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Original Article

ORIGINAL ARTICLE

Venous bicarbonate and CKD progression: a longitudinal analysis by the group-based trajectory model

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ABSTRACT

Background. Metabolic acidosis accelerates chronic kidney disease (CKD) progression towards kidney failure in animal models. Clinical trials testing the effect of bicarbonate on kidney outcomes are underpowered and/or of suboptimal quality. On the other hand, observational studies testing the same hypothesis are generally based on bicarbonate measured at a single time point.

Methods. We studied the longitudinal relationship between repeated venous bicarbonate levels and a predefined composite renal outcome (a ≥30% estimated glomerular filtration rate reduction, dialysis or transplantation) by using group-based trajectory model (GBTM) analysis. The GBTM analysis was used to classify patients based on individual bicarbonate levels over time. The relationship between trajectory groups and renal outcomes was investigated using crude and adjusted Cox regression models. A total of 528 patients with stage 2–5 CKD were included in the analysis.

Results. The GBTM analysis identified four distinct trajectories of bicarbonate levels: low, moderate, moderate-high and high. During the follow-up period, 126 patients experienced the combined renal endpoint. The hazard rate of renal events decreased dose-dependently from the lowest to the highest bicarbonate trajectory. After adjusting for potential confounders, there was a 63% risk reduction for the composite renal endpoint for patients in the high trajectory category compared with those in the low trajectory category.

Conclusion. The study found that higher bicarbonate trajectories were associated with a lower risk of adverse renal outcomes in CKD patients. These results suggest that strategies to maintain higher bicarbonate levels may benefit patients with CKD. However, further high-quality randomised trials are needed to confirm these findings and recommend bicarbonate supplementation as a strategy to delay CKD progression.

Keywords: bicarbonate, CKD, CKD progression

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KEY LEARNING POINTS

What is known:

- Metabolic acidosis accelerates chronic kidney disease (CKD) progression towards kidney failure in animal models.
- Clinical trials testing the effect of bicarbonate on kidney outcomes are underpowered and/or of suboptimal quality.
- Observational studies testing the same hypothesis are generally based on bicarbonate measured at a single time point.

This study adds:

- We studied the longitudinal relationship between repeated venous bicarbonate levels and a predefined composite renal outcome (a >30% estimated glomerular filtration rate reduction, dialysis or transplantation) by using group-based trajectory model (GBTM) analysis.
- The GBTM analysis identified four distinct trajectories of bicarbonate levels: low, moderate, moderate-high and high. During the follow-up period, 126 patients experienced the combined renal endpoint. The hazard rate of renal events decreased dose-dependently from the lowest to the highest bicarbonate trajectory.
- After adjusting for potential confounders, there was a 63% risk reduction for the composite renal endpoint for patients in the high bicarbonate trajectory compared with those in the low trajectory.

Potential impact:

- These results suggest that strategies to maintain higher bicarbonate levels may benefit patients with CKD.
- High-quality randomised trials are needed to confirm these findings and recommend bicarbonate supplementation as a strategy to delay CKD progression.

INTRODUCTION

There is substantial evidence in animal studies that metabolic acidosis accelerates the progression of chronic kidney disease (CKD) toward kidney failure [1–3]. Observational studies in various populations, including community studies and studies in CKD patients [4–10], support the hypothesis that subclinical (eubicarbonatemic) and overt metabolic acidosis [11] negatively impact the risk of CKD and CKD progression. Even though these studies coherently support the hypothesis that metabolic acidosis promotes kidney damage and accelerates kidney function loss, with the notable exception of the Chronic Renal Insufficiency Cohort (CRIC) study [12], all measured serum bicarbonate or carbon dioxide (CO_2) only at baseline and did not contemplate repeated measurements of these biomarkers.

Randomised clinical trial testing interventions aimed at correcting metabolic acidosis are the gold standard for testing whether correcting metabolic acidosis may improve kidney outcomes in CKD patients. A recent meta-analysis identified 15 trials, including 2445 participants, testing the effect of bicarbonate therapy on kidney outcomes [13]. In these trials, sodium bicarbonate retarded the decline in kidney function and reduced the risk of kidney failure by 47%, which would support findings registered in observational studies. However, most of these trials were at either an unclear or high risk of bias. The main conclusion of this meta-analysis was that, due to a lack of high-quality randomised trials, there is insufficient evidence to recommend bicarbonate supplementation as a strategy to delay CKD progression.

Awaiting adequately powered, high-quality trial results, information derived from longitudinal studies is important. As remarked, all observational studies performed so far, excluding the CRIC study [12], related just baseline bicarbonate with incident renal outcomes. This is a crude approach, and alternative methods based on repeated measurements have been developed to capture long-term exposures better. One novel method is group-based trajectory model (GBTM) analysis, a method of the family of latent class growth analysis techniques [14]. In the present study, we elected to investigate the longitudinal relationship between repeated bicarbonate measurements and a composite renal endpoint using GBTM. This method allows the description of exposures over time by adopting trajectories identified by GBTM, simplifying heterogeneous populations into homogeneous patterns or classes. With this background in mind, we applied GBTM to investigate the relationship between longitudinal trajectories of venous bicarbonate and a predefined composite renal endpoint in a cohort of stage G3–5 CKD patients in a sizable cohort of stage G3–5 CKD patients.

MATERIALS AND METHODS

Patients

We included 528 patients in this analysis out of a source population of 759 patients with stage 2–5 CKD (age 62 ± 11 years; 60% male) consecutively recruited from nephrology units in southern Italy (Calabria, Sardinia and Sicily regions) who participated in the Multiple Intervention and Audit in Renal Diseases to Optimize Care (MAURO) studies [15]. The MAURO study was a cluster randomised controlled trial in 22 renal clinics that assessed the efficacy of a multimodal quality improvement intervention to increase compliance with guideline recommendations for preventing CKD progression and cardiovascular (CV) complications in a CKD population. Patient enrolment was performed between October 2005 and October 2008. The selection criteria and the detailed clinical characteristics of this cohort are described elsewhere [16]. The study contemplated six visits over a 3-year follow-up. All patients were in stable clinical condition at enrolment and none had intercurrent infections or acute inflammatory processes. Inclusion criteria were non-acute or rapidly evolving renal diseases, age 18–75 years, non-transplanted, non-pregnant and unaffected by cancer or diseases in the terminal phase.

Measurements

Venous bicarbonate was measured by a venous blood gas test using blood gas analysers to measure pH and partial pressure of carbon dioxide. After blood sampling, syringes were immediately sealed and kept on ice. Trained technicians measured bicarbonate in the nephrology units participating in the study or the central laboratories of the hospitals of the same units within 15 minutes after sampling. The bicarbonate level was then calculated by the Henderson–Hasselbalch equation. Routine biochemical tests were measured in clinical laboratories of participating units, all applying periodic verification of the quality of standard methods. Following the MAURO study protocol, the glomerular filtration rate (GFR) was estimated by the Modification of Diet in Renal Disease (MDRD) equation [17].

Study endpoint

The predefined study endpoint was a composite renal endpoint: a decrease in GFR >30% (estimated by the MDRD equation), dialysis or kidney transplantation, which was the predefined renal endpoint of the MAURO study cohort [16].

Statistical methods

Normally distributed data were summarised as mean and standard deviation (SD), non-normally distributed data as the median and interquartile range (IQR) and categorical data as absolute frequency and percentage, as appropriate.

We followed the recommendations made for guidelines for reporting on latent trajectory studies made by van de Schotte *et al*. [18]. We applied two methods to investigate the association between bicarbonate trajectories and renal outcomes: the GBTM analysis [19] and the Cox regression model. The GBTM analysis allows the classification of patients into groups based on individual bicarbonate levels over time. The censored normal distribution (suitable for continuous data approximately normally distributed, with or without censoring) was used to model the bicarbonate values [20]. The GBTM analysis identified (based on maximum likelihood estimates) groups with similar bicarbonate trajectories. Each patient was assigned a specific trajectory according to the highest posterior probability. The distinctive features of data, parsimony, clinical judgment and latent classes observed in practice constituted a useful guideline for model selection. In defining the number of groups, we relied on the higher Bayesian information criterion (BIC) [19, 21]. We accounted for the statistical significance of polynomials starting with a trajectory shape with a cubic structure and eliminated the not significant polynomial terms [22]. In addition, analysis of the mean posterior probability of group membership (>0.70) was used to assess the fit of the final model.

The above probability relates to an individual's probability of group trajectory membership. These probabilities were calculated after the model fits using their estimated coefficients. The following criteria were also considered: the size of each group, the odds of correct classification greater than five based on the posterior probabilities of group membership and the correspondence between the estimated probability of each group and the proportion of study members assigned to that group based on the maximum posterior probability [19]. Entropy (whose value ranges from 0.00 to 1.00), which is a summary indicator of the conditional probability of membership in each group, had high values (>0.80), indicating that individuals were well classified and that there was an adequate separation between latent classes [23]. Trajectories were represented using the trajectory graph. The groups were ranked first to fourth according to bicarbonate levels (from lowest levels in group 1 to highest in group 4). We reported the intercept (with a trajectory shape with no slope) and standard error for each trajectory. To assess the association between trajectories and the study of the combined renal endpoint, we used a GBTM with a subsequent outcome on trajectory group membership analysis. This model specifically allows linking the trajectory groups with the outcome measured at or after the end of the trajectory [14].

As appropriate, baseline characteristics among trajectory groups were compared through the χ^2, analysis of variance and Kruskal–Wallis test. The level of statistical significance was set as $P < .05$.

In addition to the outcome of trajectory group membership analysis, we investigated the relationship between trajectory groups and renal outcomes by Cox regression analysis. In these analyses we considered that associated with the lowest bicarbonate values as a reference trajectory. Data were adjusted for potential confounders, i.e. variables associated ($P < .05$) with both the outcome and the trajectory groups and that did not lie in the causal pathway between bicarbonate levels and renal events. In Cox models, data were expressed as hazard rate (HR), 95% confidence interval (CI) and P-value. Data analyses were performed in Stata 16.1 for Windows (StataCorp, College Station, TX, USA).

RESULTS

The study cohort included 528 patients with stage 2–5 CKD from of a source population of 759 patients. A total of 231 patients were excluded from the analysis because they did not meet the inclusion criteria of having at least three longitudinal bicarbonate measurements over time. Patients excluded from the study did not differ from those who participated to the study regarding demographic factors and classic and CKD peculiar risk factors (see Supplementary Table 1). Enrolled patients had an average age of 62 ± 11 years, 60% were males, 49% were smokers, 33% were diabetics, 32% had background CV comorbidities and 97% were on antihypertensive treatment. The remaining demographic and clinical characteristics are provided in Table 1. As shown in Table 2, sodium bicarbonate supplements were more frequently used in patients in the low bicarbonate trajectory (10%) and not used at all in the high bicarbonate trajectory. Still, the difference across trajectories did not achieve statistical significance. Calcium carbonate was less frequently used among patients in the third and fourth trajectories than in patients in the first two trajectories. There was no difference in antihypertensive drugs and diuretic use across the four bicarbonate trajectories.

Trajectory analysis

To classify patients based on individual bicarbonate levels over time, GBTM analysis was adopted. The median number of repeated bicarbonate measurements per patient was 7. In detail, 354 patients (67%) had seven measurements, 48 (9%) had six, 48 (9%) had five, 38 (7%) had four and 40 (8%) had three bicarbonate measurements. To identify the best trajectory fitting, the order of trajectories was preliminarily investigated by testing the cubic, quadratic and linear shapes. Since these shapes did not adequately fit with observed data ($P = .78$–1.00), intercept-based trajectories were adopted. The best model (i.e. with the highest

Table 1: Demographic and clinical characteristics of CKD patients in the whole population and according to trajectory groups.

Characteristics	Whole population ($N = 528$)	Low trajectory ($n = 58$)	Medium trajectory ($n = 187$)	Medium-high trajectory ($n = 222$)	High trajectory ($n = 61$)	*P*-value
Age (years), mean ± SD	62 ± 11	59 ± 13	61 ± 11	62 ± 10	65 ± 8	.004
Male, %	60	57	62	59	59	.88
BMI (kg/m^2), mean ± SD	28 ± 5	28 ± 5	28 ± 5	28 ± 4	29 ± 6	.42
Smokers, %	49	50	51	47	48	.86
Diabetics, %	33	29	32	33	44	.26
Cardiovascular comorbidities, %	32	24	34	30	39	.27
Systolic BP (mmHg), mean ± SD	133 ±19	142 ± 22	132 ± 19	133 ± 17	131 ± 17	.0017
Diastolic BP (mmHg), mean ± SD	78 ± 10	79 ± 13	78 ± 10	78 ± 10	76 ± 10	.27
Antihypertensive treatment, %	97	100	98	96	93	.16
Haemoglobin (g/dl), mean ± SD	13.0 ± 1.8	12.3 ± 1.6	12.7 ± 1.9	13.2 ± 1.8	13.4 ± 1.6	<.001
Total cholesterol (mg/dl), mean ± SD	185 ± 44	193 ± 49	184 ± 46	183 ± 40	185 ± 43	.45
HDL cholesterol (mg/dl), mean ± SD	50 ± 17	49 ± 14	49 ± 17	50 ± 18	53 ± 18	.51
LDL cholesterol (mg/dl), mean ± SD	107 ± 36	103 ± 32	104 ± 36	108 ± 36	114 ± 37	.30
Bicarbonate	23.75 ± 3.50	19.07 ± 2.5	21.2 ± 2.3	25.1 ± 2.2	27.9 ± 2.8	<.001
PTH (pg/ml), median (IQR)	74 (52–113)	107 (65–166)	78 (56–117)	66 (47–97)	61 (53–90)	.0001
Calcium (mg/dl), mean ± SD	9.46 ± 0.57	9.4 ± 0.6	9.4 ± 0.6	9.4 ± 0.5	9.5 ± 0.6	.44
Phosphate (mg/dl), mean ± SD	3.7 ± 0.7	4.0 ± 0.9	3.7 ± 0.7	3.6 ± 0.6	3.8 ± 0.8	<.001
Albumin (g/dl), mean ± SD	4.24 ± 0.51	4.20 ± 0.44	4.15 ± 0.47	4.32 ± 0.46	4.28 ± 0.44	.005
CRP (mg/l), median (IQR)	2.31 (1.01–5.1)	2.4 (1.1–6.9)	1.9 (0.9–4.4)	2.5 (0.9–5.1)	2.8 (1.2–6.9)	.20
eGFR (ml/min/1.73 m^2), mean ± SD	36.9 ± 13.5	27.5 ± 10.1	33.9 ± 13.1	40.2 ± 12.9	42.3 ± 13.4	<.001
24-hour urinary protein (g/24 hours), median (IQR)	0.5 (0.2–1.1)	0.8 (0.5–2)	0.6 (0.2–1.4)	0.4 (0.1–0.9)	0.4 (0.1–0.8)	<.001

BMI: body mass index; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Table 2: Treatments in CKD patients in the whole population and according to trajectory groups.

Treatments	Whole population ($N = 528$)	Low trajectory ($n = 58$)	Medium trajectory ($n = 187$)	Medium-high trajectory ($n = 222$)	High trajectory (n =61)	*P*-value
Bicarbonate supplement, %	5%	10%	6%	5%	0%	.14
Vitamin D supplement, %	18%	12%	20%	21%	10%	.13
Calcium carbonate, %	9%	10%	14%	6%	5%	.035
Number of anti-hypertensive drugs, %						
1	18	19	23	14	15	.16
2	30	28	27	33	31	
3	27	24	30	24	34	
4	13	21	11	15	8	
5	3	5	2	3	3	
Calcium antagonist, %	40	50	37	40	41	.45
ACE inhibitors, %	64	71	64	64	54	.21
ARBs, %	39	43	38	39	38	.75
Diuretics, %	50	57	48	48	61	.40
Clonidine, %	34	34	30	37	36	.45

ACE: angiotensin-converting enzyme; ARB: angiotensin ii receptor blockers.

BIC, −7146.22) identified four groups that are shown in Fig. 1. The mean posterior probability for individuals ranged from 0.79 to 0.82, suggesting an overall good discrimination ability over the follow-up period (>0.70). The odds of correct classification were >5 (ranging from 10 to 89), indicating that all trajectory groups satisfied the optimal model fit criteria. The four distinct trajectories of bicarbonate (based on intercept) were labelled as low (11% of patients; mean bicarbonate 19.07 ± 2.5 mEq/L), moderate (35% of patients; mean bicarbonate 21.2 ± 2.3 mEq/L), moderate-high (42% of patients; mean bicarbonate 25.1 ± 2.2 mEq/L) and high (12% of patients; mean bicarbonate 27.9 ± 2.8 mEq/L). The patients' characteristics at baseline according to trajectories are reported in Table 1. Patients in the four trajectories groups significantly differed in age, systolic blood pressure (BP), parathyroid hormone (PTH), phosphate, 24-hour urinary protein, haemoglobin and estimated GFR (eGFR). Figure 2 shows the estimated crude and adjusted average probability of the combined renal endpoint in the four trajectory groups. Comparing the estimated average probability among the four groups showed an inverse dose–response relationship across the bicarbonate trajectories, with the low trajectory exhibiting the highest risk ($P < .001$).

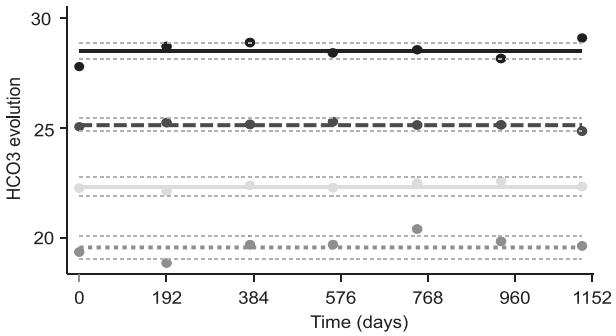

Figure 1: Venous bicarbonate trajectories as defined by GBTM over the course of CKD. The solid line is the averaged estimated trajectory, whereas the series of individual data points represent the averaged observed trajectory. The dotted lines represent the 95% CI of the serial average values.

Cox regression model

During the follow-up period [median 36.0 months (IQR 35.6–36.7)], 126 patients experienced the combined renal endpoint (GFR reduction >30%, dialysis or transplantation). Among these, 115 had a GFR reduction >30%, 10 started haemodialysis or peritoneal dialysis and 1 underwent renal transplantation. In a crude Cox regression model, the HR of renal events decreased in a dose-dependent fashion from the lowest bicarbonate trajectory (reference category, HR 1) to the moderate [HR 0.49 (95% CI 0.31–0.77)], moderate-high [HR 0.27 (95% CI 0.17–0.44)] and high bicarbonate trajectory [HR 0.15 (95% CI 0.06–0.35)] (P for trend <.001). These results were confirmed in analyses adjusting for potential confounders (i.e. age, gender, systolic BP, haemoglobin, albumin, phosphate, PTH, 24-hour proteinuria and eGFR) [moderate: HR 0.82 (95% CI 0.50–1.35), $P = .443$), moderate-high: HR 0.59 (95% CI 0.34–1.00), $P = .050$] and high: HR 0.37 (95% CI 0.15–0.95), $P = .039$; P for trend = .010]. Thus, for patients in the high bicarbonate category (27.9 ± 2.8 mEq/L), there was a 63% risk reduction for the composite renal endpoint compared with those in the low trajectory category.

DISCUSSION

This longitudinal study modelling a composite renal outcome by bicarbonate trajectories in stage G2–5 CKD patients showed a significant inverse relationship between venous bicarbonate levels and the risk of renal events, with a dose-dependent decrease in the HR of renal events as bicarbonate levels increased. These results provide observational evidence based on a robust analytical approach supporting the hypothesis that higher bicarbonate levels, and potentially bicarbonate supplementation, could mitigate the risk of adverse kidney outcomes in CKD patients.

In a study based on a medical clinic in the Bronx, NY, USA, including 5422 individuals followed for a median of 3.4 years, bicarbonate <22 mEq/L was associated with acceleration of progression of CKD [4]. Similarly, in the CRIC study, patients with bicarbonate <22 mEq/L had a doubling in the risk of CKD progression [12]. Kovesdy *et al.* [5], in a cohort of 1240 male veterans with moderate and advanced CKD, observed that patients with bicarbonate within the normal range had a lower incidence of kidney failure. Similarly, Raphael *et al.* [6], in the Multi-Ethnic Study of Atherosclerosis, reported that within the normal bicarbonate range, the circulating levels of this anion are directly associated with the risk of death, dialysis or an eGFR reduction of 50% or 25 ml/min/1.73 m^2). In the 5810 participants of the Multi-Ethnic Study of Atherosclerosis with a baseline eGFR >60 ml/min/1.73 m^2, for each SD lower baseline bicarbonate concentration, there was an 11% higher adjusted odds of rapid kidney function decline and a higher risk of incident reduced eGFR by 50% in a model adjusting for demographics, baseline eGFR, albuminuria and CKD risk factors [7]. In the study by Vallett M et al., elderly patients with bicarbonate <23 mEq/L had two-fold greater odds of a decrease in GFR to <60 ml/min/1.73 m^2 independent of the baseline eGFR [8]. In a prospective hospital-based cohort, the NephroTest

Estimated average probability of developing renal events and 95% CI

	Crude	Adjusted
	estimated average probability of developing renal events and 95% CI	
low trajectory	0.55 (0.43 - 0.67)	0.43 (0.65 - 0.54)
moderate	0.29 (0.23 - 0.36)	0.25 (0.38 - 0.31)
moderate-high	0.15 (0.11 - 0.21)	0.07 (0.15 - 0.10)
high	0.09 (0.04 - 0.19)	0.05 (0.22 - 0.11)

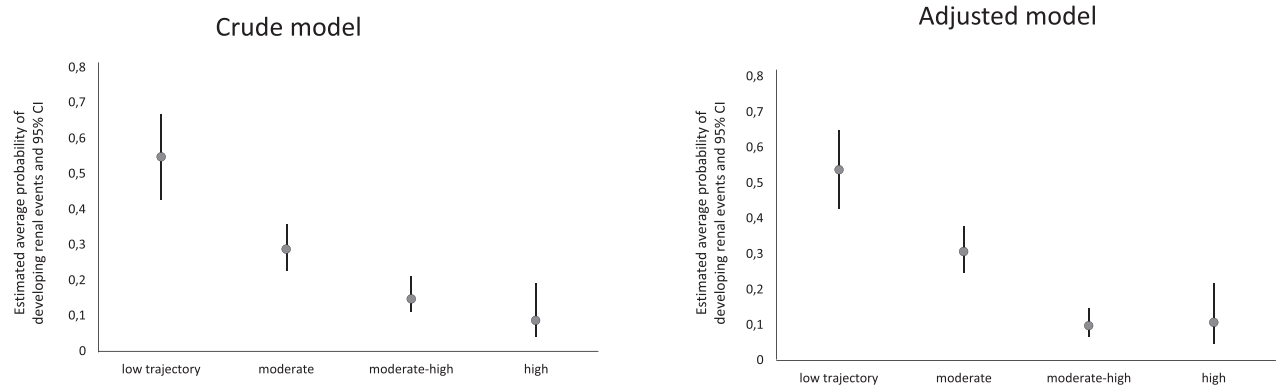

Figure 2: The crude and adjusted estimated average probability of developing renal events and 95% CIs in numerical and graphic terms. The adjusted model's data were adjusted for age, gender, systolic BP, haemoglobin, albumin, phosphate, PTH, 24-h proteinuria and eGFR.

Cohort, patients in the lowest tertile of venous total CO_2 had an increased risk of fast GFR decline but not kidney failure [8]. In the Atherosclerosis Risk in Communities Study (ARIC), individuals with a higher dietary acid load had a higher risk for incident CKD over 21 years of follow-up [9]. Finally, in a very large retrospective cohort study in >50 000 stage G3–5 CKD patients from Optum's deidentified integrated electronic health records, bicarbonate measured at baseline was linearly associated with a composite outcome including a ≥40% decline in eGFR, renal replacement therapy (chronic dialysis or kidney transplant) or all-cause mortality [10]. Even though these studies coherently support the hypothesis that metabolic acidosis promotes kidney damage and accelerates kidney function loss, it must be remarked that, with the notable exception of the CRIC study [12], they measured bicarbonate or CO_2 only at baseline and did not contemplate repeated measurements of these biomarkers over time. The approach restricting the measurement of the exposure at a single point in time is crude and many investigators seek to use alternative methods that might better capture long-term risk factor exposure, termed life course analysis, which we will comment on later on.

As to clinical trials, in a recent meta-analysis based on 15 trials, a 47% risk reduction for adverse renal outcomes by bicarbonate supplementation was registered [13]. However, among these trials, five were poor quality and six were just intermediate quality. Furthermore, only six were placebo controlled, and among these, all but one were negative, and the overall risk reduction by bicarbonate in these trials failed to achieve statistical significance.

With the lack of adequately powered, high-quality, randomised trials, longitudinal studies provide provisionally important information [24]. Among life course analysis approaches to longitudinal studies, some capture cumulative exposure, such as pack-years of cigarettes for smoking and lung cancer. Still, the assumption that the incidence rate is proportional to the total lifetime dose is questionable [25]. Other life course models extract features for standard regression approaches, such as a given change in the exposure variable over time. Mixed effects modelling is a more sophisticated approach that considers within-individual correlations, but this is difficult to interpret for public health implementation. One novel method of this family of techniques is the GBTM analysis, a method in the family of latent class growth analysis techniques [14]. This method allows the identification of latent subgroups within a population that exhibit distinct patterns over time. This can provide valuable insights into the underlying heterogeneity in the data, which may not be apparent through traditional statistical methods. GBTM is particularly well-suited for analysing longitudinal data collected over multiple time points and shows how different groups change over time, enabling a deeper understanding of life course trajectories. Furthermore, GBTM offers several model selection and validation approaches, such as the BIC and bootstrap likelihood ratio tests [14].

The present study is the first to apply GBTM analysis for analysing the relationship between longitudinal venous bicarbonate measurements and kidney outcomes. This method identified four distinct venous bicarbonate evolution patterns, i.e. low, moderate, moderate-high and high trajectories. Notably, we found that in our cohort there was a highly significant dose–response risk reduction among serum bicarbonate trajectories and the predefined composite renal endpoint. This substantial risk reduction highlights the potential benefits of maintaining higher bicarbonate levels in CKD patients. However, it is essential to acknowledge that longitudinal studies, including studies based on GBTM, are inherently limited in establishing causality. Therefore the results should be interpreted cautiously and used as a basis for further research. Our findings emphasise the need for well-designed, adequately powered randomised controlled trials to investigate the effects of bicarbonate supplementation or other pharmacologic interventions that could increase bicarbonate. A randomised trial enrolling 1600 patients to test the effect on CKD progression of veverimer, a novel polymeric hydrochloric acid binder, will be completed in 3 years [26].

In conclusion, this longitudinal study showed an inverse relationship between bicarbonate levels and CKD patients' risk of renal events. These findings call for well-powered, randomised controlled trials to further explore the effects of bicarbonate supplementation or pharmacologic interventions that increase bicarbonate. Addressing this research gap is crucial for improving the management of CKD and reducing the risk of adverse kidney outcomes.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

C.Z. conceived the idea of this study. C.Z., G.D. and G.T. designed the analytical plan. G.D., M.G. and G.T. conducted the statistical analyses. D.L. and F.M. were the coordinator and the supervisor, respectively, of the MAURO study. C.Z. and G.D. prepared the draft that was then revised according to the suggestions of the other authors. All authors approved the final version.

DATA AVAILABILITY STATEMENT

The data reported in this study will be made available to interested investigators from the sixth to the twelfth month after the publication of this study.

CONFLICT OF INTEREST STATEMENT

C.Z. is a member of the *CKJ* editorial board. No conflicts of interest are related to this paper as for the remaining co-authors.

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