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EDITORIAL COMMENT

Diagnostic, Therapeutic, and Clinical Trial Conundrum of Patients With Chronic Kidney Disease*

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The prevalence of chronic kidney disease (CKD) has exponentially increased because of an aging population and increases in obesity and its metabolic sequelae, including diabetes mellitus. Although the focus is largely on the prevention of worsening kidney function, cardiovascular disease is still the leading cause of morbidity and mortality, much more common than the risk for developing end-stage renal disease (1).

THE DIAGNOSTIC CONUNDRUM

Patients with CKD break many of the traditional cardiovascular "rules." Chest pain is less common (sensitivity 65%, specificity 66%) (2), anginal equivalents and silent coronary artery disease (CAD) are more common (3,4), assessment of symptoms on traditional grounds such as upon exertion is challenging because of reduced exercise capacity, and traditional risk factors and the Framingham risk score fare poorly in this cohort (5). In addition, noninvasive stress testing has reduced accuracy in patients with CKD (6). As such, additional markers such as proteinuria, serum cardiac troponin I in patients without acute coronary syndromes (specificity 96% to 97%), and other novel biomarkers are being investigated as markers for CAD in patients with CKD (7).

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Despite this, the prevalence of CAD and the disease complexity are high. Lee et al. (8), in this issue of *JACC: Cardiovascular Interventions*, offer interesting insights. Nearly a quarter of patients who underwent percutaneous coronary intervention had CKD, attesting to its rising prevalence. Not only did patients with CKD have a higher prevalence of traditional risk factors, but a higher proportion presented with silent ischemia. Moreover, patients with CKD had a higher prevalence of multivessel CAD, long lesions, and small vessels, attesting to the complexity of the anatomy.

THE THERAPEUTIC CONUNDRUM

The majority of cardiovascular clinical trials comparing treatment options have routinely excluded patients with CKD (9). The 3 treatment options for CAD—optimal medical therapy, percutaneous coronary intervention, and coronary artery bypass grafting—have been less well studied in the CKD cohort because randomized trials have routinely excluded them or included very small proportions. As such, one is left to extrapolate the results of trials done in non-CKD cohorts, to use results from nonrandomized studies, or to base it on expert consensus to direct care for such patients. It is not known if such extrapolation is justifiable. For example, although statin therapy has been proven effective in both primary and secondary prevention of cardiovascular disease in patients

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without CKD, the efficacy in patients on dialysis needs to be proved (10).

There has been significant progress in percutaneous coronary intervention from balloon angioplasty to the second-generation drug-eluting stents (DES), with thinner, more deliverable struts and thinner and more biocompatible polymers with consequent less inflammation and thrombogenicity, translating into faster endothelial healing with lower propensity for restenosis and stent thrombosis. These design features have vastly improved outcomes, such that the second-generation DES reduce not only restenosis but also stent thrombosis, myocardial infarction, and death compared with bare-metal stents (11). Whether this is true in patients with CKD is not known. Lee et al. (8) conclude that there is a changing paradigm of clinical events in patients with CKD, with a higher risk for non-target lesion-related outcomes rather than target lesion-related events, implying that the excess stent-related events seen previously have been mitigated with the use of second-generation DES. Although this appears to be a victory for stent development, the initial enthusiasm is quickly tempered by the data presented. The investigators base their statement on the lack of statistical significance for stent-related outcomes such as target vessel myocardial infarction ($p = 0.38$) and target lesion revascularization ($p = 0.21$), although the hazard ratios for both point to increased risk (adjusted hazard ratios: 1.38 and 1.24, respectively) in those with CKD versus those without. More important, the other composite stent-related events, such as target vessel myocardial infarction and target lesion revascularization, showed a 43% increase ($p = 0.03$), and target lesion failure showed a 50% increase ($p < 0.001$) in patients with CKD versus those without. Similarly, in a post hoc analysis of the PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study) trial, an everolimus-eluting stent was associated with a 3-fold higher rate of stent thrombosis (2.3% vs. 0.7%) and an approximately 4-fold higher rate of target lesion revascularization (12.6% vs. 3.7%) in patients with CKD versus those without, attesting to the persistent higher stent related events in patients with CKD (12). Thus, although progress has been made with second-generation DES at reducing stent-related events, it still appears to be a problem in patients with CKD. Bioabsorbable vascular scaffolds can potentially be attractive, as they are bioabsorbed within 2 to 3 years, potentially mitigating late stent-related events. However, the current-generation bioabsorbable vascular scaffolds have thicker scaffolds, are difficult to deliver in calcified, tortuous arteries, and are less suitable for small vessels, all of which are more common in patients with CKD. Moreover, the current randomized trials have excluded patients with CKD, and their efficacy in such patients needs to be proved.

In patients with CKD, there is a potential differential effect even within the subset of patients with CKD. Lee et al. (8) showed that in patients with severe CKD or end-stage renal disease, there was a 2- to 3-fold higher risk for target lesion failure or patient-oriented composite outcomes when compared with those without CKD, whereas the outcomes with mild to moderate renal function were similar to those of patients without CKD with an estimated glomerular filtration rate threshold of <40 to 45 ml/min/1.73 m^2 associated with increased clinical events.

THE CLINICAL TRIAL CONUNDRUM

There is greater consensus on the need to include patients with CKD in cardiovascular trials. However, data such as the aforementioned indicate that even among patients with CKD, the risk benefits may differ, especially in patients with severe CKD or those on dialysis. Although including a spectrum of patients with CKD and performing subgroup analysis is a potential solution, subgroup analyses themselves tend to be problematic and underpowered and at best hypothesis generating. Along these lines, the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial (NCT01471522) and the ISCHEMIA-CKD (NCT01985360) trials have been designed bearing in mind the potential differential risk/benefit ratio of therapies in patients with advanced CKD (estimated glomerular filtration rate <30 ml/min/1.73 m^2 or on dialysis) versus those without advanced CKD, randomizing patients with stable ischemic heart disease to either a conservative strategy of optimal medical therapy alone or an invasive strategy of cardiac catheterization and optimal revascularization using the latest generation DES or coronary artery bypass grafting. The trials will provide insights into the optimal management of stable ischemic heart disease across a spectrum of renal function and potentially answer the question as to whether there is a differential beneficial effect of the therapies on the basis of baseline renal function.

In summary, patients with CKD are a growing group of patients with diagnostic, therapeutic, and clinical trial conundrums, in need of

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urgent therapies to reduce their risk for cardiovascular events. Although outcomes with second-generation DES have largely improved, there is much more work needed to reduce the risk for both stent-related and non-stent-related events in patients with CKD.

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