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EDITORIAL COMMENT

Chronic Kidney Disease as a Potent Risk Modifier for CAD in Diabetics*

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With the demographic shift in the U.S. to an older and heavier population, there has been a well-documented increase in the incidence of diabetes mellitus (1). Paralleling this rise in diabetes has been a growth in the number of Americans with chronic kidney disease (CKD). Estimates of the number of adults with CKD and reduced kidney function are reported to be over 16 million (2). In fact, there is a substantial overlap of the 2 diseases, with a majority of patients with CKD also having diabetes, and both diabetes and CKD are strong risk factors for coronary heart disease (CHD) (3). Although end-stage renal disease is often expected as the disease outcome of CKD, a majority of patients with CKD are likely to die of CHD before reaching end-stage renal disease (4–6).

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The timely and accurate diagnosis of CHD is a challenge in those patients who have a preponderance of traditional cardiac risk factors along with diabetes and CKD. Such individuals might present with silent ischemia or atypical coronary syndromes or are not ideal candidates for invasive diagnostic testing (7). It is in this population that effective noninvasive strategies are needed to assist in CHD risk-stratification and guide cardiac medical management. However, when assessing patients for their likelihood of CHD and their prognosis when CHD is present, it is important to determine how much high-risk comorbidities such as diabetes and CKD affect the initial assessment of risk for CHD and then to consider how the use of a diagnostic test modifies that baseline risk and improves the predictive power for that disease.

In this issue of *iJACC*, Hakeem et al. (8) retrospectively examined the impact of CKD and diabetes in relation to myocardial perfusion defects and both cardiac and all-cause mortality over a mean of 2 years. The patient cohort consisted of 1,747 patients with "known or suspected" CHD who underwent noninvasive cardiac testing with myocardial perfusion single-photon emission computed tomography (MPS) for evaluation of ischemia. CKD (defined as an estimated glomerular filtration rate [eGFR] of <60 ml/min/1.73 m^2) was present in 20% of the subjects, with approximately the same proportion having diabetes alone and 16% suffering from both CKD and diabetes. The authors showed that presence of CKD alone, with and without diabetes, conferred a several-fold higher risk of cardiac death for the various strata of MPS perfusion defects. The incidence of death was higher with increasing severity of stress perfusion defects in all disease sub-categories, but with the relationship most pronounced in the group with both CKD and diabetes. A normal MPS conferred a lower risk in CKD patients with and without diabetes. In multivariate analysis, the presence of both CKD and diabetes were highly predictive of cardiovascular death. Likewise, perfusion defects on stress imaging and depressed ejection fraction were also significant predictors of cardiovascular death. The investigators concluded that both eGFR and myocardial perfusion defects were important factors in risk-stratification of patients being evaluated for CHD, especially in patients with diabetes mellitus.

Patients with CKD have a confluence of both traditional and nontraditional risk factors for cardiovascular disease. Beyond exhibiting a cluster of traditional Framingham risk factors (9), patients

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with CKD are subject to anemia, volume overload, left ventricular hypertrophy, poor vascular compliance, and excess oxidative stress coronary calcification, among others that have yet to be fully characterized (10). Clearly, patients with CKD have a complex metabolic milieu, and to what extent diabetes compounds this environment thereby raising the risk of CHD is unknown. In nondiabetic pre-dialysis CKD patients, we recently demonstrated a significant inverse correlation between myocardial glucose use in μmol/min/100 g and eGFR employing quantitative F18-fluorodeoxyglucse positron emission tomography as a means to measure myocardial metabolic changes (11). Myocyte-to-capillary mismatch, which is a progressive disorder in CKD, accrues with loss of renal function and is associated with a diminished vascular supply relative to the number and volume of functioning myocytes. The oxygen-poor setting might lead to diffuse myocardial ischemia with a shift in cardiac energetics from a predominance of aerobic to anaerobic metabolism, where glucose is the primary fuel. This pathologic transformation that eventually promotes myocardial fibrosis is most evident in end-stage renal disease and is associated with excessive mortality (12–15). Thus, myocardial ischemia and its metabolic consequences in CKD might account for a significant portion of the excessive cardiovascular morbidity and mortality observed across all stages of kidney disease.

Given the strength of CKD as a predictor of CHD and adverse patient outcomes in the setting of diabetes, one needs to ask what the findings of Hakeem et al. (8) inform us about cardiac risk stratification of this high-risk disease population. Although the cohort assembled for the study was substantial, it included patients who underwent MPS with "known or suspected" CHD and were likely examined for cause. The same relationship between reduced renal function and MPS might not necessarily apply to a comparable population not suspected to have CHD. Perhaps more importantly, in clarifying the roles of CKD diagnosis and the use of MPS in stratifying cardiovascular risk in diabetic patients, is the determination of how each piece of clinical information alters prior probability estimates of the disease of interest (16). It would be useful in follow-up analysis to determine the incremental utility of MPS results above and beyond determination of diabetic status and eGFR in predicting cardiac death. Whether MPS provides additive risk stratification to hemoglobin A1C, proteinuria, and other biomarkers would be an important study to undertake next.

Finally, accepting the notion that CKD represents a potent modifier to the risk of CHD in diabetes, one must ask how the acquired information from cardiovascular risk stratification impacts disease management and alters outcomes in these patients. Unfortunately, patients with CKD who have CHD do relatively poorly with established cardiac interventions, and these adverse outcomes are enhanced in diabetic patients with CKD. Coronary artery revascularization leads to significantly inferior outcomes in patients with CKD relative to their counterparts with CHD and no CKD (17,18). Thus, the diagnostic approach endorsed by MPS must be supplemented by a "new" set of therapeutic interventions that can improve the cardiovascular outcome of patients with CKD, especially in the presence of diabetes mellitus.

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