Metabolic Acidosis and Cardiovascular Disease in CKD

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Rationale & Objective: Metabolic acidosis related to chronic kidney disease (CKD) is associated with an accelerated decline in glomerular filtration rate (GFR) and the development of end-stage kidney disease. Whether metabolic acidosis is associated with cardiovascular (CV) events in patients with CKD is unclear.

Study Design: Retrospective cohort study.

Setting & Participants: The Optum De-identified Electronic Health Records Dataset, 2007–2017, was used to generate a cohort of patients with non-dialysis-dependent CKD who had at least 3 estimated GFR < 60 mL/min/1.73 m^2. Patients with metabolic acidosis (serum bicarbonate 12 to <22 mEq/L) or normal serum bicarbonate (22–29 mEq/L) at baseline were identified by 2 consecutive measurements 28–365 days apart.

Predictor: Serum bicarbonate as a continuous variable.

Outcome: Primary outcome was a composite of major adverse cardiovascular events (MACE+). Secondary outcomes included individual components of the composite outcome.

Analytical Approach: Cox proportional hazards models to evaluate the association between 1-mEq/L increments in serum bicarbonate and MACE+.

Results: A total of 51,558 patients were evaluated, 34% had metabolic acidosis. The median follow-up period was 3.9–4.5 years, depending on the outcome assessed. The adjusted hazard ratio (HR) for MACE+ was 0.964 (95% CI, 0.961–0.968). For the individual components of incident heart failure (HF), stroke, myocardial infarction (MI), and CV death, HRs were 0.98 (95% CI, 0.97–0.98), 0.98 (95% CI, 0.97–0.99), 0.96 (95% CI, 0.96–0.97), and 0.94 (95% CI, 0.93–0.94), respectively, for every 1-mEq/L increase in serum bicarbonate.

Limitations: Possible residual confounding.

Conclusions: Metabolic acidosis in CKD is associated with an increased risk of MACE+ as well as the individual components of incident HF, stroke, MI, and CV death. Randomized controlled trials evaluating treatments for the correction of metabolic acidosis in CKD to prevent CV events are needed.

Visual Abstract included

Complete author and article information provided before references.

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Cardiovascular events are the leading cause of death among patients with chronic kidney disease (CKD). In a study of over 1 million patients with CKD, the risk of cardiovascular events, defined as hospitalization for coronary artery disease, heart failure (HF), and ischemic stroke, increased progressively with advancing CKD stage.[1] The high burden of cardiovascular disease in this population reflects traditional cardiovascular risk factors as well CKD-specific risk factors.[2]

Metabolic acidosis is common in later-stage CKD because of the metabolism of dietary protein, generation of nonvolatile acids, and impaired net acid excretion.[3,4] The prevalence of metabolic acidosis, defined by a reduced serum bicarbonate level, increases as glomerular filtration rate (GFR) decreases.[5,6] Both the decrease in serum bicarbonate and net acid excretion in CKD are associated with an accelerated decline in GFR and end-stage kidney disease (ESKD) in addition to adverse musculoskeletal effects and increased mortality.[7-12] Metabolic acidosis is postulated to be a CKD-specific cardiovascular risk factor because of its negative effects on the cardiovascular system, including inflammation and activation of the renin-angiotensin-aldosterone system (RAAS).[13-15]

Prior studies have not clearly elucidated an effect of metabolic acidosis on the risk of cardiovascular events.[7,16-19] However, these observational studies were limited by their size, number of events, incomplete adjustment of covariates, and included cohorts with and without baseline cardiovascular disease. We report the findings of a large, observational, retrospective, community-based cohort study of over 51,000 adults with stages 3–5 CKD to examine the association of metabolic acidosis with HF and major adverse cardiovascular events.

METHODS

Study Design and Data Sources

This was an observational, retrospective cohort study of US patients with CKD and serum bicarbonate measurements who had at least 2 years of longitudinal follow-up observation or who died during the 2-year period. Data from January 1, 2007, to March 31, 2017, was extracted from the Optum EHR+Integrated Electronic Health Record (EHR) dataset, which is deidentified in compliance with the Health Insurance Portability and Accountability Act (HIPAA). This database is a longitudinal clinical repository that includes 81 million insured and uninsured patients from large health care providers in all 50 US states and Puerto Rico. Data elements were derived from inpatient and outpatient EHRs and administrative systems, including laboratory results, medication prescriptions, coded diagnoses and procedures,

PLAIN-LANGUAGE SUMMARY

The retention of acid in patients with kidney disease related to diet and reduced kidney function (known as "metabolic acidosis") is associated with both a faster loss of kidney function and kidney failure (dialysis or kidney transplant). Whether metabolic acidosis is harmful to the heart and brain is unknown. In this study of over 50,000 patients with kidney disease not on dialysis from the United States over a 10-year period, metabolic acidosis was associated with an increased risk of heart failure, stroke, heart attack, and death, independent of other risk factors for these negative outcomes. Studies evaluating new drugs to correct metabolic acidosis and reduce heart disease in patients with kidney disease are needed.

and provider notes extracted by natural language processing. Data cleaning by investigators included application of validity parameters to reported laboratory values (Table S1). Neither informed consent nor institutional review board approval was required as the study accesses deidentified information in compliance with HIPAA regulations and requirements.

Study Cohort

For inclusion in the initial database extract, patients were required to have at least 3 estimated GFR (eGFR) results < 60 mL/min/1.73 m^2 and at least 3 serum bicarbonate results, with at least 1 result between 12 and 29 mEq/L and at least 1 year of EHR activity. For entry into the study cohort, patients were required to have 2 consecutive valid serum bicarbonate results between 28 and 365 days apart, both between either 12 and <22 mEq/L (metabolic acidosis) or 22 and 29 mEq/L (normal per laboratory reference ranges). The first of the 2 values was considered the baseline serum bicarbonate level, and the date of the test was considered the index date. Serum bicarbonate and eGFR values collected during hospital inpatient admissions or emergency department visits with a concurrent diagnosis code of acute kidney injury (Table S1) were excluded because these may have represented acute events. In addition, patients were required to have at least 1 year of preindex EHR activity (eg, clinic visit, health care facility encounter, or laboratory test), and at least 2 years of postindex activity, unless the patient died within this 2-year period.

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[20] Baseline eGFR was defined as the mean of eGFR values from the 90 days preceding the last eGFR test on or before the index date. Patients who had evidence of long-term dialysis or kidney transplantation at baseline (diagnosis or procedure code, or outpatient eGFR result ≤10 mEq/L; Table S1) were excluded. We created analysis groups for specific outcomes that excluded patients with a history of those outcomes.

To ensure enough patients with decreased serum bicarbonate levels, an iterative patient selection algorithm was used to oversample patients with metabolic acidosis. Specifically, the selection algorithm examined records starting after 1 year of patient activity and initially searched for a qualifying pair of consecutive bicarbonate values between 12 and <22 mEq/L before examining bicarbonate values between 22 and 29 mEq/L.

Variables

The primary predictor was baseline serum bicarbonate. Information regarding the use of specific serum bicarbonate assays was not available, but they likely varied depending on local laboratory practices. Baseline serum bicarbonate was treated as a continuous variable. Demographic and clinical variables known or hypothesized to be associated with cardiovascular events were assessed at the index date and included age, sex, race, diabetes mellitus (DM), hypertension, heart failure, coronary artery disease (CAD), peripheral vascular disease (PVD), comorbidity burden as measured by the Charlson Comorbidity Index (CCI),[21] and baseline eGFR, hemoglobin, and serum albumin values. Individuals born in 1928 or earlier were assigned 1928 as their birth year to ensure HIPAA compliance. Comorbidities were defined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes according to the US Renal Data System definitions.[22] Baseline comorbidities were assessed by single occurrence of diagnosis codes and used all available data before the index date. Complete variable definitions are provided in Table S1.

Outcomes

The primary outcome was a composite of major adverse cardiovascular events (MACE+), defined as myocardial infarction (MI), ischemic stroke, incident heart failure (a new heart failure diagnosis in a patient without evidence of heart failure at baseline), heart failure admission (an inpatient admission with a concurrent diagnosis of heart failure in patients with a history of heart failure), or cardiovascular death (death within the same or next calendar month as discharge from an inpatient hospital stay involving a diagnosis code for heart failure, stroke, or MI). Secondary outcomes of incident heart failure, stroke, MI, and cardiovascular death were analyzed individually. All outcomes were identified using ICD-9-CM and ICD-10-CM diagnosis codes in all available postindex data (Table S2). Patients were excluded from analysis of secondary outcomes as follows: from incident heart failure if they had a history of heart failure before the index date and from stroke or MI analyses if they had any diagnosis code for stroke or MI, respectively, for 12 months before the index date.

Statistical Analysis

Patient characteristics were compared at baseline between the metabolic acidosis versus normal serum bicarbonate groups using the χ^2 test, t test, or 2-tailed Wilcoxon rank-sum test, as appropriate. Multivariable Cox proportional hazards models were used to model the time to MACE+, incident heart failure, stroke, MI, and cardiovascular death in each group. Patients were censored at death or loss to follow-up (defined as the patient's last known interaction with the health system through end of data availability in March 2017), but not at the development of ESKD. Fine-Gray subdistribution hazards models were used to evaluate the competing risk of noncardiovascular death in the MACE+ model. All covariates were forced into the final multivariable models. Models were adjusted for age, sex, race, eGFR, DM, hypertension, CAD, PVD, hemoglobin, and serum albumin. The proportional hazards assumption was tested by plotting Schoenfeld residuals against time and visual inspection for uniformity. Patients with missing data for any independent variable were excluded from the analysis; missing data were only relevant for laboratory measurements. Unadjusted incidence rates of MACE+, incident heart failure, stroke, MI, and cardiovascular death were assessed over the 2-year period of required data and compared between patients with metabolic acidosis or normal serum bicarbonate at baseline by χ^2 tests.

All statistical analyses were performed using SAS/STAT software version 9.4 (SAS, Inc). $P < 0.05$ was considered statistically significant.

Additional Analyses

The effect of oversampling of patients with metabolic acidosis was evaluated by constructing alternative patient cohorts without oversampling, in which the effect of serum bicarbonate on MACE+ and the individual components of incident heart failure, stroke, and MI were evaluated in Cox proportional hazards models with the same predictors. We also considered a Cox proportional hazards model with additional adjustment for urinary albumin-to-creatinine ratio (UACR) at baseline (not included in the primary analysis because of the degree of missing data).

RESULTS

Study Population and Characteristics

Of 81 million patient records located in the Optum EHR+Integrated Electronic Health Record database, 319,126 met the criteria for inclusion in the database extract. From within this extract, we identified a study population of 51,558 patients who met the data sufficiency requirements, had stages 3–5 CKD and no indication of dialysis or transplant, and who qualified for inclusion in the metabolic acidosis group (n = 17,350) or normal serum bicarbonate group (n = 34,208) (Fig 1). Baseline demographics and clinical characteristics are presented for the overall study cohort (Table 1) and for the incident heart failure, stroke, and MI analysis groups separately (Table S3). Individuals with metabolic acidosis were younger (mean age, 70 vs 74 years) and more likely to be African American (15% vs 7%). They also had more advanced CKD (eGFR 37 vs 43 mL/min/1.73 m^2), a greater burden of comorbidities (CAD, DM, heart failure, hypertension, PVD), a higher comorbidity burden as measured by the CCI, and higher UACR (277 vs 127 mg/g). The median follow-up period was 3.9 years in the MACE+ model, 4.5 years in the heart failure model, and 4.3 years in the stroke and MI models. The laboratory values missing in metabolic acidosis group versus normal serum bicarbonate group were UACR (22% vs 46%), serum albumin (12% vs 26%), and hemoglobin (4% vs 17%).

Primary Outcome

Of the entire study population, 24,873 (48%) experienced a MACE+ event within 2 years; metabolic acidosis at baseline was associated with a higher rate of MACE+ events (58% vs 44% (Fig 2). In the Cox proportional hazards model, every 1-mEq/L increase in serum bicarbonate was associated with a 4% decrease in the risk of MACE+ events (adjusted hazard ratio [HR], 0.96 [95% CI, 0.96–0.97]) (Table 2). The Fine-Gray model using the same covariates and including noncardiovascular death as a competing risk showed similar results (HR, 0.98 [95% CI, 0.98-0.99]) (Table S4). Over up to 10 years, 32,526 patients experienced a MACE+ outcome (161 events per 1,000 patient-years).

Secondary Outcomes

The 2-year unadjusted incidence rates of incident heart failure, stroke, MI, and cardiovascular death in patients with metabolic acidosis versus patients with normal serum bicarbonate were 30% versus 23%, 20% versus 17%, 17% versus 12%, and 13% versus 5%, respectively (all $P < 0.001$) (Fig 2). In the Cox proportional hazards models, the adjusted hazard ratios for incident heart failure, stroke, MI, and cardiovascular death were 0.98 (95% CI, 0.97–0.98), 0.98 (95% CI, 0.97–0.99), 0.96 (95% CI, 0.96–0.97), and 0.94 (95% CI, 0.93–0.94), respectively (Table 2), with a risk reduction of 2%, 2%, 4%, and 6%, respectively, for each 1-mEq/L increase in serum bicarbonate.

Additional Analyses

In the sensitivity analysis that did not include oversampling to identify metabolic acidosis, each 1-mEq/L increase in serum bicarbonate was associated with MACE+ and the secondary outcomes of stroke, and MI (all $P < 0.001$) but not incident heart failure ($P = 0.08$) (Table S5). In the sensitivity analysis controlling for UACR, the adjusted hazard ratio associated with a 1−mEq/L increase in serum bicarbonate was unchanged: 0.96 (95% CI, 0.96–0.97) (Table S6).

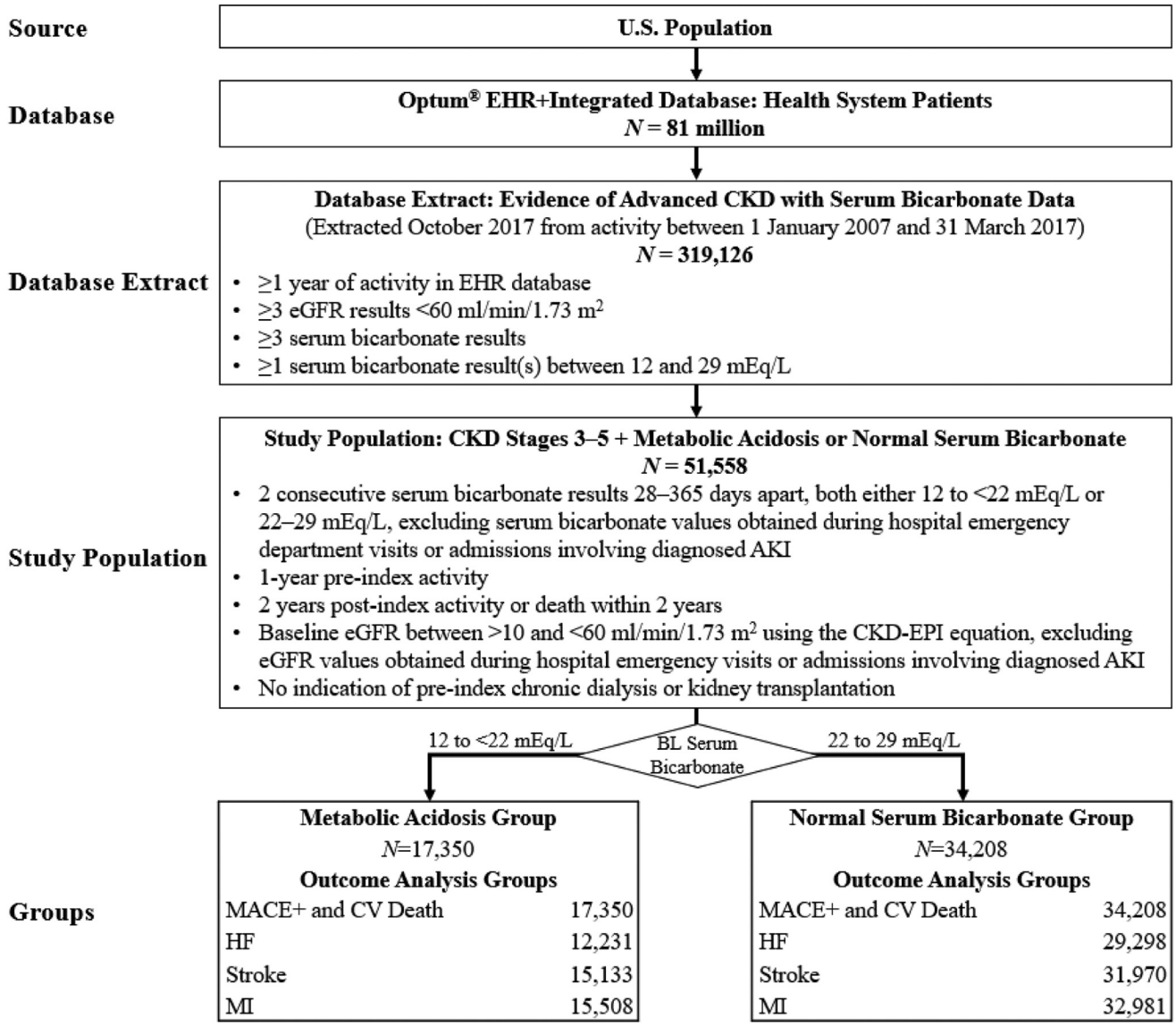

Figure 1. Study cohort selection diagram. MACE+ analysis group and cardiovascular death analysis group: n = 51,558; complete data, n = 36,917. Incident HF analysis group: n = 41,529, with 10,029 excluded; complete data, n = 28,817. Stroke analysis group: n = 47,103, with 4,455 excluded; complete data, n = 33,325. MI analysis group: n = 48,789, with 2,769 excluded; complete data, n = 34,573. Abbreviations: AKI, acute kidney injury; BL, baseline; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EHR, electronic health record; HF, heart failure; MACE+, major adverse cardiovascular event, defined as any MI, any stroke, incident HF (a new HF diagnosis in a patient without HF at baseline), or HF admission (an inpatient admission with a concurrent diagnosis of HF in a patient with comorbid HF at baseline), or cardiovascular death (death within the same or next calendar month as discharge from an inpatient hospital stay involving a diagnosis code for HF, stroke, or MI); MI, myocardial infarction.

DISCUSSION

In this large, retrospective cohort study of 51,558 patients with nondialysis stages 3–5 CKD, a higher serum bicarbonate value was independently associated with a reduced risk of incident heart failure, stroke, MI, and a composite that included cardiovascular death and heart failure admissions (MACE+), after adjustment for demographics, comorbidities, and laboratory values that included eGFR. Given the high cardiovascular event rates in the CKD population[1] and underdiagnosis and undertreatment of metabolic acidosis,[7,23] these findings suggest a potential opportunity for reduction in the risk of cardiovascular events.

Previous studies of patients with diabetes and heart failure demonstrated that metabolic acidosis was associated with an increased risk of cardiovascular events. In the Australian Fremantle Diabetes Study, lower serum bicarbonate levels were associated with an increased risk of

Table 1. Demographics and Clinical Characteristics of the Study Cohort

	Total Study Cohort (N = 51,558)	Metabolic Acidosis (n = 17,350)	Normal Serum Bicarbonate (n = 34,208)	*P* Value
Sex				
Female	27,094 (53%)	9,011 (52%)	18,083 (53%)	0.05
Male	24,464 (47%)	8,339 (48%)	16,125 (47%)	0.05
Age	72.9 ± 11.5	70.3 ± 13.3	74.3 ± 10.3	<0.001
Race				<0.001
African American	5,128 (10%)	2,585 (15%)	2,543 (7%)	<0.001
Asian	996 (2%)	398 (2%)	598 (2%)	<0.001
White	42,055 (82%)	12,866 (74%)	29,189 (85%)	<0.001
Other/Unknown	3,379 (7%)	1,501 (9%)	1,878 (5%)	<0.001
Region				<0.001
Midwest	30,683 (60%)	9,359 (54%)	21,324 (62%)	<0.001
Northeast	2,603 (5%)	1,175 (7%)	1,428 (4%)	<0.001
Other/Unknown	586 (1%)	227 (1%)	359 (1%)	0.01
South	14,107 (27%)	5,329 (31%)	8,778 (26%)	<0.001
West	3,579 (7%)	1,260 (7%)	2,319 (7%)	0.04
Baseline bicarbonate	24.0 ± 3.6	19.7 ± 1.1	26.1 ± 2.0	<0.001
Baseline eGFR, mL/min/1.73 m^2	41.2 ± 12.1	37.2 ± 13.3	43.2 ± 10.9	<0.001
CKD stage				
Stage 3a	22,431 (44%)	5,719 (33%)	16,712 (49%)	<0.001
Stage 3b	19,081 (37%)	5,987 (35%)	13,094 (38%)	<0.001
Stage 4	8,736 (17%)	4,747 (27%)	3,989 (12%)	<0.001
Stage 5, nondialysis	1,310 (3%)	897 (5%)	413 (1%)	<0.001
Comorbidities/conditions				
Hypertension	31,761 (62%)	12,879 (74%)	18,882 (55%)	<0.001
Diabetes	16,168 (31%)	7,391 (43%)	8,777 (26%)	<0.001
Coronary artery disease	14,329 (28%)	6,249 (36%)	8,080 (24%)	<0.001
Peripheral vascular disease	10,052 (19%)	5,038 (29%)	5,014 (15%)	<0.001
Heart failure	10,029 (19%)	5,119 (30%)	4,910 (14%)	<0.001
CCI	2.3 ± 2.7	3.5 ± 3.1	1.7 ± 2.3	<0.001
Additional baseline lab values				
UACR, mg/g	22 [9-81]	43 [9-315]	9 [9-81]	<0.001
Serum albumin, g/dL	3.7 ± 0.6	3.5 ± 0.7	3.9 ± 0.5	<0.001
Serum calcium, corrected, mg/dL	9.3 ± 0.6	9.3 ± 0.7	9.4 ± 0.5	<0.001
Hemoglobin, g/dL	12.2 ± 2	11.3 ± 2.1	12.6 ± 1.8	<0.001
Serum potassium, mEq/L	4.4 ± 0.6	4.5 ± 0.7	4.4 ± 0.5	<0.001

Values are presented as number (percentage), mean ± SD, or median [interquartile range]. UACR and other characteristics with non-normal distributions were assessed using the nonparametric Wilcoxon rank sum test. The reference race was White. Conversion factor for units: serum calcium in mg/dL to μmol/L, × 0.2495. Number of patients with data are reported for each test in Table S3C.

Abbreviations: CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SD, standard deviation; UACR, urinary albumin-creatinine ratio.

cardiovascular events.[24] In addition, data from a Korean heart failure registry showed that serum pH < 7.36 was associated with decreased 30-day and 1-year survival, and a decrease in serum bicarbonate (and not hypercapnia) was associated with mortality.[25] In a study of a healthy population without cardiovascular disease, metabolic alkalosis (not metabolic acidosis) was associated with an increase in incident heart failure but not cardiovascular events;[26] however, these findings may have been confounded by an increased need for diuretics among individuals with metabolic alkalosis.

To our knowledge, this is the largest observational study to date to report an association between metabolic acidosis in CKD and an increased risk of cardiovascular events, including heart failure, stroke, and MI. Previous studies in CKD populations have yielded inconsistent results regarding an association between metabolic acidosis and cardiovascular events,[7,16,18] likely due to several differences among studies, including study design, patient population, sample size, and length of follow-up. In a post hoc analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT) and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, there was no association between serum bicarbonate and adjudicated MI, stroke, coronary revascularization, or hospitalization for heart failure.[17] In the Chronic Renal Insufficiency Cohort (CRIC) study, adjudicated heart failure was more common in those with a serum bicarbonate level > 26 mEq/L (HR, 1.66 [95% CI, 1.22–2.33]; P < 0.001) but not

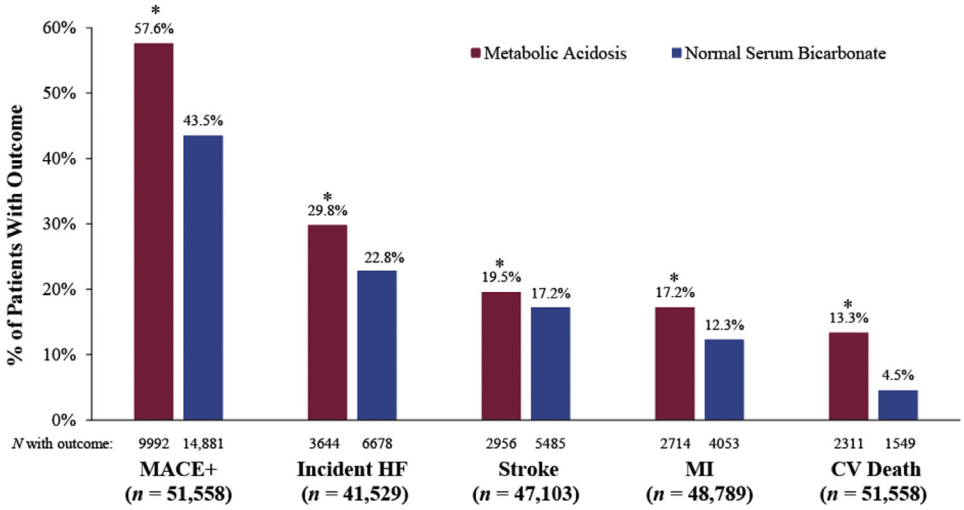

Figure 2. Unadjusted 2-year incidence rates of MACE+, incident heart failure, stroke, myocardial infarction, and cardiovascular death in the metabolic acidosis versus normal serum bicarbonate groups. Abbreviations: CV, cardiovascular; HF, heart failure; MACE+, major adverse cardiovascular event, defined as any MI, any stroke, incident HF (a new HF diagnosis in a patient without HF at baseline), or HF admission (an inpatient admission with a concurrent diagnosis of HF in a patient with comorbid HF at baseline), or CV death (death within the same or next calendar month as discharge from an inpatient hospital stay involving a diagnosis code for HF, stroke, or MI); MI, myocardial infarction. *$P < 0.001$ by χ^2 test.

in those with a serum bicarbonate level < 22 mEq/L, even after excluding those with alkali therapy, chronic obstructive pulmonary disease (COPD), or a history of cardiovascular disease. In the CRIC study, for every 1-mEq/L increase in serum bicarbonate level > 24 mEq/L, there was a 14% higher risk of heart failure (HR, 1.14 [95% CI, 1.03–1.26]),[7] but there was no difference in adjudicated MI, stroke, or PVD by acid-base status.[7,16] Our analysis differs from the CRIC study in that we excluded all patients with serum bicarbonate levels > 29 mEq/L because we were primarily interested in the risk associated with metabolic acidosis compared with patients with normal serum bicarbonate levels, and we did not want to include patients with respiratory acidosis and metabolic compensation. In a recent retrospective cohort study of kidney transplant recipients without cardiovascular events, a serum bicarbonate level < 20 mEq/L (but not < 22 mEq/L) was associated with an increased risk of cardiovascular events (HR, 2.00 [95% CI, 1.29–3.10]), which was driven by ischemic events (HR, 2.28 [95% CI, 1.34–3.90]) but not arrhythmic events or heart failure.[18] Our relative risks are smaller in magnitude but similar in direction, and may reflect differences in baseline cardiovascular risk profile of kidney transplant recipients.

The mechanism by which metabolic acidosis increases the risk of cardiovascular events is unclear. Metabolic acidosis is associated with inflammation,[10] which may contribute to endothelial dysfunction and an increased risk of cardiovascular events.[27,28] It is also associated with activation of the RAAS, as shown by elevated levels of aldosterone and endothelin,[13-15] which may contribute to kidney injury and heart failure.[29,30] In an open-label, placebo-controlled, pilot crossover trial examining the effect of oral sodium bicarbonate on vascular function in 20 patients with CKD and metabolic acidosis, sodium bicarbonate improved endothelial function as measured by brachial artery flow-mediated dilation.[31] Serum bicarbonate is associated with insulin resistance in CKD, as evidenced by a decrease in adiponectin production by adipocytes, which in turn is associated with cardiovascular events, as adipokines are potentially implicated in the pathogenesis of cardiovascular disease.[32-35] Adipokines are also implicated in the pathogenesis of heart failure via remodeling due to hypertrophy, fibrosis, and cell death.[36] Acidosis also decreases myocardial contractility and β-adrenergic response, but in the CRIC study metabolic acidosis did not correlate with left ventricular geometry, function, or relaxation.[37-39] Metabolic alkalosis, however, may be harmful because of increased precipitation of vascular calcification and activation of myoblast signaling pathways that influence cell survival.[40,41]

Although most patients with CKD are not currently treated for metabolic acidosis,[7,23] existing treatments may negate the potential cardiovascular benefits of treatment. For example, although treatment of metabolic acidosis with sodium bicarbonate reduces the rate of CKD progression, it has been associated with increased blood pressure and/or requirement for increased antihypertensive treatment in some studies.[42] Furthermore, the beneficial effects of RAAS blockade on cardiovascular outcomes in patients with CKD are negated by a high sodium intake.[43] Even though the recently conducted BASE trial did not show a change in blood pressure with sodium bicarbonate treatment, there was a dose-dependent increase in albuminuria, and the trial was conducted in a

Table 2. Factors Associated With MACE+ and Secondary Outcomes, up to 10 Years

Parameters	MACE+ (N = 36,917)[a]	Incident HF (N = 28,817)[a]	Stroke (N = 33,325)[a]	MI (N = 34,573)[a]	CV Death (N = 36,917)[a]
Age (per 1-year increase)	1.02 (1.02–1.02)	1.02 (1.02–1.02)	1.02 (1.02–1.02)	1.01 (1.01–1.01)	1.04 (1.04–1.04)
Male sex	1.04 (1.02–1.07)	1.05 (1.01–1.09)	0.97 (0.93–1.01)[b]	1.24 (1.18–1.29)	1.16 (1.10–1.22)
Ethnicity					
African American	1.29 (1.24–1.35)	1.28 (1.21–1.36)	1.27 (1.19–1.35)	1.12 (1.04–1.20)	1.31 (1.22–1.41)
Asian	0.63 (0.58–0.70)	0.64 (0.56–0.73)	0.71 (0.62–0.82)	0.66 (0.56–0.78)	0.38 (0.30–0.48)
Other race	0.890 (0.84–0.94)	0.96 (0.89–1.03)[b]	0.94 (0.86–1.01)[b]	0.68 (0.62–0.75)	0.78 (0.70–0.86)
eGFR (per 1-mL/min/1.73 m^2 increase)	1.00 (1.00–1.00)	0.99 (0.99–0.99)	1.00 (1.00–1.00)[b]	1.00 (0.99–1.00)	0.99 (0.99–0.99)
Serum bicarbonate (per 1-mEq/L increase)	0.96 (0.96–0.97)	0.98 (0.97–0.98)	0.98 (0.97–0.99)	0.96 (0.96–0.970)	0.94 (0.93–0.94)
Comorbidities					
Diabetes	1.20 (1.16–1.23)	1.22 (1.17–1.27)	1.11 (1.06–1.16)	1.16 (1.10–1.22)	1.18 (1.12–1.24)
HF	NA	NA	1.09 (1.03–1.15)	1.36 (1.28–1.44)	2.44 (2.30–2.58)
Hypertension	0.97 (0.94–1.00)	0.81 (0.78–0.85)	0.99 (0.94–1.04)[b]	0.75 (0.71–0.79)	0.84 (0.79–0.89)
CAD	2.05 (1.99–2.11)	1.53 (1.46–1.60)	1.29 (1.23–1.36)	2.56 (2.44–2.70)	1.30 (1.23–1.38)
PVD	1.31 (1.27–1.35)	1.12 (1.06–1.17)	1.29 (1.23–1.36)	1.15 (1.09–1.22)	1.34 (1.27–1.42)
Laboratory values					
Hemoglobin (per 1-g/dL increase)	0.98 (0.97–0.99)	0.95 (0.94–0.96)	1.01 (1.00–1.02)[b]	1.02 (1.01–1.04)	0.93 (0.92–0.94)
Serum albumin (per 1-g/dL increase)	0.81 (0.79–0.83)	0.73 (0.71–0.76)	0.91 (0.88–0.94)	0.82 (0.79–0.86)	0.69 (0.67–0.72)

Values are hazard ratio (95% confidence interval). The reference race was White. Individuals with baseline HF or with stroke or MI within the year preceding the index date were excluded from the incident HF, stroke, and MI analyses, respectively.
Abbreviations: CAD, coronary artery disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MACE+, major adverse cardiovascular event, defined as any MI, any stroke, incident HF (a new HF diagnosis in a patient without HF at baseline), or HF admission (an inpatient admission with a concurrent diagnosis of HF in a patient with comorbid HF at baseline), or CV death (death within the same or next calendar month as discharge from an inpatient hospital stay involving a diagnosis code for HF, stroke, or MI); MI, myocardial infarction; NA, not applicable; PVD, peripheral vascular disease.
[a]Reflects size of final analysis group subject to inclusion criteria and complete data requirement.
[b]Not statistically significant ($P \geq 0.05$).

nonacidotic population.[44] Novel treatments may avoid such trade-offs. For example, veverimer, a counterion-free, nonabsorbed polymer that selectively binds and removes hydrogen and chloride from the gastrointestinal tract, effectively corrected acidosis related to CKD compared with placebo and improved physical function and is currently being investigated in an ongoing trial for the slowing of CKD progression.[45-47]

The strengths of this study include its size, power, adjustment of most clinically relevant covariates, and generalizability given its diverse patient population. CKD and metabolic acidosis were both identified conservatively, with metabolic acidosis requiring consecutive abnormal laboratory results separated in time and CKD established by the mean of laboratory values over 3 months.

However, the study has several limitations. The requirement of a minimum of 28 days to establish a confirming index serum bicarbonate value introduces survival bias that investigators weighed against the risk of incorrectly identifying metabolic acidosis through the use of a single serum bicarbonate measurement. Comorbidities and outcomes were identified using ICD codes, but they have not been validated in this EHR.[48] Our analysis did not adjust for all factors that can influence both acid-base status and outcomes, including dietary intake (protein and fruits/vegetables[49,50]), respiratory disorders (other than COPD which is included in the CCI),[51] diuretics, and other covariates that may influence both serum bicarbonate and cardiovascular risk (eg, smoking, blood pressure,[52] and statins[53]). Metabolic acidosis was only assessed at baseline and was not modeled as a time-varying covariate, which does not reflect longitudinal CKD care (ie, GFR decline, treatment with diuretics, and oral alkali). Oversampling could have identified less severe or persistent metabolic acidosis, but this is not supported by the sensitivity analysis. Residual confounding is a concern because individuals with metabolic acidosis related to CKD may have a phenotype independently associated with cardiovascular events. Finally, ascertainment of serum bicarbonate may vary by laboratory and method of measurement and was not captured by blood gases, and as such there may be a risk of misclassification.

In conclusion, a lower serum bicarbonate level was associated with a higher risk of MACE+ in patients with CKD. Further research is needed to explain the mechanisms that drive the association between metabolic acidosis and cardiovascular events, and randomized controlled trials are needed to examine if the correction of acidosis in CKD improves cardiovascular morbidity and mortality.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Sources, measurements, and definitions.

Table S2: Comorbidity and outcome definitions by diagnosis code.

Table S3: (A) Patient characteristics by outcome analysis group. (B) Patients with lab values, analysis groups, N (%). (C) Patient with lab values, study cohort.

Table S4: Fine and Gray model of major adverse cardiovascular event (MACE+) outcome, using noncardiovascular death as the competing event (n = 36,917).

Table S5: Cox proportional hazard models from sensitivity analysis without oversampling.

Table S6: Sensitivity analyses: adding log urine ACR as covariate associated with major adverse cardiovascular event (MACE+) outcome.

ARTICLE INFORMATION

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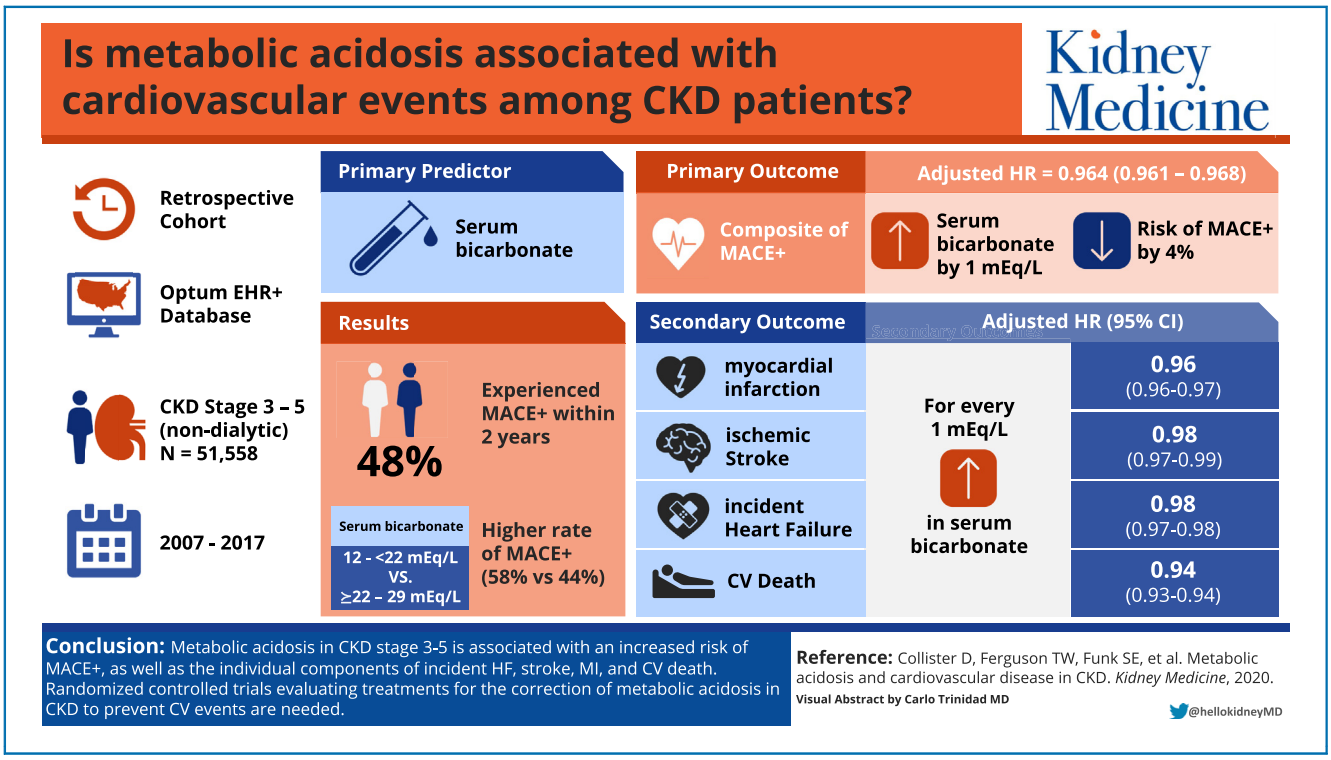
REFERENCES

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351(13):1296-1305.
2. Tonelli M, Karumanchi SA, Thadhani R. Epidemiology and mechanisms of uremia-related cardiovascular disease. *Circulation*. 2016;133(5):518-536.
3. Frassetto LA, Todd KM, Morris RC Jr, Sebastian A. Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. *Am J Clin Nutr*. 1998;68(3):576-583.
4. Scialla JJ, Appel LJ, Astor BC, et al. Estimated net endogenous acid production and serum bicarbonate in African Americans with chronic kidney disease. *Clin J Am Soc Nephrol*. 2011;6(7):1526-1532.
5. Inker LA, Coresh J, Levey AS, Tonelli M, Muntner P. Estimated GFR, albuminuria, and complications of chronic kidney disease. *J Am Soc Nephrol*. 2011;22(12):2322-2331.
6. Inker LA, Tonelli M, Hemmelgarn BR, Levitan EB, Muntner P. Comparison of concurrent complications of CKD by 2 risk categorization systems. *Am J Kidney Dis*. 2012;59(3):372-381.
7. Dobre M, Yang W, Chen J, et al. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: a report from the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis*. 2013;62(4):670-678.
8. Scialla JJ, Appel LJ, Astor BC, et al. Net endogenous acid production is associated with a faster decline in GFR in African Americans. *Kidney Int*. 2012;82(1):106-112.
9. Scialla JJ, Asplin J, Dobre M, et al. Higher net acid excretion is associated with a lower risk of kidney disease progression in patients with diabetes. *Kidney Int*. 2017;91(1):204-215.
10. Kraut JA, Madias NE. Adverse effects of the metabolic acidosis of chronic kidney disease. *Adv Chronic Kidney Dis*. 2017;24(5):289-297.
11. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. *Nephrol Dial Transplant*. 2009;24(4):1232-1237.
12. Navaneethan SD, Schold JD, Arrigain S, et al. Serum bicarbonate and mortality in stage 3 and stage 4 chronic kidney disease. *Clin J Am Soc Nephrol*. 2011;6(10):2395-2402.
13. Wesson DE, Simoni J. Acid retention during kidney failure induces endothelin and aldosterone production which lead to progressive GFR decline, a situation ameliorated by alkali diet. *Kidney Int*. 2010;78(11):1128-1135.
14. Wesson DE, Simoni J, Broglio K, Sheather S. Acid retention accompanies reduced GFR in humans and increases plasma levels of endothelin and aldosterone. *Am J Physiol Renal Physiol*. 2011;300(4):F830-F837.
15. Wesson DE, Jo CH, Simoni J. Angiotensin II receptors mediate increased distal nephron acidification caused by acid retention. *Kidney Int*. 2012;82(11):1184-1194.
16. Dobre M, Yang W, Pan Q, et al. Persistent high serum bicarbonate and the risk of heart failure in patients with chronic kidney disease (CKD): a report from the Chronic Renal Insufficiency Cohort (CRIC) Study. *J Am Heart Assoc*. 2015;4(4):e001599.
17. Schutte E, Lambers Heerspink HJ, Lutgers HL, et al. Serum bicarbonate and kidney disease progression and cardiovascular outcome in patients with diabetic nephropathy: a post hoc analysis of the RENAAL (Reduction of End Points in Non-Insulin-Dependent Diabetes With the Angiotensin II Antagonist Losartan) study and IDNT (Irbesartan Diabetic Nephropathy Trial). *Am J Kidney Dis*. 2015;66(3):450-458.
18. Djamali A, Singh T, Melamed ML, et al. Metabolic acidosis 1 year following kidney transplantation and subsequent cardiovascular events and mortality: an observational cohort study. *Am J Kidney Dis*. 2019;73(4):476-485.
19. Dobre M, Pajewski NM, Beddhu S, et al. Serum bicarbonate and cardiovascular events in hypertensive adults: results from

the Systolic Blood Pressure Intervention Trial. *Nephrol Dial Transplant*. 2020;35(8):1377-1384.
20. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367(1):20-29.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
22. United States Renal Data System. *USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2017.
23. Tangri N. Metabolic acidosis is underdiagnosed and undertreated in patients with CKD Poster presented at Kidney Week 2019 of the American Society of Nephrology; November 5-10; Washington DC. Poster FR-PO632. https://www.metabolicacidosisinsights.com/pdf/presentation-ma-underdiagnosed-and-undertreated-in-patients-with-ckd.pdf
24. Chubb SAP, Davis WA, Peters KE, Davis TM. Serum bicarbonate concentration and the risk of cardiovascular disease and death in type 2 diabetes: the Fremantle Diabetes Study. *Cardiovasc Diabetol*. 2016;15(1):143.
25. Park JJ, Choi DJ, Yoon CH, et al. The prognostic value of arterial blood gas analysis in high-risk acute heart failure patients: an analysis of the Korean Heart Failure (KorHF) registry. *Eur J Heart Fail*. 2015;17(6):601-611.
26. Kendrick JB, Zelnick L, Chonchol MB, et al. Serum bicarbonate is associated with heart failure in the multi-ethnic study of atherosclerosis. *Am J Nephrol*. 2017;45(2):118-126.
27. Recio-Mayoral A, Banerjee D, Streather C, Kaski JC. Endothelial dysfunction, inflammation and atherosclerosis in chronic kidney disease—a cross-sectional study of predialysis, dialysis and kidney-transplantation patients. *Atherosclerosis*. 2011;216(2):446-451.
28. Yilmaz MI, Stenvinkel P, Sonmez A, et al. Vascular health, systemic inflammation and progressive reduction in kidney function; clinical determinants and impact on cardiovascular outcomes. *Nephrol Dial Transplant*. 2011;26(11):3537-3543.
29. Deo R, Yang W, Khan AM, et al. Serum aldosterone and death, end-stage renal disease, and cardiovascular events in blacks and whites: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Hypertension*. 2014;64(1):103-110.
30. Kohan DE, Barton M. Endothelin and endothelin antagonists in chronic kidney disease. *Kidney Int*. 2014;86(5):896-904.
31. Kendrick J, Shah P, Andrews E, et al. Effect of treatment of metabolic acidosis on vascular endothelial function in patients with CKD: a pilot randomized cross-over study. *Clin J Am Soc Nephrol*. 2018;13(10):1463-1470.
32. Kobayashi S, Maesato K, Moriya H, Ohtake T, Ikeda T. Insulin resistance in patients with chronic kidney disease. *Am J Kidney Dis*. 2005;45(2):275-280.
33. Disthabanchong S, Niticharoenpong K, Radinahamed P, Stitchantrakul W, Ongphiphadhanakul B, Hongeng S. Metabolic acidosis lowers circulating adiponectin through inhibition of adiponectin gene transcription. *Nephrol Dial Transplant*. 2011;26(2):592-598.
34. Becker B, Kronenberg F, Kielstein JT, et al. Renal insulin resistance syndrome, adiponectin and cardiovascular events in patients with kidney disease: the mild and moderate kidney disease study. *J Am Soc Nephrol*. 2005;16(4):1091-1098.
35. Mechanick JI, Zhao S, Garvey WT. The Adipokine-Cardiovascular-Lifestyle Network: Translation to clinical practice. *J Am Coll Cardiol*. 2016;68(16):1785-1803.
36. Park M, Sweeney G. Direct effects of adipokines on the heart: focus on adiponectin. *Heart Fail Rev*. 2013;18(5):631-644.
37. Orchard CH, Kentish JC. Effects of changes of pH on the contractile function of cardiac muscle. *Am J Physiol*. 1990;258(6):C967-C981.
38. Schotola H, Toischer K, Popov AF, et al. Mild metabolic acidosis impairs the beta-adrenergic response in isolated human failing myocardium. *Crit Care*. 2012;16(4):R153.
39. Dobre M, Roy J, Tao K, et al. Serum bicarbonate and structural and functional cardiac abnormalities in chronic kidney disease—a report from the Chronic Renal Insufficiency Cohort Study. *Am J Nephrol*. 2016;43(6):411-420.
40. Mendoza FJ, Lopez I, Montes de Oca A, Perez J, Rodriguez M, Aguilera-Tejero E. Metabolic acidosis inhibits soft tissue calcification in uremic rats. *Kidney Int*. 2008;73(4):407-414.
41. Stathopoulou K, Beis I, Gaitanaki C. MAPK signaling pathways are needed for survival of H9c2 cardiac myoblasts under extracellular alkalosis. *Am J Physiol Heart Circ Physiol*. 2008;295(3):H1319-H1329.
42. Navaneethan SD, Shao J, Buysse J, Bushinsky DA. Effects of treatment of metabolic acidosis in CKD: a systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2019;14(7):1011-1020.
43. Lambers Heerspink HJ, Holtkamp FA, Parving HH, et al. Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. *Kidney Int*. 2012;82(3):330-337.
44. Raphael KL, Isakova T, Ix JH, et al. A randomized trial comparing the safety, adherence, and pharmacodynamics profiles of two doses of sodium bicarbonate in CKD: the BASE Pilot Trial. *J Am Soc Nephrol*. 2020;31(1):161-174.
45. Bushinsky DA, Hostetter T, Klaerner G, et al. Randomized, controlled trial of TRC101 to increase serum bicarbonate in patients with CKD. *Clin J Am Soc Nephrol*. 2018;13(1):26-35.
46. Wesson DE, Mathur V, Tangri N, et al. Veverimer versus placebo in patients with metabolic acidosis associated with chronic kidney disease: a multicentre, randomised, double-blind, controlled, phase 3 trial. *Lancet*. 2019;393(10179):1417-1427.
47. Wesson DE, Mathur V, Tangri N, et al. Long-term safety and efficacy of veverimer in patients with metabolic acidosis in chronic kidney disease: a multicentre, randomised, blinded, placebo-controlled, 40-week extension. *Lancet*. 2019;394(10196):396-406.
48. How good are the data? USRDS data validation special study. *Am J Kidney Dis*. 1992;20(5 Suppl 2):68-83.
49. Goraya N, Simoni J, Jo CH, Wesson DE. Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. *Kidney Int*. 2014;86(5):1031-1038.
50. Kelly JT, Palmer SC, Wai SN, et al. Healthy dietary patterns and risk of mortality and ESRD in CKD: a meta-analysis of cohort studies. *Clin J Am Soc Nephrol*. 2017;12(2):272-279.
51. Couchoud C, Bechade C, Bemrah A, Delaroziere JC, Jean G. Chronic respiratory disease: an unrecognized risk factor in dialysis. *Nephrol Dial Transplant*. 2017;32(12):2118-2125.
52. Sprint Research Group; Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373(22):2103-2116.
53. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377(9784):2181-2192.


Is metabolic acidosis associated with cardiovascular events among CKD patients?
Kidney Medicine
Retrospective Cohort
Optum EHR+ Database
CKD Stage 3 – 5 (non-dialytic) N = 51,558
2007 - 2017
Primary Predictor
Serum bicarbonate
Primary Outcome
Composite of MACE+
Adjusted HR = 0.964 (0.961 – 0.968)
Serum bicarbonate by 1 mEq/L
Risk of MACE+ by 4%
Results
48%
Experienced MACE+ within 2 years
Serum bicarbonate
12 - <22 mEq/L VS. ≥22 – 29 mEq/L
Higher rate of MACE+ (58% vs 44%)
Secondary Outcome
Adjusted HR (95% CI)
myocardial infarction
0.96 (0.96-0.97)
ischemic Stroke
0.98 (0.97-0.99)
incident Heart Failure
0.98 (0.97-0.98)
CV Death
0.94 (0.93-0.94)
For every 1 mEq/L
in serum bicarbonate
Conclusion: Metabolic acidosis in CKD stage 3-5 is associated with an increased risk of MACE+, as well as the individual components of incident HF, stroke, MI, and CV death. Randomized controlled trials evaluating treatments for the correction of metabolic acidosis in CKD to prevent CV events are needed.
Reference: Collister D, Ferguson TW, Funk SE, et al. Metabolic acidosis and cardiovascular disease in CKD. Kidney Medicine, 2020.
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