Original Article

Treatment-resistant hypertension in the hemodialysis population: a 44-h ambulatory blood pressure monitoring-based study

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Background: Uncontrolled hypertension notwithstanding the use of at least three drugs or hypertension controlled with at least four drugs, the widely accepted definition of treatment-resistant hypertension (TRH), is considered as a common problem in the hemodialysis population. However, to date there is no estimate of the prevalence of this condition in hemodialysis patients.

Method: We estimated the prevalence of TRH by 44-h ambulatory BP monitoring (ABPM) in 506 hemodialysis patients in 10 renal units in Europe included in the registry of the European Renal and Cardiovascular Medicine (EURECAm,), a working group of the European Association, European Dialysis and Transplantation Association (ERA EDTA). In a sub-group of 114 patients, we tested the relationship between fluid overload (Body Composition monitor) and TRH.

Results: The prevalence of hypertension with 44-h ABPM criteria was estimated at 85.6% (434 out of 506 patients). Of these, 296 (58%) patients were classified as uncontrolled hypertensive patients by 44-h ABPM criteria ($\geq$130/80 mmHg). Two hundred and thirteen patients had uncontrolled hypertension while on treatment with less than three drugs and 210 patients were normotensive while on drug therapy ($n = 138$) or off drug treatment ($n = 72$). The prevalence of TRH was 24% (93 among 386 treated hypertensive patients). The prevalence of predialysis fluid overload was 33% among TRH patients, 34% in uncontrolled hypertensive patients and 26% in normotensive patients. The vast majority (67%) of hemodialysis patients with TRH had no fluid overload.

Conclusion: TRH occurs in about one in four treated hypertensive patients on hemodialysis. Fluid overload per se only in part explains TRH and the 67% of these patients show no fluid overload.

Keywords: ambulatory blood pressure monitoring, fluid overload, hemodialysis, resistant hypertension

Abbreviations: ABPM, ambulatory blood pressure monitoring; AHA, American Heart Association; ASH, American Society of Hypertension; ASN, American Society of Nephrology; BIA, bio-impedentiometry; BMC, body composition monitor; BP, blood pressure; CKD, chronic kidney disease; ECW, extracellular water; ERA-EDTA, European Renal Association and the European Dialysis and Transplant Association; ESH, European Society of Hypertension; ESKD, end-stage kidney disease; EURECA-m, European Cardiovascular and Renal Medicine; NS, normotensive patients; ROC, receiver-operating characteristic; THR, treatment-resistant hypertension

INTRODUCTION

With a prevalence of about 80% [1], hypertension is a pervasive complication in patients maintained on chronic haemodialysis and it is notoriously difficult to control [2]. Resistant hypertension, a condition characterized by persistently high blood pressure (BP) notwithstanding the use of three or more antihypertensive agents of different classes including a diuretic or hypertension controlled with at least four drugs [3], is much more frequent in patients with chronic kidney disease (CKD) than

Journal of Hypertension 2020, 38:1849–1856

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Received 5 December 2019 **Revised** 27 February 2020 **Accepted** 3 March 2020

J Hypertens 38:1849–1856

DOI:10.1097/HJH.0000000000002448

without [4–7]. Resistant hypertension is also considered to be common in hemodialysis patients but no prevalence estimates in this population have been published so far. Sodium and water retention is a central feature of resistant hypertension [8], particularly in CKD patients [9] and for this reason, the definition of resistant hypertension mandates that one of the three drugs applied for hypertension control should be a diuretic agent [3]. Due to the lack of residual renal function, treatment of volume expansion in hemodialysis patients is generally pursued by intensifying dialysis ultrafiltration and/or by more frequent hemodialysis sessions[10] whereas diuretics are applied only in patients with significant residual diuresis [11,12].

The definition of treatment-resistant hypertension demands the diagnosis to be made by the gold standard measurement of BP, ambulatory BP monitoring (ABPM) [3]. This requirement also fully applies to the hemodialysis population as white coat hypertension and masked hypertension are much frequent in this population [13] and may lead to hypertension misclassification. Furthermore, the current definition requires that adherence to drug treatment be accurately assessed [3]. As alluded to before, until now, there is no study aimed at estimating the prevalence of treatment resistant in the hemodialysis population. We have, therefore, estimated the prevalence of such condition by the gold standard BP metric in this population, 44-h ABPM [1], in the European Cardiovascular and Renal Medicine (EURECA-m) Registry of hemodialysis patients. As volume overload is a dominant risk factor for hypertension in end-stage kidney disease (ESKD) [1], we also quantified fluid overload by bio-impedentiometry (BIA) in a subgroup of patients who participated into this study.

MATERIALS AND METHODS

Study population

This analysis is based on the European Renal and Cardiovascular medicine (EURECA-m) Registry, a database established in 2011 by the EURECA-m working group of the European Renal Association and the European Dialysis and Transplant Association (ERA-EDTA) to systematically collect information about hemodialysis patients from collaborating centers, including ABPM measurements. Contribution of the individual centers to data collection was approved by the ethical committees of the same centers and all patients gave their informed consent. For the present analysis, we selected patients with valid 44-h ABPM recordings, that is, more than 80% valid measurements with two or less nonconsecutive day-hours with less than two valid measurements, and one night-hour or less without valid measurement. Furthermore, ABPM recordings had to have at least 20 awake and seven night measurements per day as recommended by the 2013 ESH Guideline for ABPM [14]. A total of 506 adult patients (>18 years), all but three of Caucasian descent (1 Black and 2 Asian patients) with ESKD treated with hemodialysis in 10 Hemodialysis Units in three countries (Italy, Greece and Slovenia) were finally included in this analysis. The 44-h ABPM in these centers was applied along recommendations by Agarwal *et al.* [15], and the EURECA-m working group of the European Renal Association and European Dialysis and Transplantation Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH) [1].

Data acquisition and ambulatory blood pressure monitoring

All patients were evaluated before a midweek hemodialysis session. Prehemodialysis BP measurement were made in the nonfistula arm, according to the European Society of Hypertension (ESH) 2013 guidelines [16]. Subsequently, the ambulatory BP monitor was fitted in the nonfistula arm. The device was set to measure BP every 20 min during the daytime and every 30 min during the night-time for a complete 48-h standard intra- and inter-dialytic period, following the protocol of the EURECA-m registry [1].

During the hemodialysis session, volume withdrawal was programmed to achieve dry weight, according to standard clinical criteria, and during the interdialytic interval, patients were instructed to maintain their usual activities and their regular diet. For comparability with previous ABPM studies in hemodialysis patients, along the recommendation by Agarwal *et al.* [15] and the EURECA-m and European Society of Hypertension consensus document [1], we decided to exclude from the analysis the ABPM data recorded during hemodialysis. Thus, the duration of ABPM was 44 h.

Definitions

Hypertension was defined as prehemodialysis BP at least 140/90 mmHg or current treatment with any antihypertensive agent; ambulatory 44-h BP at least 130/80 mmHg or current treatment with any antihypertensive agent [1]. We defined treatment-resistant hypertension (TRH) as hypertension notwithstanding attempts at intensification of ultrafiltration treatment and the use of at least three antihypertensive drugs, of various classes or hypertension controlled by at least four drugs [3]. The use of loop diuretics in patients with residual diuresis was recorded but these drugs were not counted among the antihypertensive drugs needed to achieve the treatment target. This is so because loop diuretics, though probably useful to reduce the risk for hospitalization and to mitigate interdialytic weight gain, show no effect on BP in hemodialysis patients [11]. We also made an estimate of the prevalence of TRH according to the definition adopted by Agarwal *et al.* (44-h ABPM >135/>85 mmHg) [15].

Moreover, we applied phenotypes of hypertension control, that is, concordant TRH (prehemodialysis BP ≥140/90 mmHg and ambulatory-BP ≥130/80 mmHg), 'white coat' hypertension (prehemodialysis BP ≥140/90 mmHg and ambulatory-BP <130/80 mmHg) and masked hypertension (prehemodialysis BP <140/90 mmHg and ambulatory-BP ≥130/80 mmHg), as detailed in a previous review [17].

Adherence with antihypertensive treatment

Adherence with antihypertensive treatment was periodically checked by attending physicians in participating centers by asking the simple questions 'do you take the antihypertensive medication(s)?' and 'do you take all prescribed pills to lower your BP?' No pill count or other objective method for assessing adherence to treatment

was used in this study. Due to the fact that we did not apply objective methods to check treatment adherence, this study assesses apparent treatment TRH rather than true TRH.

Body fluid volume by the body composition monitor

In an unselected group of 104 patients, we tested the relationship between fluid overload and TRH. In these patients, BCM was performed before and after a midweek hemodialysis session, on the same day where 44-h ABPM was measured. Body composition and fluid status were assessed by whole body bioimpedance spectroscopy (BCM-Body Composition Monitor, Fresenius Medical Care) as described by Moissl *et al*. [18] and Machek *et al*. [19]. BCM determines fluid overload in absolute liters independently of body composition [20]. Patients are considered to be overhydrated when their relative fluid overload (= fluid overload/ECW) is at least 15% in men and at least 13% in women, which coincides with an absolute fluid overload of about 2.5 l [21].

Statistical analysis

Data were expressed as mean ± SD (normally distributed data), median and inter-quartile range (nonnormally distributed data) or as percent frequency (categorical data). Comparisons among groups were made by ANOVA/*t*-test, Kruskal–Wallis/Mann–Whitney *U* or chi-square test, as appropriate. Sensitivity, specificity, positive-predictive and negative-predictive value, as well as area under ROC curve, of predialysis BP measurement vs. 44-h ABPM were also calculated. Statistical analysis was performed with Statistical Package for Social Sciences 24 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

From a total population of 1084 patients, 620 hemodialysis patients performed the 44-h ABPM study, which was valid (i.e. conformed to the quality standard of the 2013 ESH Guideline for ABPM, see methods) in 555 patients. Among these, 28 patients were excluded as clinical information and antihypertensive treatment were missing, whereas 21 were excluded because of unavailability of peri-dialysis BP measurements. Five hundred and six patients were included in the final analysis (Fig. 1).

Among the whole population (506 patients) (Fig. 2, upper panel), 434 patients (86%) had hypertension that is, 44-h ABPM at least 130/80 or were on antihypertensive drug treatment ($n = 434$) [1]. In addition, 296 patients (58%) had uncontrolled hypertension by the same criteria (44-h ABPM ≥130/80 mmHg) and 210 (42%) were normotensive with ($n = 138$) or without ($n = 72$) drugs. Overall, 386 patients were being treated with antihypertensive drugs. Ninety-three patients (83 hypertensive patients treated with at least three drugs and 10 patients with hypertension controlled with at least four drugs) had TRH, that is, 24% of patients treated with antihypertensive drugs. The TRH prevalence by the greater than 135 mmHg/greater than 85 mmHg (44-h ABPM) threshold recommended by Agarwal *et al*., was 23%. As expected, in a sensitivity analysis counting loop diuretics as antihypertensive drugs the prevalence of TRH was higher (33%) than that in the analysis

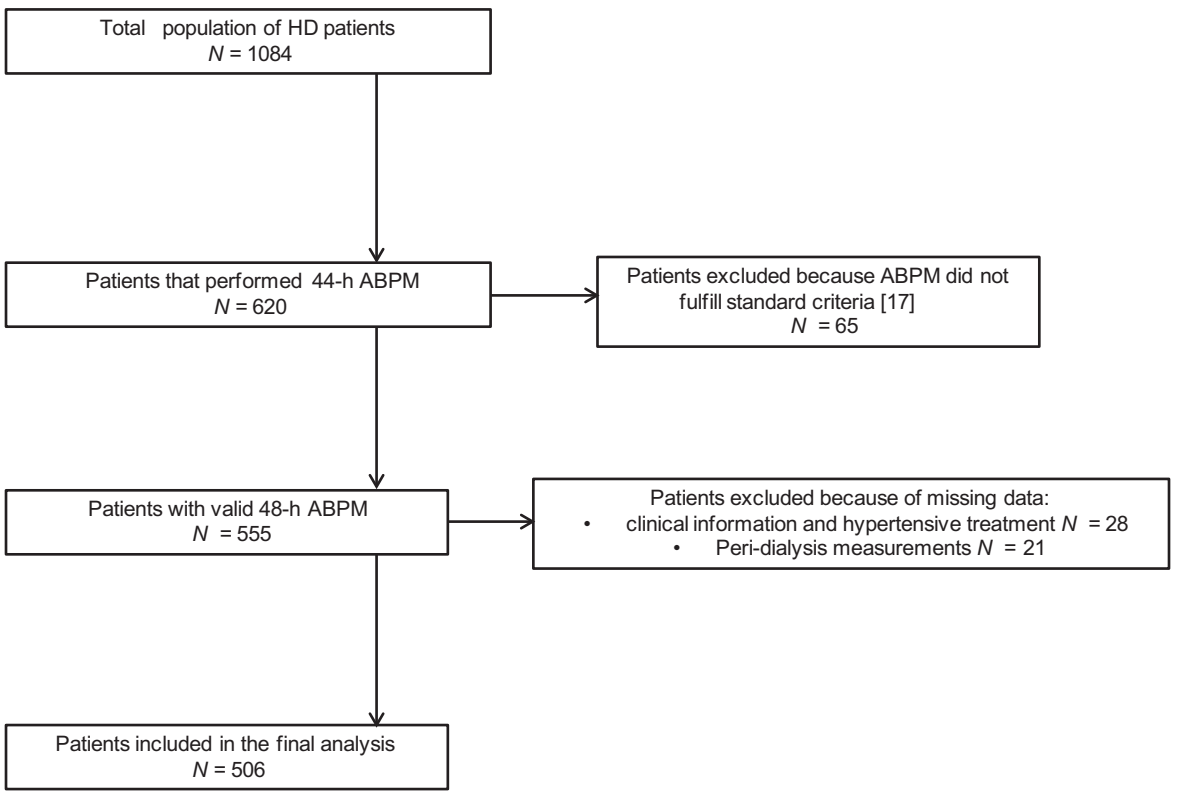

FIGURE 1 Flow chart of the study population.

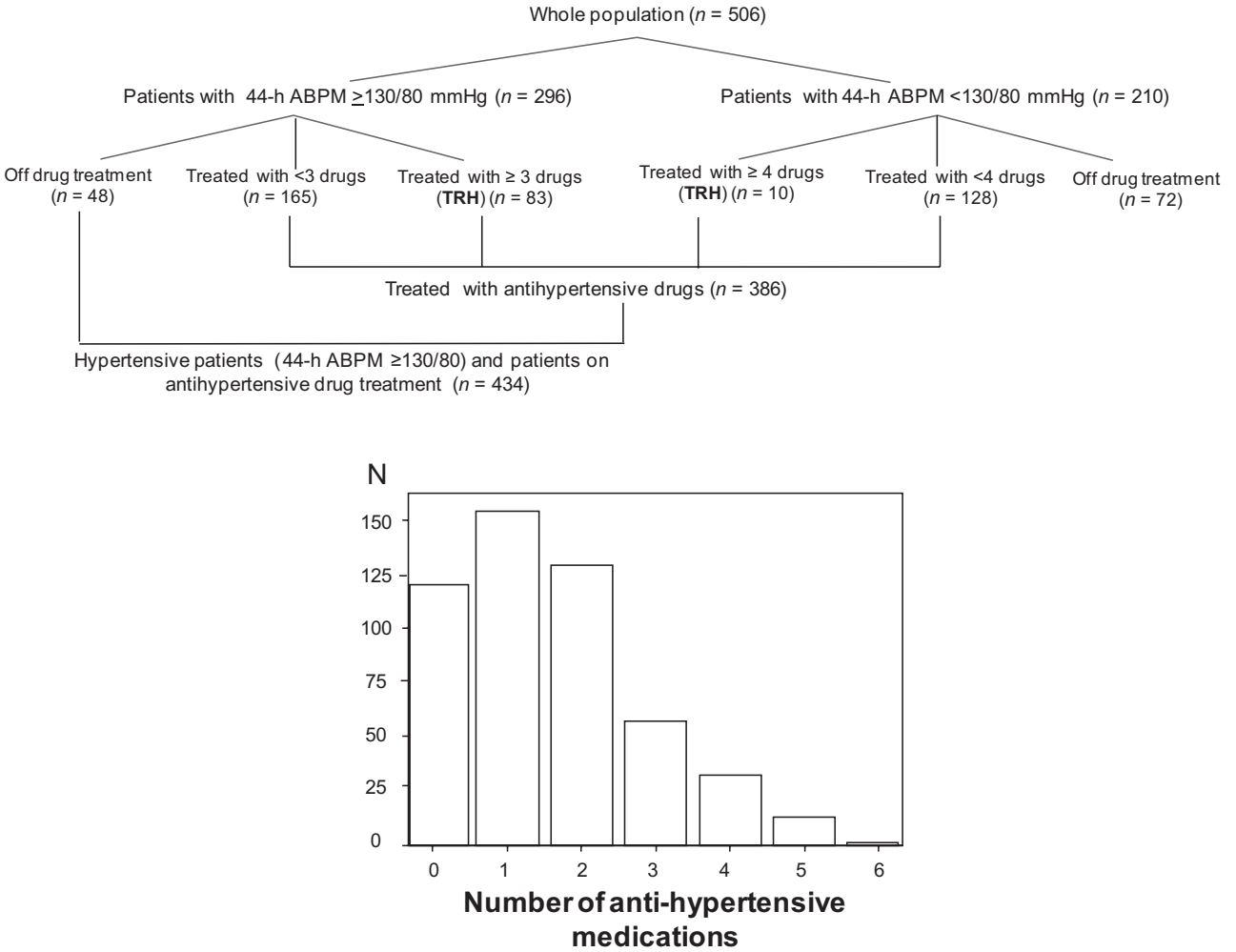

FIGURE 2 Upper panel: hypertensive and normotensive patients in the whole population, divided according to the number of antihypertensive drugs used. Lower panel: distribution of antihypertensive drugs in the study population.

excluding these drugs (24%, see above).The proportion of patients with TRH in centers participating to this study was variable but the 95% confidence intervals (CI) intervals amply overlapped (Supplementary Figure 1, http://links.lww.com/HJH/B330). Among the remaining patients with uncontrolled hypertension, 165 were being treated with less than three drugs and 48 hypertensive patients were still off antihypertensive treatment. The distribution of antihypertensive medications (Fig. 2, lower panel) being used in the whole population ranged from 0 to 6 (median: 1, IQR: 1–2). These drugs included beta-blockers (in 256, 50.6%), calcium channel blockers (in 240, 47.4%), angiotensin-converting enzyme and angiotensin II blockers (in 189, 37.4%), α-blockers (in 36, 7.1%), α-2 adrenergic agonists (in 16, 3.2%). One hundred and sixty-eight patients were treated with loop diuretics but these drugs were not counted in the number of antihypertensive drugs needed for the diagnosis of resistant hypertension (see methods).

The clinical characteristic of patients with TRH by 44-h ABPM criteria are summarized in Table 1 and face to face compared with those of hypertensive patients treated with less than three drugs and of normotensive patients (while on less than four drugs and without drug treatment) by the same criteria. On average BMI was 1 and 2 kg/m^2 lower among TRH patients than in patients with uncontrolled hypertension and normotensive patients, with or without treatment. Apart from 44-h ABPM and antihypertensive treatment intensity – which are the criteria applied for the categorization of the three groups – and dialysis vintage (higher in the normotensive group) and the proportion of patients with cardiovascular comorbidities (lower in hypertensive patients treated with less than three drugs), no additional between-groups difference emerged as for traditional (age, sex, cholesterol, smoking, diabetes) and CKD-specific (albumin, haemoglobin, CRP, calcium, phosphate) risk factors. Predialysis BP as well as day-time and night-time BP in TRH patients were very similar to those in patients with uncontrolled hypertension while on less than three drugs.

Treatment-resistant hypertension by 44-h ambulatory blood pressure monitoring and by predialysis blood pressure

Three-hundred and eight patients had uncontrolled hypertension by predialysis BP criteria and 83 of these (16%) had

TABLE 1. Clinical characteristics of treatment-resistant hypertensive patients (44-h ambulatory blood pressure monitoring at least three drugs and normotensive patients on at least four drugs), uncontrolled hypertensive patients treated with less than three drugs and normotensive patients off drug treatment or treated with less than three drugs

	Whole population	Treatment-resistant hypertensivepatients	Uncontrolled hypertensive patients treated with less than three drugs	Normotensive patients off drugs or treated with less than three drugs	*P* value
Number of patients	506	93	213	200	
Age (years)	64 ± 14	64 ± 14	64 ± 14	65 ± 15	0.41
BMI (kg/m^2)	25 ± 5	24 ± 5	25 ± 4	26 ± 5	0.004
Male sex (%)	311 (62)	55 (59)	140 (66)	116 (58)	0.26
Smokers (%)	111 (23)	27 (29)	46 (22)	38 (20)	0.22
Diabetics (%)	147 (29)	31 (34)	59 (28)	57 (29)	0.56
With cardiovascular comorbidities (%)	251 (50)	53 (57)	90 (42)	108 (54)	0.02
Dialysis vintage (months)	38 (15–84)	35 (15–70)	33 (12–71)	47 (24–109)	0.003
Cholesterol (mg/dl)	157 ± 44	161 ± 50	157 ± 43	155 ± 40	0.56
Haemoglobin (g/dl)	11.3 ± 1.2	11.1 ± 1.1	11.3 ± 1.3	11.4 ± 1.3	0.10
Albumin (g/dl)	3.9 ± 0.4	4.0 ± 0.4	4.0 ± 0.4	3.9 ± 0.4	0.04
Calcium (mg/dl)	8.9 ± 0.8	8.9 ± 0.9	9.0 ± 0.8	8.9 ± 0.8	0.50
Phosphate (mg/dl)	5.0 ± 1.4	5.0 ± 1.6	4.9 ± 1.4	4.9 ± 1.4	0.87
C-reactive protein (mg/l)	4.8 (3.4–9.0)	4.3 (3.6–5.7)	4.8 (3.1–10.1)	5.0 (3.6–12.0)	0.07
On antihypertensive treatment (%)	386 (76)	93 (100)	165 (78)	128 (64)	<0.001
Number of antihypertensive drugs	1 (1–2)	3 (3–4)	1 (1–2)	1 (0–2)	<0.001
Prepost hemodialysis weight change (kg)	2.0 ± 0.1	1.9 ± 1.0	2.0 ± 1.0	2.1 ± 0.9	0.29
Predialysis systolic; diastolic pressure (mmHg)	143 ± 23; 81 ± 15	152 ± 24; 83 ± 14	150 ± 20; 85 ± 15	132 ± 21/75 ± 14	<0.001
Predialysis heart rate (beats/min)	74 ± 9	71 ± 7	74 ± 10	75 ± 10	<0.001
44-h SBP (mmHg)	132 ± 19	145 ± 20	143 ± 11	115 ± 10	<0.001
44-h DBP (mmHg)	76 ± 12	82 ± 13	82 ± 10	66 ± 8	<0.001
Day SBP (mmHg)	133 ± 19	145 ± 21	143 ± 12	117 ± 12	<0.001
Day DBP (mmHg)	77 ± 13	83 ± 13	83 ± 10	68 ± 9	<0.001
Night SBP (mmHg)	129 ± 22	141 ± 23	140 ± 15	112 ± 15	<0.001
Night DBP (mmHg)	73 ± 13	79 ± 14	79 ± 10	63 ± 9	<0.001
White-coat hypertension [*n* (%)]	81 (16)	2 (3)	0	79 (40)	
Masked hypertension [*n* (%)]	60 (12)	12 (13)	48 (23)	0	

TRH by the same metric. Ninety-five patients had either TRH as assessed by 44-h ABPM and/or TRH as assessed by predialysis BP. Eighty-one (85%) had concordant TRH, that is, hypertension both by ABPM and predialysis criteria, and the remaining 14 (15%) had discordant TRH. Among those with discordant TRH, the majority ($n = 12$) had resistant hypertension by ABPM criteria but normal predialysis BP, that is, masked hypertension, and only two patients who were normotensive while treated with at least four drugs had TRH by predialysis criteria but normal 44-h ABPM, that is, pseudoresistant hypertension because of white coat hypertension. Predialysis BP criteria had a very good specificity (99%) and sensitivity (87%) for the diagnosis of TRH by 44-h ABPM and the discriminatory power of predialysis BP for the same diagnosis was good (area under the ROC curve: 0.93; 95% CI: 0.89–0.97).

Subgroup with body composition monitoring measurements

The 104 patients who underwent BCM studies were comparable to the whole study population for age, sex, BMI, proportion of smokers and of patients with diabetes, cardiovascular comorbidities and on treatment with antihypertensive drugs as well as for hemoglobin, serum albumin, cholesterol, and C reactive protein (*P* ranging from 0.06 to 1.0) but had a 5 mmHg higher 44-h systolic pressure ($P = 0.02$) and almost identical diastolic pressure (75 vs. 76 mmHg, $P = 0.59$). As shown in Fig. 3, fluid overload measured predialysis was much common in all groups and there was a weak, nonsignificant tendency to higher levels of fluid overload among TRH patients (2.21 l, 95% CI 1.48–2.94 l) than in hypertensive patients treated with less than three drugs (2.04 l, 95% CI 1.49–2.59 l) normotensive patients (1.53 l, 95% CI 1.03 l–2.02 l) but the overlap among the three groups was substantial. Overall, in BCM studies performed predialysis, the proportion of patients with fluid overload in the three groups was 33, 34 and 26%, respectively. The differences among the three groups were more marked in studies repeated after dialysis [TRH patients: fluid overload 0.71 l, 95% CI −0.08 to 1.50 l; uncontrolled hypertensive patients with less than three drugs: 0.42 l, 95% CI −0.20 to 1.03 l; normotensive patients (with and without antihypertensive treatment) −0.26 l, 95% CI −0.80 to 0.27 l] and the head-to-head comparison between TRH and normotensive patients achieved marginal statistical significance postdialysis ($P = 0.04$). Figure 3 also shows that postdialysis six out of 33 TRH patients (18%) had fluid overload versus three out 32 (9%) hypertensive patients treated with less than three drugs and two out 39 (5%) normotensive patients. Overall, the majority of patients with TRH had no fluid overload both predialysis (22 out of 33, 67%, Fig. 3) and postdialysis (27 out 33, 82%). Both predialysis and postdialysis total, intracellular and extracellular fluid volume did not differ in the three study groups (see Supplementary Table 1, http://links.lww.com/HJH/B331).

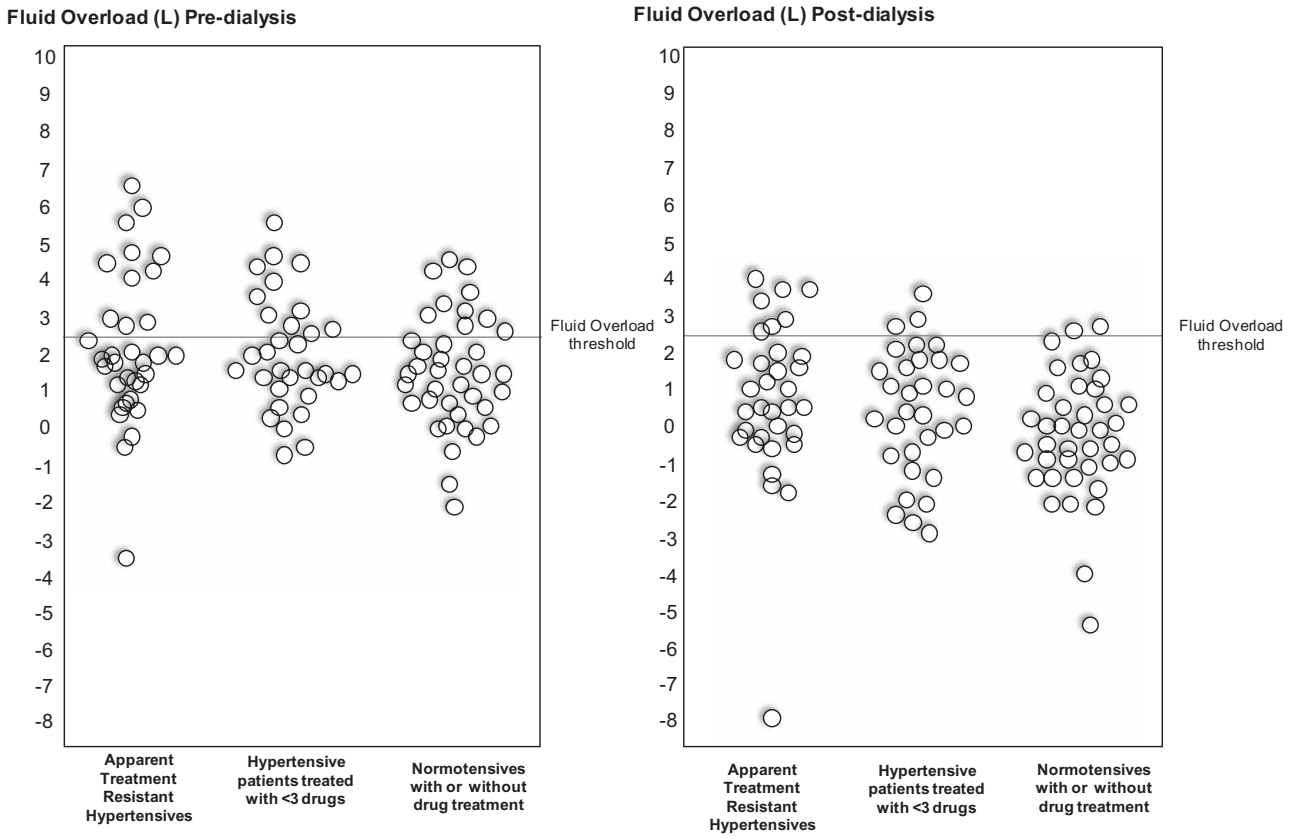

FIGURE 3 Predialysis and postdialysis fluid overload in treatment-resistant hypertension, uncontrolled hypertensive patients and normotensives. See text for details.

DISCUSSION

This multicenter study based on 44-h ABPM further again confirms the pervasive nature of hypertension in hemodialysis patients and shows that apparent TRH occurs in about one in four hemodialysis patients treated with antihypertensive drugs. Fluid overload is present in the 33% of patients with TRH but this prevalence is just marginally higher than that observed in normotensive patients. The fact that about two-thirds of TRH patients show no evidence of fluid overload predialysis suggests that factors other than volume expansion are responsible for this condition in the majority of cases.

TRH is considered as a problem of utmost clinical relevance in predialysis stage 3–5 CKD patients [9]. In population-based studies, the prevalence of TRH in CKD patients ranged from 1.6 to 24.7% [9] and was 40% in the Chronic Renal Insufficiency Cohort (CRIC) cohort [4,5]. At community level about half of hypertensive patients with uncontrolled hypertension are suboptimally treated [22] and 40% of patients with TRH are either noncompliant to drug treatment or have white coat hypertension, that is, pseudohypertension [23].

Studies on resistant hypertension at community level [22,24–27] and in CKD patients [4,5,26] were based on office BP, did not check drug adherence and did not include hemodialysis patients. Our study is the first to provide an estimate of the problem in the hemodialysis population. According to the American Heart Association (AHA), the definition of TRH should be based on ABPM or on out of office BP measurements [3]. We adopted 44-h ABPM, the method recommended for hemodialysis patients by Agarwal *et al.* [15] and by the EURECAm working group of the ERA EDTA and the Hypertension and the Kidney working group of the ESH [1] but we did not objectively assess adherence to therapy. Therefore, like previous studies in the general population and in CKD, our study provides an estimate of apparent TRH by 44-h ABPM rather than of true resistant hypertension. In studies in the general population mentioned above [22,24,25–27] the prevalence of apparent TRH ranged from 9.4 to 14.5%. The prevalence was much higher in studies focusing on the CKD population [4,5,26] where it ranged from 33 to 40%.

Until now, ABPM criteria for the diagnosis of TRH have been applied in just three studies [7,23,28]. In the first, based on the Spanish Ambulatory Blood Pressure Monitoring Registry, where adherence to treatment could not be checked, among 68 045 treated patients with essential hypertension 8295 (12%) had TRH [28]. In the second, a community-based survey in 1312 treated hypertensive patients where adherence was checked by the regularity of prescription by general practitioners and by interviewing patients, the prevalence of resistant hypertension was 22% [23], and a similar figure (23%) was registered in the third ABPM-based study, which focused on CKD patients, which again assessed drug adherence by interviewing patients [7]. In hemodialysis patients, we found a 24% prevalence of TRH by 44-h ABPM, a figure very close to that observed in the ABPM-based survey in the general population by Brambilla *et al.* [23] and to that in the sole ABPM-based

study in CKD patients by De Nicola *et al.* [7]. In general, with 76% sensitivity, 54% specificity and 0.65 area under the ROC curve, predialysis BP has quite limited ability for the diagnosis of hypertension by 48-h ABPM in hemodialysis patients [29]. In this study predialysis BP fairly well identified TRH patients in whom this condition was diagnosed by the gold standard method, 44-h ABPM. The high sensitivity (87%) and very high specificity (99%) and the good area under the ROC curve (0.93) of predialysis BP in the present study most likely depend on the fact that patients with TRH represent a subpopulation with BP values well above the hypertension thresholds of the two BP metrics – predialysis BP and 44-h ABPM – and for this reason, TRH patients are less frequently misclassified by predialysis BP. As we defined hypertension on the basis of 44-h ABPM, white coat hypertension was found just in two patients with TRH, both normotensive patients on treatment with at least four drugs.

Fluid overload is a major risk factor for TRH in the general population [30] and even more so in CKD patients [9]. In large-scale studies [31], about a half of hemodialysis patients show fluid overload predialysis. Hemodialysis patients with TRH tended to be more volume expanded than normotensive (treated or untreated) patients but the between groups overlap for fluid overload was substantial (Fig. 3). Overall, the prevalence of fluid overload among TRH patients was 33% predialysis and 18% postdialysis. Provided that patients tolerate attempts at ultrafiltration intensification beyond the level put in place in clinical practice in the present study, these data suggest that body fluid volume optimization might in theory lead to an improvement in hypertension control in about one-third of hemodialysis patients. Thus, in addition to controlling fluid overload, focus on other factors deserves at least equal attention. Accurate monitoring of adherence to drug treatment, an issue in the present study and in studies performed so far in the general [22,24,25–27] and in the CKD populations [4,5,7,26], is fundamental for labeling hypertension as 'true resistant'. Poor adherence to drug treatment is a notorious problem in dialysis patient [32] and over a half of these patients are uncompliant with antihypertensive therapy [33]. Interventions aimed at increasing adherence to treatment [34] might mitigate resistant hypertension in the hemodialysis population.

This study has limitations. The first limitation is that we could not rigorously assess adherence to therapy. Therefore, the prevalence we registered is an overestimation of true resistant hypertension. However, the same limitation applies to the three ABPM studies performed so far [7,23,28] and to studies in the general population [22,24–27] and in CKD patients [4,5,26] based on office BP. The second limitation is the fact that 44-h ABPM is not universally tolerated by hemodialysis patients, and therefore, patients that accept to undergo this test may represent a selected subpopulation. However, other BP metrics are overtly inferior to 44-h ABPM for the diagnosis of hypertension in this population. Third, we measured fluid volume in a subpopulation (20% of patients) of the EURECA-m Registry. However, this subpopulation was substantially representative of the whole EURECA-m population. Furthermore, our study is Registry-based and as such, it is less rigorous than well designed observational studies focusing on ABPM that applied random selection of patients, like the PAMELA study [35]. Finally, patients in our Registry were all but three of Caucasian descent, and therefore, studies in other ethnicities are needed to define the prevalence of TRH in non-Caucasian hemodialysis patients.

In conclusion, apparent treatment hypertension as assessed by 44-h ABPM has a 24% prevalence among hemodialysis patients, a figure is of the same order of that registered in ABPM-based studies in the general population and in CKD patients. The prevalence of predialysis fluid overload among treatment-resistant hemodialysis patients is 33% suggesting that fluid overload only in part explains TRH in these patients.

Perspectives

Hypertension is a pervasive, difficult-to-treat risk factor in ESKD patients on regular hemodialysis but the prevalence of TRH in this population is still unknown. To estimate the prevalence of TRH, we adopted the AHA criteria for the diagnosis of TRH and applied the gold standard for BP measurement (44-h ABPM) in a population of 506 patients in 10 renal units in Europe and studied the association of fluid overload with TRH. The prevalence of TRH in hemodialysis patients was 24% and the majority (67%) of patients with TRH had no evidence of fluid overload suggesting that fluid overload only in part explains TRH. Treatment of fluid overload and targeting adherence to drug treatment are needed to mitigate the burden of TRH in the hemodialysis population.

ACKNOWLEDGEMENTS

This is an original, never published study. The results were in part presented at the 2018 ERA EDTA Congress.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Sarafidis PA, Persu A, Agarwal R, Burnier M, de Leeuw P, Ferro C, *et al.* Hypertension in dialysis patients: a consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH). *J Hypertens* 2017; 35:657–676.
2. Inrig JK. Antihypertensive agents in hemodialysis patients: a current perspective. *Semin Dial* 2010; 23:290–297.
3. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, *et al.*, American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension* 2018; 72:e53–e90.
4. Tanner RM, Calhoun DA, Bell EK, Bowling CB, Gutiérrez OM, Irvin MR, *et al.* Prevalence of apparent treatment-resistant hypertension among individuals with CKD. *Clin J Am Soc Nephrol* 2013; 8:1583–1590.
5. Thomas G, Xie D, Chen H-Y, Anderson AH, Appel LJ, Bodana S, *et al.*, CRIC Study Investigators. Prevalence and prognostic significance of apparent treatment resistant hypertension in chronic kidney disease: report from the Chronic Renal Insufficiency Cohort Study. *Hypertension* 2016; 67:387–396.

6. Diaz-Buxo JA, Lowrie EG, Lew NL, Zhang H, Lazarus JM. Quality-of-life evaluation using Short Form 36: comparison in hemodialysis and peritoneal dialysis patients. *Am J Kidney Dis* 2000; 35:293–300.
7. De Nicola L, Gabbai FB, Agarwal R, Chiodini P, Borrelli S, Bellizzi V, *et al.* Prevalence and prognostic role of resistant hypertension in chronic kidney disease patients. *J Am Coll Cardiol* 2013; 61:2461–2467.
8. Pimenta E, Gaddam KK, Oparil S, Aban I, Husain S, Dell'Italia LJ, Calhoun DA. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension. *Hypertension* 2009; 54:475–481.
9. Rossignol P, Massy ZA, Azizi M, Bakris G, Ritz E, Covic A, *et al.*, ERA-EDTA EURECA-m working group; Red de Investigación Renal (REDINREN) network; Cardiovascular and Renal Clinical Trialists (F-CRIN INI-CRCT) network. The double challenge of resistant hypertension and chronic kidney disease. *Lancet* 2015; 386:1588–1598.
10. Georgianos PI, Agarwal R. Epidemiology, diagnosis and management of hypertension among patients on chronic dialysis. *Nat Rev Nephrol* 2016; 12:636–647.
11. Sibbel S, Walker AG, Colson C, Tentori F, Brunelli SM, Flythe J. Association of continuation of loop diuretics at hemodialysis initiation with clinical outcomes. *Clin J Am Soc Nephrol* 2019; 14:95–102.
12. Trinh E, Bargman JM. Are diuretics underutilized in dialysis patients? *Semin Dial* 2016; 29:338–341.
13. Agarwal R, Sinha AD, Light RP. Toward a definition of masked hypertension and white-coat hypertension among hemodialysis patients. *Clin J Am Soc Nephrol* 2011; 6:2003–2008.
14. O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G, *et al.*, European Society of Hypertension Working Group on Blood Pressure Monitoring. European society of hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens* 2013; 31:1731–1768.
15. Agarwal R, Flynn J, Pogue V, Rahman M, Reisin E, Weir MR. Assessment and management of hypertension in patients on dialysis. *J Am Soc Nephrol* 2014; 25:1630–1646.
16. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, *et al.* 2013 Practice guidelines for the management of arterial hypertension of the European Society ofHypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESCTask Force for the Management of Arterial Hypertension. *J Hypertens* 2013; 31:1925–1938.
17. Parati G, Ochoa JE, Bilo G, Agarwal R, Covic A, Dekker FW, *et al.*, European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association–European Dialysis Transplantation Association (ERA-EDTA). Hypertension in chronic kidney disease part 1. *Hypertension* 2016; 67:1093–1101.
18. Moissl UM, Wabel P, Chamney PW, Bosaeus I, Levin NW, Bosy-Westphal A, *et al.* Body fluid volume determination via body composition spectroscopy in health and disease. *Physiol Meas* 2006; 27:921–933.
19. Machek P, Jirka T, Moissl U, Chamney P, Wabel P. Guided optimization of fluid status in haemodialysis patients. *Nephrol Dial Transplant* 2010; 25:538–544.
20. Chamney PW, Wabel P, Moissl UM, Müller MJ, Bosy-Westphal A, Korth O, Fuller NJ. A whole-body model to distinguish excess fluid from the hydration of major body tissues. *Am J Clin Nutr* 2007; 85:80–89.
21. Wizemann V, Wabel P, Chamney P, Zaluska W, Moissl U, Rode C, *et al.* The mortality risk of overhydration in haemodialysis patients. *Nephrol Dial Transplant* 2009; 24:1574–1579.
22. Egan BM, Zhao Y, Li J, Brzezinski WA, Todoran TM, Brook RD, Calhoun DA. Prevalence of optimal treatment regimens in patients with apparent treatment-resistant hypertension based on office blood pressure in a community-based practice network. *Hypertension* 2013; 62:691–697.
23. Brambilla G, Bombelli M, Seravalle G, Cifkova R, Laurent S, Narkiewicz K, *et al.* Prevalence and clinical characteristics of patients with true resistant hypertension in central and Eastern Europe: data from the BP-CARE study. *J Hypertens* 2013; 31:2018–2024.
24. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. *Circulation* 2011; 124:1046–1058.
25. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. *Hypertension* 2011; 57:1076–1080.
26. Diaz KM, Booth JN, Calhoun DA, Irvin MR, Howard G, Safford MM, *et al.* Healthy lifestyle factors and risk of cardiovascular events and mortality in treatment-resistant hypertension. *Hypertension* 2014; 64:465–471.
27. Borghi C, Tubach F, De Backer G, Dallongeville J, Guallar E, Medina J, *et al.* Lack of control of hypertension in primary cardiovascular disease prevention in Europe: results from the EURIKA study. *Int J Cardiol* 2016; 218:83–88.
28. de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, *et al.* Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. *Hypertension* 2011; 57:898–902.
29. Sarafidis PA, Mallamaci F, Loutradis C, Ekart R, Torino C, Karpetas A, *et al.* Prevalence and control of hypertension by 48-h ambulatory blood pressure monitoring in haemodialysis patients: a study by the European Cardiovascular and Renal Medicine (EURECA-m) working group of the ERA-EDTA. *Nephrol Dial Transplant* 2018; 33:1872–11872.
30. Calhoun DA. Fluid retention, aldosterone excess, and treatment of resistant hypertension. *Lancet Diabetes Endocrinol* 2018; 6:431–433.
31. Zoccali C, Moissl U, Chazot C, Mallamaci F, Tripepi G, Arkossy O, Wabel PSS. Chronic fluid overload and mortality in end stage kidney disease. *J Am Soc Nephrol* 2017; 28:2491–2497.
32. Mechta Nielsen T, Frøjk Juhl M, Feldt-Rasmussen B, Thomsen T. Adherence to medication in patients with chronic kidney disease: a systematic review of qualitative research. *Clin Kidney J* 2018; 11:513–527.
33. Neri L, Martini A, Andreucci VE, Gallieni M, Rey LAR, Brancaccio D, MigliorDialisi Study Group. Regimen complexity and prescription adherence in dialysis patients. *Am J Nephrol* 2011; 34:71–76.
34. Conn VS, Ruppar TM, Chase J-AD, Enriquez M, Cooper PS. Interventions to improve medication adherence in hypertensive patients: systematic review and meta-analysis. *Curr Hypertens Rep* 2015; 17:94.
35. Bombelli M, Toso E, Peronio M, Fodri D, Volpe M, Brambilla G, *et al.* The Pamela study: main findings and perspectives. *Curr Hypertens Rep* 2013; 15:238–243.