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Association of pre-ESRD serum bicarbonate with post-ESRD mortality in patients with incident ESRD

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Abstract

Background: Serum bicarbonate or total carbon dioxide (CO_2) concentrations decline as chronic kidney disease (CKD) progresses and rise after dialysis initiation. While metabolic acidosis accelerates the progression of CKD and is associated with higher mortality among patients with end-stage renal disease (ESRD), there are scarce data on the association of CO_2 concentrations before ESRD transition with post-ESRD mortality.

Methods: A historical cohort from the Transition Care in CKD (TC-CKD) study includes 85,505 veterans who transition to ESRD from October 1, 2007 through March 31, 2014. After 1,958 patients without follow-up data, 3 patients with missing date of birth, and 50,889 patients without CO_2 6 months prior to ESRD transition were excluded, the study population includes 32,655 patients. Association between CO_2 concentrations averaged over the last 6 months and its rate of decline during the 12 months prior to ESRD transition and post-ESRD all-cause, cardiovascular (CV) and non-CV mortality were examined by using hierarchical adjustment with Cox regression models.

Results: The cohort was on average 68±11 years old and included 29% Black veterans. Baseline concentrations of CO_2 were 23±4 mEq/L and median (interquartile range) change in CO_2 were −1.8 [−3.4, −0.2] mEq/L/year, respectively. High (>28 mEq/L) and low (<18 mEq/L) CO_2 concentrations showed higher adjusted mortality risk while there was no clear trend in the middle range. Consistent associations were observed irrespective of sodium bicarbonate use. There was also a U-shaped association between the change in CO_2 and all-cause, CV, and non-CV mortality with the lowest risk approximately at −2.0 mEq/L/year and 0.0 mEq/L/year among sodium bicarbonate non-users and users, respectively and the highest mortality was among patients with decline in CO_2 >4 mEq/L/year.

Conclusion: Both high and low pre-ESRD CO2 levels (28 and <18 mEq/L) during 6 months prior to dialysis transition and rate of CO_2 decline >4 mEq/L/year during 1-year before dialysis initiation were associated with greater post-ESRD all-cause, CV, and non-CV mortality. Further studies are needed to determine the optimal management of CO_2 in patients with advanced CKD stages transitioning to ESRD.

Keywords

INTRODUCTION

Acid-base balance is important for maintaining homeostasis in humans. Serum bicarbonate or total carbon dioxide (CO_2) concentrations decline as chronic kidney disease (CKD) progresses, and metabolic acidosis is one the most common complications among patients with CKD. Several studies showed an association of low CO_2 with worsening renal function [1–3] and metabolic acidosis may exacerbate bone diseases [4, 5] and protein catabolism [6–8] in patients with CKD. Studies have also linked low CO_2 with higher mortality in patients both with and without CKD.[9–13] CO_2 concentrations rise after dialysis initiation, but the association of low CO_2 with mortality is still associated with poor clinical outcomes including higher risks of all-cause and cardiovascular (CV) mortality and hospitalization in end-stage renal disease (ESRD) patients.[14–16] Conversely, a high CO_2 level has been shown to be associated with higher mortality in pre-dialysis CKD [9], but there are mixed data in dialysis patients.[14, 3]

Correction for metabolic acidosis in CKD patients is associated with slower progression of CKD and improvement in nutritional status and bone health [1]. A recent randomized clinical trial demonstrated survival benefit of sodium bicarbonate in CKD patients [17]; however, bicarbonate therapy was associated with higher mortality in patients with lactic acidosis [18]. The consequence of normalizing CO_2 in CKD patients with metabolic alkalosis is also unclear. Therefore, CO_2 may be a surrogate marker of mortality risk in CKD and ESRD populations and using a therapeutic intervention to maintain CO_2 within certain values may improve survival in these populations.

Despite this, the cut-off levels to define high or low CO_2 are inconsistent across studies and there is little evidence to aid in the target of CO_2 concentrations among patients transitioning

to ESRD. Kidney Disease Improving Global Outcomes (KDIGO) recommends that CO_2 levels are maintained at or above 22 to 32 mEq/L.[19]. To address the knowledge gap, we examined the association between an average CO_2 before dialysis initiation and mortality after initiating dialysis in a large national cohort of US veteran patients transitioning to ESRD.

METHODS

This study was approved by the Institutional Review Boards of the Memphis and Tibor Rubin (Long Beach) Veterans Affairs (VA) Medical Centers. The requirement for written informed consent was waived due to the large sample size, patient anonymity and nonintrusive nature of the study.

Study Population and Data Source

The Transition Care in CKD (TC-CKD) study is a historical cohort of US veterans who transition to ESRD from October 1, 2007, through March 31, 2014 [18, 20–24]. The original population included 85,505 veterans derived from the United States Renal Data System (USRDS). In the current study, patients without follow-up data (n=1,958) and with missing date of birth (n=3) were excluded. We restricted our cohort to 32,655 patients who had an available serum CO_2 measurement within 6 months prior to the start of ESRD (Appendix Figure 1). In addition, we examined the association of CO_2 slopes before dialysis initiation with mortality and further excluded an additional 6,285 patients who did not meet the slope criteria. Patients were required to have 2 CO_2 measurements during their 1-year pre-ESRD period, where the last measurement had to be in the baseline period and at least 90 days from the first measure. We lastly excluded 524 patients with CO_2 slope outliers and 66 patients missing data on estimated glomerular filtration rate (eGFR) in the last year prior to transition, which resulted in a sub cohort of 25,780 patients.

Demographic, Clinical and Laboratory Measurements

Ascertainment of clinical characteristics have been previously described elsewhere [20–24]. Patient characteristics of the cohort were drawn from a composite of USRDS, VA and Centers for Medicare and Medicaid Services (CMS) databases, with the exception of marital status which was collected from VA records only. Both pre-existing comorbidity status and medication use were ascertained from VA and CMS data. Individual medications were categorized into broad groups by clinician assessment and drug class codes. We defined 6-month medication ever-use as having a prescription filled within 6 months before ESRD initiation.

Data on the eGFR at the time of transition was primarily obtained from USRDS records, and were supplemented with serum creatinine data obtained from the VA Corporate Data Warehouse (CDW) LabChem file and calculated with the CKD Epidemiology Collaboration formula [25]. Other laboratory data, including serum bicarbonate measurements, were obtained from the Decision Support System National Data Extracts Laboratory Results file. Data on body mass index (BMI) were obtained from the VA CDW Vital Signs file. In the present study, BMI and laboratory measurements including CO_2 concentration, white blood

cell, hemoglobin, albumin, corrected calcium, serum phosphorus, and serum uric acid with the exception of eGFR were averaged over the 6-month period prior to ESRD transition and were considered to be baseline. The eGFR slope was calculated using a mixed-effects (random intercept and slope) model in patients with 2 eGFR measurements in the year prior to transition.

Exposure Measurement

Our primary exposure was 6-month pre-ESRD (prelude) averaged CO_2. CO_2 concentration was measured by using CHM-S0030 carbon dioxide (CO_2) on the UniCel DxC800 autoanalyzer (SYNCHRON®). With a convenient categorization with an effort to make a good balance between granularity and statistical power, we stratified the exposure into seven categories with the following increments: <18, 18 to <20, 20 to <22, 22 to <24 (reference), 24 to <26, 26 to <28, and 28 mEq/L. The secondary exposure was the rate of change in CO_2 over the period of 1-year prior to ESRD transition using the following four categories: <−4, −4 to <−2, −2 to <0 (reference), and 0 mEq/L/yr. The rate of change in CO_2 was calculated using a mixed-effects model with random intercept and random slope among 25,780 patients.

Outcome Assessment

The main outcomes of interest for this study were all-cause, cardiovascular and non-cardiovascular mortality after transition to ESRD. We extracted data for cause of death from USRDS records and categorized them into cardiovascular and non-cardiovascular deaths. Information on censoring events, including death, were obtained from composite VA, CMS and USRDS records. Follow-up started at the ESRD transition and continued until death, kidney transplantation, loss to follow-up, or the date of final follow-up assessment for all patients (September 2, 2014 for all-cause mortality and June 30, 2014 for cardiovascular and non-cardiovascular mortality).

Statistical Analysis

Baseline characteristics of the study population were presented according to serum bicarbonate groups. We reported means ± standard deviation (SD) or medians [interquartile range] for continuous variables, where appropriate, and percentages for categorical variables. Comparisons of baseline clinical characteristics between patients with and without serum bicarbonate were done using standardized differences and are presented in Appendix Table 1. We applied a mixed-effects regression model to evaluate the trajectory of monthly population mean CO_2 concentrations over the period of 1-year pre- and post- initiation.

Potential confounders were included in the following four models of hierarchal adjustment: (i) Model 1, unadjusted; (ii) Model 2 included age, gender, race, ethnicity, and marital status; (iii) Model 3 included all covariates in Model 2 plus Charlson comorbidity index, diabetes, prior history of ischemic heart disease, congestive heart failure, atrial fibrillation, cerebrovascular disease, chronic pulmonary disease, depression, cancer, BMI, and eGFR at the time of transition; and (iv) Model 4 included all covariates in Model 3 plus serum albumin, hemoglobin, white blood cell count, corrected calcium and medications, which comprised calcium supplements, active vitamin D, non-calcium-containing phosphate

binders, erythropoiesis-stimulating agents (ESA), renin-angiotensin aldosterone system (RAAS) inhibitors, sodium bicarbonate, and loop and/or thiazide diuretics. In analyses examining CO_2 slope, we additionally included the slope for eGFR and the first available CO_2 measurement in the 1-year period prior to ESRD transition as covariates to Models 2 through 4. In sensitivity analysis, we additionally adjusted for access type, uric acid, and serum phosphate.

We examined the associations between baseline CO_2 and change in CO_2 with mortality using separate Cox proportional hazards models. We also assessed whether the association between 6-month CO_2 concentrations and post-ESRD mortality varied by medication use (sodium bicarbonate) in adjustment Model 4, stratifying patients by 6-month prelude sodium bicarbonate ever- and never-use. Restricted cubic spline functions were used to assess the associations of CO_2 and slope modeled as continuous variables with post-ESRD all-cause, cardiovascular and non-cardiovascular mortality in the adjustment Model 4. Knots were placed at the 5th, 35th, 65th and 95th percentiles. Formal tests for interaction were done using the Wald test. Effect modification by age, diabetes, cancer, and year of dialysis initiation on associations of CO_2 with all-cause death in fully adjusted models were examined and plotted.

Missing data on race, ethnicity, and marital status were categorized as "other races" (n=2), non-Hispanic (n=1), and "missing" (n=68), respectively. In the case of missing data on BMI (2.3%), eGFR at transition (2.9%), hemoglobin (9.2%), white blood cell count (8.5%), albumin (9.2%), and corrected calcium (12.9%) were imputed by means. Missing slope of eGFR (1.4%) were imputed by median. Analyses were conducted with the use of SAS Enterprise Guide, version 7.1 (Cary, NC, USA) and Stata version 14.2 (StataCorp, College Station, TX, USA).

RESULTS

Baseline demographic, clinical and laboratory characteristics

Among 85,505 US veterans who transitioned to ESRD, 32,655 were included in this study. This study population were mainly male (98%) with a mean±SD age of 68±11 years. The cohort included 29% Black patients, and the majority of patients had congestive heart failure, ischemic heart disease, and diabetes. Compared to 52,850 excluded patients, the study population were younger, less likely to be female or married; however, they were likely to have a higher prevalence of diabetes and depression (Appendix Table 1).

Mean pre-ESRD 6-month averaged CO_2 was 23±4 mEq/L. Patients with lower CO_2 were younger; more likely to be Black, Hispanic, and single or divorced; less likely to have diabetes, congestive heart failure, ischemic heart disease, atrial fibrillation, and chronic pulmonary disease; and had lower 6-month averaged BMI, hemoglobin, albumin, and corrected serum calcium and lower eGFR at transition (Table 1). They were also more likely to receive sodium bicarbonate, erythropoiesis-stimulating agents, calcium supplements, and phosphate binders, but were less likely to receive diuretics and RAAS inhibitors.

Trajectories of serum bicarbonate before and after dialysis initiation

Patients with CO_2 <24 mEq/L at baseline had a gradual decline in CO_2 during 1-year prior to initiation until between 1 and 2 months pre-ESRD when CO_2 rapidly dropped. Patients with CO_2 24 mEq/L had relatively stable CO_2, which then slightly dropped during the last 2 months prior to transition except for those with CO_2 28 mEq/L who had a small increase in CO_2 between 6 and 7 months pre-ESRD and remained stable until transition.

In the immediate months after initiation, all strata, with the exception of high CO_2 28 mEq/L, had a steep and rapid increase in CO_2 toward normal levels, which were higher than their own prelude 6-month average levels. Patients with the highest prelude 6-month averaged CO_2, had decreased CO_2 after initiation and levels plateaued to their levels between 7 and 12 months pre-ESRD. Their post-ESRD CO_2 level then remained stable throughout the rest of post-ESRD period. The differences in CO_2 between each strata were attenuated and the order was maintained when compared to pre-ESRD period (Figure 1).

Pre-ESRD CO_2 and post-ESRD mortality

During the follow up of median 1.8 (0.7, 3.2) years, 16,828 patients died with an incidence rate of 24.0 per 100 patient-years. When compared to the reference (CO_2: 22 to <24 mEq/L), higher pre-ESRD CO_2 levels were associated with greater all-cause mortality in the unadjusted model reflective of a reverse J-shape (Figure 2A and Appendix Table 2). Those associations were attenuated with additional adjustments, but a higher mortality risk was still observed for pre-ESRD CO_2 levels 26 mEq/L. The highest risk of mortality was observed for CO_2 levels 28 mEq/L (hazard ratio (HR) [95% Confidence Interval]: 1.20 [1.14, 1.27]). After full adjustment, pre-ESRD CO_2 <18 mEq/L was also associated with a higher risk of all-cause mortality (HR [95%CI]: 1.12 [1.05,1.20]). In sensitivity analysis, additional adjustment for uric acid, serum phosphate and access type did not significantly change this relationship.

The number and incidence rate of CV and non-CV deaths after transition were 5,368 (7.9 per 100 patient-years) and 10,956 (16.2 per 100 patient-years), respectively. Their associations with pre-ESRD CO_2 levels were similar to that of all-cause mortality (Figures 2B and 2C; Appendix Table 2). Both low and high CO_2 levels were associated with higher risks of CV and non-CV mortality after model 4 adjustment. The highest adjusted risks were for CO_2 levels 28 mEq/L for both CV and non-CV mortality (HR [95%CI]: 1.29 [1.17, 1.41] and 1.17 [1.09, 1.25], respectively).

Patients were then stratified by those who ever used and never used sodium bicarbonate during the 6-month pre-ESRD period. After the highest level of adjustment, the use of sodium bicarbonate modified the association between CO_2 and all mortality outcomes ($P_{interaction}$ of <0.001, 0.002, and 0.014 for all-cause, CV, and non-CV mortalities, respectively; Figure 3). The associations of low CO_2 levels with high all-cause mortality risk were observed among sodium bicarbonate users (Figure 3B) but were attenuated among non-users (Figure 3A). A similar relationship was also observed with low CO_2 levels and CV mortality, where a higher risk was observed for sodium bicarbonate users (Figure 3C and Figure 3D). Low CO_2 levels and non-CV mortality risk was attenuated irrespective of

sodium bicarbonate use (Figure 3E and 3F). The associations of high CO_2 levels with all mortality outcomes were relatively consistent between sodium bicarbonate users and non-users, yet with the exception of high CO_2 and non-CV mortality among sodium bicarbonate users, where a null association was observed (Figure 3F). Associations of CO_2 with all-cause mortality were also similar according to age, diabetes, cancer and year of dialysis initiation (Appendix Figure 2–5).

Pre-ESRD change in serum bicarbonate and post-ESRD mortality

A total of 25,780 patients were available for evaluating the association of the change in CO_2 within the 1-year post-ESRD period. During the follow up, 12,944 patients died with an incidence rate of 23.2 per 100 patient-years. In unadjusted analyses, we observed a flat and attenuated association between decreased CO_2 and mortality risk; however, this association amplified after models adjustment. In the adjusted analyses, the adjusted mortality risk was higher among patients with decline in CO_2 >4 mEq/L/year than those with decline of −2 to <0 mEq/L/year in adjusted models (Figure 4A and Appendix Table 3). Patients with increasing CO_2 showed a higher adjusted mortality risk in Models 2 and 3, but was attenuated in Model 4. There were largely consistent associations with CV and non-CV mortality outcomes (Figures 4B and C; Appendix Table 5).

Cox models using restricted cubic spline functions showed a consistent pattern of association between rate of change in CO_2 and all-cause (Figure 5A and Figure 5B), CV (Figure 5C and Figure 5D), and non-CV (Figure 5E and Figure 5F) mortality outcomes irrespective of sodium bicarbonate use ($P_{interaction}$ = 0.21, 0.77, and 0.17 for all-cause, CV, and non-CV mortalities, respectively).

DISCUSSION

From our large, national cohort of veterans with advanced CKD transitioning to ESRD, we found U-shaped associations of pre-ESRD CO_2 with post-ESRD all-cause, CV, and non-CV mortalities with the lowest risk between CO_2 of 18 to <26 mEq/L after full adjustment. In addition, a decrease in the slope of CO_2 during the 1-year pre-ESRD period was associated with higher risks of all-cause, CV, and non-CV mortality outcomes. The relationships after stratification by use of sodium bicarbonate were largely similar to that of the primary analyses.

Our study showed a U-shaped relationship between baseline pre-ESRD CO_2 and post-ESRD transition all-cause, CV, and non-CV mortalities adds to findings of prior studies. Similar to our study, an observational study investigating patients with CKD stages 2–4 from the Chronic Renal Insufficiency Cohort (CRIC) revealed a cardiovascular effect for high CO_2 levels, illustrating that there is a 14% increased risk of heart failure for every 1 mEq/L increase in CO_2 above 24 mEq/L [3]. In data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) international cohort study [14], as well as the study by Kovesdy et al. [9], which included veteran patients with moderate to advanced non-dialysis dependent CKD, the association with serum bicarbonate was also U-shaped, with higher CO_2 levels associated with the highest mortality risk. In a study by Navaneethan et al. [11], there was an association between high CO_2 levels and mortality in patients with stage 3/4 CKD, which

resulted in a J-shaped relationship between high CO_2 levels and mortality. Low and high bicarbonate were also associated with cause specific mortality. Using data over 11 years from the National Health and Nutrition Examination Survey, Al-Kindi *et al.* demonstrated higher malignancy-related mortality with bicarbonate <22 mEq/L and CV mortality with bicarbonate >26 mEq/L regardless of CKD status [27]. Thus, the predominant U-shaped association between CO_2 levels and higher mortality is consistent with previous studies.

However, a recent post-hoc analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) did not demonstrated a J- or U-shape association between serum bicarbonate concentration and CV mortality. Compared to non-diabetic patients with HCO_3 22 – 26 mEq/L, those with a serum bicarbonate <22 mEq/L had greater CV mortality regardless target systolic blood pressure either <120 or <140 mmHg; whereas, there was no increased CV mortality risk in patients with serum bicarbonate >26 mEq/L [28]. Differences between several baseline characteristics between SPRINT and our study may explain the inconsistent finding of the serum bicarbonate- mortality association. While mean age and proportion of each race/ethnicity were similar between study populations in SPRINT and lower CO_2 groups (<22 mEq/L) in our study, higher CO_2 groups (22 mEq/L) in our study were older, had greater proportion of White, but lower proportion of Black and Hispanic patients. This can be supported by previous studies that showed a paradoxically lower mortality among Black Veterans who have equal healthcare access compared to higher mortality among Black in the US general population [29, 30]. Moreover, all CO_2 groups in our study appeared to have higher significant co-morbidities including advanced stage CKD, higher proportion of CVD (20.1% vs 40 – 70%), male (64.5% vs 98%) and diabetes (0% vs 60 – 75%).

Whether the J- or U-shape association between CO_2 and mortality in CKD or ESRD patients from previous studies were consistent with our study, those studies examined the association between CO_2 and mortality either before or after ESRD transition. The uniqueness of our study is the potential predictive value of average CO_2 during advance CKD on mortality after dialysis transition.

A potential explanation for the association of higher CO_2 groups with higher mortalities, particularly those related to CV disease, which is the most common cause of mortality in CKD and ESRD patients [31, 32], is medial arterial calcification (MAC). An individual with high CO_2 is considered to have metabolic alkalosis [33]. A rodent study was done to understand the mechanism for vascular calcification in individuals with CKD [33]. They identified that alkalinization increases vascular calcification in cultured cells and rats, which suggests that MAC could be a potential mechanism behind high CO_2 concentrations and mortality risk [33]. To understand the association between high CO_2 and MAC in humans, further studies are needed. MAC is one of the most common complications associated with CV disease in patients with CKD and ESRD.[34, 35] MAC can lead to vascular stiffness and subsequently left ventricular hypertrophy (LVH), myocardial ischemia, and congestive heart failure in ESRD patients [36, 34, 37]. In addition to CKD or ESRD, diabetes, the foremost cause of ESRD, is also common risk factor of MAC [38–43].

Increased CO_2 was associated with low dietary protein intake in CKD patients [44] which facilitates muscle loss or inhibits muscle protein synthesis [45]. Loss of muscle mass can

lead to sarcopenia and subsequently increased morality [46]. High mortality in higher CO_2 groups in our study may be explained partly by low dietary protein intake. Although this group had the highest BMI which may reflect overnutrition, sarcopenic obesity may occur and is also associated with mortality [46].

Due to the nature of the U-shaped relationship between CO_2 and mortality, patients in the lowest CO_2 group also had increased post-ESRD mortality risk. Similar to Kovesdy et al. [9] and the DOPPS international cohort study [14], we also observed an association between low CO_2 and high mortality. A study by Vashistha et al. [15] analyzed the association between peritoneal dialysis or hemodialysis and mortality in patients with low CO_2 and determined that those treated with either dialysis modalities had a higher death risk with low CO_2 levels. Patients with low CO_2, although had rapid increase in CO_2 during the first month after dialysis initiation, their CO_2 remained low to the low-normal range after transition, and they likely received high dialysate bicarbonate bath during treatment, however this cannot be confirmed in this cohort. Dialysate bicarbonate is used to correct the composition of uremic blood to appropriate physiological levels by reducing uremic toxins and rectifying electrolyte and acid-base irregularities [47]. The DOPPS cohort study [47] showed that high dialysate bicarbonate bath is associated with higher all-cause and cause-specific mortality in ESRD patients. In that study, a mean dialysate bicarbonate was 35.5 ± 2.7 mEq/L and they observed an 8% higher risk of mortality from every 4 mEq/L increase in dialysate bicarbonate concentration.

An individual with low CO_2 is considered to possibly have metabolic acidosis, which has been associated with worsening renal function [1–3] as well as adverse outcomes including malnutrition or muscle wasting [48]. There is an inverse correlation between CO_2 and normalized protein catabolic rate (nPCR) [49], which is a marker of endogenous acid production [50]. Patients in the lowest CO_2 group may have had malnutrition entering into ESRD, which in turn, contributed to their higher mortality post-ESRD. These findings are consistent with a reverse epidemiology or obesity paradox, which illustrates the association between malnourished individuals and adverse CV outcomes in dialysis patients, thus indicating a higher mortality in CKD or ESRD with undernutrition [51]. Patients with a baseline pre-ESRD CO_2 level <18 mEq/L had a rapid decline in CO_2 levels compared to patients with the baseline CO_2 of 18 to 26 mEq/L and likely represent patient groups whose a prelude 1-year slope in CO_2 of more than −4 mEq/L/year. They had higher risk compared to the patients with a decrease in slope of less than −4 mEq/L/year. Therefore, it can be speculated that metabolic acidosis with a CO_2 concentration <18 mEq/L, particularly with more rapid decline in CO_2 prior to ESRD transition, may be one of the prognostic factors of mortality after ESRD initiation.

A Cochrane review [52] and meta-analysis [53] revealed that there were no evidence to support the use of sodium bicarbonate to slow CKD progression which may subsequently affect mortality. However, 2012 KDIGO clinical practice guideline for the evaluation and management of CKD suggested sodium bicarbonate use to maintain serum bicarbonate 22 mmol/L (level of evidence 2B) [19]. A recent randomized controlled trial (RCT) demonstrated improvement in kidney function and lowered mortality in stage 3 – 5 CKD patients who received sodium bicarbonate compared to those who had standard of care [17].

Another RCT revealed the efficacy and safety of novel oral selective hydrochloric acid binder from gastrointestinal tract, veverimer, which can also increase HCO_3 in CKD patients and patient-reported physical functioning [54]. Given only 45% of patients with CO_2 <18 mEq/L in our study received sodium bicarbonate, CO_2 level in our study may be affected by change in clinical practice of using sodium bicarbonate in CKD overtime during the study period between 2007 and 2014. However, subgroup analysis demonstrates associations did not differ significantly among those who initiated dialysis between 2007–2011 versus 2012–2014.

The clinical significance of the averaged CO_2 six months prior to dialysis initiation in our study may need to be elucidated by acidemic and alkalemic status, which is determined by arterial pH given these reflect cellular function [50]. An observational cross-sectional study by Yamamoto *et al.* examined the association between pre-dialysis pH or pre-dialysis bicarbonate level and mortalities in ESRD patients [55]. This study showed that pre-dialysis pH 7.40, but not pre-dialysis bicarbonate level, was associated with greater all-cause and CV mortalities compared to pre-dialysis pH 7.30–7.34. The lack of pH from an arterial blood gas, which is not routinely performed in clinically stable advanced CKD patients, limits our ability to determine true acid-base disturbance in our study population. It is unclear whether the lowest CO_2 group in our study had true metabolic acidosis, respiratory alkalosis, or metabolic acidosis with concomitant respiratory alkalosis, which probably reflects the patients' clinical conditions and may be better associated with mortality.

In addition, lower CO_2 groups in our study had a higher proportion of patients who required ESAs, although they had lower mean hemoglobin levels comparative to the higher CO_2 groups. ESAs have been a cornerstone in treating anemia in patients with CKD and ESRD [56]. ESAs do not reduce adverse outcomes associated with anemia, such as nonfatal cardiovascular events, LVH, hospitalizations, and progression of kidney disease [57]. Furthermore, a study by Streja *et al.* [56] illustrated that a higher dose of ESAs in hemodialysis patients is associated with a higher risk of mortality. Increased ESAs use among the lowest CO_2 group, especially sodium bicarbonate users, could potentially cause right shift of the oxygen-hemoglobin dissociation curve and may reflect erythropoietin resistance [58]. Likewise, it is understood from this study that among sodium bicarbonate users with low CO_2 levels there was a higher risk for all-cause mortality, which could be associated with a prolonged use of ESAs.

On the other hand, patients with higher CO_2 may have underlying precipitating and/or perpetuating factors of metabolic alkalosis such as respiratory acidosis or contraction alkalosis from chronic diuretic use. This may be suggested by up to 57% and 71% of the highest CO_2 group in our study had chronic pulmonary disease and congestive heart failure, respectively as well as 75% were on diuretics.

There are several limitations in our study. First, 52,850 patients were excluded from a total cohort of 85,505 patients, which could lead to selection bias resulting from the inclusion criteria. Moreover, there was possibility that the advanced CKD patients might die even before transition to ESRD, particularly those with the extremely low and high CO_2. This may also lead to immortal time bias. Second, our study population was reflective of the US

veteran population of male, older, non-Hispanic white patients. This may limit external validity of the results in our study. Third, data after dialysis initiation, specifically dialysate bicarbonate bath, were not available in this study. Fourth, we did not have nPCR to assess protein intake and nutritional status. Fifth, there was no arterial blood gas to indicate acid-base status. However, CO_2 is much more commonly used than arterial blood gas and is available in clinical settings; thus, our study results may still guide clinicians in clinical practice. Sixth, we do not have data regarding change in clinical practice for using sodium bicarbonate supplement in CKD during our study period between 2007 and 2014 which may affect CKD progression and mortality. Seventh, some post-ESRD factors can influence mortality in ESRD patients such as residual kidney function, and dialysis frequency (<3 or 3 times/week of HD) were not available to be incorporated into our analysis model. Furthermore, given the nature of observational study designs, we cannot prove the associations are causal and there remains the possibility of residual confounding and unmeasured confounders. However, there are strengths to this study, such as the use of a large nationally representative cohort of veterans with a large amount of laboratory data prior to the transition to ESRD.

In conclusion, among advanced CKD patients, CO_2 levels during 6 months prior to dialysis initiation (both <18 and 28 mEq/L) and pre-ESRD decline in CO_2 during 1-year before starting dialysis (i.e., >4 mEq/L/year), were associated with higher all-cause, CV, and non-CV mortalities. Further studies, especially clinical trials, are warranted to determine the optimal management of CO_2 in patients with advanced CKD stages transitioning to ESRD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS:

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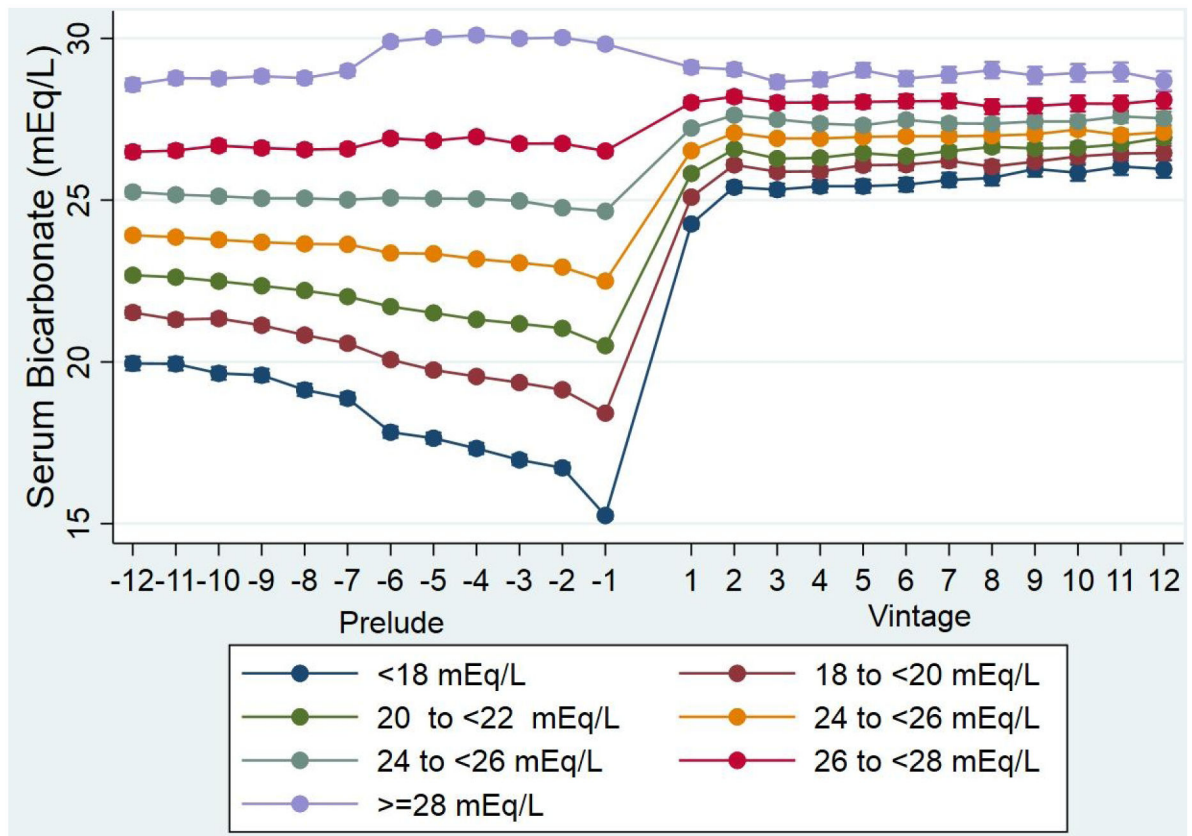
Figure 1.
Trajectories of monthly population mean serum total carbon dioxide concentrations during the pre- and post-ESRD periods across seven groups stratified by prelude 6-month averaged serum total carbon dioxide. Abbreviations: ESRD, end-stage renal disease.
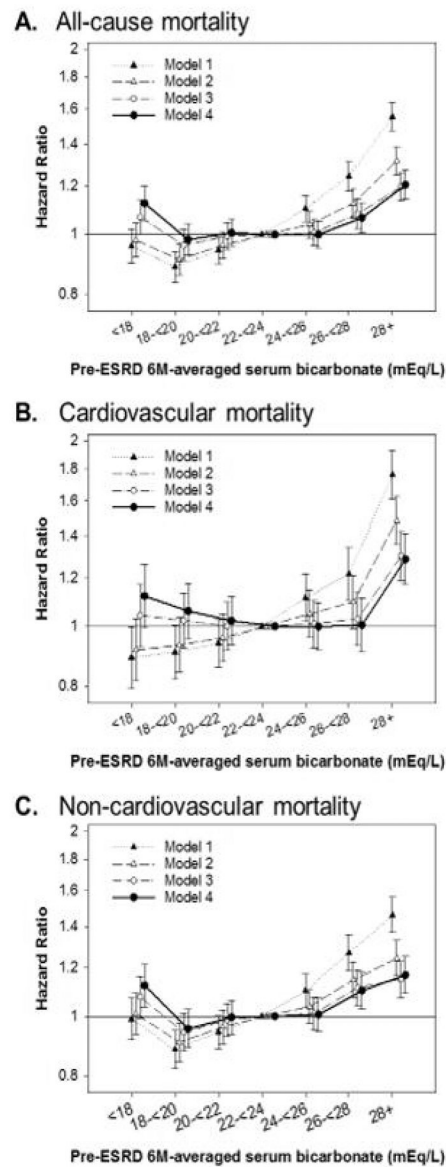
Figure 2.
Association between 6-month averaged serum total carbon dioxide concentrations before dialysis initiation and (A) all-cause, (B) cardiovascular, and (C) non-cardiovascular mortality with hierarchical adjustments.

Figure 3.
Distributions and restricted cubic splines comparing all-cause, cardiovascular, and non-cardiovascular mortality risk associated with 6-month averaged serum total carbon dioxide before dialysis initiation in Model 4 adjustment, stratified by the use of sodium bicarbonate.

Figure 4.
Association of 12-month change in serum total carbon dioxide before dialysis initiation with (A) all-cause, (B) cardiovascular, and (C) non-cardiovascular mortality with hierarchical adjustments.
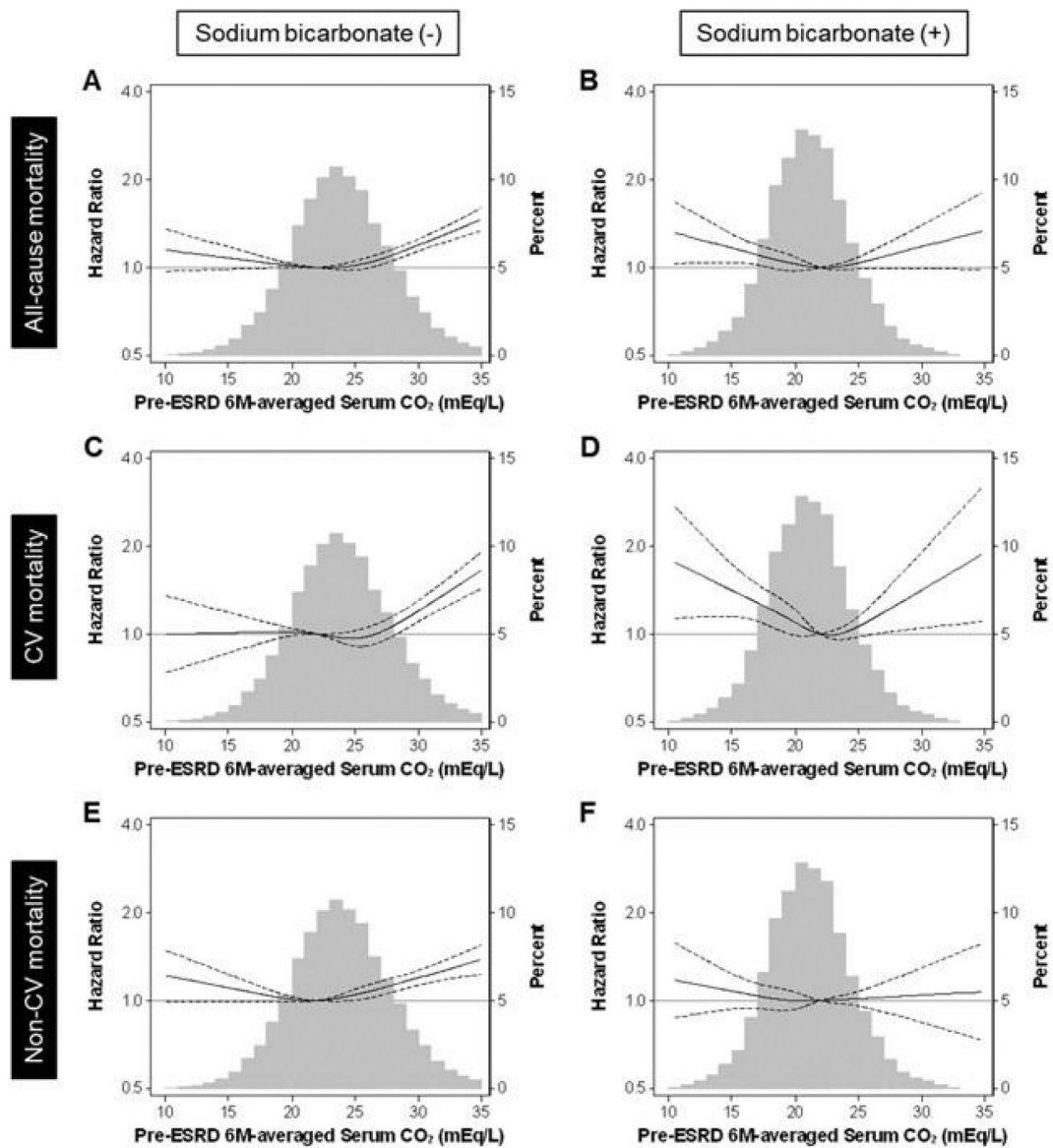
Figure 5.
Distributions and restricted cubic splines comparing all-cause, cardiovascular, and non-cardiovascular mortality risk associated with 12-month change in serum total carbon dioxide before dialysis initiation in Model 4 adjustments, stratified by the use of sodium bicarbonate.
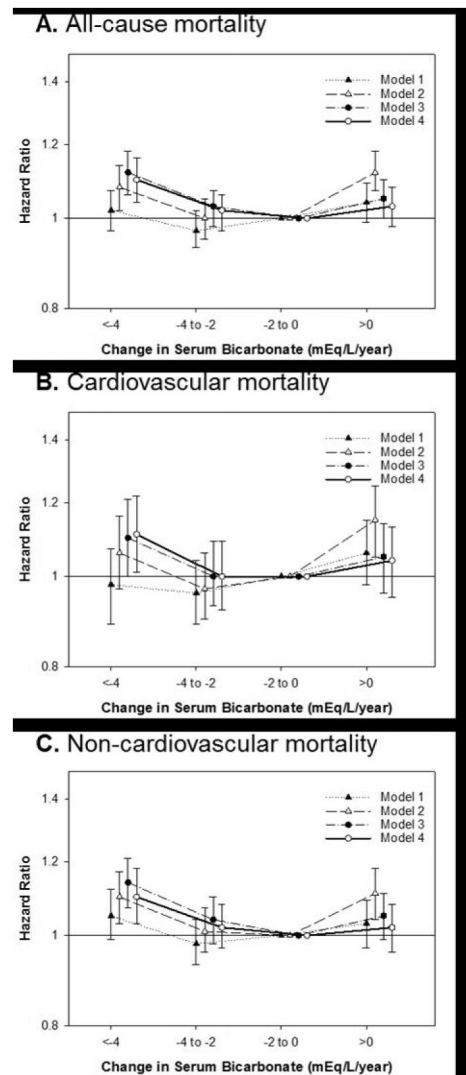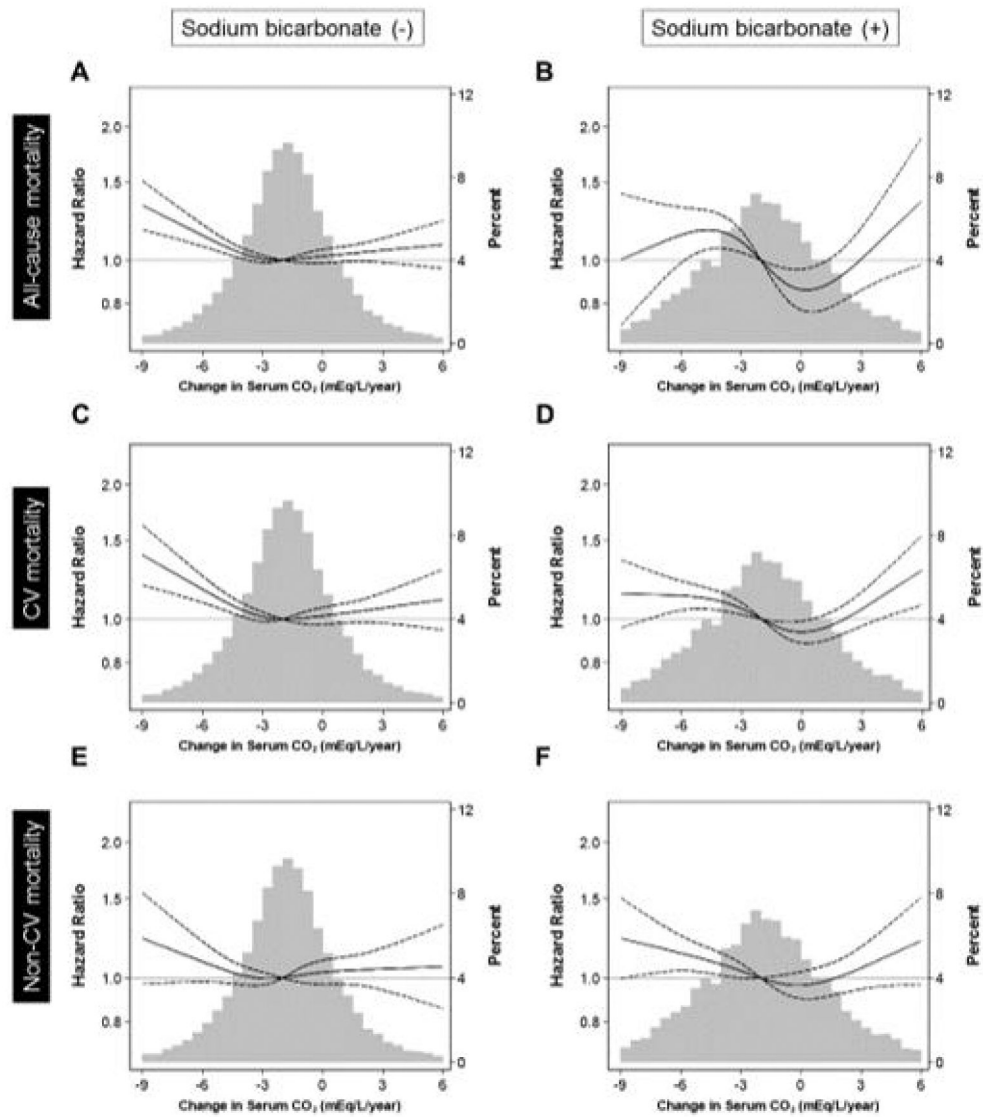
Table 1.

Baseline demographic and clinical characteristics of 32,655 US veterans with ESRD transitioning to dialysis stratified by pre-ESRD 6-month averaged serum bicarbonate.

Characteristics	Serum bicarbonate (mEq/L)						
	<18	18 to <20	20 to <22	22 to <24	24 to <26	26 to <28	28
N	2,759	3,890	6,000	6,758	5,663	3,731	3,854
Age, years	67±11	67±11	67±11	68±11	69±11	70±11	72±10
Female, %	2	2	2	2	2	2	2
Race, %							
White	61	62	61	64	68	72	78
Black	34	32	34	31	28	24	20
Other races	6	6	5	5	5	4	3
Hispanic, %	10	9	8	8	6	6	4
Marital status, %							
Married	46	49	51	53	57	59	63
Single	11	10	10	9	8	7	6
Divorced	33	32	29	27	24	24	19
Widowed	10	10	11	10	11	11	12
Vascular Access Type, %							
Arteriovenous Fistula	20	26	26	24	21	17	13
Arteriovenous Graft	3	3	3	3	2	2	2
Central Venous Catheter	77	71	70	73	77	80	85
Other	0.3	0.6	0.3	0.6	0.6	0.6	0.7
Modality, %							
Hemodialysis	96	93	93	93	93	93	94
Peritoneal Dialysis	3	5	6	6	5	4	4
Unknown	1	2	1	1	2	3	2
Charlson comorbidity index	3 (1, 5)	3 (2, 5)	3 (2, 5)	4 (2, 5)	4 (2, 6)	4 (2, 6)	4 (3, 6)
Comorbid conditions, %							
Diabetes	59	66	69	71	71	71	74
Congestive heart failure	36	37	44	50	56	61	71

Characteristics	Serum bicarbonate (mEq/L)						
	<18	18 to <20	20 to <22	22 to <24	24 to <26	26 to <28	28
Ischemic heart disease	40	44	49	53	58	64	71
Atrial fibrillation	8	9	10	13	16	20	27
Chronic pulmonary disease	28	30	33	37	40	47	57
Depression	23	25	27	26	25	26	24
Cancer	21	21	21	21	24	24	24
Body mass index, kg/m²	27.7±6.0	28.9±6.2	29.4±6.3	30.0±6.4	30.4±6.7	31.1±7.1	32.1±7.5
Estimated GFR, mL/min/1.73m²	7 (5, 10)	8 (6, 11)	9 (7, 12)	10 (7, 13)	10 (8, 14)	11 (8, 15)	12 (9, 17)
Laboratory tests							
White blood cell, 10³/µL	7.4 (6.0, 9.1)	7.4 (6.0, 9.1)	7.4 (6.1, 9.0)	7.4 (6.1, 9.0)	7.4 (6.1, 9.1)	7.4 (6.1, 9.0)	7.4 (6.0, 9.0)
Hemoglobin, g/dL	9.8±1.5	10.1±1.4	10.3±1.4	10.5±1.5	10.8±1.6	11.1±1.7	11.5±1.8
Albumin, g/dL	3.3±0.6	3.3±0.6	3.3±0.6	3.3±0.6	3.4±0.6	3.4±0.6	3.5±0.6
Corrected calcium, mg/dL	8.8±0.9	9.1±0.7	9.2±0.7	9.3±0.6	9.4±0.6	9.4±0.6	9.5±0.6
Uric Acid, mg/dL	7.8±2.1	7.9±2.1	8.0±2.0	8.0±2.1	8.1±2.2	8.3±2.3	8.6±2.6
Phosphate, g/dL	6.2±1.8	5.5±1.4	5.2±1.2	5.0±1.1	4.8±1.1	4.7±1.1	4.4±1.0
Medication use, %							
Sodium bicarbonate	45	43	33	24	15	10	5
Diuretics	63	71	75	77	75	75	75
Erythropoiesis-stimulating agents	36	37	36	33	28	21	14
RAAS inhibitors	37	43	46	48	48	49	47
Calcium supplements	23	21	19	18	16	12	9
Active vitamin D	32	35	34	33	31	26	22
Phosphate binder	20	20	21	20	16	13	8

Note: Values are expressed as mean±SD, median (IQR), or percentage, as appropriate. SI conversion factors: To convert hemoglobin to g/L, multiply by 10; albumin to g/L, multiply by 10; calcium to mmol/L, multiply by 0.25; bicarbonate to mmol/L, multiply by 1.0. Estimated GFR is a single point measurement, and is the last eGFR prior to transition.

Abbreviations: GFR, glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system.