Coronary artery disease is the number one cause of death in patients with chronic kidney disease (CKD). However, patients with impaired renal function are much less likely than patients with normal renal function to undergo left heart catheterization and coronary intervention. Patients that do receive invasive strategies experience more bleeding and higher rates of ischemic events. In this review, we examine advances in percutaneous coronary intervention—including anti-platelet therapy and drug-eluting stents—and their impact on patients with CKD.

Key words
Percutaneous coronary intervention, chronic kidney disease, coronary artery disease

Introduction and epidemiology
Cardiovascular disease remains the leading cause of mortality in patients with chronic kidney disease (CKD) and dialysis-dependent renal disease. Dialysis patients experience a mortality rate after myocardial infarction that is 15 times that in patients with normal renal function. Mortality at 1 year after myocardial infarction can reach as high as 59% in the dialysis population (1). In spite of those statistics, dialysis patients and patients with CKD that does not require dialysis are significantly less likely than patients with normal renal function to undergo coronary angiography and revascularization (2). After revascularization with percutaneous coronary intervention (PCI), renal insufficiency predicts mortality and subsequent cardiac events in a dose-dependent fashion (3).

It is already known that end-stage renal disease is an independent risk factor for stent thrombosis (4). Recently, Lambert and colleagues (5) showed that, when coupled with dipstick proteinuria, moderately severe CKD (stage 3 or 4) is an independent risk factor for stent thrombosis. Those authors retrospectively analyzed 956 patients with stage 3 or 4 CKD who had suffered an acute myocardial infarction followed by coronary stent placement. Compared with patients having lesser proteinuria, patients with proteinuria of 30 mg/dL or more were twice as likely to die and three times as likely to experience repeat myocardial infarction 1 year after stenting. Those findings were independent of lesion type and medical compliance. The authors concluded that moderate CKD and proteinuria were both associated with a significantly increased rate of stent thrombosis.

The hope has been that advances in PCI, including drug-eluting stents and dual anti-platelet therapy, will improve outcomes in all patient groups, including those with CKD. However, those advances have had only a marginal impact on patients with CKD who undergo PCI. The present review focuses on recent advances in PCI and their effects in that patient population.

Discussion

Adjunctive pharmacologic therapy, PCI, and CKD
Multiple large randomized trials have confirmed the benefits of dual anti-platelet therapy, including aspirin and clopidogrel, in the management of acute coronary syndromes and the prevention of future coronary events. However, an understanding of the interaction between CKD and those agents is only just beginning.

In the CREDO (Clopidogrel for the Reduction of Events During Observation) study, 2002 patients were randomized to receive either a 300-mg loading dose of clopidogrel or a placebo loading dose before elective PCI. Both groups received clopidogrel 75 mg daily after the PCI. Patients were followed for 1 year to
assess the combined endpoint of death, myocardial infarction, and stroke. The combined endpoint occurred less frequently in patients who received the loading dose of clopidogrel before PCI. As expected, patients with impaired renal function experienced, in a dose-dependent fashion, higher rates of death, myocardial infarction, and stroke after PCI. Surprisingly, the authors reported that, at 1 year, clopidogrel appeared to lose much of its benefit in patients with mild-to-moderate renal impairment [creatinine clearance (CCr) of 60 – 89 mL/min]. Compared with patients having normal renal function, patients with moderate CKD experienced similar rates of major adverse cardiac events after PCI with the addition of clopidogrel. Surprisingly, clopidogrel did not increase the risk of major and minor bleeding in this population (6).

In a subset of the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial, Keltai et al. investigated the effectiveness of clopidogrel after PCI for unstable angina and non–ST-segment elevation myocardial infarction (non-STEMI) in patients with CKD. The trial included 12,253 patients grouped by renal function into tertiles of glomerular filtration rate. Not surprisingly, patients in the lowest tertile experienced the highest rate of cardiovascular death, myocardial infarction, stroke, and bleeding. In all tertiles, use of clopidogrel correlated with increased minor bleeding. However, major bleeding was only moderately associated with clopidogrel use. The authors concluded that clopidogrel use is safe and beneficial in the treatment of non-STEMI in patients with CKD (7).

One of the major factors leading to adverse outcomes after PCI in patients with CKD is the lesser use of optimal medical therapy. In the EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) registry, the likelihood that a patient received aspirin, a statin, an angiotensin converting–enzyme inhibitor, or clopidogrel declined significantly with decreasing renal function (8). Multiple studies have confirmed that patients with CKD do not reach therapeutic goals for dyslipidemia, diabetes, and hypertension.

Thus, patients with CKD have worse outcomes after PCI or acute coronary syndromes. The overall use of adjunctive therapies and the ability to reach target outcomes are less in the CKD population. Furthermore, the beneficial effect of dual anti-platelet therapy is not seen in that population to the extent seen in patients with normal or near-normal renal function. The mechanisms governing these differences are unknown.

**Glycoprotein IIb/IIIa inhibitors**

Multiple studies have confirmed that glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors are effective at reducing ischemic events post PCI in the general population. However, the safety of these agents in patients with CKD has been questioned. Published in 2005, the TARGET (Do Tirofiban and Reopro Give Similar Efficacy Outcomes) trial was designed to compare the efficacy and safety of tirofiban, which is renally cleared, with that of abciximab, which is not. A multicenter trial, TARGET randomized 4623 patients to tirofiban or abciximab at the time of PCI. Patients were grouped into quartiles based on creatinine clearance (<70 mL/min, 70 – 90 mL/min, 90 – 114 mL/min, >114 mL/min). After PCI, patients were assessed for bleeding, death, myocardial infarction, and urgent target vessel revascularization at 30 days. As expected, complication rates for all endpoints increased with impaired renal function. However, no increased bleeding was seen in patients receiving tirofiban as compared with those receiving abciximab. A slight reduction in ischemic events was observed in patients who had received abciximab. The authors concluded that there is no adverse interaction between those two GPIIb/IIIa inhibitors and creatinine clearance in terms of bleeding and ischemic complications (9).

**Drug-eluting stents in patients with CKD**

Drug-eluting stents were introduced around the year 2000 as a means to slow neo-intimal growth within a stented lumen. These stents have proved successful at decreasing target vessel revascularization in the general population. To combat higher rates of target vessel revascularization and in-stent re-stenosis in patients with CKD, interest in using drug-eluting stents in that subgroup has been increasing. However, patients with end-stage renal disease and severe CKD have for the most part been excluded from large randomized trials. In multiple small nonrandomized trials (see Table I), dialysis patients receiving drug-eluting stents (as compared with bare metal stents) have experienced fewer ischemic events, less need for target vessel revascularization, and less cardiac death. However, despite the introduction of drug-eluting stents, mortality and complications from recurrent
ischemia and bleeding are proportionately higher as renal function progressively worsens (8).

The choice of a drug-eluting stent over a bare metal stent is a difficult decision and is based on a number of factors, including drug adherence, cost (use of clopidogrel on an ongoing basis), risk of bleeding from the necessary adjuvant therapy, and the overall long-term prognosis of the patient.

**Thrombolytics compared with PCI in STEMI**

Since the start of the 2000s, several studies have compared the merits of PCI with those of thrombolytics for the treatment of STEMI. Patients with CKD have not been analyzed as a subgroup in the larger landmark studies such as GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries), ISIS-3 (Third International Study of Infarct Survival), and GISSI-2 (second study by the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto). Most of the large randomized trials excluded patients with more than the milder forms of CKD.

The GRACE (Global Registry of Acute Coronary Events) multinational registry tracks patients with acute coronary events, including STEMI and new left bundle branch block. It represents the largest registry of its type, having 12,532 participants, including more than 3450 subjects with renal dysfunction. In a recently published manuscript concerning a subset of CKD patients from the registry, the patients were retrospectively stratified to treatment with PCI or thrombolysis or to neither intervention. Renal impairment was associated with increased in-hospital mortality. As compared with no reperfusion, PCI failed to reduce in-hospital mortality. Fibrinolysis did not improve in-hospital mortality in patients with normal or impaired renal function. In CKD patients, PCI was associated with an increased risk of bleeding. Fibrinolysis was associated with a higher risk of stroke. At 6 months, patients with moderate renal dysfunction showed a mortality benefit only with PCI. However, patients with severe renal dysfunction experienced significantly higher mortality if treated with either PCI or fibrinolysis than with neither treatment modality. That study highlighted the persistently poor prognosis associated with CKD in spite of the availability of modern therapies (13). Therefore, despite therapy shown to markedly improve in-hospital and later outcomes in the general population, neither PCI nor fibrinolysis demonstrated marked benefit in STEMI patients with CKD. Minor improvements in secondary and longer-term outcomes were observed in patients with moderate renal dysfunction in the GRACE registry.

**Coronary bypass grafting compared with PCI in CKD**

Drug-eluting stents have drastically changed the treatment of coronary artery disease in the 21st century, but little is known about comparative outcomes in patients with CKD who undergo bypass. Two studies published in 2009 have begun to answer questions about the risks and benefits of coronary artery bypass grafting (CABG) compared with PCI in patients with CKD and end-stage renal disease.

Manabe *et al.* retrospectively analyzed 46 dialysis-dependent patients who underwent CABG (n = 28) or PCI (n = 18). Drug-eluting stents were used in 12 of the PCI patients, and bilateral internal mammary grafts were used in 27 of the CABG patients. Patency rates for the internal mammary grafts were 100% and 84.6% (left and right arteries respectively) at 1 year. The re-stenosis rate at 6 months after PCI was 57.1%. Mortality at 2 years was similar, but major adverse cardiac event–free survival significantly favored CABG (85.9% vs. 37.1%). This small, retrospective, nonrandomized study included patients who received balloon angioplasty and bare metal stents. However, the study demonstrated the benefits of using internal mammary artery bypass in this population (14).

In a much larger study, Wang *et al.* used a comprehensive revascularization database to retrospectively analyze 1069 patients with CKD (CCr < 60 mL/min) who underwent revascularization for 2- or 3-vessel disease from January 2004 to June 2006. Of these patients, 724 underwent PCI with placement of a drug-eluting stent; 345 underwent CABG. Patients in the PCI group received a 600-mg loading dose of clopidogrel and 75 mg of the drug daily thereafter. Patients in the surgery arm underwent standard techniques, with preferential use of the internal mammary artery, and received aspirin 100 mg daily indefinitely. At 2 years, no statistical difference was observed in mortality, myocardial infarction, and stroke. However, patients who received drug-eluting stents for 3-vessel disease were more likely to require repeat revascularization (15). That finding seems to echo similar studies in patients without CKD and with multivessel disease [such as SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery)], which found that patients receiving drug-eluting stents
<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
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<th>Duration</th>
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<tr>
<td>Latif et al., 2009 (8)</td>
<td>Patients in the EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) registry stratified into 4 subgroups by CCr in milliliters per minute (&gt;75, 50–75, 30–49, &lt;30)</td>
<td>4791</td>
<td>12 Months</td>
<td>In the DES era, CKD patients receive suboptimal medical therapy post PCI; CKD predicts in-hospital bleeding, mortality, and non-fatal MI at 1 year.</td>
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<td>Yachi et al., 2009 (10)</td>
<td>Non-randomized retrospective single-center study of consecutive dialysis patients who received BMS vs. DES (sirolimus)</td>
<td>DES: 56</td>
<td>Angiography at 6–8 months</td>
<td>Compared with dialysis patients receiving BMS, those receiving sirolimus stents experienced fewer MACE (cardiac death, TLR, non-fatal MI; ( p = 0.01 )). Sirolimus stents successfully inhibited neo-intimal growth in dialysis patients.</td>
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<td>Non-CKD: 337, CKD: 222, HD: 34</td>
<td>BMS: 67</td>
<td>Clinical follow-up at 9 months</td>
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<td>Ota et al., 2009 (11)</td>
<td>Prospective analysis of patients who received DES (sirolimus), stratified by normal renal function (CCr &gt; 60 mL/min), CKD (CCr &lt; 60 mL/min), and HD.</td>
<td>Non-CKD: 337</td>
<td>2 Years</td>
<td>Compared with non-HD groups, the HD group experienced increased late lumen loss, higher re-stenosis rates, TLR, mortality, and composite MACE after receiving DES.</td>
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<td>Okada et al., 2008 (12)</td>
<td>Nonrandomized single-center study of consecutive dialysis patients who received BMS compared with DES (sirolimus)</td>
<td>DES: 80</td>
<td>1 Year</td>
<td>In dialysis patients, sirolimus stents (as compared with BMS) led to less MACE post-PCI (death, nonfatal MI, TLR, and stent thrombosis; ( p = 0.048 )).</td>
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<td>BMS: 124</td>
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CCr = creatinine clearance; DES = drug-eluting stent; PCI = percutaneous coronary intervention; MI = myocardial infarction; BMS = bare metal stent; MACE = major adverse cardiovascular events; TLR = target lesion revascularization; HD = hemodialysis; TVR = target vessel revascularization.
require repeat revascularization at a higher rate than do those receiving CABG (16).

Summary
In spite of recent advances in PCI, patients with CKD still face a poor prognosis after PCI, regardless of the type of stent used. Recent studies have showed modest clinical improvements with the use of drug-eluting stents in patients with impaired renal function. In addition, the use of mammary arterial grafts is important to improve outcomes in patients with CKD. But despite their use, outcomes after CABG are worse in CKD patients than in patients with normal renal function. These observations further reinforce the importance of primary prevention and risk-factor modification to forestall the progression of CKD and cardiovascular disease.

References

Corresponding author:
Kevin C. Dellsperger, MD, PhD, CE 549, DC 375.00, University of Missouri Health Care, One Hospital Drive, Columbia, MO 65212 U.S.A.
E-mail: Dellspergerk@health.missouri.edu