EDITORIAL COMMENT

Everolimus-Eluting Coronary Stents for Patients With Chronic Kidney Disease
What Explains the Magic?*

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Randomized, controlled trials (RCTs) comparing percutaneous coronary intervention (PCI) with coronary artery bypass graft (CABG) surgery for multivessel coronary artery disease (CAD) have routinely excluded patients with chronic kidney disease (CKD), so decisions about revascularization in this population depend on other sources of evidence (1). Several observational studies have reported that patients with CKD or end-stage renal disease requiring hemodialysis had higher mortality rates after PCI than after CABG for multivessel CAD (2,3), resulting in clinical guidelines favoring surgical therapy over PCI for this population of patients (4).

An observational study reported in this issue of the Journal (5) found that patients with CKD stage III or IV with estimated glomerular filtration rates of ~15 to 60 ml/min who had undergone PCI for multivessel CAD with everolimus-eluting stents (EES) had lower short-term mortality rates (1.0% vs. 1.7% at 30 days; hazard ratio [HR]: 0.55; 95% confidence interval [CI]: 0.35 to 0.87), and long-term mortality rates that were no different (22.7% vs. 20.5% at 2.9 years; HR: 1.07; 95% CI: 0.92 to 1.24), than those of patients who had undergone CABG. For the group with CKD stage 5 on hemodialysis, however, the study found that patients treated with EES had higher long-term mortality rates (54.3% vs. 39.1%; HR: 2.02; 95% CI: 1.40 to 2.93) than did patients treated with CABG.

Because the current study is a rigorous analysis (5), a finding of a narrowed mortality difference between PCI and CABG for patients with CKD stage III or IV is newsworthy. To put the results of the study into perspective and understand how implantation of an EES could improve the survival of patients with CKD, I review emerging information about the vasculopathy associated with CKD and new evidence of the primacy of EES implantation in PCI.

Vascular calcification is pervasive in CKD. Impaired renal excretion of phosphate (Pi) may trigger the formation of macrophage-derived matrix vesicles that facilitate hydroxyapatite nucleation, contributing to vascular microcalcification (6). Separate from spotty calcification in the intima, which may predispose the vulnerable atherosclerotic plaque to rupture (7), confluent medial calcification is the vascular hallmark of CKD.

Medial calcification develops through a mechanism analogous to bone formation and occurs in CKD independently of the traditional risk factors of diabetes, hypertension, and hyperlipidemia (8). Recent evidence suggests that extracellular Pi is transported into vascular smooth-muscle cells by a sodium Pi cotransporter, and the resultant increase in intracellular Pi induces the cells to adopt the genetic and cellular properties of osteoblasts (9). Bone disease in CKD worsens vascular calcification. High bone turnover ensures a continuous source of mineral, and low-turnover disease acts like osteoporosis in which demineralization of bone is associated with mineralization of the vascular wall (8).

Pi binders are designed to reduce Pi, but calcium-containing binders like calcium acetate theoretically exacerbate vascular calcification, particularly when they are used with vitamin D (10). The calcium-free binder sevelamer has been increasingly replacing...
calcium-containing binders in clinical practice, but there is little evidence that sevelamer improves mortality or reduces vascular calcification (11).

In addition to causing calcification, CKD may change the pattern of CAD. In an angiographic study, investigators found that patients with CKD were more likely than patients without CKD to have significant lesions within the proximal segments of the coronary arteries (12). Given the vascular findings, discerning readers may wish to understand how “spot” stenting of predominantly calcified lesions often located in the proximal segments of the coronary tree in patients with CKD could lead to favorable clinical outcomes compared with other forms of revascularization. For many interventional cardiologists, lesion calcification might elicit the use of adjunctive ablative therapies, but a serum creatinine level >2.5 mg/dl has been a common exclusion in RCTs of orbital and rotational atherectomy (13), giving little guidance for the CKD population.

The development of EES has been a major advance in PCI. Recent evidence suggests that EES are associated with lower stent-thrombosis and all-cause mortality rates than are bare metal or first-generation drug-eluting stents (14). Although lower EES-related complications may be attributed to better strut coverage or lower inflammation (15), the mechanisms cannot explain how EES perform better than other types of stents in calcified lesions or how EES could compete with surgical conduits to protect against future atherothrombotic events in long segments of the coronary tree in patients with CKD.

The current study (5) has many strengths, but an observational study is not likely to reveal pathogenetic mechanisms. The study compared outcomes in patients whose referral for EES implantation or CABG was selected but not randomly assigned. Similar to patients enrolled in other studies (2), patients referred for stent implantation in the current study were less likely than those referred for CABG to have 3-vessel disease or multivessel CAD involving the proximal left anterior descending (LAD) artery. To even out the systematic differences between the EES and the CABG groups, Bangalore et al. (5) used propensity-score matching, but some experts argue that no adjustment can eliminate prognostic imbalances when different patients are selected for different therapies (16).

A major strength of the current study (5) is its exclusive focus on the use of EES. The study thus gives relevant and timely guidance for revascularization decisions in patients with CKD and multivessel CAD. The results suggest that patients with CKD stage III or IV and multivessel CAD can undergo EES implantation as an alternative to CABG, particularly if there are mitigating factors against CABG such as frailty or significantly reduced life expectancy. However, surgical candidates with CKD stage III or IV and multivessel CAD involving the proximal LAD should probably be given the option of CABG because longer follow-up may show a survival advantage with surgery. Although a subset analysis in the report (5) suggests that patients on hemodialysis should undergo CABG in preference to PCI, revascularization decisions for patients with CKD stage V are complicated and must be individualized. Finally, the current study throws down the gauntlet for investigators to design a dedicated RCT comparing PCI with CABG for patients with CKD (1) and for experimental studies to continue to identify the pathogenetic links between the metabolic derangements of CKD and vasculopathy to codify best practices and to provide new insights into mechanisms of success of EES in the challenging milieu of CKD vasculopathy.

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