chronic kidney disease

ISCHEMIA in chronic kidney disease: improving the representation of patients with chronic kidney disease in cardiovascular trials

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Despite the high cardiovascular risk associated with chronic kidney disease, a recent systematic review confirmed that patients with kidney disease remain underrepresented in cardiovascular trials. Two ongoing trials are assessing the risk:benefit of aggressive evaluation and intervention for ischemic heart disease in patients with advanced chronic kidney disease.

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Cardiovascular disease is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD). Unfortunately, clinical trials of cardiovascular interventions frequently exclude patients with CKD, in part because of the increased risk of adverse events and often because of altered pharmacokinetics. As a result, the management of cardiovascular disease in patients with CKD is often informed by results from clinical trials that may not be generalizable to this high-risk population.

A recent systematic review confirmed that the systematic exclusion of patients with CKD from high-impact clinical trials in cardiology persists.[1] Among 371 trials published between 2006 and 2014, 57% excluded patients with CKD. Representation of patients with CKD was higher in trials that were investigating medical therapies versus procedures, but nearly 30% of medical therapy trials also excluded patients with CKD. More than half of the trials that excluded kidney disease patients used a threshold serum creatinine value; other studies excluded patients based on estimated glomerular filtration rate (eGFR) or creatinine clearance, the use of renal replacement therapy, or qualitative criteria. Overall, only 16% of trials reported outcomes in the subgroup of participants with CKD.[1]

Despite its high prevalence, the optimal management of ischemic heart disease remains controversial, with even more limited evidence to guide clinical decision making in patients with CKD. A meta-analysis of 5 randomized trials comparing medical therapy with or without percutaneous coronary intervention failed to demonstrate a significant benefit of routine revascularization in patients who were also receiving medical management.[2] Nonetheless, the most recent of the included trials was terminated early because of clear evidence of benefit in the group randomized to percutaneous coronary intervention, raising the question of whether technical advances in percutaneous revascularization may have altered the risk:benefit of early intervention.[3]

Against this backdrop, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches–Chronic Kidney Disease trial (ISCHEMIA-CKD; NCT01985360; http://www.ischemiackd.org/) is recruiting patients with moderate to severe ischemic heart disease and stage 4 to 5 CKD or end-stage renal disease in order to better define the optimal management of ischemic heart disease in this population. Participants are randomized to an early invasive strategy with cardiac catheterization and revascularization plus optimal medical therapy versus a

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conservative strategy of optimal medical therapy alone, with a primary composite end point of death or nonfatal myocardial infarction. ISCHEMIA-CKD will be the largest randomized trial to evaluate the risk:benefit of routine catheterization and revascularization in patients with moderate to severe ischemic heart disease and advanced CKD.

ISCHEMIA-CKD is an ancillary study conducted in parallel with the larger ISCHEMIA trial (NCT01471522), which will enroll participants with moderate to severe ischemic heart disease and eGFR $\geq$30 ml/min per 1.73 m^2.[4] Participants in both trials must have moderate to severe ischemia on a clinically indicated stress test, and participants with eGFR $\geq$60 ml/min per 1.73 m^2 in the parent trial undergo cardiac computed tomography angiography prior to randomization. To minimize radiocontrast exposure in patients with CKD, cardiac computed tomography angiography is not performed in ISCHEMIA-CKD or in participants in the parent trial with eGFR $<$60 ml/min. A protocol is also in place to minimize contrast exposure and optimize hydration during cardiac catheterization. Contrast-associated acute kidney injury and requirement for dialysis will be monitored as safety outcomes.

As the eGFR entry criteria are mutually exclusive, patients referred for the parent trial found to have lower-than-expected eGFR may be candidates for ISCHEMIA-CKD, increasing the efficiency of recruitment. Because of the higher anticipated cardiovascular event rates in patients with stage 4 to 5 CKD relative to persons with normal or near-normal kidney function, the ancillary study is powered to detect a difference in the primary end point with a much smaller sample size. The design of ISCHEMIA-CKD as a parallel ancillary study also allows for special consideration of safety and other issues that are unique to the CKD population without altering the design of the parent trial. A similar strategy could be used to optimize recruitment and improve the generalizability of future cardiovascular trials to patients with advanced CKD.

While ISCHEMIA-CKD will provide insights into the risk:benefit of cardiac catheterization and revascularization in patients with advanced CKD and documented ischemic heart disease, it will not directly address the important clinical question of whether and how to screen for ischemic heart disease in asymptomatic kidney transplant candidates. The Canadian-Australasian Randomized Trial of Screening Kidney Transplant Recipients (CARSK) investigators have completed a pilot trial demonstrating the feasibility of enrolling eligible kidney transplant candidates to compare selective versus routine screening for coronary artery disease (NCT02082483). Enrollment in the definitive trial has begun in Australasia, and a funding decision to enroll additional participants in Canada is anticipated in July 2016. Results of CARSK will provide insight into the risk:benefit of routine coronary artery disease screening in asymptomatic patients awaiting kidney transplantation. Together, these ongoing trials are a first step toward improving the representation of patients with advanced CKD in cardiovascular trials.

DISCLOSURE

All the authors declared no competing interests.

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