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Association of Serum Bicarbonate With Risk of Renal and Cardiovascular Outcomes in CKD: A Report From the Chronic Renal Insufficiency Cohort (CRIC) Study

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Abstract

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Background—The purpose of this study is to evaluate serum bicarbonate as a risk factor for renal outcomes, cardiovascular events and mortality in patients with chronic kidney disease (CKD).

Study Design—Observational cohort study.

Setting & Participants—3939 participants with CKD stages 2-4 who enrolled in the Chronic Renal Insufficiency Cohort (CRIC) between June 2003 - December 2008.

Predictor—Serum bicarbonate.

Outcomes—Renal outcomes, defined as end-stage renal disease (either initiation of dialysis or kidney transplantation) or 50% reduction in eGFR; atherosclerotic events (myocardial infarction, stroke, peripheral arterial disease); congestive heart failure events; and death.

Measurements—Time to event.

Results—The mean eGFR was 44.8 ± 16.8 (SD) mL/min/1.73 m^2, and the median serum bicarbonate was 24 (IQR, 22-26) mEq/L. During a median follow-up of 3.9 years, 374 participants died, 767 had a renal outcome, and 332 experienced an atherosclerotic event and 391 had a congestive heart failure event. In adjusted analyses, the risk of developing a renal endpoint was 3% lower per mEq/L increase in serum bicarbonate (HR, 0.97; 95% CI, 0.94-0.99; p=0.01). The association was stronger for participants with eGFR> 45ml/min/1.73m^2 (HR, 0.91; 95%CI, 0.85-0.97; p=0.004). The risk of heart failure increased by 14% (HR, 1.14; 95%CI, 1.03-1.26; p=0.02) per mEq/L increase in serum bicarbonate over 24 mEq/L. Serum bicarbonate was not independently associated with atherosclerotic events (HR, 0.99; 95%CI, 0.95-1.03; p=0.6) and all-cause mortality (HR, 0.98; 95%CI, 0.95-1.02; p=0.3).

Limitations—Single measurement of sodium bicarbonate.

Conclusions—In a cohort of participants with CKD, low serum bicarbonate was an independent risk factor for kidney disease progression, particularly for participants with preserved kidney function. The risk of heart failure was higher at the upper extreme of serum bicarbonate. There was no association between serum bicarbonate and all-cause mortality or atherosclerotic events.

Keywords

metabolic acidosis; serum bicarbonate; chronic kidney disease; cardiovascular morbidity

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Epidemiologic studies have shown that low bicarbonate levels are more common in patients with lower estimated glomerular filtration rate (eGFR); 19% of patients with stages 4-5 chronic kidney disease (CKD), have a serum bicarbonate less than 22 mEq/L.[1] Metabolic acidosis is an attribute of CKD because of the kidney's reduced capacity to synthesize ammonia and excrete hydrogen ions.[2] Experimental evidence suggests that metabolic acidosis contributes to progression of CKD,[1, 3, 4] but there is limited clinical evidence to support these observations. Observational studies have shown that serum bicarbonate levels are associated with renal outcomes and mortality, with optimal bicarbonate levels in the range of 24-26 mEq/L.[5-9] However, these studies were done in relatively selected patient populations (primarily non-diabetic[7, 9], primarily male[5], and small number of CKD patients[6]) limiting the ability to generalize to the overall CKD patient population. Importantly, none of these studies evaluated the association between serum bicarbonate levels and cardiovascular events. Given that supplementation of bicarbonate is already recommended in patients with bicarbonate levels <22 mEq/L by current guidelines[10] and clinical trials are being proposed using bicarbonate supplementation, it is critical to understand the epidemiologic association between serum bicarbonate levels and outcomes in a broader CKD population.

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The Chronic Renal Insufficiency Cohort (CRIC) is an observational longitudinal study of patients with CKD.[11] The large and diverse cohort of participants with CKD in CRIC allowed the opportunity to thoroughly evaluate the relationship between serum bicarbonate and outcomes while overcoming the limitations of previous epidemiologic studies. The purpose of this paper is to evaluate serum bicarbonate level as a predictor of renal outcomes, cardiovascular events, and mortality in a large cohort of subjects with CKD.

METHODS

Study Population

The CRIC study is a multicenter, prospective observational study of risk factors for cardiovascular disease, progression of chronic kidney disease, and mortality. The design, methods, and baseline characteristic of the CRIC study have been previously published.[11] Briefly, 3939 individuals aged 21 to 74 years with an eGFR between 20-70 mL/min/1.73m^2 were enrolled from June 2003-December 2008 at seven clinical centers (Ann Arbor, Michigan; Baltimore, Maryland; Chicago, Illinois; Cleveland, Ohio; New Orleans, Louisiana; Philadelphia, Pennsylvania; and Oakland, California). Exclusion criteria included inability to consent, institutionalization, enrollment in other studies, pregnancy, New York Heart Association class III-IV heart failure, human immunodeficiency virus, cirrhosis, myeloma, polycystic kidney disease, renal cancer, recent chemotherapy or immunosuppressive therapy, organ transplantation, or prior treatment with dialysis for at least 1 month. The protocol was approved by the Institutional Review Board at each study site, and participants provided written informed consent.

Data Collection

Clinical data were collected at the baseline visit by interview and questionnaire. Laboratory tests of blood and urine were measured at a central laboratory using standard assays.

The primary exposure was serum bicarbonate level performed at study entry and measured using an enzymatic procedure with phosphoenolpyruvate carboxylase on the Ortho Vitros platform at the University of Pennsylvania Core Laboratory. Thirty five participants had missing serum bicarbonate levels at baseline and were excluded from this study.

Glomerular filtration rate was assessed by the CRIC-GFR equation, a CRIC internal GFR estimating equation validated against 125-Iothalamate clearance testing that uses serum creatinine, cystatin C levels, age, sex, and race.[12] CKD was defined according to the current guidelines as follows: stage 2 CKD (kidney damage with mild decrease in eGFR [60-89mL/min/1.73m^2]), stage 3a CKD (eGFR, 45-59mL/min/1.73m^2), stage 3a CKD (eGFR, 30-44mL/min/1.73m^2), and stage 4 CKD (eGFR, 15-29mL/min/1.73m^2). We used a GFR of 45mL/min/1.73m^2 to separate participants with mild disease versus those with more advanced CKD.

Outcome Measures

The outcomes of interests were as follows: renal outcomes (50% reduction in eGFR or end-stage renal disease [initiation of either dialysis or kidney transplantation]), adverse cardiovascular atherosclerotic events (definite or probable myocardial infarction, stroke or peripheral arterial disease), congestive heart failure events, and overall mortality. Cardiovascular events were adjudicated by blinded reviewers. Participants were followed up until the occurrence of death, voluntary withdrawal from the study, or June 30, 2009, when the database was locked for analysis. The median follow-up time was 3.9 years.

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Statistical Analysis

We used descriptive statistics to compare clinical characteristics according to baseline serum bicarbonate levels by quartiles using Chi-square and ANOVA tests for categorical and continuous variables respectively.

Multivariable Cox proportional hazards models were used to model the time to death, ESRD, first atherosclerotic event and congestive heart failure event. Death was treated as a censoring event when it was not part of the outcome. Quadratic splines[13] were used to explore potential non-linearity between serum bicarbonate and the outcomes of interest. While there was a clear non-linear relationship between serum bicarbonate and heart failure events, there was an obvious linear relationship with atherosclerotic cardiovascular events, renal outcomes and mortality. Therefore a single linear term of serum bicarbonate was used in the models for end-stage renal disease or 50% decline in eGFR, atherosclerotic cardiovascular events and mortality. Additionally, a linear spline with a clinically relevant knot for serum bicarbonate at 24mEq/L was used in the model for heart failure events. Covariates adjusted in the models included demographic factors (age, sex, race/ethnicity), kidney function (eGFR and 24 hour urine protein excretion), traditional cardiovascular risk factors (systolic blood pressure, body mass index, diabetes, smoking, low-density lipoprotein cholesterol, prior history of coronary artery disease, congestive heart failure, stroke, and peripheral vascular disease) and the use of cardio-protective and reno-protective medications (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, diuretics), and levels of mineral metabolites (fibroblast growth factor 23). All models were also adjusted for clinical centers as a covariate to capture confounding at center level. In the model for renal outcome, quadratic splines of eGFR and 24 hour urine protein excretion were used to allow flexible relationships with outcome to reduce residual confounding since they are the two strongest predictors of renal outcome. Proportional hazards assumption was met based on cumulative Martingale residuals.[14] Approximately 9.4% of participants had missing covariate information and were excluded from the final analyses. Compared to participants included in the final analysis, participants excluded due to missing covariates data were not significantly different at baseline. Results are expressed as adjusted hazards ratios (HRs) with 95% confidence interval (CI).

We conducted analyses to look for interactions by race, diabetes, eGFR and proteinuria for death and renal outcomes and by diuretic use for cardiovascular outcomes. Because cardiovascular disease is closely correlated with mortality and recurrence of cardiovascular events, a secondary analysis was performed to evaluate the risk of cardiovascular events in participants without cardiovascular disease at baseline. All data analyses were conducted using SAS version 9.3 (SAS Institute Inc, Cary, NC). All statistical tests were 2-sided, and *P* values <0.05 were considered significant.

RESULTS

Baseline Characteristics

Baseline characteristics are presented in Table 1 for the entire cohort and stratified by quartile of serum bicarbonate. The mean age was 58 ± 11 (standard deviation) years, 1763 (45.2%) were female, 1895 (48.5%) were diabetic and 1631 (41.8%) were African-American. The mean bicarbonate level was 24.4 ± 3.2 mEq/L (median, 24 mEq/L; interquartile range, 22-26 mEq/L). One hundred ninety-five participants (5%) had a bicarbonate level at or below 19 mEq/L. At study entry, the mean eGFR was 44.8 ± 16.8 mL/min/1.73m^2. When stratified by quartiles of baseline serum bicarbonate levels, there were significant differences in age, race, diabetes, smoking, LDL and HDL cholesterol, diuretic and statin use, clinical site and laboratory data directly related to CKD progression:

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phosphorus, PTH, albumin, hemoglobin, FGF-23, eGFR and proteinuria. Participants in the lowest quartile were more likely to be Hispanic, smokers, with diabetes, having lower LDL and HDL cholesterol, and taking fewer diuretics. As expected, those participants had heavier proteinuria, reduced eGFR, higher phosphorus, PTH, FGF-23 and lower hemoglobin and albuminuria (Table 1). during the study follow-up, Three hundred and seventy four (24/1000 person-years) died, 767 participants (61/1000 person-years) had a renal outcome, 332 participants (23/1000 person-years) had an atherosclerotic event, and 391 participants (28/1000 person-years) had a congestive heart failure event (Figure 1).

Association of Serum Bicarbonate With Renal Outcomes

Participants in the lowest quartile of serum bicarbonate (10.3/1000 person-years) were at greater risk for development of the composite renal endpoint (progression to ESRD or 50% decline in eGFR) compared to the highest quartile (3.6/1000 person-years) (Figure 1). After adjustment for covariates including eGFR and proteinuria, serum bicarbonate level was independently associated with the development of renal outcomes (HR, 0.97 per mEq/L increase in bicarbonate; 95%CI, 0.94-0.99; p=0.01) (Table 2).

The associations between serum bicarbonate levels and renal outcomes were stronger in participants with eGFR>45 ml/min/1.73 m^2 and urine protein ≤0.2 g/24h (Figure 2). The subgroup of participants with eGFR>45 ml/min/1.73 m^2 had a 9% risk reduction in renal disease progression with each mEq/L increase in bicarbonate (adjusted HR, 0.91; 95% CI, 0.85-0.97; p=0.005). The subgroup of participants with proteinuria ≤0.2 g/24h had a 10% risk reduction in kidney disease progression with each mEq/L increase in bicarbonate (adjusted HR, 0.90; 95% CI, 0.83 - 0.98; p=0.01. There were significant interactions of serum bicarbonate with proteinuria (p=0.002) and eGFR (p=0.01). There were no statistically significant interactions with diabetes or race (p=0.5 and p=0.4, respectively).

Association of Serum Bicarbonate With All-Cause Mortality

Unadjusted and multivariable adjusted HRs for overall mortality are presented in Table 2. Results stratified by race, diabetes, eGFR and proteinuria are presented in Figure 3. After adjustment for demographic characteristics, eGFR and other CKD specific risk factors, the association between serum bicarbonate and all cause mortality was not significant (HR, 0.98; 95%CI, 0.95-1.02; p = 0.3). The associations between serum bicarbonate levels and all-cause mortality were consistent when stratified by race, diabetes, eGFR and proteinuria (Figure 3). There were no significant interactions between serum bicarbonate and race (p=0.4), diabetes (p=0.08), eGFR (p=0.6), and proteinuria (p=0.8).

Association of Serum Bicarbonate With Cardiovascular Events

The adjusted quadratic spline model demonstrated a non-linear relationship between serum bicarbonate levels and heart failure outcome (Figure 4A). Additionally, we conducted a linear spline model with a clinically significant knot at 24 mEq/L and found that for every mEq/L increase in serum bicarbonate above 24 mEq/L, there was a 14% higher risk for heart failure (HR, 1.14; 95%CI, 1.03-1.26; p=0.02) (Table 2). The association between serum bicarbonate and heart failure outcome was stronger in a subset analysis of 2387 participants without cardiovascular disease at baseline (Figure 4B). For every mEq/L increase in serum bicarbonate above 24 mEq/L, there was a 22% higher risk for a heart failure (HR, 1.22; 95%CI, 1.02 - 1.47; p=0.03).

The association was not modified by the diuretic use (Table 3). There was no difference in participants taking a thiazide diuretic versus a loop diuretic or in participants taking a high (>=80 mg/d) versus low (<80 mg/d) dose of furosemide (data not shown).

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There was no association between serum bicarbonate and atherosclerotic cardiovascular events (HR, 0.99; 95%CI, 0.95 - 1.03; p=0.6).

Sensitivity Analyses

We conducted sensitivity analyses, to exclude 91 (2.4%) participants taking any form of alkali therapy (calcium citrate, magnesium citrate, potassium citrate, sodium bicarbonate, sodium lactate, sodium citrate, sodium acetate, tromethamine, and lactated potassium saline). The associations between serum bicarbonate and the outcomes of interest were unchanged. We further excluded participants with CAD at baseline and the results were unchanged.

DISCUSSION

In a cohort of participants with chronic kidney disease, low serum bicarbonate was an independent risk factor for kidney disease progression, particularly for participants with preserved kidney function. The risk of heart failure was higher at the upper extreme of serum bicarbonate. There was no statistically significant association between serum bicarbonate levels and all-cause mortality or atherosclerotic cardiovascular events. Serum bicarbonate was independently associated with renal outcomes, even after adjustments for eGFR and proteinuria, the strongest predictors of kidney function decline. Few other studies have demonstrated an association of serum bicarbonate with adverse renal outcomes. In a cohort of patients followed in a medical clinic, progression of kidney disease was higher in those with bicarbonate ≤22 mEq/L (HR, 1.54) compared to those with bicarbonate levels of 25-26 mEq/L.[6] However, only 9% of this cohort had CKD at baseline. In the Modification of Diet in Renal Disease (MDRD) Study, the patients in the lowest quartile of bicarbonate had a higher risk of kidney failure (HR, 2.22), all-cause mortality (HR, 1.39) and the composite of all cause mortality and kidney failure (HR, 1.36) compared to patients in the highest quartile.[7] However, these associations were rendered non-significant with adjustment for eGFR. In the African-American Study of Kidney Disease study there was a 7% reduction in eGFR events per each mEq/L increase in serum bicarbonate, but the study population included only non-diabetic African Americans patients with hypertensive nephrosclerosis.[9]

It is known from experimental studies that metabolic acidosis is associated with renal hypertrophy and hyperplasia in rats.[15] Additionally sodium bicarbonate supplementation decreases tubulo-interstitial injury and slows the decline in kidney function in rats.[16] Studies in humans showed that bicarbonate supplementation slows the progression of kidney disease and improves nutritional status in patients with CKD.[17, 18] Our study supports the finding that low serum bicarbonate level is a predictor of CKD progression. It is interesting to note that bicarbonate was a better predictor of renal outcomes in patients with preserved kidney function (i.e. higher eGFR and lower proteinuria) compared with those with more advanced kidney disease. This is consistent with other biomarkers such as FGF-23 that have been shown to be better predictors at higher levels of eGFR.[19] This may provide opportunities for risk stratification in patients with early CKD, particularly since the majority of CKD patients have stage 3 CKD.

To our knowledge, this is the first study to explore the association between serum bicarbonate and cardiovascular events in patients with CKD not on dialysis. We found that the relationship between serum bicarbonate and congestive heart failure was nonlinear; the risk of congestive heart failure was highest in participants with serum bicarbonate in the alkalotic range, and also trending higher with serum bicarbonate at the lower end of the range. This is similar to the relationship between bicarbonate and mortality in other studies.[5, 8] It is important to note that patients with New York Heart Association class III

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and IV heart failure were not enrolled in CRIC since pre-existing heart failure itself may be associated with metabolic alkalosis.[20] In fact, in our data, the association was stronger after excluding participants with cardiovascular disease at baseline. Since diuretic use may induce a contraction alkalosis, and may be a surrogate for underlying heart failure we stratified our analyses based on diuretic use and found that the relationship remained consistent (Table 3).

Metabolic acidosis, a common feature of CKD, may worsen malnutrition, and inflammation in patients with CKD.[21] Chronic inflammation commonly seen in patients with kidney disease may predispose to an increased rate of atherosclerotic disease in this population.[22] While the pathways that mediate the relationship between acidosis and cardiovascular disease are not fully understood, recent mechanistic studies indicate that acidosis is associated with increased endothelin and aldosterone levels which may result in decreased GFR.[23] Though not specifically studied, it is reasonable to speculate that elevated levels of these biomarkers may also increase the cardiovascular risk.

On the other hand, the consequences of metabolic alkalosis include effects on the myocardium, central nervous system, and skeletal muscle.[24] Experimental studies looking at the effects of alkalosis on the regulation of cardiac myocytes showed that alkalosis activates specific cell kinases, which in turn, modify proteins that regulate gene transcription and cell survival.[25] The high risk of heart failure events observed at high serum bicarbonate could potentially be explained by the effect of alkalosis on regulatory proteins. Additionally, this could also be explained by subclinical congestive heart failure with respiratory acidosis and compensatory metabolic alkalosis that then manifests as admissions for CHF during follow up. Our data highlights the importance of serum bicarbonate as a risk factor for congestive heart failure in CKD, and support the need for additional studies to understand the pathophysiology of this association.

The association between serum bicarbonate and mortality was not statistically significant (p=0.3). Two recently published studies have looked at this association,[7, 8] but there were however significant differences in the patient populations between CRIC and the above mentioned studies. Compared to the MDRD Study,[7] which excluded patients with diabetes, nearly half of our population was diabetic. Diabetes in itself is a cardiovascular risk equivalent and could influence the interaction between serum bicarbonate and mortality. Naveneethan et al.[8] examined only patients with CKD stage 3 and 4, while the CRIC participants were chosen to reflect a larger CKD spectrum with a fair representation of minorities. In a cohort of 1240 male veterans, serum bicarbonate had a significant U-shaped association with all-cause mortality, with the highest mortality rate seen in individuals with baseline serum bicarbonate levels <22 mEq/L and the lowest mortality seen in persons with baseline serum bicarbonate of 26-29mEq/L.[5] In a dialysis patient population, there was also a U-shaped relationship between predialysis bicarbonate levels and mortality and hospitalization.[26]

The strength of our study lays in the robust prospective design of a well defined CKD cohort that overcomes the main limitations of previous cohorts: mostly non-diabetic[7], all male[5], non-CKD patients[6]; and bias and inability to adjust for confounding in retrospective studies[8]. To our knowledge, this is the first paper evaluating the association between bicarbonate and nonfatal cardiovascular endpoints. Additionally, we analyzed a large number of patients, with a long term follow-up, detailed adjudications of cardiovascular events, mortality and renal outcomes.

Nevertheless, there are some important limitations. As an observational study, this study is able to document the risk for these outcomes; however, this cannot necessarily prove causation, or provide detailed mechanistic pathways that may mediate the link between

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bicarbonate levels and outcomes. Furthermore, the dose of bicarbonate supplements used was unknown and we could not adjust for the acidogenic phosphate binder Sevelamer hydrochloride, which causes low serum bicarbonate and related adverse effects. However less than 7% of our population was on a phosphate binder. The diagnosis of heart failure was made using standard algorithms based on clinical, imaging and laboratory data; while these are validated in the general population,[27] they have not been validated for heart failure in the setting of CKD. Finally, these analyses report a single measurement of serum bicarbonate to predict follow-up events; whether changes in bicarbonate levels over time add incremental predictive value will need further study.

In the context of the current literature, our study supports the concept of using serum bicarbonate levels to identify patients with high risk for cardiovascular events and kidney disease progression. In addition, this epidemiologic association provides support to the notion that bicarbonate may be used as a therapeutic target to slow decline in kidney function. However, our demonstration of the association between high bicarbonate levels and heart failure may influence the dose and level of acidosis correction that clinical trials should aim to achieve. Future mechanistic studies are needed to understand the relationship between bicarbonate levels and outcomes.

In a cohort of participants with CKD stages 2 to 4, low serum bicarbonate was an independent risk factor for renal disease progression, particularly for participants with preserved kidney function. The risk of heart failure events was higher at the upper extreme of serum bicarbonate. The association between serum bicarbonate and all-cause mortality was not significant.

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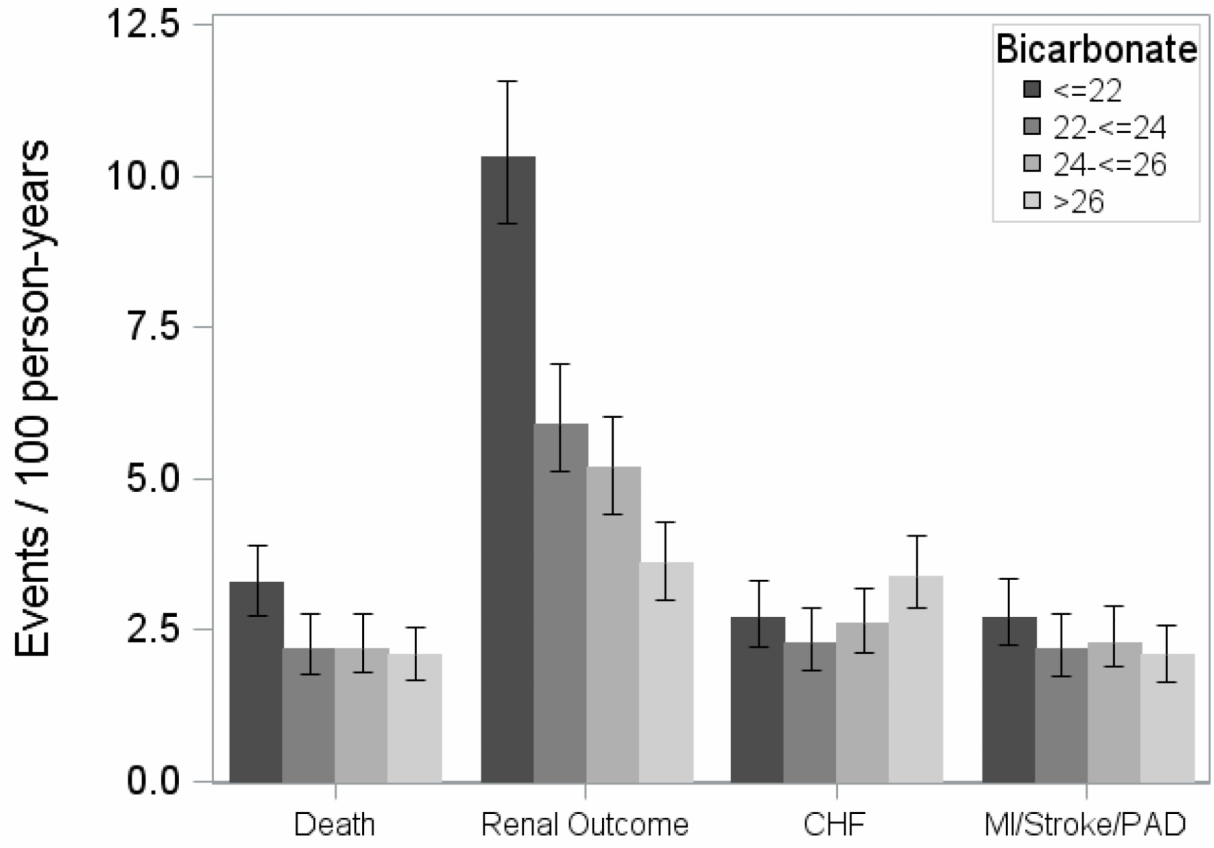

Figure 1.
Unadjusted event rates by quartile of serum bicarbonate (mEq/L).

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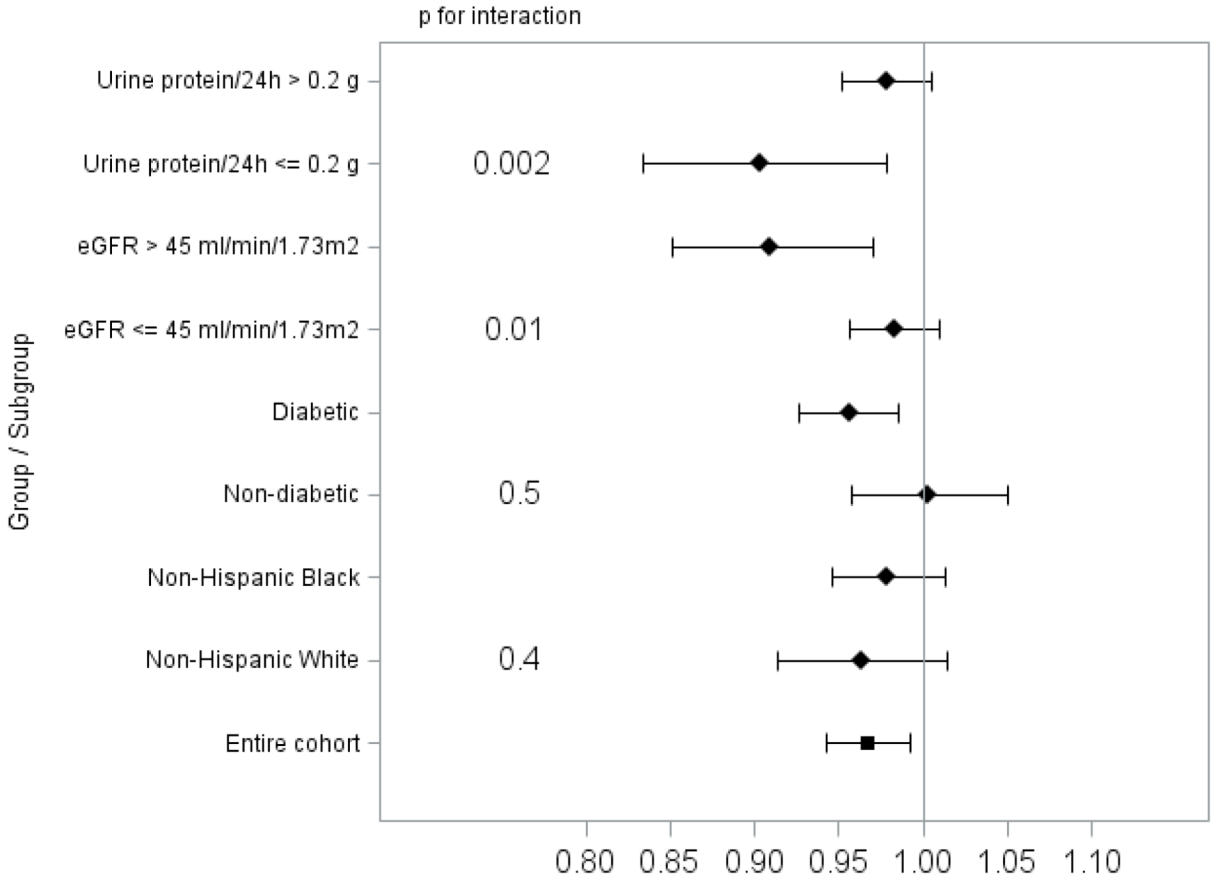

Figure 2.
Serum bicarbonate and risk of renal disease in subgroups defined by race, diabetes, eGFR and urine protein.

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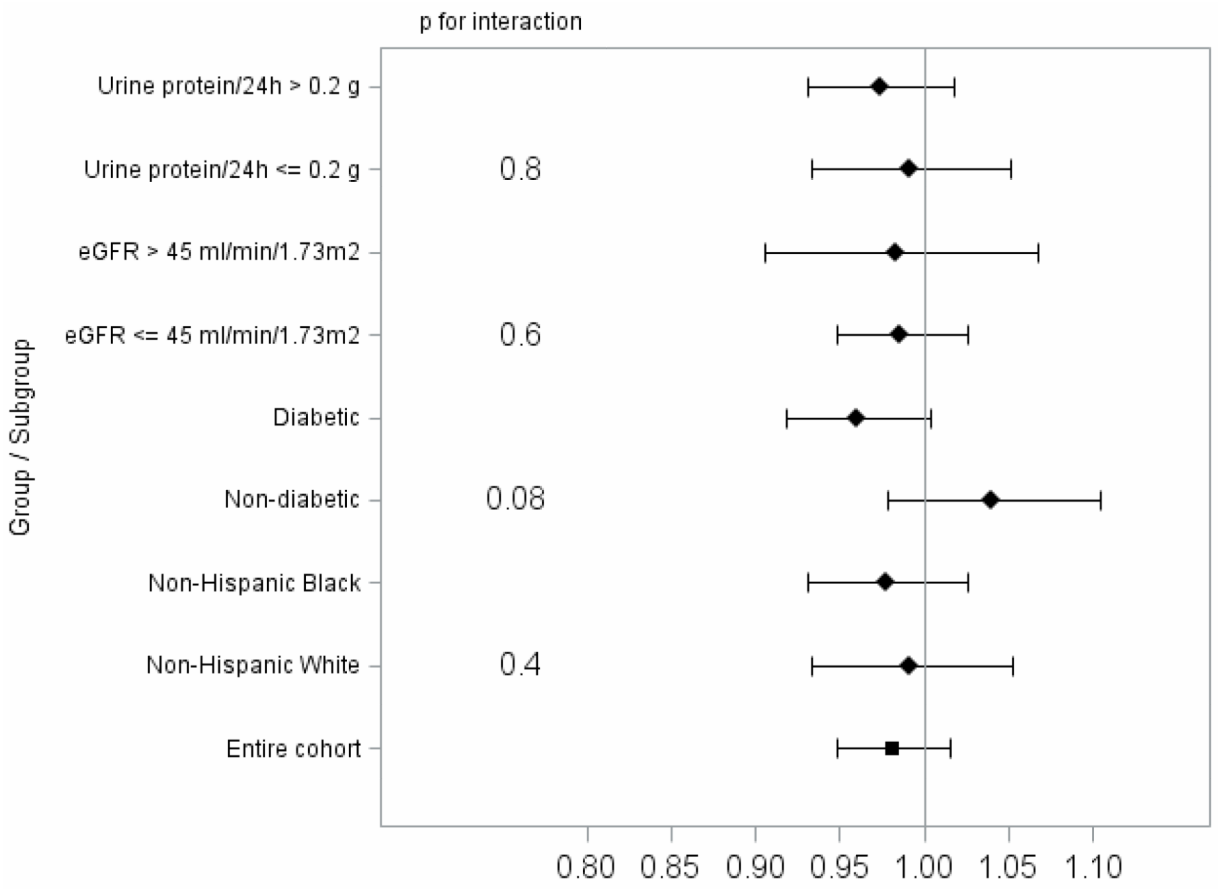

Figure 3.
Serum bicarbonate and risk of death in subgroups defined by race, diabetes, eGFR and urine protein excretion.

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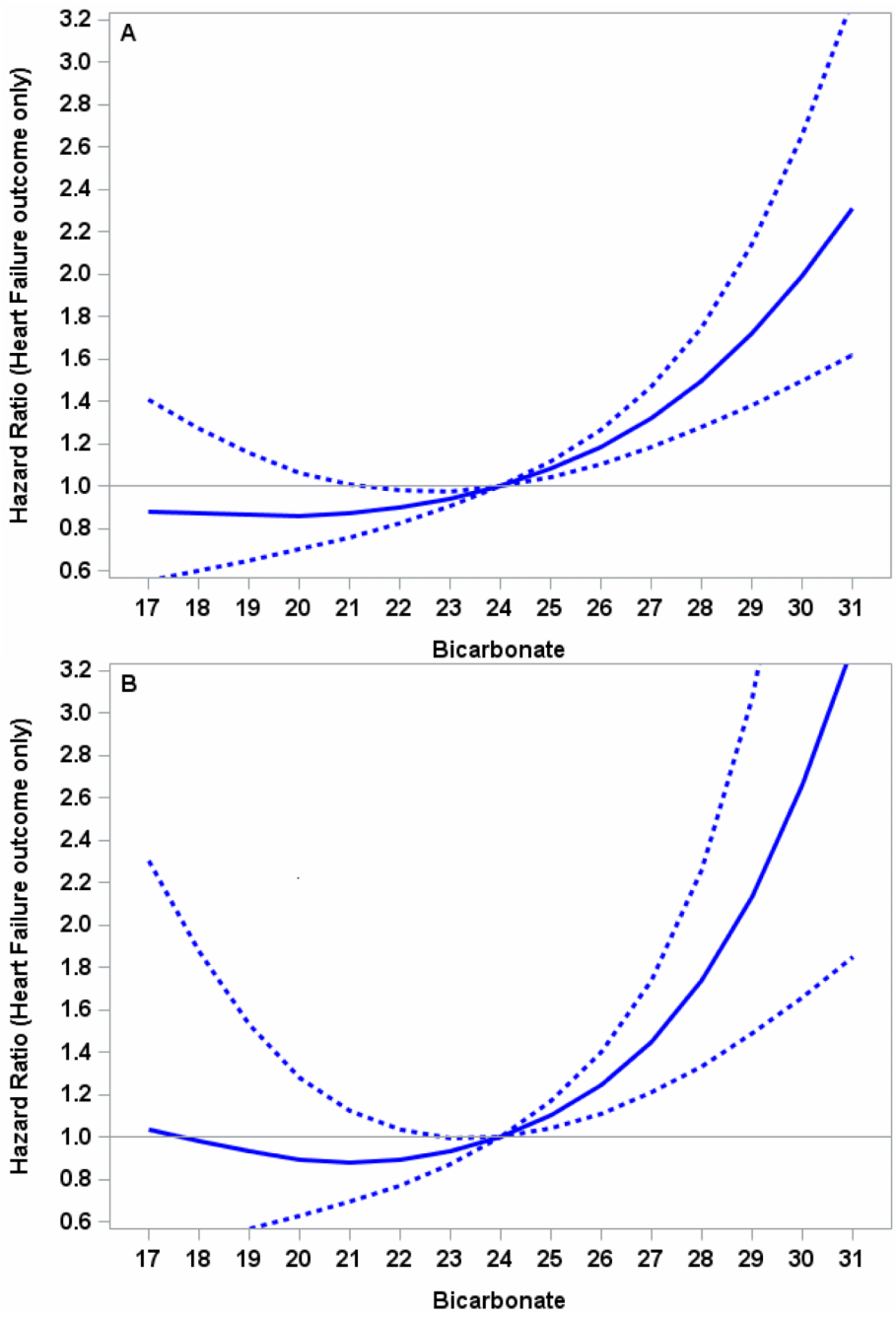

Figure 4.

Association between serum bicarbonate (mEq/L) and heart failure events (Panel A and B)
Panel A. Adjusted quadratic spline model for heart failure events
Panel B. Adjusted quadratic spline model for heart failure events excluding participants with cardiovascular disease at baseline.
The solid line represents the effect and the dashed lines represent the confidence intervals. There was a trend toward a “U shape” association between serum bicarbonate and heart failure events, though it only reached statistical significance for participants with serum bicarbonate in the alkalotic range.

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Am J Kidney Dis. Author manuscript; available in PMC 2014 October 01.

Table 1

Baseline Characteristics of All Participants and According to Quartiles of Serum Bicarbonate

Characteristic	All Participants (N=3904)	Quartiles of Serum Bicarbonate				p value
		≤22 mEq/L (n=1039)	23-24 mEq/L (n=924)	25-26 mEq/L (n=968)	>26 mEq/L (n=973)	
Serum bicarbonate (mEq/L)	24.4 ± 3.2	20.4 ± 1.8	23.5 ± 0.5	25.5 ± 0.5	28.4 ± 1.5	
Demographic and anthropometric data						
Age (y)	58.2 ±11.0	57.0 ±11.9	57.8 ±11.1	58.5 ±10.8	59.6 ±9.9	<0.001
Female sex	1763 (45.2)	440 (42.3)	427 (46.2)	444 (45.9)	452 (46.5)	0.2
Black	1631 (41.8)	400 (38.5)	367 (39.7)	400 (41.3)	464 (47.7)	<0.001
Hispanic	495 (12.7)	217 (20.9)	119 (12.9)	100 (10.3)	59 (6.1)	<0.001
Hypertension	3360 (86.1)	913 (87.9)	796 (86.1)	829 (85.6)	822 (84.5)	0.2
Diabetes	1895 (48.5)	556 (53.5)	437 (47.3)	447 (46.2)	455 (46.8)	0.003
Coronary artery disease	854 (21.9)	221 (21.3)	199 (21.5)	207 (21.4)	227 (23.3)	0.7
Any cardiovascular disease	1303 (33.4)	346 (33.3)	300 (32.5)	322 (33.3)	335 (34.4)	0.8
Current smoking	508 (13.0)	178 (17.1)	142 (15.4)	97 (10.0)	91 (9.4)	<0.001
COPD	121 (3.2)	29 (2.8)	28 (3.1)	26 (2.7)	38 (4.0)	0.4
Body Mass Index (kg/m^2)	32.1 ±7.8	31.7 ±7.4	32.4 ±8.3	31.8 ±7.5	32.5 ±8.0	0.06
Systolic blood pressure (mmHg)	128.5 ±22.2	129.4 ±21.9	127.9 ±21.9	128.3 ±22.5	128.5 ±22.5	0.5
Diastolic blood pressure (mmHg)	71.5 ±12.8	71.3 ±12.5	71.5 ±12.8	72.0 ±12.9	71.4 ±13.2	0.6
Medication use						
Aspirin	166 2(42.9)	421 (40.7)	394 (43.0)	410 (42.7)	437 (45.3)	0.2
β-Blockers	1913 (49.3)	519 (50.1)	433 (47.2)	461 (48)	500 (51.9)	0.2
Statins	2136(55.1)	608 (58.7)	47 8(52.1)	525 (54.6)	525 (54.5)	0.03
ACEi/ARBs	2668 (68.8)	735 (71)	642 (70.0)	649 (67.5)	642 (66.6)	0.1
Alkali therapy[#]	91 (2.4)	28 (2.7)	20 (2.2)	18 (1.9)	25 (2.6)	0.6
Any diuretic	2309 (59.6)	584 (56.4)	509 (55.5)	580 (60.4)	636 (66)	<0.001
Laboratory data						
CRIC eGFR (ml/min/1.73m^2)	44.8 ±16.8	37.3 ±14.7±	45.04 ±16.8	47.4 ±16.6	50.0 ±16.4	<0.001

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Characteristic	All Participants (N=3904)	Quartiles of Serum Bicarbonate				p value
		≤22 mEq/L (n=1039)	23-24 mEq/L (n=924)	25-26 mEq/L (n=968)	>26 mEq/L (n=973)	
Creatinine (mg/dL)	1.74 ±0.6	2.03 ±0.7	1.72 ±0.5	1.64 ±0.5	1.57 ±0.5	<0.001
24-h Urine protein (g/24 h)	1.07 ±2.3	1.55 ±2.9	1.08 ±2.2	0.9 ±2.0	0.75 ±2.0	<0.001
UACR ratio (mg/g)	644.6 ±1596.0	919.2 ±1881.9	673.5 ±1733.5	535.2 ±1356.5	434.7 ±1277.8	<0.001
Calcium (mg/dL)	9.2 ±0.5	9.2 ± 0.5	9.2 ± 0.5	9.2 ±0.5	9.2 ± 0.5	0.08
Phosphorus (mg/dL)	3.7 ±0.7	3.9 ±0.7	3.7 ±0.7	3.6 ± 0.6	3.6 ± 0.6	<0.001
Parathyroid Hormone (pg/ml)	75.2 ±71.5	95.6 ± 94.9	72.9 ± 61.8	68.8 ± 59.3	61.9 ± 55.9	<0.001
Albumin (g/dL)	3.94 ± 0.5	3.89 ± 0.5	3.93 ± 0.5	3.97 ± 0.4	3.95 ± 0.4	0.002
Hemoglobin (g/dL)	12.6 ±1.8	12.2 ± 1.8	12.6 ± 1.8	12.8 ±1.7	12.9 ± 1.7	<0.001
FGF-23 (RU/ml)	233.5 ± 463.7	281.0 ±523.2	240.8 ± 431.4	223.6 ± 580.5	185.5 ± 232.6	<0.001
High-sensitivity CRP (mg/L)	5.6 ± 9.8	5.8 ±10.9	5.9 ± 10.4	5.5 ± 9.6	5.1 ±8.0	0.2
Dietary protein (g/kg/d)	0.8 ± 0.4	0.8 ± 0.4	0.8 ± 0.4	0.8 ±0.4	0.8 ± 0.4	0.3
Urine urea nitrogen (g/24 h)	8.6 ±4.5	8.3 ± 4.3	8.7 ±4.4	8.7 ±4.6	8.7 ±4.5	0.1
LDL cholesterol(mg/dL)	102.8 ±35.6	98.7 ±36.6	103.9 ±36.5	103.9 ±34.7	105.0 ±34.4	<0.001
HDL cholesterol(mg/dL)	47.5 ±15.5	44.5 ±13.8	47.3 ±15.8	48.3 ±15.2	50.2 ±16.6	<0.001
CRIC Clinical Center						<0.001
Clinical Center 1	538 (13.8)	161 (15.5)	143 (15.5)	128 (13.2)	106 (10.9)	
Clinical Center 2	551 (14.1)	86 (8.3)	122 (13.2)	153 (15.8)	190 (19.5)	
Clinical Center 3	531 (13.6)	120 (11.5)	105 (11.4)	137 (14.2)	169 (17.4)	
Clinical Center 4	398 (10.2)	79 (7.6)	92 (10.0)	102 (10.5)	125 (12.8)	
Clinical Center 5	842 (21.6)	355 (34.2)	216 (23.4)	167 (17.3)	104 (10.7)	
Clinical Center 6	541 (13.9)	146 (14.1)	141 (15.3)	135 (13.9)	119 (12.2)	
Clinical Center 7	503 (12.9)	92 (8.9)	105 (11.4)	146 (15.1)	160 (16.4)	

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation.

Conversion factors for units: creatinine in mg/dL to μmol/L, ×88.4; HDL and LDL cholesterol in mg/dL to mmol/L, ×0.02586; phosphorus in mg/dL to mmol/L, ×0.3229; calcium in mg/dL to mmol/L, ×0.2495.

COPD, Chronic Obstructive Pulmonary Disease; CRIC, Chronic Renal Insufficiency Cohort (study); CRIC eGFR = estimated glomerular filtration rate based on the CRIC equation[12] ; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRP, C-reactive protein; UACR, urinary albumin-creatinine ratio; FGF, fibroblast growth factor.

[#]Alkali therapy was represented by: calcium citrate, magnesium citrate, potassium citrate, sodium bicarbonate, sodium lactate, sodium citrate, sodium acetate, tromethamine, and lactated potassium saline.

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Table 2

Serum bicarbonate and risks of kidney disease progression, cardiovascular diseases, and death

	Unadjusted Model		Adjusted Model	
	HR (95% CI)	p value	HR (95% CI)	p value
ESRD or 50% decline in eGFR *	0.88 (0.86 - 0.90)	<0.001	0.97 (0.94-0.99)	0.01
Death **	0.94 (0.91 - 0.97)	<0.001	0.98 (0.95-1.02)	0.3
Atherosclerotic events ***,1	0.96 (0.93 - 1.00)	0.03	0.99 (0.95 - 1.03)	0.6
Heart Failure ***, 2				
Serum Bicarbonate <24 mEq/L	0.96 (0.90 - 1.02)	0.2	1.00 (0.93 - 1.08)	0.9
Serum Bicarbonate ≥24 mEq/L	1.14 (1.04 - 1.25)	0.007	1.14 (1.03 - 1.26)	0.02

Note: Per 1 mEq/L increase in serum bicarbonate.

CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MI = myocardial infarction; PAD = peripheral arterial disease. ESRD, end-stage renal disease.

*Model adjusted for age, sex, race and ethnicity, clinical center, eGFR, proteinuria, systolic blood pressure, chronic obstructive pulmonary disease, diabetes at baseline, smoking, diuretic use, Angiotensin Convertin Enzyme/Angiotensine Receptor Blocker, fibroblast growth factor 23 and alkali therapy (calcium citrate, magnesium citrate, potassium citrate, sodium bicarbonate, sodium lactate, sodium citrate, sodium acetate, tromethamine, and lactated potassium saline).

**Model adjusted for age, sex, race and ethnicity, clinical center, eGFR, proteinuria, systolic blood pressure, chronic obstructive pulmonary disease, cardiovascular disease, diabetes at baseline, smoking, diuretic, Angiotensin-Converting Enzyme/Angiotensin Receptor Blocker, and alkali therapy (calcium citrate, magnesium citrate, potassium citrate, sodium bicarbonate, sodium lactate, sodium citrate, sodium acetate, tromethamine, and lactated potassium saline).

***Model adjusted for age, sex, race and ethnicity, clinical center, eGFR, proteinuria, systolic blood pressure, body mass index, chronic obstructive pulmonary disease and diabetes at baseline, smoking, low density lipoprotein cholesterol, and diuretic use and alkali therapy (calcium citrate, magnesium citrate, potassium citrate, sodium bicarbonate, sodium lactate, sodium citrate, sodium acetate, tromethamine, and lactated potassium saline).

1Atherosclerotic events were represented by myocardial infarction, stroke and peripheral arterial disease.

2Results from linear spline model with knot at 24 mEq/L.

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Table 3
Serum bicarbonate and risk of cardiovascular disease in subgroups

	Unadjusted Model		Adjusted Model *	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Heart Failure **				
No prior cardiovascular disease				
Serum Bicarbonate <24 mEq/L	0.94 (0.85 - 1.05)	0.3	0.98 (0.87 - 1.11)	0.8
Serum Bicarbonate ≥24 mEq/L	1.18 (1.01 - 1.38)	0.04	1.22 (1.02 - 1.47)	0.03
Not receiving diuretics #				
Serum Bicarbonate <24 mEq/L	0.85 (0.76 - 0.95)	0.004	0.95 (0.82 - 1.10)	0.5
Serum Bicarbonate ≥24 mEq/L	1.28 (1.03 - 1.59)	0.02	1.16 (0.90 - 1.51)	0.2
Receiving diuretics				
Serum Bicarbonate <24 mEq/L	1.00 (0.92 - 1.07)	0.9	1.03 (0.95 - 1.12)	0.4
Serum Bicarbonate ≥24 mEq/L	1.07 (0.96 - 1.20)	0.2	1.10 (0.98 - 1.24)	0.1
Atherosclerotic events ***				
No prior cardiovascular disease	0.95 (0.90 - 1.00)	0.06	1.00 (0.94 - 1.06)	0.9
Not receiving diuretics ^	0.90 (0.85 - 0.96)	<0.001	0.96 (0.90 - 1.02)	0.2
Receiving diuretics	0.98 (0.95 - 1.02)	0.4	1.01 (0.96 - 1.05)	0.8

Note: Per mEq/L increase in bicarbonate.

CI = confidence interval; HR = hazard ratio.

* Model adjusted for age, sex, race and ethnicity, clinical center, estimated glomerular filtration rate, proteinuria, systolic blood pressure, body mass index, chronic obstructive pulmonary disease and diabetes at baseline, smoking, low density lipoprotein cholesterol, and diuretic use and alkali therapy (calcium citrate, magnesium citrate, potassium citrate, sodium bicarbonate, sodium lactate, sodium citrate, sodium acetate, tromethamine, and lactated potassium saline).

** Results from linear spline model with knot at 24 mEq/L.

*** Atherosclerotic events were represented by myocardial infarction, stroke and peripheral arterial disease.

p-value for interaction test = 0.5;

^ p-value for interaction test = 0.2.