Does Serum HCO_3^- Predict Risk for Cardiovascular Disease?

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Cardiovascular disease (CVD) remains the leading cause of premature death in developed societies and identifying modifiable CVD risk factors continues to be an important goal. Patients with chronic kidney disease (CKD) suffer premature death from the full range of CVD entities at much higher rates compared to patients without CKD, and CVD risk increases with decreasing estimated glomerular filtration rate (eGFR). Consequently, CKD is an attractive model to study in which to identify CVD risk contributors that might be present disproportionately, but not exclusively in CKD patients, which when addressed might reduce the risk for subsequent CVD.

Metabolic acidosis indicated by low serum bicarbonate concentration ($[\text{HCO}_3^-]$) is associated with a further increase in the already high rate of CVD-related mortality in CKD patients [1]. Observational studies show that the more severe the metabolic acidosis as indicated by lower serum $[\text{HCO}_3^-]$, the greater the mortality in patients with stages 3 and 4 CKD [2]. These data support the need for continued study of the apparent association of metabolic acidosis and CVD risk, which might yield further insight into CVD mechanisms. If further studies subsequently affirm an association of metabolic acidosis and CVD, subsequent studies will test the hypothesis that treatment of patients with low serum $[\text{HCO}_3^-]$ due to metabolic acidosis with dietary acid reduction, done with exogenous alkali and/or a base-producing diet, reduces CVD mortality.

Despite evidence supporting that metabolic acidosis as reflected by low serum $[\text{HCO}_3^-]$ is associated with in-

creased CVD risk, other studies suggest that an acid–base contribution to CVD is more complex. For example, overall mortality was also higher in patients with higher serum $[\text{HCO}_3^-]$ [3], suggesting a “U-shaped” relationship between serum $[\text{HCO}_3^-]$ and mortality. Specifically, higher serum $[\text{HCO}_3^-]$ was associated with increased risk for heart failure, with this association being strongest in patients with eGFR >45 mL/min/1.73 m² [3]. Could it be that either extreme of serum $[\text{HCO}_3^-]$ increases CVD risk? Alternatively, might underlying syndromes that increase CVD risk concomitantly decrease or increase serum $[\text{HCO}_3^-]$?

Kendrick et al. [4] help us sift through the complexity of how, or even if, serum $[\text{HCO}_3^-]$ might be used as a predictor of CVD outcomes in studies published in this issue. They used data from the Multi-Ethnic Study of Atherosclerosis (MESA) database to examine the relationship of serum $[\text{HCO}_3^-]$ in non-diuretic users (diuretics can increase serum $[\text{HCO}_3^-]$) with CVD outcomes defined as (1) subclinical CVD (baseline left ventricular mass and aortic pulse pressure); (2) incident cardiovascular events (a composite of myocardial infarction, resuscitated cardiac arrest, stroke, coronary artery disease death, and stroke death); and (3) heart failure. Median age and eGFR of examined subjects were 62 years and 78.2 mL/min/1.73 m², respectively, and median follow-up was 8.5 years. They report that serum $[\text{HCO}_3^-]$ >25 mEq/L compared to 23–25 mEq/L was associated with a 13% greater risk for incident heart failure. Higher serum $[\text{HCO}_3^-]$ was also associated with greater left ventricular mass and higher aortic pulse

pressure, a measure of arterial stiffness. Both associations remained significant in fully adjusted models and they found no associations of serum $[\text{HCO}_3^-]$ with the other examined CVD outcomes. The authors also examined whether a potential influence of the level of dietary protein intake on serum $[\text{HCO}_3^-]$ might have confounded their results and they reported no such effect after adjustment for dietary protein density.

A notable aspect of the findings reported by Kendrick et al. [4] is that the association of higher serum $[\text{HCO}_3^-]$ with increased heart failure incidence was evident in these MESA subjects who had relatively well-preserved mean eGFR of 78.2 mL/min/1.73 m². These data are supportive of the findings of Dobre et al. [3] who also found the association of higher serum $[\text{HCO}_3^-]$ with heart failure to be strongest in patients with better preserved eGFR. Together, these data support that the association of high serum $[\text{HCO}_3^-]$ with heart failure is best evident in patients who are likely to have no metabolic acidosis and/or less acid retention. If higher serum $[\text{HCO}_3^-]$ in these 2 reports is associated with high serum pH, this alkaline milieu might create conditions that are causative for heart failure. For example, an alkaline milieu might increase vascular calcification as suggested by Kendrick et al. [4]. Vascular calcification would be expected to reduce vascular compliance and thereby contribute to the high aortic pulse pressure and resulting increased left ventricular hypertrophy associated with high serum $[\text{HCO}_3^-]$ reported by Kendrick et al. [4]. On the other hand, high serum $[\text{HCO}_3^-]$ might instead be a result of underlying heart failure. High serum $[\text{HCO}_3^-]$ has been described in heart failure, even in patients not receiving diuretic therapy [5]. This higher serum $[\text{HCO}_3^-]$ might be due to the neurohormonal disturbances of heart failure, which lead to kidney under-perfusion and stimulated electrolyte, including HCO_3^- reabsorption. The described scenarios in which high serum $[\text{HCO}_3^-]$ might be either the cause or the result of heart failure are most likely to manifest themselves in patients with comparatively preserved GFR who have little to no acid retention to titrate the excess HCO_3^- generated by either of these mechanisms.

A major challenge to determining the possible predictive value of serum $[\text{HCO}_3^-]$ for CVD risk is that most studies heretofore have not provided a complete picture of the acid-base context for the reported serum $[\text{HCO}_3^-]$. Specifically, only few studies report accompanying pH and PCO_2 to determine if a low serum $[\text{HCO}_3^-]$ is due to respiratory alkalosis or a high value to respiratory acidosis. Furthermore, most of the published studies also do not provide contextual history or physical examination

data to help determine if the serum $[\text{HCO}_3^-]$ is part of a mixed acid-base disorder. It follows that the serum $[\text{HCO}_3^-]$ in these studies is reported out of its acid-base context, making the meaning of its association with an outcome like CVD unclear. Even if these contextual data were available, observational data will not resolve if the condition reflected by the reported serum $[\text{HCO}_3^-]$ is causative of CVD or its result. Interventional studies will be needed to determine if treating the condition yielding the abnormal serum $[\text{HCO}_3^-]$ reduces CVD risk.

Kendrick et al. [4] report at least 4 important contributions to the evolving story of the potential use of serum $[\text{HCO}_3^-]$ to predict CVD risk. First, their studies affirm previous ones showing the association of increased serum $[\text{HCO}_3^-]$ with heart failure, strengthening the case for this as a real association, whether causative or a result of heart failure. Second, their reported association of increased serum $[\text{HCO}_3^-]$ and increased left ventricular mass and increased aortic pulse pressure offers a potential mechanism for the association of increased serum $[\text{HCO}_3^-]$ with heart failure through possible alkaline-pH-induced vascular calcification decreasing the arterial compliance with resulting increased left ventricular afterload. Third, their report affirms those of previous reports [3] that the relationship of increased serum $[\text{HCO}_3^-]$ with heart failure is best evident in patients with comparatively preserved kidney function. Fourth, unlike previous reports examining the potential predictive value of serum $[\text{HCO}_3^-]$ regarding CVD risk, the authors included dietary protein intake in their analysis to attempt to address an additional possible influence on serum $[\text{HCO}_3^-]$, that is, diet influence on endogenous acid production.

Deciphering the mechanisms as to how disorders of acid-base homeostasis apparently further increase CVD risk in CKD will help prevent CVD overall with its devastating consequences. Meanwhile, determining if these acid-base disorders predict CVD risk will be an important step forward and the report of Kendrick et al. [4] contributes to this evolving story. Despite this important contribution, such future studies must include pH and also preferably PCO_2 to best determine if acid-base disorders are CVD risk predictors. Such studies must then be followed by interventional ones to definitively determine if their modification indeed reduces CVD risk.

Disclosure Statement

The authors have no conflicts of interest to declare.

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