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Editorial

Cardiac Biomarkers and Prediction of ESRD

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The US National Institutes of Health have defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[1(p91)] Thus, biomarkers can be powerful tools that have the capacity to shape the diagnosis, management, and prognostic determinants of a disease entity. Biomarkers have long been in existence, with blood pressure measurements representing one of the earliest biomarkers that provided a link between the kidney and cardiovascular systems. The finding that albuminuria and decreased estimated glomerular filtration rate (eGFR), as indicators of kidney damage and loss of function, respectively, are associated with subsequent cardiovascular disease events supports this link.[2] Such evidence lends, at a minimum, prognostic value to these kidney biomarkers for determining fatal and nonfatal cardiovascular and kidney clinical end points, particularly in individuals with diabetic kidney disease.

The present controversy concerning whether microalbuminuria, and eGFR calculated using the MDRD (Modification of Diet in Renal Disease) Study equation ideally reflect the true status of the kidney does not detract from our knowledge and understanding that the pathophysiologic mechanisms involving endothelial dysfunction, atherosclerosis, activation of the renin-angiotensin system, and systemic inflammation provide a common path toward premature cardiovascular events in patients with chronic kidney disease (CKD), particularly in those with diabetic kidney disease.[3] The cardiorenal syndrome, which may be defined as "a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of 1 organ may induce acute or chronic dysfunction of the other"[4(p1)] reveals mutual risk factors that expose the dynamic interplay between heart disease and kidney injury. Importantly, longitudinal studies show that the presence of cardiovascular disease is an independent risk factor for decreasing kidney function, as well as the development of CKD.[5] Thus, it is not surprising that up to ~30% of individuals with cardiovascular disease have concurrent CKD.[6] Presently, enormous efforts are in place to identify kidney-specific biomarkers that can detect acute kidney injury (AKI) to improve its evaluation and management. Ultimately, the goal of this effort is to lessen the long-term clinical sequelae of AKI, including adverse cardiac outcomes.[7] An important challenge to the nephrology community parallels this effort in AKI treatment; namely, to uncover cardiac-specific biomarkers that could accurately predict the onset and progression of cardiac injury in patients with CKD, including end-stage renal disease (ESRD), to provide a meaningful approach to reduce the high incidence of poor cardiovascular outcomes in this population.

In this issue of the *American Journal of Kidney Diseases*, Desai et al[8] describe results of a nested cohort study of 995 persons with type 2 diabetes, CKD (eGFR, 20-60 mL/min/1.73 m^2), and anemia (hemoglobin ≤11 g/dL and transferrin saturation ≥15%) who were enrolled in TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy). The study examined whether the established cardiac-specific biomarkers, troponin T (TnT) and N-terminal pro–B-type natriuretic peptide (NT-pro-BNP), added prognostic value to currently accepted risk factors for identifying patients who would develop either ESRD or subsequent death in a population with advanced CKD. The study showed that TnT and NT-pro-BNP levels frequently were elevated in this population, with detectable TnT levels in 45% of participants and NT-pro-BNP levels >900 pg/mL in 38%. Levels of both biomarkers were higher in patients with the lowest eGFRs and the highest urine protein-creatinine ratios. After a median of 43 months, 22% of the population developed ESRD and 41% reached the composite outcome of ESRD or death. Higher levels of both cardiac biomarkers were associated independently with both ESRD and the ESRD or mortality composite outcome. Notably, the addition of TnT and NT-pro-BNP levels to prediction models resulted in a net reclassification improvement of 16.9%, with the risk score increasing in 17.2% of participants who had events, and decreasing in only 0.3% who did not have events (see Fig 5 in Desai et al[8]). The investigators conclude that measurement of TnT and NT-pro-BNP may help identify patients with CKD who are likely to require kidney replacement therapy and note that the predictive ability of these cardiac-specific risk factors in people with CKD supports a link between cardiac injury and the development of ESRD. Strengthening the results in the present study, the association of previously identified risk factors and risk markers (specifically creati-

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nine, proteinuria, hemoglobin, and albumin) with ESRD outcomes was consistent with results from the RENAAL (Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus With Angiotensin II Antagonist Losartan) Study.[9]

The present study had several limitations. Although TREAT enrolled 4,044 participants,[10] cardiac biomarkers were evaluated in only the first 1,000 participants. Nevertheless, this remains one of the largest prospective studies to investigate the relationship between cardiac-specific biomarkers and progression to ESRD. Additionally, the present study was a post hoc analysis of a very specific clinical trial population, namely type 2 diabetic patients with CKD stages 3 and 4 and anemia, who had substantial baseline comorbid conditions. Future studies could further investigate these biomarkers in a population that includes individuals with nondiabetic CKD and a larger proportion of ethnic minorities. Specific ethnic minorities, particularly African Americans, experience more rapid progression to ESRD, disproportionately contributing to health care expenditures. Therefore, uncovering biomarkers that could more efficiently target these high-risk groups would be of great benefit to improving public health. Also, several predictors of CKD progression, such as serum phosphorus and bicarbonate, were not measured. Studies show that dysregulated calcium-phosphorus metabolism in patients with CKD may contribute to coronary and vascular calcification and potentially affect cardiovascular mortality. Accordingly, inclusion of these parameters would help us understand their contribution to these serious clinical outcomes. Finally, biomarker assessment was conducted only at baseline, and changes in biomarker levels over time were not assessed. Overall, results from this study confirm findings from previous smaller studies, including a recent report from the CRIB (Chronic Renal Impairment in Birmingham) prospective cohort study (N = 383), which showed that NT-pro-BNP and TnT levels are strongly predictive of progression to ESRD and all-cause mortality in patients with CKD stages 3-5.[11]

The present study provides additional theoretical support for targeted early and more aggressive primary and secondary prevention measures in a high-risk group of patients through feasible risk stratification. For example, an elevated NT-pro-BNP or TnT level might direct earlier cardiac imaging in patients with residual kidney function who may already be at increased cardiovascular risk but have not yet had an event. In patients with ESRD, elevated levels potentially could have implications for early diagnostic testing in patients who are treated with peritoneal dialysis or for more intensive volume control for patients who are receiving hemodialysis treatment.[12-14] Studies such as these emphasize the mechanistic link between the kidney and heart and suggest that these measurements may appreciably preempt overt signs of cardiac injury.

Importantly, mortality rates of patients with CKD due to cardiovascular events can reach as high as 45.7% over 5 years, even before patients begin kidney replacement therapy.[15] Assessment of cardiac-specific biomarkers that refine risk stratification could be extremely beneficial in a large prospective interventional study. Ultimately, the greatest value in biomarkers is in guiding the most efficient and effective use of interventions. Future studies may be able to expand incrementally on the present results by first defining the utility of serial measurements of TnT and NT-pro-BNP in patients with CKD and ESRD and ultimately using these measures to target highest yield treatments to effectively decrease both kidney and cardiovascular event rates, building on experiences with similar care models used in patients with chronic heart failure.[16] The laboratory medicine practice guidelines from the National Academy of Clinical Biochemistry already advise that serial determination of cardiac troponin levels be made in patients with ESRD who are being evaluated for acute coronary syndrome.[17] However, it still is not routine practice to measure TnT and NT-pro-BNP as a screening tool to uncover underlying cardiovascular disease that potentially could be prevented in patients with CKD. Accumulating evidence, such as the study by Desai et al,[8] suggests that possible approaches to augment the utility of other cardiovascular risk indicators should be seriously considered as a goal for standard clinical practice to effectively manage and reduce cardiovascular events in patients with CKD. In addition, based on the evidence that cardiovascular risk may contribute to CKD risk, targeting cardiovascular disease prevention may potentially target CKD prevention as well.

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