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Serum Bicarbonate is Associated with Heart Failure in the Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Background—Low serum bicarbonate concentrations are associated with mortality and kidney disease progression. Data regarding associations between bicarbonate and cardiovascular disease (CVD) are scarce.

Methods—We performed a cohort study of 6229 adult participants from MESA (Multi-Ethnic Study of Atherosclerosis), a community-based cohort free of CVD at baseline. Serum bicarbonate was measured at baseline. Cardiovascular outcomes were defined as: 1) subclinical CVD (left ventricular mass (LVM) and aortic pulse pressure (PP) measured at baseline), 2) incident atherosclerotic cardiovascular events (CVE) (composite of myocardial infarction, resuscitated cardiac arrest, stroke, coronary heart disease death and stroke death), and 3) incident heart failure.

Results—During a median (IQR) follow-up of 8.5 (7.7–8.6) years, 331 (5.3%) participants had an incident CVE and 174 (2.8%) developed incident heart failure. We stratified analyses by use of diuretics because we observed a significant interaction between diuretic use and bicarbonate with

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study outcomes. Among diuretic nonusers, with adjustment, bicarbonate ≥25 mEq/L was associated with an estimated 3.0 gram greater LVM (95% CI 0.5 to 5.0) and 1.0 mmHg higher aortic PP (95% CI 0.4 to 2.0) compared to bicarbonate 23–24 mEq/L. Each 1mEq/L higher bicarbonate was associated with a 13% higher risk of incident heart failure (HR 1.13, 95% CI 1.01 to 2.11). Among diuretic users, higher bicarbonate was not associated with CVD. Bicarbonate was not associated with incident atherosclerotic CVE irrespective of diuretic use.

Conclusion—Among nonusers of diuretics in a large community-based study, higher serum bicarbonate concentrations are associated with subclinical CVD and new heart failure.

Keywords

cardiovascular disease; bicarbonate; heart failure; arterial stiffness; left ventricular mass

Introduction

The leading cause of death in both men and women in the United States is cardiovascular disease (CVD). While interventions aimed at traditional cardiovascular risk factors have resulted in improved outcomes [1], there is considerable interest in identifying novel cardiovascular risk factors. Identification of new risk factors will improve our understanding of the disease and may account for cases of CVD that cannot be explained by traditional risk factors. Metabolic acidosis, as reflected by a low serum bicarbonate concentration, may be a modifiable risk factor for CVD in patients with and without kidney disease.

Metabolic acidosis results in numerous deleterious effects such as chronic inflammation and impaired myocardial function [2]. Recent studies have also found that metabolic acidosis results in activation of the renin-angiotensin aldosterone system and vascular endothelial dysfunction [3]. Epidemiologic studies have found that lower serum bicarbonate concentrations are associated with incident and prevalent hypertension [4–6], insulin resistance [7,8], kidney disease progression [9–16] and mortality [14–18]. Collectively these data suggest that metabolic acidosis may be a risk factor for CVD. However, two studies have reported the opposite [12,19]. Both studies found that *higher* serum bicarbonate concentrations were associated with increased risk of heart failure in patients with chronic kidney disease (CKD) [12,19]. Effects of alkalosis on vascular calcification and regulatory proteins in the heart were postulated as potential mechanisms underlying these associations. It is unknown whether bicarbonate concentrations are associated with CVD in patients without CKD, for whom the causes and consequences of altered bicarbonate concentration may differ.

We examined associations between serum bicarbonate concentration and clinical cardiovascular events and subclinical cardiovascular disease in a prospective, multiethnic cohort of 6229 individuals who were initially free of clinical cardiovascular disease. A priori, we hypothesized that lower serum bicarbonate levels would be associated with a higher risk of cardiovascular disease.

Methods

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study of CVD among 6,814 community-living adults. Details of the design and recruitment for MESA have been published previously [20]. Briefly, MESA recruited adults aged 45 to 84 years from July 2000 through July 2002. Participants were recruited from Baltimore, MD, Chicago IL, Forsyth County, NC, Los Angeles County, CA, Northern Manhattan and the Bronx, NY and St. Paul MN. MESA excluded participants who had any previous diagnosis of CVD, defined by self-reported diagnosis of: myocardial infarction, angina, nitroglycerin use, atrial fibrillation, transient ischemic attack, stroke, heart failure, angioplasty, coronary artery bypass grafting, valve replacement, pacemaker or defibrillator or any other heart or arterial surgery. Institutional review board approval was obtained for each site and all participants gave informed consent. For this study we excluded participants who were missing one or more of the following: baseline measurements of serum bicarbonate (n=381), creatinine (n=25), cystatin C (n=58), urine albumin:creatinine ratio (n=39), data on cardiovascular events (n=5), education (n=23), smoking status (n=22), self-reported emphysema (n=1), systolic blood pressure (n=3), C-reactive protein (n=52), triglycerides (n=23), low-density lipoprotein cholesterol (n=113), high density lipoprotein cholesterol (n=26) or medication information (n=3). This resulted in a final analytic sample of 6229 participants (91.4%).

Measurement of Serum Bicarbonate Concentrations

MESA study personnel collected baseline serum samples in the morning after an overnight fast. Serum was frozen at −80°C, and bicarbonate was measured from thawed specimens using a pH rate-of-change method with an ion selective electrode on a Beckman DxC automated chemistry analyzer at the University of Washington. The interassay coefficient of variation across the study was 2.98%–3.19% [16].

Outcomes

Subclinical Disease—The outcomes of interest were aortic pulse pressure and left ventricular (LV) mass. PulseWave CR-2000 Research CardioVascular Profiling Instrument was used to record 30-second radial artery waveform recordings [21]. The recordings were digitized at 200Hz and exported for processing using software by Matlab (The Mathworks; Natick, MA). Assuming no brachial-to-radial amplification, the radial pressure waveform was calibrated with brachial systolic and diastolic pressures. To obtain a central pressure waveform, a generalized transfer function was applied to the radial pressure waveform. Aortic pulse pressure was computed as resting aortic systolic blood pressure minus aortic diastolic blood pressure.

Left ventricular mass was calculated from cardiac magnetic resonance imaging (MRI) images in a subset of participants (n=4,603) [22]. MESA personnel performed cardiac MRIs using scanners with 1.5-Tesla magnets. Left ventricular mass was calculated using commercially available software (MASS 4.2; Leiden, the Netherlands) by central readers blinded to other study data. The intraclass correlation coefficient for left ventricular mass was 0.98 (n=75) [22].

Cardiovascular events—Cardiovascular events were collected by study personnel through telephone interviews and scheduled follow-up exams. Hospitalization records, outpatient visits, and/or death certificates were collected and reviewed by two independent study physicians blinded to study data. Incident heart failure was defined as probable if the diagnosis was given by a physician plus the patient received medical treatment for heart failure. The MESA Events Committee defined definite heart failure as a diagnosis of heart failure by a physician plus treatment for heart failure as well as either echocardiographic or chest X-ray evidence of heart failure. Coronary heart disease was defined as definite angina, probable angina if followed by percutaneous coronary intervention or coronary artery bypass grafting, myocardial infarction, resuscitated cardiac arrest or coronary artery disease death. Ischemic stroke was defined as a focal neurological deficit lasting more than 24 hours or stroke symptoms lasting <24 hours with clinically relevant lesion on brain imaging. As in previous MESA studies [23–25], we evaluated “hard atherosclerotic CVD”, which in MESA was defined as myocardial infarction, resuscitated cardiac arrest, stroke, coronary heart disease death and stroke death.

Covariate data

Study personnel collected demographic and health information on study participants using standardized questionnaires. Medication usage was determined by questionnaire and review of pill bottles. Age, race/ethnicity and gender were self-identified. Participant’s height and weight were measured and body mass index was calculated as weight/height^2 (kg/m^2). All measurements were completed with participants wearing light clothing and no shoes. At each examination, blood pressure was measured with a Dinamap Pro100 (Critikon, Tampa, Florida) in a seated position 3 times. The second and third measurements were averaged and recorded as the blood pressure for that exam. Smoking was categorized as never, former or current smoker. Diabetes was defined as fasting blood glucose ≥ 126 mg/dL or use of glucose lowering medication. A history of emphysema was determined by self-report. Percent emphysema was available at exam 1 for some participants (n=3,622). Percent emphysema was calculated by trained readers blinded to study treatment from cardiac CT scans performed at baseline following a standardized protocol. Percent emphysema was defined as the percentage of lung voxels below −950 Hounsfield units (HU). Dietary protein density was calculated from a 120-item food frequency questionnaire that was performed at the baseline examination [26].

Fasting morning blood samples were drawn at each clinic visit and shipped to the MESA central laboratory. Serum creatinine was measured by rate reflectance spectrophotometry using thin-film adaptation of the creatinine amidohydrolase method on the VITROS analyzer (Johnson and Johnson clinical Diagnostics Inc) and calibrated to the Cleveland Clinic. Cystatin C was measured by a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Siemens AG, Munich). The CKD Epidemiology Collaboration (CKD-EPI) creatinine-cystatin C equation was used to estimate GFR. Urine albumin and creatinine were measured from spot morning collections using nephelometry and the rate Jaffe reaction, respectively. Lipid panels and C-reactive protein were measured using standard techniques at the central laboratory.

Statistical Analysis

Serum bicarbonate concentrations were examined as a continuous variable and in clinically significant categories: <21, 21–22, 23–24 and ≥ 25 mEq/L. For this analysis, a bicarbonate concentration of 23–24 mEq/L was chosen as the reference group because it is within the normal clinical range and contained the mean and median values for our study population. Multivariable linear regression models and Cox proportional hazards models were used to examine associations of serum bicarbonate concentration with subclinical disease and cardiovascular events, respectively. Prior to analysis, we considered variables that may be associated with serum bicarbonate concentration and CVD as potential covariates. Our basic model included adjustment for age, race/ethnicity, gender, attained education level, and MESA site. Model 2 included the covariates in model 1 plus diabetes, self-reported emphysema, body mass index, systolic blood pressure, smoking, antihypertensive medications, lipid-lowering medications, estimated glomerular filtration rate (eGFR), C-reactive protein, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and urine albumin to creatinine ratio. Since protein intake is the major contributor to dietary acid load [27], we performed an additional model adjusting for dietary protein density. We evaluated for heterogeneity of bicarbonate-CVD associations by diuretic use because diuretics have large effects on serum bicarbonate concentrations. Analyses were stratified by diuretic use since we observed a significant interaction between bicarbonate levels and diuretic use examining incident heart failure. Statistical analyses were conducted using SAS statistical software, and P-values <0.05 were considered statistically significant for all analyses including interaction terms.

Results

The mean (SD) age was 62 (10.3) years and mean serum bicarbonate concentration was 23.1 (1.8) mEq/L (Table 1). The median [IQR] and range of serum creatinine was 0.9 (0.8–1.1) mg/dL and 0.2 to 6.0 mg/dL, respectively. The median [IQR] and range of eGFR was 78.2 (67.2–89.1) ml/min/1.73m^2 and 6.5 to 175.9 ml/min/1.73m^2, respectively. Participants with bicarbonate < 21 mEq/L were more likely to be younger, to have diabetes, higher body mass index and higher eGFR and urine albumin to creatinine ratios. Participants with bicarbonate levels ≥ 25 mEq/L were more likely to use antihypertensive medications and diuretics. They were also more likely to be female and Caucasian, and attained higher levels of education.

Associations with Subclinical Cardiovascular Disease

There was no significant interaction between diuretic use and bicarbonate with the outcome of LVM (p=0.9 for both categorical and continuous models) and aortic pulse pressure (p>0.80 for both categorical and continuous models). Higher serum bicarbonate concentrations were associated with greater left ventricular mass and higher aortic pulse pressure in participants not using diuretics (Table 2). In participants not using diuretics (N=5216), bicarbonate ≥ 25 mEq/L was associated with a 3.0 g higher left ventricular mass compared to 23–24 mEq/L, adjusting for covariates in the fully adjusted model, and each 1 mEq/L higher bicarbonate was associated with a 0.7 g higher left ventricular mass. Similarly, in participants not on diuretics, bicarbonate ≥ 25mEq/L was associated with higher aortic pulse pressure compared to a concentration of 23–24 mEq/L (β 1.0 mmHg,

95% CI 0.4 to 2.0) in the fully adjusted model and each 1mEq/L higher bicarbonate concentration was associated with a 0.3 mmHg higher aortic pulse pressure. There was no significant association between serum bicarbonate concentration and left ventricular mass or aortic pulse pressure among the 1013 participants using diuretics. Results were unchanged after further adjustment for dietary protein density (Model 3).

Associations with Incident Cardiovascular Events and Heart Failure

Three hundred thirty one participants had an incident atherosclerotic CVD event during a median (IQR) follow-up of 8.5 (7.6–8.6) years. There were 174 incident heart failure events during a median (IQR) follow-up for 8.5 (7.7–8.6) years. There was a significant interaction between serum bicarbonate and diuretic use when examining incident heart failure (p=0.03 in model 3 when bicarbonate was examined categorically and 0.003 in model 3 when bicarbonate was examined continuously). There was no significant association between serum bicarbonate and incident atherosclerotic CVD events among either users or nonusers of diuretics (Table 3). Among participants using diuretics, bicarbonate >25 mEq/L was associated with lower risk of incident heart failure in the fully adjusted model compared with 23–24, although the association was not significant in the continuous model. Among nonusers of diuretics, in the continuous model, each 1 mEq/L higher serum bicarbonate was significantly associated with a 13% increased risk of incident heart failure in the fully adjusted model; findings were not significant in the categorical model. Results were unchanged after further adjustment for dietary protein density (Model 3).

Sensitivity Analysis

Since lung function may affect serum bicarbonate, we performed an additional analysis using a more accurate measurement of emphysema (percent emphysema by CT) in the fully adjusted model. We included 3,622 participants in whom percent emphysema was available. Higher serum bicarbonate levels were still significantly associated with increased left ventricular mass and higher aortic pulse pressure. The direction of the association between bicarbonate and incident heart failure remained the same in participants not on diuretics, but was no longer statistically significant (For each 1mEq/L increase in bicarbonate: HR 1.12, 95% CI 0.95 to 1.32). This analysis had only 86 incident heart failure events compared with 174 in the primary analysis.

To determine whether bicarbonate concentrations were associated with a specific type of heart failure we performed a sensitivity analysis examining the association of bicarbonate with preserved ejection fraction (EF) heart failure and reduced EF heart failure. Results are shown in Supplemental Table 1. Bicarbonate concentration was not significantly associated with either subtype of heart failure in the fully adjusted analysis, but the direction of the association remained the same for both subtypes. The lack of a significant association may be due to the low number of events (N=69 preserved EF events and N=80 reduced EF events).

Discussion

Contrary to our hypothesis, a higher serum bicarbonate concentration was associated with higher left ventricular mass, higher aortic pulse pressure and a higher risk of heart failure among nonusers of diuretics in a community-based, multi-ethnic cohort that was initially free of clinical cardiovascular disease. We did not observe any association between bicarbonate concentration and incident atherosclerotic CVD events.

To our knowledge, this is the first study examining the relationship between serum bicarbonate and cardiovascular events in participants with generally normal kidney function. Our results are similar to two previous studies performed in the setting of CKD [12,19]. In a study of over 3900 patients with CKD stage 2–4 from the Chronic Renal Insufficiency Cohort, each 1mEq/L higher bicarbonate concentration over 24 mEq/L was associated with a 14% increased risk of heart failure [12]. Additionally, the serum bicarbonate concentration was not associated with atherosclerotic CVD events. Similarly, an analysis from the RENAAL trial of over 2,600 participants with type 2 diabetes and CKD found that a bicarbonate level ≥27 mEq/L was associated with a higher risk of developing heart failure but not with a higher risk of atherosclerotic CVD events [19]. Together, these data suggest that higher serum bicarbonate may be a risk factor for heart failure, but not atherosclerotic CVD, among people with and without CKD.

It is important to note that the significant associations between serum bicarbonate concentrations and outcomes were observed only after detailed adjustment. Thus the association could be due to confounding. For example, it is possible that higher bicarbonate concentrations were actually a subclinical sign of heart failure rather than a causative factor. However, the high risk of heart failure observed in participants not on diuretics at higher serum bicarbonate concentrations could also be due, in part, by effects of alkalosis on arterial stiffness and left ventricular compliance, if we make the assumption that those with higher bicarbonate have higher pH. We found that higher bicarbonate concentrations were associated with greater aortic pulse pressure (a measure of arterial stiffness) and left ventricular mass. It is hypothesized that metabolic alkalosis may promote vascular calcification and stiffness. An alkaline pH increases vascular calcification in cultured cells and uremic rats [28,29] whereas acidosis inhibits calcification [30]. Experimental studies have demonstrated that acidosis prevents the production of hydroxyapatite and its soft tissue deposition by modulating the activity of several regulatory enzymes such as matrix gla-protein and alkaline phosphatase [31–34]. Vascular calcification induces arterial stiffness [34–35] and arterial dysfunction is a key factor responsible for the development of left ventricular hypertrophy [36]. Additionally, alkalosis activates specific mitogen-activated protein kinase (MAPK) signaling pathways that are involved in the regulation of cardiomyocyte cell survival and death [37].

Interestingly, we found that in participants on diuretics, a serum bicarbonate level ≥ 25 mEq/L was associated with a decreased risk of heart failure. While diuretics are a major cause of metabolic alkalosis [38], it is possible that elevated bicarbonate levels from diuretics are not harmful. Diuretics are the most effective class of drugs in preventing incident heart failure [39]. The unique preload reducing effect of diuretics may be the reason

they are superior to other drugs at preventing heart failure. Hence, elevated bicarbonate levels that result from diuretics may be different than elevated levels from a different cause. Diuretics induce metabolic alkalosis due to a “contraction alkalosis” and by increasing net acid excretion in the distal tubule resulting in increased bicarbonate production [38]. Previous studies examining the association between bicarbonate concentration and heart failure were unable to stratify by diuretic use due to more than 60% of patients being on diuretics [12]. Future studies should examine whether elevated bicarbonate levels from diuretics are different than elevated bicarbonate levels from other etiologies.

While we did not find that lower serum bicarbonate concentrations are a risk factor for CVD or heart failure, lower serum bicarbonate concentrations may still be a risk factor for other outcomes. Lower serum bicarbonate has been shown to be a significant risk factor for progression of kidney disease in patients with established CKD and relatively preserved kidney function [9–16.19]. For example, in the MESA cohort, each 1-SD lower baseline bicarbonate concentration was associated with 12% higher odds of rapid kidney function decline [16]. Additionally, studies have shown that increasing serum bicarbonate through oral bicarbonate supplementation slows kidney function decline [10,40,41]. It is hypothesized that metabolic acidosis results in increases in aldosterone, endothelin and angiotensin II levels leading to increased interstitial fibrosis and decline in GFR [10,42]. Elevated levels of these hormones are also associated with CVD [43], but our results suggest that lower bicarbonate is not a risk factor for CVD and higher bicarbonate may promote heart failure. These conflicting data demonstrate the need for randomized clinical trials examining the effect of alkali therapy on vascular calcification, cardiovascular disease and kidney disease.

Our study has limitations worth mentioning. First, this is an observational study and thus we cannot prove causation. Second, we used a single measurement of baseline serum bicarbonate concentration. Third, we did not have data regarding the use of alkali therapy in the study participants. Additionally, our observed associations may be confounded by factors that were not measured in this study. For example, lung function may affect serum bicarbonate levels. However, we were able to adjust for self-reported emphysema as well as percent emphysema by CT scan in a subset of patients and the relationships of bicarbonate persisted with left ventricular mass, aortic stiffness and heart failure. Finally, we did not have a complete description of the acid-base status of the patients (pH, PCO2 and bicarbonate level) and thus we do not know if the patients with higher serum bicarbonate levels were alkalemic. Studies have shown that patients can have alkalemia or acidemia with various serum bicarbonate concentrations [18] and future studies should obtain a complete acid-base profile.

Our study also has several strengths including the large number of participants, long-term follow-up, adjudicated cardiovascular events, and complementary measurements of subclinical CVD. Also, we examined a population free of clinical cardiovascular disease at baseline, reducing risks of reverse causation and confounding. Finally, we adjusted for established cardiovascular risk factors as well as lung function.

In conclusion, we found that higher serum bicarbonate concentrations were associated with increased risks of subclinical cardiovascular disease and clinical heart failure outcomes in a large, multi-ethnic, community-based cohort study. Our findings suggest that higher bicarbonate concentrations may be a risk factor for arterial stiffness, left ventricular mass and heart failure. Further studies are needed to determine relationships of bicarbonate concentrations and bicarbonate interventions with cardiovascular outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of study population by serum bicarbonate concentration

Characteristic	Bicarbonate Concentration (mEq/L)			
	< 21 (N=430)	21–22 (N=1733)	23–24 (N=2707)	≥ 25 (N=1359)
Age (years)	59.9 (10.1)	61.5 (10.5)	62.3 (10.2)	63.6 (9.9)
Sex				
Female	221 (51.4)	916 (52.9)	1451 (53.6)	744 (54.7)
Male	209 (48.6)	817 (47.1)	1256 (46.4)	615 (45.3)
Race/Ethnicity				
White	139 (32.3)	666 (38.4)	1075 (39.7)	538 (39.6)
Chinese-American	44 (10.2)	227 (13.1)	336 (12.4)	153 (11.3)
Black	104 (24.2)	378 (21.8)	739 (27.3)	473 (34.8)
Hispanic	143 (33.3)	462 (26.7)	557 (20.6)	195 (14.3)
Highest level of education				
High school	167 (38.8)	664 (38.3)	969 (35.8)	437 (32.2)
Some college	131 (30.5)	503 (29.0)	761 (28.1)	379 (27.9)
College graduate	132 (30.7)	566 (32.7)	977 (36.1)	543 (40.0)
BMI (kg/m^2)	29.3 (5.3)	28.6 (5.2)	28.1 (5.5)	27.7 (5.7)
Smoking status				
Never smoked	182 (42.3)	850 (49.0)	1407 (52.0)	719 (52.9)
Former smoker	153 (35.6)	610 (35.2)	991 (36.6)	517 (38)
Current smoker	95 (22.1)	273 (15.8)	309 (11.4)	123 (9.1)
Self-reported emphysema				
No	422 (98.1)	1702 (98.2)	2668 (98.6)	1336 (98.3)
Yes	7 (1.6)	30 (1.7)	36 (1.3)	22 (1.6)
Diabetes				
Impaired fasting glucose	74 (17.2)	245 (14.1)	365 (13.5)	172 (12.7)
Untreated diabetes	12 (2.8)	63 (3.6)	51 (1.9)	28 (2.1)
Treated diabetes	57 (13.3)	175 (10.1)	241 (8.9)	130 (9.6)
LDL (mg/dL)	117.4 (34.3)	117.4 (31.6)	117 (30.8)	116.5 (31.2)
HDL (mg/dL)	47.8 (13.8)	49.9 (14.5)	51.5 (15.1)	54.0 (14.8)
Triglycerides (mg/dL)	142.8 (74.2)	133.2 (68.4)	124.3 (64.5)	113.9 (58.3)
C-reactive protein (mg/L)	3.8 (5.8)	4.0 (6.3)	3.7 (5.9)	3.4 (5.1)
Serum creatinine (mg/dL)	1.0 (0.4)	0.9 (0.3)	0.9 (0.2)	0.9 (0.2)
Serum creatinin (mg/dL), median (IQR)	0.9 (0.8–1.1)	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.9 (0.8–1.1)
Albumin/creatinine ratio	46.9 (261)	28.2 (188.2)	20.6 (103.8)	18.7 (64.0)
eGFR ($mL/min/1.73m^2$)	79.9 (19.7)	79.0 (16.9)	78.1 (15.5)	76.8 (15.2)
eGFR ($mL/min/1.73m^2$), median (IQR)	82.7 (69.1– 93.7)	79.6 (67.9– 91.0)	77.6 (67.4– 88.5)	75.9 (66.0– 86.7)
Any lipid-lowering medication				
No	365 (84.9)	1452 (83.8)	2280 (84.2)	1120 (82.4)
Yes	65 (15.1)	281 (16.2)	427 (15.8)	239 (17.6)
Any hypertensive medication				

Characteristic	Bicarbonate Concentration (mEq/L)			
	< 21 (N=430)	21–22 (N=1733)	23–24 (N=2707)	≥ 25 (N=1359)
No	293 (68.1)	1151 (66.4)	1790 (66.1)	704 (51.8)
Yes	137 (31.9)	582 (33.6)	917 (33.9)	655 (48.2)
Any diuretics				
No	396 (92.1)	1548 (89.3)	2314 (85.5)	958 (70.5)
Yes	34 (7.9)	185 (10.7)	393 (14.5)	401 (29.5)

Values are expressed as mean (SD) unless otherwise specified. BMI= body mass index; LDL= low density lipoprotein cholesterol; HDL= high-density lipoprotein cholesterol; eGFR= estimated glomerular filtration rate;

Table 2

Associations of Bicarbonate Concentration with Subclinical Cardiovascular Disease

Left Ventricular Mass (N=4,603)	**Mean Difference in Left Ventricular Mass (g)**			
Bicarbonate (mEq/L)	**Unadjusted Mean (SD)**	**Model 1**	**Model 2**	**Model 3**
Diuretic Use				
< 21	150.6 (40.7)	−3.0 (−19.0 to 13.0)	−7.0 (−22.0 to 9.0)	−7.0 (−22.0 to 9.0)
21–23	154.6 (45.0)	2.0 (−5.0 to 9.0)	−1.0 (−7.0 to 5.0)	−1.0 (−7.0 to 5.0)
23–24	152.5 (43.0)	0 (REF)	0 (REF)	0 (REF)
≥ 25	145.5 (34.7)	−5.0 (−10.0 to 1.0)	−2.0 (−6.0 to 3.0)	−2.0 (−6.0 to3.0)
Per 1 mEq/L higher		−1.0 (−2.0 to 0.0)	0.2 (−1.0 to 1.0)	0.2 (−1.0 to 1.0)
P-value *		0.06	0.73	0.74
No Diuretic Use				
<21	146.8 (42.0)	2.0 (−2.0 to 6.0)	−1.0 (−5.0 to 2.0)	−1.0 (05.0 to 2.0)
21–23	144.9 (38.4)	2.0 (−0.2 to 4.0)	0.4 (−1.0 to 2.0)	0.4 (−2.0 to 2.0)
23–24	142.6 (38.5)	0 (REF)	0 (REF)	0 (REF)
≥ 25	146.3 (40.8)	1.0 (−1.0 to 4.0)	3.0 (0.5 to 5.0)	3.0 (0.5 to 5.0)
Per 1 mEq/L higher		−0.1 (−0.7 to 0.5)	0.7 (0.2 to 1.0)	0.7 (0.1 to 1.0)
P-value *		0.76	0.01	0.01

Aortic Pulse Pressure (N=5,805)	**Mean Difference in Aortic Pulse Pressure (mmHg)**			
Bicarbonate (mEq/L)	**Unadjusted Mean (SD)**	**Model 1**	**Model 2** **	**Model 3**
Diuretic Use				
< 21	61.9 (15.6)	−1.9 (−6.9 to 3.0)	−1.2 (−5.4 to 2.9)	−1.4 (−5.6 to 2.9)
21–23	65.6 (15.4)	1.7 (−0.7 to 4.0)	0.5 (−1.5 to 2.5)	0.9 (−1.1 to 3.0)
23–24	64.6 (14.5)	0 (REF)	0 (REF)	0 (REF)
≥ 25	64.7 (15.0)	−0.4 (−0.7 to 0.2)	1.2 (−0.4 to 2.7)	1.2 (−0.4 to 2.8)
Per 1 mEq/L higher		−0.3 (−0.7 to 0.2)	0.2 (−0.2 to 0.5)	0.1 (−0.3 to 0.5)
P-value *		0.26	0.36	0.54
No Diuretic Use				
<21	56.5 (13.7)	−0.3 (−2.0 to 1.0)	−0.6 (−2.0 to 0.4)	−0.7 (−1.7 to 0.3)
21–23	57.4 (14.4)	−0.2 (−1.0 to 0.6)	−0.1 (−0.7 to 0.6)	−0.1 (−0.7 to 0.6)

Aortic Pulse Pressure (N=5,805)	Mean Difference in Aortic Pulse Pressure (mmHg)			
Bicarbonate (mEq/L)	**Unadjusted Mean (SD)**	**Model 1**	**Model 2****	**Model 3**
23–24	57.9 (14.2)	0 (REF)	0 (REF)	0 (REF)
≥ 25	58.6 (15.1)	0.8 (−0.3 to 2.0)	1.0 (0.4 to 2.0)	1.2 (0.4 to 2.0)
Per 1 mEq/L higher		0.2 (−0.01 to 0.4)	0.3 (0.1 to 0.4)	0.3 (0.1 to 0.4)
P-value*		0.07	0.001	0.001

Model 1: Adjusted for age, race/ethnicity, gender, education and MESA site

Model 2: Adjusted for covariates in model 1 plus diabetes, self-reported emphysema, body mass index, systolic blood pressure, smoking, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, eGFR, C-reactive protein, urine albumin to creatinine ratio, use of antihypertensive medications, use of lipid-lowering medications.

Model 3: Adjusted for covariates in model 2 plus dietary protein density.

* P-value is for continuous comparison

** Additionally adjusted for mean arterial pressure

Table 3

Associations of Bicarbonate Concentration with Incident Cardiovascular Events and Heart Failure

Hard Cardiovascular Event (N=331)	Adjusted Hazard Ratio (95% Confidence Interval)			
Bicarbonate (mEq/L)	**Number of Events**	**Model 1**	**Model 2**	**Model 3**
Diuretic Use				
< 21	3	0.95 (0.29 to 3.15)	0.85 (0.25 to 2.89)	0.90 (0.26 to 3.06)
21–23	16	0.84 (0.47 to 1.50)	0.93 (0.52 to 1.67)	0.98 (0.54 to 1.77)
23–24	39	1.00 (REF)	1.00 (REF)	1.00 (REF)
≥ 25	24	0.56 (0.33 to 0.94)	0.65 (0.85 to 1.05)	0.71 (0.42 to 1.22)
Per 1 mEq/L higher		0.92 (0.83 to 1.02)	0.94 (0.85 to 1.05)	0.95 (0.85 to 1.06)
P-value *		0.10	0.26	0.34
No Diuretic Use				
<21	13	0.70 (0.40 to 1.25)	0.59 (0.33 to 1.06)	0.59 (0.32 to 1.08)
21–23	78	1.02 (0.76 to 1.37)	0.98 (0.72 to 1.32)	0.91 (0.66 to 1.24)
23–24	114	1.00 (REF)	1.00 (REF)	1.00 (REF)
≥ 25	44	0.97 (0.69 to 1.38)	1.01 (0.71 to 1.44)	1.02 (0.71 to 1.46)
Per 1 mEq/L higher		1.02 (0.96 to 1.10)	1.05 (0.98 to 1.13)	1.06 (0.99 to 1.14)
P-value *		0.50	0.15	0.12

Heart Failure (N=174)	Adjusted Hazard Ratio (95% Confidence Interval)			
Bicarbonate (mEq/L)	**Number of Events**	**Model 1**	**Model 2**	**Model 3**
Diuretic Use				
< 21	3	1.32 (0.38 to 4.59)	0.70 (0.19 to 2.59)	0.91 (0.25 to 3.36)
21–23	14	1.03 (0.54 to 1.95)	1.01 (0.53 to 1.95)	1.14 (0.59 to 2.21)
23–24	29	1.00 (REF)	1.00 (REF)	1.00 (REF)
≥ 25	13	0.38 (0.20 to 0.75)	0.42 (0.21 to 0.84)	0.47 (0.24 to 0.96)
Per 1 mEq/L higher		0.83 (0.74 to 0.93)	0.90 (0.79 to 1.01)	0.88 (0.78 to 1.01)
P-value *		0.002	0.07	0.06
No Diuretic Use				
<21	7	0.86 (0.39 to 1.93)	0.61 (0.26 to 1.43)	0.65 (0.27 to 1.54)
21–23	31	0.93 (0.60 to 1.45)	0.83 (0.53 to 1.31)	0.79 (0.49 to 1.26)
23–24	51	1.00 (REF)	1.00 (REF)	1.00 (REF)

Heart Failure (N=174)	Adjusted Hazard Ratio (95% Confidence Interval)			
Bicarbonate (mEq/L)	**Number of Events**	**Model 1**	**Model 2**	**Model 3**
≥ 25	26	1.26 (0.78 to 2.04)	1.30 (0.80 to 2.11)	1.23 (0.75 to 2.01)
Per 1 mEq/L higher		1.08 (0.96 to 1.21)	1.13 (1.01 to 1.26)	1.12 (1.00 to 1.26)
P-value *		0.20	0.03	0.047

Model 1: Adjusted for age, race/ethnicity, gender, education and MESA site

Model 2: Adjusted for covariates in model 1 plus diabetes, self-reported emphysema, body mass index, systolic blood pressure, smoking, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, eGFR, C-reactive protein, urine albumin to creatinine ratio, use of antihypertensive medications, use of lipid-lowering medications.

Model 3: Adjusted for covariates in model 2 plus dietary protein density. Interaction between diuretic use and bicarbonate examining incident heart failure (p-interaction = 0.03 in model 2 when bicarbonate was examined categorically and 0.003 in model 2 when bicarbonate was examined continuously).

* P-value is for continuous comparison