

A Randomized Trial Comparing the Safety, Adherence, and Pharmacodynamics Profiles of Two Doses of Sodium Bicarbonate in CKD: the BASE Pilot Trial

Kalani L. Raphael¹, Tamara Isakova,² Joachim H. Ix,³ Dominic S. Raj,⁴ Myles Wolf,⁵ Linda F. Fried,⁶ Jennifer J. Gassman,⁷ Cynthia Kendrick,⁷ Brett Larive,⁷ Michael F. Flessner,⁸ Susan R. Mendley,⁸ Thomas H. Hostetter,⁹ Geoffrey A. Block,¹⁰ Ping Li,¹¹ John P. Middleton,⁵ Stuart M. Sprague¹², Donald E. Wesson,¹³ and Alfred K. Cheung¹

Due to the number of contributing authors, the affiliations are listed at the end of this article.

ABSTRACT

Background Oral sodium bicarbonate (NaHCO_3) may preserve kidney function in CKD, even if initiated when serum bicarbonate concentration is normal. Adequately powered trials testing this hypothesis have not been conducted, partly because the best dose for testing is unknown.

Methods This multicenter pilot trial assessed the safety, tolerability, adherence, and pharmacodynamics of two doses of NaHCO_3 over 28 weeks in adults with eGFR 20–44 or 45–59 ml/min per 1.73 m^2 with urinary albumin/creatinine (ACR) $\geq 50 \text{ mg/g}$ and serum bicarbonate 20–28 meq/L. We randomly assigned 194 participants from ten clinical sites to receive higher-dose (HD- NaHCO_3 ; 0.8 meq/kg of lean body wt per day; $n=90$) or lower-dose (LD- NaHCO_3 ; 0.5 meq/kg of lean body wt per day; $n=52$) NaHCO_3 or matching placebo ($n=52$). The dose was adjusted depending on side effects. The prescribed dose at week 28 was the primary outcome; a dose was considered acceptable for a full-scale trial if $\geq 67\%$ of participants were on full-dose and $\geq 80\%$ were on $\geq 25\%$ of the per-protocol dose.

Results Mean \pm SD baseline eGFR was $36 \pm 9 \text{ ml/min per } 1.73 \text{ m}^2$, serum bicarbonate was $24 \pm 2 \text{ meq/L}$, and median (IQR) ACR was $181 (25\text{--}745) \text{ mg/g}$. Both doses were well tolerated without significant changes in BP, weight, or serum potassium. The proportions of adverse events and hospitalizations were similar across the groups. Consequently, 87% in HD- NaHCO_3 , 96% in LD- NaHCO_3 , and 87% in placebo were on full dose at week 28; and 91% in HD- NaHCO_3 , 98% in LD- NaHCO_3 , and 92% in placebo were on $\geq 25\%$ of the per-protocol dose. Mean urinary ammonium excretion was 25% lower and serum bicarbonate concentration was 1.3 meq/L higher in HD- NaHCO_3 compared with LD- NaHCO_3 at week 28. However, mean ACR increased by 12% in the lower-dose group and 30% in the higher-dose group.

Conclusions Both NaHCO_3 doses were well tolerated over 28 weeks with no significant difference in adverse events or hospitalization compared with placebo. The higher dose lowered urinary ammonium excretion and increased serum bicarbonate more than the lower dose but was associated with a greater increase in ACR. The higher 0.8 meq/kg of lean body wt per day dose of NaHCO_3 may be a reasonable choice for future trials.

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Correspondence: Dr. Kalani L. Raphael, Department of Internal

Medicine, University of Utah, 30 North 1900 East, SOM 4R312, Salt Lake City, UT 84132. Email: kalani.rafael@hsc.utah.edu

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Metabolic acidosis is a complication of CKD, occurring in approximately 15% of patients.^{1,2} Prior studies demonstrated that metabolic acidosis contributes to loss of bone mineral content and leads to skeletal muscle catabolism.^{3–6} Based on these findings, clinical practice guidelines recommended that metabolic acidosis be treated with oral alkali in patients with CKD.⁷ More recently, results from studies with small sample sizes suggested that treating metabolic acidosis slowed kidney function decline.^{8,9} Further, results from studies in hypertensive CKD support the hypothesis that alkali supplementation may preserve kidney function even in patients with normal serum bicarbonate concentrations.^{10–12} This finding is potentially important because most patients with CKD do not have overt metabolic acidosis and are not treated with oral alkali based on current practice standards. These observations raise the possibility that alkali supplementation may benefit the broader CKD population. However, sodium bicarbonate (NaHCO_3) supplementation among patients with CKD may have adverse consequences including fluid retention, hypertension, and risk of heart failure.

Before this strategy can be implemented in the general CKD population, it is critical to perform a definitive, multicenter clinical trial to determine the effect of alkali supplementation on patient safety and CKD progression. However, the dose of alkali to be studied remains uncertain. Among patients with CKD with metabolic acidosis, the dose is often titrated to achieve a serum bicarbonate level of ≥ 22 meq/L, whereas weight-based doses have been prescribed in prior studies of patients with CKD with normal serum bicarbonate concentration. Early studies using daily bicarbonate doses of 0.3–0.5 meq/kg of lean body wt found no serious adverse events,^{10–12} raising the possibility that a higher dose might be safe and possibly result in greater efficacy in a full-scale trial. In a short-term, single-center, dose-escalation study in 20 patients with CKD and 20–24 meq/L serum bicarbonate, treatment with 1.0 meq/kg of lean body wt NaHCO_3 per day for 2 weeks was well tolerated and not associated with significant adverse events.¹³ Whether doses in this range are safe and tolerable for patients with CKD with normal serum bicarbonate levels over a longer period of time is uncertain. Further, the urinary pharmacodynamics, as intermediate markers of efficacy, of various bicarbonate doses have not been rigorously evaluated in CKD and may provide further insight into dose selection.

We herein report the results of the Bicarbonate Administration to Stabilize eGFR (BASE) Pilot Trial (NCT02521181). The BASE Pilot Trial was a multicenter, randomized, double-blinded, placebo-controlled clinical trial of two doses of NaHCO_3 to aid in the selection of one that could be used in a full-scale trial of alkali supplementation in patients with CKD with a mildly reduced-to-normal serum bicarbonate concentration (20–28 meq/L). The primary objective of the study was to determine the adherence and safety of the two doses over a 28-week period. A secondary objective was to determine the effect of the bicarbonate doses on urinary ammonium excretion, urinary pH, and serum bicarbonate concentration

Significance Statement

Oral sodium bicarbonate supplementation may preserve kidney function in patients with CKD. However, the best dose to use in phase-3 trials testing this hypothesis is uncertain. The authors conducted a multicenter pilot study to assess the safety, tolerability, adherence, and pharmacodynamics of two doses of sodium bicarbonate, 0.8 and 0.5 meq/kg of lean body wt per day, over 28 weeks. They showed that the higher dose of sodium bicarbonate was well tolerated, reduced urinary ammonium excretion, and raised serum bicarbonate more than the lower dose, but it modestly increased urinary albumin excretion. These findings contribute to understanding the pharmacodynamic effects and patient acceptance of sodium bicarbonate in CKD.

over the same time period. Finally, although the study duration and sample size in each group were limited, we explored the effect of the two doses on the eGFR and urinary albumin/creatinine ratio (ACR).

METHODS

Study Design and Population

The study protocol with detailed methods are available in the Supplemental Material. Briefly, the BASE Pilot Trial was a parallel-group, randomized, double-blinded, placebo-controlled trial conducted at ten clinical sites in the United States. BASE consisted of a baseline phase (up to 12 weeks), an on-treatment phase (28 weeks), and an off-treatment phase (4 weeks). Key inclusion criteria were age > 18 years; serum bicarbonate of 20–28 meq/L; moderate-to-severe CKD, defined as an eGFR of 20 to < 45 ml/min per 1.73 m^2 with no specific ACR requirements or an eGFR of 45 to < 60 ml/min per 1.73 m^2 with random ACR of ≥ 100 mg/g; BP of $< 160/100$ mm Hg; and lean body weight of 37.5–96.0 kg.^{14,15} To facilitate enrollment, the protocol was amended after 109 participants had been randomized so that individuals in the higher eGFR category were eligible if ACR was ≥ 50 mg/g instead of ≥ 100 mg/g. Key exclusion criteria were current use of oral alkali, use of five or more antihypertensive and/or diuretic medications, serum potassium of < 3.3 or ≥ 5.5 meq/L, severe congestive heart failure (CHF), and organ transplantation.

During baseline, antihypertensive medications were adjusted to achieve a BP of $< 150/100$ mm Hg and the dose of the angiotensin converting enzyme inhibitor (ACE-i) or angiotensin receptor blocker (ARB) was maximized based on the clinical judgment of the site physician. Participants were also asked to take two placebo capsules twice daily for 2 weeks to assess adherence. Participants were eligible for randomization if placebo pill-count adherence was $\geq 80\%$, BP was $< 150/100$ mm Hg, and the ACE-i/ARB dose was judged to be optimized by the site investigator.

Participants were randomized to either higher-dose (HD) NaHCO_3 (HD- NaHCO_3 ; 0.8 meq/kg of lean body wt per day), lower-dose (LD) NaHCO_3 (LD- NaHCO_3 ; 0.5 meq/kg of lean body wt per day), HD-placebo, or LD-placebo and treated for

28 weeks (on-treatment phase). Because there were limited prior safety data for doses including HD-NaHCO₃, participants were randomized in a ratio of 4:2:1:1 to HD-NaHCO₃, LD-NaHCO₃, HD-placebo, and LD-placebo, respectively. Randomization was stratified by clinical site and was performed using permuted blocks, with randomly sized blocks of four and eight. Participants and study staff were aware of the dose level assignment (higher versus lower) but not assignment to NaHCO₃ or placebo. Participants who were assigned to the HD level were provided one half of the per-protocol dose of NaHCO₃ or matching placebo for the first 4 weeks, and at week 4 the dose was escalated to the full dose. Participants assigned to the LD level began the on-treatment phase with a full dose of NaHCO₃ or matching placebo. At the end of the on-treatment phase, participants stopped the assigned treatment and returned for a follow-up visit 4 weeks later (follow-up week 32) to assess the effect of stopping the assigned treatment on clinical and laboratory parameters.

Description of the NaHCO₃ and Placebo Capsules and Dose

NaHCO₃ of 1000 mg (12 meq) were encapsulated in size-00 capsules (Supplemental Figure 1). Identical placebo capsules contained cornstarch. The lower dose was selected because there had been favorable experience using this dose in a prior study.¹² Due to the size of the capsules and concern about the sodium load, we limited the number of capsules to six per day (6000 mg, 72 meq of bicarbonate ions). Although a prior study in patients with CKD used doses up to 1.0 meq/kg of lean body wt per day,¹³ we used 0.8 meq/kg of lean body wt per day as our higher dose so that individuals with a lean body weight of up to 96 kg could participate (versus 78 kg using a 1.0 meq/kg of lean body wt per day dose). A lower lean body weight threshold was necessary as an exclusion criterion because the number of capsules prescribed at a lean body weight of <37.5 kg would be the same if the participant was assigned to the LD or HD level. The dose was rounded to the nearest whole capsule, and half the dose was taken twice daily. Participants were informed that they could take study medications with or without their other medications and with or without food, depending on their preference.

Measurements and Sample Collection

BP and heart rate were measured three times at each study visit and the average of the second and third measurement was used for data analysis. Local clinical laboratories at each site measured urinary ACR and serum chemistries. Twenty-four-hour urine samples were collected at baseline, week 12, and week 28, and were treated with sodium fluoride to prevent bacterial overgrowth. A 24-hour urine sample was deemed acceptable for analysis if the collection duration was 20–28 hours, all voids were collected, and if sodium fluoride was added to the container. Urinary ammonium, sodium, potassium, chloride, pH, and creatinine were measured from the 24-hour samples at a central laboratory (Litholink, Chicago, IL).

At each visit, participants rated symptoms of abdominal pain, nausea, bloating, burping, or flatus as none, mild, moderate, or severe at any time since the last visit. Adherence to the prescribed treatment was assessed by pill counts at each visit.

Clinical Management during the On-Treatment Phase

Recommendations to reduce salt intake were provided by study staff at each visit. BP during treatment was targeted to <140/90 mm Hg. Fluid excess determined on clinical grounds was treated with diuretics as necessary. Dose reductions and discontinuations of the assigned treatment occurred if serum bicarbonate was ≥33 meq/L, systolic BP (SBP) was ≥170 mm Hg, diastolic BP was ≥110 mm Hg, serum potassium was <3.0 meq/L, severe fluid retention had occurred, or gastrointestinal discomfort was affecting adherence to the treatment. Rescue therapy with open-label NaHCO₃ was permitted if serum bicarbonate was ≤16 meq/L on two consecutive measurements, or if serum bicarbonate was 17–19 meq/L with refractory hyperkalemia (serum potassium ≥5.5 meq/L).

Primary and Secondary Outcomes

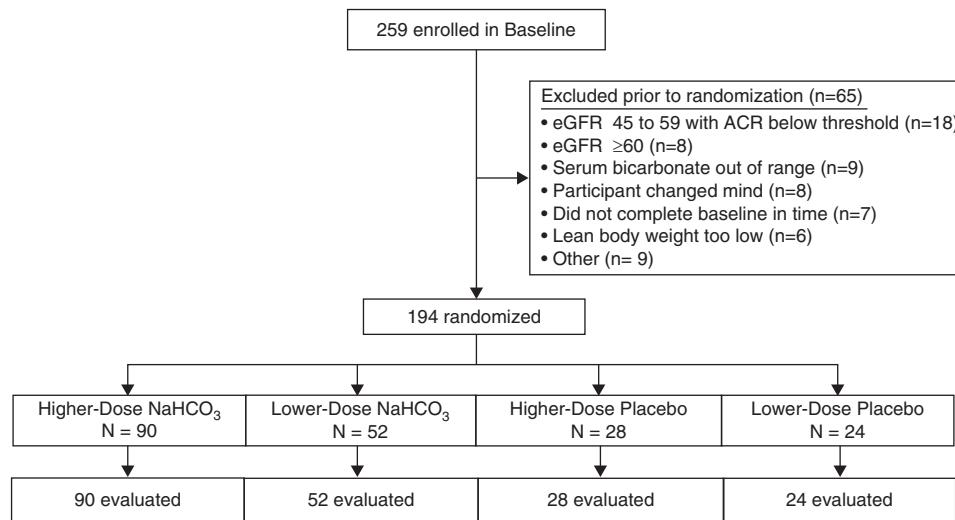
Coprimary outcomes were the percentage of participants in each dose group prescribed at week 28 (1) the full, per-protocol randomized dose of NaHCO₃; and (2) at least 25% of the per-protocol NaHCO₃ dose. We considered a dose to be feasible for use in a full-scale clinical trial if both of the following benchmarks were met: (1) at least 67% of participants were prescribed the full, per-protocol dose, and (2) at least 80% were prescribed at least 25% of the per-protocol dose at week 28 (end of treatment). The second benchmark was included because some participants might require a lower dose than intended due to side effects, yet possibly benefit from treatment in a phase-3 trial. For example, a dose would have been considered feasible if 67% of participants completed on a full dose and ≥13% completed on a dose that was less than full dose but was ≥25% of full dose. Participants who initiated maintenance dialysis, received a kidney transplant, died, or stopped attending study visits before week 28 were considered to have completed the study on zero dose.

A secondary outcome evaluated the effect of the two doses on urinary ammonium excretion, urinary pH, and serum bicarbonate at weeks 12 and 28. We reasoned the pharmacodynamic response could help guide dose selection for the full-scale trial if the NaHCO₃ doses had similar and favorable safety, tolerability, and adherence profiles.

Given the limited sample size and short duration of the trial, the effects of the two NaHCO₃ doses on the eGFR, ACR, and creatinine clearance were considered as exploratory only, as defined in the protocol *a priori*. The eGFR was calculated using serum creatinine concentration and the CKD-Epidemiology equation.¹⁶

Study Oversight

An independent committee, established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), served as both the protocol review committee



Abbreviations: ACR, urinary albumin/creatinine; eGFR, estimated glomerular filtration rate in ml/min/1.73m³.

Figure 1. Disposition of study participants from baseline to end of follow-up.

and data safety monitoring board. The study was approved by institutional review boards at each site and study participants provided written informed consent. The study was registered at clinicaltrials.gov (NCT02521181) and an investigational new drug application was filed with the Food and Drug Administration who deemed the study exempt.

Sample Size and Power Calculation

The randomization goal for the BASE Pilot Trial was 192 participants, with 88 randomized to HD-NaHCO₃, 52 to LD-NaHCO₃, and 52 to placebo (26 each in LD-placebo and HD-placebo). Detailed power estimates are presented in the Supplemental Material. The statistical power for attaining the 67% benchmark was at least 87% in HD-NaHCO₃ and at least 82% in LD-NaHCO₃ if the actual percentage prescribed the full, per-protocol dose was ≥72%. The statistical power for attaining the 80% benchmark was at least 84% in HD-NaHCO₃ and at least 80% in LD-NaHCO₃ if the actual percentage prescribed at least 25% of the randomized dose was ≥84%.

Statistical Analyses

Baseline characteristics by treatment group were summarized using means, medians, or frequencies, as appropriate. Analyses that included comparisons with placebo considered the two placebo groups jointly. Mean changes from baseline to week 12 and week 28 within randomized treatment groups were analyzed as intent to treat using linear mixed models adjusted for clinical site.¹⁷ The models were parameterized such that each outcome shared a common mean baseline value across treatment groups. An unstructured covariance matrix modeled correlations of weight-standardized urinary ammonium within participants. The covariance structure for other outcomes was selected by comparing the Bayes information criteria.¹⁸ Given their right skewness, weight-standardized

urinary ammonium and urinary ACR were natural-log transformed before analysis, and then the resulting model coefficients were converted to percentage changes of the geometric mean. Percentages of subjects who experienced various types of adverse events, including hospitalizations, were compared between treatment groups using chi-squared, goodness-of-fit tests. A significance level of 0.05 was used without adjustment for multiple comparisons. Statistical analyses were performed with SAS version 9.4 (SAS Institute) and R software (R Core Team, 2018).

Data Sharing

Data will be publicly available through the data repository of the NIDDK, National Institutes of Health (NIH). Data from the primary outcome results will be submitted to the repository within 6 months of the date of publication.

RESULTS

A total of 259 individuals enrolled in the trial and entered a baseline eligibility period. Of these, 65 did not meet the randomization criteria assessed during the baseline period; common reasons for this were random urinary ACR below the threshold in those with eGFR 45–59 ml/min per 1.73 m², eGFR ≥60 ml/min per 1.73 m², and serum bicarbonate <20 or >28 meq/L (Figure 1). A total of 194 participants were randomized over a period of 21 months to either HD-NaHCO₃ (n=90), LD-NaHCO₃ (n=52), or placebo (total n=52; n=28 for HD-placebo and n=24 for LD-placebo).

Baseline characteristics of the randomized participants overall and by treatment assignments are shown in Table 1. Mean age was 67 years, 68% were male, 35% were Black, and 9% were Hispanic. Mean SBP was 127 mm Hg and 70% were prescribed an ACE-i/ARB. Mean eGFR was 36 ml/min per

Table 1. Baseline clinical and demographic characteristics of randomized participants overall and by treatment assignment

Characteristic	Total (n=194)	HD-NaHCO ₃ (n=90)	LD-NaHCO ₃ (n=52)	Placebo (n=52)
Age (yr)	67±12	67±11	66±14	66±11
Female (no. [%])	63 (33%)	29 (32%)	21 (40%)	13 (25%)
Race/ethnicity (no. [%])				
Black	67 (35%)	27 (30%)	17 (33%)	23 (44%)
White	109 (56%)	55 (61%)	28 (54%)	26 (50%)
Hispanic/Latino	17 (9%)	8 (9%)	6 (12%)	3 (6%)
Other	15 (8%)	7 (8%)	5 (10%)	3 (6%)
Unknown or not reported	3 (2%)	1 (1%)	2 (4%)	0 (0%)
CKD stage (no. [%])				
3A	30 (15.5%)	17 (18.9%)	9 (17.3%)	4 (7.7%)
3B	107 (55.2%)	46 (51.1%)	30 (57.7%)	31 (59.6%)
4	57 (29.4%)	27 (30.0%)	13 (25.0%)	17 (32.7%)
Diabetes mellitus (no. [%])	105 (54%)	53 (59%)	27 (52%)	25 (48%)
Heart disease (no. [%])	66 (34%)	28 (31%)	18 (35%)	20 (39%)
CHF (no. [%])	20 (10%)	8 (9%)	5 (10%)	7 (14%)
COPD (no. [%])	10 (5%)	6 (7%)	4 (8%)	0 (0%)
Smoking status (no. [%])				
Never	98 (51%)	47 (52%)	26 (50%)	25 (48%)
Former	79 (41%)	39 (43%)	15 (29%)	25 (48%)
Current	17 (9%)	4 (4%)	11 (21%)	2 (4%)
Weight (kg)	95.1±22.7	95.4±22.4	96.1±25.8	93.6±20.3
Body mass index (kg/m ²)	32.5±7.5	32.8±7.9	32.8±8.4	31.6±5.9
Lean body weight (kg)	58.5±9.9	58.4±9.8	58.4±10.7	58.7±9.4
SBP (mm Hg)	127±13	127±12	127±14	127±13
ACE-i/ARB use (no. [%])	135 (70%)	60 (67%)	40 (77%)	35 (67%)
eGFR (ml/min per 1.73 m ²)	36±9	36±10	37±10	35±9
Urinary albumin/creatinine (mg/g) ^a	181 (25, 745)	176 (23, 769)	222 (58, 788)	147 (12, 593)
Serum bicarbonate (meq/L)	24±2	24±2	24±2	24±2
Serum potassium (meq/L)	4.5±0.4	4.4±0.4	4.5±0.4	4.5±0.5
Urinary ammonium (meq/d)	21±12	22±12	19±11	21±13
Urinary pH	5.8±0.5	5.8±0.5	5.9±0.5	5.8±0.6
Estimated dietary protein intake (g/d) ^b	79±29	82±31	73±25	79±30

Values are shown as number (%) or mean±SD except where indicated. COPD, chronic obstructive pulmonary disease.

^aShown as median (interquartile range).

^bCalculated as estimated dietary protein intake = 6.25×(24-h urine urea nitrogen+0.031[weight in kg]).

1.73 m² and median urinary ACR was 181 mg/g. Mean values of acid-base indices were serum bicarbonate of 24 meq/L, urinary ammonium of 21 meq/d, and urinary pH of 5.8. Clinical and demographic characteristics were distributed similarly across randomized treatment groups.

The mean (±SD, minimum, maximum) daily number of pills intended to be prescribed according to the protocol in LD-NaHCO₃ and LD-placebo was 2.5 (±0.5, 2, 4) and 2.6 (±0.6, 2, 4), respectively. The mean (±SD, minimum, maximum) daily number of pills intended to be prescribed according to the protocol in HD-NaHCO₃ and HD-placebo was 4.1 (±0.8, 3, 6) and 4.1 (±0.8, 3, 5), respectively. Over the course of the on-treatment phase, the mean (SD) dose of NaHCO₃ prescribed was 2.5 (0.7) g/d in LD-NaHCO₃ and 3.8 (1.1) g/d in HD-NaHCO₃. Overall adherence by pill count was ≥88% for each group.

Primary Outcome Results

Among participants randomized to HD-NaHCO₃, 78 of 90 (87%) completed the on-treatment phase on the full, per-protocol dose

(Table 2). Four additional participants (82 of 90, 91%) completed the on-treatment phase on at least 25% of the per-protocol NaHCO₃ dose. The most common reason for stopping or reducing the dose in HD-NaHCO₃ was gastrointestinal intolerance (*n*=6). Two safety events (high serum bicarbonate concentration; CHF with volume overload) required discontinuation of the intervention and one safety event (high serum bicarbonate concentration) led to a dose reduction.

Among participants assigned to LD-NaHCO₃, 50 of 52 (96%) completed the on-treatment phase on the full, per-protocol dose and 51 of 52 (98%) completed on at least 25% of the per-protocol dose (Table 2). One safety event (elevated BP) required a dose reduction.

In the combined placebo group, 45 of 52 (87%) completed the on-treatment phase on the full, per-protocol dose and 48 of 52 (92%) completed on at least 25% of the per-protocol dose (Table 2). Two participants reported gastrointestinal symptoms resulting in a dose reduction. Fluid retention occurred in two participants treated with placebo: one required

Table 2. Coprimary outcomes in the randomized groups

Treatment Arm	Number (%) of Participants Completing on Full Dose	Number (%) of Participants Completing on ≥25% of Full Dose	Reasons for Stopping Intervention or Reducing Dose
HD-NaHCO ₃ (n=90)	78 (87%)	82 (91%)	Gastrointestinal intolerance (n=6; 7%) Safety (n=3; 3%) Other comorbidity (n=2; 2%) Attrition (n=1, 1%) ^a
LD-NaHCO ₃ (n=52)	50 (96%)	51 (98%)	Increased BP (n=1, 2%) Other comorbidity (n=1; 2%)
Placebo (n=52)	45 (87%)	48 (92%)	Gastrointestinal intolerance (n=2; 4%) Safety (n=2; 4%) Other comorbidity (n=2; 4%) Death (n=1; 2%) ^a

A dose was considered feasible for implementation in a full-scale trial if ≥67% of participants completed the study on full-dose and ≥80% completed the study on ≥25% of the per-protocol dose.

^aParticipants who died or stopped attending study visits were considered to have completed the study on zero dose.

discontinuation of the intervention and another required a dose reduction. One participant in the placebo group died due to arrhythmia.

Changes in Urinary Ammonium, Urinary pH, and Serum Bicarbonate

Changes in mean 24-hour urinary ammonium excretion, urinary pH, and serum bicarbonate by treatment group are shown in Figure 2 and Table 3. At week 12, urinary ammonium excretion was lower and urinary pH and serum bicarbonate concentration were higher in LD-NaHCO₃ and HD-NaHCO₃, compared with placebo. There was no significant difference in urinary ammonium excretion and urinary pH between LD-NaHCO₃ and HD-NaHCO₃. However, serum bicarbonate concentration was statistically significantly higher in HD-NaHCO₃ than in LD-NaHCO₃.

At week 28, urinary ammonium excretion was lower in both LD-NaHCO₃ and HD-NaHCO₃ compared with placebo, and ammonium excretion was significantly lower in HD-NaHCO₃ compared with LD-NaHCO₃ (−25%; 95% CI, −39% to −7%). Urinary pH was higher in LD-NaHCO₃ and HD-NaHCO₃ compared with placebo, but there was no significant difference between HD-NaHCO₃ and LD-NaHCO₃. In LD-NaHCO₃, the serum bicarbonate concentration decreased from the week-20 values and was similar to the placebo group at week 28. In HD-NaHCO₃, serum bicarbonate levels at week 28 were similar to week-20 values and were consequently higher than bicarbonate levels in LD-NaHCO₃ (1.3 meq/L higher; 95% CI, 0.5 to 2.1 meq/L higher) and placebo (1.4 meq/L higher; 95% CI, 0.6 to 2.3 meq/L higher). At the week-32 visit, 4 weeks after stopping the assigned intervention, serum bicarbonate concentration decreased in HD-NaHCO₃, resulting in similar levels among the groups.

Safety and Tolerability

In addition to the two participants in HD-NaHCO₃ who had reduced the dose or stopped treatment as a result of high serum bicarbonate concentration, one participant in LD-NaHCO₃ had a single serum bicarbonate concentration

above our predefined safety threshold (≥33 meq/L) at week 32, after discontinuing treatment. No participants required per-protocol rescue therapy with NaHCO₃ during the treatment phase.

Total body weight was similar among the groups during follow-up (Figure 3A). The percentage of participants who increased diuretic therapy was similar between the groups, and the percentage that increased antihypertensive therapy was lowest, instead of highest, in HD-NaHCO₃ (Table 4). At week 12, mean SBP was higher in HD-NaHCO₃ than the other groups; however, at week 28, SBP in HD-NaHCO₃ and placebo were not significantly different from each other (Figure 3B). In HD-NaHCO₃, mean SBP was approximately 130 mm Hg after week 8, and no participants in HD-NaHCO₃ discontinued or reduced the dose because of high BP. SBP in LD-NaHCO₃ and placebo were similar at weeks 12 and 28 (Figure 3B).

Serum potassium concentration was similar between the groups during follow-up, although mean serum potassium was around 0.1 meq/L lower in HD-NaHCO₃ compared with LD-NaHCO₃ at week 28 (Figure 3C). No participants in the study had a serum potassium <3.0 meq/L. Ten participants, including three (3%) in HD-NaHCO₃, three (6%) in LD-NaHCO₃, and four (8%) in placebo, had 19 occurrences of a serum potassium of 3.0–3.5 meq/L.

Overall, there was no difference in gastrointestinal tolerability (Table 4). The percentage of participants who self-reported severe gastrointestinal symptoms at least once during the on-treatment phase was higher in the active treatment groups than placebo (Table 4) but this was not statistically significant ($P=0.39$ across the three groups). The most commonly reported severe gastrointestinal symptom was flatus in HD-NaHCO₃ (11%) and placebo (6%). In LD-NaHCO₃, the most commonly reported severe gastrointestinal symptoms were nausea (10%) and bloating (10%). Hospitalizations also occurred with similar frequency between the active and placebo groups (Table 4). Hospitalizations for CHF were uncommon ($n=3$; two in HD-NaHCO₃ and one in LD-NaHCO₃, comprising 2% in each group).

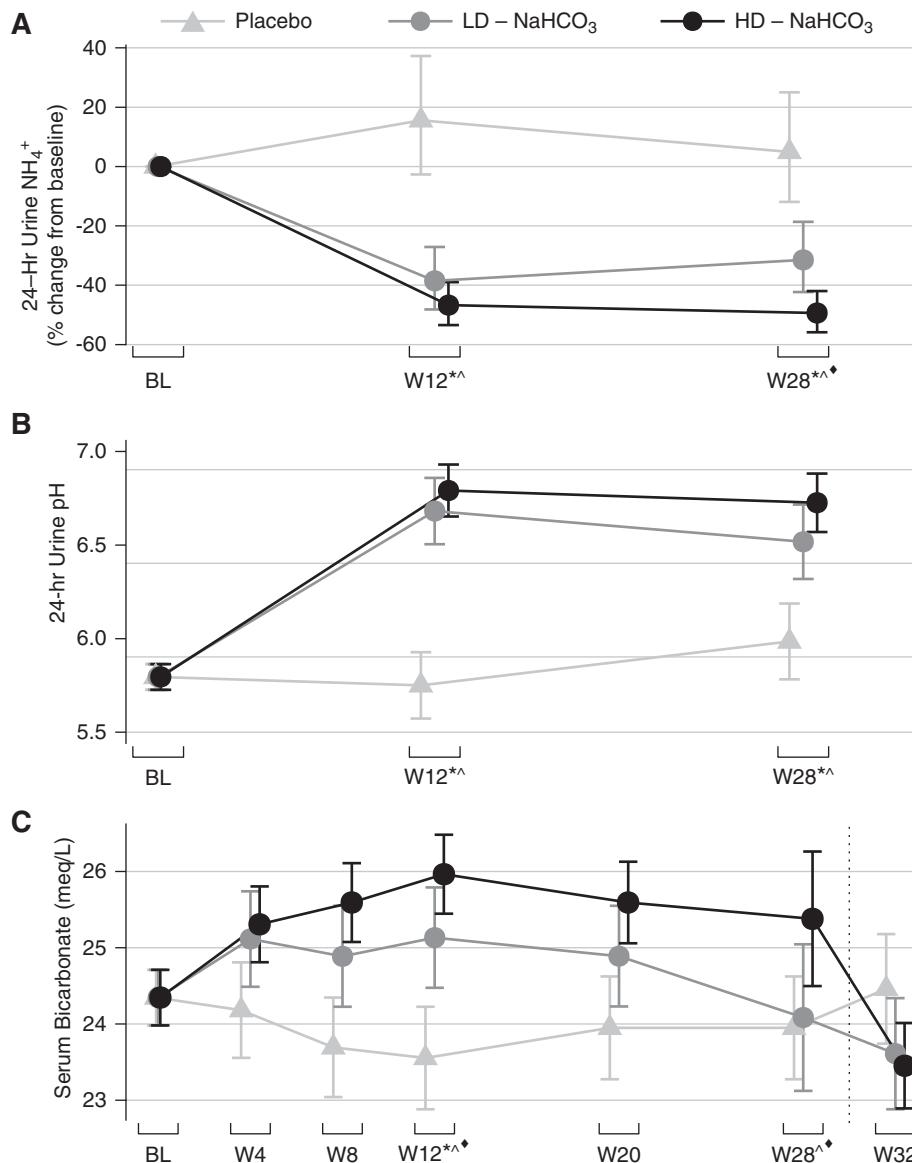


Figure 2. The higher dose of NaHCO_3 was associated with larger changes in urinary ammonium excretion, urinary pH, and serum bicarbonate concentration than the lower dose. Effect of two doses of NaHCO_3 on (A) urinary ammonium excretion, (B) urinary pH, and (C) serum bicarbonate concentration. The vertical dashed line in (C) indicates the end of the on-treatment phase. * $P<0.05$ for linear mixed model estimate of the change from baseline for LD versus placebo at the visit; ^ $P<0.05$ for linear mixed model estimate of the change from baseline for HD versus placebo at the visit; ♦ $P<0.05$ for linear mixed model estimate of the change from baseline for HD versus LD at the visit. BL, baseline; NH_4^+ , ammonium; W, week.

Changes in Urinary Sodium, Chloride, and Potassium Excretion

The mean prescribed dose of NaHCO_3 was 2.5 g (30 meq of sodium) in LD- NaHCO_3 and 3.8 g (46 meq of sodium) in HD- NaHCO_3 , and the magnitude of increase in daily urinary sodium excretion closely approximated the sodium load in each group (Table 3). Daily urinary chloride excretion was statistically significantly higher in HD- NaHCO_3 than LD- NaHCO_3 at week 28. There were no other significant differences in urinary chloride excretion among groups at baseline, week 12, or week 28. There were no differences in

urinary potassium excretion among groups during the study (Table 3).

Changes in eGFR and ACR

In exploratory analyses, we found no significant difference in the eGFR among the groups during follow-up (Figure 4A). These creatinine-based GFR estimates were unlikely to be influenced by changes in muscle metabolism related to treatment with NaHCO_3 , as there was no difference in 24-hour urinary creatinine excretion (Figure 4B) or creatinine clearance among the groups during follow-up (Figure 4C).

Table 3. Effect of two doses of NaHCO₃ on urinary and serum measurements

Measurement	Baseline	Wk 12	Wk 28
24-h urinary ammonium (meq/d)			
Placebo	16.3, 7.5–37.9	19.8, 10.5–40.8	16.7, 10.3–38.8
LD-NaHCO ₃	18.3, 7.9–30.9	10.7, 5.2–28.6 ^a	12.8, 5.5–25.7 ^a
HD-NaHCO ₃	18.9, 10.1–38.2	10.3, 3.7–30.5 ^b	10.9, 3.4–25.9 ^{b,c}
Urinary pH			
Placebo	5.7, 5.1–6.6	5.6, 5.2–6.6	5.8, 5.3–7.0
LD-NaHCO ₃	5.8, 5.3–6.5	6.8, 5.9–7.3 ^a	6.7, 5.6–7.1 ^a
HD-NaHCO ₃	5.7, 5.2–6.4	6.9, 6.0–7.3 ^b	6.9, 5.5–7.4 ^b
Serum bicarbonate (meq/L)			
Placebo	24, 22–27	23, 20–27	24, 20–28
LD-NaHCO ₃	25, 22–27	25, 22–28 ^a	25, 20–28
HD-NaHCO ₃	25, 21–28	26, 22–30 ^{b,c}	26, 22–29 ^{b,c}
24-h urinary sodium (meq/d)			
Placebo	161, 85–247	167, 73–286	162, 85–263
LD-NaHCO ₃	150, 69–220	176, 103–303	177, 90–241
HD-NaHCO ₃	156, 80–268	190, 105–298 ^b	197, 119–327 ^{b,c}
24-h urinary chloride (meq/d)			
Placebo	161, 80–231	166, 75–297	151, 81–249
LD-NaHCO ₃	148, 75–222	147, 74–257	151, 73–203
HD-NaHCO ₃	154, 70–266	144, 82–248	162, 87–257 ^c
24-h urinary potassium (meq/d)			
Placebo	53, 37–84	57, 27–100	63, 21–93
LD-NaHCO ₃	52, 30–92	58, 31–90	60, 30–84
HD-NaHCO ₃	60, 32–101	63, 38–100	61, 36–98
Random urinary ACR (mg/g)			
Placebo	147, 4.4–1494	173, 5.0–1251	176, 4.2–1488
LD-NaHCO ₃	222, 11.5–1421	213, 13.6–2017	220, 14.1–1899
HD-NaHCO ₃	176, 9.2–1433	205, 7.7–1671 ^b	195, 7.8–2265 ^b

The values shown are the median, 10th–90th percentiles of each variable.

^aP<0.05 for linear mixed model estimate of the change from baseline for LD versus placebo at the visit.

^bP<0.05 for linear mixed model estimate of the change from baseline for HD versus placebo at the visit.

^cP<0.05 for linear mixed model estimate of the change from baseline for HD versus LD at the visit.

A dose-dependent increase in ACR was observed (Figure 4D). At week 28, ACR was 12% (95% CI, –12% to 42%) higher in LD-NaHCO₃ and 30% (95% CI, 8% to 56%) higher in HD-NaHCO₃.

DISCUSSION

Prevention of progression of CKD remains a high priority in the United States and elsewhere. The number of available therapies to prevent or significantly slow down the loss of kidney function is limited. Additional clinical trials to evaluate promising treatments are needed. To obtain information to improve the design of a full-scale clinical trial to determine the effects of alkali supplementation on kidney function among persons with CKD, we conducted this pilot trial to evaluate the safety, tolerability, adherence, and pharmacodynamic profile of two oral doses of NaHCO₃ (0.5 and 0.8 meq/kg of lean body wt per day). We found both doses were well tolerated, few participants in any arm stopped or reduced the dose because of side effects, and attrition from the study was low. Although nearly one in five participants who were treated

with NaHCO₃ reported at least one episode of severe gastrointestinal symptoms, the proportion was not statistically significantly different than that experienced by persons assigned to placebo and importantly did not meaningfully decrease adherence. Of note, almost all (96%) participants assigned to the LD-NaHCO₃ group completed the on-treatment phase on the full, per-protocol dose and, in the HD-NaHCO₃ group, 87% completed the study on the full, per-protocol dose. The proportion in HD-NaHCO₃ who completed the study on full dose was similar to that in the placebo arm. Thus, in each NaHCO₃ dose group, our predefined threshold of acceptability was achieved and adherence by pill count was ≥88% in each arm during the study.

To help guide dose selection, we also characterized the effect of the two doses of NaHCO₃ on serum and urinary acid-base parameters. At week 12, both doses of NaHCO₃ lowered urinary ammonium similarly, however, at week 28 mean urinary ammonium excretion was 25% lower in the HD-NaHCO₃ arm than in the LD-NaHCO₃ arm. The mean serum bicarbonate concentration was higher in HD-NaHCO₃ than in LD-NaHCO₃ after week 8 (4 weeks after participants in HD-NaHCO₃ escalated to the full, per-protocol dose) and mean serum bicarbonate

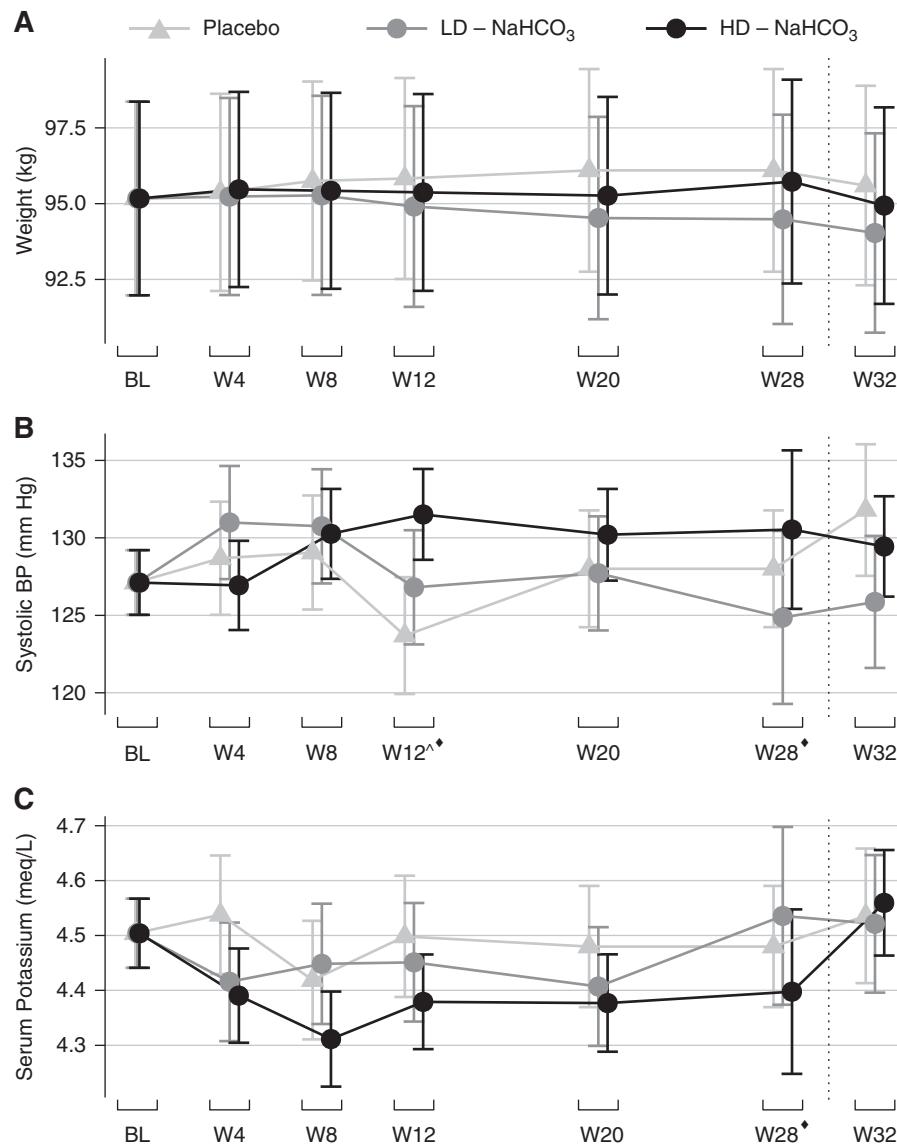


Figure 3. The doses of NaHCO₃ had no substantial effect on (A) total body weight, (B) SBP, or (C) serum potassium concentration. The vertical dashed line indicates the end of the on-treatment phase. $^{\wedge}P<0.05$ for linear mixed model estimate of the change from baseline for HD versus placebo at the visit; $\blacklozenge P<0.05$ for linear mixed model estimate of the change from baseline for HD versus LD at the visit. BL, baseline; W, week.

concentration was 1.3 meq/L higher in HD-NaHCO₃ than LD-NaHCO₃ at week 28. The magnitude of increase in urinary pH was similar between the two NaHCO₃ doses. Thus, the higher dose had a greater effect on urinary ammonium excretion and serum bicarbonate concentration than the lower dose.

These pharmacodynamic findings suggest the higher dose may be a better choice to test in studies evaluating the effect of NaHCO₃ on slowing CKD progression. Results from observational studies found higher serum bicarbonate concentrations within the normal range are associated with more favorable kidney and patient survival.^{19,20} The higher dose used in this study had a greater effect on serum bicarbonate concentration

than the lower dose, suggesting the higher dose might be more efficacious for improving hard clinical outcomes when used in future trials. In addition, ammonia activates the alternative pathway of complement within the kidney promoting tubulointerstitial fibrosis.^{21,22} Hypothetically, a greater reduction in kidney ammonia levels resulting from use of the higher dose might also have a more favorable effect on the kidney.

However, the higher dose of NaHCO₃ was associated with a modest but statistically significant increase in ACR. There was a suggestion that the lower dose increased ACR as well. These results were unexpected because prior studies had reported reductions in ACR with NaHCO₃ of 0.5 meq/kg of lean

Table 4. Effect of two doses of NaHCO₃ on diuretic and antihypertensive therapy, gastrointestinal symptoms, and hospitalizations

Event	Number (%) of Participants with Event			P
	HD-NaHCO ₃ (n=90)	LD-NaHCO ₃ (n=52)	Placebo (n=52)	
Increase diuretic therapy ^a	18 (20%)	13 (25%)	12 (23%)	0.77
Increase antihypertensive therapy ^a	20 (22%)	17 (33%)	21 (40%)	0.07
Gastrointestinal symptoms ^b				
Severe	16 (18%)	9 (17%)	5 (10%)	0.59
Moderate	22 (24%)	7 (14%)	13 (25%)	
Mild	36 (40%)	24 (46%)	24 (46%)	
None	16 (18%)	12 (23%)	10 (19%)	
Hospitalizations				
Total	16 (18%)	5 (10%)	7 (14%)	0.40
CHF	2 (2%)	1 (2%)	0 (0%)	0.57
Other cardiovascular	1 (1%)	0 (0%)	2 (4%)	0.23
Gastrointestinal	3 (3%)	2 (4%)	0 (0%)	0.38
Other	10 (11%)	3 (6%)	5 (10%)	0.57

Shown are the number (%) of participants in each group who experienced the event. In HD-NaHCO₃, the other cardiovascular-related hospitalization was for atrial fibrillation, and the gastrointestinal-related hospitalizations were for lower gastrointestinal bleed, abdominal pain, and other gastrointestinal condition. In LD-NaHCO₃, the gastrointestinal-related hospitalizations were for lower gastrointestinal bleeding and upper gastrointestinal bleeding. One person in LD-NaHCO₃ was hospitalized twice for different reasons. Hence, there were six hospitalizations in five participants in LD-NaHCO₃. In placebo, the other cardiovascular-related hospitalizations were for cerebrovascular accident and atrioventricular conduction block.

^aIncrease in diuretic or antihypertensive therapy included instances in which the dose of an agent was increased or if a new agent was prescribed.

^bShown is the highest level of gastrointestinal discomfort experienced by a participant at any time during follow-up.

body wt per day,¹⁰ NaHCO₃ of 1.0 meq/kg of lean body wt per day,²³ and sodium citrate of 1.0 meq/kg of lean body wt per day.⁹ Although the increased ACR is potentially concerning, results from prior studies found that alkali supplementation preserves eGFR, which is the outcome of greater interest.^{8,10–12,24} This includes a study that used 1.0 meq/kg of lean body wt per day of sodium citrate.⁹ Additionally, preliminary results from the Use of Bicarbonate in Chronic Renal Insufficiency (UBI) Study²⁵ showed that treatment of metabolic acidosis in patients with CKD using a mean daily NaHCO₃ dose of 1.1 meq/kg of total body weight also preserved kidney function. Changes in proteinuria were not evaluated in UBI. Because total body weight was used in UBI, the dose was considerably higher than doses prescribed here, which were based on lean body weight. Given the positive effects on kidney function observed with daily alkali doses of around 1.0 meq/kg in prior trials,^{9,25} and the greater pharmacodynamic effect on serum bicarbonate and urinary ammonium observed herein, we propose that future studies investigating the effect of NaHCO₃ on kidney function in patients with CKD and normal serum bicarbonate concentration should employ a dose of 0.8 meq/kg of lean body wt per day. Concurrently, we recommend that future studies closely monitor changes in ACR to determine if the findings observed here are reproducible.

Reasons for the modestly increased ACR observed here are uncertain. Increasing sodium chloride intake increases urinary albumin excretion.²⁶ However, urinary chloride excretion was not substantially different among the groups, suggesting sodium chloride intake remained consistent during the trial. Hence, the increase in ACR could be mediated by sodium. The increase in ACR is potentially related to the effect of urinary pH on urinary protease activity, which is inversely related

to urinary pH.²⁷ Consequently, raising urine pH with alkali could have reduced urinary protease activity leading to maintenance of the integrity of albumin and higher urinary concentrations of intact albumin determined by the assay. If confirmed in other studies, it would be important to elucidate the underlying mechanisms by which NaHCO₃ increases urinary albumin excretion.

A concern regarding long-term supplementation with NaHCO₃ in patients with CKD is sodium-mediated fluid retention leading to weight gain, peripheral edema, increased BP, pulmonary edema, and heart failure. However, in this 28-week study, no significant differences in total body weight were observed and the frequency of escalating diuretic therapy was similar among the three groups. One participant (1%) in HD-NaHCO₃ discontinued NaHCO₃ treatment for CHF with volume overload. However, two placebo-treated participants (4%) also developed fluid retention. The rates of hospitalization for CHF were low as well, with only 2% observed in each active treatment arm. One participant, assigned to the lower dose, discontinued treatment for difficult-to-manage BP. Otherwise, SBP was similar between LD-NaHCO₃ and placebo during treatment. The higher dose also did not have a substantial effect on BP. Although SBP in HD-NaHCO₃ was statistically significantly higher than the other groups at week 12, SBP was similar between HD-NaHCO₃ and placebo at week 28. Furthermore, 40% in placebo experienced an increase in the overall strength of the antihypertensive regimen as compared with 22% in HD-NaHCO₃. Differences in escalating antihypertensive treatment may account for the slightly higher mean SBP during the on-treatment period in HD-NaHCO₃. Whether this slightly higher BP accounts for the higher ACR in this group is unclear.

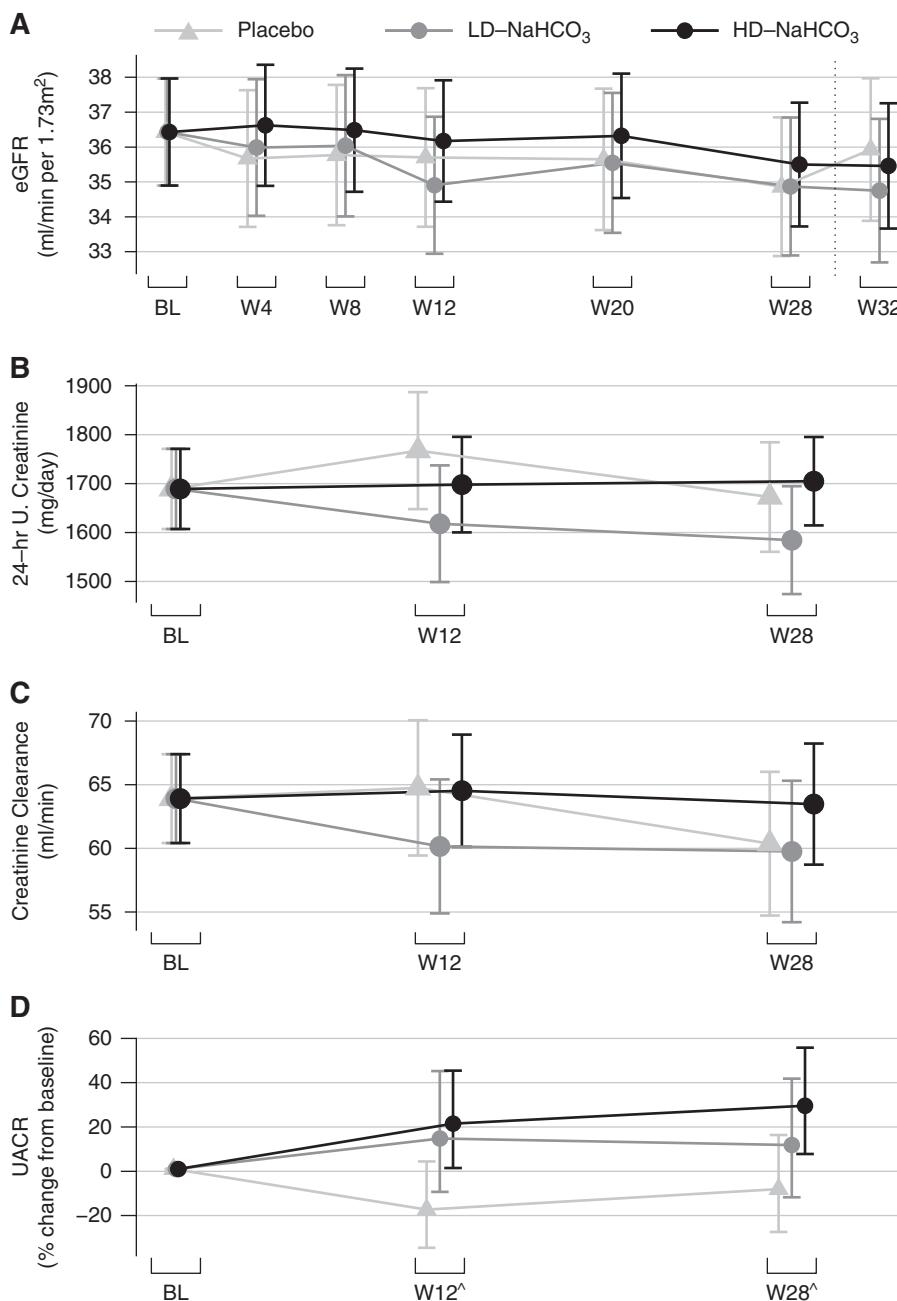


Figure 4. The doses of NaHCO₃ had no appreciable effect on (A) the eGFR, (B) 24-hour urinary creatinine excretion, or (C) creatinine clearance. However, there was a modest increase in random urinary albumin/creatinine (D). The vertical dashed line in (A) indicates the end of the on-treatment phase. [^]P<0.05 for linear mixed model estimate of the change from baseline for HD versus placebo at the visit. BL, baseline; UACR, urinary ACR; W, week.

Overall, these results suggest that doses of NaHCO₃ up to 0.8 meq/kg of lean body wt per day over 28 weeks do not cause clinically meaningful changes in fluid status or raise BP appreciably in patients with stage 3 or 4 CKD who have a baseline BP of <150/100 mm Hg. The absence of significant effects of NaHCO₃ supplementation on BP has been reported in prior intervention trials in CKD.^{8–11,23,24} Thus, sodium-mediated fluid retention appears to occur when

sodium intake is accompanied by chloride, but not with the bicarbonate anion.^{28,29}

Nevertheless, definitive conclusions about the cardiovascular safety of NaHCO₃ cannot be made due to the relatively short duration (28 weeks) of treatment and relatively small sample size, and there is reasonable concern that correcting metabolic acidosis may promote cardiovascular disease. For example, in animal models of CKD, correction of metabolic

acidosis increased vascular calcification,³⁰ and observational studies have found associations of higher serum bicarbonate above 26 meq/L with heart failure risk.¹⁹ On the other hand, correction of metabolic acidosis seems to have favorable effects on vascular function, assessed by flow-mediated dilation.³¹ Thus far, the effects of alkali supplementation on long-term cardiovascular effects have not been investigated.

Hypokalemia is another potential concern with NaHCO₃ supplementation by causing bicarbonaturia and kaliuresis or by shifting potassium intracellularly if the plasma pH rises. However, neither dose of NaHCO₃ in this study increased urinary potassium excretion. Further, serum potassium concentration was similar among the groups, and no participants experienced significant hypokalemia (<3.0 meq/L).

Prior studies testing the effect of alkali supplementation on kidney function have largely been single-center studies and most enrolled patients had hypertensive CKD.^{9–12,23} A significant strength of the BASE Pilot Trial is that it enrolled individuals at multiple institutions across the United States and half had diabetes. It is also the first study to assess the safety, tolerability, adherence, and pharmacodynamic response of two doses of NaHCO₃. Serum bicarbonate concentration was measured at local clinical laboratories, reducing concerns about falsely low serum bicarbonate levels due to measurement delays.³² The relatively short duration of the study, however, precludes definitive conclusions about long-term efficacy and safety of various doses of oral bicarbonate. Individuals with severe CHF and those with BP <150/100 mm Hg were not studied; whether NaHCO₃ doses prescribed here are safe in patients with these characteristics is uncertain.

In conclusion, an oral NaHCO₃ dose of either 0.5 or 0.8 meq/kg of lean body wt per day was well tolerated and had a favorable adherence profile over 28 weeks in persons with a mean (SD) eGFR of 36 (9) ml/min per 1.73 m² and serum bicarbonate of 24 (2) meq/L. The pharmacodynamic profile, based on changes in urinary ammonium and serum bicarbonate concentration, appears to favor using the higher dose in future full-scale trials. However, the favorable profile of the higher dose is counterbalanced by an unexpected, modest increase in ACR. These findings provide critical preliminary data to help guide dose selection in future clinical trials evaluating the effect of NaHCO₃ on CKD progression.

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DISCLOSURES

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SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at <http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2019030287/-/DCSupplemental>.

Supplemental Material. Protocol for the Bicarbonate Administration to Stabilize eGFR (BASE) Pilot Trial.

Supplemental Figure 1. Image of size 0-, 00-, and 000-capsules in relation to a US penny.

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See related editorial, "Pilot Trials in Nephrology: Establishing a BASE for Large-Scale Randomized Trials," on pages XXX–XXX.

AFFILIATIONS

¹Department of Internal Medicine, University of Utah Health and Renal Section, Veterans Affairs Salt Lake City Health Care System, Salt Lake City, Utah; ²Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; ³Department of Medicine, University of California San Diego and Renal Section, Veterans Affairs San Diego Healthcare System, San Diego, California; ⁴Division of Renal Diseases and Hypertension, Department of Medicine, George Washington University School of Medicine, Washington, DC; ⁵Division of Nephrology, Department of Medicine, Duke Clinical Research Institute, Duke University, Durham, North Carolina; ⁶Department of Medicine, University of Pittsburgh and Renal Section, Veterans Affairs Pittsburgh Health Care System, Pittsburgh, Pennsylvania; ⁷Department of Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland, Ohio; ⁸Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland; ⁹Department of Medicine, Case Western Reserve Hospitals, Cleveland, Ohio; ¹⁰Denver Nephrology, Denver, Colorado; ¹¹Renal Section, Veterans Affairs Washington, DC Health Care System, Washington, DC; ¹²Department of Medicine, Northshore University Health System, University of Chicago, Evanston, Illinois; and ¹³Health and Wellness Center, Baylor Scott & White Health, Dallas, Texas