A Piece of the Puzzle in the Cardiorenal Conundrum

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Clinical investigations in recent years have established that the presence of even mild or moderate decreases in estimated GFR (eGFR) consistently confers a significantly elevated risk for cardiovascular disease (CVD),1 the leading cause of death in the United States and most industrialized countries. Moreover, in one study of almost 28,000 people followed for 5 years, those with eGFR <90 ml/min per 1.73 m² were more likely to die than to reach dialysis; the authors surmised that most fatal events were from CVD based on the increasing prevalence of cardiac risk factors over the follow-up period.2

A related topic is the growing recognition that CKD alters the predictive ability of traditional CVD risk factors, yet the understanding of why this is remains a puzzle. This puzzle is nested within a larger puzzle of a cardiorenal conundrum, in which kidney and heart dysfunction appear intimately linked in a manner that is incompletely understood.

Although the cardiorenal syndrome typically refers to diuretic-refractory advanced heart failure seen in the setting of decreased eGFR,3 other notable cardiorenal relationships in the realm of acute coronary syndromes and cardiac-related deaths

See related article, “Type of PKD1 Mutation Influences Renal Outcome in ADPKD,” on pages 1006–1013.

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include the following: high prevalence of left ventricular hypertrophy (especially in hemodialysis patients), considered to be an independent predictor of adverse cardiac outcomes in the CKD/ESRD population (including systolic and diastolic heart failure), perhaps a consequence of anemia in CKD; short-term worsening of kidney function after acute coronary syndrome events (defined as eGFR decrease of ≥25% within 1 month) associated with recurrent CVD; and presence of albuminuria, including low levels in the traditional normal range, as a strong predictor for CVD in secondary analyses of clinical trials as well as in observational studies within general population.

The importance of lipid and inflammatory markers as predictors of CVD events has been established by the Framingham Risk Score and the Reynolds Risk Score. The question of how the presence of CKD, ideally defined as lower eGFR or presence of albuminuria, may modify these risk predictors (especially biomarkers such as cholesterol, C-reactive protein, and percentage of hemoglobin a1c used to calculate these scores) deserves more detailed study.

In this issue of JASN, Tonelli and colleagues undertook an analysis of the predictive ability of LDL cholesterol (LDL-C) for subsequent myocardial infarction (MI) events in >800,000 adults without ESRD from the Alberta Kidney Disease Network. They report that higher LDL-C is a substantially weaker predictor of MI in those with CKD (defined in categories of eGFR 60–89.9 and 15–59.9 ml/min per 1.73 m²) than those without (defined as eGFR ≥90 ml/min per 1.73 m²). Moreover, the lower the eGFR, the smaller was the hazard ratio for MI.

Strengths of this investigation include the large sample size available for analysis and the ability to link medication, diagnoses, and hospitalization data with laboratory data in this universal healthcare system. The authors also performed multiple sensitivity analyses, including limiting the study population to those with medication data, those who had ST-elevation MIs, and those without previous MI to support the consistency of their findings. Furthermore, additional analysis using time-varying (updated) variables as well as presentation of the hazard ratios for LDL-C across different eGFR categories reflects sophisticated statistical approaches, which further lends confidence that the reported results are less likely to be subject to study bias from nonrandom missing data.

Important limitations that deserve mention, however, include the relatively short follow-up time (median 48 months), lack of medication data in approximately two-thirds of the study population, and lack of quantitative albuminuria information or inflammatory markers of interest. As with any large administrative database study, potential misclassification of clinical outcomes and missing data are always of concern. In addition, this observational study reports observed associations without the ability to provide further insights into underlying pathophysiologic mechanisms of the cardiorenal conundrum. Although the investigators propose that based on these findings, patients with CKD may benefit from statin therapy to lower C-LDL below the current recommended thresholds, which were developed in primarily non-CKD study cohorts, a sizeable randomized intervention trial is needed before this can become standard of care for medical management.

Further study of kidney dysfunction and cardiovascular risk represents an important area of health care research, and several questions for investigation deserve to be addressed. Do measures of kidney function (eGFR and albuminuria) provide additional and independent predictive value for incident CVD risk above and beyond that provided by current prediction models of CVD risk as suggested by a very recent study of >400 CKD patients in Taiwan? If so, might the results vary by sex, ethnicity, and age between different categories of eGFR and microalbuminuria? Moreover, are inflammatory biomarkers potential mediators in the association between kidney function and CVD? If yes, seeing that the most established widely used marker of LDL-C used in the management of CVD may not be as well correlated with CVD events in CKD patients, which specific inflammatory markers may be effective targets and risk monitors in the high-risk CKD patients? Is the cardiorenal conundrum due simply to diffuse vascular disease in two of the most vascular organs in the body or are there other neurohormonal factors yet to be recognized, which mediate the associations between kidney and heart disease?

Perhaps most critically, the continuing attention to solving the cardiorenal conundrum draws additional focus on the outcomes data, which suggest that those with CKD are less likely to receive aggressive cardiac interventions, including medications such as β-blockers and statins as well as cardiac catheterization and angioplasty, yet stand to benefit at least as much as non-CKD patients from such therapies. The knowledge gap of CVD in CKD is further exacerbated by the frequent exclusion of participants with overt CKD from cardiovascular disease clinical trials. The very large total at-risk population of CKD and ESRD patients who will experience morbidity and mortality from CVD is calling out for more research to lead directly to improved management and outcomes as soon as possible. Let us continue the very important work of answering this call.

DISCLOSURES

J.L. is employed by Genzyme Corporation, a Sanofi company. The comments expressed in this editorial do not represent those of the company, nor is this topic directly related to any of her current working projects.

REFERENCES


