Coronary Revascularization in Diabetic Chronic Kidney Disease/End-Stage Renal Disease: A Nephrologist’s Perspective

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Coronary artery disease (CAD) has become a familiar problem for nephrologists, requiring collaboration with interventional cardiologists and cardiac surgeons. Coronary risk is magnified in both patients with chronic kidney disease (CKD) and patients with ESRD (1). Cardiovascular disease frequently leads to death before ESRD is reached (2). Recent data indicate that moderate renal failure is a predictor of myocardial infarction (MI) and death (3), independent of other clinical variables (4,5). Both the National Kidney Foundation (6) and the American Heart Association (7) now list CKD as an independent cardiovascular risk factor. Cardiovascular complications, including sudden death, are the principal cause of morbidity and mortality in patients who are on long-term dialysis, accounting for 44% of all-cause mortality. In patients who are on renal replacement therapy, the relative risk for dying from cardiac causes is higher by a factor of at least 10, and the relative risk for death as a result of MI is five times that of the general population (8). A recent report from the US Renal Data System database indicated 59% 1-yr mortality in long-term dialysis patients after an acute MI (9).

The risk for cardiac and all-cause death is also higher in patients with diabetes, even after adjustment for confounding factors (10–12) (Figure 1). Cardiovascular disease accounts for almost three fourths of deaths of patients with diabetes, almost entirely as a result of CAD (13). Patients with diabetes have twice the incidence of acute coronary syndromes, twice the mortality from acute MI, and worse short- and long-term outcomes (14). Diabetes is associated with poorer outcomes for both coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI), a term that includes percutaneous transluminal coronary angioplasty (PTCA), stent implantation, and techniques for plaque modification and thrombus aspiration. Patients with diabetes represent approximately 25% of revascularization procedures that are performed annually in the United States (15). Diabetic ESRD is the highest risk group for cardiac death (16). In a recent study of new dialysis patients who were asymptomatic and had no known cardiac history, significant lesions were present in 83% of patients with diabetes (17).

Nonetheless, the optimal CAD treatment in this population remains uncertain. PCI and CABG are the definitive options for coronary revascularization (18). PCI have dramatically changed the management of CAD, rising in prevalence, whereas the number of surgical revascularizations remains static (Figure 2). PCI are being used in patients with varying degrees of renal failure (18). The most common indications are critical stenosis found in stable angina, unstable angina, or acute MI (although a large proportion of these may have noncritical stenosis). However, patients who have diabetes and undergo PCI have worse angiographic and clinical outcomes than individuals without diabetes (19) and also are at greater risk for complications. Diabetes roughly doubles the incidence of restenosis compared with individuals without diabetes (20–22). Renal insufficiency is also associated with poorer short- and long-term outcomes. Preliminary data suggest that aggressive therapy is underutilized in dialysis patients who experience acute MI (23), yet as the number of patients with diabetes and CKD grows, it is likely that the number of coronary revascularization procedures will also increase.

What are the indications for coronary revascularization in the patient with diabetes and CKD/ESRD, and the expected results? Treatment of medically refractory or inadequately treated patients with CAD accounts for the majority of coronary interventions, whereas others are treated for acute coronary syndromes. Additional patients will be discovered to have CAD when screened for atypical symptoms or in anticipation of noncardiac surgery, including kidney transplantation. Patients with pretransplantation diabetes and symptomatic CAD or positive noninvasive screening tests should undergo coronary angiography (24–26). This article reviews the distinguishing features of CAD in the population with diabetes and CKD/ESRD and assesses recent developments, including drug-eluting stents (DES) and aggressive antiplatelet therapy. Coronary bypass surgery data are presented as the comparator therapy to PCI.

Diabetes and CKD as Coronary Risk Factors

Diabetes is an independent risk factor for CAD, promoting both the initiation and the progression of atherosclerotic dis-
ease (27). The risk is enhanced to the extent that mortality in individuals who have diabetes and no history of cardiac events matches that of individuals who do not have diabetes and have survived an MI (28). Patients with diabetes have more diffuse disease and more silent ischemia. Patients who have diabetes and undergo PCI have more three-vessel disease, more total occlusions, more significant lesions, and left ventricular systolic function that is impaired (29). Less than half of the increase in cardiovascular events in diabetes seems to derive from traditional risk factors such as dyslipidemia and hypertension (30). Traditional risk factors did not distinguish patients with CAD in a study of patients with diabetes and ESRD (31). Excessive cardiovascular risk in patients with diabetes is instead attributed to enhanced platelet activity, inflammation, hypercoagulability, and endothelial dysfunction (14). Thrombosis is a major determinant of the progression of atherosclerosis (32). Activation of platelets is heightened in diabetes. Adhesion of platelets is increased because of enhanced surface expression of glycoprotein IIb/IIIa, which mediates adhesion by binding to von Willebrand factor (33). The role of increased generation of thrombin is evidenced by increased elevated concentrations of fibrinogen, fibrinopeptide A, and thrombin-antithrombin complexes in blood, particularly in patients who have diabetes and clinical vascular disease.

Even mild CKD now has been established as a coronary risk factor. In patients with CKD, the problem of occult yet significant coronary disease is increasingly understood (34). In a recent report, 30 asymptomatic patients with stage 5 CKD and no history of angina pectoris or MI underwent coronary angiography at the initiation of dialysis. More than half had significant coronary stenoses, a third of whom had severe luminal narrowing (17).

As with diabetes, CAD in CKD exists independent of other conventional risk factors. Two risk factors, anemia and disordered mineral metabolism (especially hyperphosphatemia), have been shown consistently in patients with ESRD. Although not unique to the CKD population, inflammation, like hypertension, may be more prevalent. Suggestive data also support a role for oxidative or carbonyl stress and elevated inflammatory and prothrombotic factors [C-reactive protein, fibrinogen, IL, factor VII, and lipoprotein (a)] (3). Compared with the general population, elevated creatinine levels have been associated with increased cardiovascular risk by a factor of 2 to 4 (35). In patients with even mild degrees of kidney impairment or microalbuminuria, the independent risk for a clinical cardiovascular event is significantly increased (36) and has been compared in magnitude to the similar risk related to diabetes (37). In a recent analysis of 8600 patients who had a mean (± SD) GFR of 70.9 ± 23.5 ml/min and underwent coronary angiography in the Intervention Heart Study, when adjustments were made for known coronary risk factors, even moderate kidney impairment increased the risk for MI and death (4). Go et al. (38) reported an independent, graded association between decreased estimated GFR and risk for cardiovascular events, below a GFR of 60 ml/min. Other studies have also associated renal impairment with increased in-hospital and postdischarge mortality after acute MI (39,40).

Analysis of genetic risk profiles in diabetic CKD/ESRD is ongoing (41,42). Diabetes and CKD both are precursors to accelerated vascular calcification, with calcium and phosphorous deposition (43). The composition of involved coronary arteries of patients with diabetes and kidney failure resemble each other (44). Atherosclerotic occlusive plaque morphology in both diabetes and ESRD is accompanied by marked subintimal calcification and is associated with medial thickening as a result of hypertrophy and hyperplasia of vascular smooth muscle cells. Clinically, medial calcification also seems to correlate

![Figure 1.](image1.png) Comparative coronary heart disease risk in chronic kidney disease (CKD) and ESRD, relative to risk in actual population as predicted from the Framingham study (12). Framingham risk computation assumed age 60 yr, male gender, diabetes, hypertension, low HDL level, and nonsmoker. Micro-, microalbuminuria; Gross, overt proteinuria.

![Figure 2.](image2.png) Rising prevalence of percutaneous coronary intervention (PCI) procedures. Shown are adjusted admission rates for cardiovascular procedures in ESRD period prevalent patients from the US Renal Data System database. Adapted from reference (1), with permission.
with CAD, a relationship that possibly is based on vessel stiffness, increased pulse pressure, left ventricular hypertrophy, and compromised coronary perfusion (45). Nondialed patients with diabetes and CKD, like patients with ESRD, have a greater prevalence and severity of vascular calcification by electron beam computed tomography than control subjects without diabetes (46). Of the two predominant vascular processes involving calcification—atherosclerotic plaque or vessel media—it is not clear whether the computed tomography findings are detecting biomineralization of atheroemboli or medial calcification (47). Recent studies correlating coronary calcification with angiographic stenosis have had mixed results (48–50). Although coronary calcification correlates with atherosclerotic plaque burden, an important predictor of cardiovascular outcomes, it may not be indicative of occlusive coronary stenosis by angiography (27).

Plaque morphology and coronary anatomy may have therapeutic implications for this high-risk population, whenever operative or angioplasty repair is considered. Severely calcified vessels may be inoperable. In patients who do not have renal disease and undergo PCI, coronary calcification is associated with dissection, risk for MI, and decreased 5-yr survival. Heavy arterial or plaque calcification could contribute to small luminal diameters and higher reoclusion rates after balloon angioplasty procedures. In one recent study, the EBCT calcium score was compared with complications of angioplasty (45). The calcium score in unsuccessful PTCA segments was significantly higher than in ones with successful results.

Conventional Treatment of CAD in Diabetes

**CABG**

Since the first CABG in 1968, CABG revascularization has been viewed as more effective than medical therapy and has provided the comparator group for trials of PTCA and coronary stenting. In the general population, patients seem to benefit from CABG compared with medical therapy when left main stenosis, multivessel disease with proximal left anterior descending lesion, or three-vessel disease and poor LV function is present. CABG reduces morbidity in patients with acute coronary syndromes and may reduce mortality (49–51), compared with medical therapy. Most large, randomized, prospective studies that have compared CABG with PTCA in the general population have shown similar morbidity and mortality outcomes in both groups but a higher rate of secondary target vessel revascularization as a result of restenosis in the PTCA group (52). Relative clinical superiority but no mortality benefit of CABG over PTCA has been established in clinical trials for revascularization of left anterior descending and multivessel disease. A meta-analysis of four relatively small trials that compared CABG and stent implantation found no mortality differences but fewer revascularizations with stents (53). A recent analysis of adverse events in CABG trials reported overall rates of in-hospital morbidity of 1.7 and 30-d mortality of 2.1% (54), consistent with other large published series (55).

CABG superiority in subgroups with diabetes may be less certain (56), with the greatest potential survival advantage in patients with left internal mammary artery (LIMA) graft. No trials have been designed to compare surgical revascularization with medical therapy in patients with diabetes. No prospective trials have compared CABG with PCI in a population with diabetes, although post hoc analysis of trials has also suggested favorable results with CABG in patients with diabetes. The Arterial Revascularization Therapy Study (ARTS) compared the relative efficacy of CABG and multivessel bare metal stenting and showed no difference in mortality in the subset of patients with diabetes (17%) at 1 yr but clinically necessary revascularization in twice as many patients who had diabetes and were randomly assigned to stent implantation versus CABG (57), although most patients did not receive current antiplatelet agents. This advantage was more pronounced than in individuals without diabetes. In cardiac surgery candidates, patients with diabetes have a higher risk profile than patients without diabetes: They are older and have more extensive CAD and a greater incidence of previous MI, poorer cardiac function, and more angina and heart failure at the time of presentation. Subgroup analysis of large trials has established that CABG outcomes are less favorable when performed in patients with diabetes. The widely known Bypass Angioplasty Revascularization Investigation (BARI) reported in 2000 that for patients who had diabetes and symptomatic multivessel disease, CABG resulted in improved 5-yr survival (81%) versus PTCA (65%) (58), although <20% had diabetes (Figure 3). In fact, the outcome advantage for CABG in the entire study group disappeared when patients with diabetes were eliminated from the analysis. Patients with diabetes had a higher incidence of three-vessel disease and lower ejection fraction in the study and lower 5-yr survival than individuals without diabetes. The 15% absolute improvement in mortality was largely confined to patients who underwent CABG with an arterial (LIMA) conduit, which may be less susceptible to disease progression in diabetes, and was due to reduced post-MI mortality. Complete revascularization was achieved more often with CABG. However, only a minority of patients who underwent revascularization in a survey would have been BARI eligible (56). A large

![Figure 3. Improved survival with coronary artery bypass grafting (CABG) versus conventional percutaneous transluminal coronary angioplasty (PTCA) in patients with diabetes and symptomatic multivessel coronary artery disease (CAD). Data from the Bypass Angioplasty Revascularization Investigation (BARI) study (58).](image-url)
observational study of >50,000 patients with multivessel disease had outcomes reported from cardiac registries reported in a recent study. CABG was associated with higher adjusted long-term survival outcomes than stenting (59). The CABG group included 25% patients with diabetes, and the stented group included 33% (P < 0.001). When the subgroup with diabetes was analyzed, hazard ratios were generally lower for CABG than after stenting.

Several studies have also established that isolated CABG in patients with diabetes is associated with increased morbidity and mortality compared with individuals without diabetes, despite angiographic evidence of comparable graft patency in patients with diabetes (60). Diabetes is associated with reduced short-term survival after isolated CABG. The incidence of perioperative wound infections, renal failure, neurologic complications, post-CABG graft thrombosis, and rehospitalization is higher in patients with diabetes. A recent meta-analysis reported an odds ratio for 30-d mortality after CABG in patients with diabetes versus individuals without diabetes to be 1.57 (54).

Much less is known about the effect of CKD and ESRD in patients who undergo CABG surgery. The presence of proteinuria is a predictor of cardiovascular disease and death after CABG (61). In the ARTS, 25% of patients had CKD at entry. CABG was associated with a reduced risk for revascularization compared with PCI. Of note, CKD was associated with a nearly two-fold risk for death, MI, or stroke compared with those with normal kidney function (57). In a recent meta-analysis, data were too sparse in patients with renal disease to draw any conclusion (54). However, the newly published Kidney Disease Outcomes Quality Initiative guidelines, emphasizing that outcomes in dialysis patients with established CAD are worse than in the general population, support CABG as preferred therapy in ESRD patients with three-vessel or left main coronary disease (6). For acute coronary syndromes in the general population, CABG is preferred for left main CAD or CAD not suited for PCI, although the need for emergency CABG has decreased significantly.

PTCA

In studies that used PTCA in the 1990s, the group with the least favorable results for target vessel revascularization was patients with diabetes (62), with poorer long-term results attributed to a nearly two-fold higher incidence of restenosis, related to residual stenosis at the angioplasty site (63) and to progression of CAD in other arteries. Several reports indicated that the risk for restenosis after successful PTCA was increased in patients with diabetes (64). Acute angiographic success rates for PTCA in patients with diabetes were comparable to results in individuals without diabetes (85 to 95%) (15), whereas more major adverse cardiac events and poorer long-term outcomes were consistently described (65). In a report from the National Heart, Lung, and Blood Institute registry, even despite more extensive and diffuse atherosclerotic disease, patients with diabetes had angiographic success rates and completeness of revascularization similar to individuals without diabetes (66). However, patients with diabetes were more likely to require repeat PTCA or bypass surgery and had twice the 9-yr mortality as individuals without diabetes (35.9 versus 17.9%).

Conventional Treatment of CAD in CKD/ESRD

Like diabetes, CKD is associated with rapid progression of diffuse severe CAD (67). However, virtually all early clinical studies of revascularization have routinely excluded patients with ESRD. Patients with CKD have traditionally been viewed as at lower risk for complications than patients with ESRD (68), except for the differential risk of renal deterioration as a result of contrast nephropathy. In addition, revascularization by either method is associated with more complications than in patients without kidney impairment. The Mayo Clinic risk score model for complications after PCI, validated in the National Heart, Lung, and Blood Institute’s Dynamic Registry, identified CKD as a predictor of major procedural complications (69). Complete revascularization with PCI ranges from only 25 to 50% (67), and subsequent restenosis rates may not be accompanied by clinical symptoms in patients with CKD. Patients who have CKD and undergo PCI are more likely to have peripheral vascular disease, cerebrovascular disease, hypertension, and diabetes and may have asymptomatic coronary disease (70). Major adverse outcomes at long-term follow-up are similar to those of patients with severe kidney failure (68). In a retrospective cross-sectional study of >1000 patients, Reinecke et al. (71) reported reduced long-term outcomes after PCI even in patients with creatinine levels of 1.3 mg/dl. In a small study, mean survival time was reduced by 25% in patients with CKD compared with control subjects (72). Proteinuria is also a determinant of mortality after PCI (61).

ESRD is associated with acceptable initial procedural success rates but lower long-term survival than in control subjects. Many studies have shown inferior outcomes with coronary balloon angioplasty compared with CABG in dialysis patients (73), with a 60 to 80% incidence of restenosis after angioplasty. Restenosis rates among hemodialysis patients are twice that of patients with normal renal function (74). The largest ESRD population studied remains the US Renal Data System national database between 1978 and 1995 (75). In nearly 7000 dialysis patients who underwent a first PCI, the 2-yr survival rate was roughly 50%. Using the Cox regression model in this retrospective comparison, Herzog et al. (75) showed that dialysis patients in the United States had better survival after CABG surgery than after PCI. Because of perioperative mortality events, the relative survival advantage of CABG was not present in the first 6 mo. The risk for cardiac death after CABG surgery in patients with diabetes was approximately twice that of the patients without diabetes.

Contrast Nephropathy

Not only does diabetic CKD confer risk for major adverse cardiac events, prolonged hospitalization, and greater cost for patients who undergo PCI, but also it is risk factor for contrast nephropathy, a noncardiac complication associated with increased morbidity and mortality, including temporary dialysis or even permanent impairment of kidney function. In large
series of patients who underwent coronary angiography and intervention, the incidence of contrast nephropathy ranges from 3.3 to 16.5%, depending on the diagnostic criteria used. Up to 4% required short-term dialysis (76,77). In a recent report of patients with diabetes at a single tertiary care center, contrast nephropathy after PCI was evident in 15% of control subjects versus 27% of those with CKD (78). Contrast nephropathy was among the predictors of higher 1-yr mortality rates. Patients with diabetes and CKD are at the highest risk, with mortality >50% should dialysis become necessary (76). Coronary angiography studies indicate that the risk for contrast nephropathy in a patient with diabetes and a creatinine >2.0 mg/dl correlates with the severity of kidney impairment, on the order of 25 to 40% (79).

The best proven strategy for prevention is intravenous saline hydration (80), which can be achieved with a 0.9% saline solution at 1 ml/kg per min from 12 h before until 12 h after the angiography procedure. Patients with congestive heart failure require special consideration, as excessive fluids may cause respiratory deterioration, whereas overdiuresis may cause hypovolemia and increase the risk for contrast nephrotoxicity. Of note, however, a recent single-center, randomized, controlled trial suggested superiority of sodium bicarbonate over sodium chloride, particularly in patients who undergo cardiac catheterization (81). To a lesser degree, available data on efficacy and safety from some studies support the use of acetylcysteine at the time of coronary angiography (600 mg orally twice daily the day before to the day after angiography). Isosmolar nonionic contrast agents in reduced volume (82) promote better protection from renal injury than a high- or low-osmolar agent, as well as minimize the risk for potential volume overload after the angiographic procedure. When possible, coronary interventions may need to be done sequentially rather than as a single procedure. Prophylaxis against contrast nephropathy was achieved by periprocedural hemodialfiltration in one study of patients with a serum creatinine >2 mg/dl, approximately one third of whom had diabetes. The majority of patients had single-vessel PTCA and stenting (83).

**Restenosis**

As noted, patients who underwent conventional PTCA in early trials frequently required subsequent revascularization, in comparison with CABG-treated patients. Among the clinical factors that determined outcomes with PTCA were renal failure and diabetes. Each condition now has become a recognized risk factor for restenosis of coronary stents. Patients who develop ischemic symptoms between the first and eighth months after PTCA need to be evaluated for restenosis. Stents have been shown to improve outcomes by reducing restenosis rates (84).

In patients with diabetes, the large incidence of restenosis after coronary angioplasty renders the procedure less effective than in individuals without diabetes. Despite similar procedural success rates as patients without diabetes, patients with diabetes are more likely to require repeat revascularization procedures. Factors that influence restenosis in patients with diabetes were reported recently by West et al. (10) in a multivariate analysis of 16 published interventional trials of >30,000 patients, 13.5% of whom had diabetes. Restenosis was 50% higher in the patients with diabetes (31.1 versus 20.6%) at 6 mo after angiography. In more limited data, ESRD is also associated with restenosis after stent placement. After coronary stenting, rates of restenosis in dialysis patients relative to nonrenal control subjects range from no increase to a doubling; Azar et al. (85) reported an approximate two-fold increase in restenosis rates in dialysis compared with nonrenal control subjects in a retrospective case-controlled study. A recent small study of dialysis patients who received DES reported no repeat interventions as result of restenosis at 1 yr but lacked angiographic or noninvasive follow-up (86).

Restenosis is a response to vascular injury. Candidate mechanisms in the patient with diabetes involve the vascular endothelial response to balloon and stent instrumentation during the intervention. Factors that were cited in a recent review by Karha and Bhatt (87) were increased neointimal proliferation, extensive platelet aggregation and adhesion, increased vascular inflammation, impaired endothelial function, impaired fibrinolytic activity, hyperinsulinemia, and hyperglycemia. Smaller vessel caliber was the principal determinant of in-stent restenosis in the study by West et al. (86). Initial hyperglycemia predicted more pronounced neointimal proliferation after carotid stenting in a recent report (88). Advanced glycation end products have been reported to play a role in neointimal formation in animal models of arterial injury, and high serum advanced glycation end product levels may be a risk factor for in-stent stenosis in patients with diabetes (89).

**Coronary Stents**

**Conventional Stents**

The BARI and other trials, which formed the basis for popular recommendations that CABG was superior to PTCA in candidate patients with diabetes and multivessel CAD (90), were conducted before the stent era. Since BARI, advances in surgery (more arterial conduits, minimally invasive surgery) have had less impact than advances in PCI (coronary stenting, antiplatelet therapy). Several randomized trials demonstrated lower restenosis rates with conventional coronary stents compared with PTCA. A reduction of restenosis by 10 to 20% with stents versus angioplasty alone is expected in patients without diabetes. In a meta-analysis of six studies that comprised 6236 patients (1166 with diabetes) who underwent coronary stenting, the average restenosis rate among patients with diabetes was 37% compared with 26% in patients without diabetes. However, the odds ratio of restenosis associated with diabetes decreased from 1.61 to 1.30 after controlling for age (84). Coronary stent placement also improved clinical outcomes of patients with diabetes. Limited data on conventional stents in ESRD are available. In the study of the US Renal Data System database by Herzog et al. (75), fewer than half of the PCI patients underwent stenting, and neither DES nor intensive anti-platelet therapy was used. In the subgroup of patients with diabetes and ESRD, the risk for cardiac death was lower after CABG compared with PTCA but not after conventional stenting. Randomized survival comparisons between standard angioplasty and coronary stenting in patients who have diabetes...
and are on dialysis have not been done, but the impact of kidney disease in patients who have diabetes and are treated with stents and current antiplatelet agents at a single center was reported in 2004 (78). Mortality rates were dramatically higher in patients who had diabetes and had CKD or were on dialysis (Figure 4). Because restenosis may be difficult to diagnose clinically in ESRD, Kidney Disease Outcomes Quality Initiative guidelines recommend provocative stress imaging at 12 to 16 wk after PCI with conventional stents. Potential complications of coronary stenting in patients with diabetes and CKD are shown in Figure 5. The incidence of acute complications of PCI has decreased to 2 to 4%. Thrombotic events remain the primary cause of mortality after PCI. Diabetes and renal failure are two key predictors of stent thrombosis (91).

**DES**

In the past few years, DES have replaced conventional stenting in over 80% of PCI procedures. The introduction and market penetration of DES have dramatically changed the management of patients with coronary artery disease. The majority of all coronary intervention procedures in the US now include DES placement. The safety and efficacy of coated stents drugs have been proved for sirolimus and paclitaxel. Each agent produced a significant reduction in the incidence of in-stent stenosis in single vessel CAD reported from prospective multicenter randomized trials (Table 1). Large, clinically relevant differences in rates of MI and death compared with bare metal stents in the first year of follow-up have not been shown (92).

Sirolimus, or rapamycin, binds to the cytosolic receptor FK506-binding protein, forming a complex that inhibits the mammalian target of rapamycin. The drug inhibits several regulators of cell-cycle progression and migration of smooth muscle cells, resulting in both antiproliferative and anti-inflammatory properties. *In vivo*, it is delivered from a polymer-encapsulated stent. After balloon predilation, 80% of the drug is released within 30 d of stent placement. The largest trial randomly assigned approximately 1100 patients who had de novo coronary artery lesions and were undergoing coronary intervention with sirolimus-coated versus bare metal stents (93). The sirolimus stent virtually eliminated in-stent neointimal hyperplasia and significantly reduced restenosis after coronary revascularization. Overall, sirolimus reduced the rate of revascularization four-fold, from 16 to 4%. Approximately one quarter of enrolled patients had diabetes. In the analysis of the subgroup with diabetes, patients with diabetes were shown to have a higher rate of restenosis compared with those without diabetes, with an odds ratio of 2.39, but for patients with diabetes, the risk in the sirolimus-coated stent group was reduced to 17.6 versus 50.5% in the standard stent group. Major cardiac adverse events were reduced to 9% in the treated group with diabetes compared with 25% with the conventional stent (94). Late luminal loss and restenosis, although reduced in patients with diabetes, remained higher than in patients without diabetes. Patients with diabetes and DES had a 35% revascularization rate after 1 yr of stent placement. However, outcome data were limited to 2 yr of follow-up.

Paclitaxel was similarly shown to reduce restenosis and target vessel revascularization in patients with single-vessel CAD. Paclitaxel binds to microtubules and stabilizes microtubule assembly, inhibiting cell cycles that are dependent on microtubular turnover. It inhibits the proliferation and migration of vascular smooth muscle cells (95). The TAXUS IV trial confirmed the effectiveness of paclitaxel-coated stents on in-stent stenosis reported in earlier trials (96). Unlike the sirolimus trials, most patients did not have follow-up angiography, and revascularization was based on clinical indications. Only one third of enrolled patients with diabetes underwent follow-up angiography. In the analysis of the subgroup with diabetes, the paclitaxel arm had a relative risk for developing angiographic restenosis of only 0.19 compared with patients with diabetes in the bare metal stent arm (97).

Although the core indication for DES has been single-vessel CAD (including ostial atherosclerotic lesions and in-stent restenosis in bare metal stents), other indications are emerging. In the ARTS II trial, sirolimus DES are being evaluated in patients...
with multivessel disease. Approximately one quarter of enrolled patients have diabetes. Initial results indicate that revascularization outcomes for the more complex patients of ARTS II were only slightly worse than the CABG group from the ARTS I study (98). Although DES in clinical trials cut target vessel restenosis and late luminal loss by 50 to 80%, data primarily have included patients with relatively simple lesion morphologies. Inadequate information on medical management of CAD is available for the major trials. Predictors of stent thrombosis included diabetes and renal failure. Some major trial data support a lower late luminal loss rate and less obstructive intimal proliferation with the sirolimus stent (99). The two stents that currently are in competition in the United States are undergoing direct comparison in the REALITY Trial outside the United States. On the basis of limited available studies, they are currently viewed as having equal efficacy.

In addition, device trials have not been powered sufficiently to determine adequately differences within subsets of patients with diabetes (100). Patients who have diabetes and are treated with DES do remain at relatively high risk for restenosis (101), so subsequent revascularization rates may remain higher than CABG-treated patients. In addition, patients with advanced CKD were not admitted to the major trials. There are few data on sirolimus or paclitaxel stents in the dialysis population.

Concurrent Medical Management

A second major change in the routine management of PCI has been the use of more potent antiplatelet and antithrombotic adjunctive therapy. Vascular injury leads to platelet activation and aggregation. Antiplatelet therapy during and after PCI is currently viewed as having equal efficacy.

### Table 1. Drug-eluting stents commercially available in the United States

<table>
<thead>
<tr>
<th>Stent</th>
<th>Cypher™</th>
<th>Taxus™</th>
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</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>Sirolimus</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Class</td>
<td>Immunosuppressant</td>
<td>Antineoplastic</td>
</tr>
<tr>
<td>Primary actions</td>
<td>Inhibits cell-cycle progression</td>
<td>Inhibits cell replication</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Cordis Division, Johnson &amp; Johnson</td>
<td>Boston Scientific</td>
</tr>
<tr>
<td>Major trial</td>
<td>SIRIUS</td>
<td>TAXIS IV</td>
</tr>
<tr>
<td>Duration of antiplatelet therapy</td>
<td>3 mo</td>
<td>6 mo</td>
</tr>
</tbody>
</table>

Platelets of patients with diabetes are larger and more reactive than normal, and platelet activation in diabetes is associated with increased expression of the glycoprotein IIb/IIIa receptor. Despite the increase in baseline platelet aggregation, GPIIb/IIIa inhibition can achieve the same degree of platelet inhibition as in patients without diabetes, and the mortality benefit of blockade is magnified in patients with diabetes (102). Three randomized studies have shown that IIb/IIIa blockers reduce combined death or infarction by 40 to 62% in patients with diabetes (103). In a recent meta-analysis of large-scale trials of intravenous IIb/IIIa inhibitors for acute coronary syndromes, inhibition was associated with a significant mortality reduction in patients with diabetes but not in patients without diabetes, especially after PCI (104). The BARI II trial will compare the effects of revascularization plus aggressive medical therapy with aggressive medical therapy alone in patients with diabetes and CAD (105). Aspirin-clopidogrel (Plavix, Sanofi-Aventis, New Jersey) combination has also become standard treatment after PCI. The antiplatelet agent clopidogrel inhibits adenosine diphosphate–induced platelet aggregation (106) and has clinical efficacy with aspirin to reduce cardiac event rates beyond 1 mo after PCI (107). A dose of 300 mg is standard for angioplasty procedures, followed by 75 mg/d for 3 (sirolimus) or 9 (paclitaxel) mo. Clopidogrel inhibition of platelet aggregation seems to be unaltered in ESRD. In addition to GIIb/IIIa procedural anticoagulation, the new direct thrombin inhibitor bivalirudin (Angiomax, The Medicines Company, New Jersey) may cause less bleeding risk than heparin (108). Renal clearance is the primary route of elimination of bivalirudin (109). Despite dosage adjustment, the risk for complications increases with decreasing renal function (110).

The use of adjunctive antiplatelet and antithrombotic agents poses potential risks for hemorrhage in patients with ESRD. Patients with kidney impairment have been excluded from most studies that evaluated adjunctive therapy. Neither kidney impairment nor dialysis alters the effect of clopidogrel on platelet inhibition. Abciximab can be used with caution in dialysis patients, because clearance of the drug is not altered in renal failure, and no dosing changes are necessary (111) (use of tirofiban, an alternative agent that is cleared by the kidneys, is problematic in renal insufficiency, although dosing guidelines exist). Increased bleeding has been reported with abciximab in
renal failure, but overall safety is acceptable in CKD. Data on its use in dialysis patients are inadequate.

Of note, patients with CKD/ESRD may be less likely to receive other adjunctive therapies for acute MI, such as β blockers, converting enzyme inhibitors, and thrombolytics. Patients with diabetes and acute coronary syndromes may benefit from intense glycemic control. Long-term risk factor management in patients with diabetes and with CKD/ESRD and CAD may also include statins, angiotensin-converting enzyme inhibitors, and effective glycemic control. However, no benefit of LDL cholesterol lowering by atorvastatin on cardiovascular death and nonfatal MI was evident in hemodialysis patients with type 2 diabetes in a recent study (112). In a recent prospective, randomized study, the thiazolidinedione oral hypoglycemic agent rosiglitazone reduced restenosis after conventional stent PCI by 54% at 6 mo in patients with type 2 diabetes (89). Class effects of the drug include improving inflammation.

Conclusion
Both diabetes and kidney disease are associated with inferior CAD outcomes, regardless of the therapeutic approach. Existing guidelines for kidney patients are consistent with cardiology recommendations of CABG for left main or three-vessel disease in the general population. No guidelines are specific for patients with diabetes and CKD/ESRD and with CAD. The algorithm recommended in Figure 6 suggests an approach that is independent of the stage of CKD and assumes that the benefit of coronary revascularization exceeds the risk for renal failure as a result of the evaluation/intervention.

Significant advances in PCI as well as in adjunctive therapy continue to have an impact on choices for individual patients. Despite surgical advances in the use of multiple arterial conduits, cardiopulmonary bypass techniques, and “off-pump” bypass, a growing number of previous CABG candidates are being treated with DES, and the use of multivessel PCI is increasing. DES stents, the major breakthrough in PCI, and more aggressive periprocedural antithrombotic treatment have improved the efficacy of PCI. DES reduces early restenosis by approximately 50%. Some patients will have lesions that are unsuitable for PCI, primarily as a result of chronic occlusion or calcific CAD. CABG with LIMA grafting should be considered in patients with extensive and diffuse CAD, particularly with depressed LV function. The decision to proceed with surgery should be based on technical feasibility and acceptable operative risk. For all revascularized patients with diabetes, generalized disease progression must be slowed, using a comprehensive approach directed at derangements of diabetes and CKD, which worsen CAD.

Prospective trials continue to be needed for the growing population of patients with diabetes and CKD/ESRD and with CAD to define further their best treatment. In the future, direct comparison of PCI and CABG in the patient with diabetes will be made in the BARI-IID Trial (103) (which will compare initial surgical or interventional revascularization with medical therapy versus medical therapy alone) and the FREEDOM Trial (113) (which will compare CABG with the sirolimus-eluting stent in patients with diabetes and multivessel disease). The nephrologist will need to be aware as the indications and expected results of coronary revascularization evolve further, to provide optimal total care of the patients with diabetes and kidney disease.

References

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Figure 6. PCI versus CABG algorithm for elective coronary revascularization in patients with diabetes and CKD/ESRD.
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