Coronary Artery Revascularization in Chronic Kidney Disease

Time for a Randomized Trial

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Coronary artery revascularization procedures, performed via coronary artery bypass grafting (CABG) or percutaneous (PCI) methods, are among the most commonly performed therapeutic interventions worldwide with >1 million performed annually in the United States alone. The relative merits of each approach have been examined in numerous landmark clinical trials that inform practice guidelines and daily clinical decision making. Although the percutaneous comparator to CABG in early studies usually included balloon angioplasty or bare metal stents, recent studies reflect iterative advances in both stent technology and contemporary medical therapy. Despite this large evidence base, however, routine exclusion of patients with underlying chronic kidney disease (CKD) persists in many clinical trials. In the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) and Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) studies, for example, patients were excluded with serum creatinine levels exceeding 2 mg/dL and severe renal disease, respectively. The public health implication of such systematic under-representation is highlighted by the fact that CKD is present in >40% of all patients undergoing PCI and ~30% of those receiving CABG. In addition, renal dysfunction confers a strong, independent, and graded risk for morbidity and mortality after PCI or CABG. The high prevalence of CKD in patients requiring revascularization, coupled with the excess cardiac risk associated with this condition, has motivated consensus statements and clinical investigations examining the impact of PCI and CABG in this high-risk population.

See Article by Chan et al

It is within the context that Chan et al have reported their findings comparing CABG to PCI with drug-eluting stents (DES) in a large cohort of patients with CKD in this issue of Circulation: Cardiovascular Interventions. Using data from a provincial registry in Ontario, Canada, the authors identified 4006 patients with CKD and multivessel coronary artery disease undergoing index revascularization between 2008 and 2011. Most patients (n=3010) underwent CABG, whereas PCI with DES was performed in 996. The cohort reflected the high prevalence of comorbid risk factors expected in patients with CKD with an average age of ~75 years and diabetes mellitus present in >40% of participants. Of note, few patients (n=211; 5.3%) were receiving dialysis at the time of revascularization. Patients were followed up for an average of ~2 years and the authors compared early and late clinical outcomes between groups in the overall sample and in a propensity-matched cohort. Independent predictors of late adverse events were identified using multivariable modeling. Salient findings from this report include a substantial advantage for CABG over PCI that emerged as early as 30 days, lack of differences in stroke rates between groups, and an independent hazard for late adverse events associated with DES use. Findings were unchanged in the propensity-matched cohort and persisted after multivariable adjustment.

As CKD is associated with a unique and diffuse atherosclerotic phenotype, these results are concordant with the current revascularization paradigm favoring CABG over PCI in patients with diffuse or complex coronary artery disease. Randomized trial data, for example, has demonstrated the accentuated benefits of CABG over PCI with DES in other patient cohorts with extensive atherosclerosis, such as diabetes mellitus or those with intermediate to high Synergy Between PCI With TAXUS and Cardiac Surgery (SYNTAX) scores. Although patients were matched for degree of coronary artery disease in this study, nonobstructive and angiographically inapparent disease is strongly linked with risk for subsequent adverse events and provides a rationale for more complete revascularization with CABG in patients with diffuse atherosclerosis.

The current report is also consistent with and extends previous comparisons between CABG and PCI performed in dialysis cohorts. Although these earlier studies suggested an advantage for CABG over PCI in dialysis patients, the magnitude of benefit observed by Chan et al in their predominantly nondialysis population is much larger than that observed in the setting of dialysis-dependent CKD. More specifically, Chan et al demonstrated an absolute unadjusted 7.4% reduction in late mortality risk, substantially higher than the 3% difference noted by Charytan et al at a similar time point. These differences may reflect excess mortality risk after CABG in the early postsurgical period in patients with versus without dialysis, thereby mitigating long-term benefits from surgical bypass. Alternatively,
it is possible that nonatherosclerotic mechanisms contributing to cardiovascular mortality that are minimally modified with CABG, such as myocardial fibrosis, left ventricular hypertrophy, and electrolyte disturbances, increase in importance as renal function worsens. Supporting this hypothesis are findings by Hakeem et al.\textsuperscript{13} showing that rates of sudden cardiac death increase as renal function worsens even in the absence of any inducible ischemia. This concept, as articulated by Herzog et al.,\textsuperscript{14} provides a rationale for the attenuated impact of other interventions that reduce cardiovascular risk via atherosclerotic-mediated mechanisms, such as statins, in dialysis patients.

In the present report, Chan et al also noted an increased hazard for late mortality associated with DES use, an association that persisted after multivariable and propensity adjustment. This result contrasts with those of a recent network meta-analysis suggesting that newer-generation DESs yield mortality reductions comparable with CABG when either is compared with medical therapy, whereas first generation DESs confer less benefit.\textsuperscript{15} Whether the observed mortality risk observed by Chan et al is uniform or varies by DES type is unknown; however, as this information was not collected as part of the study. In addition, the possibility of residual and unmeasured confounding influencing the point estimates for mortality associated with DES use is a relevant consideration given the observational study design. Although the authors used propensity matching, several baseline differences persisted in the matched cohort. In addition, adherence to dual antiplatelet therapy, an important risk factor for stent thrombosis,\textsuperscript{16} was not included as a covariate in adjusted analyses. Dual antiplatelet therapy compliance as a potential mediator of DES-attributable mortality in the setting of CKD may be particularly relevant given the increased bleeding risk observed in such patients. The limitations of an observational study notwithstanding, it is also plausible that the prothrombotic state associated with CKD may amplify stent thrombosis risk, contributing to excess mortality after DES implantation. Previous studies, for example, have shown that renal dysfunction is an independent risk factor for stent thrombosis.\textsuperscript{17} Modulation of platelet reactivity and the coagulation cascade are potential mechanisms by which CKD may promote stent thrombosis.\textsuperscript{18}

A somewhat surprising result from the present study was the lack of differences in stroke risk between groups throughout the study period. In fact, in the propensity-matched cohort late stroke rates were identical at 2.4% in both CABG and PCI groups. Although this rate is comparable with the CABG arms in both FREEDOM and SYNTAX trials, it is much higher than the ≈1.5% stroke rate observed in the PCI arms of these randomized studies. These differences might reflect a chance finding or selection bias favoring PCI in patients at higher risk for stroke in the context of nonrandom treatment allocation. Although the prevalence of cerebrovascular disease was compared at baseline, prior stroke per se was not included as a baseline clinical parameter. In addition, stroke rates were numerically higher with PCI as compared with CABG in the unmatched population, suggesting baseline imbalances in preexisting risk factors for stroke between groups. As the authors mention this finding warrants further study, particularly as concerns for stroke are among the most important considerations for patients and may even outweigh those of death.\textsuperscript{19}

The study by Chan et al represents an important and clinically relevant contribution to the growing body of literature examining revascularization approaches in high-risk patients with underlying CKD. Although the authors are to be commended for this work, results from observational studies can generate hypotheses, not answer them. A randomized trial to address this issue is long overdue and is needed if we are to provide the highest quality and optimal level of care to the many patients with CKD and coronary artery disease who will need coronary revascularization.

Disclosures

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References


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