.55]). The risk of hypoglycaemia was also significant higher in patients with a high SU dose (adjusted HR 3.12 [95% CI 2.68–3.62]) and with current glibenclamide use (adjusted HR 7.48 [95% CI 4.89–11.44]). Results for gliclazide, the currently recommend SU of first choice, showed a similar risk of hypoglycaemia compared to other SUs.

Conclusions: SU-treatment in patients with a renal function below 30 mL/min/1.73 m2 should be considered with caution, especially the use of glibenclamide. In contrast with several guidelines, gliclazide does not seem to be superior compared to glimepiride, glipizide and tolbutamide.

939. Adjusting for the Effect of Switching Basal Insulin Treatment on the Risk of First Severe Hypoglycaemia

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Background: Long-acting basal insulin analogues have shown a positive effect on the balance between glycaemic control and hypoglycaemia risk compared to insulin NPH (Neutral Protamine Hagedorn). Hazard ratio (HR) estimates of the risk of severe hypoglycaemia (SH) using standard methods may be biased in the presence of insulin switching.

Objectives: The objective of this study is to estimate and compare the incidence of first SH among type 2 diabetes mellitus (T2DM) patients treated with insulin detemir, glargine and NPH, accounting for insulin switching with the use of Marginal Structural Models (MSM).

Methods: T2DM patients aged >40 who initiated use of detemir, glargine or NPH during 2006-2009 were identified from the Finnish health care registers. The patients were followed until discontinuation of insulin treatment, death, end of 2009 or first SH event. In the MSM the causal effect of insulin use on the risk of first SH was estimated by applying the inverse of the probability to switch as weights in the Cox's Proportional Hazard (Cox PH) model. The probability to switch (from NPH to detemir or glargine) was estimated using logistic regression adjusting for both fixed and time dependent covariates on several time grids.

Results: Out of the total population of 27 267 patients, 5 292 (19.4%) initiated detemir, 11 980 (43.9%) initiated glargine and 9 995 (36.7%) initiated NPH. The mean follow-up time was 0.9 years and mean time to first switch was 1.0 years. From NPH initiators, 593

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(5.9%) switched to detemir and 936 (9.3%) switched to glargine. Only 87 (0.5%) patients switched from detemir or glargine to NPH. In the MSM, using a 90 day time grid, the hazard ratio (HR) for first SH for insulin detemir and glargine compared to NPH was 0.71 (95% CI: 0.51, 0.98) and 0.80 (95% CI: 0.63, 1,01), respectively. For comparison, the HRs using the traditional Cox PH with adjusting for switching were 0.73 (95% CI: 0.53, 1.00) and 0.78 (95% CI: 0.62, 0.97), respectively.

Conclusions: The lower risk of first SH when using insulins detemir or glargine over NPH remains after accounting for time dependent insulin switch by MSMs. The results hold for a wide range of time grids.

940. Cancer Risk Among Insulin Users: Comparing Analogues with Human Insulin in the CARING Five-Country Study

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Background: Observational studies suggest an association between certain insulin analogues and increased cancer risk. However, methodological shortcomings, short follow-up, and small sample size, have hindered interpretation and generalization of findings.

Objectives: The primary aim was to compare the risk of cancer at ten specific sites (prostate, breast, lung, colorectal, bladder, pancreas, liver, corpus uteri, melanoma of skin, and non-Hodgkin lymphoma) between the users of insulin glargine or detemir and human insulin.

Methods: In this retrospective study of new insulin users, we used cancer and prescription data from the Norwegian, Swedish, Danish and Finnish National Health Registries and the Clinical Practice Research Datalink from the United Kingdom. We assessed the cumulative insulin exposures in a time-dependent manner. Effect of exposure on cancer incidence was examined by applying multivariate Poisson models to the semi-aggregate data on five cohorts.

Results: During a mean follow-up of 4.6 years, a total of 1.45 million person-years accumulated, and 21,298 cancer cases occurred among 327,040 new insulin users. For 0-0.5 years of glargine exposure relative to that of human insulin, we found an increased risk of colorectal (RR = 1.49, 95% CI: 1.02 -2.17), and endometrial (1.81, 1.09-3.00) cancers in women, for 2-3 years an increased risk of melanoma cancer (2.18, 1.05-4.52) in women, and a decreased risk of pancreas cancer (0.34, 0.17-0.67) in men, for 3-4 years a decreased risk of liver cancer (0.36, 0.14-0.93) in men, for 4-5 years an increased risk of lung cancer (2.18, 1.05-4.52) and melanoma of skin (3.50, 1.67-7.39) in women, for >6 years a decreased risk of liver cancer (0.22, 0.05-0.93) in men. Similarly, comparisons between detemir and human insulin revealed only a few random associations. Altogether, no trends with longer cumulative use were observed for any of the 10 studied cancer outcomes.

Conclusions: Present large-scale study found no major differences in risk of any of the studied cancers between human insulin and different insulin analogues.

941. Comparative Effectiveness of Glinides vs. DiPeptidyl Peptidase-4 Inhibitors in Diabetic Patients

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Background: Glinides and DiPeptidyl Peptidase-4 Inhibitors (DPP-4Is) are both second-line oral glucose-lowering-drugs (GLDs). To date, there is no evidence to prefer one over another.

Objectives: To compare all-cause mortality of glinides vs. DPP-4Is in diabetic patients.

Methods: This new-users cohort study used data from the representative sample of the French national healthcare insurance system database (EGB). Patients newly treated with glinides or DPP-4Is between 2007 and 2012, and aged ≥ 18 years at initiation were eligible for inclusion in the study. They were followed from initiation until occurrence of outcome (all-cause-death), withdrawal of database or December 31, 2013. For every 3-month periods of follow-up, patients were classified as exposed if they received at least one delivery of glinides or DPP-4Is. Parametric g-formula was used to estimate hazard ratio comparing the effectiveness of glinides to that of DPP-4Is adjusted on baseline and time-varying confounders (age, gender, length of diabetes, cancer, cardiac failure, coronary heart disease, neuropathy, nephropathy, use of lipid lowering agents, number of other GLDs, use of insulin). We repeated the estimation process on 500 samples of size 385,300 subjects randomly selected with replacement from the original dataset to estimate confidence interval for the hazard ratio (HR) of all-cause-death.

Results: Of the 7,706 patients included in the study, 51% were men; median age was 65 years (interquartile range, IQR: 57-75). In the trimester before initiation of glinides or DPP-4Is, 24.9% of patients had no other GLDs, 46.2% had one other GLDs, and 28.9% had two or more other GLDs. The median time of follow-up was 3.1 years (IQR: 2.0-4.1) and 729 all-cause-deaths were identified. The HR of all-cause death of DPP-4Is vs. glinides was 0.88 (95% CI 0.67; 1.12).

Conclusions: In real life, effectiveness of DPP-4I and glinides seems comparable in term of mortality. Preference of prescription of such drugs should thus be based on safety profile or life-style considerations.

942. Association Between Type 2 Diabetes Mellitus and Cancer – a Methodological Approach

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Background: Despite thorough research regarding the association between type 2 diabetes mellitus (T2DM) and the incidence of cancer still no consensus whether T2DM increases the risk of cancer has been reached.

Objectives: This observational study investigates whether design and different criteria influence the association between T2DM and the incidence of cancer.

Methods: Data from the PHARMO Database Network, an administrative database network of pharmacies, hospital, general practitioners and other settings, was linked to the Eindhoven Cancer Registry, including data on all newly diagnosed cancer patients. The association between T2DM and breast, colorectal and prostate cancer was studied using a non-matched and a matched design. Three different analyses were performed using different criteria for the censoring or exclusion of persons with incident diabetes during follow-up. Incidence rates were compared using competing-risk models. Age-adjusted hazard ratios (HR) were determined per gender.

Results: The non-matched cohort study included >15,000 persons with T2DM and >210,000 persons without DM, in the matched cohort study this was >22,000 and >65,000 persons, respectively. In the non-matched, as well as in the matched, cohort study, using three different criteria, similar non-significant risks of breast cancer were found (non-matched cohort study: HR ranging from 0.96 to 1.02, matched cohort study: HR ranging from 1.02 to 1.05). An increased risk of colorectal cancer was seen in all analysis designs; non-significant in males (HR ranging from 1.07 to 1.15) and significant in females (HR ranging from 2.04-2.16). All analyses showed a non-significant decreased risk of prostate cancer in males (HR ranging from 0.78 to 0.93).

Conclusions: Different designs and criteria did not alter the association between T2DM and breast, colorectal or prostate cancer. The robustness of these results supports the finding that there is no association

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between T2DM and breast cancer and an association between T2DM and colorectal and prostate cancer.

943. Association of Type 2 Diabetes And Glucose-Lowering Drugs With Risk Of Recurrence Or Death Following Breast Cancer: A Population-Based Cohort Study

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Background: Type 2 diabetes (T2D) may adversely impact breast cancer (BC) prognosis, but data regarding breast cancer recurrence (BCR) are sparse. T2D treatment regimens may modify BC prognosis.

Objectives: To investigate the association of T2D and its treatment with BCR and mortality.

Methods: All incident early-stage BC patients diagnosed during 1996-2006 in Denmark were identified in the Danish Breast Cancer Group registry. T2D before BC diagnosis or incident T2D during follow-up were ascertained from the Danish National Patient Registry and National Prescription Registry. We used Cox regression to compute adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of BCR and mortality for (1) T2D present before BC diagnosis, and (2) T2D diagnosed after BC diagnosis, further classified by glucose-lowering therapy as time-varying exposure lagged by 6 months. Follow-up began on the BC surgery date, or, in analyses of incident T2Ds, on the T2D diagnosis date, and continued until BCR/death, emigration, or 31/12/2012.

Results: Among 27,221 breast cancer patients, 1069 patients (4%) had T2D before BC diagnosis. Median follow-up was 6.3 years; 4699 patients (17%) developed BCR. Compared with patients without T2D, T2D was associated with increased mortality [HR = 1.65 (95% CI 1.41-1.94)] but not BCR [HR =1.00 (95% CI 0.85-1.17), taking competing risk of death into account].

987 (4%) patients developed incident T2D during follow-up (median = 2.9 years). Incident T2D was associated with HR = 1.64 (95% CI 1.34-2.01) for mortality and HR = 1.18 (95% CI 0.98-1.42) for BCR. Compared with metformin-based therapy, other treatment regimens not including metformin predicted increased BCR [HR = 1.21 (95% CI 0.74-1.99)] and mortality [HR = 1.47 (95% CI 0.76-2.84)].

Conclusions: T2D before BC diagnosis was not associated with BCR, but was correlated with increased mortality. Incident T2D after cancer diagnosis was correlated with increased rates of BCR and mortality. Metformin-based T2D therapy may be associated with lower BCR and mortality than other therapies, but risk estimates were imprecise.

944. Safety and Efficacy of Sofosbuvir with Simeprevir with or without Ribavirin for Hepatitis C Genotype 1 with Severe Renal Impairment: A Meta-Analysis of Cohort Studies

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Background: A strong relation between hepatitis C and chronic kidney disease (CKD) has come in light. The management of hepatitis C in patients with severe renal impairment continues to be a challenge because of failure of conventional therapies. Only limited evidences were available, with no clear consensus on the use of Sofosbuvir with Simeprevir for treating hepatitis C genotype 1(HCV-1) in severe CKD.

Objectives: To study the efficacy and safety of combination of Sofosbuvir and Simeprevir with or without ribavirin in severe renal impairment (GFR<30 ml/min./1.73 m2).

Methods: A systematic review was carried out using Pubmed; Cochrane Library; ClinicalTrials.gov; WHO International Clinical Trials Registry; conference proceedings from European Association for the Study of the Liver and the American Association for the Study of Liver Disease congress. Reference lists of all relevant articles upto Feb 2016 were studied. Sustained virological response-12 (SVR-12) and drop-out rate was assessed as a measure of efficacy and tolerability,

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retrospectively. Quality of studies was evaluated by using Newcastle Ottawa scale. Heterogeneity was assessed by Cochrane Q-statistics test and I2 statistics. Random effect model was used to summarize the SVR12 and dropout rate.

Results: This meta-analysis included 4 clinical studies (Prospective cohort: 3; Retrospective cohort: 1), with 56 patients of HCV-1 along with severe CKD. Of all, 59% (33) were found to have cirrhosis and 70% (39) were on dialysis. SVR-12 pooled estimate was found to be 0.897 (95% CI; 0.957-0.772; P<0.01). Pooled estimates of dropout rate was found to be 0.040 (CI 95%; 0.011- 0.137; P<0.01). Of all, 98% (55) of the patients completed the treatment. Only one subject discontinued treatment due to worsening of renal function. Mild adverse events included anemia (27%), insomnia (9%), headache (9%), fatigue (22%), nausea (13%), loss of appetite/diarrhea (4%), and rashes (9%).

Conclusions: Sofosbuvir with Simeprevir in a combination with or without ribavirin was found to be significantly effective with good tolerability in HCV-1 patients with severe CKD.

945. Metabolic Syndrome Associated to Antiretroviral Therapy: A Cross-Sectional Analysis

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Background: Metabolic syndrome (MS) - presence of multiple metabolic risk factors for type 2 diabetes and cardiovascular diseases - has been strongly associated to antiretroviral therapy (ART).

Objectives: Estimate the prevalence of MS and of two MS related-parameters among HIV-infected patients on ART.

Methods: A chart review was performed in a cross-sectional analysis of a historical cohort including treatment-naïve HIV-infected adults (n = 247), initiating ART from 2001 to 2005 and followed-up for a maximum of five years. Two endpoints were evaluated considering any time after ART initiation: i) MS - presence of three concomitant abnormal levels of triglycerides (≥150 mg/dl), HDL-cholesterol < 40 mg/dl - men /< 50 mg/dl -woman) and fasting blood glucose (≥ 100 mg/dl) - "MS patients" and ii) presence of two concomitant MS-related parameters - "high-risk MS patients". Descriptive analyses were performed by estimating absolute and relative frequencies of variables. Pearson's chi-squared test was employed to compare the frequency of MS and according to selected variables (= 0.05). Odds ratios (OR), with 95% confidence intervals were used to estimate the strength of association between MS and exposure variables. Mantel-Haenszel test was performed to obtain OR adjusted for confounders.

Results: Laboratory test results were available for 225 patients, being 78.7% of these (n = 177) eligible for MS prevalence calculation. Most patients were male (61.3%), with mean age of 37 ± 9.7 years and initiated ART with non-nucleoside reverse-transcriptase inhibitors (60.8%). A total of 68 (46.9%) patients had CD4 cell count < 200 cells/mm3 and one-thirty had viral load > 100.000 copies/ml at baseline. MS was detected in 19 patients, corresponding to a prevalence of 10.7% (CI95% = 6.6-16.3). Approximately 6.0% (13/225) of patients had two abnormal test results. A gender-adjusted association was found for MS and age ≥ 37 years (OR = 2.87; CI95% = 1.02 - 8.11).

Conclusions: High proportion of "high-risk" MS and MS patients was found after ART initiation. The monitoring of metabolic abnormalities should be part of the everyday practice of health professionals who care HIV/AIDS patients on lifelong ART.

946. Analysis of Regimen Changes Due to Adverse Drug Reactions Associated with Antiretroviral Therapy in HIV Patients

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Background: The adherence to antiretroviral (ARV) drugs is crucial to achieve and prolong viral load suppression and avoid drug resistant to Human immunodeficiency virus (HIV). HIV patients have been normally prescribed various drug combinations and prone to have more adverse reactions (ADRs). The serious ADRs might result in long hospitalization or life threatening such as serious cutaneous reactions

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associated with nevirapine or lamotrigine in previous studies. The effective drug regimen should be concerning the less adverse events or drug interactions.

Objectives: The objectives of the study are to estimate the magnitude of regimen change due to ADRs and to describe the pattern of ARV regimen change due to ADRs in Thai HIV patients.

Methods: The cross sectional study was performed in ADR reports occurred in patients using ARV drugs from spontaneous drug surveillance system in Thailand until year 2014. The selected case is defined as at least one ARV drugs reported in case reports.

The risk factors of ADR were analyzed. Number of patient/number of prescription who took ARV drug from National Health Securities Office (NHSO) was collected.

Inferential statistics hypothesis testing using Chi-square or Fisher Exact test for categorical data were performed. Reporting Odds Ratio (ROR) will be calculated. Comparison of incidence will be constructed with the HIV-NAT project to evaluate the tendency of ADRs associated ARV drug use.

Results: ADR associated with ARV drugs were identified in 18,332 reports from the drug surveillance database. The majority of patients were from outpatients with ADRs reported around 76%. The mean age is 37.0 (IQR 31-42 years). 72% of ADRs reports were non seriousness. Total of 4,877 were serious, 81% of those resulted in prolong hospitalization. 1% was reported death.

GPO-Vir was the most drugs used (39.07%). The incidence of ADRs equaled 0.056 (95%CI 0.051-0.06). The high incidence of Lipodystrophy from GPO-Vir was 0.0386 (95%CI 0.0353 -0.0425).

Conclusions: The incidence of ADRs cases was also high in many combination drugs regimen. The results have led to improve the guidelines of treatment about ARV therapies in Thailand.

947. Real-World Effectiveness of HCV Infection from an Irish National HCV Registry

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Background: Hepatitis C (HCV) infection is a major public health problem and a leading cause of chronic liver disease. The high acquisition costs of the direct-acting antiviral agents (DAA) for the treatment of HCV raises the question of affordability. Given this, it was recognised in Ireland that robust real-world data was required to determine the effectiveness of these new treatments, and a national HCV registry was established to determine the real-world impact.

Objectives: To evaluate the effectiveness of DAA regimens for treatment of HCV infection in the post-reimbursement era in Ireland.

Methods: The Irish national HCV treatment registry utilizes a prospective, longitudinal, observational methodology. Data for this study were collected between June 2012 and November 2015. All patients meeting criteria for treatment were enrolled in the registry. Demographic data, sustained virological response (SVR) rates, relapse rates and discontinuation rates were captured and entered into a secure electronic platform.

Results: A total of 808 patients (68% male, median age of 49 years (range 18-84 years)) have commenced treatment since June 2012. A protease inhibitor (PI)-based regimen in combination with pegIFN and RBV (PR) was the treatment of choice for 355 patients, of whom 27% were cirrhotic. 453 patients with cirrhosis received interferon-free (IFN-free) treatment, of whom 27% had advanced liver disease (CTP B/C and/or decompensation). The genotypic profile of this cohort was 67% GT1, and 27% GT3. The SVR rate ranged from 45%-73% in the PI-based regimens. In the IFN-free regimens, the SVR rate in GT1 patients ranged from 86%-89%. In GT3 patients, the SVR rate was between 31%-75%.

Conclusions: The national HCV registry provides information on the effectiveness of these costly treatment regimens in the post-reimbursement setting. Following the introduction of IFN-free regimens in Ireland, the SVR rates in GT1 patients are higher than the SVR rates in the cohort treated with protease inibitor-based regimens. A poor response to SOF/LDV was demonstrated in GT3 patients (31%). Initial results are more promising for those GT3 patients treated with SOF/DCV (67%) or SOF/PR (75%).

948. The Association Between the Use of Oral Fluoroquinolones and Neuropsychiatric Events: A Self-Controlled Case Series Study

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Background: Oral fluoroquinolones (FQ) have been reported to be associated with the acute neuropsychiatric events in numerous case reports. However, few population-based studies have investigated this association.

Objectives: To estimate the incidence rate ratio (IRR) of acute neuropsychiatric events among patients prescribed oral FQ in Hong Kong.

Methods: We used the self-controlled case series method to conduct the analysis using data collected from the Clinical Data Analysis and Report System in Hong Kong. Patients with at least one oral FQ prescription and a neuropsychiatric event between 2001-2013 were identified. Those with a history of neuropsychiatric events were excluded. The rates of event occurrence during risk periods were compared to the non-risk periods to estimate the IRR. The risk periods were predefined as before, during and after FQ exposure. Poisson regression adjusted for age was used. The crude absolute risk of having a neuropsychiatric event during current FQ use was also estimated.

Results: There were 291,751 oral FQ prescribed to 166,325 patients between 2001-2013. A total of 4,287 patients were included in the analysis. An increased risk was observed in current FQ use [IRR: 2.12 (95% Confidence Interval 1.58-2.83)] and 1-7 days immediately after FQ completion [1.90 (1.30-2.75)]. There was no increased risk observed in other risk periods. A total of 50 neuropsychiatric events occurred during current FQ use. The estimated crude absolute risk of having a neuropsychiatric event during current FQ use was 1.70 (1.30-2.26) case per 10,000 oral FQ prescriptions.

Conclusions: The findings of this study supports an association between the use of oral FQ and neuropsychiatric events. The association is acute and appeared to be short-term. However, based on the estimated crude absolute risk, the occurrence of such event is rare.

949. Incidence of Myelosuppression in Patients with Longer-Term Exposure to Linezolid in an Outpatient Claims Database

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Background: Linezolid is indicated for treating antibiotic resistant skin and soft tissue infections often occurring in immunocompromised patients, particularly infections caused by Gram-positive bacteria. However, there have been reports of myelosuppressive events associated with long exposure >14 days) to linezolid.

Objectives: To assess the incidence of myelosuppression (MS) among patients exposed to linezolid using a claims database.

Methods: Adults exposed to linezolid from 2000-14 were selected from a claims database and followed up for 42 days past end of treatment. MS was separately defined using either ICD-9 codes or lab values by the occurrence of at least one of the following: anemia (AN), thrombocytopenia (TH) or neutropenia (NU). MS definitions were: AN (hemoglobin <9.5 g/dL; ICD-9 283.x, 284.x, 285.9x), NU (neutrophil count <1000/mm3; ICD-9 288.00, 288.03, 288.09) and TH <75,000 platelets/ mm3; ICD-9 287.4x, 287.5x). Cumulative incidence of MS was computed and patients were censored at the time of first event.

Results: A total of 15,908 patients with a linezolid script were identified and 1,889 events of any MS (11.9%) were observed using ICD-9 only definition. MS incidence by days of exposure (0-14, 15-28, >28 days) were relatively similar: 12.2, 9.7 and 11.4% respectively. Anemia, thrombocytopenia and neutropenia occurred in (8.9-10.8%), (1.9-2.2%), (0.4-1.2%) of patients, respectively. Lab values were available in 5,058 (32%) patients. Overall MS events (n = 278, 5.5%) did not substantially differ by increasing duration of exposure days (0-14, 15-28, >28): 5.2, 7.9, 4.6% respectively. Anemia, thrombocytopenia and neutropenia occurred in (4.4, 6.5, 3.0%), (0.7, 1.8, 0.8%) and (1.1,1.7, 1.6%) of patients per exposure period, respectively.

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Conclusions: Incidence of MS outcomes were greater using ICD-9 codes compared to lab values perhaps due to missing lab values for patients with MS in the database. No apparent trend with increasing duration was observed using either method for classifying MS. However, without chart review it is not clear whether ICD9 or lab values are more accurate.

950. Intravenous Vancomycin and the Risk of *Clostridium difficile* Infection

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Background: Antibiotic exposure is the most important modifiable risk factor for Clostridium difficile infection (CDI). Intravenous (IV) vancomycin is frequently prescribed to inpatients as empiric and definitive treatment for a range of infectious diseases. Evidence on the role of IV vancomycin in CDI etiology is conflicting, in part because IV vancomycin is not commonly prescribed as a single agent.

Objectives: The purpose of this study was to evaluate the impact of IV vancomycin on the risk of hospital-acquired (HA) CDI.

Methods: We conducted a retrospective cohort study of all patients hospitalized on a general medical, surgical, or intensive care unit within the US Department of Veterans Affairs (VA) health care system between January 1, 2011 and December 31, 2013. All patients who received at least one antibiotic not known to increase the risk of CDI (neutral antibiotics) as their first treatment regimen were included. Patients who received IV vancomycin in addition to the CDI-neutral antibiotic (IV + N) were matched to up to 3 patients with no IV vancomycin (N only) on propensity score. Pre-treatment variables in the propensity model included outpatient antibiotics in the prior 30 days, comorbidities, history of CDI, and age. Relative risks and risk differences and 95% confidence intervals were estimated using modified Poisson and log-binomial regression.

Results: During the study period, 115,908 patients were eligible for inclusion in the study, and 31,822 IV + N patients were matched to 84,047 N only patients. Less than 1% (514, 0.4%) of patients developed HA-CDI. After accounting for baseline characteristics, IV + N patients were 1.83 (95% CI 1.53 – 2.19) more likely to develop HA-CDI compared to patients who received N only. The adjusted risk difference comparing IV + N patients to N only patients was 0.3% (95% CI 0.2 – 0.4%).

Conclusions: Although the receipt of IV vancomycin increased the risk of HA-CDI among patients receiving a CDI-neutral antibiotic nearly 2-fold, the absolute increase in risk was very small. It appears that IV vancomycin is not a substantial contributor to HA-CDI risk among inpatients on CDI-neutral antibiotics, but additional work is required to confirm our observations.

951. Clarithromycin Resistance to Helicobacter Pylori: A Prospective Insight from Malaysia

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Background: The frequency of resistance to antibiotics in H. pylori isolates is enormously increasing worldwide.

Objectives: This study determined the clarithromycin resistance rate to H. pylori strains isolated in patients with gastric pain in Malaysia.

Methods: A prospective study was conducted on 220 patients in gastroenterology wards in tertiary hospitals in Malaysia. H. pylori detection was done using polymerase chain reactions, histological examination and culture tests. H. pylori clarithromycin resistance was determined by bacterial cultures using disc diffusion method.

Results: Around 55% of the cases of H. pylori infection were detected by using PCR. From the obtained

cultures, 41% were clarithromycin resistant using agar diffusion method. Samples free of H. pylori by PCR and positives by histological examination were also negatives by reel time PCR.

Conclusions: Bacterial resistance to antibiotics is the only significant determinant of treatment success. The rate of clarithromycin resistance is higher in obtained results of this study. This rate should be further confirmed by a reel time PCR in a larger sample. Continued monitoring of antibiotic resistance should be carried out to minimize antibiotics resistance in Malaysia.

952. Antibiotics and Infection/Colonization by Carbapenem-Non-Sensitive P. aeruginosa: A Nested Case-Case-Control Study

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Background: In France, about 30% of nosocomial Pseudomonas aeruginosa (PA) are carbapenem-resistant and responsible of severe infections. The role of exposure to antibiotics other than carbapenem is unclear.

Objectives: We conducted a case-case-control study to identify other antibiotics than carbapenem associated with isolation of a carbapenem-non-sensitive PA among adults in intensive care units (ICU).

Methods: Case-case-control study nested in DYNAPYO cohort: non-sensitive cases (inpatient colonized/infected by carbapenem-non-sensitive PA), sensitive cases (inpatient colonized/infected by carbapenem-sensitive PA) compared to the same controls (inpatient never colonized/infected by PA) matched according to ICU, length of stay and hospitalization's period. Setting: 1808 inpatients hospitalized in ICU included in DYNAPYO prospective multicenter cohort screened for PA weekly. Antibiotics exposure: Expressed in cumulative duration of treatment by antibiotic classes. Confounding factors: Inpatients severity (SAPS II), exposure to inpatient colonized by carbapenem-non-sensitive PA (colonization pressure), cumulative duration of treatment by carbapenem (except ertapenem). Statistical analysis: Two logistics regressions.

Results: We identified 59 non-sensitive cases, 83 sensitive cases matched with 142 controls. The cumulative duration of treatment by Penicillin M, Aminopenicillins ± clavulanic acid, 1st-2nd generation cephalosporins was a risk factor for isolation of carbapenem-non-sensitive PA after adjustment for cumulative duration of treatment by carbapenem and SAPS II (OR = 1.10; IC95% [1.010–1.201]). The cumulative duration of treatment by Piperacillin ± Tazobactam and Ticarcillin ± clavulanic acid was a protective factor for isolation of carbapenem-sensitive PA after adjustment for cumulative duration of invasive ventilation (OR = 0.868; IC95% [0.772–0.976]).

Conclusions: In this study, used of DYNAPYO cohort allowed us to take into account colonization pressure and to have a valid definition of cases. We identified other antibiotics associated to isolation of carbapenem-non-sensitive PA. These results must be used to define probabilistic treatment protocol in ICU.

953. Drug Interactions as a Potential Instrumental Variable: The Example of Effectiveness of Antibiotic Therapy in Exacerbated COPD Patients

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Background: Exacerbations in COPD patients are associated with serious limitations, reduced quality of life, hospital admissions and death. The effectiveness of antibiotic therapy is debated since part of exacerbations is caused by bacterial infections and unnecessary prescriptions may lead to bacterial resistance. Confounding by indication is a major threat to the study of this type of intervention in current practice. Instrumental variables can enhance the validty by control of both measured and unmeasured confounding.

Objectives: To examine to what extent antibiotic therapy prevents a worsening of severe exacerbations in COPD patients in general practice.

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Methods: We designed a retrospective cohort study in which COPD patients with severe exacerbations with first prescription of an antibiotic were compared with similar patients that were not exposed with same age and gender. Study data were derived from the University Groningen prescription database IADB.nl. The outcome was defined as a prescription of prednisolone or increased dose of respiratory medications after 15 to 30 days. Use of an interacting drug as potential instrumental variable was used to adjust for the unmeasured confounding.

Results: 11,042 COPD patients with severe exacerbations were included; 5,873 were exposed to an antibiotic and 5,169 were unexposed. A higher incidence of the outcome was found in those who were exposed to antibiotics and the relative risk (RR) adjusted for high-risk comedications was 1.03 (CI 95%: 0.93- 1.14). Prescription of an antibiotic was 18 times less prevalent when an interacting drug was prescribed at the time of index date. After correcting for unmeasured confounding by the instrumental variable interacting drug, the association between exposure to an antibiotic and the outcome was estimated at 0.67.

Conclusions: A 33% reduction of worsening of an exacerbation in COPD patients after antibiotic therapy was found in this study which agrees with similar effects as obtained from trials. Interacting drugs can be considered a potential instrumental variable for drug effectiveness research.

954. Clinical Outcome Difference Of The Patient Treated With Generic Piperacillin-Tazobactam And Innovator In Severely Infectious Patients In Medical Intensive Care Units

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Background: Generic drugs had the same active substance, the same pharmaceutical form and the same therapeutic indications as the brand formulation, they had been done bioavailability and bioequivalence tests. However whether they have same clinical efficacy is uncertain.

Objectives: The study aims to compare the efficacy of generic piperacillin-tazobactam and innovator in severely infectious patients in medical intensive care units (MICU).

Methods: Chart review had been performed for patients who were admitted to medical ICU between January 2010 and March 2014 in Kaohsiung Chang Gung Memorial Hospital. All patients either received generic piperacillin-tazobactam or innovator for first line antibiotic were screened. The primary end point was comparison of survival rate between the two patient groups. The secondary end point was sequential organ failure assessment (SOFA) score differences before and after treatment.

Results: A total of 161 patients who fulfilled the criteria were enrolled, including 49 patients treated with generic piperacillin-tazobactam and 112 patients with innovator. Acute Physiology and Chronic Health Evaluation (APACHE) II score were compatible (generic: 28.29 ± 4.73 vs. innovator: 28.96 ± 4.87, p = NS). The 7-, 14-, 28-day and in hospital mortality rates were also compatible (generic vs. innovator; 7d: 10.2% vs. 4.5%, 14d: 16.3% vs.9.8%, 28d: 32.7% 22.3%, in hospital: 36.7% vs. 32.1%, p = NS). The mean antibiotic using day of the two groups were 7.5 ± 4.142 vs. 6.4 ± 3.415, p = 0.101. Trend of decrease in SOFA score was noted although not significantly (generic: 0.90 ± 3.58 vs. innovator: 1.83 ± 2.84, p = 0.079).

Conclusions: Although there were favorable trends over decrease in SOFA score and mortality. No statistically significant difference was noted between generic piperacillin-tazobactam and innovator therapy groups in our study population.

955. Effectiveness of Adalimumab and Etanercept for the Treatment of Rheumatoid Arthritis in the Public Health System (SUS) Belo Horizonte, Minas Gerais, Brazil

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Background: The biological disease-modifying anti-rheumatic (bDMARDs) medicines including the anti-TNF alpha medicines have become firmly established in the management of patients with rheumatoid arthritis (RA). However, they are considerably more expensive than synthetic DMARDs such as cyclosporine and methotrexate. This needs to be considered within resourced constrained environments.

Objectives: To evaluate the effectiveness of bDMARDs in clinical practice among a cohort of patients with RA in the Brazilian Public Health System.

Methods: Individuals with RA treated with anti-TNF agents, adalimumab and etanercept, were included within an open prospective cohort study. These two were chosen as their funding was approved after infliximab. The Clinical Disease Activity Index (CDAI) was used to assess effectiveness of bDMARDs at baseline, 6 and 12 months of follow-up. The Health Assessment Questionnaire and EuroQol-5D were used provide further data on functionality and quality-of-life.

Results: 137 patients completed one year of follow-up. The average mean age of patients was 54.43 years and disease duration 9.0 years, 90% were female, 41% white and 60% married. The most widely used bDMARD was adalimumab (76%). Both adalimumab and etanercept significantly reduced disease activity as measured by CDAI during a 1-year of follow-up ($p<0.001$). 46.7% patients achieved remission or low disease activity at 1 year, with no difference between adalimumab and etanercept ($p=0.066$). Higher bDMARD effectiveness at 12 months was seen with patients who spent a longer time in higher education and had better functionality at the beginning of bDMARD treatment.

Conclusions: In this real-world drug utilization study, half of RA patients achieved the target of remission or low disease activity with adalimumab or etanercept use, demonstrating that the bDMARDs are feasible alternatives for the treatment of RA to sDMARDs. The remaining patients are having their therapeutic options reviewed, including potential switching to other therapies, to improve their RA. This will be the subject of further research.

956. The Associations Between Bullous Pemphigoid and Drug Use: A Prescription Sequence Symmetry Analysis

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Background: Bullous pemphigoid (BP), the most common autoimmune blistering disease, is increasing in incidence and conveys a high mortality. The mechanism of the autoantibodies formation in BP has not yet been fully elucidated, but it is widely accepted that a strong correlation with chronic use of various medications may exist.

Objectives: To understand the associations between BP and drug use by prescription sequence symmetry analysis (PSSA), a new method established by Hallas in 1996 for signal detection of safety issues in datasets.

Methods: The National Health Insurance Research Database of Taiwan from 2001 to 2012 was used in this retrospective study. A cohort of patients whose diagnosis have been coded as BP (ICD-9 code 694.5) for at least three times were recruited. The chronological order of diagnosis of BP and medication use constituted the basis of PSSA. Sequence ratios (SR) were calculated, and 95% confidence intervals (CI) were determined with a normal approximation to the binomial distribution. To validate the study, thiol containing drugs (e.g., captopril and flupenthixol) group, a well-known trigger of BP was tested as positive control; systemic corticosteroids, a first-line therapy for BP, was tested as negative control.

Results: A total of 6,656 BP patients (3619 male and 3037 female) were included.

A positive association was identified between thiol-group drugs and BP with a SR 4.31 (CI: 3.22–5.78), while the negative association was noted in systemic glucocorticoid with a SR 0.20(CI: 0.16–0.25). The SR of 4 top drug classes were 2.89 (2.34-3.56) for

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tertiary amines belladonna alkaloids, 2.1 (1.68-2.62) for class III anti-arrhythmics, 2.36 (2.09-2.66) for adrenergic and dopaminergic agents, and 2.69 (1.74-4.16) for quaternary ammonium peripheral muscle relaxants.

Conclusions: Our study provided further support of the association between thiol-group drugs and BP. Furthermore, we identified new categories of drug, which will provide a new window for further investigations on the pathogenesis of BP.

957. Safety and Efficacy/Effectiveness of 2nd-Line Treatments in Immune Thrombocytopenia (ITP): A Systematic Review of the Literature

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Background: ITP is a rare platelet disorder leading to an increased tendency to bleed. Patients who fail initial treatment or relapse may require 2nd-line therapy, yet definitive guidelines in this setting are lacking, presumably because of a paucity of relevant rigorous clinical research.

Objectives: To systematically review studies evaluating the safety and efficacy/effectiveness of therapies used to treat ITP in the 2nd-line setting (splenectomy, azathioprine, cyclophosphamide, cyclosporine A, danazol, dapsone, eltrombopag, mycophenolate mofetil, rituximab, romiplostim, and vinca alkaloids), with a focus on randomized controlled trials (RCTs).

Methods: Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, PubMed, EMBASE, and clinicaltrials.gov were searched. Studies in the 1st-line setting; with n <20; or in children, pregnant women, or patients with secondary thrombocytopenia were excluded. In RCTs with either a placebo or standard-of-care (SOC) arm, outcomes of bleeding, platelet response, and use of rescue therapies were summarized and indirectly compared using forest plots of calculated risk/response ratios.

Results: Final abstraction was performed on 165 articles. Most studies were observational and none were interventional head-to-head comparisons. Twelve RCTs with a placebo or SOC arm were identified and studied either rituximab or one of two thrombopoietin-receptor (TPO-R) agonists (romiplostim, eltrombopag). Patients receiving one of these therapies tended to have a lower risk of bleeding and rescue therapy use and an increased likelihood of platelet response vs patients receiving placebo/SOC, particularly in trials of a TPO-R agonist (eg, the range of response ratios for overall platelet response was 1.81 [95% CI: 1.37-2.37] – 34.28 [95% CI: 2.20-533.41] for romiplostim vs placebo/SOC; 1.40 [95% CI: 0.27-7.18] – 14.00 [95% CI: 2.10-93.45] for eltrombopag vs placebo; and 0.86 [95% CI: 0.60-1.22] – 1.09 [95% CI: 0.85-1.40] for rituximab vs placebo).

Conclusions: High-quality RCT data are still lacking for most ITP treatments used in the 2nd-line setting.

958. Patient Characteristics and Overall Survival (OS) in the Post-Docetaxel Metastatic Castration-Resistant Prostate Cancer (mCRPC) Community Setting

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Background: The mCRPC treatment landscape has evolved substantially with the approval of new therapies.

Objectives: To assess treatment sequences, patient characteristics, and OS in post-docetaxel mCRPC pts.

Methods: mCRPC pts (N = 629) receiving docetaxel, cabazitaxel, abiraterone, or enzalutamide after 1st-line docetaxel, in 5/2011- 10/2014 were identified using electronic medical records from US community oncology practices. OS, evaluated from 2nd-line therapy initiation, was assessed using Cox regressions, adjusting for metastasis site, prostate-specific antigen

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(PSA), hemoglobin, alkaline phosphatase (ALP), albumin levels, and year of 2nd-line therapy initiation.

Results: After 1st-line docetaxel, 123 pts (20%) received 2nd-line cabazitaxel (median age: 72 years) and 506 (80%) received 2nd-line androgen receptor-targeted therapy (ART) (abiraterone: 330, enzalutamide: 173, combination: 3; median age: 73 years).54 and 141 pts subsequently received additional treatment lines following cabazitaxel or ART, respectively. While pts receiving 2nd-line cabazitaxel vs ART had similar disease prognosis profiles at 1st-line therapy initiation, at 2nd-line therapy initiation they had higher mean PSA (387 vs 234 ng/mL) and ALP (182 vs 167 u/L), lower mean hemoglobin (10.8 vs 11.5 g/dL), and more presented with a intermediate or high Halabi risk score (62% vs 48%; JCO 2014:32;671–7); all $p<0.05$. Although not statistically significant, a trend suggested longer OS for pts receiving 2nd-line cabazitaxel (hazard ratio [HR] for cabazitaxel vs ART: 0.79, 95% CI: 0.59–1.06). Among selected patient subgroups, cabazitaxel was associated with significantly longer OS: Halabi high-risk (HR 0.48, 0.24–0.93, $p=0.0296$); albumin < lower limit of normal (HR 0.43, 0.23–0.80, $p=0.0077$); hemoglobin <11 g/dL (HR 0.60, 0.40–0.90, $p=0.0135$).

Conclusions: Most pts (80%) received ART post-docetaxel. Although pts receiving cabazitaxel post-docetaxel had more poor-prognosis characteristics, for pts with Halabi high-risk scores or low albumin or hemoglobin, cabazitaxel may be associated with longer OS compared with ART.

959. Withdrawn by Author

960. The Quality of Warfarin Therapy Among Atrial Fibrillation Patients in Finland - Results from the FinWAF Registry

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Background: Warfarin is an anticoagulant that has been used to reduce the risk of stroke and thromboembolic events in atrial fibrillation (AF) patients for decades. It has narrow therapeutic index. Hence, continuous monitoring and adjustment of the dose of warfarin are important in order to avoid bleeding and thrombotic complications.

Objectives: The objective of this study was to investigate the overall quality of warfarin therapy in Finnish AF patients.

Methods: The FinWAF Registry contains real-life data on AF patients from national population and healthcare registers in Finland, linked with prothrombin time measurements expressed as international normalized ratio (INR). The quality of warfarin therapy was calculated as time in therapeutic range (TTR) defined as percentage of time with INR 2.0 – 3.0 during the previous 60 days. The proportion of days and patients with poor TTR (≤40%), moderate TTR >60%) and with good TTR >80%) was summarized. Incidence rates of stroke, overall mortality and adverse bleeding events were determined for different TTR levels.

Results: The FinWAF Registry included 54568 AF patients, representing more than half of all anticoagulated AF patients in Finland. Average follow-up time was 3.2 years during the 5-year study period (2007 – 2011). The average number of INR measurements per patient was 57 (range 1 – 586) with approximately 1.5 INR samples collected monthly. Excluding 6 months from treatment initiation, TTR was poor, moderate and good for 19%, 66% and 48% of total follow-up time, respectively. Furthermore, 12%, 40% and 15% of patients maintained poor, moderate and good TTR levels for over 70% of their follow-up time, respectively. Incidence rates of all studied outcomes decreased with increasing TTR.

Conclusions: TTR was good for nearly half of the total follow-up time but only few patients were able to maintain this level constantly. In addition, although the proportions of patients with constantly poor and good TTR were similar (12% vs. 15%), poor TTR comprised lower proportion of the total follow-up time (19% vs. 48%). In the future, treatment could be potentially improved by identifying factors associated with TTR.

961. Antiplatelet and Anticoagulant Prescriptions and Breast Cancer Recurrence: A Danish Nationwide Prospective Cohort Study

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Background: Laboratory studies suggest that drugs that inhibit platelets and coagulation impair the growth and dissemination of breast cancer cells. Use of antiplatelet and anticoagulant prescription drugs therefore may improve breast cancer prognosis.

Objectives: To investigate the association between antiplatelet and anticoagulant prescriptions and breast cancer recurrence.

Methods: Our study cohort consisted of all women diagnosed with early-stage breast cancer during 1996-2008 who were included in the Danish Breast Cancer Group (DBCG) registry. We retrieved information on antiplatelet and vitamin K antagonist (VKA) prescriptions from the National Prescription Registry, and information on breast cancer recurrence from the DBCG. Follow-up began on the breast cancer diagnosis date and continued until breast cancer recurrence, emigration, death, or 31 December 2012, whichever occurred first. We used Cox regression models to estimate associations between drug exposure, modelled as time-varying exposures lagged by one year, and breast cancer recurrence, accounting for competing risks of mortality and adjusting for potential confounders. Associations are reported as recurrence hazard ratios (HRs) with 95% confidence intervals (95%CI).

Results: We identified 34,474 patients with 234,746 person-years of follow-up (median = 7.1 years), during which 4,751 recurrences were diagnosed. 1,496 (4%) women received at least one prescription for platelet inhibitors and 1,619 (5%) received at least one prescription for VKAs. Both crude and adjusted HRs showed no evidence of an association between exposure to either platelet inhibitors [HRcrude = 0.75 (95%CI = 0.58-0.97); HRadjusted = 0.88 (95% CI = 0.68-1.15)], or VKAs [HRcrude = 1.05 (95% CI = 0.85-1.29); HRadjusted = 1.17 (95%CI = 0.95-1.44)] and recurrence.

Conclusions: Our study suggests no notable reduction in breast cancer recurrence associated with prescriptions for platelet inhibitors and VKAs.

962. Safety And Efficacy Of New Oral Anticoagulants, And Low Molecular Weight Heparins Compared To Aspirin Associated With Total Knee And Hip Replacement

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Background: There has been much debate recently on the best type of antithrombotic agent following elective total joint replacement (TJR) surgery.

Objectives: To compare rates of venous thromboembolism (VTE), gastro intestinal (GI)-bleeding and mortality events, with use of new oral anticoagulants (NOAC) or low molecular weight heparins (LMWH) compared to aspirin in patients undergoing TJR.

Methods: A population based retrospective cohort study was performed using the Clinical Practice Research Datalink (CPRD). Patients ≥18 years of age who had undergone total knee (TKR (n = 3,261)) or hip replacement (THR (n = 4,016)) between 2008 and 2012 were included. Within this population three cohorts were selected, based on their first prescription within the 35 day period after surgery: Use of NOACs only, LMWHs only, and aspirin only. Incidence rates were calculated and Cox proportional hazard models were fitted to estimate the risk of VTE, GI-bleeding and all-cause mortality with the use of NOACs and

LMWHs compared to aspirin use after TKR and THR. We statistically adjusted our analyses for lifestyle factors, comorbidities and concomitant drug use.

Results: TKR and THR patients currently on LMWHs had higher risk of VTE (HR = 3.3 (1.0-10.9) and HR = 42.7 (10.0-183.5) respectively). Although higher incidence rates were found, use of LMWHs or NOACs was not associated with a significantly increased risk of GI bleedings and all-cause mortality in THR and TKR patients.

Conclusions: In contrast to a similar or better safety and efficacy profile of NOACs and LWMHs, as compared to aspirin, reported in previous studies, we found a similar (or increased) risk of VTE, GI-bleeding, and all-cause mortality.

963. Outcomes Associated With Non-Adherence To Anti-Hypertensives And Statins

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Background: Non-adherence to medicines is associated with poorer patient outcomes. As hypertension and dyslipidaemia are asymptomatic, adherence can be an issue due to the lack of perceived treatment benefit.

Objectives: To determine the effect of non-adherence in relation to: (i) blood pressure in anti-hypertensive use and (ii) LDL and total cholesterol levels in statin use.

Methods: Design: Retrospective cohort study with health assessments linked to pharmacy claims data.

Setting: Community dwelling participants aged ≥ 50 years from 2009-2011. Means-tested subset of the population.

Exposures: The proportion of days covered (PDC) for each of five classes of antihypertensive medication (WHO ATC: C02, C03, C07, C08, and C09) and all statins (C10AA) during 12 months prior to the health assessment. The average PDC was calculated and adherence assumed at PDC ≥80%.

Main outcome measures: (i) Mean systolic and diastolic blood pressure (BP) measurement (from two recordings) and (ii) total cholesterol (TC) and LDL cholesterol levels.

Statistical analysis: Multivariable linear and logistic regression, adjusting for covariates including age, gender, smoking status, chronic disease, educational level and BMI. Adjusted regression coefficients ( ) or adjusted odds ratios (OR) are presented with 95% confidence intervals (CI). Targets for reaching TC≤ 5mmol/L and LDL≤3.5mmol/L were used.

Results: There were n = 998 receiving anti-hypertensive medications, with n = 567 (56.8%) adherent. For systolic BP the adjusted coefficient for adherent vs non-adherent was non-significant = -1.11 (95%CI -3.81, 1.59), but was significant for diastolic BP = -2.14 (95%CI -3.64, -0.65). There were n = 771 receiving statins and having blood lipid data, with 482 (62.5%) adherent. Adherent subjects were more likely to reach target TC (OR = 1.79, 95%CI 1.27,2.52) and LDL (OR = 1.65, 95%CI 1.12,2.41).

Conclusions: Adherence to anti-hypertensive medication reduced diastolic but not systolic BP and adherence to statins improved targets for TC and LDL cholesterol. The results support improving adherence amongst patients taking anti-hypertensive and lipid lowering therapy for optimal patient outcomes.

964. De-Novo Post-Diagnosis Statin Use And Mortality In Women With Stage I-III Breast Cancer

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Background: Preclinical evidence suggests an anti-cancer role for statins, through inhibition of cell proliferation and oncogene signalling effects. Epidemiological studies have investigated the role of statins in reducing cancer-specific mortality, however, there is conflicting evidence due to varying

methodologies. Some studies included patients with pre-diagnostic statin exposure, making it difficult to attribute benefit to post-diagnostic exposure.

Objectives: This study investigates associations between statin-use initiated after a breast cancer diagnosis (de novo), and breast cancer-specific and all-cause mortality.

Methods: Women with newly diagnosed stage I-III breast cancer were identified from the National Cancer Registry of Ireland and linked national prescription refill data (N = 4243). Women who initiated de-novo statin therapy post-diagnosis were identified (N = 837). Multivariate Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for associations between post-diagnosis statin use and breast cancer and all-cause mortality. We also investigated whether associations between statin use and mortality were modified by the type of statin (lipophilic, hydrophilic), statin intensity (high; >80% for one year) or breast tumour characteristics (ER status).

Results: Almost 20% of women initiated statins (mean on-treatment intensity of 86%). No association was found between de-novo statin initiation and breast cancer-specific mortality (HR 0.88, 95% CI 0.66, 1.17). Similar null associations were found in women taking a statin at high-intensity (HR 1.03, 95% CI 0.71, 1.50) and in those with high intensity exposure for at least 2 years (HR 1.02, 95%CI 0.63, 1.65). There was no effect modification by type of statin, or ER status at diagnosis.

Conclusions: The results from our study suggest that initiating statin use after a diagnosis of stage I-III breast cancer is not associated with a reduction in breast cancer-specific or all-cause mortality. Therefore, it is important to determine whether there may be a specific molecular subgroup of patients for whom statin initiation after a breast cancer diagnosis may be beneficial.

965. The Association Between Statin Use and Risk of Cancer Among Elderly Medicare Beneficiaries

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Background: Recent studies have shown that statin users have lower risks of developing cancer. However, most of observational studies failed to control for healthy user effects. Patients filling statins are more likely to partake in other healthy behaviors, and achieve better outcomes, compared to those who don't fill statins. Hence, failure to control for healthy user effects leads to underestimate the cancer risk associated with statin use.

Objectives: The objective of this study is to explore the association between statins and the risk of cancer among the elderly, after controlling for healthy user effects.

Methods: A retrospective case-control study was conducted using data from the Medicare Current Beneficiary Survey (MCBS) linked to the Medicare claims from 2007 to 2010. The study sample consisted of Medicare beneficiaries aged> 65 years and free of cancers at baseline. Exposure to statins was identified based on self/proxy's reports or pharmacy claims. Five controls were matched to each case on age, sex, race and year of initial interview. Adjusted odds ratios (AOR) were calculated by using logistic regression models.

Results: We identified 242 cancer cases and 1,210 non-cancer controls. During the 2-year follow up period, 18% cases and 19% controls received statins, respectively. Compared with non-users, individuals filling statins had a similar risk of developing cancer (AOR, 0.90; 95% confidence interval [95%CI] 0.64-1.38), after controlling for demographics, socioeconomics, self-rated health status, health seeking behaviors, and comorbidities. The prevalence of health-seeking behaviors, i.e. using of preventative care, were higher among individuals who filled statins than those who did not (71.5% vs. 62.5%). However, adjusting health seeking behavior had no significant impact on altering the risks of cancer among the users vs. non-users of statins.

Conclusions: Our findings suggested that statin use was not associated with reduced risks of cancers among the Medicare beneficiaries aged 65 years and older. There is no evidence of healthy user effects on altering the risk of cancer associated with statin use. Further studies are warranted to conduct on a larger population.

966. Beta Blockers and Cancer Prognosis – the Role of Immortal Time Bias: A Comprehensive Systematic Review and Meta-Analysis

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Background: Experimental and observational studies have suggested beneficial effects of beta blocker use on cancer survival. However, results were inconclusive and there have been concerns that the observed associations might have resulted from immortal time bias.

Objectives: The aim of this systematic review and meta-analysis was to summarize existing evidence, paying particular attention to the potential source of immortal time bias.

Methods: A systematic literature search was performed in PubMed and ISI Web of Science according to a predefined protocol following the PRISMA and MOOSE guidelines. Studies investigating the association between beta blocker use and overall or cancer-specific survival were included. Summary estimates were derived in meta-analyses using random effects models. The potential influence of immortal time bias was investigated in meta-analyses by computing the pooled effect estimates for all studies and studies excluding the ones deemed to be prone to immortal time bias.

Results: After full-text review, 30 studies including 88,026 cancer cases were identified of which 11 were deemed to be prone to immortal time bias. Including all studies in the meta-analysis, beta blocker users had a significantly better overall (hazard ratio (HR) 0.88, 95% confidence interval (CI) 0.79-0.97) and cancer-specific (HR 0.78, 95% CI 0.67-0.90) survival. Excluding the studies deemed to be prone to immortal time bias resulted in HRs (95% CIs) of 1.00 (0.93-1.07) and 0.92 (0.84-1.00), respectively. Besides a significant benefit for overall survival among melanoma patients, none of the subgroup analyses by cancer site and beta blocker type showed significant associations.

Conclusions: In our systematic review, we found no evidence for an association between beta blocker use and survival after excluding studies deemed to be prone to immortal time bias. Our results support suggestions that the proposed beneficial effect of beta blockers on cancer survival might be based on immortal time bias.

967. Protection Against Colorectal Cancer with Use of Low-Dose Aspirin: Selection Bias Is Unlikely Based on Results Using Three Different Study Designs

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Background: Evaluation of drug–outcome associations needs an appropriate and unbiased study design.

Objectives: To evaluate the potential role of selection bias in the association between new use of low-dose aspirin (75–300 mg) prescribed for the prevention of ischemic cardio- or cerebrovascular events (CVD/CeVD) and risk of colorectal cancer (CRC).

Methods: Using The Health Improvement Network (2000–2013), we followed different cohorts of patients, who varied in their demographic, lifestyle and clinical characteristics, for up to 13 years to identify first ever cases of CRC. In Studies 1 and 2, the cohorts were new-users of low-dose aspirin and a comparator cohort (non-users of low-dose aspirin in Study 1 and new-users of paracetamol in Study 2). In Study 3, a single cohort of individuals näive to low-dose aspirin at start of follow-up were observed. Controls were selected using incidence sampling to obtain an unbiased estimate of the incidence rate ratio (RR). Current use of low-dose aspirin was use ending 0–90 days before the index date (CRC date for cases and a random date for controls). Because low-dose aspirin use could change during follow-up, exposure was analyzed according to actual use, irrespective of exposure status at baseline. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by logistic regression.

Results: Mean age at start of follow up was 64 years in Studies 1 and 2, and 53 years in Study 3. RRs (95% CIs) for CRC with current low-dose aspirin use were: 0.66 (0.60–0.73) in Study 1, 0.71 (0.63–0.80) in Study 2 and 0.69 (0.64–0.74) in Study 3. No duration of use or dose–response relationships were seen. When aspirin was used for prevention of secondary

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CVD/CeVD, ORs (95% CIs) were 0.61 (0.55–0.68) in Study 1, 0.60 (0.53–0.68) in Study 2 and 0.62 (0.54–0.72) in Study 3. Corresponding estimates for primary CVD/CeVD prevention were 0.75 (0.68–0.81), 0.71 (0.63–0.79) and 0.78 (0.68–0.89).

Conclusions: Low-dose aspirin is associated with a significantly reduced risk of CRC. The consistency of our findings across study designs makes this protective effect unlikely explained by selection bias.

968. New Use of Statins and the Risk of Achilles or Biceps Tendon Rupture: A Propensity-Score Matched Cohort Study

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Background: Case reports and analyses of pharmacovigilance data suggested that statin use may increase the risk of tendinopathies and tendon ruptures. The only previous observational cohort study observed no association between statin use and tendon rupture, although only in patients aged ≤65 years.

Objectives: We aimed to assess the association between new onset statin use and incident Achilles or biceps tendon rupture.

Methods: We performed a propensity score-matched sequential cohort study, using data from the Clinical Practice Research Datalink. Exposed patients had ≥1 statin prescription within one of 9 sequential 2-year enrolment blocks between 1995 and 2014, and were matched 1:1 on a propensity score (PS, including potential confounders and variables associated with the risk of tendon ruptures) to patients without a statin prescription in the respective block (random enrolment date within the block) . All patients were aged ≥45 years and had ≥3 years of statin free active history in the database before cohort entry. Patients were followed in an 'as treated' approach until they either had a recorded Achilles or biceps tendon rupture, they completed 5 years of follow up, or until they were censored for change in exposure status or another censoring criterion. We calculated hazard ratios (HR) with 95% confidence intervals (CI) applying Cox proportional hazard regression in the overall cohort (crude and multivariable) as well as in the PS-matched cohort. Subgroup analyses were performed by gender and age </≥65 years).

Results: We observed a crude HR of 1.32 (95% CI 1.21-1.44) in the overall cohort, which attenuated after multivariable adjusting (HR 1.02, 95% CI 0.92-1.12) as well as after PS-matching (HR 0.96, 95% CI 0.84-1.09). Crude HRs were higher in women than in men, but remained around unity in both sexes after multivariable adjusting and after PS matching. Subgroup analyses by age also revealed non-significant HRs around unity in both age-groups.

Conclusions: The results of this PS-matched cohort study do not suggest that statin use is associated with an increased risk of tendon rupture, irrespective of gender or age.

969. Impact of Treatment with Lipid-Lowering Drugs on Longitudinal and Secular Decrease in Total Cholesterol Levels. The Tromsø Study 1979-2008

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Background: Cholesterol level surveillance is necessary to study population disease burden and understand the effect of lifestyle and lipid-lowering drug (LLD) use. Previous studies show a cholesterol decline in recent decades, but lack data to follow long-term trends in blood cholesterol combined with information on LLD treatment in individuals born in different decades.

Objectives: To assess secular and longitudinal trends in total cholesterol levels and examine the impact of LLD treatment.

Methods: We examined changes in age-specific cholesterol levels and LLD use by repeated measurements in 37,968 women and men born 1905-1977 examined up to five times between 1979 and 2008 in the population-based Tromsø Study. LLD data is based on questionnaire data validated in a prescription registry (NorPD).

Results: Mean total cholesterol decreased from 1979 to 2008 in both sexes and all age groups. LLD use was rare in 1994 and increased substantially between 1994 and 2008, especially in persons older than 50 years.

In birth cohorts born 1940-77, mean total cholesterol levels increased with age up to 2001 and decreased thereafter. Among those born 1910-39, the cholesterol decrease was evident after 1994-95.

The secular trends showed that the decrease in mean cholesterol was not explained by LLD use in persons younger than 50 years. Among those aged 50 years and older, the drop in mean cholesterol from 1994 to 2008 was 1.09 and 1.00 mmol/L in women and men, respectively (in LLD non-users 0.88 and 0.73 mmol/L in women and men, respectively).

The longitudinal trends showed that in those aged 45-74 years in 1994 followed to 2008, the estimated drop in cholesterol was 0.65 mmol/L in women and 1.00 mmol/L in men, respectively (in LLD non-users 0.28 and 0.58 mmol/L in women and men, respectively).

Conclusions: We found a secular decrease in mean cholesterol in all age groups, a decrease with age and time in birth cohorts, and a larger decrease among LLD users compared to non-users.The explained cholesterol decrease due to impact of LLD as shown in the longitudinal trends, probably represent an upper limit, 58% in women and 42% in men, respectively.

970. Fertility Treatment and the Risk of Cardiovascular Diseases in the Offspring

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Background: As 2-3% of all children are born with fertility treatment, the safety of the hormones used as part of this treatment is of great importance. Exposure to high doses of hormones such as gonadotropin or clomiphene in the early stage of fetal development can not be avoided. In studies conducted so far, inconclusive results on the association between these hormones and cardiovascular malformations in the offspring have been found.

Objectives: The aim of this study was to examine whether hormones used in fertility treatments increase the risk of cardiovascular diseases in the offspring.

Methods: We conducted a case-control study in which 132 children, having ≥ 3 prescriptions of cardiovascular drugs before their fifth birthday, were compared with 24856 controls. Information about drug use was retrieved from the prescription database IADB.nl. Primary exposure was defined as use of gonadotropin and other ovulation stimulants (ATC: G03), (anti) gonadotropin-releasing hormones (ATC: H01CA and H01CC) or analogues (ATC: L02AE). A subanalysis was limited to cases receiving ≥ 3 prescriptions for cardiovascular drugs during their first year of life. We applied regression analysis to compute odds ratios (ORs) and 95% confidence intervals (95% CI).

Results: The percentage of exposure to hormones used in fertility treatment was 6.8% among cases compared to 3.5% among controls. After adjustments for age of the mother at delivery, gender of the child, and birth year, exposure to hormones is pointing to an increased risk for developing cardiovascular diseases (aOR [CI95%] 1.94 [0.98-3.84]). When limiting the analysis to cases below the age of 1 (n = 86), the risk was significantly increased with aOR 2.67 (1.28-5.57).

Conclusions: This study shows that hormones used in fertility treatments seem to increase the risk of cardiovascular diseases notably during the first year of life.

971. Effectiveness of Ezetimibe on Blood Lipids in Real-Life Clinical Practice

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Background: Ezetimibe is currently approved in France as monotherapy for patients in whom statins are contraindicated or who are intolerant to statins, and as addition to a statin for patients who have not achieved control of their hypercholesterolaemia with statins alone.

Objectives: To assess the use of ezetimibe in real life and its impact as lipid-lowering therapy.

Methods: 48-month prospective, nationwide cohort study conducted between 2008 and 2013 in France at the request of the French National Authority for Health.

Results: Over 700 physicians (94% general practitioners and 4% cardiologists) recruited and characterised 3,395 eligible adult patients started on ezetimibe for no longer than three months, of whom 3,215 (94.7%) entered the analyses. Patients were naturalistically followed for up to 4 years with no visits formally planned. Blood lipids were reported by physicians every twelve months and lipid-lowering medicines utilisation every six months during telephone interviews to patients in-between two annualvisits to the physician. 9 314 person-years of follow-up were accumulated.

Mean age at inclusion was 61.5 years (standard deviation (SD): 10.7) and 54.6% were males. Stratification by cardiovascular risk returned: 29.3% low, 32.4% moderate and 11.4% high for primary prevention, and 26.9% for secondary prevention. Ezetimibe exposure at inclusion was 33.1% monotherapy, 13.2% ezetimibe added to a statin, and 53.7% fixed association ezetimibe - simvastatin. Exposure to ezetimibe remained stable during follow-up with a treatment interruption rate of 12.5 per 100 person-years of follow-up. LDL-C was 4.1 mmol/L (SD: 1.1) at baseline and decreased by 23.8% (SD: 28.8) in the first 12 months, reaching –27.3% (SD: ¬28.3) at 48 months. Adjusting for baseline clinical characteristics and risk factors, interruption of lipid-lowering treatment at least once during follow-up was associated with a lower probability of LDL-C progression to the lower tertile (OR: 0.38, 95% confidence interval: 0.31 – 0.45).

Conclusions: In this population with incident exposure to ezetimibe, LDL-C decreased by one quarter in the first year after treatment onset and remained stable over the 4-year follow-up.

972. Clinical Characteristics, Lipid Treatment and Goal Attainment in a Familial Hypercholesterolemia Cohort in the Netherlands: A Cross Sectional Study

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Background: Patients with familial hypercholesterolemia (FH) develop cardiovascular disease much earlier in life compared with non-FH patients. Aggressive lowering of low-density lipoprotein cholesterol (LDL-C) is therefore warranted by current guidelines for this patient population.

Objectives: Describe lipid-modifying treatment (LMT) patterns and LDL-C goal attainment in a large cohort of FH patients in the Netherlands.

Methods: Using the PHARMO Database Network, patients aged ≥18 years with an LDL-C measurement in 2012 (index date) and ≥2 years' continuous enrolment prior to index were selected. FH was defined based on recorded diagnosis by a general practitioner and/or by Dutch Lipid Clinic Network criteria (score ≥6). Patients with a prescription for LMT within 45 days of index were considered to be taking the medication.

Results: 209,929 patients had a valid LDL-C value, of whom 1132 FH patients were identified. Mean (standard deviation [SD]) age was 57 (14) years; 43% were male. Approximately 33% had co-morbid diabetes and 42% had hypertension. The mean (SD) LDL-C was 138 (57) mg/dL. Overall, 54% were being treated with LMT, with 13% receiving high-intensity statin (atorvastatin 40/80 mg, rosuvastatin 20/40 mg, or simvastatin 80 mg). Of those on high-intensity statins, 24%

also used ezetimibe. Only 4% achieved LDL-C <70 mg/dL and 23% LDL-C <100 mg/dL.

Conclusions: These data suggest the majority of FH patients in the Netherlands are undertreated and not at goal. This underscores the need for improving treatment rates with LMT, including add-on treatment options in those not able to achieve goals on statins alone.

973. Modelling Of Average Endpoint Postponement For Cardiovascular Outcomes In Statin Trials

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Background: The 'average postponement of the endpoint' (APEP) has been proposed as an expression of the magnitude of effect of preventive drugs. Presenting effect sizes using this measure has been shown to be in better agreement with patient preferences than conventional outcome measures, including the "number needed to treat". We have previously demonstrated that statin treatment postpone all-cause mortality during the trials' running time with an average of 11.2 days in a meta-analysis.

Objectives: To conduct a meta-analysis of modelled APEP for other cardiovascular outcomes in statin trials, such as myocardial infarctions, strokes, and cardiovascular death.

Methods: We identified 15 statin trials that fulfilled our inclusion criteria. We calculated the APEP by calculating the area between Kaplan-Meier survival curves. Our novel method for APEP modeling allows estimation of APEP without Kaplan-Meier curves, by fitting of survival curves. The modelled APEP for 17 different cardiovascular (CV) outcomes was computed on the basis of (1) hazard ratio or relative risk (2) the cumulative event rate in the untreated group and (3) the trial's running time. The modelled APEPs were subjected to a meta-analysis, using inverse variance weighting in a random effects model.

Results: The APEPs for the 17 CV related outcomes varied between 2 and 18 days.

For four outcomes, cardiovascular mortality, non-cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke, the APEP was 11.6 (2.6-20.6), 2.0 (-4.0-7.9), 18.0 (6.5-29.4) and 2.4 (1.2-3.6) days, respectively.

Conclusions: Based on modelled APEP estimates, preventive statin treatment provides relatively small average postponement of CV outcomes during the trials' running time.

974. Blood Pressure-Lowering Effect of Spironolactone in Hypertensive Patients Without Heart Failure

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Background: Lowering blood pressure (BP) to target in patients with hypertension results in greatly reduced cardiovascular risk and mortality. But achieving BP control in a diverse clinical population remains difficult. Spironolactone, an aldosterone antagonist, is mostly prescribed for heart failure patients but not often considered in patients with hypertension only.

Objectives: To determine the effect of spironolactone on systolic BP (primary endpoint), and diastolic BP and serum K+ (secondary endpoints) in patients with hypertension.

Methods: We conducted an observational study using electronic medical record data from the Indiana Network for Patient Care. This patient population is representative of patients in the state of Indiana, USA. Participants, diagnosed with hypertension but not heart failure, received spironolactone during 2003 – 2014. We compared the BP and serum K+ within two years before and after receipt of spironolactone

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using regression analysis adjusting for age, sex, race, major comorbidities, and medication adherence.

Results: The analysis included 6,287 patients (65% female, 21% African American). Mean age of the patients was 60 ± 14 (SD) years. Comorbidities included diabetes (44%); depression (36%); cardiovascular diseases including coronary artery disease (25%), stroke (10%), myocardial infarction (6%); and chronic kidney disease (21%). Concurrent antihypertensive medications included ACE inhibitors (40%), angiotensin II receptor blockers (23%), beta-blockers (45%), and thiazide (33%) or loop diuretics (46%). Mean prescription refill adherence ranged from 54% to 70%. On average systolic BP reduced by 3-5 mmHg and diastolic BP by 2-3 mmHg after spironolactone prescription ($P<0.001$ for each), and JNC-7 goal BP increased from 54% to 70% ($P<0.001$). Mean change in serum K+ was 0.04 mEq/L ($P < 0.001$); however, the proportion of patients with hyperkalemia did not significantly differ > 5 mEq/L, $P=0.13$; > 6 mEq/L, $P=0.49$).

Conclusions: Adding spironolactone to the antihypertensive regimen significantly improved BP control. Aldosterone blockade with spironolactone may be a reasonable consideration for the management of hypertension.

975. Effectiveness of Ticagrelor Compared to Clopidogrel in Reducing the Risk of Major Adverse Cardiovascular Events in Patients with Coronary Heart Disease After Percutaneous Coronary Intervention

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Background: Antiplatelet therapy is recommended in patients with coronary heart disease (CHD) who had percutaneous coronary intervention (PCI) procedure to reduce major adverse cardiovascular events (MACE). There has been a lack of population-based studies that showed the superior effectiveness of ticagrelor over clopidogrel and similar studies have not been conducted in Indonesia yet.

Objectives: To investigate the effectiveness of ticagrelor compared to clopidogrel reducing the risk of MACE in patients with CHD after PCI.

Methods: A retrospective cohort study with 1 year follow-up was conducted. 361 patients consisted of 111 patients with ticagrelor exposure and 250 patients with clopidogrel exposure. The primary outcome was MACE, defined as a composite of repeat revascularization, myocardial infarction, or all-cause death. The association between antiplatelet exposure and the MACE was analyzed with Cox proportional hazard regression, adjusted for sex, age, comorbids, PCI procedures, and concomitant therapy.

Results: MACE occurred in 22.7% of the subjects. Clopidogrel had a significantly higher risk of MACE compared with ticagrelor (28.8%, vs 9.0%, hazard ratio (HR): 1.96 (95% CI 1.01 to 3.81, $p <0.001$). There were no significant differences in risk of repeat revascularization (20.40% vs 5.40%, HR: 2.32, 95% CI 1.00 to 5.42, $p=0.05$), myocardial infarction (11.60% vs 3.60%, HR: 2.08, 95% CI, 0.73 to 5.93, $p=0.17$), and death (1.60% vs 1.80%, HR: 0.77, 95% CI, 0.14 to 4.25, $p=0.77$).

Conclusions: Clopidogrel had a higher risk of MACE compared to clopidogrel in patients with CHD after PCI, but there were no significant differences in the risk of repeat revascularization, myocardial infarction, and all-cause death.

976. The Comparative Effectiveness of 4th Line Anti-Hypertensive Agents in Patients with Resistant Hypertension: A Meta-Analysis

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Background: Recent evidence points to the effectiveness of spironolactone vs placebo in the treatment of resistant hypertension (RH). However, placebo is rarely a realistic treatment choice in uncontrolled hypertension.

Objectives: Using meta-analysis, we assessed the effectiveness of alternative 4th line anti-hypertensive agents in comparison to 4th line spironolactone/eplenerone in patients with RH.

Methods: Pubmed, EMBASE and the Cochrane library were systematically searched for randomised and non-randomised studies that compared any 4th line anti-hypertensive agent to spironolactone/eplenerone in RH. Clinicaltrials.gov and the reference lists of included articles were also searched. Data extraction and quality appraisal was carried out in duplicate. The outcome was change in systolic BP, measured in the office, at home or by ambulatory blood pressure monitoring (AMBP). A random effects model was used to pool the data. Statistical heterogeneity was assessed using the I2 test. Sensitivity analyses were carried out according to study design and method of BP measurement.

Results: From 2,506 records, we identified 1 RCT and 5 observational studies according to our inclusion criteria with 877 included patients. The mean age was 57.3yrs, 29.5% female, 41.4% diabetic, mean eGFR of 83.7 ml/min and mean BMI of 29.8 kg/m2. The baseline systolic BP was 143.1 mmHg. Other 4th line agents included bisoprolol, doxazosin and furosemide. When all the data was pooled, spironolactone reduced systolic BP by -7.49mmHg (95% CI 6.47 – 8.51) more than the active comparator. When limited to studies that measured 24hr AMBP, spironolactone reduced BP by 11.16mmHg (95% CI 8.77 – 13.54) relative to the comparator. Analysing observational studies only, spironolactone reduced systolic BP by 10.7mmHg (95% CI 9.07 – 12.46).

Conclusions: On the basis of this meta-analysis, spironolactone reduces systolic BP more effectively than other potential 4th line treatment options in RH. The comparative effectiveness of 4th line agents with regard to clinical outcomes such as myocardial infarction and stroke now needs to be determined.

977. New Statin Use And Left Ventricular Structure: Estimating Long-Term Associations In The Multi-Ethnic Study of Atherosclerosis (MESA)

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Background: Recent treatment guidelines in the United States have increased the number of statin-eligible individuals. While statins show a modest reduction in heart failure hospitalization in meta-analyses of statin primary and secondary prevention trials, the mechanism is unclear. Only small and short-term studies have evaluated statins in relation to changes in heart structure.

Objectives: To estimate the association of new statin use with 10-year changes in the left ventricle.

Methods: We used data from the MESA, which collected data on statin use at five clinic exams over ~10 years, and conducted cardiac magnetic resonance (CMR) imaging at baseline and the ~10 year exam. Participants were free of known cardiovascular disease (CVD) and did not use statins at baseline. Cumulative statin use was estimated between exam intervals for each positive report of current use. Primary outcomes were the change in left ventricular mass index (LVMI; % predicted by height, weight and sex relative to a healthy population) and mass-to-volume ratio (MVR). Associations were estimated in multivariable linear regression analyses, adjusting for baseline age, race, sex, CVD risk factors (e.g. smoking and lipids), anti-hypertensive use by class, exercise, health insurance, and coronary artery calcium.

Results: 3113 participants (53% female; 60% non-white) had a valid CMR scan and no statin use at baseline; 2431 returned for a follow-up CMR after a median of 9.4 years. LVM averaged 120.2 g at baseline and 123.1 g at follow-up. We excluded 42 participants with an incident myocardial infarct. Statins were started by 36% of participants; use ranged from 0-8 years (mean: 1.4). Each additional year of new statin use was not associated with less 10-year progression in LVMI (-0.33, 95%CI: -0.68, 0.01), unindexed LVM (-0.20 g, 95%CI: -0.60, 0.20), or MVR (-0.002, 95%CI: -0.006, 0.003). Results were robust to techniques to account for missing data.

Conclusions: We found no association between statin use and changes in left ventricular mass over ~10 years in a diverse population without clinical CVD at

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baseline, which contrasts with findings from previous studies.

978. Effectiveness Of Preventing Stroke Between Different Rhythm Control Agents For Atrial Fibrillation: Retrospective Cohort Study From A Nationwide And Single-Center Database

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Background: Atrial fibrillation (AF) is a significant risk factor for ischemic stroke. Rhythm control is an important treatment strategy. However, this treatment contains different drugs of choice, but the effect of each agent on stroke reduction remains unknown.

Objectives: To evaluate the comparative effectiveness of rhythm control agents and their combinations on stroke reduction within two Taiwanese electronic health databases.

Methods: We performed two population-based retrospective cohort studies using Taiwanese electronic health data. First, we used the National Health Insurance Research Database (NHIRD; 2006-2010) to identify 3 groups among total of 86,566 AF patients: 1) amiodarone-alone users (n = 40,299), 2) propafenone-alone users (n = 10,943), and 3) amiodarone/propafenone users (n = 1,088). We also used the National Taiwan University Hospital (NTUH; 2007-2013) database to identify the following groups among 3,460 AF patients : 1) amiodarone (n = 1,434), and 2) other rhythm control agents (n = 812). Medication possession ratio (MPR) of amiodarone was also calculated. The definition of amiodarone MPR was cumulative days of amiodarone use for each prescription divided by study period. Within each data source, Cox regressions was used to estimate the risk of stroke associated with use of different rhythm control agents, and covariates including age, sex, CHA2DS2-VASc score, comorbidities and comedications were adjusted.

Results: Within the NHIRD database, amiodarone-alone users had a higher risk of stroke compared to propafenone-alone users (HR, 1.17; 95% CI, 1.08-1.26), but the risk of stroke was not increased in amiodarone/propafenone-combined users compared to propafenone-alone users (HR, 1.10; 95% CI, 0.89-1.36). Within the NTUH database, amiodarone-alone users had no higher risk of stroke compared to other rhythm control agents users (HR, 1.16; 95% CI, 0.67-1.99), but the risk of stroke was higher for amiodarone users when MPR was $> 25\%$ compared to $\leq 25\%$ (HR, 2.37; 95% CI, 1.30-4.30).

Conclusions: Amiodarone may be associated with an increased risk of stroke in AF patients.

979. The Impact of Comorbidity with Heart Failure on Treatments and Outcomes in Patients with Acute Coronary Syndrome

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Background: Clinical trials have reported the benefits of aspirin, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI) angiotensin receptor blockers (ARB), statins, and clopidogrel for reducing the incidence of morbidity and mortality after acute coronary syndrome (ACS).

Objectives: To assess the differences between treatments and outcomes for ACS patients with and without heart failure (HF).

Methods: We conducted a retrospective cohort study of patients who had a hospitalization for ACS recorded in the claims-based Taiwan National Health Insurance Research Database (NHIRD) between January 1, 2006, and December 31, 2010. Patients were classified

according to their usage combination of aspirin, beta-blocker, ACEI/ARB, statin and clopidogrel. Patients were categorized into five groups based on the number of different types of these five medications that were dispensed (1, 2, 3, 4 or 5). Those dispensed aspirin alone were the reference group. Multivariable Cox regression was used to determine the risk of re-hospitalization for ACS associated with use of number of medications.

Results: Among 212,110 patients with ACS (dispensed 2 types of medication: 8,653; prescribed 3types: 21,643, dispensed 4 types: 25,354; dispensed 5 types: 5,599; dispensed aspirin alone: 1,608), compared with patients dispensed aspirin alone, the relative hazards of risk of re-hospitalization for ACS for patients dispensed 2, 3, 4, 5 types of medication are 0.82 (95% CI, 0.77-0.87), 0.83 (95% CI, 0.77-0.88), 0.76 (95% CI, 0.71-0.82), 0.72 (95% CI, 0.66-0.79). Among patients with HF, the risk of re-hospitalization for ACS decreased only when patients were dispensed one kind of medication (HR, 0.86; 95% CI, 0.77-0.96).

Conclusions: Among ACS patients without HF, the risk of re-hospitalization for ACS decreased with increasing number of types of anti-platelet and/or antihypertensive therapies. However, this finding was not observed among ACS patients with HF. The outcomes and effects of treatment among ACS patients with HF are different from those without HF.

980. Population-Based Effectiveness and Safety of Different Antiplatelet Regimens as Secondary Prevention for Ischemic Stroke/Transient Ischemic Attack

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Background: Different antiplatelet regimens are used for secondary prevention after ischemic stroke (IS)/transient ischemic attack (TIA), but studies on the relative effectiveness and safety of each regimen in daily practice are lacking.

Objectives: To assess the relative effectiveness and safety of several antiplatelet regimens as secondary prevention in patients after an IS/TIA in clinical practice.

Methods: A cohort study was conducted using the Clinical Practice Research Datalink. Patients aged ≥ 18 years with a first diagnosis of IS/TIA in 1998-2013 were identified. Antiplatelet exposure was categorized into aspirin-dipyridamole, aspirin-only, clopidogrel-only, aspirin-clopidogrel, other regimens, and no-antiplatelet exposure. The primary effectiveness outcome was a composite endpoint of nonfatal IS, nonfatal myocardial infarction (MI), or cardiovascular (CV) death; and the safety outcome was major bleeding. Time-dependent Cox regression analysis was used to assess the association between antiplatelet regimens and CV effectiveness and major bleeding outcomes.

Results: We followed 20,552 IS/TIA patients for a median duration of 2.3 years. There were 5,714 composite events during follow-up. All regimens were effective in reducing the primary effectiveness outcome compared to no-antiplatelet exposure. Aspirin-only, clopidogrel-only, aspirin-clopidogrel and other regimens were significantly ($p < 0.05$) less effective compared to aspirin-dipyridamole (HR: 1.35, 1.12, 1.40, and 1.27, respectively), adjusted for age, sex, lifestyle factors, disease history and CV comedications. All other regimens were also significantly ($p < 0.05$) associated with a higher relative risk of major bleeding compared to aspirin-dipyridamole (HR: 1.21, 1.32, 1.78, and 1.37, respectively), adjusted for age, sex, alcohol use, liver and renal disease, major bleeding history and comedications.

Conclusions: Compared to aspirin-dipyridamole, all other antiplatelet regimens are less effective in reducing the risk of nonfatal IS, nonfatal MI or CV death, and associated with a higher risk of major bleeding in patients with IS/TIA.

981. Age-Stratified Outcome Of Genotype-Guided Dosing Algorithm For Acenocoumarol And Phenprocoumon

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Background: Age seemed to affect the interaction between coumarins and genotype in the European pharmacogenetics of anticoagulant therapy (EU-PACT) trial, which tested the benefit of pharmacogenetic dosing algorithm for acenocoumarol and phenprocoumon.

Objectives: We conducted further analyses of the data to assess the effect of genotype-guided dosing stratified by age and the influence of potential factors such as comorbidities and comedications in different age categories.

Methods: Data from the acenocoumarol/phenprocoumon arm of the EU-PACT trial was used. 325 patients treated with acenocoumarol and 159 patients treated with phenprocoumon were included in this study. The outcomes of the EU-PACT trial (percentage of time in therapeutic range (TTR) for the International Normalized Ratio (INR, 2.0 to 3.0) during the initial 12 weeks of therapy and the percentage of time below and above the range) were compared between the genotype guided group and the control group in younger <75 years) and older (≥75 years) patients by using independent t-test and were adjusted for sex, height, weight and co-medications.

Results: Among younger phenprocoumon users, TTR during the first 12 weeks in the genotype-guided group (n = 55) was 9.5 % (95% confidence interval (CI): 1.3 to 17.8) higher than the control group (n = 63) with a remarkable lower percentage of time above range (difference: -9.6%, 95%CI: -19.0 to -0.2) and similar percentage time with the International Normalized Ratio (INR) below 2. Older patients dosed by the genotype-guided algorithm (n = 24) spend more time above the range (difference: 27.5%, 95%CI: 12.9 to 42.0). For acenocoumarol users, there were no significant differences between the genotype-guided and control group for most outcomes, except for a lower percentage of time with INR below 2 among older patients, in which 47 the genotype-guided spent 9.9% (95% CI: 1.0 to 18.8) more time than the control group.

Conclusions: Using a genotype-guided algorithm for phenprocoumon benefitted younger patients more, while it could increase the risk of overdose in older patients. This effect was not confounded by the concomitant medication and comorbidity.

982. Incidence of Intracranial Bleeds in New Users and Non-Users of Low-Dose Aspirin in the UK

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Background: Low-dose aspirin protects against ischemic cardiovascular disease and colorectal cancer yet may increase the risk of bleeding.

Objectives: To establish the incidence of intracranial bleed (ICB) in new users and non-users of low-dose aspirin using data from The Health Improvement Network.

Methods: Two cohorts aged 40–84 years from 2000–2012 were identified – new-users of low-dose aspirin (75–300 mg; exposed cohort N = 199,079) and an individually matched comparator cohort of non-users of low-dose aspirin at start of follow-up (mean age 59.6 years). Matching was by age, sex and primary care practitioner visits in the previous year. Cohorts were followed for up to 14 years to identify incident cases of intracranial bleed (ICB), with validation through manual review of patient records and linkage to hospitalization data. Incidence rates (IRs) with 95% confidence intervals (CIs) were calculated overall and stratified by sex, age at start of follow-up and type of ICB: intracerebral hemorrhage (ICH), subdural hematoma (SDH) and subarachnoid hemorrhage (SAH). To minimize the possibility of changes in aspirin use during follow-up, IRs for ICB subtypes were restricted to 1 year follow-up when computed separately for the exposed and non-exposed cohorts.

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Results: 1635 cases of ICB were identified after a median follow-up of 5.39 years (n = 757 for ICH, n = 490 for SDH and n = 388 for SAH) in the two cohorts. IRs (95% CI) per 10,000 person-years (pyrs) were 7.32 (6.97–7.68) overall, 3.39 (3.16–3.64) for ICH, 2.19 (2.01–2.40) for SDH and 1.74 (1.57–1.92) for SAH. Rates of ICB were similar in men and women and increased with age; IRs (95% CIs) were 7.42 (6.93–7.93) for men, 7.22 (6.73–7.74) for women, 4.01 (3.67–4.38) for <65 years, 9.24 (8.54–10.00) for 65–74 years, and 15.51 (14.24–16.90) for ≥75 years. Comparing the exposed and non-exposed cohorts after 1 year of follow-up, IRs (95% CI) per 10,000 pyrs were 4.22 (3.39–5.24) vs. 3.34 (2.61–4.28) for ICH, 2.55 (1.93–3.38) vs. 1.33 (0.90–1.96) for SDH and 2.03 (1.48–2.78) vs. 2.71 (2.06–3.56) for SAH.

Conclusions: ICB incidence increases markedly with age. Low-dose aspirin is associated with a small increase in the risk of ICH and SDH.

983. An Evaluation of the Effect of Spironolactone on the Risk of New Onset of Diabetes in a Population-Based Study of Patients with Heart Failure

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Background: The non-selective mineralocorticoid receptor antagonist spironolactone is an established treatment for heart failure (HF). However, some evidence suggests that it may have a deleterious effect on glucose homeostasis.

Objectives: The objective of this study was to assess whether spironolactone may increase the risk of developing diabetes in a large cohort of HF patients.

Methods: We studied a population-based cohort of patients hospitalized with a primary diagnosis of HF using two administrative databases: the Quebec government administrative database of hospital discharges (MED-ECHO) and the Quebec medical services and prescription claims database (RAMQ) from January 1995 to December 2009. Patients were categorized as new users of spironolactone and non-users. The primary outcome was the new-onset diabetes.

Results: The cohort consisted of 5,773 patients hospitalized with a primary diagnosis of HF, of which 873 were new users of spironolactone. The incidence of new-onset of diabetes was greater in spironolactone users (6.3 per 100 person-years) than in non-users (4.1 per 100 person-years). This increase was significant in both the crude, unadjusted model, with a hazard ratio (HR) of 1.31; 95% CI: 1.08-1.58; p = 0.005, and in an adjusted Cox proportional hazard model (HR: 1.25; 95% CI: 1.03-1.52; p = 0.0259). A propensity-matched cohort analysis revealed consistent results.

Conclusions: HF patients treated with spironolactone in the community appear to have modest increased risk of new-onset of diabetes compared to non-users. Further investigations using large randomized controlled trials will be necessary to confirm the results from this population-based observational study.

984. Novel Oral Anticoagulants and Risk of Gastrointestinal Bleeding: A Systematic Review

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Background: In recent years, a new class of anticoagulants, novel oral anticoagulants (NOACs) (e.g., dabigatran, rivaroxaban, edoxaban), has been approved for treatment of atrial fibrillation (AF), providing advantages (e.g., no monitoring requirement) over warfarin treatment. However, recent post-marketing case reports and other observational data suggest NOACs may be associated with a greater risk of gastrointestinal (GI) bleeding compared with warfarin.

Objectives: To review and evaluate the risk of GI bleeding associated with NOACs compared with the warfarin treatment using published data from randomized controlled trials (RCTs).

Methods: Following a specific protocol, a systematic review of PubMed, EMBASE, and the Cochrane Registry of Clinical Trials was conducted to identify RCTs (in English) among non-valvular AF patients comparing NOACs to warfarin. Abstracts were independently

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reviewed by two researchers with a third reviewer providing input.

Results: Out of 9 RCTs identified, edoxaban and rivaroxaban were each assessed in 4 studies and dabigatran was assessed in 1 study. In one study, high-dose edoxaban [1.51% vs. 1.23%, RR = 1.23 (95% CI 1.02-1.50)], but not low-dose [0.82% vs. 1.23%, RR = 0.67 (95% CI 0.53-0.83)], was associated with an increased GI bleeding risk compared to warfarin. The other 3 edoxoban studies assessed GI bleeding in a composite bleeding events measure and showed an increased risk associated with the high-dose compared to warfarin. In 2 rivaroxaban studies, major GI bleeding was more common in rivaroxaban-treated patients compared with warfarin-treated patients (4.5% vs. 0.6%; 3.2% vs. 2.2%). In another study, as a proportion of bleeding-related events, GI bleeding was more common in rivaroxaban-treated patients. By contrast, one study did not find an increased risk of GI bleeding with rivaroxaban treatment. Compared to warfarin, dabigatran was also associated with an increased risk [1.51% vs. 1.15%, RR = 1.50 (95% CI 1.19-1.89)].

Conclusions: In this systematic review of RCTs among AF patients, NOACs appear to be associated with a greater risk of GI bleeding compared with warfarin. The risk may be dose-related, but that warrants further investigation.

985. Rivaroxaban vs. Phenprocoumon Use in Germany and Risk of Bleeding: A Claims Data Analysis Based on 80,000 Patients

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Background: Rivaroxaban (RVX) is an increasingly used new oral anticoagulant (NOAC) licensed i.a. for stroke prevention in atrial fibrillation (AF) and treatment of venous thromboembolism (VTE). Clinical trials compared RVX to warfarin, but not to the standard of care in Germany, phenprocoumon (PPC). Recent insights regarding defective devices used to measure blood clotting rates in the control group of these trials raised new questions about the risk of bleeding associated with RVX as compared to standard drugs.

Objectives: To characterize new users of RVX versus PPC in Germany and to assess and compare bleeding rates in both groups using claims data.

Methods: Based on data from the German Pharmacoepidemiological Research Database (GePaRD) from 2011 to 2013 a cohort of new users of RVX or PPC was established. Comedication, comorbidity, potential indication as well as the thromboembolic and the bleeding risk scores (CHA2DS2-VASc and HAS-BLED) were assessed. Crude incidence rates (IRs) per 1,000 person years (PY) were estimated for any bleeding leading to hospitalization and the sub-types intracerebral, gastrointestinal and urogenital bleeding. A nested case-control analysis (NCCA) will be applied to compare the adjusted risk of these bleeding events between new users of RVX and PPC using conditional logistic regression.

Results: The study cohort included 31,596 new RVX users and 48,965 new PPC users. Main indications were AF (40%) and VTE (23%). New users of RVX were younger (median 69 vs. 71 years) and had less cardiovascular comorbidity (31 vs. 46% in users with AF). The CHA2DS2-VASc was lower in RVX users while HAS-BLED was similar in both groups. The overall crude bleeding rates were slightly lower in new RVX users compared to new PPC users (overall IR: 17.58 per 1,000 PY (95% CI: 15.98-19.29) vs. 19.60 per 1,000 PY (18.43-20.83)).

Conclusions: New users of RVX and PPC differed regarding cardiovascular comorbidity and thromboembolic risk score. Therefore the crude IRs should be interpreted with caution. As the delivery of further data for the NCCA is pending the results will be presented only at the conference.

986. Risk Factors for Major Bleeding Events in Rivaroxaban Users with Atrial Fibrillation: A Nested Case-Control Study

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Background: Rivaroxaban is a novel oral anticoagulant indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF). Anticoagulation therapies carry a risk of major bleeding (MB), for which patient characteristics may play a role.

Objectives: To examine risk factors for MB within a cohort of rivaroxaban-treated patients with NVAF.

Methods: Data from the United States Department of Defense were examined using a nested case-control design. Cases with MB were selected by a validated claims-based algorithm that approximated the definition of MB used in clinical trials. Incidence density sampling was used to identify five controls without MB for each case. Controls had the same year of entry into the cohort and were at risk for a MB event at the time of each matched case's event (index date). Potential risk factors of MB included demographic characteristics and comorbidities from the 12 months prior to the index date. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from multivariable conditional logistic regression models to identify risk factors for bleeding.

Results: Among 542 MB cases and 2,710 controls, cases were older and had more comorbidities. Cases who had intracranial hemorrhages were more likely to die or have subsequent hemiparesis than those who had bleeds in other locations. The large majority of cases without hemiplegia/hemiparesis or a fatal hemorrhage experienced gastrointestinal bleeding. Based on the multivariable modeling, prior gastrointestinal bleeding (OR: 2.76; 95% CI: 1.98–3.85), vascular disease (OR: 1.82; 95% CI: 1.47–2.24), anemia (OR: 1.80; 95% CI: 1.43–2.26), heart failure (OR: 1.56; 95% CI: 1.26–1.94), and increased age (OR: 1.05 per year; 95% CI: 1.03–1.06) were identified as the strongest risk factors for MB ($p<0.0001$ for all).

Conclusions: Several risk factors for MB during rivaroxaban use were identified, although some findings may have been affected by unmeasured confounding effects. These risk factors may assist in the development of clinical management strategies.

987. Outcomes of Intravenous Corticosteroids in Patients Undergoing Coronary Artery Bypass Grafting Surgery

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Background: Corticosteroids reduce the risk of atrial fibrillation in patients undergoing coronary artery bypass graft (CABG) surgery, but their impact on mortality and safety outcomes is uncertain.

Objectives: To compare mortality, markers of safety outcomes, and length-of-stay (LOS) between patients undergoing CABG surgery with versus without perioperative intravenous corticosteroids (IVCS) exposure.

Methods: Using a nationally representative US inpatient database, we identified patients who underwent CABG between 2003 and 2014. IVCS use was based on in-hospital administration of methylprednisolone, dexamethasone, or hydrocortisone on the day of surgery. Study outcomes -- mortality, insulin administration, antibiotic administration, overall LOS, and intensive care unit (ICU) LOS -- were assessed during the in-patient stay beginning the day after surgery. Propensity score matching was used to adjust for a large number of potential confounders. Cox proportional hazard models, stratified on geographic region, were used to estimate hazard ratios (HRs) for all-cause mortality and insulin and antibiotic administration. Differences in mean LOS and ICU stay were estimated using linear regression models.

Results: Of 401,816 eligible CABGs patients, 80,691 (20%) involved IVCS administration on the day of surgery; of which 49% used methylprednisolone. The mean age of patients was 66 (standard deviation [SD], 11) years old of whom 28% were females. During post-operative in-hospital follow-up, there were more deaths among IVCS users (n = 1,940) compared to non-users (n = 1,483); HR, 1.27 (95% confidence interval [CI], 1.18 to 1.36). IVCS users were more likely to receive antibiotics (HR, 1.17; 95% CI, 1.07 to 1.29) and insulin (HR, 1.03; 95% CI, 1.0 to 1.06). On average, IVCS users spent one more day in the ICU (7 [SD, 8] days vs. 6 [SD, 7]). There was no difference in overall LOS.

Conclusions: In a large population of patients undergoing CABG surgery, perioperative use of IVCS was associated with post-operative in-hospital death and markers of safety outcomes, as well as longer ICU stay.

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988. The Impact of Comorbidity and Age on Treatments for Acute Coronary Syndrome

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Background: Acute coronary syndrome(ACS) is a major cause of death and hospital admissions among the elderly. Clinical trials have reported benefits of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, beta-blockers, clopidogrel, and statins for reducing the incidence of morbidity and mortality after ACS. However,little is known about the impacts of comorbidities and age and their possible association with re-hospitalizations on the treatments of ACS patients.

Objectives: To assess the associations between ten relatively common comorbidities – atrial fibrillation, dementia, diabetes mellitus, heart failure, hypertension, hyperlipidemia, liver disease, peripheral vascular disease, renal disease, and schizophrenia – and re-hospitalization for ACS, and between the age of patients and re-hospitalization for ACS.

Methods: A retrospective cohort study of patients having a hospitalization for ACS recorded in the claims-based Taiwan National Health Insurance Research Database from 2006-2010. A patient was defined as having ACS if they had a discharge diagnosis code of 410.xx, 411xx, or 414xx. The primary outcome was re-hospitalization for ACS, defined as the patients having a inpatient record of ACS after the index ACS event. Multivariable Cox regression was used to determine the relationship between the number of medications dispensed and re-hospitalization for ACS, overall and by sex and age groups.

Results: Among 212,110 patients with ACS, the mean age was 66.0 (SD, ± 12.9) years, and 34.6% were female. A higher number of medications dispensed was associated with a lower risk of re-hospitalization for ACS. No association between a higher number of medications and a decreased risk of re-hospitalization for ACS was observed among the youngest age group (age<45 years old) or oldest age group (age≥75 years old). A non-significant additive effect was found among patients with renal disease, heart failure, and dementia.

Conclusions: Higher number of medications was observed to reduce re-hospitalization of ACS in patients aged between 45 and 75. The results may provide information toward decision-making in personalized ACS medicine based on the different comorbidities and age.

989. Health-Related Quality of Life and Burden of Disease in Patients Suffering from an Acute Coronary Syndrome: Evidences from the Use of Validated Instruments in the PGRx-3 Real World Dataset

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Background: The value of measuring patients' Health-Related Quality of Life (HRQoL) in observational studies is increasingly recognized due to its implications, among others, in describing the burden of diseases and comparing the effectiveness of interventions.

Objectives: To analyse the HRQoL of patients suffering from Acute Coronary Syndrome (ACS) registered in the Pharmacoepidemiology General Research eXtension System (PGRx-3) and to describe the associated humanistic burden.

Methods: PGRx-3 is a newly developed information system comprising multi-national prospective real world datasets designed to identify risk factors of multiple diseases, quantify the associated burdens, describe their management and the outcomes achieved. Patients from UK, France, Italy, Germany, Spain and

US are being recruited by their physicians. Information from medical records is complemented with a set of validated Patient-Reported Outcomes Measures (PROMs). Responses to EQ-5D 5L were compared with the respective population norms (RPNs) to identify the associated burden of disease and analyzed considering key socio-demographic and clinical variables by means of bivariate tests and multivariate models.

Results: The PGRx-3 ACS sample included 1048 ACS cases, of which 678 patients (69.8% males, mean age-SD-=66.16-11.26-, 50.6% with non-ST elevated myocardial infarction) fulfilled the EQ-5D 5L. No differences in relevant socio-demographic variables were found between responders and non-responders ($p>0.05$). Mean utility scores found across all countries were lower than those published in their RPNs (i.e. range of differences-total populations-: 0.074 - 0.206). Moderate to extreme symptoms of anxiety/depression were reported in 17.8% of incident and 19.8% of recurrent ACS patients ($p=0.606$). Adjusted EQ-5D index scores and VAS values were higher in incident subjects ($p< 0.05$).

Conclusions: An important humanistic burden of disease with a substantial presence of psychological symptoms has been evidenced by means of the inclusion of a validated PROM in the PGRx-3 system.

990. Switching of Angiotensin Receptor Blockers to Angiotensin-Converting Enzyme Inhibitors in Patients with Hypertension: Is It a Cost-Saving Strategy?

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Background: Switching Angiotensin Receptor Blockers (ARBs) to Angiotensin-Converting Enzyme Inhibitors (ACEIs) is a common strategy to improve ACEIs/ARBs prescribing efficiency but its clinical and economic impacts are unclear.

Objectives: To evaluate the impact of ARBs switching on the incidence of hypertension (HT) related cardiovascular complications and HT-related medical resource use.

Methods: This retrospective study used data from the UK Clinical Practice Research Datalink (CPRD) in linkage with Hospital Episode Statistics (HES) from April 2006 to March 2012. Hypertensive patients who stopped ARBs and switched to ACEIs within 30 days were followed from the first prescribing date of ARBs to switching date (pre-switching period) and then to either the end of the study period, patients left the dataset or died (post-switching period). Incidences of individual and composite HT related complications (stroke, myocardial infarction, angina, heart failure, and chronic renal failure) and costs of HT related resource use (GP visits, antihypertensive drugs, hospitalisations and outpatient attendance) between pre- and post-switching periods were compared using multilevel, mixed-effect regression. Unit costs based on 2012 National Health Service reference cost and British National Formulary were used to calculate costs.

Results: Of the 470 included patients, 19 and 21 patients in the pre- and post- switching period developed at least one HT-related complication. Compared with the pre-switching period, there was no significant difference in the incidence of individual complications or composite outcome (OR: 0.9, 95%CI: 0.4, 2.0). Switching of ARBs was associated with a reduction in the total medical cost of £329 (95%CI: -534, -205), antihypertensive drugs costs of £177 (95%CI: -246, -148) and hospitalisation costs of £105 (95%CI: -251, -31).

Conclusions: Switching of ARBs to ACEIs was found to be a cost-saving strategy as it was associated with an overall cost saving without an increase in the incidence of HT-related complications. Further study is needed to compare the cost-effectiveness between switching and non-switching patients.

991. Characteristics of Different Antihypertensive Medication Users in Observational Comparative Effectiveness Studies: A Literature Review

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Background: While randomized trials are primarily designed to provide evidence on efficacy of new drugs, observational comparative effectiveness research using electronic health record data provides evidence on effectiveness and safety of drugs in routine medical practice. Early evaluation of effects of emerging therapies is challenging mainly due to confounding (channeling bias).

Objectives: To explore trends in differences in confounder distributions between users of antihypertensives over time since launch.

Methods: A PUBMED search was conducted, followed by a focused literature review on observational comparative effectiveness studies of antihypertensives (angiotensin converting enzyme inhibitors, ACEIs), calcium channel blockers (CCBs) vs. diuretics (D) and beta blockers (BB)) since the launch of ACEIs/CCBs. For each study, information was extracted on baseline characteristics, duration of follow-up, exposure, and outcome. Differences in patient characteristics between ACEIs versus D, ACEIs vs. BB, CCB vs. D, and CCB vs. BB were assessed over calendar years.

Results: Forty observational studies on comparative effectiveness and safety of antihypertensive medications published between 1996 - 2013 were included for the analysis. Major patient characteristics often reported in the studies were age, gender, body mass index (BMI), baseline systolic and diastolic pressures, smoking, diabetes, dyslipidaemia, stroke, ischaemic heart disease, and heart rate. The mean differences in baseline systolic and diastolic blood pressure and smoking status between users of ACEI and D, ACEIs and BB, CCB and D as well as CCB and D decreased over calendar time. No pattern was observed for age, gender, diabetes, and BMI.

Conclusions: Groups of antihypertensive medications users become more similar in some patient characteristics at later times after launch. However, this was not observed for all characteristics and no time window could be identified that is optimal for observational comparative effectiveness research.

992. Withdrawn by Author

993. Cholinesterase inhibitors and Risk of Adverse Cardiac Events: Synergic Effects of Cardiosuppressive Drugs in Dementia Patients

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Background: Cholinesterase inhibitors (ChEIs) may cause adverse cardiac events such as atrioventricular block from increased parasympathetic activity. The potential risk can be much higher in older patients already on cardio-suppressive drugs (CSs).

Objectives: To assess the risk of adverse cardiac events in dementia patients on ChEIs who are concurrently on medications that suppress heart rate or cardiac function.

Methods: We conducted a cohort study of initiators of ChEIs or memantine (reference) using 5% Medicare data. The concurrent use of CSs including alpha or beta blockers (BB), non-dihydropyridine calcium channel blockers, digitalis, antiarrhythmic drugs, and cholinomimetic drugs (CMs), e.g. bethanechol was examined. The outcome was adverse cardiac events identified by inpatient or emergency department ICD-9 codes for sino-/atrio-ventricular block, bradycardia, syncope and syncope-related consequences, e.g., hip fracture. We used Cox regression to estimate adjusted hazard ratios (HRs) for ChEIs, CSs, and synergistic effects between ChEIs and CSs. To quantify synergistic effects, we calculated attributable proportions due to interaction (API) and synergy index (SI).

Results: Among 62,283 new users (49,826 donepezil and 12,457 memantine) with mean age of 82, 73% female, and 81% White, higher outcome rates (per 1000 person-years) were observed in patients receiving donepezil (322) vs. memantine (292). The adjusted HRs were only slightly elevated for donepezil (HR 1.2; 95% confidence interval [CI] 0.9-1.3), BB (HR 1.2; 95%CI 1.0-1.5), or CMs (HR 1.2; 95%CI 0.8-1.6) by itself. However, we found significant positive synergistic effects for donepezil + BB (HR 1.5; 95% CI 1.3-1.7, API 13%, SI 1.6) and for donepezil + CMs (HR 1.7; 95%CI 1.0-1.9, API 16%, SI 1.6).

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Conclusions: The risk of adverse cardiac events was only slightly elevated for ChEIs, BBs, or CMs by itself. However, the risk was much higher with concurrent use of ChEIs and BB or CMs. As polypharmacy is common in the elderly, clinicians should use caution when prescribing ChEIs in patients who are already on BBs or CMs, e.g., bethanechol until proven otherwise by further studies.

994. Medication Therapy Modifies the Association Between Longitudinal eGFR and Cardiovascular Events Among Adults with CKD

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Background: Single time-point eGFR values are used for risk prediction in CKD. Various applications of longitudinal eGFR modeling have been shown to predict cardiovascular events.

Objectives: We jointly modeled longitudinal eGFR and CV events, and tested for modifying effects of medications (beta blockers, ACEI/ARB, statins) on the eGFR association with CVD outcomes.

Methods: A cohort of Geisinger primary care patients with stage G3-G4 CKD(1/1/2001 to 6/30/2012) who had a minimum of 4 outpatient eGFR values and 6-months follow-up was retrospectively assembled. Exclusion criteria included a history of dialysis, renal transplantation, myocardial infarction(MI), heart failure(HF), or TIA/stroke. Patients were followed through 12/31/2012 for the first occurrence of MI, HF, or stroke (CVD), or were censored at ESRD, death or end of study. EGFR was modeled using a random intercept and slope model with a flexible spline transformation of time to capture non-linear trends. Time to CVD was modeled using Cox Proportional Hazard regression.

Results: 17,958 patients met cohort criteria (mean age 68.7 y, 38% male, mean baseline eGFR 51 mL/min) and contributed 103,104 person-years of follow up. Among the patients 28%, 29% and 29% had an active prescription for beta blocker, ACEI/ARB, and statins at time of eligibility, respectively. 2081 (12%) patients developed CVD. In fully adjusted models, each 5 mL/min/1.73m2 decrease in current eGFR was associated with a HR of 1.08 (95% CI 1.06, 1.10). Similarly, each 2 mL/min/1.73m2/year eGFR decrement was associated with a HR of 1.16 (95% CI 1.09, 1.22). Beta blockers and ACEI/ARBs modified the eGFR slope associations, such that the associations were significantly greater among those with an active prescription at cohort entry.

Conclusions: Longitudinally modeled eGFR and time-dependent eGFR slope each independently associates with CVD risk among patients with moderate and advanced CKD. The relative prognostic value of static, single time point eGFR vs. joint modeling of eGFR warrants investigation.

995. Risk Of First Hip Fracture Associated With Incident Benzodiazepine And Related Drug Use In Persons With And Without Alzheimer's Disease

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Background: Although hip fractures are more frequent in persons with Alzheimer's disease (AD), there are no studies on the impact of benzodiazepine and related drug (BZDR) use on hip fracture incidence.

Objectives: To investigate whether BZDR use is associated with increased hip fracture risk in persons with and without AD.

Methods: Design: Retrospective cohort study.

Setting: The register-based MEDALZ cohort included all community-dwelling persons diagnosed with AD in Finland during 2005-2011 (n = 70,718) and their matched comparison persons without AD.

Exposure: BZDRs included benzodiazepines and Z-drugs (ATC classes N05BA, N05CD, and N05CF). With one-year washout period, incident BZDR use

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was extracted from Prescription register data and modelled with the PRE2DUP method.

Main outcome measure: Hip fracture recorded in the Hospital Discharge register. Persons with previous hip fracture were excluded from the analyses.

Statistical analyses: Time with BZDR use was compared with time without BZDR use separately in persons with and without AD. The risk of first hip fracture in relation to incident BZDR use and its duration was analyzed with Cox regression models and confidence intervals (CI), applying BZDR use as a time-varying exposure. Further, age-adjusted hip fracture rates were investigated.

Results: In total, 21.1% (n = 9,782/46,373) of persons with and 12.8% (n = 11,871/92,746) of persons without AD initiated BZDR use during the follow-up (median = 2.8 years). During BZDR use, age-adjusted hip fracture rates were 2.5 (95% CI = 2.2-2.9) and 1.3 (95% CI = 1.1-1.6) per 100 person-years in persons with and without AD, respectively.

BZDR use, compared with nonuse, was associated with increased risk of hip fracture among persons with and without AD (HR = 1.5 [95% CI = 1.3-1.7] and HR = 1.8 [95% CI = 1.5-2.2], respectively). The association between BZDR use and increased risk of hip fracture remained significant for one year (in persons with AD) or longer (in persons without AD).

Conclusions: BZDR use seems to increase the hip fracture risk in persons with and without AD. Rationalizing the pharmacological treatment of AD might decrease the hip fracture rate.

996. Association Between Exposure to Benzodiazepines and Related Drugs and Total Hip Replacement Survivorship in Arthritis: A Population-Based Cohort Study of 246 940 Patients

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Background: Total hip replacement (THR) is successful in treating hip arthritis. Prosthetic survivorship may depend on medications taken by the patient; particularly, the role of benzodiazepines (BZDs) and related drugs (Z-drugs) with THR revision has been poorly investigated.

Objectives: Our objective was to compare THR short-term survivorship according to level of BZDs and Z-drugs exposure.

Methods: Were included all patients aged 40 years or older, having undergone primary THR from January 1, 2009, through December 31, 2012, for arthritis, according to French national health insurance databases. Outcome of interest was THR revision, including any surgical procedure in which the implant or any component was changed or removed. Follow-up started the day the primary THR was performed. Observations were right-censored on December 31, 2014, if neither revision nor death had yet occurred. Exposure of interest was the cumulative defined daily dose per day (cDDD/day) of BZDs and Z-drugs dispensed within 6 months before or after inclusion. We defined four exposure groups; cDDD/d = 0: unexposed; <0.08: low exposure;]0.08-0.38]: medium exposure; >0.38: high exposure. THR survivorship was assessed according to level of BZDs and Z-drugs exposure, in univariate and multivariate Cox models adjusted for patient, THR and implanting center characteristics.

Results: The study cohort comprised 246 940 individuals: mean age at baseline, 69.9 years; women, 57.9%; unexposed: 51.7%; low exposure: 16.7%; medium exposure: 15.9% ; and high exposure: 15.7%. During the median 45-month follow-up, 9043 individuals underwent prosthetic revision. Adjusted hazard ratios in low, medium and high exposed groups were 1.18 (95%CI, 1.12-1.26; P<0.001), 1.32 (95%CI, 1.24-1.40; P<0.001) and 1.37 (95%CI, 1.29-1.45; P<0.001), respectively, compared to unexposed.

Conclusions: Exposure to benzodiazepines and z-drugs is associated with an increased risk of THR revision, with a dose-response relationship. Cautious prescribing is therefore needed as well as careful history examination and assessment of risk for patients with a hip prosthesis.

997. Benzodiazepine Use During Hospitalization: Automated Identification of Potential Medication Errors and Systematic Assessment of Preventable Adverse Events

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Background: Benzodiazepines and "Z-drug" GABA-receptor modulators (BDZ) are amongst the most frequently used drugs in hospitals. Adverse drug events associated with BDZ can be the result of preventable medication errors related to dosing, drug interactions and comorbidities.

Objectives: The present study aimed to evaluate inpatient use of BDZ and related medication errors and adverse drug events.

Methods: We conducted an observational study within a pharmacoepidemiological database derived from the clinical information system of a tertiary care hospital. We developed algorithms that identified dosing errors and interacting comedication for all administered BDZ. Associated adverse drug events and risk factors were validated in medical records.

Results: Among 53081 patients contributing 495813 patient-days BDZ were administered to 25626 patients (48.3%) on 115150 patient-days (23.2%). We identified 3372 patient-days (2.9%) with comedication that inhibits BDZ metabolism, and 1197 (1.0%) with lorazepam administration in severe renal impairment. After validation we classified 134, 56, 12, and 3 cases involving lorazepam, zolpidem, midazolam and triazolam, respectively, as clinically relevant medication errors. Among those there were 23 cases with associated adverse drug events, including severe CNS-depression, falls with subsequent injuries and severe dyspnea. Causality for BDZ was formally assessed as 'possible' or 'probable' in 20 of those cases. Four cases with medication errors and associated severe adverse drug events required administration of the BDZ antagonist flumazenil.

Conclusions: BDZ use was remarkably high in the studied setting, frequently involved potential medication errors related to dosing, co-medication and co-morbidities, and rarely cases with associated adverse drug events. We propose the implementation of automated medication error screening and validation for the prevention of BDZ-related adverse drug events.

998. Effectiveness and Safety of Smoking Cessation Pharmacotherapy: A Retrospective Cohort Study

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Background: Smoking is the leading preventable cause of death in North America. Smoking cessation pharmacotherapies have been shown to potentially increase the risk of cardiovascular and neuropsychiatric adverse events.

Objectives: To assess the relative effectiveness and safety of bupropion and nicotine replacement therapies (NRT) vs varenicline.

Methods: Design and Setting: Using US MarketScan administrative data, 3 cohorts of new users of bupropion (n = 98,319), NRT (n = 19,753), and varenicline (n = 395,598), aged 18 to 99, excluding patients with a diagnosis of depression or antidepressant in the prior 12 months, were studied in the period Jan 2007 to June 2013.

Exposures: Dispensings of bupropion (Zyban® and generic 150mg ER only), NRT, and varenicline.

Outcomes: One-year incidence of re-starting smoking cessation therapy (as a proxy for treatment failure) and of CV and neuropsychiatric events.

Statistical analysis: Odds ratios (OR) from propensity score adjusted logistic regression analysis.

Results: Bupropion was associated with a higher rate (35.3%) of therapy re-initiation within 1-year versus varenicline (17.4%) [adjusted (OR) = 2.60, 95% CI: 2.56-2.64]. NRT had the lowest re-initiation rate (14.4%). Bupropion was associated with a 8% lower 1-year CV risk versus varenicline [OR = 0.92 (0.89-0.95)]. NRT was associated with a 9% increased 1-year CVD risk versus varenicline [OR = 1.09 (1.04-1.14)]. There was no significant association between NRT and varenicline in ischaemic heart disease [OR = 1.03 (0.98-1.09)], heart failure [OR = 0.85 (0.41-1.74)], or peripheral artery disease [OR = 0.96 (0.87-1.07)]. Bupropion and NRT were associated with a relative increased risk of a neuropsychiatric hospitalization [OR = 1.57 (1.39-1.77)] and [OR = 1.35 (1.11-1.64)], respectively.

Conclusions: Bupropion was less effective than varenicline and NRT. CV risk was comparable between varenicline and NRT users and lower among

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bupropion users. Neuropsychiatric hospital admissions were less likely in varenicline users, but a large change in the OR estimate with adjustment suggests potential residual confounding.

999. Association Between Buprenorphine/Naloxone Sublingual Tablet And All-Cause Mortality In Patients Receiving Medication Assisted Treatment For Opioid Addiction In UK

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Background: Buprenorphine/naloxone (B/N) sublingual tablet (SLT) is an effective treatment for opioid addiction. Its long-term impact on mortality is yet to be explored.

Objectives: To evaluate the association between B/N SLT and all-cause mortality in comparison with buprenorphine SLT and methadone.

Methods: In The Health Improvement Network (THIN) database, all new users of B/N SLT, buprenorphine SLT, and/or methadone aged 18 years and older during 2007-2014 were included. Two study designs were employed. In a cohort design, patients entered exposure groups based on the first drug received, and were followed until the first event of death, transfer out, or the end of the study period. Cox's proportional hazard model was used to compare the all-cause mortality among the three groups. In a nested case-control design, up to 5 controls per each death case were randomly selected in each risk set after matching on age, sex and length of follow-up. Conditional logistic regression was used to estimate the association of all-cause mortality with "current" and "recent" use of B/N SLT relative to the "past or never" use of any of the three treatments.

Results: The cohort analysis included 3,284 patients, with 320 in the B/N SLT group, 692 in the buprenorphine SLT group, and 2,272 in the methadone group. After controlling for age, sex, baseline charlson comorbidity, smoking status, alcohol use and cohort entry year, the adjusted hazard ratios for buprenorphine SLT and methadone relative to B/N SLT were 1.24 ($P=0.66$) and 5.02 ($P<0.01$), respectively. The nested case-control analysis included a total of 311 death cases and 1,514 controls. After controlling for the baseline characteristics, the adjusted odds ratios were 0.65 ($P=0.44$) and 1.00 ($P=1.00$) for "current" and "recent" B/N SLT use relative to "never or past" use, respectively.

Conclusions: B/N SLT is not associated with increased all-cause mortality compared to buprenorphine SLT, and is associated with significantly reduced all-cause mortality compared with methadone.

1000. Hypnotic Drug Use and Cardiovascular Events in Treated Hypertensive Patients

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Background: Recent reports suggest insomnia as a factor of hypertension. We have little understanding about blood pressure (BP) among Japanese hypnotics drugs users who are treated with antihypertensive drugs.

Objectives: This study aims to understand characteristics of hypertensive patients of Japanese hypnotics drugs users and non-users, and to investigate in what way their BP influences the incidence of cardiovascular events.

Methods: This is a retrospective matched cohort study using the receipt data on medical treatments and drug dispensing and the data on routine health checkups, provided by the Japan Medical Data Center. The outpatients who started antihypertensive drugs between January 2008 and December 2010 and were prescribed them twice and more were identified with the database. Patients using hypnotics drugs were identified with the database for one-year period after starting antihypertensive drug treatment; non-exposures were matched by age group, sex, and the period of antihypertensive drug treatment at the index date. Index date was the first date of that antihypertensive and hypnotic drugs were simultaneously used. Kaplan-Meier estimates and Cox proportional-hazards regression model was applied to examine the incidence of cardiovascular events.

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Results: There were 757 and 1038 patients prescribed hypnotics drugs and matched patients, respectively. The exposed showed lower BP, higher use of antihypertensive and psychoneurotic drugs compared to matched non-exposures at the date closest to the index date. Hazard ratio (HR) of cardiovascular events were higher in the exposure group; crude HR = 1.62 [95%CI 1.25-2.09] $p<0.001$, adjusted HR = 1.70 [1.21-2.39] $p=0.002$. The longer exposed patients showed a higher HR of cardiovascular event.

Conclusions: Hypnotics use among users antihypertension drugs may be at higher risk of cardiovascular events. However, this study focused on drug utilization only, and other important factors such as exercise, diet, and sleep hours were not available. Further investigation of the relationship between insomnia, treatment with antihypertensive and hypnotic drugs, and cardiovascular events is necessary.

1001. First-Line Disease Modifying Therapies in Preventing Multiple Sclerosis Relapse – A Nationwide Observational Study in Taiwan

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Background: Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system, which is rare in Asian populations. Interferons (INF) and glatiramer acetate(GA) are major medications for MS and recognized as first-line disease-modifying therapy (DMT). Clinical trials of these drugs in Asian population are scanty. It is crucial to evaluate their clinical benefits in real-world setting.

Objectives: The aims of this study were to evaluate the comparative effectiveness of first-line DMT for preventing MS relapse in ethnic Chinese population.

Methods: We retrieved patients with MS and receiving INF 1A, INF 1B, or GA to conduct a retrospective cohort study by using National Health Insurance Research Database between 2001 and 2009. The patients were classified according to their initial DMT. Those died within the first year after diagnosis were excluded. Adherence of DMT was measured by proportion of days covered (PDC), each calculated by the total number of days of DMT supply divided by 180-days in the 2-year follow-up period. Good adherence was defined as a PDC $>=0.8$. We defined hospitalization due to MS or optic neuritis and receiving parenteral corticosteroid as a relapse. We performed proportional hazard regression and Kaplan-Meier estimation to examine their effectiveness in delay the first relapse after receiving treatments.

Results: Six hundreds and thirty one patient were recruited(427 in INF 1A, 161 in INF 1B, and 43 in GA group). Median following time was 1677 days. In comparison to INF 1A, The OR of INF 1B and GA were 1.1855(CI: 0.92-1.52), and 1.51 (CI: 0.98-2.32) respectively. Two events (or more) prior to initiation of DMT was associated with higher risk of relapse (OR = 1.103, CI: 1.00 -1.21). Males had lower risk than females (OR = 0.72, CI:0.53 - 0.96). Hospital levels and geographic regions did not affect the risk.

Conclusions: There is no significant difference of relapse-free survival among three first-line DMTs. Females, and those who had more pre-treatment events were associated with higher risk of relapse. The major limitation of our study is the case number, especially in the GA group.

1002. Comparison of the Effectiveness of Duloxetine versus Pregabalin/Gabapentin for Treatment of Diabetic Peripheral Neuropathy

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Background: Peripheral neuropathy (DPN) is common among patients with diabetes mellitus. Its clinical management is challenging, and response to existing treatments is often inadequate. The comparative effectiveness of duloxetine, pregabalin/gabapentin, and duloxetine + pregabalin/gabapentin is unknown but could help to determine appropriate treatment of DPN, especially within subgroups.

Objectives: To compare the effectiveness of duloxetine, pregabalin/gabapentin, and duloxetine + pregabalin/gabapentin on alleviating symptoms of DPN.

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Methods: We conducted a prospective cohort study in Kovai Medical Center from March 2015 - September 2015. Eligible patients who had type 1 or type 2 diabetes, were newly diagnosed with DPN, and newly initiated treatment with duloxetine alone, pregabalin/gabapentin alone, or combination duloxetine + pregabalin/gabapentin. Neuropathic symptoms were evaluated between 3 clinic visits with a time gap of 30 days each over a time period of 6 months using the Short - Form McGill Pain Quetionnaire (SF-MPQ). Results were analysed using two way ANOVA and Pearson correlation co-efficient.

Results: Forty eligible patients who completed the protocol (15 patients treated with duloxetine alone; 12 with pregabalin/gabapentin; 13 with duloxetine + pregabalin/gabapentin). A significant decrease in neuropathic pain was observed among patients treated with duloxetine alone (change in pain symptoms, 5.86 points; $p < 0.01$) or with duloxetine + pregabalin/gabapentin (change in pain symptoms, 4.30 points; $p < 0.01$). However, no change in pain symptoms were observed among patients treated with pregabalin/gabapentin (change in pain symptoms, 0.80 points; $p = 0.32$).

Conclusions: Duloxetine monotherapy and duloxetine + pregabalin/gabapentin had comparable effects on DPN symptoms while pregabalin/gabapentin had little effect on these symptoms. Larger prospective studies with longer follow-up should be conducted to further evaluate the effectiveness of these agents on DPN..

1003. Comparative Safety of Long-Acting Opioids for Non-Cancer Pain

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Background: The use of opioid analgesics for non-cancer pain in the U.S. has increased markedly and has been accompanied by an increase in deaths and hospitalizations due to opioid toxicity. The safety of long-acting opioids, particularly transdermal fentanyl and oxycodone, is a concern, but little is known about the relative safety of this class of drugs.

Objectives: To compare the risk of death in patients with chronic non-cancer pain receiving transdermal fentanyl or oxycodone slow release (SR) and those receiving morphine SR.

Methods: We conducted a retrospective cohort study in 50,658 patients enrolled in Tennessee Medicaid who filled prescriptions for the three commonly used long-acting opioids: transdermal fentanyl (n = 8,717), oxycodone SR (n = 14,118), or morphine SR (n = 27,823) between 1/1/1999 through 12/31/2011. To decrease the risk of detecting deaths related to a serious disease, patients with cancer, end-stage renal disease, serious cardio-respiratory disease, history of organ transplant, serious neuromuscular diseases, feeding problems, other end-stage organ damage, HIV, and drug abuse were excluded. The primary outcome was out-of-hospital mortality. Relative risk was estimated with the use of Cox Hazard models; time-dependent propensity scores were used to adjust for multiple potential confounders.

Results: There were 689 deaths during 44,385 person-years of follow-up. The all-cause mortality rate among study subjects was 155/10,000 patient-years. All-cause mortality was not significantly different in patients using transdermal fentanyl compared to morphine SR (adjusted HR = 0.96, 95% C.I.: 0.77-1.21). However, patients taking oxycodone SR had 21% lower mortality risk (adjusted HR = 0.79, 95% C.I. 0.66-0.95) than those receiving morphine SR. Sensitivity analyses, including propensity score–matched cohorts and follow-up restricted to the first year of evaluation yielded similar results.

Conclusions: Patients taking long-acting opioids for non-cancer pain have a high mortality risk. Our findings indicate that there is a significant decreased risk of death in patients taking oxycodone SR compared to those taking morphine SR.

1004. Efficacy of Anticonvulsant, Antidepressant and Opioid in Treating Neuropathic Pain – A Systematic Review and Meta-Analysis

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Background: The management of neuropathic pain is challenging due to its etiological complexity.Several pervious systematic reviews focused on select pharmacotherapies in specific type of neuropathic pain, hence the evidence of efficacy is lacking.

Objectives: This study aimed to summarise the efficacy of pharmacotherapies from randomised controlled trials (RCTs) conducted in different types of neuropathic pain.

Methods: A systematic review was conducted by searching electronic databases, Ovid MEDLINE (1996-2015) EMBASE (1974-2015) PsychINFO (1806-2015),Cochrane Central Register of Controlled Trials(1974-2015) and PubMed.Fully published,double-blind RCTs that assessed efficacy of oral and topical pharmacological interventions(anticonvulsants, antidepressants opioids,cannabinoids,topical capsaicin and lidocaine)for neuropathic pain were included. Pooled rate ratios(RRs)of proportions of patients archived 50% pain reduction comparing interventions and placebo and the corresponding 95%confidence interval (95%CI)were calculated by using the Mantel-Haenszel method within a fixed-effect meta-analysis.

Results: Of the 187 RCTs (28782 patients) included in this systematic review,170 were placebo-controlled and 17 were active-controlled trials.The efficacy of anticonvulsants varied in different types of neuropathic pain. Pooled RR of gabapentin compared against placebo was 1.56(95%Cl:1.31,1.87) in postherpetic neuralgia and 2.23(95%Cl:1.60,3.10) in painful diabetic neuropathy patients.Various doses of pregabalin were significantly effective in patients with postherpatic neuralgia and painful diabetic neuropathy. However, pooled RR for pregabalin was 0.86(95%CI:0.7,1.06) in patients with HIV associated neuropathic pain Pooled RR for antidepressants (duloxetine) in painful diabetic neuropathy pain and opioids (morphine,oxycodone) in peripheral neuropathic patients were1.54 (95%Cl:1.34,1.78)and 1.55(95%Cl:1.16,2.07) respectively.

Conclusions: The efficacy of current pharmacotherapies varied in different types of neuropathic pain conditions. Due to a lack of head to head study,a further network meta-analysis is needed to evaluate the efficacy between active comparators.

1005. Impact of Pre-Admission Opioid Treatment on One-Year Mortality After Non-Surgical Intensive Care Admission

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Background: Preadmission opioid use may worsen the prognosis of patients admitted to an intensive care unit (ICU), but data are limited.

Objectives: The aim of this study was to examine the impact of pre-admission opioid-use on one-year mortality following non-surgical admission to an ICU.

Methods: Using Danish registries, this cohort study included all patients admitted to an ICU between 2005 and 2014. Patients who had a surgical procedure other than endoscopy or minor surgery on the day of or one day prior to ICU were excluded. Patients were categorized according to timing of last redeemed opioid-prescription prior to admission into either: current (0-30 days prior), recent (31-365 days prior), former (365+ days prior), or non-user. Patients were followed for 1 year, until 31 December 2014, emigration, or death, whichever came first. Primary outcome was all-cause mortality at 30-days and 31-365-days following ICU-admission. Mortality was estimated using Kaplan-Meier method (1-survival) and crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) were estimated using Cox-regression. Adjusted models included age, gender, socioeconomic factors, co-medication, and comorbidity.

Results: The study included 125,326 ICU-patients; 14% were current opioid users, 15% recent users, 30% former users, and 41% no-users. The 30-day mortality was 34% for current users, 27% for recent users, 23% for formers users and 19% for non-users. After confounder adjustment, current users remained at an elevated risk within the first 30 days following ICU-admission (adjusted HR = 1.24 CI 1.20-1.29) compared to non-users. No association remained for recent or former users. A similar pattern was evident for 31-365-day all-cause mortality: absolute mortality was 6% among current users, 5% for recent users, 3% for formers users, and 2% among non-users. From 31-365-days, both current users and recent users remained at elevated risk with an adjusted HR = 1.47 CI 1.39-1.55 and an adjusted HR = 1.18 CI 1.11-1.25, respectively.

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Conclusions: Current use of opioids is associated with a slightly increased risk of one-year mortality following ICU-admission.

1006. Is Use of Antiepileptic Drugs Associated with an Increased Cataract Risk? A Case-Control Analysis

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Background: Several antiepileptic (AE) drugs such as phenytoin, valproate and carbamazepine have been associated with cataract in previous case reports. One case-control study reported an increased risk of cataract surgery in patients exposed to clonazepam (OR 1.5, 95% CI 1.1-2.1) or carbamazepine (OR 1.4, 95% CI 1.05-1.8). The results were based on a small number of patients and need to be confirmed in additional population-based studies.

Objectives: To explore the association between use of AE drugs and the risk of cataract.

Methods: We conducted a case-control analysis within the UK-based Clinical Practice Research Datalink (CPRD). Cases (≥ 40 years) had either an incident cataract diagnosis or a recorded cataract extraction (i.e., the index date, i.d.). Individuals with a history of cancer, alcoholism, HIV were excluded. Cases and controls were matched 1:1 on age, sex, calendar time, general practice, and number of years of history in the CPRD prior to the i.d. We assessed the number of prescriptions for antiepileptic drugs before the index date and conducted conditional logistic regression to derive Odds ratios (ORs) with 95% confidence intervals (CI). The contribution of various potential confounders (co-morbid conditions or exposure to other drugs previously associated with cataract development) was evaluated in univariate models, and final results were adjusted for BMI, smoking, hypertension, diabetes, and oral steroids. In a sensitivity analysis (to account for the non-acute onset of cataract) we shifted the i.d. backwards for two years.

Results: A total of 185,702 cataract cases and the same number of matched controls were identified. Long-term use (≥ 25 prescriptions) of the following AE drugs was associated with a statistical significantly increased risk of cataract: clonazepam (adj. OR 1.32, 95% CI 1.02-1.70), gabapentin (adj. OR 1.33, 95% CI 1.12-1.58) and pregabaline (adj. OR 1.92, 95% CI 1.40-2.63). In the analysis with the shifted i.d., long-term valproate exposure was also associated with an increased cataract risk (adj. OR 1.25, 95% CI 1.06-1.49).

Conclusions: According to our study, several AE drugs seem to be associated with cataract development.

1007. Estimating the Association of Adverse Health Outcomes Using Three Anticholinergic Medication Toxicity Scales

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Background: Medications with anticholinergic (AC) properties are commonly used and known to cause adverse health outcomes (AHO). AC toxicity scales have been developed as a clinical tool to measure the risk of AHOs, however no scale has been identified as a gold standard.

Objectives: To examine the association between AC toxicity and agitation and ataxia using measures of toxicity generated by a novel scale (ATS) compared to two existing scales (ARS, ACB).

Methods: A retrospective cohort study consisting of 194,279 patients on AC monotherapy from 2001-2013 was conducted using the IMS LifeLink PharMetrics database. A list of 17 prescription drugs was compiled and consisted of identified medications and assigned toxicity levels. The primary outcomes of interest are agitation and ataxia. Descriptive statistics were utilized to describe patient demographics. Poisson

regression was used to calculate incidence rates and risk ratios, and 95% confidence intervals, for each outcome. Spearman rank correlation was used to estimate the correlation between the outcomes of interest and levels of toxicity measured by the different scales.

Results: Incidence rates varied by toxicity level and outcome across scales. After adjusting for age, the risk of agitation and ataxia was greatest in the highest toxicity level compared to the lowest, as measured by the ATS scale (agitation Relative Risk 3 v. 1 = 3.44, 95% Confidence Interval: 3.10-3.82, p< .0001; ataxia RR 3 v. 1 = 1.71, 95% CI: 1.65-1.78, p< .0001). Among current scales, relative risk estimates of the highest toxicity level compared to the lowest level demonstrated a protective relationship (p< .0001).

Conclusions: Toxicity levels measured by the ATS scale more accurately discriminate the risk of AHOs compared to current scales. ATS methodologies for determining toxicity levels are superior in comparison to the ARS and ACB scales. Additional comparative exploration of the ATS scale to current scales is imperative to establish sound medication toxicity levels as a means of estimating the risk of experiencing an AHO among exposed patients.

1008. Psychiatric Medication and School Performance in Primary School Children: An Explorative Study

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Background: Treatment with antipsychotics or stimulants can reduce severe symptoms of psychiatric disorders, however, data on school performance on such treatments are lacking.

Objectives: We aimed to explore school performance among children using antipsychotic drugs or methylphenidate.

Methods: A cross-sectional study was conducted using a pharmacy database linked to academic achievement scores at the end of primary school (Dutch Cito-test). Cito-test scores were obtained for children on antipsychotic therapy, methylphenidate treatment and reference children, and compared using analyses of covariance. Differences in subgroups as gender, ethnicity, household income, concurrent treatment of antipsychotics and methylphenidate, and late starters versus early starters (start date < or > 12 months before the Cito-test) were tested.

Results: 7000 children could be linked to their Cito-test score. At the time of the test, 45 children were on treatment with antipsychotics and 377 with methylphenidate. Scores were different in both treatment groups across gender and in the antipsychotics users on levels of household income (p<0.05).Children using antipsychotics and methylphenidate scored on average 3.1 c.q. 2.1 points lower than the reference peer group (534.5 ± .1) after adjusting for confounders. We found no significant differences between concurrent versus only methylphenidate treatment. Scores of children starting early with antipsychotics were significantly higher than late starters (533.7 ± 1.7 vs. 524.1 ± 2.6), while early starters with methylphenidate scored significant lower compared to the late starters (536.9 ± 1.5 vs. 532.3 ± .5).

Conclusions: This first exploration showed that children on antipsychotic and methylphenidate treatment have lower school performance compared to the reference group. This indicates that both treatments do not normalize school performance. Differences in scores were most noticeable for girls and initiation of the treatment. Due to the observational cross-sectional nature of this study, no causality can be inferred, but the results indicate that school performance should be monitored and causes of underperformance despite treatment warrants more research.

1009. Risk of Parkinson's Disease In The Users Of Antihypertensive Agents: An Evidence From The Meta-Analysis Observational Studies

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Background: Antihypertensive agents, especially calcium channel blockers have been shown to inhibit oxidative stress, inflammatory response and are neuroprotective. Observational studies had reported that use of other antihypertensives like ACE inhibitors

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and ARBs may also show an association in reducing the risk of PD. However, epidemiological studies found an association between the use of antihypertensives and the risk remains uncertain. We conducted a meta-analysis to investigate relationship between use of antihypertensives and PD risk.

Objectives: This study aimed to examine the association between antihypertensive use and risk of Parkinson's disease (PD).

Methods: Literature search was done in PubMed, EMBASE and PsycInfo databases till November 2015. Observational studies evaluating the association between antihypertensive drug use and risk of PD were included. Pooled Odds Ratio (OR) and 95% confidence intervals (CIs) were calculated using random-effects model. Subgroup and sensitivity analyses were also performed.

Results: Seven relevant studies (3 case control and 4 cohort studies) were included, these consisting a of 26,63,004 subjects consisting of 12,120 PD cases. A significant association was observed between use of any antihypertensive agents especially calcium channel blockers. There was significant heterogeneity (I2 = 75%) and no publication bias (Beggs P = 0.2) was observed. As compared to non-use of antihypertensive drugs, the pooled OR for use of angiotensin converting enzyme inhibitors is 0.99 (95% CI 0.78 - 1.20), for angiotensin II antagonists is 0.89 (95% CI 0.77 - 1.08), for beta blockers is 1.24 (95% CI 1.12 - 1.38), and for calcium channel blockers is 0.82 (95% CI 0.71 - 0.93).

Conclusions: The present analysis shown that long term use of calcium channel blockers has shown a significant reduction in risk of Parkinson's disease. In case of ACE inhibitors and ARBs we did not found any significant reduction. Use of beta blockers shown an increased risk of PD. However, studies with large sample size and dose relationships are required to strengthen our hypothesis.

1010. Risk of Mortality in Patients with Parkinson'S Disease Exposed to Domperidone

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Background: Domperidone is used for treating gastrointestinal symptoms in patients with Parkinson's disease (PD). Domperidone use has been linked to cardiovascular and cardiotoxicity side effects that increase the risk of mortality.

Objectives: To determine the risk of mortality in PD patients exposed to domperidone.

Methods: We conducted a matched cohort study using data from the Clinical Practice Research Datalink database (1987–2011). Cohort entry (index date) was the first recorded PD diagnosis date, with no prior exposure to PD medications. PD patients (N = 5,114) were matched 1:1 to non-PD controls. The primary outcome was all-cause mortality. Cox proportional hazard models estimated hazard ratios (HRs) of mortality risk in PD patients using domperidone compared to controls. PD patients were stratified by domperidone use (current, recent, past), disease duration, and disease severity. Secondary analyses for PD patients only, stratified current domperidone use by average daily dose (ADD) and domperidone duration (never use as referent). Time-dependent adjustments were made for comorbidities and drug use.

Results: PD patients with current use of domperidone had a 2.4-fold increased risk in mortality [adjusted (adj) HR = 2.40, CI 1.95-2.94] compared to non-PD controls. This risk was attenuated when use became more distant. Substantial increases in mortality were identified among current users of domperidone with 5+ years since PD diagnosis [adj HR = 3.33, CI 2.34-4.72] and current users with severe PD [adj HR = 2.90, CI 1.81-4.63].

Compared to patients never exposed to domperidone, current use was associated with a 2-fold increase in mortality (adj HR = 2.00, CI 1.64-2.45). Mortality risk was highest in current users receiving a moderate (15 - 30mg) ADD [adj HR = 2.16, CI 1.55-3.01], and those starting domperidone in the previous month [adj HR = 2.97, CI 2.06-4.27].

Conclusions: Current use of domperidone in PD patients results in a more than 2-fold increased mortality risk. Risk is highest within the first month of use and for patients with more severe PD. Domperidone

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should be considered with caution for treating gastrointestinal symptoms in PD patients.

1011. Outcomes of Three Treatment Strategies in Bipolar Disorder Using Conventional Mood Stabilizers and Antipsychotic Drugs

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Background: Second-generation antipsychotics (SGAP) are increasingly used in bipolar disorder to the detriment of the conventional mood stabilizers (MS). However, their benefit-risk ratio remains unknown as a long-term treatment in this indication.

Objectives: To compare outcomes between 3 therapeutic strategies in bipolar disorder using the French national health insurance (CNAMTS) claim database linked to the hospital discharge databases: i) MSs (lithium, valpromide, divalproate, carbamazepine, lamotrigine) without SGAP; ii) SGAPs approved for bipolar disorder (aripiprazole, olanzapine, risperidone, quetiapine) without MS; iii) combination of the two above categories.

Methods: A historical cohort study was conducted in 20,086 patients, aged 21 years and over, newly treated using one the 3 treatment strategies in 2011-2012, with at least 2 dispensings of the considered treatment and diagnosed with a bipolar disorder in the 4 years prior to treatment initiation. Several outcomes considered as markers of treatment failure were identified over 12 months: treatment discontinuation, switch, or addition, psychiatric hospitalization, suicide attempt and death. For each treatment strategy, the cumulative incidence of treatment failure was calculated while adjusting for covariates by propensity score weighting. Covariates included sociodemographics, drug use and comorbidities at baseline.

Results: A total of 8,225 patients (40.9%) received MS, 9,342 (46.5%) SGAP, and 2.519 (12.5%) both MS and SGAP. After one year, one of the outcomes considered had occurred in 75.7% (95%CI: 74.9-76.3) of patients using MSs, in 75.3% (74.6-76.0) of patients using SGAPs, and in 60.5% (58.3-62.6) of patients with treatment combination. The adjusted difference in cumulative incidence for SGAP compared with MS was 0.40% (95%CI -0.59;1.38 $p=0.4$) in whole population, -2.2% (-3.3;-1.2 $p<0.002$) in patients under 65 year-old, and 6.7% (4.1;9.1 $p<0.002$) in patients 65 years and over.

Conclusions: Bipolar disorder was more frequently treated with SGAPs than with MSs. Treatment failure rate appeared dramatically high and SGAPs not better than MSs.

1012. Use of Antipsychotics and Risk of Recurrent Stroke Events: A Population-Based Retrospective Cohort Study in Taiwan

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Background: Antipsychotics have been used in treatment of psychological diseases. Recent researches indicated an increasing risk of developing cerebrovascular adverse events due to the use of antipsychotics. It is necessary to compare the risk of recurrent stroke among different antipsychotics.

Objectives: The aim of this study was to assess the risk of different antipsychotics on recurrent stroke events among stroke patients.

Methods: This is a nationwide population-based retrospective cohort study using administrative claims data National Health Insurance Research Database in Taiwan. A total of 200,546 stroke patients who have been discharged after their first stroke events between 2006 and 2010 were enrolled. Seven groups were identified:

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(1) Non antipsychotics user (n = 166,992), (2) Chlorpromazine user (n = 2,288), (3) Haloperidol user (n = 7,807), (4) Flupentixol user (n = 2,461), (5) Risperidone user (n = 5,263), (6) Quetiapine user (n = 12,939), (7) Other antipsychotics user (n = 2,796). Cox proportional hazard model with time-dependent covariates were performed to estimate the risk of rehospitalization for stroke associated with the use of antipsychotics during the follow-up period.

Results: During the six-year follow-up, antipsychotic users have higher risk on rehospitalization for stroke compared to non-users. Risk of rehospitalization for stroke were higher in Chlorpromazine user (adjusted HR = 1.117; 95% CI0.983-1.270), Haloperidol user (adjusted HR = 1.668; 95% CI 1.557-1.787), Flupentixol user (adjusted HR = 1.520; 95% CI 1.342-1.721), Risperidone user (adjusted HR = 1.786; 95% CI 1.652-1.930) and Quetiapine user (adjusted HR = 1.687; 95% CI 1.603-1.776).

Conclusions: Using antipsychotics among stroke patients was associated with higher risk of rehospitalization for stroke. Caution should be taken when prescribing antipsychotics to patients with high risk for stroke.

1013. Antipsychotic Use and Risk of Hospitalisation or Death Due to Pneumonia in Persons with and without Alzheimer's Disease

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Background: Antipsychotics have consistently been associated with higher risk of pneumonia, but although persons with dementia are particularly susceptible to pneumonia, only one small study assessed the risk of pneumonia in relation to antipsychotic use among persons with Alzheimer's disease (AD).

Objectives: To investigated whether incident antipsychotic use in general, or specific antipsychotics are related to higher risk of hospitalisation or death due to pneumonia in persons with AD or a matched comparison cohort without AD.

Methods: The MEDALZ cohort includes all persons with AD who received a clinically verified AD diagnosis in Finland in 2005-2011 (N = 60,584, n with incident pneumonia 12,225). A matched comparison cohort without AD diagnosis (N = 60,584, n with incident pneumonia 6,195) was used to compare the magnitude of risk. Results were adjusted for a propensity score derived from comorbidities, concomitant medications and sociodemographic characteristics. Sensitivity analyses with case-crossover design were conducted.

Results: Antipsychotic use was associated with higher pneumonia risk (adjusted hazard ratio, 95% confidence interval (CI) 2.01, 1.90-2.13) in the AD cohort and somewhat higher risk in the non-AD cohort (3.43, 2.99-3.93). Similar results were observed with case-crossover analyses (odds ratio 2.02, 95% CI 1.75-2.34 in the AD cohort, 2.59, 1.77-3.79 in the non-AD cohort). The three most commonly used antipsychotics (quetiapine, risperidone, haloperidol) had fairly similar associations with pneumonia risk.

Conclusions: Regardless of applied study design, treatment duration, or the choice of drug, antipsychotic use was associated with higher risk of pneumonia. Thus, the risk-benefit balance should be considered when antipsychotics are prescribed. Especially old persons should be closely monitored.

1014. Antidepressant Use and Outcomes in Combination with Contraindicated Comedication in a Tertiary Care Hospital

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Background: Most antidepressants are known to prolong the QT-interval and may therefore cause life-threatening cardiac arrhythmia, particularly in combination with other QT-prolonging drugs.

Objectives: This study aimed to determine frequency, monitoring and outcomes of QT-prolonging

antidepressant use in combination with contraindicated co-medication in clinical practice.

Methods: Comparative cohort study using our pharmacoepidemiological database derived from electronic medical records at a tertiary care hospital. Validated algorithms identified antidepressant users with formally contraindicated co-administered other QT-prolonging drugs. Frequencies of ECG monitoring and validated adverse events were determined and compared to a randomly selected control cohort of antidepressant users without contraindicated co-medication.

Results: Among all 82358 hospitalizations 6670 (8.1%) were exposed to at least one of 26 different antidepressants. Co-administration of explicitly contraindicated QT-prolonging drugs occurred in 585 (52.0%) and 532 (49.9%) of all users of citalopram and escitalopram, respectively. In patients with contraindicated combinations with citalopram and escitalopram ECG monitoring was documented in 186 hospitalizations (17.3%), and among those there were 11 cases (5.9%) with a validated drug-related prolonged QTc interval. In the control cohort 57 (11.4%) had ECG monitoring, and there were 4 cases (7.0%) with a prolonged QTc interval. Of note, all 4 had co-administered drugs known for QT prolongation but without an explicit contraindication. The relative risk for QT-prolongation in those with contraindicated therapy vs. the control group was 0.8 (95%CI 0.3-2.5). We identified no cases with life-threatening arrhythmia.

Conclusions: Antidepressant users were frequently exposed to contraindicated additional QT-prolonging co-medication, but ECG-monitoring was only performed in a minority of those patients. QT-prolongation was not found more frequently than in patients without formally contraindicated co-medication, who may be exposed to a combination of several QT-prolonging drugs each without a formal contraindication.

1015. Applying a Novel Anticholinergic Toxicity Scoring System to a Retrospective Cohort of Managed Care Patients

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Background: Many commonly used medications have anticholinergic (AC) properties. Overuse or combined use of such medications can lead to adverse events (AE) ranging from subtle changes in mood and cognition to overt acute AC toxicity. Existing scales assign a level of AC toxicity to medications, but most scales are based on clinician judgment and may not be useful for predicting patient-level risk of AC-related AEs.

Objectives: Demonstrate the applicability of a novel AC toxicity scoring system (ATS) using a retrospective cohort study to examine the association between ATS scores and AC-related AEs.

Methods: Computational molecular modeling techniques were used to develop the ATS based on muscarinic receptors M1-M5, resulting in a score ranging from 0-1 for each receptor that can be added or used alone. The PharMetrics Legacy Health Plans Claims Data, a large database of paid medical and pharmacy claims representative of managed care enrollees in the United States, was used to identify a cohort of patients age 5+ with at least one fill between 2002-2013 from a list of 25 eligible medications. ATS scores were assigned to patients for each eligible medication filled during their study period, with scores added across receptors and medications. Logistic regression was used to estimate the association between receptor-specific and total ATS score, and urinary retention (UR) and tachycardia (AEs thought to be primarily associated with MA3 and MA2, respectively).

Results: 287,614 patients were included (mean age = 18 years; 44% male). Increasing receptor-specific ATS scores were associated with an increased risk of UR (odds ratio (OR) = 1.8, 95% confidence interval (CI) = 1.5-2.1) and tachycardia (OR = 1.3, 95% CI = 1.2-1.4). Associations between total ATS score and each AE were smaller but still statistically significant ($p<0.05$).

Conclusions: Receptor-specific ATS scores have the potential to predict risk of AC-related AEs. Such a scoring system has important implications in observational research and in clinical settings, where scores can be assigned to patients based on current medications and used to identify at-risk patients.

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1016. A Novel Molecular-Based Anticholinergic Toxicity Scoring System as a Basis for Assessing Drug-Induced Anticholinergic Burden

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Background: Many common medications potentially interact with muscarinic acetylcholine (MA) receptors through poly-pharmacologic interactions, leading to anticholinergic (AC) adverse events, such as delirium, urinary retention, and tachycardia, particularly among elderly patients. There is a critical need for rational assessment of the relative and cumulative AC toxicity burden induced by medications.

Objectives: To develop a novel AC toxicity scale (ATS) based upon molecular similarity computational techniques that is directly applicable to the clinical assessment of AC toxicity.

Methods: We screened prescription AC drugs of interest against bioactivity databases using a novel bioinformatics method that includes millions of chemicals annotated for known interactions with human receptors. The ATS score is based on each drug's receptor-specific propensity to interact with MA receptors and is derived from molecular similarities between the drug and known bioactives.

Results: Using a subgroup of 25 common AC medications, our approach yielded individual ATS scores for all 5 MA receptors (M1-M5) ranging from 0 to 1.0 and total ATS scores (sum of all 5 individual receptor ATS scores) ranging from 0.3 to 5.0. Using a large medical and pharmacy claims dataset (PharMetrics Legacy Health Plans Claims Data), the population weighted total ATS scores were correlated (R2 = 0.71) with the overall AC clinical burden (mean number of AC adverse events per patient) for the 25 drugs. A strong correlation (R2 = 0.86) was achieved between a population-weighted M3 receptor ATS score and urinary retention, a M3 receptor-specific AC outcome.

Conclusions: The molecular-based ATS scores offer potential advantages over current empirical AC scoring systems including a strong physicochemical basis for drug-receptor interactions and the integration of bioactivity databases. The positive associations between population-weighted ATS scores and overall and specific AC adverse events suggests that ATS holds a promising methodology for predicting patient adverse event risks in clinical practice.

1017. Tolerability/Safety Profile of Cariprazine in Treating Psychotic Disorders/Bipolar Disorder: A Systematic Review with Meta-Analysis of RCTs

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Background: Cariprazine, a novel antipsychotic agent, was recently approved for treating schizophrenia, bipolar mania. Sample sizes of published randomized clinical trials (RCTs) are small; previous meta-analyses included few RCTs and did not specifically investigate the tolerability/safety profile of cariprazine.

Objectives: To systematically review the tolerability and safety of cariprazine versus placebo.

Methods: Clinical trials registers and electronic databases up to January 2016 were searched. A meta-analysis was conducted to investigate outcomes, including risks of discontinuation due to adverse events (AEs), extrapyramidal side-effect (EPS) related events, metabolic syndrome and cardiovascular-related events.

Results: 3,512 subjects in eight RCTs were included. The risk of discontinuation due to AEs for cariprazine was similar to placebo (risk ratio (RR) =0.99, 95% confidence interval (95% CI) 0.71-1.38). Cariprazine was associated with about a 3-fold higher risk of EPS-related events compared to placebo, including risk of treatment-emergent akathisia (RR = 3.63, 95% CI 2.59-5.07) and use of anti-parkinson medication (RR = 2.79, 95%CI 1.63-4.75). There was a statistically significant higher risk of 7% change in weight with cariprazine (RR = 1.77, 95%CI 1.14-2.75). No

significant differences in results were found in other metabolic parameters or cardiovascular-related events.

Conclusions: There was a higher risk of EPS-related adverse events and slight increase in body weight with cariprazine. No significant effect on prolactin level or cardiovascular parameters system was found. EPS were the main short-term adverse reaction to cariprazine reported in the limited number of patients studied. Further clinical and post-marketing pharmacovigilance studies are needed to investigate the long-term safety of cariprazine.

1018. The Risk of Depression, Euphoric Mood and Sedation with the Use of Dextromethorphan in Different Indications. Results from a Systematic Review and Meta-Analysis of Randomised Clinical Trials

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Background: Dextromethorphan (DMP), an antitussive agent, is one of the active ingredients in many OTC cough and cold medicines around the world. Many other indications have been studied in randomized clinical trials (RCTs) with DMP, such as amyotrophic lateral sclerosis, reduction of pain, sedation, detox of alcoholism, opioid withdrawal, and pseudobulbar affect.

Objectives: To provide reliable assessment of unintended effects in central nervous system (CNS) with the use DMP in RCTs in different indications through a systematic review and meta-analysis (SR&MA).

Methods: This SR&MA was registered with PROSPERO database (CRD42015016631) for an evaluation of the safety profile of DMP in CNS.

The search strategy involved randomised clinical trials using DMP in different indications, and spanned from January 1990 to December 2015 in Medline, EMBASE and Cochrane Library databases. This SR&MA was conducted following the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses). The outcomes of interest evaluated were the number of adverse events reported. Analysis of odds ratio (OR), 95% confidence intervals (95%CI) and p-values as generated from the x2 were calculated; heterogeneity was assessed using the I2 test. Sub-analysis by doses (low$<$120 vs high$\geq$120mg/day) and number-needed-to-harm (NNH) were performed.

Results: Sixty-two RCTs were included with 5,987 subjects. Evidence of associations, mainly in the CNS, were in accordance to published data; however, the subgroup DMP-high-dose ($\geq$120mg/day) showed 3 undescribed associations for depression OR 2.83 (1.06-7.53), p = 0.037, I2 = 0.0%; euphoric mood OR 19.53 (2.25-169.5), p = 0.007, I2 = 0.0%, and sedation OR 51.32,(3.02-873.3), p = 0.006, I2 = 0.0%. The NNH were 4.5, 2 and 3.6 respectively.

Conclusions: The associations of depression, euphoric mood and sedation are not described in the summary of product characteristics of Robitusin® (DMP's brand name in the US and UK) for the treatment of cough or Nuedexta® (DMP-quinidine) for the treatment of pseudobulbar affect. Further studies are needed to confirm these findings.

1019. The Risk of Dizziness with the Use of Dextromethorphan in Different Indications; Not a Rare Risk as Described in Label. Results From a Systematic Review and Meta-Analysis of Randomised Clinical Trials

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Background: Dextromethorphan (DMP), an antitussive agent, is an OTC product; other indications have been studied in randomised clinical trials (RCTs), like amyotrophic lateral sclerosis, reduction of pain, sedation, detox of alcoholism, opioid withdrawal, and treatment of pseudobulbar affect. In the label (summary of product characteristics) of Robitusin® (DMP's brand name in the US and UK) and other OTC products for the treatment of cough, the effect of dizziness is marked as 'rare' (incidence: $\geq$1/10,000 to $<$1/1,000).

Objectives: To provide reliable assessment of unintended effects in central nervous system (CNS) with the use DMP in RCTs in different indications through a systematic review and meta-analysis (SR&MA).

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Methods: This SR&MA was registered in PROSPERO database (CRD42015016631). The search strategy involved RCTs using DMP in different indications, from January 1990 to December 2015 in Medline, EMBASE and Cochrane Library databases. This SR&MA was conducted following the PRISMA statement. Outcomes evaluated were number of adverse events in CNS. Analysis of odds ratio (OR), 95% confidence intervals (95%CI), heterogeneity using the I2 test, sub-analysis by doses (low <120 vs high ≥120mg/day) and number-needed-to-harm (NNH) were performed.

Results: Sixty-two RCTs were included with 5,987 subjects. Associations, mainly in the CNS, were in accordance to published data; however, the risk of dizziness was quantified as follows (OR (95%CI), p-value, I2 in % and NNH):

DMP-alone vs Placebo/Comparator 2.88 (2.22-3.73), 17.34%, 4.9

DMP-combinations vs Placebo/Comparator 2.05 (1.44-2.91), I2 13.82%, 15.2

DMP + Quinidine vs Placebo/Comparator 2.57 (1.67-3.96), I2 0.0%, 8.9

DMP≤120 mg/day vs Placebo/Comparator 2.15 (1.50-3.08), I2 16.55%, 14.9

DMP>120 mg/day vs Placebo/Comparator 8.82 (2.14-36.39), I2 32.17%, 4.4.

Conclusions: The risk of dizziness in different groups with DMP is higher (very common (≥1/10); or common (≥1/100 to <1/10)) than the described in the label of Robitusin® and other OTC products. The label of a product should reflect the real incidence of adverse events.

1020. Risk of Myocardial Infarction (MI) Associated with Acute Exacerbations of COPD (AECOPD): Effect Modification by Cardiovascular Drugs

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Background: Chronic obstructive pulmonary disease is a common progressive disease characterised by airflow limitation which is not reversible. Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are worsening of symptoms of cough, dyspnoea and sputum production and are often triggered by infections. Previous studies have suggested that AECOPD may represent periods of increased risk of myocardial infarction (MI) for those with COPD.

Objectives: We aimed to use a within person design to investigate whether use of beta-blockers modifies the relationship between AECOPD and risk of MI.

Methods: We identified COPD patients with both an AECOPD and a first MI between 01/01/04-31/03/14 from the UK Clinical Practice Research Datalink (CPRD) and Hospital Episodes Statistics using previously validated algorithms. We performed a self-controlled case series to make within person comparisons of the rate of MI in the 91 days following onset of an AECOPD compared to their own stable periods for both frequent (≥2 per year) and infrequent exacerbators <2 per year) measured in the year before entry to the study. Analyses were adjusted for the effects of season and we controlled for age in 5 year age bands. We then investigated effect modification by beta-blockers, defined as at least one prescription in the year before entry to the study.

Results: We included 3,886 COPD patients with a first MI. Risk of MI was elevated in the 91 days following an AECOPD compared to stable periods for both frequent (IRR 1.19, 95% CI 1.08-1.31), and infrequent exacerbators (IRR 1.49, 95% CI 1.30-1.71). The effect of AECOPD on MI was modified by use of beta-blockers for both frequent (users IRR 1.08, 0.92-1.27; non-users IRR 1.27, 1.12-1.44; p for interaction 0.006) and infrequent exacerbators (users IRR 1.44, 1.18-1.76; non-users IRR 1.55, 1.27-1.89; p for interaction 0.001).

Conclusions: AECOPD represent a period of increased risk of MI for those with COPD. The effect of AECOPD on risk of MI is lower in beta-blocker users.

1021. Inhaled Corticosteroids and the Risk of Hospitalization for Pneumonia. Results from the OUTPUL Study

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Background: Inhaled corticosteroids (ICS) are used in combination with long acting beta-agonists (LABA) to treat chronic obstructive pulmonary disease (COPD). ICS treatment has been shown to be associated with a reduction of exacerbations, but may also increase the risk of pneumonia.

Objectives: To assess whether use of ICS, with or without LABA increases the risk of pneumonia in COPD patients.

Methods: A population based cohort study was performed using linked hospital and drug prescriptions databases in Lazio region. Patients aged 45+, discharged with COPD diagnosis in 2006-2009 were enrolled and followed from cohort entry until first admission for pneumonia, death, or alternatively, study end (31 December 2012). Cases of pneumonia were identified through a validated alghoritm. A nested case control approach was used to estimate the rate ratio (RR) associated with current or past use of ICS adjusted for age, gender, number of exacerbations in the previous year and comorbidities (including heart failure, diabetes mellitus, hypertension, chronic kidney disease, cerebrovascular diseases, psychiatric diseases). Current was defined, all subject with last prescription of ICS in the 60 days prior the case date. Past users were those subject with last prescription between 61 and 365 days previous the case date. Current use was classified according to three levels (high, medium, low), using the Medication Possession Ratio.

Results: The cohort included 19288 patients, 3141 had an event of pneumonia (incidence rate: for current use 87/1000py, for past use 32/1000py). The adjusted RR of hospitalization for pneumonia associated with current respect to no use was 2.29 (95%CI: 1.99-2.63); for past use RR 1.23 (95%CI: 1.07-1.42. A significant increasing trend in the risk was detected starting from the medium doses. For older patients (80+), the rate was higher than for younger patients, both for current and for past use.

Conclusions: ICS use is associated with an excess risk of pneumonia requiring hospitalization. The effect was greatest for those prescribed higher doses and in very elderly.

1022. Risk of Cardiovascular Events After Glucocorticoid Treatment: A 24-Year Population-Based Cohort Study

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Background: Excess endogenous cortisol has been linked to thromboembolic risk. However, studies on long-term risk of cardiovascular events after glucocorticoid treatment are sparse.

Objectives: To examine the association between glucocorticoid use and risk of cardiovascular events.

Methods: Using Danish medical databases we conducted a 24-year population-based cohort study in north Denmark from 1990 to 2013. We identified 53,891 patients with first-time prescription of oral glucocorticoids in the study period. Using the Danish Civil Registration System we constructed a comparison cohort, consisting up to 5 individuals randomly sampled from the general population, matched on year of birth, sex, and calendar year of the first-time glucocorticoid treatment. The cohorts were followed until one of the outcome diseases (pulmonary embolism, deep venous thrombosis, myocardial infarction, stroke), death, emigration or 30 November 2013. We used Cox proportional hazards regression to compute hazard ratios (HRs) with 95% confidence intervals (CIs) for each outcome, controlling for age, gender and calendar year.

Results: Median follow-up time was 8.3 years (interquartile range [IQR]: 2.7-15.5 years) for patients with glucocorticoid treatment and 6.5 years (IQR: 2.6-12.7 years) for members of the comparison cohort. 54% of patients were females, and the median age at first-time prescription/index date was 59 (IQT: 43-72) and 58 (IQT: 42-71) for the treated patients and their matched comparators, respectively. Compared with the general population cohort, risk of pulmonary

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embolism and deep venous thrombosis was increased among patients with glucocorticoid treatment during 24 years follow-up, adjusted HR: 1.77 (95% CI, 1.58-1.98) and 1.88 (95% CI, 1.73-2.05), respectively. The risk of myocardial infarction increased only marginally for patients treated with glucocorticoid (adjusted HR: 1.10 (95% CI, 1.04-1.17)). The stroke incidence was similar in the two cohorts throughout follow-up, HR: 0.99 (96%CI, 0.94–1.04).

Conclusions: Use of oral glucocorticoids was associated with an elevated risk of venous thromboembolism, but not for myocardial infarction and stroke.

1023. Risk of Idiopathic Pulmonary Fibrosis (IPF) in Patients Exposed to Statins and Other Lipid Lowering Agents

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Background: Idiopathic pulmonary fibrosis (IPF), the most common interstitial lung disease (ILD), is an irreversible interstitial pneumonia with a dismal prognosis. There is conflicting evidence on the relation between statin use and IPF.

Objectives: To assess the relation between statins and IPF and ILD, and compare the risk of IPF and ILD in high versus low-potency statin users.

Methods: We used the HealthCore Integrated Research Database to establish a cohort of new-users of statins and other lipid lowering agents ≥50 years old with ≥6 months of continuous health plan eligibility prior to the first lipid-lowering agent dispensing. IPF was identified by a validated algorithm. ILD, included as a secondary outcome because an ILD that the clinician attributed to statin therapy would not be classified as idiopathic, were identified using applicable ICD-9 diagnosis codes. We controlled confounding using propensity scores and estimated the incidence rate ratio of IPF and ILD for use of statins versus other lipid-lowering agents.

Results: We analyzed 714,474 statin users and 106,428 patients who used other lipid-lowering agents. Mean age of each group at the initiation of therapy was 60 years. Among statin users, we identified 274 IPF cases and 10,751 ILD cases. Among other lipid-lowering agent users, we identified 39 IPF cases and 1,878 ILD cases. The RR estimate for IPF was 1.13 (95% CI 0.80 – 1.58) for statin users versus users of other lipid- lowering agents, and 0.80 (95% CI 0.42 – 1.51) for users of high versus low potency statins. The RR estimate for ILD was 0.87 (95% CI 0.83 – 0.91) for statin users versus other lipid-lowering agent users and 1.35 (95% CI 1.23-1.49) for high versus low potency statin users.

Conclusions: We did not identify a relation between statin use and IPF, however statin-users had a lower risk of ILD than did users of other lipid lower agents. High potency statin users had an increased risk of ILD, compared to low potency statin users.

1024. Increased Risk of Stroke with Co-Exposure of Acute Respiratory Infection and NSAIDs Use: A Nationwide Case-Crossover Study

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Background: Previous evidence suggests that acute respiratory infection (ARI) and NSAIDs (nonsteroidal anti-inflammatory drugs) use are each associated with an increased risk of stroke. However, it is unclear if simultaneous exposure to both further increases risk of stroke.

Objectives: To assess the joint effect of ARI and NSAIDs use on risk of ischemic and hemorrhagic stroke.

Methods: We conducted a retrospective case-crossover study by Taiwan's National Health Insurance Research Database. All patients who had an incident hospitalization with either ischemic or hemorrhagic stroke between 2007 and 2011 were enrolled for analysis. The date of hospital admission with stroke was the index date. We compared the following exposure status between the case (1- to 7-day before the index date) and matched control periods (366- to 372-day before index date): co-exposure to ARI and NSAIDs,

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ARI only, NSAIDs only, or no exposure. Multivariable conditional regression models were used to estimate adjusted odds ratios (aORs) of stroke associated with NSAIDs and ARI co-exposure.

Results: We identified 23,618 patients with ischemic stroke and 5,900 patients with hemorrhagic stroke. Co-exposure to ARI and NSAIDs was associated with a significantly increased risk of ischemic stroke (aOR, 2.28; 95% CI, 2.00-2.59) and hemorrhagic stroke (aOR, 2.30; 95% CI, 1.72-3.08). There was an increased risk of ischemic stroke associated with exposure to ARI only (aOR, 2.11; 95% CI, 1.90-2.33) or NSAIDs use only (aOR, 1.37; 95% CI, 1.29-1.46). And there was also an increased risk of hemorrhagic stroke associated with ARI only (aOR, 1.59; 95% CI, 1.28-1.98) or NSAIDs use only (aOR, 1.50; 95% CI, 1.31-1.71).

Conclusions: Co-exposure to ARI and NSAIDs use may further increase risk of both ischemic and hemorrhagic stroke.

1025. The Key Role of Inhaler Use in COPD: A Real-Life Study

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Background: Errors in inhaler use are frequent and may impact effectiveness of treatment in COPD.

Objectives: To update data on device mishandling, including new devices, in real life setting in France.

Methods: Cross-sectional observational study was conducted in primary care between March and Oct 2015. Physicians had to include COPD patients ≥40 years old, current or ex-smokers (≥10 pack-years), treated ≥1 month with a studied device. They completed a standard procedure to check inhaler technique and documented natural history of COPD. Patients were requested to take a puff of their inhaler without any instructions. They were observed and rated by the physician. Critical errors (i.e. substantially affect dose delivery) were defined prior to the study by experts and not revealed to physicians. For each device, patient inhaler technique was classified as: no error, non critical error and critical error.

Results: 212 GPs and 50 pulmonologists recruited 2935 patients treated with at least 1 studied device: Breezhaler®(n = 876), Diskus®(n = 452), Handihaler®(n = 598), pressurized Metered Dose Inhaler (pMDI, n = 422), Respimat®(n = 625) and Turbuhaler® (n = 420). Among 3393 inhalation technique evaluations, 25% was performed without any error, 45% with non critical error and 30% with at least 1 critical error. The proportion of subjects who read the package leaflet is lower in case of critical error (53.9%; 95% CI, 50.8 to 56.9) vs no error (69.1%; 95% CI, 66.0 to 72.2). Critical errors are respectively made in 15.4%, 21.2%, 29.3%, 32.1%, 43.8%, 46.9%, of inhalation assessment tests with Breezhaler®, Diskus®, Handihaler®, Turbuhaler®, pMDI and Respimat®. For patients treated ≥3 months, frequency of moderate to severe exacerbations within the 3 previous months is higher in case of critical error 38.5% (95% CI: 35.4 to 41.5) vs. no error 32.1% (95% CI: 28.9 to 35.4). Similar results are obtained for hospitalizations or emergency room visits: 6.9% (95% CI: 5.3 to 8.5) vs. 3.3% (95% CI: 2 to 4.5).

Conclusions: Inefficient inhaler technique remains frequent and is associated with recent severe exacerbations of COPD. Prospective studies are needed to confirm that efficient inhaler technique improves clinical outcomes in COPD.

1026. LABA Safety in Actual Medical Practice: Results from the Longitudinal, Time-Dependent Analyses of the ASTROLAB Data

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Background: The safety of Long-Acting -agonists (LABAs) remains an issue in asthma. The ASTROLAB FP-7 European project aimed to assess LABA safety in actual medical practice.

Objectives: To assess the risk of severe asthma exacerbations (SAEx) in patients receiving LABAs in LABA/ICs fixed-dose combinations (FDCs) or in single LABAs (free combination with ICs or in monotherapy).

Methods: ASTROLAB included persistent asthma patients (6-40 yrs) prescribed ≥ 6 months out of 12 of one of 4 therapy patterns: ICs without LABAs, LABAs without ICs, LABAs and ICs in separate canisters (LABA + ICs) and LABA/ICs FDCs. Patients were prospectively followed for ≥ 12 months, with collection of data on drug exposure and severe asthma exacerbations (SAEx: courses of oral steroids and/or unplanned medical contacts for asthma) by computer-assisted telephone interviews every 4 months and monthly text messages. Generalized linear mixed models were used to assess the risk of SAEx during follow-up, according to time-dependent exposure to single LABAs and LABA/ICs FDCs, adjusted for baseline severity and concomitant therapy.

Results: Among 908 patients (mean age = 21.8, 46.6% women), those under ICs without LABA, LABAs without IC, LABAs and ICs in separate canisters and FDCs were 28.9%, 3.0%, 9.1% and 59.0% at inclusion, respectively. After adjustment for baseline severity, increased risks were observed under single LABA exposure and LABA/ICs FDCs: OR = 1.24, 95%CI = [0.75-2.04] and OR = 1.03, 95%CI = [0.75-1.31], respectively.

Conclusions: Non significantly increased risks were observed under the two LABA exposures (FDCs and single LABAs). However, the risk was 24% higher in patients under single LABAs, while it was only marginally increased (3%) for FDCs. The data suggest that FDCs have a satisfactory safety profile while the safety of single LABAs should be verified on larger patient counts.

1027. Development of a Risk Model for Uncontrolled Pneumonia in Hospitalized Patients

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Background: Care of inpatients with community-acquire pneumonia (CAP) has been one of core metrics to determine hospitals' quality of care. Real-time models that can predict admissions with uncontrolled CAP may assist in directing care to patients at greatest need for intervention.

Objectives: This study aimed to identify risk factors for uncontrolled CAP, and construct a dynamic risk model that can be implemented in hospitals' electronic health record systems to prioritize patients at greatest risk.

Methods: We established a retrospective cohort from the two largest University of Florida (UF) affiliated hospitals including admissions aged ≥ 18 years with CAP between January 2012 and October 2013. We identified risk factors for development of uncontrolled CAP from literature, clinician inputs and a technical expert panel. All risk factors were operationalized allowing for automated EHR retrieval. Uncontrolled CAP was defined using respiratory signs (respiratory rate, oxygen levels [SaO2, PaO2 or PaO2/FiO2] or mechanical ventilation) and other clinical symptoms (temperature, heart rate or leukocytosis) exceeding thresholds. For each of the first three hospital days, we used multivariate logistic regression with a full, expert selected and backward eliminated set of risk factors, to predict uncontrolled CAP on day 4.

Results: A total of 527 cases of uncontrolled pneumonia (13.3%) occurred in 3,973 at-risk days during the study period. C-statistics varied from 0.71 for hospital day 1 to 0.77 for hospital day 3 and 0.73 for a model combining all 3 days. Strong predictors included anemia (Odds ratio (OR) = 1.33 [95% CI 1.06-1.67]), inappropriate initial CAP therapy (OR = 1.52 [1.17-1.99]), enteral feeding (OR = 1.67 [1.30-2.14]), liver

injury (OR = 1.31 [1.04-1.66]), PPI or H2-antagonist use (OR = 1.90 [1.49-2.41]), septic shock (OR = 2.53 [1.88-3.40]), uremia (OR = 1.42 [1.08-1.85]) and other viral respiratory infection (OR = 2.35 [1.23-4.49]).

Conclusions: The dynamic risk models for uncontrolled pneumonia achieved satisfactory predictive validity. All risk factors were operationalized from discrete EHR fields and allow full automation for real-time prediction of patients who develop uncontrolled CAP.

1028. Severe Acute Liver Injury Risk Among Temozolomide Treated Brain Cancer Patients in the HealthCore Integrated Research Environment

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Background: Temozolomide (TEMODAR®, Merck & Co, Inc.) is an alkylating agent approved in 1999 and indicated in the US for treatment of adult patients with glioblastoma multiforme (GBM). There have been post-marketing reports of hepatic injury in temozolomide treated patients.

Objectives: To assess the relation, if any, between temozolomide exposure and severe acute liver injury (SALI) in brain cancer (BC) patients.

Methods: We conducted a retrospective case-control study nested within a cohort of patients with malignant BC in the HealthCore Integrated Research Database[SM] (HIRD). Patients were identified by having two medical claims with BC diagnosis on different dates, the latter of which defined the index date. Cohort members were followed forward from this index date to identify potential SALI cases. Potential SALI cases were adjudicated by independent medical record review and confirmed cases were matched on age and calendar year of index date to five controls using incidence density sampling. We assessed the relation between temozolomide exposure and SALI using conditional logistic regression models, controlling for variables that changed the temozolomide effect estimate by more than 10%.

Results: An initial cohort of 11,799 BC patients yielded 250 potential SALI cases. Medical records were obtained for 113, of which 61 were confirmed by adjudication and matched to 305 controls. Temozolomide exposure was more common among controls (22.0%) than cases (18.0%), and no SALI cases were currently exposed at the time of the event. Current/recent temozolomide exposure (≤30 days of SALI date) was not associated with increased SALI risk in adjusted models (Odds Ratio [OR]: 0.62; 95% Confidence Interval [CI]: 0.21-1.85). A sensitivity analysis that included potential SALI cases without medical record information revealed no association between temozolomide use and SALI risk (OR: 1.04; 95% CI: 0.70-1.54).

Conclusions: We found no increased SALI risk associated with temozolomide exposure. Although results were based on small numbers of confirmed SALI cases, sample size was sufficient to rule-out large relative increases in SALI risk (OR > 2).

1029. Proton-Pump Inhibitor Induced Risk of Liver Cancer: A Nested Case-Control Study

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Background: Proton pump inhibitors (PPI) are used in treating gastroesophageal reflux and peptic ulcer. However, omeprazole was found to be associated with liver damage and might be a carcinogen.

Objectives: Whether long-term PPI use will increase the risk of liver cancer (HCC) in patients without hepatitis.

Methods: We conducted a nested case-control study in a cohort in Taiwan National Health Insurance Research Data in 2003-2013. Cases with incident HCC were matched by incidence density sampling to controls who remained without HCC at the date of the cancer diagnosis for the corresponding case. We identified prescriptions duration between omeprazole index date and cancer diagnosis date. A patient receiving ≥28 cumulative defined daily doses (cDDD)

was defined as a user. Adjusted odds ratios (AOR) were calculated using conditional logistic regression adjusted for other comorbidities. For comparison, a similar nested case-control analysis was performed for other types of PPIs, which included dexlansoprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole.

Results: There were 12812 cases and 128073 matched controls. The AOR for HCC associated with omeprazole was 1.12 (95% confidence interval [CI], 0.97-1.28). In considering the use of omeprazole according to cDDD, the AOR was 1.11 (95% CI, 0.95-1.30), 1.19 (95% CI, 0.93-1.53) and 0.95 (95% CI, 0.62-1.45) in patients exposed to omeprazole 28-90, 91-180, and >180 cDDD, respectively, when compared with those exposed to 0-27 cDDD. However, we found HCC had a stronger association with other types of PPIs with an AOR of 1.22 (95% CI, 1.01-1.48). A dose–response effect was found in patients exposed to other PPIs 91–180 and >180 cDDD. The AOR was 1.17 (95% CI, 0.94-1.46), 1.21 (95% CI, 0.96-1.53) and 1.34 (95% CI, 1.04-1.73) in the group of 28-90, 91-180 and >180 cDDD, respectively, when compared with the group of 0-27 cDDD.

Conclusions: Omeprazole was not significantly associated with the risk of HCC, but a long-term exposure to other PPIs might increase the risk of HCC. Further investigation is warranted to study whether the increased risk is associated with stimulation of DNA-damaged cell or any symptom associated with the use of PPIs.

1030. The Risk of Alcohol-Related Mortality in Patients with Psoriasis: A Population-Based Cohort Study Using Linked Primary Care, Hospital and Mortality Records

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Background: An excess risk of all-cause mortality has been observed in patients with psoriasis, a disease which may be associated with unhealthy lifestyle behaviours such as smoking and alcohol misuse.

Objectives: To investigate whether patients with psoriasis have an elevated risk of alcohol-related deaths.

Methods: A cohort of patients with psoriasis was identified between 1998 and 2014 using the Clinical Practice Research Datalink, linked to the Hospital Episode Statistics and to the Office of National Statistics (ONS) mortality records. Up to 20 comparison patients without psoriasis were matched by age, gender and general practice to each patient with psoriasis. Alcohol-related deaths were identified via the ONS mortality records. Cox proportional hazard regression with shared frailty was used to estimate the relative risk of alcohol-related deaths. Analyses were adjusted to account for age, gender, depression, anxiety and area-level social-economic status. Sensitivity analyses included restricting the study to: i) an incident cohort of patients with psoriasis and comparison group; and ii) patients with at least six months follow-up.

Results: The cohort included 98,933 and 1,517,977 patients with and without psoriasis respectively, followed-up for a median (IQR) of 4.6 (6.6) years. Mean age at index date was 44 years (19); 55.76% were female. The alcohol-related mortality rate was 0.48/1,000 person-years [0.43-0.54] for the psoriasis group compared to 0.24/1,000 person-years [0.23-0.25] for the comparison group. The age-and-gender adjusted HR of alcohol-related death for psoriasis was 1.94 [1.71-2.20], whereas the fully adjusted HR was 1.83 [1.62-2.07]. Sensitivity analyses confirmed the results of the primary analysis with the fully adjusted HR of alcohol-related death for psoriasis being: i) 1.89 [1.61-2.23] and ii) 1.83 [1.61-2.09], respectively.

Conclusions: People with psoriasis have almost double the risk of dying due to alcohol-related deaths compared to the general population. The results suggest the need for improved detection and management of alcohol misuse in patients with psoriasis in clinical practice.

1031. Ophthalmic Adverse Effects In Cancer Patients Treated With MEK Inhibitors: A Meta-Analysis

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Background: Treatment with MEK inhibitors reduced neoplastic disease progression and improved the response rate, particularly in melanoma. However, these drugs were also associated with ophthalmic iatrogenics.

Objectives: This meta-analysis aims to evaluate the risk of ophthalmic adverse effects associated with MEK inhibitors.

Methods: A literature search was conducted in Pubmed from its inception until December 2015. Eligible studies were Phase II and Phase III randomized clinical trials (RCTs) including cancer patients which have been designed to evaluate the efficacy and safety of MEK inhibitors (binimetinib, cobimetinib, selumetinib and trametinib) versus placebo or active control. Overall risk of ophthalmic adverse effects, chorioretinopathy, retinal detachment, blurred vision, uveitis and eye hemorrhage were the assessed outcomes. Peto odds ratios (ORs) with the 95% confidence intervals (CI) were pooled. Between-study heterogeneity was assessed using I^2 statistics. Sensitivity analysis was conducted to evaluate the influence of type of cancer (melanoma vs non-melanoma) and RCT' phase in risk estimates.

Results: Eleven RCTs were included in this meta-analysis, one evaluating cobimetinib, six evaluating trametinib and four evaluating selumetinib. RCT evaluating binimetinib did not meet the inclusion criteria. Overall, MEK inhibitors were associated with an increased risk of ophthalmic adverse effects (OR 1.73; 95%CI 1.33-2.24; p<0,0001; I2=83,3%). An increased risk was also estimated for chorioretinopathy (OR 4.96; 95%CI 2.62-9.41; p<0,0001; I2=0%), retinal detachment (OR 7.01; 95%CI 2.99-16.47); p<0,0001; I2=0,0%), blurred vision (OR 1.92; 95% CI 1.21-3.05; p=0,006; I2=47,6%), but not for uveitis (OR 0.99; 95%CI 0.14-7.03; p=0,991; I2=3,6%) or eye hemorrhage (OR 0.72; 95%CI 0.04-12.39; p=0,824; I2=32,5%). Risk estimates did not significantly changed when results were stratified according to type of cancer or RCT' phase.

Conclusions: Treatment with MEK inhibitors seems to increase the risk of ophthalmic adverse effects. A need for monitoring the safety of this class of drugs exists. Regulators, clinicians and other healthcare professionals must, together, be involved in this process.

1032. Impact Of Anti-Inflammatory Drugs On Risk Of Depression And Anxiety After Intensive Care Requiring Mechanical Ventilation

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Background: Critically ill patients are at increased risk of mental illness, including depression and anxiety. Critically ill patients exhibit high levels of inflammation, which plays a role in mental illness.

Objectives: To examine the impact of pre-admission use of nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, statins, or a combination of these on risk of depression and anxiety after intensive care requiring mechanical ventilation.

Methods: Nationwide registry-based cohort study including all patients >18 years) treated with mechanical ventilation in Danish intensive care units during 2005-2013. We excluded patients with a diagnosis of psychiatric disorders or use of antidepressants, anxiolytics, or antipsychotics within a year prior to intensive care. Use of NSAIDs, glucocorticoids, statins, or combinations of these was identified from filled prescriptions.

We computed 3-year risk of depression and anxiety diagnosis and/or prescriptions for antidepressants and anxiolytics in users and nonusers of these anti-inflammatory drugs using the cumulative incidence method, accounting for death as a competing risk. The risk of depression and anxiety was compared using Cox regression hazard ratios adjusted for potential confounding factors (e.g. comorbidity and socio-economic status). Propensity score matched analyses will be presented.

Results: We included 50,631 patients: 16,089 current statin users, 4,696 current NSAID users, 2,550 current glucocorticoid users and 2,259 combination users. Comparing current users with non-users the 3-year risk of anxiety and depression was 17.8% vs. 19.9%

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(adjusted HR 0.85; 95%-CI 0.80-0.89) for statin, 20.7% vs. 18.3% (adjusted HR 1.10; 95%-CI 1.02-1.19) for NSAIDs, 17.4% vs. 19.1% (adjusted HR 1.05; 95%-CI 0.95-1.18) for glucocorticoids, 18.8% vs. 19.1% (adjusted HR 1.04; 95%-CI 0.94-1.16) for combinations.

Conclusions: NSAIDs are associated with a slightly elevated risk of depression and anxiety after intensive care treatment. Glucocorticoids or combinations did not alter the risk. Statins may be associated with a protective effect.

1033. Utilization of Belatacept in Renal Transplant Recipients in USA

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Background: The high incidence of acute rejection is a major concern for using belatacept in renal transplant recipients.

Objectives: To investigate the utilization and clinical outcomes of belatacept in real clinical settings.

Methods: We conducted a retrospective cohort study based on the Scientific Registry of Transplant Recipients (SRTR) data. We included solitary kidney transplant adult recipients, and received belatacept or tacrolimus or both during transplant surgery after June 1st, 2011 and followed up to December 2nd, 2014. The primary 1-year outcome included: composite patient death or graft loss and incidence of biopsy-proven acute rejection (BPAR). The secondary 1-year outcomes included mean estimated glomerular filtration rate (eGFR, mL/min/1.73m2), the incidence of new-onset diabetes after transplantation (NODAT). Recipient and donor's characteristics were adjusted in Multivariate Cox model. Subgroup analyses were conducted in the patients with or without Lymphocyte-Depleting (LD) inductions.

Results: The study included 50,244 recipients, with 417 receiving belatacept + tacrolimus, 458 receiving belatacept-alone, and 49,369 receiving tacrolimus-alone. The rates of composite patient death or graft loss in the two belatacept regimens were noninferior to that of the tacrolimus group. The rates of BPAR were similar between belatacept + tacrolimus and belatacept-alone in all recipients (16.8% vs 18.8%), whereas, were significantly higher than those in the tacrolimus-alone group. The use of LD induction drugs was associated with lower BPAR rates in the recipients who received belatacept-alone (14.6% vs 23.1%, $P=0.02$). eGFR was no different between belatacept- and tacrolimus-treated patients at 12 months. The risk of NODAT was significantly lower in the two belatacept groups than in the tacrolimus-alone group (1.7% vs 2.2% vs 3.8%, respectively, $P=0.01$). In multivariate Cox analyses, belatacept-alone shows a significant higher risk of BPAR than tacrolimus-alone (aHR: 2.36, $P<.0001$), and belatacept + tacrolimus (aHR:1.88, $P=0.002$).

Conclusions: Combining belatacept with tacrolimus or LD induction can reduce acute rejection. Further investigation on detailed regimen of belatacept is necessary for its safe use.

1034. Future Perspectives of Study of Acute Liver Transplant (SALT): What Is Going on Since 2007?

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Background: SALT-I created a network of European liver transplant centres (LTC), also accumulated considerable data on drug-exposed acute liver failure leading to registration for transplantation (ALFT) over the years 2005-2007. The national coordinators of these centres have expressed a desire to continue this collaboration.

Objectives: To extend SALT as EURO-SALT project.

Methods: SALT-II follows the same methodology as SALT-I extending the retrospective part for 7 years (2008-2014). SALT-III is the prospective study of drug-exposed ALFT in LTC with anticipated duration of case recruitment ≥2.5 years. Blood sample is drawn and kept for genetic and drug detection. EURO-SALT is envisaged in 10 countries; five from original SALT (France, Ireland, Italy, Netherlands, UK), five new (Denmark, Finland, Germany, Spain, Sweden). i)

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Retrospective part (SALT-II methodology) will evaluate a 10-year period (2005-2015), providing the risk evaluation of drug-associated ALFT for a 10 year-period in 10 countries. ii) Prospective part (SALT-III methodology) will build a surveillance network of European LTC, thus providing real-time assessment of emerging risks related to drugs newly introduced to the market, allowing for earlier signal identification of a major drug-related public health issue. Prospective case inclusion period of EURO-SALT is anticipated from 2017 to 2020 in 10 countries, depending on the start year of EURO-SALT.

Results: In France, data analyses of SALT-II and case inclusion in SALT-III ongoing smoothly. ANSM has expressed its interest in EURO-SALT and financed a feasibility study, EURO-SALT(f) scheduled for 2016.

Conclusions: This study has been proven feasible by SALT-I study, even on a wider scale. The new methods to be developed are use of hospital information systems to store and extract case data, systematic retrieval of blood samples for pharmacokinetic, toxicological and pharmacogenetic evaluation of drug hepatotoxicity, identifying possible co-factors or drugs that might worsen the prognosis or outcome of the initial liver injury. Linking to claims databases could provide more exposure information. This is a novel issue that has not been yet studied systematically.

1035. SALT-III: Prospective Study of Drug-Exposed Acute Liver Failure (ALF)

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Background: In SALT-I (Study of Acute Liver Transplant) similar per-user risk of ALFT between NSAIDs and a 3-fold higher rate of ALFT in non-overdose paracetamol users were found. SALT-II extends the retrospective part to 2008-2013, thus increasing power. SALT-III takes advantage of this network of liver transplantation centres (LTC) to do a prospective case-population surveillance of ALFT.

Objectives: To develop LTC network for the identification of drug-related ALFT, and to compute event rates for the drugs from the exposure data provided by the national healthcare insurance system.

Methods: Prospective case-population study of drug-exposed ALFT cases in LTC. Inclusion period is 2 years. ALFT cases will be further examined if with/without defined clinical cause. Drug exposure will be investigated for all ALFT cases using all available data including evidence of drug dispensation. Blood samples are drawn and kept for further genetic analyses. The reference population is the whole country populations. The numerator of the incidence rate in the case-population study is the number of ALFT cases where the patient was exposed to the drug(s) of interest within 30 days prior to index date. The denominator of the incidence rate is the population exposure to the drug(s) of interest, determined from the national healthcare insurance system as number of patients exposed per year, and as number of DDD dispensed for the drug and within the drug's ATC class. Incidence rates to the general population will then be computed adjusted for risk factors.

Results: The estimated number of all-cause ALFT cases to be included is 120 over the study period, based on SALT- I results. To date, 29 ALFT cases are included.

Conclusions: The study is ongoing smoothly in France with the enthusiastic collaboration of the LTC. The prospective nature allows for real-time assessment of emerging risks related to drugs newly introduced to the market, thus earlier signal identification of a major drug-related public health issue. Furthermore, determining genetic risk factors will help clarifying underlying conditions. Finally, the methodology will serve for EURO-SALT project.

1036. Comparison of Outcomes Following a Switch from a Brand to an Authorized vs. Independent Generic Drug

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Background: Authorized generic drugs are chemically identical to brand drugs and marketed under the brand drug's new drug application, which is supported by trial data on efficacy and safety. Independent generics are required to demonstrate bioequivalence to the brand drug, but their approval does not require data to demonstrate comparable clinical outcomes.

Objectives: To compare health services use and likelihood of medication discontinuation between authorized and independent generic drugs, which serves as a proxy brand vs. generic comparison that minimizes possible brand drug perception bias.

Methods: A retrospective cohort study was conducted using claims and electronic medical records data from a regional U.S. healthcare system. Seven drugs with authorized and independent generics marketed between 1999 and 2014 were evaluated, including alendronate, amlodipine, citalopram, gabapentin, paroxetine, sertraline, and simvastatin. Eligible adult patients received a brand drug within 6 months preceding generic entry and then switched to an authorized or independent generic within 30 months following generic entry. All-cause emergency department visits, hospitalizations, and medication discontinuation were measured during 12 months following the index brand-to-generic switch date. Multivariable logistic regression models assessed how generic type was related to these outcomes, controlling for pre-index covariates.

Results: Among 5,234 unique patients on a brand drug of interest prior to generic entry, 4,900 (93.6%) switched to a generic within 30 months of generic availability. Patients using authorized vs. independent generics had a similar likelihood of all-cause hospitalization (OR = 1.14; 95% CI 0.91-1.43) and medication discontinuation (OR = 1.04; 95% CI 0.91-1.19), but a slightly higher likelihood of ED visits (OR = 1.33; 95% CI 1.11-1.61).

Conclusions: Similar likelihood of hospitalization and medication discontinuation between authorized and independent generics indirectly supports similar outcomes for generic compared with brand drugs. The finding of higher ED visits with authorized generics needs further investigation.

1037. Potential Prescribing Omissions Among older US Adults According to START Criteria

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Background: Potential prescribing omissions (PPOs) increase the risk of adverse outcomes in older adults. PPOs are an important part of potentially inappropriate prescribing (PIP). In Europe, PPOs have been identified using the Screening Tool to Alert doctors to Right Treatment (START) criteria. US data using these criteria are lacking.

Objectives: To describe the extent of PPO in older US adults using the 2015 START criteria.

Methods: We used a national random sample of Medicare beneficiaries covered by fee-for-service Parts A, B, and D in at least one month from 2007-2013. We estimated the prevalence of PPO as a ratio of the number of older adults without the recommended prescription for 4 months after the qualifying diagnosis, divided by the number of older adult beneficiaries with the diagnosis during the month. We also estimated prevalence of PPO using an adapted version of START criteria in which we excluded beneficiaries with contraindications to the recommended treatment or who received second line treatments. We identified new diagnoses of interest after a 12-month washout period without a diagnosis nor treatment for that condition to avoid counting patients having stopped medication due to side effects as PPO. Over the counter (OTC) drugs were excluded on these results because lack of data.

Results: A total of 43,430 patients and 1,734,089 observations were included during the study period. The mean ± SD age was 76.6 ± 7.8 years (38.2% of aged ≥80), 64.7% were women, and 85.4% were white. A total of 33,601 beneficiaries and 588,153 observations had at least one diagnosis included in START criteria. The most common PPOs were lack of bisphosphonates among beneficiaries on maintenance corticosteroid therapy (45,748 of 53,445; 85.6%) and lack of ACE inhibitors among patients with a new acute myocardial infarction (922 of 1,164; 79.2%).

Conclusions: PPOs are highly prevalent among older US people between 2007 and 2013 according to START Criteria. START criteria are more difficult to implement in claims data than other forms of PIP and suffer from the lack of data on OTC drugs. Nevertheless, strategies to monitor PIP to improve quality of care should include highly prevalent PPOs.

1038. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Population-Based Case-Control Study

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Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions. Previous hospital-based case-control studies identified allopurinol, aromatic antiepileptics, sulphonamide antibiotics (mostly cotrimoxazole, i.e. sulfamethoxazole/trimethoprim), oxicam analgesics, and nevirapine as the main culprit drugs. Other antibiotic classes and other specific drugs have been associated with insufficient evidence.

Objectives: To quantify the risks for SJS/TEN associated with the use of specific drugs.

Methods: We conducted a matched (1:4) case-control study using the UK-based Clinical Practice Research Datalink. Cases were 488 patients with a incident diagnosis of SJS/TEN between 1995 and 2014 (validation presented separately). In conditional logistic regression analyses (multivariable if ≥3 exposed cases/controls), we calculated odds ratios (OR) for SJS/TEN and first-time prescription of various drugs ≤84 days before SJS/TEN onset. For drugs with potential for confounding by indication we performed the same analyses excluding the last 14 days before SJS/TEN onset.

Results: We observed increased OR for most previously identified main culprit drugs (i.e. carbamazepine, lamotrigine, phenytoin, allopurinol [insufficient numbers for oxicam analgesics and nevirapine]), but also for aminopenicillins, quinolones, and cephalosporins. The OR for SJS/TEN were increased in association with trimethoprim only use (OR 9.35, 95% CI 3.62-24.18), but not for other sulphonamide antibiotics. We further observed previously unreported associations for COX-2 inhibitors (crude OR 24.17, 95% CI 2.91-200.77), omeprazole (OR 4.25, 95% CI 1.34-13.49), and lansoprazole (OR 5.85, 95% CI 1.39-24.64).

Conclusions: The observed associations between SJS/TEN and previously identified culprit drugs support the findings of previous studies and corroborate the validity of this SJS/TEN study population (first large SJS/TEN study population from a longitudinal database). Our results further suggest that trimethoprim may trigger SJS/TEN. The observed associations of SJS/TEN with COX-2 inhibitors, omeprazole, and lansoprazole remain to be confirmed in further research.

1039. Stevens - Johnson Syndrome Associated with Dimenhydrinate

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Background: Dimenhydrinate is in the ethanolamine group of histamine receptor H1-antagonists which used for the relief of allergic conditions. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare immune-mediated severe cutaneous adverse reactions and drug-induced. Antibacterial sulfonamides, anticonvulsants, nonsteroidal anti-inflammatory drugs and allopurinol are the most drug or drug groups commonly implicated for SJS and TEN. Previously, Dimenhydrinate is rarely found to induce SJS and TEN.

Objectives: To identify SJS-Dimenhydrinate cases from the spontaneous ADRs reporting system.

Methods: The spontaneous ADRs reports, sent to the national pharmacovigilance center, Ministry of Public Health, Thailand until year 2013 were analyzed. The inclusion criteria were the serious outcome of Stevens-Johnson syndrome. Furthermore, the SJS was

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categorized as certain related to Dimenhydrinate, as evaluated by the Naranjo adverse drug reaction probability assessment tool.

Results: Until 2013, thirty-six cases of SJS-Dimenhydrinate were reported to the national pharmacovigilance center, Thailand. We found two cases out of thirty-six which Dimenhydrinate was the only suspected drug and the Naranjo algorithm causality assessment resulted in certain. One was female, age 85 years, receiving Dimenhydrinate for dizziness. Patient developed SJS within 24 hours and requiring hospitalization. Another was female; 16 years old developed SJS after prescribing in the same day. No history of drug allergy was noted in both patients.

Conclusions: SJS-Dimenhydrinate was uncommon. Although the two cases in Thailand were very rare but the reaction was very serious. Additionally, there were none contributing factors. The mechanism of actions and gene specification of SJS-Dimenhydrinate studies were fewer. Safety risk communication of SJS-Dimenhydrinate to the healthcare professionals is imposed.

1040. Mapping of Existing Data Sources for the Conduct of Real-World Studies in Duchenne Muscular Dystrophy (DMD) in North America and Europe

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Background: Duchenne muscular dystrophy (DMD) is a genetic disorder characterized by progressive muscle wasting and weakness. This rare disease primarily affects boys, representing about 1 in 3,500 male births worldwide. Evidence generation on the safety and effectiveness of new therapies increasingly requires the collection of insight from routine clinical settings or real world data (RWD). In rare diseases, although it is recognized that a number of local registries exist, the availability of RWD remains limited. To data, no repository of such information has been created for DMD.

Objectives: To identify and characterize existing RWD sources that record treatment patterns and disease management for DMD patients in North America (US, Canada, Mexico) and Europe (EU 27).

Methods: Existing data sources were identified through a systematic literature search, using Medline and Embase (1/01/2006-22/01/2016). Search strategies combined the following concepts, using MeSH and Emtree terms: DMD, RWD, and countries of interest. Clinical trials, case reports/series, literature reviews, or opinions were excluded. Identified abstracts were screened for relevance. Retained data sources were reviewed in depth in order to extract the following characteristics in a standardized matrix: country, type, number of patients, availability of disease-specific variables (i.e., biomarkers, PRO etc.), healthcare utilization, linkage capabilities, and access policy.

Results: Literature search yielded 994 abstracts (332 from North America (NA) and 662 from EU). Following screening, respectively for NA and EU, 45 and 60 publications corresponding to 23 and 44 potential databases were retained for in-depth review. Disease registries were the most common, accounting for 24 (35.8%) of sources followed by medical records and EMRs (N = 8, 25.4%). Data elements available in each data source and usefulness for observational research will be presented.

Conclusions: Having a repository of existing RWD sources for rare diseases such as DMD is key to support future clinical research on the safety and effectiveness of new treatments.

1041. Mapping of Existing Disease-Specific Data Sources in Latin America for the Conduct of Real-World Studies

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Background: Safety and cost-effectiveness assessment of new drugs increasingly require the collection of disease-specific variables. Given the importance of having fit-for-purpose data sources, while ensuring efficiencies in preventing duplication of data collection, absence of a central repository of longitudinal and disease-specific data sources in Latin America (LATAM) represents a major challenge.

Objectives: i) Identify and characterize existing real-world data sources in LATAM for 5 selected disease areas: hematology/oncology; immunology; infectious diseases; metabolism; central nervous system (CNS); ii) Determine the usefulness of identified data sources for observational research.

Methods: For each disease area, a list of required data elements for the conduct of real-world studies was developed. Then, a systematic literature search was conducted using Medline, Embase and LILACS (1 Jan 2005-7 Dec 2015). Search strategies combined the following concepts, using MeSH and Emtree terms: Disease of interest, disease-specific variables, and countries of interest. Clinical trials, case reports, case series, literature reviews, or opinions were excluded. Identified abstracts were screened for relevance. Web sources were also searched. For each data source, the following characteristics were extracted through in-depth review of papers: country, type, availability of disease-specific variables (i.e., biomarkers, PRO), healthcare resource utilization, linkage capacities, and access policy.

Results: Literature search yielded a total of 13,379 abstracts. Following screening, 852 publications (6.4%) were retained for in-depth review, corresponding to a total of 534 potential databases to which pragmatic searches added 122 data sources. Most of these originated from Brazil (36.4%, n = 239) and were registries (31.1%, n = 204). Qualitative assessments of data sources regarding the availability of data elements and usefulness for observational research will be presented.

Conclusions: Having a repository of real-world data sources in Latin America will be key to inform the conduct of future observational research.

1042. Mapping Of Existing Disease-Specific Data Sources For The Conduct Of Pharmacoepidemiologic Studies In China

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Background: In recent years, there has been an increasing interest in drug safety and effectiveness research in Asia, especially in China. Although fit-for-purpose data sources appear to be available in China, the characteristics of the data included in such databases and the feasibility of conducting pharmacoepidemiologic studies remain poorly examined to date.

Objectives: i) Identify and characterize existing data sources for two selected diseases, representing respectively highly prevalent and rare diseases in China: Lung cancer and Duchenne muscular dystrophy (DMD); ii) Determine the usefulness of identified data sources for observational research.

Methods: A literature review was conducted using Medline and Embase (1 Jan. 2010-26 Jan. 2016). Search strategies combined the following concepts, using respectively MeSH and Emtree terms: Disease of interest, real-world data and China. Clinical trials, case reports/series, literature reviews or opinions were excluded. Identified abstracts were screened for relevance. In addition, pragmatic web searches have been conducted in English, Simplified and Traditional Chinese. For each retained data source, the following characteristics were extracted: type, setting, availability of patient and disease-specific variables (clinical, biomarkers, laboratory values, etc.), linkage capabilities and access policy.

Results: A total of 1,311 and 65 publications were found, respectively for lung cancer and DMD, out of which 205 and 5 abstracts (15.6% and 7.7%) met the inclusion criteria, corresponding to a total of 114 and 4 potential databases. Most of the sources consisted of disease registries (n = 27, 23.7% for lung cancer and n = 2, 50.0% for DMD). For lung cancer, other sources included: cohorts with ad hoc data collection (n = 26, 22.8%), surveys (n = 11, 9.6%), EMRs (n = 7, 6.1%) and administrative claims (n = 4, 3.5%). Details on each data source will be presented.

Conclusions: Several real-world data sources have been identified in China and the availability of data

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elements suggests that they could become a valuable resource for pharmacoepidemiologic research.

1043. Assessment and Comparison of Competitiveness Between Clinical Trial Protocols: A Simulation Approach Using Publicly Available Registered Clinical Trials

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Background: Clinical trials that target similar patient populations can compete for patients for recruitment. In fact, competitive trials may come from the same sponsor. As sponsors designs new clinical trials, it is important to understand how competitive trials may be in comparison to the landscape of other trials. Therefore we developed a process for comparing protocols on key eligibility criteria and determining the competitiveness between them and compared three non-small cell lung cancer (NSCLC) trials for competitiveness.

Objectives: To demonstrate a unique method for comparing competitiveness between clinical trial protocols.

Methods: Key eligibility criteria were identified for the three NSCLC trial protocols obtained from www.clinicaltrials.gov. For each criterion, we identified the distribution in target patient population using published literature, hospital-based claims data and electronic medical records (EMR) data. We generated a pseudopopulation of patients with clinical and demographic values obtained via sampling from health data-based distributions. We assessed key eligibility criteria to determine how many simulated patients in our pseudopoulation were eligible for each clinical trial, and how many were eligible for more than one trial. For sake of simplicity, we restricted analysis to comparisons between two trials at a time. We defined competitiveness as the total number of simulated patients who were eligible for both trials (intersection) divided by the number of patients who were eligible for either trial (union): Cpe = T1 ∩ T2 / T1 ∪ T2.

We generated survival-like curves to illustrate the impact of each criterion on inclusion into each trial and Venn diagrams to illustrate relative size of trial inclusion and overlap.

Results: Competitiveness of trial comparisons ranged from 0% for mutually exclusive trials to 100% for completely overlapping trials, with the average competitiveness of the NSCLC trials of 13%.

Conclusions: This method demonstrated useful in comparing and assessing competitiveness between clinical trial protocols. Future work will include temperospacial development.

1044. Progress and Future of Medical Information Database Network (MID-NET®) Project

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Background: PMDA, the Japanese regulatory agency, has reinforced post-marketing drug safety measures by implementing pharmacoepidemiological approaches since FY2009. In FY2011, Ministry of Health, Labor and Welfare (MHLW) and PMDA initiated the new project called as "MID-NET® (Medical Information Database Network)" for establishing a new Electronic Medical Records (EMR) database including data from the 23 hospitals in Japan. This system is the first, largest and real-time Japanese EMRs database which stores various linked-data such as pharmacy claims and laboratory test values. Here, we report the progress and future of MID-NET®.

Objectives: To efficiently utilize EMRs for quantitative drug safety assessment through establishment of a new database system.

Methods: MID-NET® project consists of 5 steps; 1) Development of database with analytical system in each hospital and PMDA. 2) Data quality check. 3) Verification of the system operation. 4) Trial utilization of MID-NET® by MHLW / PMDA and 23 hospitals. 5) Full-implementation of MID-NET®.

Results: PMDA has successfully completed developing a closed network among the 23 hospitals in Japan. EMRs in each hospital were stored in the standardized format (HL-7). Currently, a validation process of data

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quality and analytical system is the final stage to ensure validity and integrity of results for regulatory decision making. Recently, we have started trial utilization of MID-NET®.

Conclusions: PMDA has developed EMRs database with analytical system for drug safety assessment. We will continue to make efforts for establishing the MID-NET® system aiming for its full implementation in 2018. The MID-NET® system will be highly valuable in pharmacoepidemiological drug safety assessments, resulting in contributing to more effective safety measures and advancing public health.

1045. A Framework for Rapid Medical Product Safety Assessment: FDA's Sentinel Toolkit

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Background: The US FDA's Sentinel Program uses customizable analytic tools (ie, modular programs) to rapidly provide descriptive information across a large distributed electronic healthcare data network. These results help inform more complex analyses.

Objectives: To describe Sentinel "Level 1" modular program querying capabilities that support medical product safety surveillance activities.

Methods: Sentinel includes 16 data partners (DPs) that together have healthcare information for over 193 million individuals contributing 351 million person-years of quality-checked data from 2000 to 2015. Each DP routinely transforms its healthcare data into the Sentinel Common Data Model and stores the transformed data locally, within its firewall. DPs execute standardized modular programs distributed securely by the Sentinel Operations Center (SOC) and only return de-identified, aggregated results needed for the analysis. Level 1 programs use customizable parameters such as inclusion/ exclusion criteria, enrollment requirements, and flexible exposure and outcome definitions based on medical product use, diagnosis and procedure codes to perform unadjusted analyses. Complementary tools to perform confounder adjustment (Level 2 and 3 analyses) are also available (not described here).

Results: Modular programs can describe: 1) background rates 2) uptake, use, and persistence of medical products 3) health outcomes following medical product exposure 4) concomitant medical product use 5) health outcomes during concomitant use 6) frequently observed diagnoses, procedures, or drug dispensing and 7) baseline distributions of potential confounders. Analyses can be stratified by age group, sex, year, month, comorbidity score, or healthcare utilization metrics. In 2015, the SOC supported 57 FDA Level 1 requests that evaluated nearly 1,500 unique sets of query parameter combinations and generated over 80 reports. Requests typically take 4 weeks to complete from the time query parameters are finalized.

Conclusions: These publicly available modular programs are the backbone of Sentinel's distributed querying system, contributing to the FDA's ability to rapidly generate information on medical product safety questions.

1046. Lessons Learned from the Assembly of the SENATOR Drug File

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Background: The potential benefits of clinical decision support systems (CDSS) are well established. The European Union has funded the development and clinical trial of a new Software ENgine for the Assessment and optimization of drug and non-drug Therapy in Older peRsons (SENATOR). SENATOR is an ambitious project which aims to develop a high-powered software engine capable of efficiently assessing the clinical status, pharmacological and non-pharmacological therapy of elderly, multi-morbid patients in order to define the optimal drug therapy, highlight risk of adverse drug reaction (ADR), provide guidance on best value drug brand for selection and also to advise non-pharmacological treatment.

Objectives: Lacking an existing multinational drug file suitable for use in SENATOR, a comprehensive combined drug file from sites in six participating E.

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U. countries (Belgium, Iceland, Ireland, Italy, Spain and the UK) needed to be assembled. This lengthy process required input from all sites as well requiring one site (Ireland) to coordinate.

Methods: The creation of the drug file consisted of five steps;
- Consultation and planning
- Assembling the raw data
- Data verification and error checking
- Streamlining for SENATOR
- Continual Updating.

Results: The end result of this 5 step process was the creation of two drug files; a larger, comprehensive drug file and a second version streamlined for use in SENATOR. Ultimately, the assembly proved to be a challenging process, from which many lessons were learned.
- The consultation and planning phase was essential to the success of the process.
- The raw data collection was comprehensive, but ultimately captured some unnecessary data.
- Data verification and error checking was a time consuming process but the errors uncovered highlight its importance
- The importance of considering end-user suitability was demonstrated by the significant streamlining process.
- Continual updating is an important consideration and the design of SENATOR's drug file simplifies the addition new products.

Conclusions: The lessons learned from this experience will prove valuable in guiding future research and serve as a reference point for future assembly of multinational drug files for use within a CDSS.

1047. An eResearch Query Definition Library: Methods and Value

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Background: Widespread adoption of electronic health records (EHRs) results in a wealth of data in structured/codified and unstructured/uncodified electronic formats. Research studies seeking to use these data require translation of narrative research protocols into EHR-friendly queries. This involves interpretation of the protocols, distillation into distinctive query-level components and determination of appropriate code value sets (list of ICD-9 codes, procedure codes, medication codes, etc.). In addition, for studies conducted across multiple disparate EHR data sources, it is essential to ensure queries are conducted in a consistent and comparable manner. EHR-friendly query definitions provide the necessary granularity of information needed to conduct consistent queries across multiple EHR data sources.

Objectives: The objective is to develop and demonstrate the value of a curated EHR research query definition library to improve efficiency of EHR research queries.

Methods: A standard format for electronic research query definitions was established following federal EHR certification standards. A logic format was developed to articulate the research protocol into informaticist terms that lead to data analyst-friendly query statements. Healthcare industry standard vocabulary terminologies are used to develop code value sets. A hosting library was developed to maintain version control and repurposing of developed definitions.

Results: Our query definition format, content and time-savings were validated through an iterative process with multiple healthcare informatics systems across a variety of disease therapy areas, including but not limited to: cardiovascular, CNS/neurology, metabolics, nephrology, oncology, pulmonology/respiratory, etc.

Conclusions: An EHR-compatible format for research query definitions expedites the process of data query and analysis. Our Query Definition Library of protocol-specific validated query definitions standardizes queries and expedites future definition development. It also provides ready access to curated standardized EHR-compatible research query definitions to support clinical research studies.

1048. Integrating ICD-10-CM Coding into RWE Research Using US Healthcare Databases: Challenges for Valid Research Practices

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Background: In October 2015, US healthcare providers transitioned to the ICD-10-CM version of the WHO's disease classification system. The expanded coding scheme offers more granularity and a dramatic increase in the number of disease codes. This greater complexity results in only a small number of direct, 1:1 mappings between ICD-9 and ICD-10, creating a significant challenge for researchers using EMR and claims databases, who now must define disease cohorts and study outcomes with both coding systems.

Objectives: This study illustrates the impact on analytic results when disease definitions do not integrate equivalent ICD-9 and ICD-10 codes.

Methods: ICD-9 to ICD-10 mapping tools, such as CMS's General Equivalence Mappings (GEMs), bridge differences between coding schemes to yield meaningful clinical comparisons. We evaluated the risk of adverse outcomes among patients exposed to tricyclic antidepressants (TCAs) vs. SSRIs using UBC simulated claims data, first using GEMs to define our outcome then repeating the analysis without GEMs. We then compared the estimated relative risk, Screening Rate Ratio (SRR), and mean time to event for the two approaches.

Results: We identified 112,499 patients with TCA exposure and 297,187 patients SSRIs exposure. The largest difference observed was for unspecified corneal deformity. The GEMs-based SRR was 12.1 vs. 16.9 using ICD-9 and 7.3 using ICD-10. Also, without GEMS the mean time to event was affected, as seen in the acute salpingitis and oophoritis results for TCA patients: 26.6 days with GEMS vs. 11.0 days for ICD-9 and 89.0 days for ICD-10.

Conclusions: An ICD-9 to ICD-10 mapping tool is important for generating analytic results that accurately evaluate all diagnostic information in the study population. Researchers need to understand the impact that the expanded ICD-10 codes have on their study design, and become familiar with resources available for code mapping. Supplementing crosswalk tools with clinical knowledge is critical to avoiding imperfect mappings. These challenges extend into the future as retrospective database analyses including both ICD-9 and ICD-10 codes become the norm.

1049. Assessing the Gaps in Turning Data into Insights Using Real World Evidence

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Background: IBM Watson Health, launched in April 2015, is building a platform with robust data and analytic capabilities to shorten the time to insights for life science companies leveraging big data and cognitive computing.

Objectives: In January 2016, IBM conducted a workshop with pharmacoepidemiologists and executives from several pharmaceutical companies to determine their biggest challenges and needs in their Real World Evidence (RWE) analytical practice. One notable finding was the challenge in harnessing insights from emerging data sources like wearables, mobile, and medical devices.

Methods: We employed IBM's design thinking methodology to facilitate a two-day workshop with eleven pharmacoepidemiologists from small and large pharmaceutical companies. Collaborative activities were led by a design team to understand key user unmet needs and industry gaps. Overall we sought to solicit information from participants to better understand the challenges and hurdles to providing decision support and insights from RWE.

Results: RWE is a massive space with tremendous opportunity. Adoption of our products will require a paradigm shift in how the pharmaceutical industry accesses and uses emerging as well as traditional sources of data, conducts analysis, and distributes findings. Users are looking for a cognitive solution to summarize and highlight user opportunities in the data that may have not otherwise been identified. There is a desire to work in a more collaborative environment with the ability to easily link data from multiple sources with the goal of moving toward precision medicine. Stakeholders including payers, regulators, and providers are also needed to participate in the formulation of the ecosystem for adoption.

Conclusions: Participants confirmed that traditional sources of data like claims, laboratory, and EHR data is still very important to their analytic activities. In addition, participants have not yet embraced exogenous data (weather, wearable, social, behavioral). However, if the value of this type of data can be demonstrated, then users are open to including it in their work.

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Facilitating insights from traditional and emerging sources is an open need in this community.

1050. Comparative Assessment of US Healthcare Databases and Linkage Capabilities for Pharmacoepidemiology Studies

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Background: Population-based pharmacoepidemiology studies rely on information on exposures and outcomes that occur in general populations in clinical practice. Real world data can be used to conduct these studies, however different types of databases (e.g., claims, electronic medical record (EMR)) have different uses and linking disparate databases can expand their end use (e.g., linking medical claims to EMR). Real world data are commonly used in pharmacoepidemiology studies and it is important to systematically assess the utility of these data sources.

Objectives: Assess data availability and linkage capabilities across United States (US)-based data assets for pharmacoepidemiology studies, using data at IMS Health as an example.

Methods: An analysis of IMS Health US data assets was conducted. First a framework was created to define key required data elements for pharmacoepidemiology based on 13 domains of the Observational Medical Outcomes Partnership (OMOP) common data model. Second, 7 commonly used IMS databases were systematically reviewed—including PharMetrics Plus (PMTx+), Ambulatory EMR (AEMR), and Oncology EMR (OncEMR)—to determine which data sources contained elements of interest.

Results: All 7 datasets contained patient-level cohorts. PMTx + contained variables in 11 of 13 OMOP domains for $>$ 98 million patients in 2014. The AEMR and OncEMR databases contained information mapping to all domains, but for smaller cohorts. A Health Insurance Portability and Accountability (HIPAA) compliant deterministic algorithm allows linkage across datasets to create cohorts with variables that map to all key domains. Linkage use cases relevant to pharmacoepidemiology studies will be presented.

Conclusions: Real world data assets contain the data elements in selected OMOP domains necessary for pharmacoepidemiology studies. Single data assets do not likely cover all data elements, but have a large potential cohort size. Depending on the research question, studies using all OMOP domains are feasible by linking across datasets. Additional variables can be added by linking to other data sources, such as registries that include patient-reported outcomes.

1051. Impact of the US ICD-9 to ICD-10 Code Transition on Clinical Research

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Background: International Classification of Diseases (ICD) diagnosis codes are commonly used for clinical research to identify target patient populations, describe clinical characteristics, and/or determine health outcomes. Since 1978's 9th revision (ICD-9), the US has maintained the Clinical Modification (ICD-9-CM), adding morbidity detail and procedure codes to ICD-9. As of Oct 2015, the US mandates the 10th revision (ICD-10-CM) for federal insurer claims, an update approaching the ICD-10 codes used globally. Researchers must understand how this transition impacts healthcare data sources they commonly use, particularly on electronic medical record (EMR) data sources compared to health claims databases.

Objectives: To demonstrate the impact of the ICD-9-CM to ICD-10-CM code transition on US EMR and claims data sources.

Methods: Two US data sources were selected for this analysis based on size, broad coverage, and data availability: an EMR data source covering $>$150 hospitals and $>$1,500 other healthcare facilities across the US and a charge master database covering $>$350 hospital units across the US. All documented diagnosis codes (both ICD-9-CM and ICD-10-CM) were observed in the patient diagnosis and problems lists for the 3 months before and 3 months after the adoption of ICD-10-CM (01 Jul 2015 - 31 Dec 2015).

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Results: In both data sources, >99% of codes observed between July and Sept were ICD-9-CM and between Oct and Dec were ICD-10-CM. While there was a stark transition in Oct 2015, some ICD-10-CM codes were present prior and some ICD-9-CM codes were present after. Though these accounted for <1% of the codes observed, they still accounted for ~20k codes in the EMR and ~500k codes in charge master data sources, which can have a significant impact on a study.

Conclusions: Researchers understanding the impact of this diagnosis code transition can design retrospective studies recognizing the appropriate diagnosis code value sets for the correct time periods. In addition, given significant differences between ICD-9 and ICD-10, researchers must ensure that patients identified using one coding scheme match appropriately to those identified using the alternate.

1052. Leveraging NLP-Assisted Semi-Automated Chart Review for Detecting Rare Clinical Events from Narrative Clinical Notes

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Background: Rare clinical events are difficult to identify in electronic medical records (EMRs), as they are seldom defined by specific diagnosis code. Traditionally, they are extracted utilizing costly and time-consuming manual chart review; however, rare events may require review of such a large array of records that manual chart review becomes impractical. Natural language processing (NLP) can be a solution; however, the number of events are often too few to adequately train an automated NLP system.

Objectives: To demonstrate the use of NLP-assisted, semi-automated chart review to determine rates of rare clinical events in the U.S. Department of Veterans Affairs (VA).

Methods: Several rare clinical event studies were identified over the course of research. Here we present one example: identification of patients diagnosed with a specific subtype of cancer. Patient identification was determined using structured data, and relevant clinical notes were mined for keywords related to the subtype. Clinical annotators manually reviewed the resulting snippets of text and identified actual instances of the subtype. A full chart review of the documents associated with these events was completed for validation and reproducibility.

Results: >360,000 patients were included with a diagnosis of the general type of cancer. From those patients, 5,848,293 EMR notes were obtained. NLP-assistance using keywords/phrases significantly narrowed down the number of relevant clinical notes and highlighted the resulting keywords/phrases. This allowed for a much faster manual chart review process, which resulted in identification of ~1,200 (0.3%) patients with the specific subtype.

Results for other examples will be presented.

Conclusions: This demonstrates the ability to identify rare clinical events from EMR clinical notes when full NLP is not sufficient and without the need for costly and time-consuming full manual chart review. This NLP-assisted semi-automated chart review approach maintains a large sample size for clinical research while managing workload necessary to extract meaningful information from EMR.

1053. AugMed; Augmented Reality Application for Unobtrusive Medical Adherence Measurement

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Background: Medication adherence is a significant factor in improving patient outcomes. There are various methods available for measuring adherence, such as self-reporting questionnaires, Medication Event Monitoring System pill bottle caps and pill counts, but each method has its disadvantages.

Objectives: To improve the promising adherence method of pill counts by alleviating its negative implementation barriers.

Methods: The application has been developed in the UNITY game development platform utilizing

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Qualcomm's Vuforia AR plugin and is available for the majority of mobile devices. A simple Medication box is used as the Augmented Reality target. The user enters the medication name, start date and medication interval and the application displays the expected doses that should have been consumed from the medication box. When the augmented reality scene is rendered, as soon as the medication box enters the mobile device's view, the compartments that should be empty are covered with red tiles. In that fashion the mobile app's user can at a glance and without alerting the patient immediately measure adherence of the patient to the prescribed medication.

Results: The AugMed medicinal adherence AR application is basing unobtrusive adherence measurement on two pillars. One is the ubiquitous nature of mobile devices (phones, tablets) that do not intrude as a technological presence. The other is the familiar notion of informal carer visitation or cohabitation in a patient's space that does not create a set of dependencies, stigmas, or intrusions that pharmacist visitations with MEMS pill bottles, or pill counts can inflict. Furthermore the engagement of informal carers (siblings, children etc.) removes the social awkwardness of a distant professional intruding on the patient's schedule.

Conclusions: Through a simple mobile Augmented Reality application and the recruitment of an informal carer (patient sibling, spouse, friend, parent or child, according to demographic), an immediate and straightforward means of adherence measurement can be provided with very low obtrusiveness that can be altered to an almost stealth measurement according to the particular challenges in each patient.

1054. Medication Safety Infrastructure at Saudi Hospitals: A Descriptive Cross-Sectional Pilot Study

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Background: The success of hospital medication safety program depends on hospital information system, pharmacy services infrastructure, and the interactions of health care providers with information.

Objectives: The aim is to explore hospital information System (HIS) and Pharmacy Information System (PIS) infrastructure adopted to improve the hospital medication safety, and to investigate how often do the hospital committees discuss the safety related issue in Riyadh hospitals, Saudi Arabia.

Methods: A cross-sectional survey targeted pharmacy managers in hospitals in Riyadh City in fall 2014. The survey gathered information about HIS , PIS, patient's safety related information collected in the PIS, the safety related activities within the Pharmacy and Therapeutics Committee (P&TC).

Results: Of the 30 hospitals pharmacies, 23(76.6%) pharmacy managers responded, only 21(70%) hospitals pharmacies met the inclusion criteria. Out of 21 hospitals, 18(85.7%) hospitals have Electronic Medical Record (EMR), 14(66.67%) hospitals have Computerized Physician Order Entry (CPOE), 6(30%) hospitals have Bar Code Medication Administration (BCMA) and 6(30%) hospitals have the Clinical Decision –Support Systems (CDSSs) .Patient Discharge Counseling Services (PDCS) provided in 7(33.3%) hospitals, while Inpatient Clinical Pharmacy Services (ICPS) provided in 13(61.9%) hospitals. 17(81%) hospitals have abilities to detected Drug-Drug interaction, 4(19%) detect incorrect dose and duration ,and 9 (42.9%) detect Drug- Disease interaction. Drug allergy, disease history , medication history, adverse drug reactions are collected in 13(61.9%) hospitals, 10(52.4. %) hospitals, 14(66.7%) hospitals, and 13 (61.9%) hospitals PIS, respectively. Of 20 hospitals' P&TC, 10(50%) hospitals discuss the adverse event reports each meeting, while 11(55%) discuss the medication error reports in each meeting. Only 10(50%) hospitals have detracted committees for medication safety.

Conclusions: Only 6(30%) hospitals have integrated system that support medication safety program, however, further study on the quality of medication safety program is recommended to ensure the achievement of program goals.

1055. Representativeness of Electronic Medical Records to Support Novelty (A Novel Observational Longitudinal Study of Patients with Asthma and/or COPD)

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Background: NOVELTY is a global 3-year observational study of 14,800 patients aged ≥12 years (≥18 years in most countries) with asthma and/or COPD designed to describe patient characteristics, treatment patterns and burden of illness over time and to identify phenotypes and endotypes associated with differential outcomes. The feasibility of using electronic medical records (EMRs) as a complementary data source for NOVELTY was assessed using IMS Health and Anolinx EMR databases.

Objectives: The objective of this analysis was to evaluate the representativeness of these EMR databases.

Methods: French (FR), German (DE), Italian (IT), Spanish (ES), UK, Nordic (Sweden, Denmark, Norway), US, Australian (AU) and Japanese (JP) EMRs were assessed. The representativeness was evaluated against national statistics including patient distribution by age and gender, physician distribution by age, gender and specialty, and geographical coverage.

Results: Country-specific assessment data were retrieved from all databases, including a mixture of primary and specialty care datasets except Nordic countries where the single EMR database had reached national coverage (50-90%). EMR patient age and gender were generally representative of national statistics with a few exceptions, e.g., male and female patients (younger than 15 years) in IT and ES were under-represented by approximately 12%, and JP patients aged 65–84 years were over-represented for both genders by 6–7%. Physician data were available from FR, DE, IT, UK and AU and were generally representative in age and gender, except for IT data which under-represented female physicians by 16%. EMR records were representative of both primary care physicians and respiratory specialists, except that AU, IT and UK EMRs did not cover specialists. The EMRs generally represented geographical coverage with a slight predominance to some specific regions in FR, UK, US and AU.

Conclusions: The EMRs sampled were generally representative of national data and confirm the concept of the EMR-based feasibility assessment approach in support of the NOVELTY study design.

1056. The Effect of Intensified Anti Tuberculosis Therapy on Patient's Health Status (Symptoms, Activity and Respiratory Impact)

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Background: Tuberculosis (TB) is a leading cause of global morbidity, yet there is limited information regarding its impact on health status and quality of life (QoL). The control and eliminations program had been addressed using the multi drugs during intensive and maintenance treatment. Indonesia as TB endemic areas has a limited of data regarding impact of therapy on the health status of TB patients.

Objectives: To evaluate health status of patients including the symptoms, activity and respiratory impact after 2-months intensified and 4-months maintenance anti-TB therapy.

Methods: This study used cohort data of 6 months period treatment in adult, new diagnosed lung TB patients in Respiratory Hospitals and Primary Health Centers in Yogyakarta, Indonesia. The health status and quality of life evaluated using translated and validated St. George Respiratory Questionnaires, in which contained 51 questions with scale 1-5 for symptoms (fever, cough, breathing difficulties, wheezing, chest complaint etc), any limited activities due to the illness, and its impact on on social work and health perception. The measurement was done before treatment, after 2-months intensified and 4-months maintenance anti-TB therapy.

Results: In total 87 patients completed treatment were enrolled, age were 39.2 ± 14.4 years, 60.0% were male, 40.7% were smokers and BMI were 18.3 ± 2.3. The score of health status for symptoms, activity and impacts were 49.5 ± 14.4; 43.5 ± 28.5; 39.8 ± 19.8 respectively. The health status were not significantly improved after intensified therapy (30.7 ±

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21.0; 31.7 ± 25.9; 26.6 ± 21.7 respectively). In contrast, after maintenance therapy, patient's symptoms, activities and respiratory impact were significantly better compared to baseline (12.7 ± 14.9; 19.9 ± 20.2; 11.5 ± 17.3 respectively). The QoL was also significantly increased from 0.70 ± 0.22 at baseline to 0.86 ± 0.13 and 0.91 ± 0.12 after intensified and maintenance therapy.

Conclusions: TB patient in Indonesia has lower health status and QoL. But the health status including the symptoms, activities and respiratory impact and QoL after 2-months intensified and 4-months maintenance anti-TB therapy were improved.

1057. Patient-Reported Outcomes in Adults Suffering from Acute Coronary Syndrome: A Comprehensive Analysis from the Pharmacoepidemiology General Research eXtension System (PGRx-3)

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Background: The measurement of Patient-Reported Outcomes (PROs) has taken a central place in real-world studies to inform comparative effectiveness research. Besides, it provides valid data on adherence, Health-Related Quality of Life (HRQoL) and others related with the challenging decisions faced by patients and clinicians.

Objectives: The aim was to study the adherence to medication in patients suffering from Acute Coronary Syndrome (ACS), their HRQoL and the productivity impairment.

Methods: Patients were recruited via the Pharmacoepidemiology General Research eXtension information system (PGRx-3). Comprehensive real-world physician and patient data captured serves to describe targeted diseases, their management and the related burden in different countries: UK, France, Italy, Germany, Spain and USA. The following PROs were administered: The 8-item Morisky Medication Adherence Scale (MMAS-8), the EQ-5D 5L and the Work Productivity Activity Impairment (WPAI-GH). Parametric and non parametric bivariate tests and multivariate models were applied.

Results: PGRx-3 currently has 1,048 ACS cases registered, of which 678 patients (69.8% males, mean age-SD-=66.16-11.26-, 64% incident cases) fulfilled the EQ-5D: no differences in key variables were found between responders and non-responders; $p>0.05$). Rates of low adherence (MMAS-8$<$ 6) were similar between incident and recurrent patients (9.1% vs 12.8%, respectively; $p=0.244$). In adjusted models, emotional well-being and living condition were significantly associated with adherence. Regarding HRQoL, at long term (6-24 months after the event), a relevant proportion of patients reported slight to extreme affectation in pain/discomfort and anxiety/depression (60.9% and 46.5%). Finally, only 33.1% of patients $<$65 years) were employed.

Conclusions: Although moderate to high levels of adherence have been found, the evidenced impact on relevant domains of patients' HRQoL demands additional research and attention to reduce the burden of illness in this population.

1058. Association Between Quality of life and Medication Use for Baby Boomers and Older People, by Cardiovascular Disease Status

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Background: Analysis on the association between the use of prescription medicines and quality of life (QoL) is limited. Exploring the QoL between different generations helps to inform prescriber and health policy to better meet the needs of aging populations in regard to quality use of medicines.

Objectives: To explore the association between QoL and medication use for baby boomers (born between 1946 and 1964) and older people (born before 1946) with and without cardiovascular disease (CVD).

Methods: We conducted a linear regression analysis to determine the relationship between QoL and

medication use using data from the North West Adelaide Health Study (2004-2006). Patients were included if they participated in the clinic assessment during which data were collected on medication use, demographics, and QoL using the Short Form 36 (SF36).

Results: A total of 2,029 (1177 baby boomer; 852 older people) participated in the clinic assessment. The SF36 Physical Component Score (PCS) among patients with self-reported CVD was lower than those without CVD for baby boomers (43.28 [95% CI, 39.84-46.73] versus 48.73 [95%CI, 48.22-49.24]) and older adults (37.10 [95%CI, 35.19-39.01] versus 42.83 [95%CI, 42.02-43.65]).

For baby boomers, without CVD, a higher use of prescription medicines was more strongly associated with a lower PCS (=-0.366) than for baby boomers with CVD and PCS (=-0.331) despite a higher prevalence of use of prescription medicines in these age groups with CVD. Older adults taking prescription medicines with CVD and no CVD both had lower PCS (=-0.402 versus =-0.399) and MCS (=-0.175 versus =-0.132). Baby boomers with CVD taking polypharmacy had an association with lower PCS (=-0.225). For both CVD and no CVD older adults taking polypharmacy associated with lower PCS (=-0.302 versus =-0.158) and MCS (=-0.123 versus =-0.064).

Conclusions: Those without CVD but taking medications were generally more likely to have lower QoL, suggesting that medications for CVD may improve QoL for baby boomers. Further studies are warranted to investigate which types of medications are associated with lower PCS and MCS.

1059. Do GPs Adhere to the Guidelines? A Study Based on Statins Prescriptions

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Background: The National Institute for Health and Care Excellence (NICE) guideline for the prescription of statins (2006 – 2014) stated that statin therapy should be initiated to people aged below 75, whose 10-year risk of experiencing a cardiovascular diseases (CVD) event is greater than 20%.

Objectives: To explore General Practitioners (family doctors) habits in statins prescription and quantify the proportion of prescriptions which are prescribed according to the guideline.

Methods: Using data from The Health Improvement Network (THIN) UK primary care database in the years 2007 - 2008 we identified individuals who have been prescribed statins for the first time, and for whom a Framingham risk score has been recorded on the computer system. In addition we identified individuals who, in the year prior to initiation of statins, had records of systolic blood pressure, total and HDL cholesterol and smoking habits, as needed to calculate the risk score. This allowed us to calculate the risk score for people who did not have it recorded, even though they were prescribed statins. We explored the GPs decision to record the risk score as a binary outcome (i.e. the missingness of the risk score). We then analysed its relationship to various factors by means of logit regression.

Results: Among the 8672 individuals who initiated a statin therapy, only 848 (9.8%) had a risk score recorded by the GP in the database. Additionally 5316 (61.3%) had the components of the risk score recorded but not the risk itself, leaving 2503 individuals (28.9%) prescribed statins without any recorded risk score.

GPs were less likely to record a risk score if the individuals were diabetic (OR 1.93, 95%CI 1.55 to 2.43), female (OR 1.83, 1.58-2.13) or aged less than 60 years (OR 1.23, 1.05-1.44). Availability of BMI, at a lower level of significance (OR 1.18, 1.02-1.38), also influences the decision to prescribe statins without the need for the risk score.

Conclusions: Many people are prescribed statins in general practice without any recorded CVD risk score. This suggests that GPs may not adhere to guideline when prescribing statins. Our study represents the first attempt to shed some light on this phenomenon.

1060. Costs Analysis Of Traditional And New Oral Anticoagulants: A Retrospective Analysis In A Local Health Authority In Northern Italy

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Background: Oral anticoagulants modify blood clotting capacity and are widely used for long-term prevention or treatment of thrombosis. The traditional drugs are vitamin K antagonists, while the new agents target either factor Xa or thrombin.

Objectives: To evaluate the burden for the NHS of treatment with traditional (TAO) and new anticoagulants (NAO), considering direct pharmaceutical costs and related events.

Methods: Data were retrieved from administrative databases; they included the register of residents in the province of Cremona, dispensed drugs, hospitalizations and outpatient care. A retrospective drug utilization study was conducted, enrolling subjects≥40 years old with at least one prescription of drugs with ATC codes B01AA, B01AE or B01AF during the period January 1st, 2013–September 30th, 2015. Volume of use was estimated. All anticoagulant prescriptions, hospitalizations for thrombotic or hemorrhagic events and blood monitoring in outpatient services occurring during follow-up (stratified by type of anticoagulant) were considered for the cost analysis. Volume of costs (in total and for person-time) was estimated for TAO and NAO users,stratified by type of cost (pharmaceuticals, hospitalizations and outpatient care).

Results: A total of 10,206 patients received at least one prescription of anticoagulants in the study period: 83% were TAO users. Overall, 83,590 prescriptions of oral anticoagulants were cashed, 87% of which for TAO. On average, NAO users were prescribed 381.3 DDD, as opposed to310.6 DDD for TAO. Annual pharmaceutical costs were €37.13 per person for TAO and €521.71 for NAO. Annual outpatient costs were 6.7 times higher for TAO users compared to NAO users; yearly costs of hospitalizations per user were higher by €112.3 in TAO patients compared to NAO users. Overall, the excess per capita expenditure of NAO vs. TAO was estimated at €237.81 per year.

Conclusions: Treatment with NAO is more expensive than TAO; the difference is entirely attributable to the direct cost of these drugs. These savings deserve further investigations, to ascertain if they may be explained by differences in health-related outcomes.

1061. The Healthcare Costs of Heart Failure During the Last Five Years of Life: A Retrospective Cohort Study

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Background: Evidence on the economic impact of heart failure (HF) is vital in order to predict the cost-effectiveness of novel interventions.

Objectives: To estimate the healthcare costs of HF during the last five years of life.

Methods: Adults who died with HF in 2012/3 were identified through linked English Office of National Statistics mortality data and Clinical Practice Research Datalink (CPRD) primary care data. CPRD and linked Hospital Episode Statistics admissions data were used to estimate the cost of primary care prescriptions and primary care and hospital admission healthcare with 95% confidence intervals (CI). Generalized least squares regression was used to estimate the relationship between costs, HF diagnosis and patient characteristics.

Results: In the last 90 days of life of 1,555 identified patients, healthcare costs were £8,912 (95% CI £8,436-9,388) per patient, more than 90% of which were for inpatient or critical care. In the last 90 days, patients spent on average 17.8 days (95% CI 16.8-18.8) in hospital and had 8.8 (95% CI 8.4-9.1) primary care consultations. Most (59%) patients were in hospital on the day of death. Mean quarterly healthcare costs were significantly higher after diagnosis than preceding diagnosis (by £1,479, 95% CI £1,286-1,671). Younger patients and patients with higher comorbidity had higher costs.

Conclusions: Healthcare costs increased sharply at the end of life and were dominated by hospital care. There is potential to save money by implementation and

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evaluation of interventions known to reduce HF hospitalizations, particularly at the end of life.

1062. Racial Differences in Productivity Loss Attributable to Rheumatoid Arthritis Among Patients Taking Disease-Modifying Antirheumatic Drugs (DMARDs)

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Background: Disease burden may vary among working-aged Rheumatoid Arthritis (RA) patients. There is limited literature about the burden of RA and differential impact of RA treatments among minority populations and their loss of productivity.

Objectives: To examine the association between racial/ethnic differences and loss of productivity among RA patients in the US, including a subsample taking Disease-Modifying Antirheumatic Drugs (DMARDs).

Methods: In a pooled cross-sectional analysis of Medical Expenditure Panel Survey (MEPS) data from 2010-2013, we identified 232 full-time employed adult patients with any RA prescription medication event, including DMARDs, glucocorticoids, and NSAIDs. The following racial/ethnic groups were included: Non-Hispanic Whites (Whites), Non-Hispanic Blacks (Blacks), Hispanics, and Others. Impact on productivity, our main outcome variable, was measured as annual wage income loss and days absent from work (absenteeism). We used log-linear regression to control for sociodemographic variables and RA-related treatments. Additionally, we evaluated the impact of DMARDs on loss of productivity among the aforementioned ethnicities. We weighted the estimates to account for complex survey design.

Results: The overall weighted sample size of RA patients analyzed was 1,976,969. The majority of the patients were women (70%) and ages 45-64 (45%). About 68% were Whites, 18% were Blacks, and 9% were Hispanics. Among patients with any RA prescription event, wages increased 25% among Blacks (p-value = 0.02) compared to Whites. In sub-sample taking DMARDs compared to those using other RA medications, absenteeism increased 1.06 times among Whites and decreased by 72% among Blacks (p-values $<$ 0.0001), while wage loss decreased in Whites, Blacks, and Hispanics (2%, 30%, and 24%, respectively; p-values $<$ 0.0001).

Conclusions: With DMARD treatment compared to other RA treatment, absenteeism was higher among Whites while wage loss decreased among all ethnic sub-groups, but remained present. Future studies should explore racial variances associated with access, adherence and effectiveness of various DMARD treatment strategies.

1063. Patient Monitoring – the Hidden Costs of Treatment with Antipsychotics

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Background: Antipsychotics are an important treatment option for patients with schizophrenia. Drug treatment costs not only comprise the costs of the drug itself but also the costs of monitoring the patient. During treatment patients need to be monitored to determine the effectiveness and safety of pharmacotherapy.

Objectives: We assess the proportion of patient monitoring costs as a part of antipsychotic treatment costs in patients with schizophrenia.

Methods: Monitoring instructions were extracted from the Summary of Product Characteristics (SmPC) and monitoring was defined as a statement to do something prior to or during drug use. Total drug treatment costs were determined as the sum of drug costs and patient monitoring costs. Drug costs were acquired from the Dutch Healthcare Institute by selecting the lowest price using the Defined Daily Dose during one year of treatment including the pharmacy dispensing fee. Patient monitoring costs were calculated for laboratory and physical tests. Unit prices for laboratory tests were obtained using prices from the Dutch Healthcare Authority 2014 including laboratory order costs. Costs for physical tests were calculated based on costs for the specific test or for a consultation. Costs for a

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consulation were obtained from the Dutch guidelines for cost research, methods and standard price units for economic evaluations in health care.

Results: Mean drug treatment costs were €461 (range €100 - €1660) per drug per year, with a proportion of minimal required patient monitoring costs ranging from 0 to 83%. Over one third of antipsychotics (37%) had a proportion of >20% mandatory monitoring costs. A proportion of 0% and 0-20% was found for 47% respectively 16% of the antipsychotics. The proportion of patient monitoring costs was highest for olanzapine (83%; €230/€277), clozapine (70%; €412/€590) and risperidone (47%; €47/€100).

Conclusions: Total drug treatment costs consisted of >20% mandatory monitoring costs for over one third of all antipsychotics. Proportions may increase when patents expire. We advocate to use drug treatment costs including monitoring costs for decision making in clinical practice for antipsychotics.

1064. Assessment of Predictive Ability of SLANSS and ID Pain Questionnaires in Assessing Pain Related Outcomes in Chronic Non-Cancer Neuropathic Pain Conditions

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Background: Diagnosing and assessing treatment outcomes in neuropathic pain (NP) is challenging. Commonly used treatment outcomes in pain clinical trials and practice are pain intensity (PI) and quality of life (QoL). However correlation between changes in PI and QoL is poor. New markers of treatment outcomes are needed.

Objectives: Assess the predictive ability of NP screening questionnaires for treatment outcomes, clinically relevant optimum cut off, correlation between NP screening questionnaires scores and PI and QoL.

Methods: Adult patients of either gender with chronic severe non-cancer NP were recruited. PI, QoL, disability and NP screening questionnaires (SLANSS and ID-pain) scores were assessed at baseline and 1 month post treatment.

ROC curve analysis was done to determine area under curve (95% CI), Youden's index (YI) to assess MCIDs (Minimal Clinically Important Difference) to assess predictive value. Correlation coefficient was calculated between screening questionnaires and various outcomes using SPSS 15.0.

Results: 56 patients with mean (SD) age of 44.3 (4.8) were recruited. 50% were males and 57% had low back pain. Mean (SD) PI was 7.99 (1.1) and 56% observed decreased PI after treatment. AUC for S-LANSS and ID-pain was 0.778 (0.614 - 0.896) and 0.719 (0.550 - 0.852). Based on YI MICD for S-LANSS is >2 (sensitivity 90.9% and specificity 81.5%) and for ID-pain >0.5 (sensitivity 81.8% and specificity 66.67). A positive correlation between PI and disability ($r=0.31$, $P<0.05$) and ID-pain ($r=0.37$, $P<0.05$), and negative correlation between PI and QoL ($r=0.22$, $P<0.05$) was found.

Conclusions: There is significant positive correlation between various pain related outcomes and NP screening questionnaires scores. S-LANSS and ID-pain questionnaires can be used as an outcome measure to assess the patient's progress/performance of an intervention.

1065. A Qualitative Study to Develop Patient Materials on Opioid Use in Orthopaedic Surgery

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Background: The American Academy of Orthopaedic Surgeons recognizes the unintended consequences of focusing on opioids for pain management.

Objectives: Develop patient-focused educational materials and scripting for a randomized trial to reduce opioid use following total hip and total knee arthroplasty (THA/TKA).

Methods: Qualitative study with open-ended, structured interviews (n = 18) at Kaiser Permanente Northwest. A purposeful sampling method identified surgeons, advice nurses, physical therapists, physician assistants and patients. Patients were recent THA/TKA cases in the top tertile of opioid use after surgery.

Interview guides captured feedback consistently. Provider interviews explored their approach with

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THA/TKA patients on: pain management; barriers to opioid titration; and recommendations/changes on educational materials to support pain management and opioid-reduction. Patient interviews explored their experience, understanding, and beliefs surrounding opioids; and recommendations on important content. A qualitative methodologist conducted content analysis to identify key themes.

Results: Recommendations for content in patient educational materials and scripting included:

- Clear descriptions of how opioids work in the body, how to taper, non-opioid pain management options, and problems from over-use (e.g. side effects, and pain masking)
- Messaging on how long to expect to use opioids and type of pain to expect
- Providing a visual timeline for patients to reinforce pain medication titration expectations and home or physical therapy exercises, especially during the acute phase
- Emphasis on the multi-modal approach to pain management and the importance of a balance between opioids for recovery vs over-use
- Explanations to chronic opioid users that their pain and its management may vary from opioid-naïve patients
- Provide education and messaging multiple times prior to and after surgery.

Conclusions: Patients and providers agreed that clearly stated verbal and written messaging is needed beyond what has typically been done regarding opioid expectations; the resulting materials are being tested in an ongoing trial.

1066. What Is the Evidence on Financial Toxicity of Cancer Treatment?

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Background: Cost of cancer treatment in the United States has skyrocketed. Patients and cancer survivors are faced with difficult choices to bear, some of which are lifetime debt, bankruptcy, inability to cover cost, other financial and life sacrifices These financial and other life sacrifices substantially increase towards the end of life treatment and leave cancer patients' families and survivors with continuing hardships.

Objectives: To explore the determinants of cost of cancer care and the limits of the patient involvement to manage the challenge of cost of care.

Methods: A literature search is conducted using the following databases: Ovid MEDLINE, Embase, CINAHL, PsycINFO, and SCOPUS. Studies are evaluated with evidence tables generated with the key appropriate guidelines of the EQUATOR network: "Enhancing the Quality and Transparency of Health Research" Systematic reviews are evaluated by the AMSTAR criteria: Assessment of the Methodological Quality of Systematic Reviews.

Results: Several studies have been identified that investigated the cost or burden of cancer care. Cost of cancer care increased to over $100,000 per year. Multiple myeloma, bladder cancer, and lung cancer appear to be forthcoming in expenditures and financial toxicities left for families of patients to bear. Several solutions and future research directions are suggested, such as, developing country-specific cost-effectiveness methodology to evaluate the cost of treatment, stratification of cost of cancer care by specific ethnic and socio-economic groups, increasing psychosocial support to cancer patients, survivors and their families. The most interesting is an agglomeration of suggestions made by a large number of oncologists to the pharmaceutical industry. Yet, the ripples of these effects are yet to be seen in accolades.

1067. Measuring Outcomes Among Metastatic Prostate Cancer Patients in Administrative Claims Data Using the Center for Medicare and Medicaid Services Oncology Care Model

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Background: -Centers for Medicare and Medicaid Services proposed new payment and healthcare delivery models for cancer care (Oncology Care Model (OCM)). OCM defined treatment episodes begin with chemotherapy and last 6 months. Patients receiving chemotherapy after the initial episode would initiate a subsequent treatment episode.

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Objectives: This analysis examines real world treatment patterns for metastatic prostate cancer (mPCa) in context of OCM treatment episodes and evaluates OCM performance metrics.

Methods: A retrospective analysis was conducted using administrative claims data from the MarketScan® Commercial and Medicare databases (1/1/2011-12/31/2014). mPCA patients were included if they were treated with enzalutamide (n = 463) or abiraterone (n = 1,313). Index date was the first treatment date and patients were continuously enrolled for one year post-index. Outcomes included the proportion of patients requiring second OCM treatment episodes within 6 months after the first episode and the proportion experiencing prostate cancer-specific emergency department (ED) visits and hospitalizations.

Results: Over 56% of enzalutamide and 66% of abiraterone patients initiated a second treatment episode with their initial drug. Approximately 6% of enzalutamide patients were also dispensed abiraterone and 8% of abiraterone patients were also dispensed enzalutamide during their initial treatment episode. ED visits occurred during the first treatment episode for 10% of enzalutamide and 7% abiraterone patients and within 6 months after the first treatment episode for 14% enzaluatimide and 10% abiraterone patients. Approximately 15% of enzalutidmide and 14% of abiraterone patients had a hospitalization during the initial treatment episode. Approximately, 20% of both cohorts had a hospitalization within 6 months of the first treatment episode.

Conclusions: Long-term continuous oral chemotherapy requires multiple OCM treatment episodes and may include more than one drug. Administrative claims data is an effective tool to evaluate performance measures and treatment patterns during OCM treatment episodes.

1068. Quality of Life of Patients with Diabetes Mellitus Types 1 and 2 from a Reference Health Care Center in Minas Gerais, Brazil

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Background: The evaluation of the impact of diabetes mellitus (DM) on patients' quality of life (QoL) has been used to improve our understanding of how different health dimensions are influenced by the disease characteristics. This is important as compliance with multiple medications is a concern in patients with DM. It is also important to assess QoL in the real-world to better target interventions.

Objectives: Evaluate the QoL and DM-associated factors in patients with DM in a real-world setting.

Methods: Patients > 18 years old attending the Endocrinology Department of the University Hospital of the Federal University of Minas Gerais (HC-UFMG), Brazil, were enrolled. They were interviewed by pharmacy undergraduate students trained in interview techniques regarding their sociodemographic, clinical and QoL characteristics from October 2013 to June 2014. The QoL of the patients was measured using the EuroQol questionnaire (EQ-5D), which allows the comparison of individual patients' QoL with predicted values derived from a population sample, which can subsequently be used to derive a single utility measure. Descriptive analysis, correlation, linear regression, univariate and multivariate analysis were performed.

Results: We interviewed 346 patients who agreed to participate. Of these, 67% were women, 59% with Type 2 DM, and 32% Type1 DM. Some did not know there type or admit they had DM. DM 1 patients had a mean QoL of 0.7369, with retinopathy, depression, dyslipidemia and a serious hypoglycemic crisis significantly reducing patients' QoL. Patients with DM type 2 had a mean QoL 0.6582, with hypertension, neuropathy, depression, cancer and dyslipidemia significantly reducing their QoL. Reduced QoL also correlated with a lack of physical exercise. Males had a better quality of life than females ($p = 0.016$).

Conclusions: The results point to the need for better disease monitoring and control, and effective educational activities that contribute to patients' self-care

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to improve their QoL. The goal is also to reduce medicine use where possible.

1069. Impact of Patient Counseling on Medication Adherence Behavior and Quality of Life in Diabetics of Telangana Region

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Background: Diabetes mellitus has become an international healthcare crisis, alarming the requirement of new approaches to prevent and treat it. Increasing the medication adherence and improving the health related quality of life is the need for hour. Carbohydrate rich diet and Poor compliance to medications due to economical and other barriers leading to poor quality of life of diabetics of Telangana, making its a need of hour to check the influence of Patient counselling and its impact on overall quality of life.

Objectives: Evaluate the impact of patient counseling on medication adherence behavior and HQoL in diabetics of Telangana region.

Methods: The current Study was carried Satyam Diabetic Clinic, Warangal, a secondary care hospital in Warangal city of telangana state with a turnover more than 300 diabetics per day Study was conducted on a convenient sample (N = 287), which was divided into intervention (n = 148) and control group (n = 139). Total patients were interviewed using a pretested, structured, close ended Brief Medication Questionnaire (BMQ), to assess medication adherence behavior and Audit of Diabetes Dependent Quality Of Life (ADDQoL), a diabetes disease specific questionnaire to assess QoL. The intervention group received patient counseling, whereas the control group deprived of counseling till the end of the study. Suitable statistical methods were used to interpret the data.

Results: We found intervention reduced beliefs-barrier from 19% to 0.4% and recall-barrier from 30% to 21% in intervention group and beliefs-barrier from 17% to 0.5% and access-barrier from 30% to 4% in control group. In intervention group, QoL significantly improved (i.e. negative impact decreased by 43% from first to final follow up). Significant correlations (C.I. 0.3512-0.9996, p = 0.0189, r = 0.9841) were found between QoL and medication adherence.

Conclusions: The improved HQoL profiles and enhanced compliance behavior in test group signify the importance of patient counseling. The study results are in line with the earlier findings emphasizing the importance of patient counseling to obtaining the outcomes desired.

1070. Cost-Effective Approach in Management of Diarrhoea in Nigeria: A Decision Analytical Model

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Background: Diarrhoea is the leading cause of death in Nigerian children under 5 years. There are several recommended approaches to prevent and treat diarrhoea. Implementing the most cost-effective approach will save resources in Nigeria.

Objectives: This study evaluated the current trends for management of diarrhoea to determine the most cost-effective

approach. 1. The 'no treatment' approach; 2. the preventive approach; 3. the integrated management of childhood illness (IMCI) for diarrhoea; 4. combination of rotavirus vaccine with IMCI for diarrhoea were evaluated.

Methods: The study employed decision analytic modelling. Markov cohort model conducted from the patient's perspective was used to quantify cost and effectiveness of the four interventions. The markov model had a life cycle of 260 weeks for 1000 children with asymptomatic diarrhoea. Disability adjusted life years (DALYs) averted was used to quantify clinical outcome. The average cost of treatment for the 1000 patient was tracked over the Markov cycle model for

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the four interventions and results were presented in 2015 US Dollars. Probabilistic cost-effectiveness analysis was performed using Monte Carlo simulation, and results presented as cost-effectiveness acceptability frontiers. Expected value of perfect information (EVPI) was conducted for the hypothetical population.

Results: From the cost-effectiveness acceptability frontier, the IMCI approach had the highest probability of being cost-effective when the patient is willing to pay any amount that is not above $1200 to avert a DALY. When the patient is willing to pay any amount above $1200 to avert a DALY, the IMCI plus rotavirus vaccine approach emerges as the most cost-effective. The value of perfect information for 'IMCI for diarrhoea' and 'IMCI for diarrhoea plus rotavirus vaccine' were $386,585 and $4,688,300.88 respectively.

Conclusions: Based on cost-effectiveness, study perspective, sustainability and affordability, IMCI for diarrhoea is the most cost-effective option for childhood diarrhoea.The Nigerian government should consider rotavirus vaccination as part of national programme of immunization as it is very cost-effective.

1071. Resource Utilization of Adult Patients with Sporadic Angiomyolipoma in the Netherlands

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Background: Renal angiomyolipomata (AML) are nonmalignant, highly-vascularized lesions that usually present sporadically. Sporadic AML (sAML) require frequent monitoring, can grow over time, may be associated with significant complications, and can necessitate burdensome interventions such as embolization and nephrectomy.

Objectives: This study documents the health care resource utilization (HCRU) associated with sAML.

Methods: This was a retrospective, longitudinal cohort study conducted using medical chart data from patients with sAML treated at the University Medical Center – Utrecht, a major specialty center in the Netherlands, from 1995 to 2015. Patients were classified into cohorts based on the longest diameter of their largest AML at diagnosis (small: <3.5cm; large: ≥ 3.5cm). Those with only small AML were further classified by number of AML (≤ 5 vs. >5). HCRU rates per patient per year (PPPY) for scans, specialist visits, embolizations, and nephrectomies were reported and compared across cohorts using rate ratios (RR).

Results: Fifty-three patients with sAML were included (85% female; median [range] age 54 [25-79] years and follow-up time after sAML diagnosis 3.7 years [1 day-14 years]). At diagnosis, 26 (49%) had large AML. Among patients with small AML, 6 (23%) had >5 AML. Rates of scans, specialist visits, and embolizations or nephrectomies were 1.44, 1.73, and 0.03 PPPY, respectively. One (2%) and 6 (11%) patients, respectively, underwent embolization and nephrectomy during follow up. Patients with larger AML had higher rates of scans ($RR = 1.25$, $P = 0.047$) and displayed a trend toward a higher rates of embolization or nephrectomy ($RR = 4.67$, $P = 0.149$). Patients with more numerous small AML had higher rates of scans and specialist visits ($RR = 2.39$-2.78, $P \leq 0.001$).

Conclusions: The presence of large or numerous sAML is associated with higher rates of health care resource use. More than 10% of patients underwent nephrectomy after sAML diagnosis. Alternative treatment options for patients with sAML are needed to help avoid costly interventions.

1072. Costs with Medicines and Services in the Treatment by Patients with Schizophrenia

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Background: Schizophrenia is a severe mental disorder, chronic and debilitating, affecting 0.3 to 0.7% of the population and is associated with a significant financial and social impact on patients, families, caregivers and society in general.

Objectives: To describe the costs with high cost drugs, outpatient and hospital services used for patients with schizophrenia attended by Brazilian Public Health System (SUS) from January 2000 to December 2010.

Methods: We analyzed a nationwide cohort developed through deterministic-probabilistic linkages of administrative records of SUS national databases. We included patients received the following antipsychotics: clozapine, olanzapine, quetiapine, risperidone and ziprasidone; had the diagnosis ICD-10 for schizophrenia and were treated between January 2000 and December 2010. We conducted an analysis of costs, we stratified the individual cost by procedure category and we describe on median. Monetary values were adjusted for inflation to January 2015. Brazilian Reais (BRL) were converted to United States Dollars (USD) using the purchasing power parity of the World Bank at a conversion factor for 2014 (USD1 = 1.69 BRL).

Results: We included 241,079 patients. High cost drugs represented 82.9% of the total cost, followed by hospitalizations (9.8%) and outpatient care (7.3%). Atypical antipsychotics represented 93.8% of the cost with high cost drugs and had a median cost USD 517.33. Psychiatric hospitalization was used in 8.0% of patients, represented 67.0% of the cost with hospitalizations and had a median cost USD 1,074.08. Outpatient psychiatric care was used in 11.6% of patients, represented 74.9% of the cost with outpatient care and had a median cost USD 303.56.

Conclusions: Atypical antipsychotics were responsible for the majority of the schizophrenia treatment cost. This finding may be related to the cost of medicines to the healthcare system and its continuous use. Psychiatric hospitalizations account for higher median cost and a lower percentage of use and outpatient psychiatric care had lower median cost. These results suggest ensure the quality in use of atypical antipsychotic and encourage the use of outpatient services over hospitalization.

1073. Some Statistical Considerations in Estimating a Disease Progression Model for Chronic Obstructive Pulmonary Disease (COPD)

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Background: To develop statistical models predicting disease progression and outcomes in chronic obstructive pulmonary disease (COPD).

Objectives: To estimate associations between attributes of COPD and to develop a model that predicts economic and health outcomes associated with COPD progression.

Methods: We utilized data from a three year cohort study of COPD patients to estimate the associations between central COPD attributes (exacerbations, lung function, exercise capacity, and signs/symptoms) while adjusting for co-morbidities, body composition (BMI), biomarkers, smoking history, age, and gender. As disease progression endpoints we used the total score of the St. George's Respiratory Questionnaire (SGRQ) and mortality. We applied random coefficient models to assess the relationships between the central COPD attributes longitudinally and thereby describe patient trajectories over time. As appropriate, non-linear functional forms were explored to characterize the nature of the data. Endogeneity among the central attributes of COPD was addressed by time-lagging in the regression models.

Results: We found that exacerbations in the preceding 12-months were associated with an average decline in lung function (FEV1) of up to 10 ml ($P<0.05$) and with a reduced exercise capacity (6 minute walk test) of 13 meters ($P<0.0001$). A 1% increase in FEV1 % predicted was also associated with a 5% reduction in the probability of experiencing dyspnoea on most days/week ($P<0.0001$). All central attributes were found to significantly impact disease progression, measured by the SGRQ, with the largest estimated effect for dyspnoea on most days/week (18 point increase in the SGRQ score; $P<0.0001$). Lung function and exercise capacity, however, were the only significant predictors of mortality ($P<0.05$).

Conclusions: The use of appropriate analytical techniques to account for the longitudinal nature and endogeneity of COPD attributes enables the estimation

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of their impact on important health outcomes. Our results confirm the expected associations between the central attributes of COPD and their effect on patient health status (SGRQ) and mortality.

1074. What Are Patient's Willing to Pay for Pharmacogenomic Testing?

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Background: Implementation of pharmacogenomics (PGx) has been restricted to medical centers with substantial institutional support given the limited reimbursement rates. Expansion to patient populations willing to pay out-of-pocket could facilitate wider adoption.

Objectives: To determine patient's willingness to incur out of pocket costs for PGx testing.

Methods: The Mayo Clinic's Right, Drug, Right Dose, Right Time Protocol is tasked with preemptive PGx testing with integration of clinically actionable PGx variants into the electronic health record. RIGHT participants were sent a survey assessing their experiences with and understanding of PGx. Patients self-reported health status, the number of prescription medications, interest in additional PGx testing, and available financial resources. We assessed the patient's willingness to pay for PGx testing by the following question: "If PGx tests were available, what would be the maximum out-of-pocket cost you would be willing to pay?" Using logistic regression, we assessed factors associated with a willingness to incur costs.

Results: 869 (86%) completed the survey (55% females, mean age 59 years) and 70% indicated that they would ask for additional PGx testing if it became available. Overall, 42% of the patients were not willing to incur out of pocket costs. After adjusting for all other variables, fewer financial resources remained strongly associated with being unwilling to incur any out-of-pocket costs (cut back to pay bills odds ratio (OR) = 1.4; little to spare OR = 2.2; difficulty paying bills OR = 15.3, P for trend < 0.001). Likewise, older patients and women were less likely to be willing to incur out-of-pocket costs.

Conclusions: Patients are interested in PGx testing but a majority would only do so if it was completely reimbursed. A patient's financial situation is a key driver of a willingness to incur out-of-pocket costs. These findings add empiric evidence to the concern that future benefits of PGx testing may be disproportionately allocated to patients with more financial resources and support the need for a national conversation about reimbursement given that advances in clinical medicine often result in widening health disparities.

1075. Policy Options to Lower Prescription Drug Prices in the United States

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Background: Policy makers and the general public are once again expressing concern about high prices and high levels of spending for branded prescription drugs in the United States. The U.S. spends considerably more per capita on branded drugs than other countries; the U.S. typically pays the highest prices for branded drugs; spending on pharmaceuticals in the U.S. is approaching $400 billion; and the rates of growth of drug prices in the U.S. have returned to double-digit levels, reaching 12.2% in 2014.

Objectives: We evaluated policy options implemented to reduce U.S. branded drug costs.

Methods: We identified policy options to reduce U.S. branded drug costs using a two-step process that combined expert opinion with a structured literature review of 343 peer-review articles. We then developed and applied seven criteria to the most commonly cited policies. Finally, we considered unresolved empirical issues that are particularly important in any discussion of the merits of various policy proposals.

Results: Approximately 40 policies were identified that clustered into five categories: revising the patent system; encouraging research to increase development of new drugs; altering pharmaceutical regulation; decreasing market demand; and developing innovative pricing policies. The most promising policies are currently being evaluated with respect to whether they: (1) promote incentives for innovation, (2) ensure equitable access to drugs, (3) reduce spending on drugs, (4) encourage generic adoption, (5) lower administrative burden, (6) require legislative action, and (7) are likely to have unintended consequences.

Conclusions: While dozens of policies have been advanced to address the high cost of branded prescription drugs in the United States, these policies tend to focus on a limited number of fundamental market mechanisms that effect drug pricing. The most commonly proposed policies can be differentiated based on dimensions that may assist policy-makers, payers and other stakeholders seeking to meaningfully address the high cost of branded products in the United States.

1076. The Role of Real-World Data in Single Technology Appraisal Submissions in the United Kingdom

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Background: The role of real-world data (RWD) in single technology appraisal (STA) submissions is to complement evidence collected from clinical trials and contextualise the anticipated real-world use of a technology. The potential for RWD to strengthen reimbursement submissions has been increasingly recognised, although little research has been conducted to ascertain their use.

Objectives: To determine the frequency and type of RWD incorporated in manufacturers' submissions to the National Institute for Health and Care Excellence STA process. A secondary objective was to identify the Evidence Review Group (ERG) and the Appraisal Committee's explicit requests for RWD.

Methods: We reviewed STA guidance and manufacturers' submissions for technologies indicated for solid tumours (January 2010 to December 2015). We extracted information describing the type of RWD used to support clinical effectiveness, safety or the following types of economic model inputs: comparators and treatment patterns, disease progression, survival, and resource utilisation. We classified the type of RWD according to a pre-defined hierarchy of evidence. Additionally, we extracted critiques and recommendations made by ERG and the Appraisal Committee regarding RWD and future research that could be informed by RWD.

Results: Overall, 48 STAs in solid tumours were identified. Among those, five were terminated or withdrawn and three were multiple technology appraisals, thus leaving 40 STAs for extraction. Approximately 80% of STAs included RWD; in the remainder, RWD was either absent or unclear. In less than 10% of STAs, RWD informed clinical effectiveness and safety. More frequently, RWD was used to inform survival (e.g. extrapolation beyond the duration of the randomised controlled trial) or resource utilisation. In several STAs, the ERG or Appraisal Committee explicitly requested RWD or critiqued their validity.

Conclusions: RWD inform central components of STA submissions. Our findings emphasize that these data should be collected using robust research designs, with high external validity; failure to do so may contribute to the Committee's uncertainty of the plausibility of the submitted evidence.

1077. Withdrawn by Author

1078. Assessment of Pharmacist Interventions of Drug Related Problems Among Patients with Impaired Renal Function

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Background: Studies report poor quality and gaps in the care of Chronic Kidney Disease (CKD) patients with their attendant complications and drug related problems. Clinical outcomes after pharmacist intervention need to be studied.

Objectives: To characterize pharmacist interventions among patients with CKD.

Methods: This randomized, prospective, open-labeled interventional study was carried out in the inpatient wards of a tertiary care hospital during the period October 2014 to March 2015. Patients with a primary diagnosis of CKD of any stage and etiology and who consented to participate were included in the study. Patients with cancer, undergone organ transplantation, significant liver disease and alcohol and substance abuse were excluded. Patients were randomized into test or control group. The control group received the standard of care provided at the hospital. Test group received a pharmacist's review in addition to standard of care. A clinical pharmacist reviewed treatment charts to identify drug therapy problems and communicated appropriate changes or recommendations to the nephrologist. Categorical data is expressed as percentage and continuous data as mean ± SD. Parametric data was analyzed using two-tailed t-test with significance set at 0.05.

Results: Among 833 patients included in the study, a total of 250 DRPs were identified from 245 patients. DRPs occurred at a rate of 1.02 per patient in the study population. Out of 250 DRPs, 105 (42%) were Manifest problems and 145 (58%) were found to be Potential problems. 117 (46.8%) of DRPs occurred in the test group whereas 133 (53.2%) were seen in the control group. Most common DRP was adverse drug reactions (21.6% in Test and 22.4% in control group), followed by therapy requiring dosage adjustment (4.8% in test, 5.6% in control group). Most common interventions by pharmacist were drug being stopped (49.6%), new drug started (26.4%) and dose changes (17.4%).

Conclusions: Adverse drug reactions are the most common problem for this group of patients. Future studies must concentrate on developing measures to prevent them. Harm due to non-intervention in the control group can be surmised.

1079. New Chronic Disease Medication Prescribing by Nurse Practitioners, Physician Assistants, and Primary Care Physicians: A Cohort Study

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Background: Medications to treat and prevent chronic disease have substantially reduced morbidity and mortality; however, little is known about prescribing of chronic disease medications by different primary care providers.

Objectives: To examine prescribing of new chronic disease medications by nurse practitioners (NPs) and physician assistants (PAs) compared to primary care physicians (PCPs).

Methods: We obtained prescribing data from IMS Health's XponentTM on all primary care NPs, PAs, and PCPs in Pennsylvania regularly prescribing anticoagulants, antihypertensives, oral hypoglycemics, and/or HMG-Co-A reductase inhibitors pre- and post-introduction of five new drugs in these classes that varied in novelty (i.e., dabigatran, aliskiren, sitagliptin or saxagliptin, and pitavastatin). We constructed three measures of prescriber adoption during the 15-month post-FDA approval period: 1) any prescription of the medication, 2) proportion of prescriptions in the class for the medication, and 3) time to adoption (first prescription) of the medication. Descriptive statistics were used for the first two measures; to assess time to first adoption, we used the Kaplan-Meier method to compute the proportion of providers who had adopted the new drug in the 15 months post-FDA approval.

Results: By 2011, more PCPs had prescribed each of the new medications than APCs (e.g., 44.3% vs. 18.5% vs. 20% for dabigatran among PCPs, NPs, and PAs). Across all drug classes, the new medications accounted for a larger share of prescriptions in the class for PCPs followed by PAs, followed by NPs (e.g., dabigatran: 4.9% vs. 3.2% vs. 2.8%, respectively). Mean time-to-adoption for the new medications was shorter for PCPs compared to NPs and PAs (e.g., dabigatran, 7.3 vs. 8.2 vs. 8.5 months; P all medications <0.001).

Conclusions: PCPs were more likely to prescribe each of the new medications per each measure of adoption. Differences in the rate and speed of drug adoption between PCPs, and NPs and PAs may have important implications for care and overall costs at the population level as NPs and PAs continue taking on a larger role in prescribing.

1080. Electronic Medication Histories: Highlighting Potential Adverse Drug Events

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Background: Medications are an important aspect of patient safety with 3-5% of all prescriptions written in primary care resulting in an adverse drug event (ADE) with one-third being serious. Access to electronic medication histories (e-Rx) may improve prescribing safety and decision-making.

Objectives: To describe the distribution of drug alerts based on alert category, the type of medication and the association with sex, age group, and access to eRX.

Methods: A population descriptive study used data from an electronic prescribing and drug management project, combining information from physician billing, health administrative data, pharmacies and participating physicians. Information on dispensed prescriptions was available for all patients with public drug insurance. All dispensed prescriptions on the index date were verified for drug-drug contraindications and therapeutic duplication using the drug knowledge database from Vigilance Santé. Frequency distributions for categorical variables were calculated.

Results: From 58 261 prescriptions, 14 775 (25.4%) drug alerts occurred for 7 143 patients; 66.1% of alerts were from physicians who had access to the eRx and 3 815 (53.4%) of patients received two or more alerts. Contraindications occurred nearly twice as much as duplications for men and women. Contraindications were the most frequently reported cause (78.0%) of alerts for patients $>$ 65 years, whereas duplications (53.9%) were the most common for $<$ 65 years. The top 3 medications receiving duplication alerts for those $>$ 65 years were antidepressants (Venlafaxine, 1.4%; Trazodone, 1.2%; Citalopram, 0.9%) and for contraindications were: Calcium Carbonate (2.3%), Levothyroxine (1.6%), and Warfarin (0.9%). The top 3 medications receiving duplication alerts for those $>$ 65 years were: Temazepam (1.0%), Lorazepam (0.9%), and Citalopram (0.7%), and for contraindications were: Calcium Carbonate (11.1%), Levothyroxine (7.7%), and Warfarin (5.4%). These results were similar for males and females.

Conclusions: Patients are at risk for ADE related to antidepressant and benzodiazepine duplications as well ass contraindication for calcium supplements. Access to the eRx does not seem to reduce this risk.

1081. Longitudinal Trend and Forecast in Taiwan Pharmaceutical Industry and International Trade (2009-2018)

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Background: The development of pharmaceutical industry can reflect changes in demand and supply of medicine in a country. Little attention has been given to the past and future trends of pharmaceutical market and international trade in Taiwan.

Objectives: This study aims to examine trends in the total size of pharmaceutical market in Taiwan and its growth, including western and Chinese medicines. We also forecasted these measurements up to and including year 2018 based on the current patterns.

Methods: The yearly statistic data regarding pharmaceutical industry and international trade were obtained from annual reports of pharmaceutical industry published by Taiwan's Ministry of Economic Affairs (2009-2013). We estimated yearly pharmaceutical market size, value of output and volume of international trade. In addition, using a time series design with ARIMA models, we estimated the past trends and predict future trends up to the year 2018.

Results: The pharmaceutical market size grew from US$ 39.67 million in 2009 to US$ 48.10 million in 2013 (growth rate: 21.26%) in Taiwan, and it was predicted to reach US$ 58.33 million in 2018. Value of

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output grew from US$ 2,250 million in 2009 to US$ 2,471 million in 2013 (growth rate: 9.84%) in Taiwan, and it was predicted to reach US$ 2,715 million in 2018. Overall volume of imported and outported products rose from US$ 2,066 million in 2009 to US$ 2,694 million in 2012 and from US$ 354 million in 2009 to US$ 495 million in 2012 respectively.

Conclusions: This is a critical study to better understand the pharmaceutical industry and trade in Taiwan. Our findings indicate a substantial increase of medicine demand over the last few years, especiallty for western medicies, and this trend would keep continuously in the future.

1082. Trends in the Use of Prescription Medications with Risk Evaluation and Mitigation Strategies Among U.S. Adults: 2003-2004 to 2011-2012

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Background: Despite the implementation of Risk Evaluation and Mitigation Strategy (REMS) by the Food and Drug Administration for high risk prescription medications, there is limited information on the use of these medications in the U.S. adult population.

Objectives: To examine trends in the prevalence of REMS medication use among US adults overall and by therapeutic drug class.

Methods: Prevalence of REMS medication use was estimated over a ten-year period using nationally representative data from the National Health and Nutrition Examination Survey (NHANES). Five consecutive two-year NHANES cycles were included (2003-2004 to 2011-2012), resulting in 29,765 noninstitutionalized US adult participants. To identify prescription medications with a REMS, we extracted data from the FDA website which includes a list of all active and inactive REMS medications. REMS medication use was defined as the use of at least one REMS medication in the last 30 days.

Results: The use of at least one REMS medication among US adults slightly increased from 14.4% [95% CI 12.8%-15.9%] in 2003-2004 to 15.6% [95% CI 13.4%-17.7%] in 2011-2012. Psychotropic and analgesic REMS medications were the most commonly used therapeutic drug classes; among psychotropic medication users the use of a REMS psychtropic medication (such as gabapentin and zolpidem) increased from 31.0% to 34.7% during this time period (p-value <0.05). Trends in REMS medication use by therapeutic class often differ from the trends seen in the overall therapeutic class. For example, the use of antidiabetic medications increased (from 6.2% to 8.0%) while the use of REMS antidiabetic medications among antidiabetic medication users decreased (from 1.9% to 1.5%).

Conclusions: Despite the implementation of the REMS and growing drug safety concerns, more than one in seven adults in the U.S. use at least one medication with REMS. The majority of therapeutic drug classes have experienced an increase in REMS medication use. To improve safety, regulators need to review the impact of REMS on the use of medications as well as the adverse events they are intended to mitigate.

1083. Trends in Medicines Procurement by the Brazilian Federal Government from 2006 to 2013

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Background: The costs of medicines pose a growing burden on healthcare systems worldwide. A comprehensive understanding of how procurement is being carried out provides strong support for the development of effective policies.

Objectives: This investigation examined the Brazilian federal pharmaceutical procurement data provided by the Sistema Integrado de Administração de Serviços Gerais (SIASG) database from 2006 to 2013.

Methods: Medicine purchases were aggregated in terms of volume (number of packages purchased) and expenditure (number of packages purchased multiplied by unit price) for each year. Data on expenditure were adjusted for inflation using the Extended National Consumer Price Index (IPCA), December 31th, 2013. In order to study the cumulative proportion of the purchased therapeutic groups, Lorenz

curves were plotted. Cost-variance analysis was performed to determine the impact of each factor, price and volume, on the total expenditure variation.

Results: The annual expenditure on medicines increased 2.72 times (172%), while the purchased volume of drugs increased 1.99 times (100%). A limited number of therapeutic classes dominated expenditure each year. Drugs for the treatment of infectious diseases monopolized expenditures from 2006 to 2009, being replaced by antineoplastic and immunomodulating agents from 2010 on. Immunosuppressants (L04), in particular, concentrated, after 2010, one third of all purchases, showing the most substantial expenditure increase of the period, more than 25,000%.

Conclusions: The overwhelming price-related increase caused by L04 class is bound to have an important impact on healthcare supply system sustainability. If Brazil continues to select and incorporate costly drugs and purchase them at the same rate, the system may not hold, given the same level of financing.

1084. Good Practice Guidelines for Designing, Conducting, Analyzing and Reporting Cross-National Comparison Drug Utilization Studies

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Background: Cross-national comparison drug utilization (CNC DU) studies provide valuable information about the medicines use in different countries or regions by examining patterns of prescribing, dispensing and consumption of medicines.

Objectives: To develop good practice guidelines for designing, conducting, analyzing and reporting of CNC DU studies, to reduce the risk of bias in exposure estimation.

Methods: A group of experts from IMI-Protect, EuroDURG and WHO CC for Pharmaceutical Policy and Regulation, examined previous articles that address the comparability of CNC DU studies. A review template (RT) for CNC DU studies was constructed to: address their main methodological issues, standardize the information extraction, assess the risk of bias in the exposure estimation of each country or region compared, and evaluate the validity of the comparison between countries or regions.

To test the validity and reliability, we used the RT on a test sample (16 articles) derived from a literature search with the following criteria: (1) drug utilization studies comparing exposure data on consumption volume, (2) comparison of at least two countries or regions, (3) published between 2000-2015. Each article was reviewed by at least 4 researchers using the RT, to analyze inter-observer agreement in risk of bias assessment.

The information gathered was used to develop good practice guidelines for designing, conducting, analyzing and reporting CNC DU studies.

Results: The resulting guidelines cover the following areas: reliability and validity of population and drug coverage, and drug terminology. Biases affecting accuracy and precision of exposure estimates were identified.These guidelines and the RT will assist researchers in the development of CNC DU by highlighting the most common and potential limitations of these studies as well as to recommend procedures to overcome them.

Conclusions: Following standardized guidelines will enhance the validity and reliability of CNC DU studies, and facilitate their peer review, correct interpretation of CNC DU studies, and adequate translation into pharmaceutical policy decision-making.

1085. Sale of Phthalate Containing Drugs in Denmark from 2004 to 2012

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Background: The effect of phthalate exposure on human reproduction, development and cancer risks is controversial. Not commonly recognised, phthalates are used as excipients in a number of drug formulations. The European Medicines Agency and the U.S. Food and Drug Administration have set a maximum daily exposure level for diethylphthalate (DEP) and dibutylphthalate (DBP) of 4.0 and 0.01 mg/kg/day, respectively.

Objectives: To estimate the sale of dibutyl- and diethylphthalate containing drugs in Denmark from 2004 to 2012.

Methods: National data on annual sale of medications (tablets only) were accessed from www.medstat.dk for each substance, specified by single drug formulation. Data from the Danish Medicines Agency on phthalate content per tablet were merged with data on total sale for each drug formulation and substance. We used the 'defined daily dose' (DDD) as the unit of sale.

Results: Several of the identified drugs exceeded the permitted daily exposure of DBP. Multienzymes had 24.6-43.6 mg per DDD (phthalate-containing sale: 4.765.800 DDD; 43% of total sale). Mesalazine had 12.5-26.4 mg per DDD (10,142,100 DDD; 27%) and budesonide had 12.6 mg per DDD (25,600 DDD; 1%). Lithium had 7.6 mg per DDD (12.921.800 DDD; 66%) and bisacodyl had 1.42 mg per DDD (35.155.200 DDD; 41%)

Other drugs had high levels of DEP, but did not exceed the permitted daily exposure. Multienzymes had 43.9 mg per DDD (4.765.800 DDD; 43%) and didanosine had 12 mg per DDD (273.600 DDD; 84%). Naproxen had 10.4 mg per DDD (1.568.200 DDD; 5%) and theophylline had 8.5 mg per DDD (18.044.200 DDD; 79%)

The 7 most frequently sold drugs containing any type of phthalate (DPB, DEP and three high-molecular phthalates: hypromellose- polyvinyl acetate- and cellulose acetate phthalate) were dipyridamole (82,060,692 DDD; 75%), bisacodyl (35,155,200 DDD; 41%), dipyridamole combinations (22,672,900 DDD; 56%), theophylline (18,044,200 DDD; 79%), sulfasalazine (17,130,500 DDD; 65%), lithium (12,921,800 DDD; 66%) and mesalazine (10,142,100 DDD; 27%).

Conclusions: Sales of phthalate-containing drugs in Denmark from 2004 to 2012 were substantial, and phthalate exposures from several drug preparations exceed the regulatory exposure limit introduced in 2014.

1086. Use of Proton Pump Inhibitors Among Adults: A Danish Nationwide Drug Utilization Study

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Background: The use of proton pump inhibitors (PPIs) has increased over the last decade.

Objectives: To provide detailed utilization data on PPI use over time, with special emphasis on duration of PPI use and concomitant use of ulcerogenic drugs.

Methods: Using the nationwide Danish Prescription Registry, we identified all Danish adults filling a PPI between 2002 and 2014. Using descriptive statistics, we described the (i) distribution of use between single PPI entities, (ii) development in incidence and prevalence of use over time, (iii) measures of duration and intensity of treatment, and (iv) prevalence of use of ulcerogenic drug among users of PPI.

Results: We identified 1,617,614 adults using PPIs during the study period. The prevalence of PPI use increased four-fold during the study period to 7.4% of all Danish adults in 2014. PPI use showed strong age-dependency, reaching >20% among those aged ≥80 years. The proportion of users maintaining treatment over time increased with increasing age, with <10% of those aged 18-39 years using PPIs two years after their first prescription, compared to about 40% among

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those aged ≥80 years. The overall use of ulcerogenic drugs among PPI users increased moderately, from 35% of users of PPI in 2002 to 45% in 2014.

Conclusions: The use of PPIs is extensive and increasing rapidly, especially among the elderly.

1087. Utilization Of Tacrolimus And Pimecrolimus In Europe: Results from the JOint European Longitudinal Lymphoma and Skin Cancer Evaluation (JOELLE) Study

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Background: Tacrolimus and pimecrolimus are indicated for the treatment of atopic dermatitis.

Objectives: To assess utilization of tacrolimus and pimecrolimus in children and adults from a study across health databases in four European countries.

Methods: Multicenter database cohort study comprising the PHARMO Database Network in the Netherlands, Danish and Swedish national registers, and the UK Clinical Practice Research Datalink (CPRD). RTI-Health Solutions acted as coordinating center. New users of tacrolimus and pimecrolimus were selected from the date of first availability of tacrolimus (2002 in all data sources and pimecrolimus (2002 in Denmark and 2003 in the other data sources) through 2011. In Sweden, prescription data was available from 2006 and new users of tacrolimus and pimecrolimus were selected from that starting point. New users were identified by ATC codes in PHARMO, Denmark and Sweden, and by Gemscript codes in CPRD. Use was assessed for children <18 years) and adults.

Results: The study included 19,948 children and 66,127 adults treated with tacrolimus, and 23,840 children and 37,417 adults treated with pimecrolimus. Denmark and Sweden contributed the largest proportion of users (48% and 27%, respectively, children and adults combined). The median follow-up of new users of tacrolimus in children ranged from 2.2 years in Sweden to 4.2 years in CPRD, and in adults from 2.2 years in Sweden to 3.6 years in Denmark and CPRD. The median (min-max) number of tacrolimus prescriptions per patient in children ranged from 1 (1-46) in Sweden to 2 (1-132) in CPRD, and in adults from 1 (1-83) in Sweden to 1 (1-145) in CPRD. The utilization of pimecrolimus showed similar trends to that of tacrolimus in both children and adults. Few patients switched between tacrolimus and pimecrolimus.

Conclusions: Utilization of tacrolimus and pimecrolimus did not vary substantially across European data sources. Most patients received a single prescription. No large difference in utilization patterns was seen between tacrolimus and pimecrolimus.

1088. Impact of Safety Warning on Domperidone Prescribing in Ireland

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Background: Domperidone has been widely available as an over-the-counter or prescription-only medicine since the 1970s. Following cardiac toxicity concerns, an EU safety review in 2014 recommended that the maximum oral dose be set at 30mg for adults, and use should be limited to one week, and contraindicated in those with cardiac disease or in conjunction with QT-prolonging drugs/potent CYP3A4 inhibitors.

Objectives: To investigate the impact of these safety warnings on the prescribing of domperidone in Ireland.

Methods: Data obtained from the HSE–PCRS pharmacy claims database were used to identify the study cohort (aged 18+), prescribed domperidone from Jan

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2014 to Oct 2015. The dose was available for each claim and concomitant prescription with the following drug classes was identified and calculated as a percentage of the total number of claims: anti-arrhythmics (class IA & III C01BA0; C01BD0), macrolide antimicrobials (J01FA) and the SSRIs citalopram and escitalopram (N06AB04; N06AB10). Prescribing patterns were investigated before and after the issue of the safety advisory (May 2014) Segmented regression analysis was used to examine change in trend before and after May 2014.

Results: A total of 397,572 claims for domperidone were identified in the patient cohort during the study period. Overall, there was a significant decline in domperidone prescribing during the study period (from 22,226 to 15,691 claims, $p = 0.012$), which did not significantly change after the warning. No significant change in co-prescription of SSRIs or anti-arrhythmic agents was observed over time; co-prescription with any macrolide significantly increased after the safety advisory compared to trends before ($p = 0.031$). In those aged 60+ years, 10% of claims ($n = 1332$) were for doses > 30mg/day at the start of the study; there was no significant change in trend after the May advisory.

Conclusions: The safety warnings concerning domperidone appeared to have had little effect on prescribing patterns in Ireland. Of concern is the continuing co-prescription with drugs known to increase the risk of QT-prolongation, in all ages, including the 60 + year age group.

1089. Initiation of Anti-TNF Therapy in Patients with Inflammatory Bowel Disease in France Between 2011 and 2013: A Nationwide Study Based on Medico-Administrative Databases

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Background: Tumour necrosis factor inhibitors (anti-TNFs) are active but expensive drugs that induce and maintain remission in patients with Crohn's disease (CD) and ulcerative colitis (UC). But there is an ongoing debate about the use of anti-TNF as first line treatment for patients with inflammatory bowel disease (IBD).

Objectives: To assess the trends in anti-TNF prescription and the conditions of prescription of these drugs in newly treated patients with IBD in France between 2011 and 2013.

Methods: Data were extracted from the French health insurance and hospital claims databases (SNIIRAM/PMSI). We identified IBD patients by hospital discharge diagnoses or eligibility for serious and costly long term disease (ALD), both encoded in ICD-10 (Crohn's disease, CD: K50, Ulcerative colitis, UC: K51, Unclassified: both K50 and K51). Patients with other indications for anti-TNF were excluded. Finally, patients who initiated adalimumab or infliximab between 2011 and 2013 were selected (no anti-TNF during the previous 12 months).

Results: The number of IBD patients initiating anti-TNF increased from 4,571 to 5,875 between 2011 and 2013 (+29%). In particular, the number of anti-TNF new users who were not prescribed any immunosuppressants (IS) in the 12 months before anti-TNF initiation increased from 2,100 to 3,007 (+43%). These patients were more frequently hospitalized or operated for IBD in the 12 months before anti-TNF initiation than those previously treated with IS (47% vs. 40% for CD and 44% vs. 32% for UC). In parallel, the number of patients initiating anti-TNF combined with IS increased by 50%, reaching 570 patients in 2013. A majority of these patients were hospitalized or operated for IBD in the 12 months before initiation (59% for CD and 61% for UC).

Conclusions: This study shows a rapid increase in new prescriptions of anti-TNF for both CD and UC in France between 2011 and 2013. These results suggest a change in medical practices, with anti-TNF agents prescribed more often as first-line maintenance treatment, preferentially to patients with a history of hospitalization for IBD.

1090. Treatment Patterns of Thiopurines in a Danish Population Diagnosed with Inflammatory Bowel Disease: A Drug Utilization Study

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Background: Thiopurines (TH), including azathiopurine and 6-merceptopurine, play an important role in the maintenance treatment of patients with moderate-to-severe inflammatory bowel disease (IBD). Knowledge about utilization patterns are helpful in the evaluation of whether the actual use of TH in clinical practice corresponds with existing treatment guidelines.

Objectives: To characterize the Danish IBD population initiating TH in the period of 2009–2014 based on demographic, clinical and treatment factors and to describe the TH drug utilization patterns.

Methods: This drug utilization study was based on data from Danish nationwide population registers. Descriptive analyses of drug utilization patterns among persons with at least one primary diagnosis of IBD initiating TH treatment from 2009-14 were performed. Information on in- and outpatient contacts and prescription redemptions was included. The study presents number of incident users by demographic characteristics and in relation to clinical and treatment factors.

Results: A total of 5781 out of 33130 persons (17.5%) with a primary diagnosis of IBD between 2009 and 2014 initiated TH treatment (median age: 35 years, 51% females). In the study population, 44% were diagnosed with ulcerative colitis, 43% with Crohn's disease and 13% were registered with both diagnoses. A total of 47782 prescription redemptions of TH occurred in the period with a median of 4 prescription redemptions (ranging from 1-74). Approximately one fourth had only redeemed a TH prescription once. Forty percent of the study population initiated treatment within 0.5 years after first IBD diagnosis, whereas a minority initiated TH treatment before first IBD diagnosis (3%). Before entering the TH cohort, 3704 persons had been hospitalized (median = 2 hospitalizations) and 5406 persons had at least one outpatient contact (median = 2 outpatient contacts) with IBD.

Conclusions: In contrast to other studies on selected populations, the findings of this study are representative for the entire country population and bring important insights into TH treatment patterns in the IBD population.

1091. Drug Utilization Patterns of Tumor Necrosis Factor Inhibitor Agents in a Population with Inflammatory Bowel Disease from 2009 to 2014 in Denmark

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Background: The utilization patterns of tumor necrosis factor inhibitor (TNFI) agents in patients with inflammatory bowel disease (IBD) are not completely understood. Insights into TNFI utilization patterns can help identify subgroups with unusual drug use.

Objectives: To characterize IBD patients initiating TNFI treatment in Denmark 2009 to 2014 and to study drug utilization patterns of TNFI use among these patients.

Methods: We identified persons initiating treatment with TNFI during 2009 and 2014 who were diagnosed with IBD in the same period in the nationwide Danish patient register (TNFI inception cohort). All TNFI treatments are monitored at the hospital setting. The TNFI inception cohort was linked with register information on prescription redemptions of thiopurines and steroids, IBD related hospital contacts and TNFI treatments at the hospital.

Results: Out of 33130 persons with at least one primary diagnosis of IBD between 2009 and 2014, 4560 (13.7 %) initiated treatment of TNFI (TNFI inception cohort). In the TNFI cohort, 2143 (47%) have been registered only with Crohn's disease (CD), 1828 (40%) only with ulcerative colitis (UC) and 589 (13%) with both CD and UC diagnoses from 2009 to 2014. The cohort consisted of 53% women and 17% were younger than 20 years of age at cohort entry. Prior to entering the TNFI inception cohort, 3007 (66%) and 4120 (90%) had redeemed at least one prescription of thiopurines or steroids, respectively. The majority (76%) in the TNFI cohort used one type of TNFI, whereas 22% used two types, and 1% used three types

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of TNFI in the study period. Persons in the TNFI inception cohort had a median of 9 treatments registered (ranging from 1 and 145) and minority (2.9%) has only one treatment registered.

Conclusions: Examining drug utilization patterns is important since it provides insights into treatment patterns of IBD and can be used to monitor TNFI use in the IBD population and thereby potentially identify patient subgroups in need of treatment optimization.

1092. Dispensing Patterns of Prescription-Only Antiobesity Preparations in South Africa

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Background: Obesity is a major global public health problem. It is one of the most serious and prevalent non-communicable diseases of the 21st century. South Africa is undergoing a rapid epidemiological transition. The highest rate of obesity and overweight among adults in sub-Saharan Africa was found in South African women at 42%. Studies on the prescribing patterns of antiobesity products in South Africa are limited.

Objectives: The aim of the study was to investigate the dispensing patterns of prescription-only antiobesity preparations in South Africa using a pharmacy dispensing database to establish a baseline for further research.

Methods: A retrospective, cross-sectional drug utilisation study using electronic dispensing records of community pharmacies in South Africa was conducted on a database of approximately 54 million records. All patients who received one or more antiobesity medications in ATC group A08 in 2013 were included in the study. Descriptive statistics were calculated.

Results: A total of 27 703 patients were prescribed 52 555 products for antiobesity medication during 2013. The average age of patients was 41.71 (SD = 11.37) years, with male patients on average older than female patients (46.09 and 40.02 years, respectively). More females (72.19%) were dispensed antiobesity products, and females received their prescriptions on average at a younger age than male patients. Five active ingredients were dispensed. Phentermine was prescribed the most, accounting for 92.44% of all the antiobesity prescriptions, followed by orlistat (6.08%), phendimetrazine (1.36%), D-norpseudoephedrine (0.06%) and diethylpropion (0.05%). Most patients (79.44%) received only short-term therapy (one or two prescriptions for an antiobesity product during the year). A small percentage (0.30%) of young patients (18 years and younger) received antiobesity products, despite the fact that the safety of these products in children has not been proven.

Conclusions: Phentermine was the most commonly dispensed active ingredient, followed by orlistat. Females were prescribed most antiobesity preparations. Further studies on patient outcomes and the cost-effectiveness of these products should be conducted.

1093. Characteristics of Patients Prescribed Prucalopride versus an Active Comparator in England, Wales, and Northern Ireland

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Background: Prucalopride is currently licensed in the European Union for treatment of chronic constipation for women (approved in 2009) and men (approved in 2015) in whom laxatives have been ineffective. Given prior safety experience with other 5-HT4 agonists, a multidatabase study is planned to evaluate cardiovascular safety of prucalopride.

Objectives: To describe baseline characteristics of patients who were newly prescribed prucalopride versus polyethylene glycol (PEG), focusing on cardiovascular risk factors.

Methods: Adult new users of prucalopride were identified in the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network

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(THIN), from April 2010 through May 2014, by following a common protocol in both databases. Aggregate data were pooled after resolution of duplicate practices. Prucalopride patients were matched to PEG patients (5:1) by age, sex, calendar year of index prescription, and practice (CPRD only). Patient demographics, baseline comorbidities and comedications, and prescribing patterns for each cohort are described.

Results: The pooled data included 1,037 new users of prucalopride and 5,867 new users of PEG; 95% of patients were female and 66% were aged 18-54 years. History of hospitalization for cardiovascular disease was similar for each cohort (acute myocardial infarction: 0.5% vs 0.6%; stroke: 0.3% vs 0.7%; ischemic heart disease: 3.3% vs 2.8%), but the prucalopride cohort had a higher proportion of patients taking antihypertensive medications (48.0% vs 42.4%). More patients using prucalopride had gastrointestinal-related visits than PEG patients: 55.8% vs 11.1% had ≥2 outpatient visits for constipation, and 15.4% vs 6.3% had ≥2 outpatient visits for irritable bowel syndrome.

Conclusions: Differences in prior history of gastrointestinal disease may be due to selective channeling, because prucalopride is indicated for patients in whom laxatives have been ineffective. Despite the similarity in measured cardiovascular risk factors observed between the cohorts, accounting for channeling may control for important unmeasured confounding and will be important in the analysis of cardiovascular outcomes.

1094. Influence of Health Insurance Policy on Oral Anti-Hyperglyecemic Agents in Korean Diabetic Patients

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Background: The Ministry of Health and Welfare of Korea changed the coverage of national health insurance for the first line treatment of diabetes mellitus (DM) using oral anti-hyperglycemic agents (OHA) in July of 2011, where only metformin (MET) monotherapy as first line OHA should be reimbursed. However, the impact of this policy change on the utilization pattern of first line OHA has not been evaluated.

Objectives: To evaluate the influence of health insurance policy on the choice of first line OHA.

Methods: We used the National Health Examinee 2002-2013 database of the National Health Insurance Service of Korea. It was a 10 year follow-up data of 510,000 subjects who underwent national health screening from 2002 to 2003 to which all prescription and diagnosis information in claims database was merged. The DM patient was defined with more than 2 claims with diagnosis in a year, and new OHA user was defined as DM patients initiating OHA which was not prescribed prior 24 months. We counted the number of new OHA users from 2004-2013 in every month, and calculated proportion of OHA monotherapy by therapeutic group of OHA in MET, SU, a-GI, MEG, TZD, DPP4. Monthly proportion of OHA initiation was described, and influence of the insurance policy was evaluated in level and trend of OHA initiation using interrupted time series analysis.

Results: We identified 45,490 new OHA users from the database. Steady and gradual changes in MET and SU was observed: The proportion of new OHA users initiating MET monotherapy gradually increased from 10.6% in 2004 to 60.3 % in 2013. For SU, the proportion decreased to 6.6% in 2013 though it was 60.3% in 2004. Segmented regression analysis revealed that the clinical practice guideline in 2007 did not related to a significant level change in the utilization level of MET and SU. However, statistically significant 16.4% increase in MET initiators ($p<0.01$) and 5.6% decrease in SU initiators ($p<0.01$) were observed immediately after insurance policy change.

Conclusions: The health insurance policy was related to a statistically significant increase in MET use and decrease in the SU as the first line monotherapy of DM.

1095. Pattern of Use of Incertin-Based Medicines in a Large Sample of the Italian General Population

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Background: Incretin-based medicines (IBM) are hypoglycemic agents which have been available on the European market for almost a decade. Although they are increasingly used for type 2 diabetes, their pattern of use in clinical practice is poorly investigated.

Objectives: To describe the pattern of use of IBM in a sample of the Italian general population.

Methods: In this population-based drug utilization study, administrative data from Tuscany (Italy) were used. At January the 1st of each year between 2008 and 2014, active subjects aged ≥18 with at least one year of look-back were selected. All prescriptions of antidiabetics (ATC A10*) dispensed for outpatient consumption and reimbursed by the National Health Service were analyzed. Annual trends of IBM incidence and prevalence of use were observed per pharmacological subgroups: dipeptidyl-peptidase 4 inhibitors (DPP4i) and glucagon like peptide 1 analogues (GLP1a). Characteristics of new IBM users (age, sex, previous antidiabetic therapies) were also described per year of initiation.

Results: On a total population of almost 3,3 millions adults, 31,750 patients received ≥1 prescription of IBM between 2008 and 2014. During the study period, incidence of use of IBM increased from 0.4‰ to 1.4‰, with a peak in 2011 (2.3‰). The highest incidence of use was observed in 2013 for DDP4i (2.1‰) and in 2011 for GLP1a (0.5‰). Prevalence of use increased from 0.2‰ to 1‰ for GLP1a and from 0.2‰ to 5.8‰ for DPP4i. Prevalence of use showed similar trends in antidiabetic users (GLP1a:0.4-1.6%; DPP4i:0.4-9.3%). Among IBM new users, the percentage of women decreased from 50.9 in 2008 to 43.5 in 2014 while the portion of those aged ≥65 years increased from 30 to 61.1%. Patients on hypoglycemic monotherapy during the year preceding the first IBM prescription also increased from 23.4 to 32.9%.

Conclusions: IBM use in Tuscany rose steeply during the first half of the observation period and started to stabilize in the second. DPP4i have rapidly become the drugs of choice for the vast majority of new IBM users. Moreover, IBM are increasingly started in elderly patients and considered as first add-on hypoglycaemic treatment.

1096. Changes in Diabetes Therapy One Year Before and After Discharge from a Heart Failure Hospitalization Among Patients with Type II Diabetes

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Background: The incidence of heart failure (HF) is 2- to 5-fold higher in people with diabetes compared to those without. The extent to which evidence based recommendations are followed in the selection of antidiabetic therapy following HF diagnosis is not clear.

Objectives: To assess the change in diabetes therapy one year before and after hospitalization due to HF among patients with type II diabetes.

Methods: This is a retrospective analysis using Truven's Health Analytics Commercial database (2008-2014). The cohort included diabetic patients with first hospital admission with a primary or secondary diagnosis of HF (ICD-9: 428.0) . Patients were required to have at least 12 months of continuous enrollment prior and after hospitalization. The proportion of patients on specific antidiabetic therapy was compared between the 12- month before and after hospitalization using McNemar's test.

Results: A total of 5723 patients were identified (mean age, 56 years; 59% male; and 85% discharged home). The most commonly prescribed medications in the pre-admission period were: insulin (48.5 %), followed by sulfonylureas (22.2%), and thiazolidinediones (TZDs) (9.0%). The use of the following antidiabetic therapy was significantly higher in the post-index compared to the pre-admission period: insulin (55.6% vs. 48.5%; $P < .0001$), DPP-4 inhibitors (9.4% vs 8.4%; $P < .0001$), and metformin-DPP4 inhibitors combination (3.84% vs. 3.44%; P

<.0001). In contrast, the use of antidiabetic therapy significantly decreased for the following therapy: sulfonylureas (20.7% vs. 22.2%, P < .0001), TZDs (4.2% vs. 9.0%, P < .0001), metformin-sulfonylureas combination (2.2% vs. 3.5%, P < .0001), and metformin-TZDs combination (0.4% vs.1.0%, P <.0001).

Conclusions: There was a significant change in diabetes therapy after HF hospitalization. A significant increase was observed for insulin and DPP-4 but the use of TZDs and sulfonylureas decreased following hospitalization. These findings raised concerns that antidiabetic medications with documented unfavorable cardiovascular risk profile (e.g., TZDs) are still being prescribed for diabetic patients after HF diagnoses.

1097. Impact of Pioglitazone Withdrawal in France: A Study Using Data from the National Healthcare Insurance System

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Background: In 2011, pioglitazone was withdrawn from the French market with regard to a potential risk of bladder cancer.

Objectives: To study the public health impact of pioglitazone withdrawal (PW) in France considering i) trends in antidiabetic uses, and ii) changes in hospitalisation/death rates in diabetic patients following PW.

Methods: Two populations were considered: i) the general population of affiliates to the Echantillon Généraliste de Bénéficiaires (EGB), a 1/97th sample of the French national healthcare insurance system beneficiaries, for the 2010-2013 time period; ii) a cohort of patients identified from the EGB, all having received at least one reimbursment for a non-inulinic antidiabetic between 01/04/2011 and 31/07/2011 (date of PW). In the first population, the changes observed along the period within the monthly numbers of reimbursements observed for each non-insulinic antidiabetic drug classes were studied using through times series explored using Unobserved Component Models (UCM). In the second population, post-withdrawal incidences of all-cause hospitalization and of all-cause death among pioglitazone users and non-pioglitazone users was compared using a proportional subdistribution hazards (PSH) model.

Results: Over the period studied for the exploration of changes in reimbursment, reimbursements of antidiabetics increased in the EGB from roughly 22,000 in 01/2010 to 29,000 in 01/2014. PW was accompanied by a significant increase in sulfamides reimbursements (+277.9 reimbursements/month, 95%CI: 149.3-406.9), and glinides (+50.9; 5.3-96.6). No significant associations were found between PW and the time series of metformine, GLP-1 agonists, and alpha-glucosidase inhibitors. In the cohort of antidiabetic users at the time of PW (1102 pioglitazone users, 17,980 other antidiabetic users), pioglitazone use at the time of withdrawal was not associated with a higher rate of hospitalization or death.

Conclusions: If significant changes were observed in the use of some antidiabetic drugs after PW, and potentially because of PW, the results herein presented suggest that this did not result in an adverse impact on diabetic types II population health.

1098. Nationwide Trends in Glucose-Lowering Drug Use in Denmark, 1999-2014

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Background: The glucose-lowering treatment armamentarium has increased substantially during the past decade. Unselected population-based prescription data are needed to monitor shifting trends in diabetes drug use in real-world populations.

Objectives: We examined nationwide population-based time trends in the utilization of glucose-lowering drugs in Denmark from 1999 to 2014.

Methods: We retrieved nationwide sales statistics from the Register of Medicinal Products Statistics through Medstat.dk and reported the total number of users and the prevalence of users per 1,000 inhabitants

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in 1-year intervals for all glucose-lowering drug classes.

Results: The annual prevalence of glucose-lowering drug users increased more than 2-fold between 1999 and 2014, from 19 per 1,000 inhabitants (n = 98.362) to 41 per 1,000 (n = 233,230). Metformin use increased 7-fold during the period and was by far the most frequent used glucose-lowering drug in 2014 (30 per 1,000, 72% of all glucose-lowering drug-users), whereas use of sulfonylurea decreased considerably (6 per 1,000 in 2014). By 2014, the newer drug-classes, i.e. the glucagon-like peptide 1 (GLP-1) receptor agonists, the dipeptidylpeptidase-4 (DPP-4) inhibitors, and the sodium-glucose co-transporter 2 (SGLT-2) inhibitors have reached a significant position in the treatment of Danish diabetes patients with 4 per 1,000, 6 per 1000 and 1 per 1,000 inhabitants, respectively. Use of GLP-1 receptor agonists and SGLT-2 inhibitors was almost exclusively seen in persons aged 40-79 years. The 1-year prevalence of thiazolidinedione users peaked in 2007 at 1 per 1,000 and fell to only 0.03 per 1,000 in 2014. The prevalence of long-acting insulin users rose from 2004 onwards (7 per 1,000 in 2014), while users of intermediate-acting and mixed formula insulins decreased much and reached 4 per 1,000 and 3 per 1,000 users in 2014, respectively.

Conclusions: Use of glucose-lowering drugs has continuously increased and the pattern of glucose-lowering drug use has changed substantially, reflecting the recommendations of metformin as first-line treatment. The newer glucose-lowering drug-classes have been well-received.

1099. Treatment of Polycystic Ovary Syndrome in UK Primary Care 2004-2012

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Background: Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder affecting millions of women worldwide. The treatments of PCOS are diverse; however, little is known about their use in routine clinical practice.

Objectives: To investigate treatments prescribed in UK primary care to women with PCOS, including oral contraceptives, intrauterine devices, clomiphene, metformin, spironolactone, gonadotrophins, cyproterone, flutamide, eflornithine, weight control/loss drugs, lipid regulators, acne-related drugs.

Methods: We identified 6,013 women with a specific PCOS diagnosis and 5,807 with symptoms indicative of PCOS in The Health Improvement Network database from 2004 to 2014. For these women, we calculated the number and proportion with a prescription for one of the drugs of interest at any point prior to PCOS index date. Among the women without a prescription prior to their PCOS index date, we calculated the cumulative proportions of women with a prescription over the 2 years after the diagnosis.

Results: For women with a diagnosis and symptoms indicative of PCOS, over 40% of women had previously been prescribed a combined oral contraceptive (COC), approximately 30% had been prescribed acne-related drugs, and over 18% had been prescribed progestin oral contraceptives (POC) at the time of their first PCOS record (index date). For women without relevant prescriptions prior to their PCOS index date, acne-related drugs, COC and metformin were the most commonly prescribed drugs in the 24 months after their diagnosis. For cases with a specific PCOS diagnosis, metformin was the drug most commonly prescribed, with more than 5% of diagnosed cases receiving a prescription on their index date and over 20% receiving a prescription in the 24 months after their diagnosis. For women with symptoms of PCOS, acne-related drugs were the drugs most commonly prescribed.

Conclusions: Both women with diagnoses and symptoms of PCOS were often prescribed drugs for acne treatment. Metformin prescribing is commonly initiated after a PCOS diagnosis.

1100. Increase In Prescribing Of Systemic Tetracyclines And Isotretinoin For Treatment Of Acne Vulgaris In Norwegian Adolescents From 2005 To 2014

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Background: Acne is affecting 80-85% of all teenagers. Tetracyclines are recommended as first choice for severe acne, and - if not sufficient effect - isotretinoin could be prescribed. Both therapy options have disadvantages; antibiotic use gives side effects, influences the normal gut microbiota and contributes to antibiotic resistance, and isotretinoin may precipitate severe side effects.

Objectives: We aimed to investigate the prescribing of systemic drug therapy for the treatment of severe acne in adolescents over a 10 year period.

Methods: The Norwegian Prescription Database (NorPD) covers prescriptions to all persons living in Norway. The study population consisted of 14-24 year old users of the recommended tetracyclines or isotretinoin in the period 2005-2014 (102,586 individuals). The one-year period prevalence was calculated as the number of patients who had redeemed at least one prescription during the year divided by the mean population. If the user had no redeemed prescriptions in the preceding 12 months he/she was defined as a new user. The incidence rate was defined by the number of new users during the year divided by the mean population.

Results: In the period 2005-2014, a total of 95,993 and 26,316 individuals filled a prescription of tetracyclines and isotretinoin, respectively. For tetracyclines, the prevalence in women increased from 1.6% in 2005 to 2.8% in 2014, and in men from 2.0% to 2.4%. For isotretinoin, the prevalence in women increased from 0.1% to 0.8%, and in men from 0.3% to 1.0%. From 2005 to 2014, the incidence rate of isotretinoin use increased from 0.1% to 0.6% in women compared to an increase from 0.3% to 0.7% in men. For tetracyclines, the incidence increased from 1.2% to 2.1% in women and from 1.4% to 1.7% in men.

Conclusions: Increased prescribing rates for drugs used for severe acne were observed in the period 2005-2014. Tetracyclines were most commonly prescribed, but isotretinoin was increasingly prescribed. The prevalence and incidence of use of tetracyclines showed a greater increase in women compared to men.

1101. Retrospective Study on Antibiotics Usage Employing Who ATC DDD Methodology

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Background: Antibiotics are the primary drugs employed in hospitals worldwide . At times this usage may be irrational which can emerge immediate resistance to microorganisms. DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults.

Objectives: To study the use of antibiotics usage and their pattern using DDD/100 bed-days WHO scale and compare the usage with sensitivity pattern of for the corresponding period.

Methods: Relevant antibiotic prescribing pattern and the disease conditions for which antibiotics were

Prescribed in the in-patients admitted were collected.Information on the common organisms isolated during culture and sensitivity testing and their antibiotic sensitivity patterns were collected for the period of 2010-2014. DDD/100 bed-days of the antibiotics was calculated for the study period and compared with the corresponding antibiotic sensitivity pattern.

Results: The DDD per 100 bed day of oral antibiotics increased from 40.7 DDD/100 bed days to 50.3 DDD/100 bed days while that of injectable antibiotics increased from 33.1DDD/100 bed days to 41.2 DDD/100 bed days from 2010-2014.The highly used oral antibiotic was found to be amoxicillin having average usage of 9 DDD/100 bed days. For parenteral use it was found to be amoxicillin (6.5 DDD/100 bed days). The most common gram negative organism isolated during the study period was Psuedomonas aeruginosa and its sensitivity pattern showed increased sensitivity to amikacin and reduced sensitivity to piperacillin and tazobactam in four years. For the gram negative organisms like Methicillin Resistant Staph Aureaus the sensitivity to Amikacin remained stable over these four years.

Conclusions: The present study highlighted the level of antibiotic use in a tertiary care hospital over a period of four years. The use of antibiotic increased over this period and the anti-microbial sensitivity pattern remained fairly stable within this period. If the trends

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are followed over long periods, it would be useful to identify emerging drug use trend and corresponding sensitivity pattern.

1102. Travel Time to Pharmacy Influence the Use of Antibiotics in Norway

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Background: Travel time to health services is one important factor that can influence the use of medications such as antibiotics. Norway is a sparsely populated country with a population density of 17 persons per square kilometre. Research on out-of-hours services in Norway show that increased distance to these services leads to less use. However it is not known whether the same will be observed with travel time to pharmacies.

Objectives: To study the effect of travel time to pharmacies on antibiotic use in Norway.

Methods: We collected coordinates from Norwegian households (N: 2.1 Mill) from the Norwegian Mapping Authority. We then used the Google Maps API to estimate the travel time to the nearest pharmacy and it was then aggregated to municipality level (N:430).

Median travel time was categorised into 4 equal sized groups (quartiles)

We used aggregated data from the Norwegian Prescription database (NorPD) to get the antibiotic use per municipality. Finally we used crowd-sourced data containing spatial data on longitude/latitude for municipality centres. We linked all these data on municipality level (N:411). Age and sex was not included, as the total antibiotic consumption, in contrast with most other drugs, does not have a strong relationship to age and sex.

A Quantile regression model was used to study the association between travel time and the outcome, antibiotic use. The model included the 25%, 50% and 75% quantiles.

Results: After adjusting for number of inhabitants in municipality as well as latitude, the group with the longest median travel time $>$ 40 min) was associated with a lower use of antibiotics in all quantiles. The effect was strongest in the lowest quantile (25%) with 5.73 percentage points (CI:4.16-7.29) , and decreased to 4.31 (CI:3.26-5.35) percentage points in the 50% quantile and 3.72 (CI:2.10-5.34) in the 75% quantile of antibiotic use.

Conclusions: It seems that travel time to pharmacies influence the use of antibiotics in Norway. Further work including travel time to general practitioners in the analyses is needed. We believe that that travel time should be investigated as an explanatory variable when differences in drug consumption is observed between geographical locations.

1103. Antibiotic Prescribing Trends for Urinary Tract Infections (UTI) in a U.S. Network of Primary Care Clinics Serving Low-Income Populations

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Background: Uncomplicated UTI is the most commonly treated bacterial infection in primary care settings. Often treatment is prescribed empirically without urine culture or antibiotic susceptibility results. With increasing prevalence of multidrug-resistant bacteria, prudent prescribing must be supported by limiting use of broader spectrum agents. Socioeconomic factors are known to influence medication use but little data are directly available from low-income clinics.

Objectives: To assess fluoroquinolone (FQ) and other broader-spectrum antibiotic use among adult females treated for UTI in a national network of primary care clinics serving low-income populations.

Methods: We collected 2009-2014 data from the OCHIN network of 442 clinics across 18 states. Clinic visits for females age $>$18 with a UTI diagnosis were included. Patient visits with chronic UTI or other infectious disease diagnoses, or prior UTI within 30 days were excluded. Antibiotic prescriptions and duration of therapy were summarized and compared by year (Cochran-Armitage test).

Results: Among 32,818 visits, 36.5% resulted in a FQ prescription followed by trimethoprim-

sulfamethoxazole (TMP-SMX, 34.4%) and nitrofurantoin (21.2%). Over 6 years, TMP-SMX use decreased from 39.3% in 2009 to 30.5% in 2014 ($p<0.01$); FQ use did not change significantly; and cephalosporin use rose from 3.0% to 6.2% ($p<0.01$). Among FQ and cephalosporin prescriptions, 8-14 day regimens were ordered in 11.8% and 18.2% of visits, respectively, and >14 day regimens (possibly reflecting prophylaxis) in 33.0% and 32.8%, respectively.

Conclusions: TMP-SMX and FQ each represented over a third of antibiotics prescribed for UTI. Use of TMP-SMX, a recommended first-line agent in the U. S., declined over time. Yet broader spectrum FQ were prescribed consistently and cephalosporin use increased; these agents are associated with emergence and spread of multidrug resistance, especially when use is unnecessary or prolonged. More research is needed to improve empiric antibiotic prescribing in low-income primary care settings to limit the spread of antibiotic resistance.

1104. Antibiotic Prescribing in Hospital, a Comparison Point Prevalence Study Between Ireland and Norway

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Background: Surveillance of antibiotic use is an important part of antibiotic stewardship. Sales data has been used for antibiotic surveillance in hospitals, but this method lacks information about choice of therapy, dosages and indication for use. This information may be collected by point-prevalence surveys (PPS).

Objectives: To compare the use of antibacterials among hospitalised patients in Ireland and Norway with regard to diagnosis, therapy choice and doses. Moreover, to relate the data to national Guidelines in the respective countries.

Methods: A one-day PPS was carried out 10 February 2016 in one general hospital in Ireland and one in Norway at departments of general medicine and surgery. A standardized Norwegian PPS spreadsheet was translated to English. The data collectors in both countries were trained in advance. All patients using systemic antibacterials (ATC group J01) were eligible for the PPS. The following were recorded: indication for use, antibiotic name, formulation, dosage and whether microbiological tests were taken. The main outcome measures were number of patients prescribed antibacterials and therapy pattern according to indication and Guidelines recommendations. The data is presented as descriptive statistics.

Results: Of the hospitalized patients, 32.7% and 36.9% were prescribed antibiotics in respectively Ireland and Norway. Lower Respiratory Tract Infection was the most common indication for antibiotic prescribing in both countries, 41.5% (Norway) and 35.6% (Ireland) The antibacterial most often used were cefuroxime in Norway (n = 11) and co-amoxiclav (n = 21) in Ireland.

Conclusions: Approximately one third of patients were prescribed antibiotics in both countries. The prescribing seems to be in consistence with the Guidelines in the respective countries.

1105. Knowledge, Attitude, and Perception of Physicians Towards Prescribing Antibiotics Use for Upper Respiratory Tract Infections in Holy Makkah, Kingdom of Saudi Arabia

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Background: Upper respiratory tract infection is most frequently reported among in community. Majority of such infections are viral oriented and does not require antibiotics. Physicians attitude and perception may result to inappropriate antibiotics use, resulting to antimicrobial resistance in general.

Objectives: Aim of this study was to study and analyze physicians belief about antibiotics prescribing

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towards upper respiratory tract infections and their perception about antimicrobial resistance.

Methods: A knowledge attitude practice questioner was adopted from previous study to find out physicians attitude towards prescribing antibiotics for upper respiratory tract infections. Simple random stratified sampling was used to select representative sample of parents.

Results: One hundred and three physician completed the questioner (54% male and 45 % female) responded among physicians. Most of them were resident 64% versus 23 % specialist and 12 % were consultant. Sixty eight of the physicians believed that antimicrobial resistance is a significant problem in Saudi Arabia. While 51 % only think that it's a significant problem in their clinics. Interestingly, 45 % think that the level of awareness and Knowledge of healthcare providers about antimicrobial resistant is adequate in their facility while only 32% were aware of any antimicrobial stewardship programs that have been implemented in Saudi Hospitals. Most of them strongly agreed that the reasons of antimicrobial resistance are poor monitoring (42%) and due to that he patient doesn't finish his medication (43%).

Tonsillitis was the most common cause for prescribing antibiotics by physicians (62%).Cefuroxime was the most prescribed first line treatment for uncomplicated urinary tract infection (39%) while Amoxicillin/Clavulanate was the most common as a second line treatment (24%).

Conclusions: This survey will outline physicians perceptions and can highlight gaps in physicians knowledge about antimicrobial resistance to develop appropriate policies at ministry of health level.

1106. Trends in Utilization of Antibiotics in Norway - Do We Reach the National Goals?

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Background: Antibiotic overuse leads to antimicrobial-resistant infections which may harm patients. The Norwegian National Strategy Against Antibiotic Resistance 2015-2020 states the goals for rational use of antibiotics in all sectors. The Norwegian Prescription database (NorPD) and the Norwegian Drug Wholesales Statistics database are key data sources for assessing consumption of antibiotics in the Norwegian population.

Objectives: To present trends in utilization of antibiotics in Norway in the light of the specific targets in the National Strategy; reduce the total use of antibiotics in 2020 by 30 percent (measured in DDD/1000 inhabitants/day (DID)) as compared to 2012 and reduce the number of prescriptions to 250 prescriptions per 1000 inhabitants per year.

Methods: Sales of antibiotics were captured from the two Norwegian drug databases. The NorPD was the basis for descriptive analyses related to the number of users and the number of prescriptions. The NorPD contains all drugs prescribed and dispensed by Norwegian pharmacies since 2004. Individual data on inpatient use are not included. Data from the wholesales database provided longitudinal statistics. The main outcomes were the amount of antibiotics used (measured in DID), number of prescriptions and number of users.

Results: The overall use of antibiotics has increased from 14.5 DID in 2000 to 17.4 DID in 2012, thereafter it declined to 15.1 in 2015, a 13.5% reduction. In primary care (NorPD), the use has declined since 2012 from 13.9 DID to 12.4 DID in 2015. The proportion of narrow-spectrum antibiotics dispensed has declined and accounted for 26% of the total consumption in 2015. The number of prescriptions/1000 inhabitants/year decreased from about 450 in 2012 to about 390 in 2015. In the Norwegian population 22% received antibiotics at least once during 2015. Norwegian municipalities showed a considerable variation in the proportion of the population receiving antibiotics, from 6% to 33%.

Conclusions: To achieve the goals of the National Strategy against antibiotic resistance for reduced antibiotic use in 2020, further efforts are needed.

1107. Trends In The Utilization Of Allergy Medications

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Background: Allergic disorders are widespread diseases which are occurring with increasing frequency. New and safer allergy medications have become available, and these can also be purchased without a prescription.

Objectives: To identify and understand trends in the use of allergy medicines.

Methods: Total sales of allergy medications (1988-2014), measured in defined daily doses (DDD), were retrieved from Nordic drug databases. Information about the number of users was obtained from the population-based prescription registries in Norway, Sweden and Denmark for the year 2014. The prescription registry in Norway was the basis for descriptive analyses related to gender, age and season variations. The main outcomes were the amount of drugs used nationwide, measured as DDDs per 1000 inhabitants per day and the proportions of drug users in specific population segments.

Results: In Norway, total sales of systemic allergy medications (2nd and 3rd generation antihistamines) increased tenfold over the last 25 years. Use of systemic antihistamines (all systemic antihistamines included) increased considerably (threefold) in all Nordic countries during the period 2001-2014, and the use was highest in Norway. There were large gender differences; in Norway, twice as many females as males were users in the age group 50-59 years. Season variations in use of allergy medications were pronounced for both genders, with utilization that varied in parallel with the pollen seasons. The season variations were largest in the younger age groups.

Conclusions: The strong rise in the use of allergy medicines in recent decades was primarily accounted for by a general increase in the incidence of allergic diseases. The differences between the Nordic countries can partly be explained by dissimilarities in drug policy and pricing of allergy medications.

1108. Dispensing Patterns of Anthelmintic Drugs by a Community Pharmacy Group in South Africa

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Background: It is estimated that over two billion people worldwide, especially in developing regions of sub-Saharan Africa, Asia and the Americas are infected with one or more species of helminths. Little is known about the prescribing and use of anthelmintic drugs outside the government sector in South Africa.

Objectives: The primary aim of this study was to describe the dispensing patterns of anthelmintic products, dispensed by a group of community pharmacies in South Africa, in order to identify further research needs.

Methods: A retrospective, cross-sectional drug utilisation study was conducted on a 2013 community pharmacy dispensing database from 327 pharmacies in South Africa. Anthelmintics provided free of charge by the government as part of current prevention and treatment programmes were not included in the study. Basic descriptive statistics were calculated.

Results: A total of 252 248 anthelmintic products were dispensed to 176 931 patients (66.02% females) during 2013. The average age of patients was 40.20 (SD = 11.93) years. Less than one percent of the total number of products (n = 2 212; 0.88%) were dispensed to children below 12 years of age. Four anthelmintic active ingredients were dispensed, namely albendazole, mebendazole, praziquantel and niclosamide. Mebendazole dominated the dispensing of anthelmintic products, constituting 95.33% of the number of products and 92.61% of the cost of products dispensed in ATC subgroup P02. Mebendazole was followed by albendazole (4.35% of products). Most products (71.36%) dispensed were originator products, with only mebendazole and albendazole having generic equivalents that were dispensed. Dispensing patterns for mebendazole peaked in January and December, and there was also a slight increase in July (three traditional holiday months in South Africa). The majority (74.66%) of products for praziquantel were dispensed in the northern provinces of South Africa (North-West, Gauteng, Limpopo and Mpumalanga).

Conclusions: Mebendazole was the anthelmintic of choice in this study. The low percentage (0.88%) of

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children younger than 12 years who were dispensed an anthelmintic product needs to be investigated.

1109. NOACs: Are We Prescribing Appropriately?

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Background: The Novel Oral Anticoagulants (NOACs) are increasingly prescribed in the healthcare setting. In Ireland, 25,364 patients were on a NOAC as of October 2015. (1) However, there are many potential difficulties associated with their use- ie. The need to dose-adjust for age, creatinine clearance (CrCl) and weight. In addition, analysis of the GMS prescribing database has illustrated that over 20% of patients on NOACS receive medications expected to interact with NOACs, with >50% of patients receiving doses that have not been proven superior to warfarin in clinical trials. (1)

Objectives: To examine prescribing trends and errors in a large teaching hospital with a strong pharmacy commitment.

Methods: Cross-sectional data was collected from 30 inpatients over a 3 week period from internal medicine and cardiology wards. Information collected included the type of NOAC; Apixiban, Dabigatran and Rivaroxaban, as well as the indications, doses, age, weight, serum creatinine and creatinine clearance, hepatic impairment and potential drug interactions. Data was inputted and analysed via Microsoft Excel.

Results: In line with the HSE- Medicines Management Programme (HSE-MMP) recommendations, (2) the majority of patients were on Apixiban (57%). Rivaroxaban prescriptions constituted 33% and the remaining 10% were prescribed Dabigatran. Of the patients on Apixiban, 70% were on the recommended 5mg BD dose. Only 10% of patients were on a NOAC for an inappropriate indication, including valvular Atrial fibrillation and post PCI. An inappropriate dose for the CrCl was found in 11%. Potential drug interactions were common, with 63% of patients concomitantly taking a cautioned or contraindicated medication. NSAIDS, including aspirin were the most common (33%). Macrolides were prescribed in 10% of patients. 1 patient was on Dronedarone and 1 patient on Heparin.

Conclusions: In hospitals with ongoing pharmacist input, prescribing errors in relation to NOACs are lower than the national average. (1) However, concurrent prescribing of cautioned or contraindicated medication remains high, reflecting the ongoing need to assess risk-benefit ratio when prescribing NOACs.

1 General Medical Services database.
2 Medicines Management Programme 2015.

1110. General Pharmacological Treatments Preceding A Primary Chronic Immune Thrombocytopenia Diagnosis

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Background: Patients with chronic immune thrombocytopenia (cITP), even those unexposed to Immunosuppressants, have increased risk of infection both before and after cITP diagnosis. The findings suggest that infection might not only be related to the treatment but also to the disease itself. It is possible that patients with cITP may seek help due to early symptoms before diagnosis of cITP and that infection is a secondary finding. If this is correct cITP should also be associated with increased prescription of other drugs before the cITP diagnosis.

Objectives: To investigate the pattern of medications in adult patients with primary chronic ITP during the year before the cITP diagnosis.

Methods: From the Swedish Patient Register 1,087 adults (18 years or older) with a diagnosis of primary cITP between 2006 and 2012 were identified. The International Classification of Diseases, tenth revision, codes D69.3 and D69.4 were used to identify the patients. Data on pharmacological treatment were obtained from the Swedish Prescribed Drug Register. ATC codes A11-12, C02-03, C07-10, M, and N02 were used to investigate the pattern of dispensed drugs. The Standardized Incidence Ratios (SIR; the ratio of the observed to the expected number of prescriptions dispensed), and 95% confidence intervals, were estimated as a measure of relative risk for pharmacological treatment during the year preceding the cITP diagnosis. The expected numbers of drug treatment

was calculated using the rates from the general population, divided into strata of sex, age (in five-year groups), and year of diagnosis.

Results: The associations for overall drug prescription (SIR = 0.97, 95% 0.95-0.99) and majority of the studied drugs were close to unity. The only statistically significant increased risks were for calcium (SIR = 1.28, 95% CI 1.03-1.58), bisoprolol (SIR = 1.39, 95% CI 1.03-1.85), and codeine- containing medicines (SIR = 1.33 95% CI 1.02-1.70).

Conclusions: The pattern of dispensed drugs does not support the hypothesis that diagnosis of infection would be a secondary finding after medical examinations due to early symptoms of ITP. The statistical significant findings can be due to multiple statistical testing.

1111. Evolving Australian, and Northern European, Utilisation Patterns for Immunosuppressants After Transplantation

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Background: The increasing utilisation of and expenditure on immunosuppressant medications is a worldwide challenge as more people successfully live with transplanted organs.

Objectives: To characterise utilisation and expenditure patterns for mycophenolate, tacrolimus, cyclosporin, sirolimus and everolimus in Australian transplant recipients between 2010-2014, including use of the newer formulations and compare these patterns to Norwegian, Danish, Swedish and the Netherlands use.

Methods: Australian utilisation and expenditure were captured through Pharmaceutical Benefits Scheme and Highly Specialised Drug databases. Norwegian, Danish, Swedish and Netherlands utilisation were retrieved from their respective healthcare databases. Utilisation was compared as defined daily dose per 1000 population per day. Data on kidney transplant recipients, the predominant group prescribed these medicines were obtained from international transplant registries.

Results: From 2010-2014 Australian utilisation of mycophenolate, tacrolimus and everolimus increased 1.5-fold, 1.7-fold and 1.7-fold respectively. Conversely, cyclosporin utilisation decreased by 5% while sirolimus remained unchanged. Australian utilisation was significantly lower than Northern European countries (2013; Chi-squared $p<0.0001$ in all cases); however overall utilisation in Australia was increasing at a faster rate. Australian expenditure increased by AUD $10 million over the 5-years to AUD$95 million. In contrast to previous use, new formulation EC-MPS doubled over 5 years to 26% of mycophenolate use, and XR-Tac increased from 0 to 10% of tacrolimus use in this 5 year period.

Conclusions: In line with changing evidence, use of calcineurin inhibitors in Australia has moved from cyclosporin to tacrolimus, similar to changes in Northern Europe. With an increased number of people living with transplants, the observed growth predicted from the comparison Northern European data, and the switching to newer, more expensive formulations, this group of medicines will continue consuming an increasing share of Australian pharmaceutical expenditure.

1112. Trends in Prevalence of Lung Cancer and Targeted Therapies Utilization for Lung Cancer Treatment in Taiwan (2004-2013)

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Background: Lung cancer is one of the most commonly diagnosed cancers and a leading cause of cancer deaths in Taiwan. Use of targeted therapies has improved quality of cancer care and survival globally, but these innovative and expensive drugs have led to increases in pharmaceutical expenditures. The economic burden of targeted therapies has increased markedly, but little is known about their use specifically for lung cancer treatment in Taiwan.

Objectives: This study first examined the prescribing pattern of targeted therapies for lung cancer treatment in light of the prevalence of lung cancer in Taiwan. We also examined trends in use and expenditures of antineoplastic agents in Taiwan and estimated market shares by prescription volume and costs of targeted therapies overtime.

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Methods: A retrospective observational study of the utilization of targeted therapies for treatment of lung cancer. Yearly claims data for antineoplastic agents were retrieved from Taiwan's National Health Insurance Research Database (2004-2013). We calculated yearly prevalence of lung cancer, prescribing rate of targeted therapies, and market shares by prescription volume and costs for each class of antineoplastic agents (including targeted therapies). Using a time series design with ARIMA models, we estimated trends in use and costs of targeted therapies.

Results: The estimated prevalence of lung cancer increased from 128 to 198 per 100,000 population during 2004-2013, an average rate of 6.08% increase per year. The prescribing rate of targeted therapies increased from 3.35% in 2004 to 40.21% in 2013. Among all antineoplastic agents, market share of targeted therapies grew from 1.27% in 2004 to 37.86% in 2013, but contributed 2.87% of antineoplastic agent costs in 2004 and grew to 45.58% in 2013.

Conclusions: Targeted therapies are increasingly used for lung cancer treatment in Taiwan, representing substantial economic burden. It is important to establish mechanisms to monitor their use and outcomes.

1113. Trends in Erlotinib Use for Non-Small Cell Lung Cancer, 2007-2012

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Background: Erlotinib is the first FDA approved and guideline recommended targeted therapy for locally advanced or metastatic (stage IIIB/IV) non-small cell lung cancer (NSCLC), with evidence of survival benefits demonstrated in clinical trials.

Objectives: To examine the trends in erlotinib use over time among older patients with stage IIIB/IV NSCLC and to describe characteristics of users versus non-users.

Methods: We used SEER-Medicare claims and included patients aged 65 and older with stage IIIB/IV NSCLC diagnosed during 2007-2012. Patients were required to be enrolled in Medicare Parts A, B, and D for 6 months prior to diagnosis through death or the end of the study period. We examined changes in erlotinib utilization by estimating proportion of patients receiving erlotinib by year, time from diagnosis to treatment, and utilization by patient characteristic, including demographics, socioeconomic status, and cancer characteristics.

Results: More than 10% of newly diagnosed stage IIIB/IV NSCLC patients were treated with erlotinib each year, although the proportion treated declined over time. The proportion of users initiating within 6 months of diagnosis increased from 46% to 60% between 2007 and 2012. Overall, erlotinib users were of similar age (median 75 years) and stage (70% stage IV) as non-users, but users were significantly more likely to be women (59% vs 48%), married (52% vs 42%), and of non-Hispanic ethnicity with races other than White or black (21% vs 7%). Non-users were more likely to live in less urban/rural (14% vs 9%, $p<.05$) and higher poverty (28% vs 22%, $p<.05$) areas.

Conclusions: Targeted therapy presents promising treatment alternatives for NSCLC. However, erlotinib uptake was low among Medicare beneficiaries with only 10% of advanced NSCLC patients using the drug over time. Limited utilization may be due to its high price and limited evidence outside of trials. Evaluating the uptake of new technologies and characteristics of patients receiving innovative treatments can highlight gaps in care and differences between patients treated in trials and in the real world.

1114. Oral Anticancer Drugs Use in France: A Population-Based Study

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Background: The number of new oral anticancer drugs (OAcD) emerging on the market has increased during the last decade but few data are currently available on their "real-life" use.

Objectives: To estimate use of OAcD in France from 2006 to 2013 and to describe users profile using outpatient data from the French healthcare insurance database.

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Methods: A yearly cross-sectional study was conducted from 2006 to 2013 within the EGB (Echantillon Généralistes des Bénéficiaires), a random 1/97 permanent sample from the French national health insurance database. Usage patterns of OAcD were explored among prevalent users (at least one reimbursement of OAcD over each studied year) and incident users (no OAcD reimbursement within the year prior to the first OAcD reimbursement over each studied year) and categorized according to their pharmacological class (Hormone Therapy (HT), cytotoxic, Targeted Therapy (TT) and others). Besides baseline characteristics described for both prevalent and incident users, comorbidities were summarized for incident users only using the Charlson index score estimated within the year prior to the first OAcD reimbursement.

Results: Prevalent and incident OAcD users frequencies remained broadly stable from 2006 to 2013 (0.6%; 0.3%). Considering OAcD classes, incident use of TT increased (+6.0%) while incident use of HT and cytotoxic decreased (-6.4%; -1%) over the seven-year study period. The male to female sex ratios were stable in prevalent (0.4) and incident users (0.5) for each year of the study period. Mean age increased slightly from 2006 to 2013 for prevalent users (58 yrs (±19) to 59 yrs (±20)) as incident users (56 yrs (±20) to 57 yrs (±20)). Incident users' comorbidities at treatment initiation remained broadly stable from 2006 to 2009, then slightly decreased to 2013: 33% to 26% had a Charlson index score ≥ 5. This trend concerned essentially cytotoxic (33% to 22%) and HT incident users (34% to 27%).

Conclusions: This study showed an increase in TT use balanced by a decrease in HT and cytotoxic use between 2006 and 2013 in France. These trends are associated with a change in the users profile especially over the last 2 years.

1115. Uptake and Cost of Capecitabine versus 5-FU Among Commercially-Insured Colorectal Cancer Patients

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Background: Capecitabine, an oral pro-drug to 5-fluorouracil (5-FU), approved May 2001 for metastatic colorectal cancer (CRC), allows for less invasive, more convenient treatment. However, the cost of oral cancer medications may be prohibitive, affecting their uptake compared to infused alternatives.

Objectives: We investigated the uptake and cost of capecitabine over time, including generic capecitabine, which was approved September 2013.

Methods: We selected patients' first treatment with capecitabine or 5-FU from MarketScan Commercial data (2002-2014). Patients were ages 18-64, had 6 months' prior medical and pharmacy coverage, a diagnosis of CRC and no prior breast cancer diagnosis. The proportion of patients treated with capecitabine versus 5-FU was calculated by year. Non-capitated costs of index capecitabine fills were calculated annually for branded and generic products and inflation-adjusted to 2014 dollars.

Results: We identified 11,314 capecitabine-treated and 28,502 5-FU-treated patients. Between 2002-2014, capecitabine market share increased from 20% to 34%, with generics accounting for 74% of index capecitabine fills in 2014. The median cost/fill for capecitabine increased from $1,411 to $3,767 from 2002-2013. Median cost of generic fills in 2014 was $3,458, versus $4,089 for brand capecitabine. Out-of-pocket (OOP) cost was <$50 for 85% of patients in 2002, compared to 56% in 2013. In the same time period, patients paying >$500 rose from 0 to 6%. In 2014, median and mean OOP cost for generic fills were $10 and $63, compared to $40 and $237, respectively, for brand fills.

Conclusions: Uptake of capecitabine as initial fluoropyrimidine therapy for CRC has increased since approval, but most patients still receive 5-FU. Median inflation-adjusted cost of capecitabine fills has increased by 2.7 times since 2002. Although generic capecitabine had significant uptake in 2014, the median cost was similar to the branded product, and 2.5 times higher than 2002 branded costs. Mean and median OOP costs for generic products were lower, but OOP costs were <$50/fill for >50% of patients prior to generic entry.

1116. Consumption and Expenditure of Non-Targeted and Targeted Cancer Drugs in Ecuador

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Background: Cancer drugs are important drivers of pharmaceutical expenditures worldwide. In 2008 Ecuador (a South-American country, 14.5 million inh. in 2010), launched a new constitutional framework assuring free access to cancer care, including non-targeted and targeted (biologicals) cancer drugs.

Objectives: To describe the longitudinal pattern of consumption and expenditures of cancer drugs in the 6 main cancer care hospitals in Ecuador from 2010 to 2013, comparing non-targeted vs. targeted drugs.

Methods: Cancer drugs corresponding to L01, L02, L04, H01 and G03 (ATC) were extracted from administrative databases collecting information from 6 Ecuadorian hospitals serving around 70% of the country's population. L01XC, E and X were classified as targeted oncologic drugs. The consumption is expressed as the percentage of patients exposed to the drug and as the total number of units dispensed in one year. The database included the expenditure per drug per patient, this is expressed as the mean expenditure per unit calculated for targeted vs. non targeted drugs.

Results: The total number of treated patients (51.8% female, age 52.8 SD ± 19.6 years old) varied from 12791 in 2010 to 14890 in 2013. The dispensed units increased from 1.6 million in 2010 to 2.1 million in 2013 (or from 131 to 143 per patient). Ecuador's total expenses in cancer drugs raised from USD 13.5 to USD 30.4 million in the studied period (or from USD 1061 to 2042 per patient). The percentage of exposed patients to targeted drugs raised from 12.1% (2010) to 16.1% (2013). The mean price for these targeted drugs was USD 678.5 per unit, more than 20 times the mean price for the non-targeted drugs (USD 29.4).

Conclusions: This is the first study in Latin America showing empirical evidence on the utilization of cancer drugs using population-based administrative secondary sources. In Ecuador the expenditures on cancer drugs have doubled from 2010 to 2013 mainly due to an increasing consumption pattern of expensive targeted drugs, seriously burdening the public health budget aimed to accomplish the free access to medicines policy.

1117. A Comparative Study to Evaluate Treatment Patterns & Resulting Utility in Patients of Head & Neck Cancers Under Private Payment Scheme and Government Reimbursement Scheme

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Background: Access to quality cancer care remains a challenge in a developing world due to poor insurance coverage of the patients and limited support from government.

Objectives: This study was conducted to compare the treatment patterns and resulting quality adjusted life year (QALY) in patients of Head & Neck cancers under private payment scheme (PPS) and government reimbursement scheme (GRS) in India.

Methods: In a prospective study treatment orders of patients on chemotherapy for head & neck cancers were reviewed for six treatment cycles to assess treatment patterns in an oncology hospital. Treatment patterns were reviewed with respect to National Cancer Comprehensive Network (NCCN) guidelines. EQ-5D-5L instrument was administered to assess patient utility and calculate QALY with treatment during each cycle. Treatment patterns and resulting patient utility were reviewed and compared among patients of PPS and GRS.

Results: A total of 104 patients (n = 49 under PPS, n = 55 under GRS) were enrolled in the study after obtaining their informed consent. Majority of the patients under PPS were on Paclitaxel based regimen (63%) followed by primary protocol ((Docetaxel + Cyclophosphamide + Fluorouracil, (8%)).Most of the patients under GRS were treated with Cisplatin with radiation therapy (82%) and none of the eligible patients under GRS had privilege of treatment with primary protocol due to restricted formulary of the scheme. Treatment compliance to NCCN guidelines for patients under PPS and GRS was 89% and 58%

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respectively. Common adverse events like vomiting, constipation, neutropenia, fatigue and myalgia were higher in patients under GRS than PPS. QALY gained by patients under PPS and GRS after six cycles was 0.024 and 0.014 respectively ($p<0.05$).

Conclusions: Treatment patterns in patients under PPS were well compliant to NCCN guidelines. Limited budget and restricted formulary of government scheme in a developing country does not allow clinicians to prescribe required anti-cancer medicines and supportive care. Patients under GRS can be benefited with more utility with additional increment in the budget.

1118. Identification & Resolving of Medication Related Problems Associated With Management of Co-Morbidities in Cancer Patients — A Role of Medication Therapy Management Service

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Background: A role of Medication therapy management (MTM) service in ensuring appropriate care of co-morbidities in cancer patients was explored.

Objectives: This study was conducted to study the nature and extent of medication related problems (MRPs) associated with management of co-morbidities in cancer patients.

Methods: This was a prospective interventional study conducted for a period of six months at private cancer center. All the cancer patients with co-morbidities were followed by clinical pharmacists on daily basis under provision of newly implemented MTM service. All the MRPs identified by clinical pharmacists pertaining to management of co-morbidities were discussed with concerned clinicians for necessary actions. After discussion, appropriate suggestions were provided to resolve all MRPs.

Results: A total of 267 MRPs were identified in 197 patients from 251 patients followed. The most common MRPs identified were drug-drug interactions (44%) followed by failure to receive drugs (16%), untreated indication (14%), adverse drug reactions (10%), drug use without indication (8%), sub therapeutic doses (6%) and over dose (2%). The common reasons for MRPs were poorly maintained paper medical records (38.5%), lack of coordination among treating physicians, pharmacists and nurses (18%), literacy status of the patients and medication non adherence (16%), unavailability of full time general physician (15.5%) and high patient load (12%). A total of 244 interventions were made to resolve the identified MRPs. MTM service resolved these MRPs by altering medication orders of interacting drugs (44%), re-initiating previously prescribed treatment for co-morbidities (14%), prescribing newer treatments for untreated indications (14%), correcting under dose & over doses (8%), discontinuing drugs without indications (6.5%) and prescribing symptomatic treatment for ADRs (6%). Acceptance of MTM initiated treatment changes by clinicians was 96%.

Conclusions: MTM service by clinical pharmacists can contribute to rationalize the drug therapy of co-morbidities in cancer patients.

1119. Impact of Regulatory Action on Prescribing of Renin-Angiotensin System Blockers in the UK

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Background: RAS blockers are used to treat hypertension, diabetes and heart failure. Combination use from two different classes was thought to provide cardio- and nephroprotective effects despite uncertainty around long term efficacy and safety. In 2014 an EU review concluded co-prescribing of RAS blockers from two different classes was associated with an increased risk of hyperkalaemia, hypotension and impaired renal function compared to monotherapy and advised against this practice.

Objectives: Assess the impact of regulatory action on prescribing trends of RAS blockers in UK primary care.

Methods: RAS blocker prescriptions from 01/01/2009-30/06/2015 were extracted from the Clinical Practice Research Datalink to estimate incidence and prevalence of prescribing by quarter. Two different RAS blockers prescribed on the same day constituted co-prescription.

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Results: 879,555 patients were prescribed a RAS blocker (12,372,343 prescriptions issued) during the study period. The median number of prescriptions per patient was 9 (IQR 4-16). Prevalence of prescribing increased steadily from 462,414 in 2009 Q2 to 514,226 prescriptions per million pyrs in 2015 Q2, while incidence decreased from 10,833 to 7,573 prescriptions per million pyrs. Conversely, prevalence of co-prescribing decreased steadily from 2,481 to 1,450 co-prescriptions per million pyrs. Incidence of co-prescribing increased during 2009 from 11 to 40 co-prescriptions per million pyrs but remained relatively constant at 58 co-prescriptions per million pyrs on average thereafter with a slight reduction in the quarter after the EU review. The majority of co-prescriptions were for an ACE inhibitor + ARB (~96%) while an ACE inhibitor or ARB + renin inhibitor accounted for ~4%.

Conclusions: In recent years, there has been a decrease in the prevalence of RAS blocker co-prescribing and a constant incidence rate despite an increase in overall RAS blocker prescribing. It is reassuring that the overall co-prescribing of RAS blockers from two different classes has fallen in line with the recommendations, although trends were showing a decrease prior to this. This is likely due in part to prior publication of the data used in the EU review.

1120. Antiplatelet Treatment and Long-Term Mortality After Acute Myocardial Infarction in Real-World Data

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Background: Cardiovascular diseases are the leading causes of death and myocardial infarction (MI) accounts for nearly half of cardiovascular-related deaths.

Objectives: We characterize long-term treatment patterns and all-cause mortality of patients with acute MI using real-world data.

Methods: All patients who experienced an MI between 1/2009 and 12/2010 among adult members of a large health organization in Israel (Maccabi Healthcare Services) were assessed using linked, longitudinal electronic medical records. Patients with a history of CVA or TIA were excluded from the study to focus on those whose antiplatelet treatment wouldn't substantially be influenced by bleeding risk. Multivariable Cox proportional hazards regression models were used to assess all-cause mortality over more than 5 years.

Results: We identified 1521 eligible incident MI patients who survived 60 days from hospital release (75% men, mean age = 64.7 ± 14.2 y). Among them, 8.5% and 5.7% remained untreated at 30 and 60 days post MI (17.8% and 13.0% of women, and 5.4% and 3.2% of men, respectively, $p<0.001$). Women were significantly less likely than men ($p<0.01$) to be seen by a cardiologist (74% and 90%), and to be treated with dual antiplatelet therapy (DAPT, clopidogrel + aspirin) (52% and 70%, respectively). Among men, but not among women, treatment with aspirin alone was independently associated with higher all-cause mortality compared to treatment with DAPT [adjusted hazard ratio (HR) 1.80 (95% CI: 1.21-2.68) and 1.14 (0.69-1.86) among men and women, respectively]. However, women had no excess risk for all-cause mortality compared to men [HR = 0.93 (0.70-1.23), adjusted for type of treatment and other confounders].

Conclusions: The study results indicate that a considerable proportion of post-MI patients go untreated with APT and without seeing a cardiologist, particularly among women. Initial treatment with aspirin alone was associated with worse survival among men but not among women. There was limited power to assess associations observed among women. Further efforts are required to assess how gender may drive disease management and subsequently prognosis among patients experiencing an MI.

1121. Treatment Changes Among Users of Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation

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Background: Patients with atrial fibrillation discontinuing anticoagulant therapy are left unprotected against ischaemic stroke. Further, switching between oral anticoagulants may be associated with a transiently increased risk of bleeding or thromboembolism. However, real-life data on the occurrence of anticoagulant switching and discontinuation are sparse.

Objectives: To examine switching between oral anticoagulants as well as discontinuation of non-VKA oral anticoagulants (NOACs) among Danish patients with atrial fibrillation.

Methods: We conducted a nationwide drug utilization study including all registered Danish atrial fibrillation patients initiating a NOAC between August 2011 and October 2015. Changes in anticoagulant treatment, including switching and discontinuation, were assessed including evaluation of patient characteristics predicting these changes.

Results: We identified 43,477 patients with atrial fibrillation initiating NOAC therapy within the study period. The majority (56.9%) initiated dabigatran and one third had previously used VKA. Within one year, 10.6% switched to VKA, 4.7% switched to another NOAC, and 15.6% discontinued treatment. The frequencies of switching to VKA and discontinuation were highest among NOAC users with young age <55 years) and low CHA2DS2-VASc score (≤1). The majority of patients (87.3%) stopping NOAC treatment had a CHA2DS2-VASc-score ≥1.

Conclusions: Switching from VKA to NOAC, and to a lesser extent from NOAC to VKA, was common, as were early treatment discontinuation. The majority of treatment changes were observed in patients at increased risk of stroke. More knowledge on the risks of bleeding and thromboembolism associated with switching and discontinuation of NOACs in real-life is warranted.

1122. Differences in Recording of Characteristics Among Patients Prescribed Oral Anticoagulants Using Primary Care and Cardiologist Data in Germany

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Background: Electronic health records are frequently used in pharmacoepidemiology. Interpretation of such research can be impeded by data quality. German primary care physician (PCP) and specialist data are cumulatively built up through patient visits, and patients can move between physicians, potentially affecting continuity of care and availability of medical history.

Objectives: To assess differences between PCP and cardiologist data in the recording of characteristics of patients with non-valvular atrial fibrillation (NVAF) initiated on oral anticoagulants (OACs) for stroke prevention.

Methods: Patients with NVAF who were newly treated with an OAC between Dec-2012 and Oct-2014 in Germany were selected from IMS Disease Analyzer. Baseline demographic characteristics, history of stroke risk factors and bleeding events were examined in two separate panels from PCPs and cardiologists (it is not possible to identify patients across panels). Patients could have initiated multiple OACs; analysis was conducted for each OAC exposure.

Results: Of 22,151 OAC exposures in the PCP data and 2,584 in the cardiologist data, computerised medical data prior to baseline was greater in the PCP data (PCP vs. cardiologist: median 8 vs. 5 years), while AF diagnosis was recorded closer to baseline (median 4 vs. 18 months prior). Patients in the PCP data were older (median 76 vs. 73 years). Stroke risk factors were more common in the PCP data (PCP vs. cardiologist: 17% vs. 6% had stroke/TIA; 17% vs. 4% thromboembolism; 40% vs. 29% congestive heart failure; 86% vs. 77% hypertension). In the PCP data, 7% had previous gastrointestinal (GI) ulceration, 17% previous GI bleed and 26% any previous bleeding event whereas these were all <2% in the cardiologist data.

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Conclusions: Much lower recording of history of stroke and bleeding events were found in cardiologist data compared to primary care data. This could represent differing spectrums of patients or, more likely, there may be incomplete information on medical history in cardiologist data; the use of this panel alone is not recommended for outcomes research.

1123. Differences in Statin Users and Non-Users with Bacteremia

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Background: Evidence suggests statins may have protective effects in patients with inflammatory conditions. In comparing clinical outcomes among statin users and non-users, it is important to understand differences between these patient groups.

Objectives: To identify differences between statin users and non-users with bacteremia.

Methods: A retrospective study was conducted using Optum Clinformatics with matched Premier hospital data among adult (≥18 years) patients with a primary diagnosis of bacteremia during a hospital admission between 2010-2012. Medication use was identified from both outpatient prescriptions and medications given during the hospital admission. We included patients with at least two consecutive days of the same antibiotic therapy within the first two days of admission. Incident statin use was defined as initiation of stain therapy in the 30 days prior to admission or during the admission. Non-users included patients with no statin use for 6 months or more prior to the hospital admission. Chi-square, Fisher's Exact, T-Test, or Wilcoxon Rank Sum tests were used to evaluate differences.

Results: Our study included 298 statin users: 209 (70%) initiated in the 30 days prior to admission and 89 (30%) after admission. Of those initiating prior to admission, 34% continued statin therapy during the admission. We identified 2,048 non-users. Among statin users vs. non-users, significant ($p<.0001$) differences in age (mean age-59.3 vs. 51.5 years) and gender (40% vs. 54% females) were observed. Transfer to skilled nursing facility was significantly higher among statin users than non-users (13.8% vs. 7.0%, $p<.0001$). Marital status, race, and admission type were similar between statin users and non-users. Emergency room was the admission source for 29% of statin users and 16% of non-users ($p<.0001$). Inpatient mortality was significantly lower among statin users (2.7% vs. 7.7%, $p<.001$) and length of stay was significantly higher compared to non-users (mean-8.6 vs.7.4, $p<.01$).

Conclusions: Statin users and non-users with bacteremia were different in terms of age, gender and admission source. As in other research, mortality was lower among statin users, however, length of stay was longer among these patients.

1124. Concurrent Use of Proton Pump Inhibitor and Clopidogrel Plus Aspirin in the U.S. Ambulatory Setting Between 2003 and 2011

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Background: In 2009, the FDA warned the public of the interaction between clopidogrel and proton pump inhibitors (PPI), which can reduce the antithrombotic effect of clopidogrel via CYP2C19 inhibition. Although the controversy over concurrent use of PPIs and clopidogrel has continued after the FDA announcement, little research has been conducted to assess a change in use of gastrointestinal (GI) prophylaxis in patients on clopidogrel before and after the 2009 announcement.

Objectives: The objective of this study was to assess trends in use of PPI or GI prophylaxis among physician office visits documented with dual antiplatelet therapy (DAT: clopidogrel plus ASA) in the United States from 2003 to 2011.

Methods: The National Ambulatory Medical Care Surveys (NAMCS) and the National Hospital Ambulatory Medical Care Surveys (NHAMCS) from 2003 to 2011 were used to examine office visits made by patients aged 18 and above. PPI included omeprazole, lansoprazole, pantoprazole, esomeprazoel, rabeprazole, and dexlansoprazole. GI prophylaxis included PPI, H2 blocker, misoprostol, and sucralfate. The weighted annual numbers of PPI use were estimated from all physician office visits. The weighted annual proportions of PPI or any GI prophylaxis use were calculated among visits documented with DAT.

Results: The weighted number of annual ambulatory visits in which PPI was recorded increased from 41.6 million in 2003 to 78.5 million in 2011. The annual proportion of concurrent PPI use among visits documented with DAT was 19.4% in 2003 and peaked at 29.1% in 2004. The proportions of PPI use decreased to 18.6% by 2008, but steadily increased to 25.6% by 2011. Similar patterns were shown for the annual proportions of concurrent GI prophylaxis use during the 9-year period. The proportions of GI prophylaxis use increased from 16.8 to 29.0% during 2008-2011, widening the gap between the proportions of PPI use and those of GI prophylaxis.

Conclusions: Overall, concurrent use of GI prophylaxis in visits in which DAT was documented was low. Compared to 2009, concurrent use of PPI or GI prophylaxis among visits documented with DAT increased in 2011.

1125. Sex Differences in Factors Predicting the Type of Bladder Antimuscarinics Initiated in Medicare Nursing Homes Residents

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Background: While not curative, bladder antimuscarinics (BAM) can pose important health risks for older adults. Sex is an important factor in the clinical decision process and understanding which other factors impact prescription behaviors is important for optimizing therapy.

Objectives: To examine what sex-specific factors predict the type of BAM initiated in nursing home (NH) residents.

Methods: Design: Retrospective cohort, new user design to identify incident BAM users following NH admission using Medicare claims data and Minimum Data Set assessments (MDS).

Setting: Medicare certified NH- residents continuously eligible for Medicare benefits between 01/01/07 and 12/31/08, including Part D and that were prescribed BAM after NH admission.

Variables: Patient characteristics, medications, and NH characteristics from Medicare enrollment files and reimbursement claims (pharmacy, inpatient and outpatient). Patient health status and assessment results derived from MDS. Outcome defined as type of BAM initiated after NH admission (selective, non-selective extended release, non-selective immediate release), derived from pharmacy claims.

Statistical analysis: Multinomial regression using generalized estimating equation approach to identify factors predicting type of BAM initiated by sex.

Results: Between 01/01/07 and 12/31/08, we identified 12,899 NH residents that initiated BAM; 13.38% of the new users were prescribed selective BAM, 45.56% were prescribed non-selective extended release, and 41.07% prescribed non-selective immediate release medications. Significant predictors of BAM in both sexes included region of NH location, body mass index, cognitive performance score, CHESS, activities of daily living, and measures of bladder continence. A history of fracture and fall-related injuries were significant predictors of type of BAM use in women. Race and indicators of balance were significant predictors of type of BAM use in men.

Conclusions: Type of BAM initiation differs by sex. Non-pharmacological continence management strategies were not predictive of type of BAM initiation, which suggests prescribers weight other factors more heavily when prescribing BAM.

1126. Patterns of Use of Antimuscarinic Drugs to Treat Overactive Bladder in Denmark, Sweden and the United Kingdom

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Background: In December 2012, mirabegron, a drug with a novel mechanism of action to treat overactive bladder (OAB), was approved in Europe.

Objectives: We characterized users and patterns of use of available antimuscarinic OAB drugs in Denmark, Sweden, and the UK before the approval of mirabegron, as a component of a multidatabase safety study for these drugs.

Methods: We identified new users of OAB drugs aged 18 years or older without cancer from the Danish National Registers (2004-2012, n = 72,917), Swedish National Registers (2006-2012, n = 130,944) and UK CPRD (2004-2012, n = 119,912). Therapy episodes, created by concatenating prescriptions for the same drug with gaps up to 60 days, could end due to no refill or end of follow-up, drug switch, or add-on. We added 7 days to allow for suboptimal compliance (Sweden, UK). Users were followed until disenrollment, cancer or death.

Results: Mean age was 66 years in Denmark and Sweden and 62 years in the UK. About 70% of UK patients and 60% of Danish and Swedish patients were female.

In Denmark, of the 224,680 therapy episodes, 4% were darifenacin, 9% fesoterodine, 2% oxybutynin, 39% solifenacin, 35% tolterodine and 12% trospium.

In Sweden, of the 240,141 therapy episodes, 8% were darifenacin, 13% fesoterodine, 5% oxybutynin, 35% solifenacin, 37% tolterodine, and 3% had more than one treatment. Trospium was not available.

In the UK, of the 245,800 therapy episodes, 0.3% were darifenacin, 3% fesoterodine, 28% oxybutynin, 27% solifenacin, 26% tolterodine, 6% trospium, and 10% had more than one treatment.

About half of the index episodes (the episode with which the patient entered the cohort) in the three populations consisted of one prescription. In Danish, Swedish and UK cohorts, 93%, 83% and 81% of episodes, respectively, ended because of no refill. Solifenacin was the drug most patients added on or switched to.

Conclusions: In these three cohorts of similar age and sex distributions, about half of the episodes consisted of one prescription, and most episodes ended due to no refill. The preferred drugs were tolterodine and solifenacin; oxybutynin use was minimal in Nordic countries compared to the UK.

1127. Impact of the Introduction of Newer Long Acting Reversible Contraceptive (LARC) Methods on LARC Use in a Commercially Insured Population

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Background: NA

Objectives: To assess the impact of the introduction of newer LARC methods on LARC use relative to all contraceptive users.

Methods: Using a US insurance claims database (01/1999-03/2014), we studied women using LARC or short acting reversible contraceptive (SARC) methods. The proportion of women using LARC relative to all contraceptives (LARC + SARC) was reported yearly. Four time periods corresponding with the approval of a new LARC method, that is, Jan-2001 (new intrauterine device [IUD]), Jul-2006 (new implant), and Jan-2013 (new IUD), were identified. Generalized estimating equation models were utilized to identify the impact of time periods and patient characteristics on the use of LARC over SARC methods.

Results: A total of 1,040,978 women met inclusion criteria. LARC use increased yearly from 0.6% (1999) to 16.6% (2013) among all contraceptive users. Time periods associated with the introduction of a newer LARC method were significant predictors of LARC use; women in 2006 2012 and 2013 2014 were respectively 3.7-fold (95%CI: 3.57-3.74) and 6.6-fold (95%CI: 6.43-6.80) more likely to use LARC over SARC relative to women in 2001 2006. The increase in LARC use was especially pronounced in young women. Compared to women aged 18 to 24 in 2001 2006, women aged 18 to 24 in 2006 2012 and in 2013 2014 were respectively 6.4-fold (95%CI: 5.91-6.86) and 14.7-fold (95%CI: 13.59-15.89) more likely to use LARC over SARC method.

Conclusions: This broadly representative commercial claim-based study showed that the proportion of women using LARC increased over time and that the

introduction of newer LARC methods corresponded with significant increases in overall LARC use.

1128. Withdrawn by Author

1129. Use Of Cyproterone Acetate/Ethinylestradiol In The United Kingdom Prior To And Following Recent Updated Guidance: Prescribing Patterns Using A National Primary Care Database

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Background: Cyproterone acetate combined with ethinylestradiol (CPA/EE) is indicated for moderate to severe acne and hirsuitism in women of reproductive age. The updated UK label for CPA/EE explicitly states that CPA/EE should not be used concomitantly with another hormonal contraceptive (HC) in order to minimize any potential increased risk of thromboembolism with exposure to a high oestrogen dose.

Objectives: To investigate prescribing patterns of CPA/EE in the UK including concomitant prescribing of CPA/EE with other HCs before and after the 2013 label guidance.

Methods: The study population included all women with a first prescription (index date) for CPA/EE in The Health Improvement Network during three calendar years: 2011, 2012 and 2014. Before the start of the calendar year containing the index date, women were required to have at least 1 year recorded history and have had no prescription for CPA/EE in the previous year nor before the index date in that year. Treatment characteristics evaluated included the number of CPA/EE treatment episodes, duration of use, and concomitant use of CPA/EE and another HC (either a 28-day cycle HC or a long-acting reversible contraceptive).

Results: The proportion of new CPA/EE users per 1000 women was 1.6 in 2011 (2760/ 1,736,683), 1.6 in 2012 (2,923/1,800,027) and 1.3 in 2014 (2341/ 1,869,071). During each calendar year, most CPA/EE users had only one uninterrupted episode of use (83% in 2011, 81% in 2012 and 78% in 2014). More than two separate CPA/EE episodes were observed among only 2–3% of users across calendar users. The median duration of CPA/EE use was 3 months (inter-quartile range [IQR] 3–6) in both 2011 and 2012 and 4 months (IQR 3–7) in 2014. Concomitant use of CPA/EE and another HC was rare, 1% of CPA/EE users in 2011 and fewer than 0.5% of CPA/EE users in both 2012 and 2014.

Conclusions: The proportion of CPA/EE new users has remained stable across recent years. Few women are currently prescribed CPA/EE concomitantly with another HC. Most women receive CPA/EE in line with UK prescribing advice.

1130. Cyproterone Acetate/Ethinylestradiol Prescribing in the UK

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Background: Cyproterone acetate with ethinylestradiol (CPA/EE) is indicated for moderate to severe acne and for hirsuitism in women of reproductive age. The updated UK label in 2013 reiterated that CPA/EE should only be used for the treatment of acne when antibiotic acne therapy has failed.

Objectives: To determine the indication for CPA/EE among new users before and after 2013.

Methods: Women with a first prescription (index date) for CPA/EE in The Health Improvement Network were identified during three calendar years: 2011, 2012 and 2014. Before the start of the year containing the index date, women had at least 1 year recorded history and also had no prescription for CPA/EE in the previous year nor before the index date in that year. Diagnoses for any hyperandrogenic conditions including acne, menstrual problems, visits for contraception and prior acne treatment were assessed in the year before the index date. Women could have more than one diagnosis at start of CPA/EE therapy. Manual review of patient records, including free-text,

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was conducted for a random sample of 200 CPA/EE users during 2011–2012.

Results: In each calendar year most new CPA/EE users were aged 15–25 years (55% in 2011 and 2012, 56% in 2014); mean age, 23 years in all years. The percentage of women with a record of any hyperandrogenic condition was 61% in 2011, 62% in 2012 and 63% in 2014. Corresponding percentages were 51%, 54% and 55% for acne, 7%, 7% and 6% for polycystic ovary syndrome (PCOS), and 4%, 3% and 3% for hirsuitism. In the manual review, the recorded diagnosis was acne in 77% of women, hirsuitism in 9.5% and PCOS in 9.5%. The majority of CPA/EE users with an acne diagnosis had a record of acne therapy, 83% in 2011 and 2012, and 84% in 2014. Among CPA/EE users without an acne diagnosis, approximately half had a record of acne therapy; 50%, 54% and 52%, respectively. Overall, the majority of CPA/EE users had a prior acne diagnosis and/or treatment, 76% (n = 2091) in 2011, 79% (n = 2296) in 2012 and 78% (n = 1834) in 2014.

Conclusions: Before and after 2013, the majority of UK women starting treatment with CPA/EE had a condition in line with its approved indication and had received prior acne treatment as per guidance.

1131. Use of Emergency Contraceptives in Two European Countries

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Background: Emergency contraceptive pills (ECPs) are used to prevent unwanted pregnancies and may reduce abortion rates. Despite the recent legislation recommendations at the EU level to ease access to ECPs, member states differs in the sales category of this drug group. In Hungary all ECPs are prescription only medicines, while in Portugal, ECPs are available as over the counter products, even outside community pharmacies (i.e. authorized stores). In both countries ECPs are not reimbursed products (i.e. patients pay the full price).

Objectives: To compare the scale and pattern of ECP use and quantify abortion rates in Hungary and in Portugal.

Methods: National sales data was obtained for both countries for 2013. ECP use was expressed as number of occasions (=DDDs or packages) per 1000 female population aged between 15 and 49 years and per year. Demographic and abortion data was derived from Eurostat.

Results: Portugese ECP consumption was 54.8, while Hungarian ECPs use was 26.27 occasion/1000 female aged 15-49 years/year. In Portugal, 7.5 % of packages were sold outside the pharmacies in 2013. In both countries levonorgestrel products were much more popular than ulipristal (in Hungary levonorgestrel shared: 92,5% vs. ulipristal shared 7,5%, while in Portugal it shared 99,8% vs. 0.2 %). For abortion rates we found opposite values: it was 15/1000 female aged 15-49 yrs/year in Hungary versus 7.4 per 1000 female aged 15-49 yrs/year in Portugal.

Conclusions: ECP use in Portugal was twice as much as in Hungary, while abortion rates was half of the Hungarian value. While association between the two outcome measures cannot be derived from these data, the findings are interesting and requires further research.

1132. Characteristics of New Users of Osteoporosis Drugs Changed Over Time, Yet High Compliance with Therapy Remained Stable

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Background: Oral bisphosphonates are the primary drugs used to treat osteoporosis and prevent fragility fractures.

Objectives: To examine the characteristics of new initiators of oral bisphosphonate therapy, and estimate one-year compliance with therapy by sex, and over time.

Methods: We identified community-dwelling seniors initiating (new users) oral bisphosphonate therapy in Ontario from April 2002 to March 2011. Compliance with therapy was estimated using the proportion of days covered (PDC = total days supplied in 365 days/365; capped at 100%) in the year following treatment initiation. Patient characteristics (1-year lookback

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period) and compliance with therapy were summarized by fiscal year of treatment initiation, and stratified by sex.

Results: We identified 62,990 men and 257,767 women initiating oral bisphosphonate therapy (mean age = 75.2 years, SD = 6.8). Patient characteristics changed over time. A larger proportion of men initiated therapy (13% in 2002/03 to 25% in 2011/12) and use of some medications decreased (e.g., etidronate: 88% to 5%, benzodiazepines: 25% to 18%, NSAIDs: 35% to 22%), while use of other medications increased (e.g., ARBs: 4% to 17%, statins: 24% to 44%) over time. Compliance with therapy was similar in men and women. The proportion with compliance ≤20% declined over time reflecting measurement error induced by a change in the typical days supply at index (from 90 days in 2002/03 to 30 days in 2011/12). The proportion with compliance ≥80% remained relatively stable over time at around 55%.

Conclusions: The characteristics of patients starting oral bisphosphonate therapy changed over time reflecting changes in osteoporosis management and healthcare delivery. However, estimates of high compliance have remained relatively stable. Understanding practice changes and measurement error in calculation of measures of adherence are important to inform and interpret results of pharmacoepidemiologic analyses.

1133. Early Analgesics Among Workers' Compensation Claimants with Low Back Pain from 1998-2009: A Population-Based Study in British Columbia, Canada

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Background: Studies describing opioid use patterns soon after work injury are mostly from the US and rely on workers' compensation prescription claims data that may be incomplete. Little is also known about early dispensing of other analgesics.

Objectives: To describe prescription analgesic patterns within 8 weeks of a low back work injury and their temporal trends using a province-wide network of all prescriptions dispensed from community pharmacies.

Methods: We identified workers with low back workers' compensation claims and ≥1 compensated lost workday from 1998-2009 (n = 97124). Administrative data from Pharmanet and Population Data BC were linked. Data on opioids, non-steroidal anti-inflammatories (NSAIDs) and skeletal muscle relaxants (SMRs) were used to describe patterns of early dispensing and trends by injury year.

Results: The proportion of claimants dispensed opioids, NSAIDs and SMRs within 8 weeks was 27.8%, 40.7% and 24.8%, respectively. Codeine, naproxen and cyclobenzaprine were most common. Prevalence of early dispenses increased from 1998-2009: 25.6 to 30.6% for opioids (+19.5%), 35.0 to 45.4% for NSAIDs (+29.7%) and 19.5 to 34.2% for SMRs (+75.4%). Among those dispensed opioids, codeine dispensing decreased (95.7% 1998, 80.0% 2009), while tramadol (0.9% 2005, 12.9% 2009) and strong opioids, namely oxycodone (4.5% 1998, 13.7% 2009), increased. Median time to first dispense was 6, 4 and 3 days for opioids, NSAIDs and SMRs, respectively, decreasing one day for opioids and NSAIDs from 1998-2009. Mean (SD) cumulative days supply was 12.3 (11.8), 18.3 (11.7) and 14.1 (9.9) days, respectively, for opioids, NSAIDs and SMRs, increasing for NSAIDs and SMRs over time. Mean daily morphine-equivalent dose was 31.5 (SD 31.1), increasing from 26.4 in 1998 to 35.3 in 2009.

Conclusions: Short courses of analgesics were frequently dispensed soon after injury in this Canadian sample and increased over the study period, namely SMRs. Opioid dispensing, while common, was generally conservative, though strong opioid dispensing increased over time. Future research should examine predictors of early analgesic choice and associated outcomes.

1134. Intra-Articular Injection Switching Patterns Among Patients with Knee Osteoarthritis: Data from the Osteoarthritis Initiative

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Background: Intra-articular injections such as hyaluronate and corticosteroid injections are recommended and increasingly used in osteoarthritis (OA). Studies of switching patterns in this population are scarce.

Objectives: To describe and evaluate longitudinal use of intra-articular injections among adults with radiographically confirmed knee OA.

Methods: We used 9 years of follow-up data from the Osteoarthritis Initiative and included participants with at least one knee with radiographically confirmed OA (Kellgren-Lawrence grade (K-L) ≥2) at baseline. Among the 415 participants newly initiating hyaluronic or corticosteroid injections, we identified 79 participants switched injection type during 9 years of follow-up. Switching users were then matched to 336 non-switchers by the frequency of distribution of follow-up times between the first initiation and switch. We calculated the prevalence of switching, continuation, and discontinuation after the index injection. Average yearly changes in symptoms and physical performance between one year before initiation and one year before switching by types of injections use were calculated.

Results: Nearly 1 in 5 of those initiating injections use had ≥ 1 switch. Among hyaluronate initiators, 24.0% switched to corticosteroid injections. Among corticosteroid initiators, 17.6% switched to hyaluronate injections. Approximately 40% reported switching after one year. Discontinuation was common (60.4%: hyaluronate; 58.3%: corticosteroid). At the year before switching, switchers had lower physical function as measured by The Western Ontario and McMaster Universities Arthritis Index (18.7 versus 16.6; $p<0.05$), lower quality of life as measured Knee Injury and Osteoarthritis Outcome Score (49.9 versus 55.1; $p<0.05$), larger changes in WOMAC pain (0.8 versus 0.2; $p<0.05$) and changes in WOMAC physical function (1.4 versus 0.3, $p<0.05$), relative to non-switchers.

Conclusions: Switching injection type and discontinuation of injections were frequent raising questions regarding the longer-term efficacy of these agents and reflecting on-going challenges in symptom relief for those with OA in the real-world setting.

1135. Factors Associated with Use of Disease Modifying Agents for Rheumatoid Arthritis in the National Ambulatory Medical Care Survey (NAMCS)

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Background: The first-line of treatment for Rheumatoid Arthritis (RA) is traditional disease-modifying antirheumatic drugs (DMARDs). However, RA management has changed in recent years due to increased used of (relatively more effective) biological DMARDs. Factors that influence access to the relatively expensive biological DMARDs will help understand the healthcare utilization patterns among adults with RA.

Objectives: To evaluate the factors associated with use of any and biological DMARDs among patients with RA.

Methods: We conducted cross-sectional analysis on visits recorded in NAMCS from 2005-2012 with a diagnosis of RA. The primary outcome was DMARD use (traditional and/or biological). We included prescription records of all RA-related treatments such as traditional and biological DMARDs, glucocorticoids, gold preparations, immunosuppressants, and NSAIDs. We used Anderson Behavioral Model to identify factors affecting healthcare utilization by an individual. The sociodemographic determinants of any DMARD use or biological DMARD were assessed using logistic regression.

Results: Of 859 visits with a RA diagnosis code, 464 (~52%) were prescribed DMARDs while 173 (19.3%)

were prescribed biological DMARDs. The distribution of DMARD prescriptions versus other treatments was significantly higher among individuals with private insurance (57%) and with <3 comorbidities (56%) while biological DMARDs was significantly lower among older (≥65) vs. younger adults (~14%) and among those with ≥3 comorbidities (13.7%). In fully adjusted models, individuals with ≥3 comorbidities were 64% (05% CI 0.47-0.86) less likely to receive any DMARDs and 60% (95% CI 0.39-0.90) less likely to receive biological DMARDs versus those with < 3 comorbidities. African Americans were 60% (95% CI 0.36-0.98) less likely to receive any DMARDs versus Whites.

Conclusions: Majority of visits had a DMARD prescription however, the frequency of traditional DMARD prescriptions were higher than biologicals. Individuals with ≥3 comorbidities were less likely to receive biological DMARDs and African Americans are less likely to receive any DMARDs as compared to Whites.

1136. Trends of Allopurinol Use in Norway and in Hungary

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Background: Hyperuricemia is a very common laboratory finding. Due to recent new theories on the risks of hyperuricaemia the consumption of allopurinol traditionally used to treat symptomatic crystal deposition-related disorders (i.e. gout) might change.

Objectives: To describe the trends and compare the prevalence of allopurinol use in Norway and in Hungary in the light of gout (and hyperuricaemia) prevalence.

Methods: This observational descriptive study refers to the period of 2003-2014. Data on the number of dispensed allopurinol packages in Hungary was obtained from the National Health Fund Administration (NHFA). The Norwegian data was retrieved from the Norwegian prescription database (NorPD), a nationwide registry including sales of prescription medicines in primary care. Consumption data was expressed in DDD per 1000 inhabitants per day (DID) and as prevalence of persons prescribed these medicines annually at least once. ATC/DDD index, 2015 was used.

Results: In Hungary allopurinol use increased from 3.9 to 14.8 DID, and the prevalence of allopurinol use increased gradually to 4.45% in 2014. The proportion of 300 mg tablets increased from 42% to 68 % of DIDs According to a recent large scale national point prevalence study the prevalence of hyperuricaemia was 14.7 % in Hungary, while prevalence of gout increased from 0.65 % to 2.08 % during the study period.

In Norway allopurinol use increased from 2.3 to 3.4 DID, proportion of 300 mg tablets increased from 37% to 45% of DIDs. In Norway the prevalence of gout is estimated to be around 1%, no data is available for hyperuricaemia. The annual prevalence of allopurinol use in Norway increased from 0.7% to 0.9%.

Conclusions: Hungarian allopurinol use was above and increased much more sharply than the Norwegian one. Increasing use can be partly explained by using higher doses in both countries. The inter country differences can be partly explained by the differences in the gout prevalence. Moreover Norwegian allopurinol exposure is in line with the gout prevalence data, while in Hungary it implies that not only patients with gout but also patients with asymptomatic hyperuricaemia are treated with allopurinol.

1137. Psychotropic Drug Use in Subjects Presenting with a Cancer Diagnosis

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Background: Studies have reported that diagnosis of cancer is associated with a two-fold prevalence increase of anxiety and/or mood disorders as compared to the general population.

Objectives: Using the French insurance claims database EGB (Echantillon Généraliste des Bénéficiaires), we described time trends of psychotropic drug dispensations in subjects presenting with a cancer diagnosis.

Methods: Between 2009 and 2012, every subject covered by the French Insurance system with a first cancer ALD (long-term disease) registration (index date) was included in the study. ALD registration allows

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reimbursement of medical costs for the given condition. The prevalence of psychotropic drug use was assessed 3 mths, 3-6 mths, 6-9 mths and 9-12 mths before and after the index date. Using ATC codes (N06 and N05), psychotropic drug dispensations were classified as hypnotics, anxiolytics, antidepressants, and antipsychotics. Trends of psychotropic dispensations were described overall and according to the localization of cancer before and after the index date.

Results: A total of 7909 subjects with a first cancer ALD were identified between 2009 and 2012. Breast (n = 1504), prostate (n = 1245), colorectal (n = 793), and pulmonary cancers (n = 602) were the most frequent cancers. Among all subjects, 23.4% initiated a psychotropic drug after index date and this ranged from 16 to 30% according to cancer localization. Anxiolytics were the most frequent (30 to 70% according to the cancer localization), followed by hypnotics (20 to 30%) and antidepressants (about 20% for all cancer localizations). The highest prevalence of psychotropic use was during the 3 mths before and after index date: 1.5 to 2-fold higher as compared to the rest of the studied period.

Conclusions: in this study, the occurrence of cancer is associated with psychotropic drug use, in particular anxiolytics. Psychotropic dispensations are the highest over the 3 mths preceding and following ALD registration. This may be related to anxiety when performing diagnostic investigations, or perception of the disease and/or the treatment after diagnosis. Delayed date of the ALD registration regarding the real date of cancer diagnosis may also explain these trends.

1138. Predicting Rehospitalization in Patients Treated with Antipsychotics: A Prospective Observational Study

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Background: Prediction of rehospitalization in patients on antipsychotics is important to identify patients in need of additional support to prevent hospitalization.

Objectives: The aim of this study was to identify factors that predict rehospitalization in patients treated with antipsychotics at discharge.

Methods: In this prospective observational study, adult patients suffering from schizophrenia, psychotic or bipolar I disorders who had been hospitalized in a psychiatric hospital for ≥7 days and treated with oral antipsychotics at discharge were included. The outcome was rehospitalization within six months after discharge. A prediction model for rehospitalization using Cox proportional hazards was constructed including: patient/disease and medication characteristics, patients' attitude towards medicine use, and health care professional assessments for all patients. The patients were stratified by diagnosis (schizophrenia and non-schizophrenia) and the prediction model was assessed for both groups.

Results: 87 Patients were included and 33.3% of them were rehospitalized within six months after discharge. The variables that predicted rehospitalization for all patients were e.g. duration of hospitalization, residential situation, patients' attitude towards medicine use, and health care professional assessments (such as whether the physician and the nurse discussed antipsychotic adherence during hospitalization, and whether the nurse asked the patient if he/she was adherent to medication). This model had an AUCROC of 0.82. Rehospitalization for patients with schizophrenia could be predicted (AUCROC =0.71) by GAF score, age, and harm score. Rehospitalization was predicted (AUCROC =0.73) for non-schizophrenia patients with GAF score, residential status, adherence predicted by the physician, and rehospitalization predicted by the nurse.

Conclusions: Rehospitalization was predicted by a combination of variables from the patient/disease and medication characteristics, patients' attitude towards medicine use, and health care providers assessment. These variables can relatively easily be assessed at discharge to predict rehospitalization within 6 months after discharge.

1139. Persistence of Antipsychotic Medications in Patients with Schizophrenia: A Cross-National

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Study from the Asian Pharmacoepidemiology Network (AsPEN)

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Background: The Surveillance of Health Care in Asian Network (SCAN) Project was launched to gain a better understanding of drug utilization patterns of population covered in each participating site database in the Asia pharmacoepidemiology Network (AsPEN).

Objectives: To compare the persistence of antipsychotic medications (APMs) in patients with schizophrenia among Taiwan, Hong Kong, Japan and the US.

Methods: We used 5% United States Medicare database, the Japan Medical Data Center Database (JMDC), a 4% random sample of the Taiwan's National Health Insurance Research Database (NHIRD), a 1% random sample of the Hong Kong's Clinical Data Analysis and Reporting System (CDARS), which were converted to a common data model. We identified new users of single oral APMs with schizophrenia aged 18-64 years old. We considered the first prescribed APM as the index agent and the prescription date as the index date. Patients without exposure of APMs for 1 year prior to index date were considered as new users. The outcome was the persistence of index agent defined as treatment duration from the index date to an earliest date of any of the following: discontinuation, switching, addition of 2nd agent, and any hospitalization.

Results: We identified a total of 4721, 76, 22314 patients with schizophrenia newly prescribed single oral APMs and the mean age was 37 (standard deviation [SD] 12), 39 (SD 13), 45 (SD 11) in Taiwan, Hong Kong and the US respectively, 43%-60% were male. The most frequently used APM in Taiwan was sulpiride (36%), but risperidone was the most frequently used APM in Hong Kong (46%) and the US (28%). The most persistence rate of APM in Taiwan was sulpiride (9.2%, 95% confidence interval [CI] 8.8-9.6), Hong Kong was risperidone (8.3%, 95% CI 5.6-17.8) and the US was olanzapine (37.1%, 95% CI 35.3-38.9).

Conclusions: Despite sulpiride is a first generation APM, it has better persistence in Taiwan, while the second generation APMs has better persistence in other countries. The most frequently used APM and the most persistence of APM in the US were different. Attributes to such discrepancy need further studies.

1140. Long-Acting Injectable Antipsychotics: Patterns of Use and Determinants of Treatment Failure in a Northern Italy Area

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Background: Long-Acting Injectable AntiPsychotics (LAI-AP) have gained renewed interest, especially with marketing of new formulations.

Objectives: To describe LAI-AP utilization in Community Mental Health Centers (CMHCs) of Bologna area (2010-2015), investigating incidence, treatment failure and associated factors.

Methods: Drug utilization and historical cohort designs were performed retrieving demographic characteristics, diagnoses and prescriptions of Bologna CMHCs' patients from the local Mental Health information system. All new treatment cycles, defined as absence of LAI-AP prescription in the previous 6 months (1/7/2010-31/12/2015), were selected and incidence rates on AP users were estimated. The first LAI-AP prescription of each patient represented the cohort entry-date. Each subject was followed up for six months to evaluate therapy discontinuation/ interruption or hospitalization for psychiatric diagnosis, as treatment failure proxies. Multivariate analyses were

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performed to identify socio-demographic and clinical characteristics associated with treatment failure.

Results: The LAI-AP annual incidence rate was stable throughout years (about 5% out of AP users). The cohort (844 patients) was mainly represented by schizophrenic-like disorders (51%). In the six months preceding the index date, 32% of patients had never used oral AP. During follow-up, 21% of patients was classified continuous, 27% discontinuous, and 52% interrupters. Treatment discontinuation/interruption was lower in users of first generation LAI-AP (OR: 0.59; 95%CI: 0.38-0.91) and in patients with previous hospitalization (OR: 0.50; 0.34-0.72). The risk of hospitalization increased in case of previous admissions (OR: 2.77; 1.92-3.99) and was reduced in continuous patients (OR: 0.51; 0.31-0.85), without differences between first and second generation drugs.

Conclusions: New prescriptions of LAI-APs use remained stable and limited in over the past 5 years. Continuous use of long-acting agents, especially the first generation ones, seems to play a role in avoiding treatment failure and deserves further evaluation.

1141. Incident Use of Benzodiazepines in France from 2006 to 2012: A Population-Based Study

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Background: International guidelines have been formulated to improve benzodiazepine (BZD) use, and it might be expected that BZD use, in particular new use, has decreased in the past years.

Objectives: To estimate the incident use of BZD in France. This study was part of the DRUGS-SAFE program funded by the French Medicine Agency (ANSM).

Methods: Yearly repeated cross-sectional study conducted from 2006 to 2012 within the French national healthcare insurance system. BZD new users defined as users with no BZD reimbursement in the year prior to the date of first dispensing of BZD over each year.

Results: The incident use of BZD use steadily decreased: -4.8% in 2012, relative to the estimated incidence in 2006. This decrease concerned hypnotic BZD and was more pronounced in patients aged 18-64 years than in those aged 65 years and older. Regarding anxiolytics, the incidence of use remained stable for the class; however, it decreased for long half-life BZD (bromazepam, prazepam), this being counterbalanced by an increase for short half-life BZD (alprazolam, oxazepam). Finally in 2012, the overall incidence of use was 5.9%. This incidence was 0.5% in patients under 18 years; 7.2% in those aged 18-64 years; 7.7% in those aged 65 years and older. The highest incidence of use was observed among women aged 18-64 years (8.8%). The incidence of use was 4.0% for anxiolytic BZD and 1.6% for hypnotic BZD; both were higher among women. Relative to the number of prevalent users of BZD estimated in 2012 by the ANSM, new users would represent around 1/3 of BZD users, and 1/4 of hypnotic BZD users. Alprazolam was the most prescribed BZD at treatment start in 2012 (3.8%) despite bromazepam remained the most incident BZD (1.5%) in patients aged 65 years and older.

Conclusions: Although the prevalence of BZD use remained stable over the study period according to recent reports, the incidence of BZD use slightly decreased in France. These results could indicate that treatment duration did not decrease over the period. Even if the incidence of long half-life BZD decreased to the benefit of short half-life BZD, as guidelines recommend, the most incident BZD in the elders in 2012 was a long half-life BZD.

1142. Utilization Patterns of Antidepressants in France from 2007 to 2012: A Population-Based Study

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Background: Clinical guidelines on antidepressant (AD) treatment are often poorly respected, with too short duration of treatment and inadequate congruence between diagnosis and AD treatment.

Objectives: To describe utilization patterns of AD in France. This study was part of the DRUGS-SAFE program, funded by the French Medicine Agency (ANSM).

Methods: A yearly repeated cross-sectional study was conducted from 2007 to 2012 within the French national healthcare insurance system. Utilization patterns of AD were explored in new users (no AD reimbursement in the year prior to the first dispensing of AD over each studied year). Explored characteristics were i) for first treatment episode (index episode): initial prescriber, combination or switch of AD, episode duration; ii) for the first year of treatment: number of treatment episodes, cumulative annual duration of treatment.

Results: In 2012, the incidence of AD use was 2.8% and was highest in patients aged 75 years and older (4.7%). General practitioners initiated 77% of new treatments. Most of new users (93%) received one class of AD during the first treatment episode, a selective serotonin re-uptake inhibitor in more than half cases. About 16% of patients aged 75 years and older had at least one tricyclic dispensing. The majority of new users (82%) had index episode duration of less than 6 months (92% of new users aged 16-24 years vs. 76% in those aged 75 years and older; 92% in new users with at least one tricyclic dispensing). Single dispensing of AD was found in 51% of new users (59% in new users aged 16-24 years; 49% in those aged 75 years and older). During the year following the first dispensing, 68% of new users had a single episode of treatment, and 23% two episodes. About 70% of patients had a cumulative annual duration of treatment of less than 6 months. No relevant evolution of AD utilization patterns was observed between 2007 and 2012.

Conclusions: Despite guidelines that recommend treatment duration of at least 6 months after remission to reduce the risk of relapse/recurrence of depression and anxiety disorders treated by these drugs, early discontinuation of AD treatments remains frequent, especially in the youngest.

1143. Trends and Prescription Patterns of Anti-Alzheimer Drugs Used in Japan from 2010 to 2015: A Descriptive Study Based on Pharmacy Claims Databases

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Background: Donepezil had been the only drug used in management of Alzheimer's disease (AD) for more than ten years until 2011, when three novel anti-AD drugs were released in Japan. However, only a few studies have investigated the change in trends and prescription patterns of the anti-AD medications used in Japan.

Objectives: To compare and describe the trends in prescription of the anti-AD drugs among Japanese outpatients, before and after the release of the new drugs in 2011.

Methods: It was a descriptive study using pharmacy claims databases, which consist of outpatient-prescription data obtained from community pharmacies across Japan. The patients aged 20 years or older who received first administration of anti-AD drugs (donepezil, memantine, rivastigmine, or galantamine) between Jan 2010 and Sep 2014 were included for analysis. They were divided into two groups based on the initial year of taking an anti-AD drug; 2010-2011 (group1) and 2012-2014 (group2). Patient characteristics, the proportion of monotherapy in AD treatment, and the discontinuation of treatment within a year were summarized for each group.

Results: A total of 103,592 patients (group1: 28,581, group2: 75,011) were prescribed anti-AD medication during the study period. In group1 and group2, the mean (±SD) ages were 79.6 (±7.4) and 80.9 (±7.3) years, female patients were 64.0% and 64.5%, elderly patients (≥80 years) were 25.0% and 32.2%, and patients prescribed 5 or more non-AD drugs were 33.8% and 39.8%, respectively. 99.0% and 94.3% of patients received any anti-AD drug as monotherapy in group1 and group2, respectively. Among these, donepezil prescription accounted for 92.3% and 59.6%. Finally, the patients who withdrew from treatment within a year were 40.5% and 41.5%, respectively.

Conclusions: While the proportion of donepezil monotherapy decreased after the release of new drugs in 2011, the proportion of monotherapy remained the same. Similarly, there was no apparent difference in patient characteristics throughout the study period.

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1144. Evaluation Of Antidepressant Drug Use In Populations In the UK and Quebec

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Background: In order to study comparative effectiveness and safety of antidepressant (AD) drugs across countries, there is first a need to understand the way these drugs are being prescribed in each setting.

Objectives: To estimate the use of ADs in adults in UK and QC.

Methods: A retrospective cohort of individuals, with at least one AD prescription between 1 Jan 2009 and 30 April 2014, was identified in each country using prescriptions from electronic health record systems. To be included in the cohort, individuals had to be adult users of AD therapy, with 2 years of follow-up from the date of the first prescription. ADs were grouped as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) or serotonin antagonist reuptake inhibitors (SARIs). Analysis involved the calculation of proportions that go on to have a treatment gap, switch drug group, combine drug groups or stop treatment during follow-up.

Results: SSRIs accounted for the highest proportion of initially prescribed ADs in each country, with higher levels observed in UK (56%) compared with QC (42%). The second most commonly initially prescribed ADs were TCAs in UK (30%) and SNRIs in QC (17%) while SARIs had the lowest prescribed rates (1.2% in UK vs 9% in QC). Approximately 70% of subjects in QC discontinued treatment compared with only 47% in UK. Across all drug groups, a greater proportion in UK had a treatment gap (44% vs 18% on average), after which the majority (80% on average) in both settings returned to an AD in the same group. Even though more drug groups were involved in switching to an AD in a different group after a treatment gap in UK, similar proportions in both countries were observed (11% on average).

Conclusions: There is wide variation across countries in AD drug prescribing over the 2-year follow-up period, indicating differences between settings in prescribing habits and/or patient populations. This has important implications when considering subsequent comparative safety studies of ADs across international boundaries.

1145. Use of Antidepressants Under the Financial Crisis in Greece

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Background: Under the current financial crisis in Greece, an effort has been made by the Greek authorities to encourage generic use, in order to lower medicinal cost.

Objectives: The purpose of this work was to study trends in antidepressant sales and in utilization of generics in Thessaloniki, the second largest city in Greece, during the years of the financial crisis.

Methods: Two samples of antidepressants registered sales corresponding to the years 2012-2013 and 2014-2015 were collected for the study. The samples corresponded only to a small amount of sales from the market of Thessaloniki. All classes of antidepressants and their relative ratios in the sales were estimated, and the percentage of generics in the sale of each medicine was calculated out of a variety of brand names in each class of antidepressants. The amount of medicines was estimated in Defined Daily Doses (DDDs) of the reference drug and its generics. The comparison of the two samples was made by using the statistical package SPSS.

Results: Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) have displaced older antidepressants in both study samples. Generic use corresponded to 26% of total sales in the sample of the years 2012-2013 and 32% of total sales in the sample of the years 2014-2015. During the last two years the percentage of generics increased from 36% to 52% in sertraline

sales, from 44% to 56% in venlafaxine sales and from 53% to 65% in citalopram sales.

Conclusions: Under the financial crisis in Greece, an increase in generic use was observed in antidepressant sales in the market of Thessaloniki.

1146. Assessment of the Impact of Medical Fee Schedule Revision on Polypharmacy of Psychotropic Agents in Japan

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Background: National Health Insurance (NHI) medical fee schedule introduced a financial incentive aiming to reduce the number of concurrent prescriptions in each anxiolytic and hypnotic agents to less than three agents in 2012 revision and 2014 revision. Little is known about the impact of these revisions.

Objectives: To assess the impact of fee schedule revisions on polypharmacy and overdose and to explore factors affecting the prescription trend.

Methods: Japanese large claims database with 4 million subscribers by Japan Medical Data Center (JMDC) was used to analyze prescription trends. Anxiolytic and hypnotic agents between October 2011 and July 2015 were assessed. Polypharmacy was defined as concurrent prescriptions with three or more anxiolytic agents or hypnotic agents. Anxiolytic and hypnotic agents were converted to diazepam equivalent and more than 15mg/day was defined as overdose. The proportion of prescriptions with polypharmacy of anxiolytic or hypnotic agents and the overdose was evaluated by year. Logistic regression was performed to evaluate trend and interrelated factors.

Results: Average of 510,596 anxiolytic and 441,784 hypnotic prescription per year was obtained. The proportion of polypharmacy of anxiolytic agents was 1.6% in 2012 and 0.8% in 2014, hypnotic agents was 5.2% in 2012 and 2.5% in 2014. The adjusted odds ratio of polypharmacy prescription of anxiolytic and hypnotic agents in 2014 were 0.51 (0.49-0.53) and 0.47 (0.46-0.48) lower compared to those in 2012 (95% CI). The proportion of overdosed prescriptions was 14.9% in 2012 and 14.0% in 2014. There was no significant change in overdose.

Conclusions: This study showed a trend reducing polypharmacy prescription of psychotropic agents over time. The trend of decreased dose in psychotropic agents was not observed.

1147. Trend and Prescription Patterns of Antipsychotic Medications (APMs) in Asia and US: A Cross-National Comparison Study

Chien-Chou Su[1], Edward Chia-Cheng Lai[4], Kenneth K. C. Man[5], Kiyoshi Kubota[2], Yukari Kamijima[2], Shinya Kimura[6], Paul Stang[3], Martijn Schuemie[3], Patrick Ryan[3], Yinghong Zhang[4], Ian C. K. Wong[7], Soko Setoguch-Iwata[4] and Yea-Huei Kao Yang[1]

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Background: The Surveillance of Health Care in Asian Network (SCAN) Project was launched to gain a better understanding of drug utilization patterns of population covered in each participating site database in the Asia pharmacoepidemiology Network (AsPEN).

Objectives: To investigate trends and prescription patterns of APMs among Taiwan, Japan, Hong Kong and the US.

Methods: We used 5% United States Medicare database, the Japan Medical Data Center Database, 4% sample of Taiwan's National Health Insurance Research Database, 1% sample of the Hong Kong's Clinical Data Analysis and Reporting System, which were converted to a common data model. We identified a cohort of patients initiating APMs who had 6 months eligibility for no use of APMs. We described the characteristics of the APM new user cohort, assessed the types and frequency of APMs and calculated incidence, prevalence and rates of each APMs use by calendar years. The denominator of rates was calculated by person-year.

Results: We identified a total of 28070, 82641, 1267, 2481 initiators of APMs aged ≥65 in Taiwan, the US, Hong Kong and Japan, respectively. Sulpiride was

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the most frequently used APM in Taiwan (48%) and Japan (37%), but quetiapine and haloperidol were the most frequently used APMs in the US (34%) and Hong Kong (58%), respectively. We included a total of 91801, 61841, 1743, 59945 patients aged less than 65 patients from Taiwan, the US, Hong Kong and Japan. Similar with elderly group, we found sulpiride was most frequently used in Taiwan (64%) and Japan (44%) and haloperidol was most frequently used in Hong Kong (25%). Specifically, the most frequently initiated APM in the US was quetiapine (26%). The most prevalent and prescribed APM in Taiwan and Japan was sulpiride, but the US was quetiapine. In Hong Kong, haloperidol was most prevalent and prescribed APM in patients aged ≥65, but in aged less than 65 patients was risperidone.

Conclusions: The trends and prescribing patterns of APMs varied among the four countries. We found that the most frequently used APM was sulpiride in Taiwan and Japan. Quetiapine and haloperidol were the most frequently used APMs in the US and Hong Kong.

1148. Antipsychotic Use in Dementia: A Comparison Between Three European Countries

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Background: Antipsychotic (AP) use in dementia is an important public health concern due to an increased of stroke and all-cause mortality. Despite the dug safety recommendations by regulatory agencies, APs are currently misused to different extents in dementia patients across European countries.

Objectives: To compare AP utilisation in persons >65 with dementia in the UK, Italy and the Netherlands over 4 years of follow-up.

Methods: Persons >65 with a dementia diagnosis and >1 year of database history were identified in three GP databases from 2008-2012: The Healthcare Improvement Network (THIN, UK), Health Search Database (HSD, Italy) and Integrated Primary Care Information (IPCI, Netherlands). Antipsychotic (AP) prescriptions were identified by ATC codes N05A* except N05AN. The quarterly prevalence of AP use overall, by class (conventional or atypical) and for most commonly used antipsychotics was estimated and compared among countries.

Results: Overall, 61,330 (3%) persons with dementia were identified in THIN, 11,553 (3%) in HSD and 14,396 (4%) in IPCI. The use of APs overall was initially similar in 2008: 13% in the Netherlands, 14% in the UK and 17% in Italy; this increased significantly in Italy (31% in 2012) but remained stable in the UK and Netherlands. Conventional APs were commonly used in Italy and the Netherlands in 2008 (10% prevalence for both), increasing more in the Netherlands (6%) and Italy (15%) by 2012; in the UK the use of this class was stable at 4 to 5% during the study. Atypical APs were preferred in the UK (10% prevalence throughout the study) and Italy (8% in 2008 increasing to 19% in 2012); in the Netherlands the prevalence was stable at 5% throughout the study. The most interesting trend was single AP use was for quetiapine which was low in the Netherlands (1% throughout the study) but more common in the UK (6% throughout the study); in 2008, prevalence in Italy was 4% increasing to 14% by 2012.

Conclusions: The use of APs among dementia patients differs substantially among the three European countries studied.

1149. Antipsychotic Prescription Trend in Hong Kong from 2004 to 2014

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Background: Antipsychotics are extensively used for the treatment of various mental distress and affective disorders including schizophrenia, bipolar disorder and in some cases, severe anxiety or depression. Current situation of antipsychotics use in HK is a serious public health issue but has not yet been studied. Therefore it is of interest to explore the unknown prescribing trend of antipsychotics in HK.

Objectives: To describe the prescribing trend of antipsychotics prescriptions in the Hong Kong public hospital system.

Methods: Prescription and dispensing records were retrieved from the Hong Kong Hospital Authority Clinical Data Analysis and Reporting System (CDARS), in the study period from 1st Jan 2004 to

31st Dec 2014. The prevalence of antipsychotic prescriptions were investigated and with the corresponding 95% confidence intervals (CIs) were obtained.

Results: A total of 256,848 patients were prescribed with antipsychotics in the study period. Females represented 57.1% (n = 132,869) of patients on antipsychotics. The prevalence of antipsychotic prescribing increased steadily, from 1.050% (95% CI = [1.042%-1.057%]) in 2004 to 1.507% (95% CI = [1.498%-1.516%]) in 2014. The prescribing of conventional antipsychotics dropped from 643,996 to 381,639, a 40.7% reduction from 2004 to 2014, while atypical antipsychotics increased from 186,660 to 656,664 prescriptions, representing an increase in volume by 2.5 times in the same period. The number of depot injections decreased from 85,248 (9.9%) in 2005 to 76,725 (7.4%) in 2014. Haloperidol is the most frequently prescribed antipsychotic, however proportion of patients on which decreased from 41.7% (n = 29,356) to 27.0% (n = 29,427). The most popular atypical antipsychotic was quetiapine in 2014, proportion of patients on which was 23.5% (n = 25,657).

Conclusions: The prevalence of antipsychotic medication prescribing in Hong Kong is increasing in the study period. Atypical antipsychotics are becoming more widely used in place of conventional antipsychotics. Due to the increasing usage, further research is required to assess the safety and effectiveness associated with antipsychotics.

1150. Antipsychotic Prescribing in a Tertiary Hospital Under the Financial Crisis in Greece

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Background: Under the current financial crisis in Greece, an effort has been made by the Greek health authorities and by Greek physicians to lower medicinal cost.

Objectives: The purpose of this work was to study trends in antipsychotic prescribing and in utilization of generics in outpatients of a tertiary Hospital of Thessaloniki, during the years of the financial crisis.

Methods: Two samples of antipsychotic prescriptions corresponding to the first four months of the years 2009 and 2015 were collected from the archives of the Psychiatry Outpatient Department of the AHEPA Hospital in Thessaloniki, Greece. All proprietary names of antipsychotics and their relative ratios in the prescriptions were estimated, and the percentage of generics in prescriptions was calculated. The amount of prescribed medicines was estimated in Defined Daily Doses (DDDs) of the reference drug and its generics. The comparison of the two samples was made by using the statistical package SPSS.

Results: The total number of prescriptions increased from 21,879 DDDs in 2009 to 47,373 DDDs in 2015. Haloperidol, risperidone, olanzapine, quetiapine and perphenazine/amitryptiline were the most prescribed antipsychotics in both samples, accounting for 83% of all antipsychotics prescribed in 2009 and 79% of all antipsychotics prescribed in 2015. Generic prescribing increased dramatically from 2009 to 2015, corresponding to 24% of total antipsychotic prescriptions in 2015 and 4% of total antipsychotic prescriptions in 2009. The percentage of generics was high for olanzapine (61%), risperidone (60%) and amisulpride (60%) in 2015, while in 2009 the percentage of generics was high only for risperidone (19%).

Conclusions: The total number of prescriptions and the percentage of generics in antipsychotic prescribing were much higher in 2015 than in 2009. These results reflect an increase in the number of people seeking medical advice in the National Health System, and an increase in the efforts of Greek physicians to lower medicinal cost.

1151. Time-to-First Discontinuation in New Users of Second Generation Antipsychotics in Older People

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Background: Consensus guidelines worldwide recommend the duration of exposure to antipsychotics not exceed 12 weeks, unless justified for mental illnesses like schizophrenia and severe psychotic symptoms which require longer treatment. Previous studies have found differences in discontinuation rates between first and second generation antipsychotics (SGAs). However, there has been limited information

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on time-to-first discontinuation (TTFD) for SGAs at a population level in a real world setting in older people.

Objectives: To examine and compare discontinuation rates in new SGA users in older people aged 65 years and over.

Methods: A cohort of 30, 297 SGA new users (365 days without pre-exposure to antipsychotics) were followed for antipsychotic discontinuations from 1 January 2006 to 31 December 2012. Data for oral formulations were extracted using a de-identified unique variable to merge the New Zealand (NZ) Ministry of Health Pharmaceutical claims collection and other healthcare databases. Low dose SGA new users were selected following current NZ Formulary dosage recommendations. The TTFD and adherence were defined using (dispensing gap $\geq$ 91 days between last and first dispensing claim plus days of last medicine supply, while cut-off for variable medication possession ratio $\geq$ 0.8), respectively. Kaplan-Meier curves and Cox regression analysis were used to estimate and adjust the cumulative probability and risk of TTFD of SGAs therapy.

Results: The overall TTFD in SGA new users was 192.3 days (95%CI: 177.6, 206.9), mean age at dispensing was 80.9 SD (8.1) and 60.3% were females. The TTFD was shortest for risperidone 101.3 (95% CI: 85.0, 117.7; p=0.03) compared to clozapine 68.3 (95% CI: 43.7, 92.9). The adjusted all-cause TTFD risk for risperidone, olanzapine, quetiapine or ziprasidone (Hazard ratios 0.54, 0.29, 0.22 and 0.08, respectively) were significantly lower than clozapine (positive comparator). The TTFD was associated with older age and adherence but independent of sex and deprivation scores.

Conclusions: Finally, differences in TTFD in SGA new users may be attributed to varying potency, monitoring requirements and tolerability of antipsychotic medicines. Ziprasidone used in continuation therapy had the lowest rate of discontinuation among older people.

1152. Prevalence, Time Trends and Utilization Patterns of Psychotropic Polypharmacy: Evidence from Children and Adolescent Medicaid Beneficiaries, 1999-2010

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Background: Psychotropic utilization is on the rise in children and adolescents. The public concern of this increased use is significantly high because evidence behind safety and effectiveness profiles for psychotropics, let alone Psychotropic Polypharmacy (PP), remains weak.

Objectives: To estimate the prevalence, time trends, and state-level variation of any, same, and multi-class PP among fee-for-service youths enrolled in Medicaid.

Methods: Utilizing pharmacy dispensing billing records from 29 Medicaid States from 1999 to 2010, we constructed ten cohorts of beneficiaries' between 0 and <18 years of age who received at least one psychotropic agent and had at least two years of continuous enrollment. To define PP. we considered any period were dispensed days' supply of qualifying psychotropic drugs overlapped more than 45 days. All psychotropic medications indicated to treat mental disorders were included. Same and multi-class PP rates were stratified by age and states.

Results: On average, 692,485 children were included in each 2-year cohort. Approximately 20% of the sample received PP. Multi-class PP is more prevalent in 15-17 years of age than 6-9 years (20.9 % and 16.3 % respectively), suggesting a steeper PP trajectory for adolescents. For same-class PP, there was a constant upward trend over time. For example, CNS stimulants, in 1999-2001 reported a prevalence of 0.1% whereas in 2008-2010 it increased to 0.6%. For alpha-agonists, between 1999-2001 and 2008-2010, the prevalence of PP increased from 0.0005 % to 0.2% respectively. Regional utilization ranged, for multi-class PP, from 6.1% in Illinois to >36% in several Midwest states. For same-class antidepressants, it ranged from 0.4% in Illinois to 6.4% in Minnesota. For same-class antipsychotics, it ranged from 0.1% in Louisiana to 4.6% in Nebraska.

Conclusions: We found an increasing trend of PP coupled with significant variation across the examined US states. A more granular assessment that considers patient characteristics and local contextual factors is warranted.

1153. Prevalence, Time Trends and Utilization Patterns of Psychotropic Polypharmacy: Evidence from Adult Medicaid Beneficiaries, 1999-2010

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Background: Most benefit/risk treatment profiles among psychotropics favor monotherapy medication regimes over Psychotropic Polypharmacy (PP) but the latter remains a common prescription practice. Yet, little is known about the extent of this practice throughout Medicaid.

Objectives: This study aims to estimate the prevalence, utilization time trends, and state-level variation of any, multi, and same-class PP among adult beneficiaries of fee-for-service Medicaid.

Methods: A retrospective cohort study over a 10-year period (1999-2010) analyzed any, multi, and same-class PP use in 29 Medicaid states. Ten 2-year cohorts of beneficiaries between 18 and 64 years of age who received at least one psychotropic medication and two years of continuous enrollment were constructed. To define PP, we considered any period were dispensed days' supply of qualifying psychotropic medications overlapped more than 45 days. All psychotropic medications with on-label indication to treat a mental disorder were included. Multi and same-class PP were analyzed by age and individual states.

Results: On average, 788,302 adult beneficiaries were included in each 2-year blocks. Almost 50% of adults received any-class PP between 1999 and 2001. In the 2008-2010 period, it increased to almost 60%. Same-class antidepressant use increased from 10.9% in 1999-2001 to 13.2% in 2008-2010. Between 1999-2010, an increasing trend of multi-class PP was observed between adults aged 18-29 years and those aged 40-49 years (30% to 42% respectively). On the contrary, a downward trajectory was observed for those above 50 years of age. Regionally, multi-class PP utilization was higher than 40% in 62% of the states. For same-class antidepressants, 19 out of 29 states reported utilization rates higher than 9%. For same-class antipsychotics, only one state had rates higher than 9%.

Conclusions: Almost half of adults in the study period received PP. A closer look of the factors mediating its use such as contextual settings and individual characteristics of the beneficiaries should help understand more how much of this trend may reflect inappropriate care.

1154. Comparing the Increase in the Cost of Drug Prices Among Multiple Sclerosis Drugs: Anticipated vs. Market Prices Between 2010-2015

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Background: Recently, a number of Multiple Sclerosis(MS) disease modifying therapies(DMTs) have become newly available, including the introduction of oral therapies such as dimethyl fumarate and fingolimod. Rituximab has also been used to treat MS although off label. Regardless of the increase in options, cost of MS DMTs has increased dramatically.

Objectives: To investigate pricing trajectories of MS DMTs, specifically glatiramer acetate(GA), rituximab (RTX), natalizumab(NTZ), fingolimod(FTY) and dimethyl fumarate(DMF) between 2010-2015 following the introduction of the first oral DMT, FTY.

Methods: We used the Average Wholesale Price (AWP) as a conservative estimate for the actual market drug price per year and compared it to the expected annual price of each drug per year using the Consumer Price Index(CPI) for Prescription Drugs. Changes in annual AWP pricing for each DMT was estimated from monthly reported AWP values obtained from the RED BOOK® for every year following the approval of a DMT and adjusted for the for a 15% discount rate. Similarly, changes in CPI rates, obtained from the Bureau of Labor Statistics were used to estimate, changes in expected increase of each DMT per year since approval. The actual versus expected AWP for DMTs were compared using descriptive statistics and estimates of annual relative increase from 2010 AWP values.

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Results: The discounted AWP annual prices in 2015 of GA, NTZ, FTY and DMF are $63,419, $64,357, $72,365, and $71,829, respectively. From 2010-2015, the average rate of increase in the actual price of all DMTs was 4.38 times greater than the average rate of increase in their expected prices. GA had the greatest change in actual price, increasing at a rate of 5.85 times higher per year in actual vs expected price. RTX had the least change increasing at a rate of 2.28 times greater per year in actual vs. expected price.

Conclusions: Rate of costs for MS DMTs is substantially greater than the CPI rates of inflation for prescription drugs. There is a critical need to address these dramatically increasing MS DMT prices.

1155. The Nudge, the Push and the Mole: Management of Long-Acting Oxycodone

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Background: Long-acting oxycodone was introduced to Canada in 1999 with the promise of less addiction and an imperative to treat chronic non-cancer pain as basic human right. Supported by considerable promotion, the resulting growth in oxycodone is now considered a key component in the "opioid epidemic". Calls for rationale use have resulted in policy and formulation changes to curtail the problematic use of oxycodone.

Objectives: The objective was to assess the impact of policy and formulation changes on the use of long-acting oxycodone.

Methods: A longitudinal utilization analysis was conducted in Manitoba, Canada of oxycodone/opioid use from 2001 to 2014, using the Drug Program Information Network Database. To allow comparison, all opioid use was converted to oral morphine equivalents. The impact of the change to restrict formulary coverage of oxycodone (2009/10) and the release of a tamper-resistant formulation (2011/12) was assessed using segmented regression analysis on quarterly long-acting oxycodone users.

Results: There was a 626% increase in users and a 1034% increase in morphine equivalents of long-acting oxycodone use between 2001 and 2009. A change in coverage criteria restricting use of oxycodone (the nudge) produced a significant decline in use ($p<0.0001$). The change to a tamper-resistant formulation (the push) sustained but did not enhance this decline. Long-acting oxycodone has been largely replaced by long-acting hydromorphone and short acting oxycodone while overall population opioid use continued to increase.

Conclusions: The nudge of a simple inexpensive policy change can have a large impact on opioid choice. The full impact of a push-like full market replacement of a patent-extending tamper-resistant formulation remains to be understood. As we suppress one opioid, the use of other opioids rises to replace it. Like a game of "whack a mole", this evaluation suggests that while policy and formulations changes may be helpful there really is no substitute for careful patient-level opioid stewardship.

Results and conclusions are those of the authors; no official endorsement by Manitoba Health, Healthy Living and Seniors, or MCHP is intended or should be inferred (HIPC#2012/2013-08).

1156. Exploring Factors linked to In-Patient Hospitalisation Amongst Non-Cancer Pain Patients Prescribed Long-Term Strong Opioids in UK Primary Care

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Background: Management of persistent non-cancer pain (PNCP) is complex, and as chronic opioid (COT) use for PNCP becomes common hospitalisations of PNCP on COT is less clear.

Objectives: To quantify in-patient admissions in non-cancer patients prescribed strong opioids long-term in UK primary care, and explore factors of influence.

Methods: A longitudinal study using the Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics data in England was conducted from 2000 to 2010. Adults prescribed four strong opioids (morphine, buprenorphine, fentanyl, oxycodone), with no cancer diagnosis 12 months prior to first prescription date (index date) were included. Total day's supply was calculated for each patient-year and long-term use (≥ 90 days in a year) was included. Both

baseline (demographics, pain condition, comorbidity, socioeconomic status, smoking) and time-dependent variances (general practice visits, co-prescribed neuroleptics, high dose user) associated with number of hospitalisations were assessed using generalized estimating equations. High dose use was defined as average oral morphine equivalent dose >180mg/day in a year.

Results: In total, 49,477 were identified as long-term strong opioids users. Fourty-three percent (n = 21,552) had one or more pain conditions diagnosed 6 months before the index date, and 20.3% had more than one physical or psychological comorbidity. Forty percent (n = 19,952) of users had a recorded hospital admission during follow-up. Strong opioid users aged >60 years (aOR:1.2; 95%CI: 1.1-1.3; p<0.001), those who had more GP visits per year (aOR:1.8; 95%CI: 1.6-1.9; p<0.001), had more pain diagnoses (aOR:1.1;95% CI: 1.0-1.2; p<0.001), co-morbidities including psychiatric conditions (aOR:1.5; 95%CI: 1.3-1.7; p<0.001), used high dose strong opioids (aOR:1.2; 95%CI: 1.1-1.3; p<0.001) and co-prescriptions of neuroleptic medications were associated with hospital admissions.

Conclusions: Elderly, greater co-morbidities and high opioid doses were significantly associated with increased odds of hospital admissions. Additional research relating COT to hospitalisation outcomes are needed.

1157. Non-Buprenorphine Opioid Utilization Among Patients Using Buprenorphine/Naloxone

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Background: Buprenorphine/Naloxone is commonly used to treat opioid dependence, however it remains unclear to what extent buprenorphine patients receive prescription opioids while under treatment.

Objectives: To characterize patterns of opioid utilization among incident buprenorphine/naloxone recipients in the United States.

Methods: We used anonymized, individual-level, all-payer pharmacy claims data from the IMS Health LifeLink LRx database to identify incident users of buprenorphine/naloxone between January 2010 and August 2013. We limited our study to patients 18 years or older who filled at least 1 buprenorphine/naloxone prescription (index fill) with at least a 6-month window of observed claims activity prior to and following this index fill. We defined each patient's first buprenorphine/naloxone treatment episode as the date of their index fill until the first day of a gap where the patient had no buprenorphine/naloxone on-hand for 90 or more days. We calculated measures of non-buprenorphine opioid utilization prior to, during and after their first buprenorphine treatment episode.

Results: Of the 94675 incident buprenorphine/naloxone users meeting the inclusion criteria, 50% were female and 50% were between 27 and 46 years of age. The median length of the first treatment episode was 113 days (IQR 30 to 401). Patients filled a median of 6 (IQR 2 to 19) buprenorphine/naloxone fills during the first treatment episode. Of these patients, 27.4% filled at least one opioid prescription 1 year prior, during and 1 year after their first treatment episode and 10.7% filled no opioids. Overall, non-buprenorphine opioid utilization declined slightly during buprenorphine/naloxone treatment then increased after the first treatment episode. The median morphine milligram equivalents per opioid day supplied 1 year prior, during and 1 year after the first treatment remained stable at 44mg (IQR 30 to 79), 40mg (IQR 28 to 78) and 43mg per day (IQR 29 to 85), respectively.

Conclusions: Despite the fact buprenorphine/naloxone is primarily used to treat opioid dependence, a substantial proportion of patients fill prescriptions for opioids prior, during and after their first treatment episode.

1158. Opioid Utilizations in Patients with Diabetes

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Background: As patients with diabetes (DM) suffer from nociceptive and neuropathic pain, they rely on

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painkillers to reduce symptoms. Since non-opioid medications often fail to manage pain, these patients can be prescribed opioid medications. Given the potential for addiction and negative outcomes, it is important to understand the magnitude of opioid utilization in this population.

Objectives: To describe the utilization patterns of opioids in patients diagnosed with DM.

Methods: The 2-year longitudinal data of the Medical Expenditures Panel Survey (MEPS) (Panel 17, 2012-2013) were linked to the medical condition and the prescribed medicines data. Using a cross-sectional design, 18-years or older diabetic patients were compared with a non-diabetic control group to examine their opioids utilization. The control group was selected through 1:1 matching on age, gender, and MEPS data collection round. In addition, to evaluate opioid initiation/use in newly diagnosed diabetic patients, we restricted the analyses to those first reporting DM during rounds 2nd, 3rd, or 4th and their controls and investigated opioid use at the following round. Analyses were conducted using conditional logistic regression adjusted for demographics and comorbidities.

Results: Among the 1354 patients diagnosed with DM (weighted estimate: 11.24 % US population) (weighted estimate: 51.03% females, weighted mean [SE] age: 59.78[0.68]), 49 (weighted %: 4.38) filled a prescription for opioids. In the control group, 36 participants (weighted %: 0.41) reported opioids. The odds ratio (OR) with 95% confidence interval (CI) was 1.37 (0.89-2.12) (unadjusted) and 1.21(0.70-2.08) (adjusted). When looking at newly diagnosed diabetic patients (N = 184), 11 (weighted %: 7.27) filled a prescription for opioids on the following round, as compared to seven (weighted %: 5.62) in the control group; unadjusted OR of 1.57 (95% CI: 0.61-4.05) and the adjusted OR of 29.01 (95% CI: 0.64->999.99).

Conclusions: Our study suggests that patients with DM were more likely to fill a prescription for opioids. Given that our estimates were not statistically significant, further studies are need to evaluate the magnitude of using opioids in patients with type 1 or 2 DM.

1159. Impact of State Laws to Reduce Prescription Drug Abuse on High-Risk Opioid Prescribers

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Background: Prescription drug monitoring programs (PDMPs) and pill mill laws have been implemented to reduce opioid-related injuries.

Objectives: To evaluated the impact of Florida's PDMP and pill mill law on high-risk prescribers.

Methods: We used IMS Health's LRx Lifelink database in Florida (intervention state) and Georgia (control state). We selected Georgia because it had not implemented a pill mill or PDMP law during our analysis period and is right next to Florida. The pre-intervention, intervention, and post-intervention periods were: July 2010-June 2011, July 2011-September 2011, and October 2011-September 2012. High-risk prescribers are those in the top 5th percentile of opioid volume during four consecutive calendar quarters. We applied comparative interrupted time series models to evaluate policy effects on clinical practice patterns and prescribers' monthly prescribing measures. We included 38,465/18,566 prescribers who had prescribed opioid in Florida/Georgia in the pre-intervention period. We also performed secondary analyses that examined subsets of these prescribers.

Results: We identified 1,526 (4.0%) high-risk prescribers in Florida, accounting for 67%/40% of total opioid volume/prescriptions. Relative to lower-risk prescribers, they wrote about sixteen times the number of monthly opioid prescriptions (79 vs. 5, $p<0.01$), and were more likely to have prescription-filling patients receive opioids (47% vs. 19%, $p<0.01$). Following policy implementation, Florida's high-risk

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providers experienced large relative reductions in the number of opioid patients and opioid prescriptions (-536 patients/month, 95% confidence intervals [CI] -829 to -243; -847 prescriptions/month, CI -1498 to -197), morphine equivalent dose (-0.88 mg/month, CI -1.13 to -0.62), and total opioid volume (-3.88 kg/month, CI -5.14 to -2.62). Low-risk providers did not experience statistically significantly relative reductions, nor did policy implementation affect the rank order of high vs. low prescribers.

Conclusions: High-risk prescribers are disproportionately responsive to state policies. However, opioids-prescribing remains highly concentrated among high-risk providers following policy implementation.

1160. Drugs Used in Intentional Drug Overdose: Findings from the National Self-Harm Registry Ireland

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Background: Intentional drug overdose (IDO) is the most common form of hospital treated self harm. To date there has been no detailed breakdown of individual drugs frequently used in self-harm in Ireland.

Objectives: To examine the profile of persons who present to hospital following IDO and to determine the drugs frequently used in these acts.

Methods: We included data from the National Self-Harm Registry, on presentations involving IDO (ICD-10 codes X60-64) to 36 emergency departments in Ireland, from 1st January 2012 to 31st December 2014. Self-poisoning with substances other than drugs were excluded. Drugs were classified according to the Anatomical Therapeutic Classification system.

Results: During the study period 18,329 IDO presentations were recorded. The majority of presentations were made by women (10,767,59%), with presentations peaking for persons aged 15-24 years (5,195,28%). Alcohol was involved in 41% (7,446) of acts. Half of presentations involved polydrug use (6,961,53%) and where the quantity of drugs was known, 49% of acts involved the ingestion of over 20 tablets (7,217).

Two-thirds (12,021,66%) of IDO's involved the use of nervous system acting drugs, mainly psycholeptics (4,827,40%) including anxiolytics (2,309) and hypnotics and sedatives (1,736). Antidepressants were involved in 14% (2492) of all IDO's. Illegal drugs were used in 5% of atcs, including cocaine (309, 2%) and heroin (233,1%).

Of the most frequently used drugs, seven were prescription only and four were benzodiazepines (2,916,16%). Paracetamol containing medicines were the most common drugs used (2845,16%) followed by Diazepam (1367,8%) and Alprazolam (558,3%). Sedatives namely Flurazepam and Zopiclone were involved in 6% of presentations (991).

Conclusions: Intentional drug overdose occurs most often in women, in those aged under 25 and is associated with alcohol misuse. Prescription drugs, specifically psycholeptics and antidepressants are frequently taken in IDO. Paracetamol was the most common drug used in IDO. There is a need to review prescribing practices, adherence to medication prescriptions among at-risk populations and existing restrictions to accessing drugs frequently used in IDO.

1161. Asthma Hospitalization Differences Between Generics and Brand of Montelukast

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Background: Asthma hospitalization, mostly due to severe exacerbations, is an indication for uncontrolled asthma symptoms. Montelukast, categorized as leukotriene receptor antagonists (LTRA), is prescribed as a long term control medication. In 2012, the Food and Drug Administration has approved generic versions of Montelukast. More than 90% of patients switched from brand to generics by the 4th quarter of 2012.

Objectives: The main aim is to assess the differences in hospitalization due to asthma between generics and brand Montelukast.

Methods: The study population draws from the Truven MarketScanR database. The study periods is defined as two periods. The first one, from 1st July

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2011 – 30th June 2012, is prior to the approval of Montelukast generics. The second period, which is from 1st July 2013 – 30th June 2014, is after the generics entered the market.

Patients included in the study must have 6 months' available information prior the study period, full enrollment during two study periods, at least 2 ICD-9 asthma code (493xx) in the outpatient setting or 1 ICD-9 asthma code in the inpatient setting and at least one Montelukast prescription. We excluded patients with COPD, Cystic Fibrosis, Bronchiectasis, Bronchiectasis, Embolism, Bronchopulmonary dysplasia or Congestive heart failure.

Results: 3,521 patients are identified as switchers to generics before the second study period starts. Since patients in two periods are the same, there is no differences in sociodemographic and socioeconomic characteristics. The proportion of asthma hospitalization among patients using the brand is 3% compared to 1.9% in patients taking the generics (P-value <0.01). In both periods, pre and post, patients younger than 12 years old have a higher proportion of hospitalization due to asthma compared to asthma patients older than 12 years old (P-value<0.01).

Conclusions: Compared to the brand version, generics Montelukast show more protective effect in hospitalization due to asthma.

1162. Trends in Asthma Medications Use in the United States from 2008-2014

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Background: Asthma is one of the major public health challenges worldwide. In 2010, the prevalence of asthma in United States was 8.4%, and accounted for 25.7 million patients. Since 2008 the market has seen major changes. The U.S Food and Drug Administration has issued asthma medications safety communications, changed labels; and more than 10 generic asthma medications were approved.

Objectives: The main aim is to assess the trends in asthma medications' use in the United States from 2008 to 2014.

Methods: This is a cross-sectional study. The study's populations are obtained from MarketScan Commercial Claims. The data is retrieved separately for each year. Patients must have no gap in insurance enrollment, at least 12 months' of continuous enrollment, at least one Asthma ICD-9 code, a drug cohort indicator, and at least one prescription claim of any of the following asthma medications: Inhaler corticosteroids (ICS), Leukotrienes Modifiers (LTRA), Long Acting Beta 2 Agonists (LABA), ICS + LABA, Short Acting Beta 2 Agonists (SABA), Mast Cell Stabilizers, Omalizumab, and Theophyllines. If a medication lost patent during the study period, further analysis was performed to assess the prevalence changing between brand and generic versions.

The prevalence of each medications was calculated as the number of patients with an ICD-9 code for asthma taking the study medications divided by the total number of eligible patients in a particular year.

Results: More than 600,000 asthma patients were identified in each year from 2008 – 2014. The only preventive asthma medication that increased between 2008-2014 is ICS (3.6%). Both LTRA and ICS + LABA decreased by 6 percent since 2008. Patients younger than 12 years old, stopped using LTRA by almost 10%. In the 3rd quarter of 2012, more than 90% of asthma patients who using Montelukast had shifted from brand to generic versions.

Conclusions: The utilization of asthma medications has dramatically changed since 2008 which could be attributed to safety warnings, and more so due to generic versions approved for marketing.

1163. The Role of Patient Characteristics in Dosage Form of ICSLABA Prescriptions

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Background: Prescribing patients with both an inhaled corticosteroid (ICS) and a long-acting beta-agonist (LABA), which delivers complimentary anti-inflammatory and long-term bronchodilator effects, is the most frequently prescribed maintenance regime for chronic obstructive pulmonary disease (COPD). Despite the introduction of a fixed-dose combination (FDC) budesonide/formoterol ICSLABA inhaler to the Department of Veterans Affairs' (VA) National Formulary in 2011, ICSLABA is prescribed as both

a FDC inhaler and in separate, but overlapping monotherapy inhalers (OM).

Objectives: To determine whether patient characteristics are associated with the dosage form of ICSLABA initially prescribed following COPD diagnosis among patients within the VA.

Methods: We identified a cohort of newly diagnosed COPD patients with their first/index prescription for an ICSLABA filled between 01/01/07 and 12/31/14. Patients were categorized according to the type of budesonide/formoterol ICSLABA prescribed (FDC or OM). Multivariate logistic regression models assessed the likelihood of index prescription being OMs after the formulary change, considering demographic and clinical factors as predictors.

Results: 1,046,835 COPD patients filled a prescription for a COPD medication between 01/01/07 and 12/31/14, 2014, with 518,513 (50%) being newly diagnosed patients. Of the new patients, 30,349 (5.8%) received prescriptions for a budesonide/formoterol ICS/LABA as their index prescription. The majority of FDC prescriptions were filled after 2011 (99%), whereas the majority of OM inhalers were prescribed before 2011 (84%). Patients with both a COPD and asthma diagnosis were 1.40 (CI:1.16,1.70) times more likely to be prescribed an OM than a FDC after 2011 compared to COPD patients without asthma.

Conclusions: As expected, prescribing practices for ICSLABA varied considerably across time, whereas there was a significant change in proportion of prescription type that occurred in parallel with a VA addition of a budesonide/formoterol FDC inhaler to the formulary. The presence of comorbid conditions, such as asthma, explains some of the occurrence of OM prescriptions after the inclusion of a FDC ICSLABA on the VA formulary.

1164. Montelukast Use 1998-2015 - A Danish Nationwide Drug Utilization Study

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Background: Montelukast is a leucotriene receptor antagonist that has been approved as an oral add-on therapy to inhaled corticosteroids in persons with uncontrolled asthma despite of treatment with inhaled corticosteriods. Although the drug has been on the market for 18 years, no study has described nationwide utilization patterns of montelukast.

Objectives: We aimed to describe baseline characteristics and the trend in period prevalence of montelukast use among all adults (≥18 years) in Denmark from its market entry in 1998 to 2015.

Methods: We extracted all prescriptions from the Danish Registry of Medicinal Products Statistics for montelukast (ATC: R03DC03) in the period 9 February 1998 to 31 December 2015.

We used data from the Danish Civil Registration System to calculate annual prevalences. We estimated the duration of therapy by counting the number of filled prescriptions per user.

Results: We identified 85,849 montelukast users from 1998 to 2015 filling 895,155 prescriptions. 31,824 (37.1%) filled only one prescription, whereas 21,192 (24.7%) and 36,977 (43.1%) filled 2-4 and 5+ prescriptions, respectively. The median number of DDDs filled per prescription was 28 (InterQuartile Range [IQR] 28-98). The median age of montelukast users at their first prescription was 52 years (IQR 38-66), and 40% were male. The trend in yearly period prevalences showed a 2.2 fold increase from 189/100,000 users in 1998 to 413/100,000 in 2015.

Conclusions: The number of users of montelukast has increased two-fold since its market entry in 1998. The median age at first prescription is high considering the marketed indication. More than one-third of users only filled one prescription.

1165. Variability in the Consumption of Inhaled Beta2-Adrenergic Bronchodilators in 10 European Countries, 2007-2011

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Background: Inhaled short- and long-acting beta2-agonists (SABA, LABA) and long-acting beta2-agonists in combination with corticoids (LABA + ICS) are used for the treatment of asthma and chronic obstructive pulmonary disease.

Objectives: To assess the variability in the use of SABA, LABA and LABA + ICS across 10 European countries between 2007 and 2011.

Methods: We conducted a population-based cross-sectional study with data retrieved from the Multi-Integrated Database Analysis System (MIDAS, IMS Health) for Denmark (DK), France (FR), Germany (DE), Italy (IT), Netherlands (NL), Norway (NO), Poland(PO), Spain (ES), Sweden (SE) and United Kingdom (UK). Analyses were stratified in SABA, LABA and LABA + ICS. Annual volume sales were expressed in defined daily doses/1,000 inhabitants/day (DID). Population denominators were extracted from EUROMEDSTAT. To assess the country-specific trends of inhaled bronchodilators we conducted a two-stage analysis. First, we fitted a linear regression model for each country with a first-order autoregressive covariance structure for the error terms. Second, we modelled the between-countries variability with respect to their regression coefficients, assuming that the random effects followed a normal distribution. All analyses were conducted in SAS University Edition software.

Results: Country-specific linear regressions showed an increased use of LABA + ICS in all countries, of SABA in FR, DE, PO and UK and of LABA in DK, GE, NL and PO. . The between-country variability showed a global intercept (standard error, [se]) of 12.08 (2.15), $p=0.0003$ for LABA + ICS; 4.34 (0.52), $p<0.0001$ for LABA; and 14.11 (3.02), $p=0.001$ for SABA. The global slope (se) for LABA + ICS was 0.78 (0.14), p-value = 0.0004. For SABA and LABA, the global slope (se) was -0.03 (0.09), $p=0.75$ and -0.06 (0.06), $p=0.33$, respectively.

Conclusions: There was an overall significant increase in the use of LABA + ICS with an overall non-significant decrease in the use of SABA and LABA during the study period. The average use of inhaled beta2-adrenergics in 2007 was higher for SABA and LABA + ICS than for LABA.

1166. Characteristics of New Users of Aclidinium Bromide in the United Kingdom

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Background: Aclidinium bromide, a long-acting antagonist of lung M3 receptors (LAMA), was approved in Europe in 2012 as maintenance bronchodilator treatment to relieve symptoms in adults with chronic obstructive pulmonary disease (COPD). As part of the pharmacovigilance plan, a drug utilization study in several European countries is ongoing.

Objectives: To describe the characteristics of new users of aclidinium, tiotropium, and other LAMAs (glycopyrronium and umeclidinium) in the United Kingdom (UK).

Methods: Observational cohort study of new users of LAMAs in the Clinical Practice Research Datalink in the UK, between 2012 and 2015. New users were identified through recorded general practitioner prescriptions. Patients with COPD were identified through Read codes and ICD-10 hospital discharge codes in Hospital Episode Statistics. Annual age- and sex-standardized prevalence of use of each LAMA was estimated using the 2013 adult European Union population. Descriptive statistics were performed to characterize new users of LAMAs.

Results: We identified 3,604 new users of aclidinium, 30,705 new users of tiotropium, and 3,288 new uses of other LAMAs. The standardized annual prevalence of use per 100,000 adults ranged from 0.6 in 2012 to 80.2 in 2015 for aclidinium, from 1,442.8 in 2012 to 1,254.8 in 2015 for tiotropium, and from 33.6 in 2013 to 76.9 for other LAMAs. Approximately 53% of users of

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aclidinium and 51% of users of tiotropium or other LAMAs were men. The percentage of users aged ≥60 years was higher in users of aclidinium and other LAMAs (80%) than in users of tiotropium (77%). The percentage of former smokers was higher in users of aclidinium and other LAMA (57%) than in users of tiotropium (53%). A higher proportion of users of aclidinium (92%) than users of tiotropium (82%) or other LAMAs (88%) had a recorded diagnosis of COPD. A higher proportion of users of aclidinium (43%) than users of tiotropium (37%) or other LAMAs (39%) had severe or very severe COPD.

Conclusions: In this study, new users of aclidinium in the UK were older, more frequently former smokers, and had more severe COPD than new users of tiotropium and new users of other LAMAs.

1167. Predictors for the Prescription of Aclidinium Bromide as Compared to Tiotropium Bromide Using German Claims Data

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Background: Aclidinium bromide (aclidinium) and tiotropium bromide (tiotropium) are long-acting anticholinergics for the long-term treatment of chronic obstructive pulmonary disease (COPD). In early benefit assessment, no proof of an added benefit was found by German authorities, but dispensations of aclidinium continuously increased since its launch.

Objectives: To determine potential predictors for initial prescription of aclidinium compared to tiotropium.

Methods: Retrospective cohort study based on claims data from one statutory health insurance provider included in the German Pharmacoepidemiological Research Database. The study population comprised patients with a first dispensation of aclidinium or tiotropium between October 1st and December 31st, 2012, after an aclidinium/tiotropium-naïve period of one year. Age, sex, COPD-related variables, Charlson-Comorbidity-Index (CCI), time spent in hospital, history of renal disease (potential contra-indication) and characteristics of the prescribing physician were considered as potential predictors and their impact was assessed with multivariable logistic regression.

Results: During the study period, 544 insurants received an index prescription of aclidinium (61% women, median age 69 years) and 4,379 insurants started tiotropium therapy (58% women, median age 71 years). Patients living in rural areas were more likely to receive aclidinium (OR: 1.43; CI: 1.1-1.87). A pulmonologist as the prescribing physician (1.91; 1.55-2.35), participation in the Disease Management Program for COPD (1.26; 1.01-1.57), chronic use of corticosteroids (1.75; 1.25-2.44) and history of renal disease (1.46; 1.03-2.07) increased the likelihood of receiving aclidinium. In contrast, COPD hospitalizations (0.5; 0.32-0.8), hospitalization time (0.95; 0.92-0.97) and CCI (0.89; 0.84-0.95) increased the likelihood of receiving tiotropium.

Conclusions: Both clinical factors and aspects of care were identified as predictors for an aclidinium prescription. The strongest predictor was a pulmonologist as the prescribing physician. General comorbidity increased the probability to receive tiotropium.

1168. Patterns of Roflumilast Use for the Treatment of COPD Across Three Distinct Populations: Findings from the Roflumilast Pass Study

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Background: Roflumilast is an oral selective phosphodiesterase-4 inhibitor indicated for the treatment to reduce the risk of COPD exacerbations that was approved in the European Union (2010) and United States (US) (2011). A post approval safety study (PASS) is currently ongoing in three countries.

Objectives: The key objective of the Roflumilast PASS study is to evaluate the long-term safety of roflumilast in the treatment of COPD, with focus primarily on 5-year all-cause mortality. The sub-analysis describes exposure to roflumilast for treatment of COPD, using real-world data from Sweden (SWE), Germany (GER) and the US.

Methods: A common study protocol was used across study sites. We identified patients aged ≥40 years with

a diagnosis of COPD, who were newly exposed to roflumilast in 2011 among study sites. Country-specific datasets included information on in- and out-patient visits, pharmacy dispensations, and deaths at the patient level. We described information on the number of roflumilast dispensations during follow-up, days' supply (DS) (days covered by a dispensation), number of days between roflumilast dispensations, and percentage of exposure time (sum of DS divided by follow-up time).

Results: We identified 1304 (SWE), 3604 (GER), and 2269 (US) initiators of roflumilast. The median number of dispensations was 2.0, 2.0 and 1.0 and the median length between dispensations was 30.0, 31.0, and 30.0 days, respectively for the sites. The mean DS for the 1st dispensation was 49.5 (SWE), 50.1 (GER), and 45.8 (US) days, ranging between (30,120) in SWE, (1,150) in GER, and (7, 90) in the US. The median gap in days between roflumilast dispensations was -1 days for SWE and GER, and 0 days for US. The percentage exposed time for the 2011 calendar year was 54.9% (SD: 145.4), 68.0% (SD: 38.2), and 80.0% (SD: 32), for SWE, GER, and US, respectively.

Conclusions: Among the study sites, the majority of newly initiating patients' follow-up time was exposed (exposed time) throughout the 2011 calendar year, with minimal gaps between dispensing. Exposure data will continue to be updated over the course of the roflumilast PASS study.

1169. COPD Patients Initiating Roflumilast in Sweden, Germany and the United States: Findings from the Roflumilast PASS Study

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Background: Roflumilast is an oral selective phosphodiesterase-4 inhibitor indicated for the treatment of severe chronic obstructive pulmonary disease (COPD) patients associated with chronic bronchitis and a history of exacerbations. A post approval safety study (PASS) is ongoing in Sweden, Germany and the United States (US).

Objectives: The objective of this subanalysis was to describe comorbidities, COPD drug treatment, healthcare resource utilization and moderate exacerbations in roflumilast exposed and in unexposed background COPD population using real-life data from healthcare registries in the three countries.

Methods: COPD patients aged over 40 years were identified during 2011-2013 in Sweden, 2010-2011 in Germany and 2011 in the US. Patients exposed to roflumilast were described at the time of treatment initiation and compared to the unexposed background COPD population at a fixed date. *A moderate exacerbation* was defined as acute use of systemic corticosteroids and/or systemic antibiotics during 12 months and *triple therapy* as a dispensation of long-acting muscarinic antagonist, long-acting $_2$-agonist and inhaled corticosteroid during 4 months prior to date of comparison.

Results: In Sweden, Germany and the US, 3257, 5084 and 2269 initiators of roflumilast were identified. The mean ages (years) were 70.9, 67.4 and 71.2 among exposed and 71.3, 63.9 and 70.9 among unexposed, respectively. In all three countries roflumilast-exposed patients had higher prevalences of asthma, emphysema, pneumonia/influenza and osteoporosis than unexposed patients. In Sweden, Germany and the US the percentage of patients with COPD hospitalizations was 32.9, 29.8, 21.6 in exposed and 5.0, 1.8, 2.5 in unexposed. The prevalence (%) of moderate exacerbations was 85.3, 81.0, 74.8 in exposed and 48.5, 27.9, 58.1 in unexposed, and the percentage on triple therapy was 65.3, 53.6, 48.4 in exposed and 17.6, 3.8, 6.9 in unexposed, in the three countries respectively.

Conclusions: In Sweden, Germany and the US, roflumilast-initiating patients represent the more severe spectrum of COPD with more comorbidities, more moderate exacerbations and higher use of healthcare resources.

1170. Treatment of Patients with Pulmonary Tuberculosis in China

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Background: Although different drugs have been marketed for anti-tuberculosis therapy, the actual use of these medications for pulmonary tuberculosis treatment in clinical practice is rarely reported in China.

Objectives: To characterize the patients and describe medications used in the treatment of pulmonary tuberculosis at a pulmonary specialty hospital in Beijing China.

Methods: Relevant clinical data from the hospital Healthcare Information System were mapped into a common data model. Patients with a diagnosis of pulmonary tuberculosis who received continuous care (having had at least 3 consecutive visits with no gap longer than 45 days) from January 1, 2012 to December 31, 2014 and treated with any anti-tuberculosis drugs at the hospital were included in the study. All medications recommended by the Chinese Society for Tuberculosis guidelines for the treatment of pulmonary tuberculosis were included in the analysis.

Results: During the study period, there were 13,707 patients with continuous care diagnosed as pulmonary tuberculosis and 12,824 were treated with anti-tuberculosis medications. Median age at first diagnosis for males was 38 years, and for female was 32 years (Wilcoxon rank-sum test, $p<0.001$). More than 40% were in the 16 – 30 years age group. The median treatment duration was 260 days, and 4,710(36.7%) patients had anti-tuberculosis therapy for less than 180 days. For overall period of therapy, isoniazid (INH), ethambutol (EMB), pyrazinamide (PZA), rifampicin (RFP) and rifapentine (RFT) were the most prevalent medications, used in 12,121(94.5%), 11,462(89.4%), 8,087 (63.1%), 7,139(55.7%) and 6,589(51.4%) patients respectively, with little difference between genders. The combination of INH, EMB, PZA and RFP was the most common combination therapy, used in 3,129(40.1%) male patients and 2,207(44.0%) female patients.

Conclusions: Patients had a younger age at diagnosis than reported in previous publications, and female patients had a younger age at first diagnosis than males. INH, EMB, PZA, RFP and RFT were the most prevalent medications and the combination of INH, EMB, PZA, and RFP was the most common combination therapy in the treatment of pulmonary tuberculosis.

1171. Prevalence and Factors Associated with Prescription of Overlapping Monotherapy Inhalers of Corticosteriods and Long-Acting Beta-Agonists Among US Veterans

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Background: Combination therapy with an inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA), which delivers complimentary anti-inflammatory and long-term bronchodilator effects, is the most frequently prescribed maintenance regime for chronic obstructive pulmonary disease (COPD). Despite the introduction of a fixed-dose combination (FDC) ICS/LABA inhaler to the Department of Veterans Affairs (VA) national formulary in 2011, ICS and LABA continue to be prescribed as overlapping monotherapy (OM) inhalers – separate prescriptions filled on the same day.

Objectives: To determine the prevalence and factors associated with overlapping ICS and LABA monotherapy inhalers prescribed following COPD diagnosis within the VA healthcare system.

Methods: We identified a cohort of non-asthmatic COPD patients who filled an ICS/LABA prescription between 2007-2014. Newly diagnosed patients were defined as having 1-year baseline data without COPD diagnosis code. Prescriptions were categorized according to the form of ICS/LABA prescribed (FDC or OM). Mulitvariable logistic regression analyses assessed differences between new cases who were first prescribed an OM ICS/LABA versus those who were first prescribed an FDC after 2011. We also assessed differences between patients who switched from OM ICS/LABA to FDC following the 2011 formulary addition.

Results: A total of 303,962 COPD patients filled a ICS/LABA prescription between 2007-2014, of which 158,679 were newly diagnosed patients. First prescriptions for newly diagnosed patients in the West and the Northeast were approximately 20% less likely to be OM ICS/LABA compared to new patients in the South. Black patients were 25% less likely than white patients to switch to FDC following the formulary change (OR:0.75, $p<0.01$).

Conclusions: Although the majority of ICS/LABA prescriptions after 2011 were FDC inhalers, geographical and racial differences suggest that patient characteristics, at least in part, explain the continued use of OM ICS/LABA prescriptions after the formulary addition.

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