Supplementary Material

TECHNICAL APPENDIX

Analyses of time-updated serum bicarbonate

Our analyses of time-updated serum bicarbonate utilized marginal structural models (MSM) which applies inverse probability weighting in a discrete time logistic regression model.[1] A substantial body of work has emerged demonstrating the usefulness of statistical tools like marginal structural models in the areas of HIV and CKD.[2, 3] Briefly, MSM is a two-step approach wherein models were first fit to predict mean serum bicarbonate levels during follow-up (i.e., the exposure of interest), and second, inverse-probability weighted structural models were fit for the outcomes. In both models, the data structure was set up so that each individual could contribute multiple records, each a year in length, depending on the number of annual study visits. For example, an individual with five study visits contributed five records in the data set.

In the first step (i.e, calculating the exposure weights), the serum bicarbonate measure at each study visit was divided into three categories: <22, [22-26] and >26 mmol/L. A multinomial logistic regression model was fit on the categorical serum bicarbonate measures with adjustment for concurrent age, gender, race/ethnicity, clinical center, eGFR, proteinuria, diabetes, systolic blood pressure, cardiovascular disease at baseline, chronic obstructive pulmonary disease, tobacco use, diuretic and alkali medication used, Low Density Lipoprotein, Fibroblast Growth Factor 23, High-sensitivity C-reactive protein. We calculated the weights that were used in the second step based on the predicted probability of observing a history of serum bicarbonate

categories during all study visits that were the same as what were observed. The weight for a particular study visit was calculated as one over the cumulative probabilities of the observed serum bicarbonate history up to that visit, calculated as the product of the probabilities of the observed serum bicarbonate categories up to that visit.

To improve model stability and statistical efficiency, we stabilized the weights by multiplying the estimated probability of observed serum bicarbonate history conditional on baseline predictors only (i.e., baseline: age, gender, race/ethnicity, eGFR, proteinuria, diabetes, systolic blood pressure, cardiovascular disease at baseline, chronic obstructive pulmonary disease, tobacco use, diuretic and alkali medication used, Low Density Lipoprotein, Fibroblast Growth Factor 23, High-sensitivity C-reactive protein.).[1, 2] This was done by fitting a second model for categorical serum bicarbonate using the baseline predictors only.

In the second step, we fit a logistic regression model for the outcome, i.e., heart failure by applying the final weight derived in the first step to the study visit level data using the GENMOD procedure in SAS 9.3 (SAS Institute, Cary, NC). In the model, we included the mean bicarbonate level up to the current study visit and the time since enrollment to allow the baseline hazard to change linearly over time. In addition, we included in the model the baseline only predictors from the stabilizing weights deriving the numerator weight in the first step. We also refit the model by summarizing the serum bicarbonate history as the percent of time being spent in each serum bicarbonate category.

REFERENCES

1. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11:550-560

2. Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of hiv-positive men. *Epidemiology*. 2000;11:561-570

3. Brunelli SM, Joffe MM, Israni RK, Yang W, Fishbane S, Berns JS, Feldman HI. History-adjusted marginal structural analysis of the association between hemoglobin variability and mortality among chronic hemodialysis patients. *Clin J Am Soc Nephrol*. 2008;3:777-782

Table S1. Multivariable-adjusted hazard ratios for time-updated serum bicarbonate on heart failure or death composite outcome in the Chronic Renal Insufficiency Cohort (CRIC) using Marginal Structural Models.

	Marginal Structural Model Hazard Ratio (95% Confidence Interval)
Composite of Heart Failure or Death	
Continuous serum bicarbonate	Per 1 mmol/L increase in mean bicarbonate over time*
	1.05 (1.02 - 1.08)
Categorical serum bicarbonate	
(Reference [22- 26 mmol/L])	
Serum Bicarbonate < 22 mmol/L	1.07 (0.82 - 1.40)
Serum Bicarbonate > 26 mmol/L	1.47 (1.17 – 1.85)

*Results generated from a Marginal Structural Model with updated mean serum bicarbonate over time.
All models are adjusted for age, gender, race/ethnicity, clinical center, eGFR, proteinuria, diabetes, hypertension, cardiovascular disease at baseline, chronic obstructive pulmonary disease, tobacco use, diuretic and alkali medication used, Low Density Lipoprotein, Fibroblast Growth Factor 23, High-sensitivity C-reactive protein.
In order to evaluate the risk of events for participants with bicarbonate belonging to any category only a certain percent of time, the risk should be multiplied by that percent (i.e. if a participant spends 50% of the time with bicarbonate > 26 mmol/L, the risk of mortality is 36*0.5 = 18%)

Table S2. Multivariable-adjusted hazard ratios for time-updated serum bicarbonate on atherosclerotic events in the Chronic Renal Insufficiency Cohort (CRIC) Study using Marginal Structural Models. Total of 3586 participants were included in the model. There were a total of 482 atherosclerotic events.

	Marginal Structural Model **Hazard Ratio (95%Confidence Interval)**
Atherosclerotic Event[^]	
Continuous serum bicarbonate	Per 1 mmol/L increase in mean bicarbonate over time*
	1.01 (0.97 - 1.05)
Categorical serum bicarbonate	
(Reference [22- 26mmol/L])	
Serum Bicarbonate < 22 mmol/L	1.12 (0.79 - 1.60)
Serum Bicarbonate > 26 mmol/L	1.16 (0.85 - 1.58)

*Results generated from a Marginal Structural Model with updated mean serum bicarbonate over time.
All models are adjusted for age, gender, race/ethnicity, clinical center, eGFR, proteinuria, diabetes, hypertension, cardiovascular disease at baseline, chronic obstructive pulmonary disease, tobacco use, diuretic and alkali medication used, Low Density Lipoprotein, Fibroblast Growth Factor 23, High-sensitivity C-reactive protein.
In order to evaluate the risk of events for participants with bicarbonate belonging to any category only a certain percent of time, the risk should be multiplied by that percent (i.e. if a participant spends 50% of the time with bicarbonate > 26 mmol/L, the risk of mortality is 36*0.5 = 18%)
[^]The three categories of serum bicarbonate, [22-26], <22 and > 26 mmol/L, had the following distribution of CRIC participants: 2071, 610, and 905, with corresponding 265, 98, and 119 atherosclerotoc events in each group respectively.