Percutaneous coronary intervention in patients with chronic kidney disease: where’s the evidence?

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More than 1,000,000 percutaneous coronary interventions (PCIs) are performed annually in the USA [1]. This growth in PCIs has been largely supported by many randomized clinical trials (RCTs) that have demonstrated the benefit of PCI in the context of acute coronary syndromes (ACS) and certain subsets of patients with chronic coronary artery disease. However, in the real world, many PCIs are performed in patients not represented in the RCTs. The ‘average’ overall benefit and risk of using a standardized therapy such as PCI and its concomitant antithrombins may not be applicable to these patients. An important example of a higher-risk patient subset frequently treated with PCI in the real world but excluded from RCTs is patients with chronic kidney disease (CKD).

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Over 19 million adults in the USA are estimated to have CKD, with an additional 500,000 requiring chronic dialysis [2,3]. These patients have a high prevalence of coronary artery disease and are at increased cardiovascular risk when admitted for ACS. Despite the fact that 30–60% of patients with coronary artery disease also have concomitant CKD, major cardiovascular disease trials frequently exclude these patients from their studies [4,5]. A recent paper by Coca et al. examined RCTs for chronic congestive heart failure and acute myocardial infarction treatments that were listed as class I or II recommendations in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines. Of the 153 trials reviewed, 86 (56%) excluded patients with CKD. Furthermore, in the trials that included patients with CKD, only four (3%) reported a subgroup analysis of treatment stratified by renal dysfunction [6].

As a result, few data exist from RCTs to guide decisions concerning PCI in patients with CKD. The majority of our evidence in this patient subset comes from observational registries or post hoc subgroup analysis of RCTs. The presumption of similar efficacy of PCI and the concomitant use of antithrombotic adjuncts in patients with CKD is challenging given the known differences in the pathophysiology of cardiovascular disease in these patients and their well-recognized qualitative platelet abnormalities and coagulation disorders [7].

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The literature has been very consistent in showing an increased risk of PCI in patients with CKD. Specifically, periprocedural complications such as in-hospital bleeding, myocardial infarction and death are much higher, approaching an increased relative risk of two- to eight-fold [8,9]. In addition, dozens of registries have shown worse short- and long-term clinical outcomes after PCI, including death, when these patients are compared with patients with normal renal function [10,11]. However, this may be due to the overall greater risk of cardiovascular events in this high-risk group. Thus, the more pertinent question is whether patients with CKD undergoing PCI do better or worse than...
those treated with medical therapy alone. In a retrospective study of 4758 high-risk patients admitted with ACS, patients with CKD who underwent PCI had superior long-term survival. Of the 1654 patients with significant renal dysfunction defined as an estimated glomerular filtration rate of less than 60 ml/min/1.73 m², only 232 underwent PCI while 1078 were treated with medical therapy alone [4]. This probably represents strong selection bias that influenced the operator’s decision to proceed with invasive therapy that cannot be fully adjusted for the given limited variables in the registry. Patients deferred to medical therapy alone were likely to be sicker and less suitable for an invasive procedure owing to more severe coronary artery calcification and difficult coronary anatomy [12,13]. Therefore, the data supporting the use of PCI over medical therapy in patients with CKD is extremely limited and fraught with confounding data in the absence of a RCT. To date, there have been no RCTs that have directly examined the risk:benefit ratio of PCI over medical therapy in patients with CKD.

In addition to the paucity of data substantiating PCI as efficacious in patients with CKD presenting with ACS or stable angina, controversy also exists regarding the optimal antithrombotic regimen for high-risk patients with CKD undergoing PCI. Commonly used pharmacologic adjuncts to PCI, such as the glycoprotein (GP) IIb/IIIa inhibitors eptifibatide and tirofiban, are cleared by the kidneys and would be expected to lead to increased plasma levels in patients with CKD. On the one hand, the increased levels of platelet inhibition might be expected to increase the risk of bleeding. However, this may also decrease the likelihood of periprocedural ischemic end points through an enhanced suppression of platelets. The latter benefit was suggested in a post hoc subgroup analysis of the Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrin Therapy (ESPRIT) trial [14]. In this retrospective analysis, it appeared that a greater magnitude of the treatment effect of eptifibatide was observed in patients with lower calculated creatinine clearances [15]. However, other post hoc analyses of RCTs have not found a greater beneficial effect of GP IIb/IIIa with increasing CKD [16]. Abciximab, a GP IIb/IIIa inhibitor that is cleared through the reticuloendothelial system, has become the GP IIb/IIIa inhibitor of choice in patients with severe renal insufficiency and dialysis given its consistent therapeutic levels independent of renal dysfunction. Unlike the RCTs that showed no increased risk of bleeding with abciximab over placebo, registries have suggested an increased risk of bleeding in patients with CKD versus patients with normal renal function. This risk of bleeding with abciximab did not significantly increase with increasing levels of renal insufficiency [17]. Therefore, the true risk and benefit of these agents in patients with CKD are uncertain. Recent studies have exposed the risk of both excess dosing and the inappropriate administration of antiplatelets and anticoagulants in patients with CKD, which has led to increased adverse events [18,19].

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Despite a firm evidence base, thousands of patients with concomitant coronary artery disease and CKD will continue to be treated based on the average overall benefit and risk observed in the RCTs. In the absence of definitive data to guide us, treating to the mean may appear to be the best option available. However, the presumption of the benefit of cardiovascular therapies to patients with CKD was recently challenged with the publication of the Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) [20]. The impetus of this study was to evaluate the benefit of statin therapy for patients on hemodialysis where the benefit in the general population and patients with CKD were well supported. Surprisingly, despite a mean 43% reduction in LDL, rosuvastatin had no effect on the primary end point of nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes. The lack of a benefit of statin therapy in this study suggests that cardiovascular disease in patients with CKD differs from patients without CKD, and translations of therapeutic benefit from the non-CKD population may be unwarranted. An important distinction between a therapeutic efficacy trial involving a drug such as rosuvastatin...
and coronary revascularization deserves mention. PCIs in patients with CKD have procedure specific risks such as acute renal failure, access site bleeding and periprocedural myocardial infarction and stroke that are substantial trade-offs to patients receiving medical therapy alone. All of these must be considered in the risk:benefit analysis. Owing to the increased risk of these complications with PCI in patients with CKD, a rigorous assessment of the potential benefits of PCI over medical therapy is paramount.

Moving forward, we propose two key solutions that will better inform the treatment of patients with CKD in cardiovascular medicine. First, the NIH should advocate for pragmatic clinical trials where the trial design requires the inclusion of patients with significant renal dysfunction and prespecified subgroup analysis of the efficacy of treatment in these patients. This would add significant insight into the risks and benefit of new therapies in these important patients. For example, imagine that the COURAGE trial had included a significant number of patients with CKD [21]. This would allow clinicians to translate the findings of this prespecified subgroup to their substantial population of patients with CKD. Second, with the American Recovery and Reinvestment Act of 2009, a sudden influx of research funds have been allocated towards the development and dissemination of research assessing the comparative effectiveness of healthcare treatments. A particular focus of this effort has been towards patients under-represented in clinical trials, such as patients with CKD. To understand the complexities and strengths of using nonrandomized data, guidelines have emerged to ensure valid retrospective comparative effectiveness research questions, appropriate analyses to address bias or confounding and standardized reporting [22-24]. Through the application of these new techniques, we must begin to better evaluate these high-risk subsets of patients in large registries. This will allow us to provide more accurate and reliable point estimates of the potential benefits and risks of specific therapies and make more informed decisions for our patients.

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