Impact of Chronic Kidney Disease and Diabetes on Percutaneous Coronary Intervention Outcomes

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Abnormalities of glucose metabolism and chronic kidney disease (CKD) complicate treatment and outcomes for patients undergoing percutaneous coronary intervention (PCI). Likely causes of the complicating effects of diabetes include hyperglycemia, abnormalities of microvascular perfusion, and a prothrombotic and proinflammatory state. CKD predisposes to atherosclerosis, adds to the mortality and morbidity risk of cardiovascular disease (CVD), and increases risks for patients undergoing PCI. The complexity of the renal dysmetabolic syndrome and its close association with CVD must be taken into account when developing a therapeutic plan for these patients. Clinical data support the use of abciximab for patients with disturbances of glucose metabolism or with CKD who are undergoing PCI. The use of drug-eluting stents reduces the rate of target vessel revascularization and restenosis.
[Rev Cardiovasc Med. *2006;7(suppl 4):S38-S48*]

Key words: Percutaneous coronary intervention • Diabetes • Chronic kidney disease • Drug-eluting stents • GP IIb/IIIa inhibitors • Abciximab

Percutaneous coronary intervention (PCI) has evolved since the first percutaneous transluminal coronary angioplasty (PTCA), performed on a discrete 3 mm, mid-left anterior descending artery stenosis by Andreus Gruentzig in 1977. Now it is commonplace for interventional cardiologists to be challenged by very complex anatomic subsets, including calcified lesions in tortuous vessels, chronic total occlusions, and complex bifurcation disease, and they have become expert at recognizing such complex anatomic characteristics. However, a gap remains in prospectively identifying and taking into account

complex and higher-risk physiologic characteristics, including abnormalities of glucose metabolism and chronic kidney disease (CKD). Knowledge of the implications of these higher-risk physiologic subsets will allow us to improve the care these patients receive.

Glucose Metabolism

Abnormalities of glucose metabolism extend from the prediabetic conditions of impaired glucose tolerance and impaired fasting glucose to frank diabetes. Almost 35 million Americans—20% of all people in the middle-adult years and 35% of the elderly (age ≥ 65 years) population—have some degree of abnormal glucose tolerance. This higher-risk group will account for a significant proportion of cardiovascular disease (CVD) and premature mortality in the United States. About 25% of the nearly 1.5 million surgical and percutaneous coronary revascularization procedures performed annually in the United States occur in patients with diabetes. Even though diabetes has been categorized as a coronary disease–equivalent risk factor, only a minority of diabetic patients have their hyperglycemia, hyperlipidemia, and/or hypertension treated to achieve goal levels, and only 7.3% attain recommended goals for all 3 factors.[1]

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Diabetes increases the risk of developing coronary, cerebrovascular, and peripheral arterial disease up to 4-fold.[2] Approximately 30% of hospitalized patients with acute myocardial infarction (MI) have diabetes, compared with a diabetes prevalence of 6% to 8% in the general population. Diabetes is also a major risk factor for adverse outcomes in patients with unstable angina (UA). Clinical outcomes in diabetic patients are worse for each additional manifestation of coronary artery disease. In-hospital and long-term mortality rates after acute MI are twice as high among individuals with diabetes as among those without diabetes. Most patients with insulin resistance harbor a prothrombotic state, characterized by elevated plasma levels of plasminogen activator inhibitor-1 and other defects of coagulation. A prothrombotic state may interfere with endothelial function and promote atherogenesis. Furthermore, following coronary plaque rupture, a prothrombotic state can promote propagation of thrombi and exacerbate an acute coronary syndrome (ACS).

Diabetic patients who present with UA are more likely to develop MI, and diabetic patients with MI are more likely to die than are nondiabetic individuals with MI.[3] In the OASIS (Organization to Assess Strategies for Ischemic Syndromes) registry, a 6-nation UA outcome study, diabetes was associated with a 57% increment in mortality compared with nondiabetics.[4] The SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial of revascularization found a 9% increase in mortality among diabetic patients with cardiogenic shock complicating MI, compared with nondiabetics (67% vs 58%, $P > .001$).[5] After MI, the 1-month mortality rate is increased in diabetic patients by 58%.[6]

The impact of prediabetic conditions such as impaired fasting glucose is evident in patients who have undergone coronary artery bypass graft (CABG) surgery: the relative risk of 30-day and 1-year mortality compared to nondiabetics for patients known to be diabetic was 1.7 and 2.9, respectively, and 1.8 and 1.6 for prediabetics, respectively.[7] There is probably no single characteristic of the biology of the dysglycemic patient that can explain the acceleration of atherosclerosis and the increased incidence of adverse events in diabetes. The discussion here focuses on some of the potential biological culprits.

Hyperglycemia

Acute hyperglycemia is associated with platelet activation in diabetic patients.[8] In patients with acute MI, hyperglycemia increases the inflammatory process.[9] Blood glucose levels have been shown to be an independent predictor of mortality in patients with acute MI treated with thrombolytics, independent of known diabetes status.[10] Whether this represents a state of "stress hyperglycemia" due to elevated catecholamines, unrecognized diabetes, or a prediabetic condition is not clear. Hyperglycemia was also found to be predictive of impaired epicardial flow before reperfusion therapy; 1 study found 28% TIMI (thrombolysis in MI) flow grade 3 in euglycemic patients and only 12% when glucose levels on admission were > 140 mg/dL ($P < .001$).[11]

Chronic hyperglycemia is known to induce vascular endothelial cell damage with resultant vasomotor dysfunction, increased cellular proliferation, and excessive extracellular matrix formation. Chronic hyperglycemia leads to an accumulation of glycated end products, resulting in

augmentation of the inflammatory response to vascular injury and increased smooth muscle cell proliferation. These effects may be reversed by improved glycemic control.[12] In 239 patients undergoing elective PCI, optimal glycemic control (Hb A1c ≤ 7%) was associated with a lower rate of target vessel revascularization (TVR) than occurred in patients with glycemia not optimally controlled (defined as an Hb A1c > 7; 5% vs 34%, $P = .02$).[13] Patients with optimally controlled diabetes had rates of TVR similar to those of nondiabetic patients. Similarly, a fasting blood glucose ≥ 110 mg/dL was associated with a significant increase in mortality following PCI.[14]

Diabetic patients have abnormalities of microvascular perfusion that may be evident in those who present with acute MI and are treated with primary PCI.[15] Among patients with successfully restored epicardial blood flow, diabetics were much less likely to have normalization of tissue myocardial perfusion or resolution of ST segment elevation. The cause(s) of these abnormalities may include the prothrombotic and proinflammatory state known to exist in diabetics. This status is associated with upregulation of intercellular adhesion molecule-1 and monocyte chemoattractants, as well as direct platelet-leukocyte binding (leukocyte-platelet aggregates) with release of inflammatory cytokines and subsequent accumulation of microthrombi and leukocytes in capillaries with microvascular obstruction. The ability of the platelet glycoprotein (GP) IIb/IIIa inhibitor abciximab to disaggregate platelet as well as leukocyte–platelet aggregates may contribute to the salutary effects of this agent in improving microvascular flow, left ventricular function, and clinical outcomes when used as adjunctive pharmacotherapy during primary PCI, as shown in the ADMIRAL (Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up) and CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trials (Table 1).[16,17] Abciximab has been observed to reduce both platelet-monocyte interactions and Mac-1 expression when given to patients with acute MI who are undergoing PCI.[18] How this has implications in the diabetic populations presenting with acute MI is not clear. In a subgroup analysis of the CADILLAC trial, the net reduction in the diabetic population was not observed.[19]

A meta-analysis of placebo-controlled PCI trials evaluating the efficacy of abciximab for diabetic patients following PCI found a reduction of 1-year mortality from 4.5% to 2.5% (P = .031) when this agent was used.

Treatment of Diabetic Patients With Obstructive Coronary Artery Disease

In acute coronary syndrome, platelet antagonist therapies may be more clinically effective in diabetic than in nondiabetic subjects. A meta-analysis of the diabetic subpopulation enrolled in 6 large-scale trials of intravenous GP IIb/IIIa inhibitors in the medical management of ACS demonstrated that these agents reduced mortality by ~25% at 30 days among the patients with diabetes but had no apparent survival benefit in nondiabetic patients.[20]

The use of abciximab at the time of stent placement reduces the risk of death, MI, and TVR through 6 months for diabetic patients.[21] A meta-analysis of placebo-controlled PCI trials evaluating the efficacy of abciximab for diabetic patients following PCI found a reduction of 1-year mortality from 4.5% to 2.5% ($P = .031$) when this agent was used. In particular, a marked reduction of mortality from 7.7% to 0.9% ($P = .018$) was observed when abciximab was compared with placebo for diabetic patients undergoing multivessel PCI (Figure 1).[22] In a study comparing the administration of the small-molecule inhibitor

Table 1
Comparison of 30-Day Events in the CADILLAC trial Diabetic and Nondiabetic Patients

	No Abciximab (n = 1030)	Abciximab (n = 1052)	Relative Risk (95% CI)	*P*
30 Days, %				
Death	2.2	1.9	0.85 (0.47-1.53)	.49
Reinfarction	0.9	0.8	0.87 (0.34-2.22)	.76
Disabling stroke	0.2	0.1	0.48 (0.04-5.21)	.54
Ischemic TVR	4.4	2.5	0.57 (0.35-0.91)	.02
Composite	7.0	4.6	0.65 (0.46-0.93)	.01
Recurrent ischemia	8.9	7.3	0.82 (0.61-1.09)	.14
Any TVR	4.7	2.6	0.55 (0.35-0.87)	.009

CI, confidence interval; TVR, target vessel revascularization. Adapted with permission from Tcheng JE et al.[17]

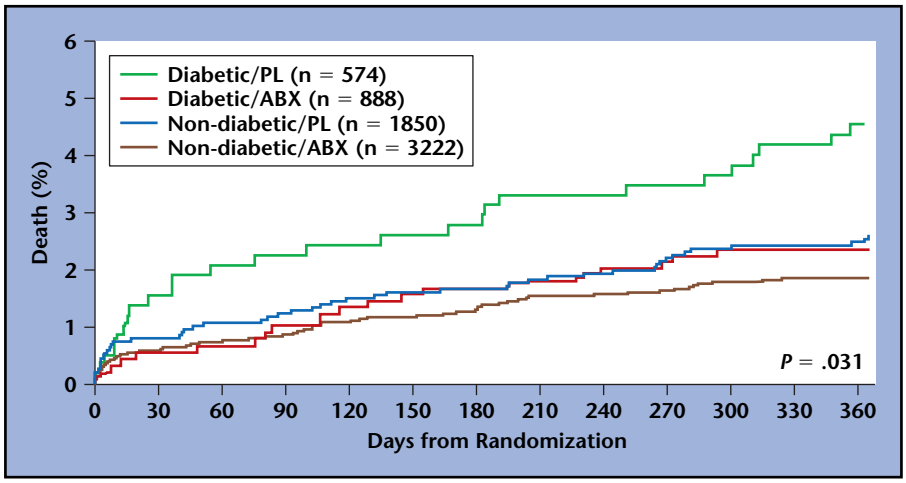

Figure 1. *The Kaplan-Meier curves are shown for 1-year mortality in diabetic and nondiabetic patients randomized to either placebo (PL) or abciximab (ABX). Adapted with permission from Bhatt DL et al.*[22]

tirofiban and abciximab, similar outcomes were observed among diabetic subjects undergoing stent-based PCI.[23]

The risk of restenosis and other adverse clinical outcomes associated with PCI is greater in diabetic than in nondiabetic patients.[24,25] Although the Diabetes Abciximab Stent Evaluation trial did not show a restenosis benefit with abciximab in patients undergoing elective stent implantation,[26] a reduction of in-stent late lumen loss and/or angiographic or clinical restenosis did accompany abciximab administration (vs placebo) in both the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial) and ISAR-SWEET (Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics?) randomized trials.[21,27]

The BARI (Bypass Angioplasty Revascularization Investigation) study found the 5-year survival rate was better for diabetic patients treated with bypass surgery than for those undergoing PTCA.[28] Stents were not employed in BARI because the study took place before these were introduced. Restenosis rates are lower in diabetic patients treated with stents than in those undergoing balloon angioplasty.[29] In the diabetic population included in ARTS (Arterial Revascularization Therapy Study), short-term outcomes for diabetic patients undergoing bare metal stent placement were similar to those for patients undergoing CABG, with the exception of a higher stroke rate and longer hospital stay for the surgically treated cohort (Table 2).[30] One-year event-free survival was lower for diabetic patients treated with stents than for those treated with CABG surgery, and much of that difference was related to the requirement for repeat revascularization procedures (Table 3).[30]

Diabetes is also associated with an increase in short-term mortality and morbidity in patients undergoing CABG. In a retrospective cohort of

Table 2
Short-Term Outcome (Up to Discharge)

	Diabetes			Non-diabetes		
	Stent (n = 112)	CABG (n = 96)	*P*	Stent (n = 488)	CABG (n = 509)	*P*
Death, n (%)	3 (2.7)	2 (2.1)	.780	3 (0.6)	6 (1.2)	.208
Cerebrovascular events, n (%)	0	4 (4.2)	.041	3 (0.6)	3 (0.6)	.848
MI, n (%)	3 (2.7)	3 (3.1)	.848	11 (2.3)	17 (3.3)	.097
Q-wave, n (%)	3 (2.7)	2 (2.1)	.780	11 (2.3)	16 (3.1)	.144
Repeat revascularization						
CABG, n (%)	4 (3.6)	0	.173	7 (1.4)	1 (0.2)	.113
PTCA, n (%)	1 (0.9)	0	.354	8 (1.6)	3 (0.6)	.197
Event-free, n (%)	101 (90.2)	87 (90.6)	.762	456 (93.4)	479 (94.1)	.665
In-hospital stay, days	5.2 ± 4.1	13.2 ± 9.2	<.001	4.5 ± 4.7	11.2 ± 5.7	<.001

CABG, coronary artery bypass graft; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty. Adapted with permission from Abizaid A et al.[30]

Table 3
ARTS Trial: One-Year Outcomes

	Diabetes			Non-diabetes		
	Stent (n = 112)	CABG (n = 96)	*P*	Stent (n = 488)	CABG (n = 509)	*P*
Death, n (%)	7 (6.3)	3 (3.1)	.294	8 (1.6)	14 (2.8)	.412
Cerebrovascular events, n (%)	2 (1.8)	6 (6.3)	.096	7 (1.4)	6 (1.2)	.722
MI, n (%)	7 (6.3)	3 (3.1)	.294	25 (5.1)	21 (4.1)	.453
Q-wave, n (%)	6 (5.4)	2 (2.1)	.222	22 (4.5)	20 (3.9)	.649
Repeat revascularization:*						
CABG, n (%)	9 (8.0)	0	<.001	19 (3.9)	3 (0.6)	<.001
PTCA, n (%)	16 (14.3)	3 (3.1)	<.001	57 (11.7)	15 (2.9)	<.001
Event-free, n (%)	71 (63.4)	81 (84.4)	<.001	372 (76.2)	450 (88.4)	<.001

*P = .04 for diabetes (stent) vs non-diabetes (stent). CABG, coronary artery bypass graft; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty. Adapted with permission from Abizaid A et al.[30]

more than 146,000 patients undergoing CABG in 1997, the 30-day risk-adjusted mortality was 23% higher for diabetic than nondiabetic patients. Diabetic patients exhibited higher rates of infection, MI, renal failure, stroke, or multisystems failure.[31] In a meta-analysis of the diabetic patients enrolled in the EAST (Emory Angioplasty versus Surgery Trial), CABRI (Coronary Angioplasty Bypass Revascularization Investigation), and RITA (Randomised Intervention Treatment of Angina) trials, there was no difference in 5-year mortality for patients undergoing PCI versus CABG.[32]

The most effective means to reduce PCI-related restenosis has been the introduction of drug-eluting stents. An analysis of the diabetic cohort enrolled in the TAXUS-IV trial of the paclitaxel-eluting TAXUS versus bare metal Express stent (Boston Scientific, Natick, MA) showed a reduction of 9-month binary angiographic restenosis from 34.5% to 6.4% (Express vs TAXUS, respectively; $P < .0001$) and of the 12-month rate of TVR from 20.9% to 7.4%, respectively.[33] No difference between stent types was observed in the 1-year mortality rate or in the composite endpoint of death or MI. GP IIb/IIIa inhibitors were administered in the majority of diabetic patients studied. In an analysis of patients enrolled in the SIRIUS (Sirolimus-eluting Stent in the Treatment of Patients with de novo Coronary Artery Lesions) randomized trial of the sirolimus-eluting CYPHER versus bare metal Bx Velocity stent (Cordis, Miami Lakes, FL), the 12-month target lesion revascularization rates were reduced from 26.4% to 8.4% (Bx Velocity vs CYPHER, respectively; $P = .0002$).[34] In SIRIUS, diabetes was a significant determinant for target lesion revascularization (odds ratio 1.74, $P = .007$) by multivariate analysis. In the ISAR DIABETES (Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-eluting and Sirolimus-eluting Stents?) trial, 250 diabetic patients undergoing PCI were randomized to either the CYPHER or TAXUS stents.[35] The primary endpoint of angiographic late lumen loss did not meet the predefined non-inferiority criteria for the TAXUS stent. Angiographic restenosis was observed more frequently in the TAXUS than in the CYPHER stent group (16.5% vs 6.9%, respectively; $P = .03$).

Chronic Kidney Disease

It is estimated that 20 million adults in the United States have chronic kidney disease, with 8 million adults classified as having moderate to severe disease.[36] The prevalence of CKD increases with age and adds to the cardiovascular burden already borne by the fast-growing elderly segment of the US population.[37,38] The classification of CKD is based on guidelines from the National Kidney Foundation (Table 4).[37]

Most patients are not diagnosed with CKD until the disease has progressed to stage 3. Relying on serum creatinine (SCr) as the standard measure of renal function has led to a systematic overestimation of renal function and underestimation of the incidence of CKD (Table 5).[37]

Cardiovascular Disease and CKD

A significant proportion of patients undergoing coronary angiography

Table 4
Definitions of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)	US Prevalence (1000s)	US Prevalence (%)
1	Kidney damage with normal or increased GFR	≥ 90	5900	3.3
2	Kidney damage with mildly increased GFR	60-89	5300	3.0
3	Moderately decreased GFR	30-59	7600	4.3
4	Severely decreased GFR	15-29	400	0.2
5	Kidney failure	< 15 or dialysis	300	0.1

Data for stages 1-4 from NHANES III (1988-1994), based on population of 177 million with age ≤ 20 years. Data for stage 5 from United States Renal Data System (1998) include about 230,000 patients treated by dialysis and assume 70,000 additional patients not on dialysis. GFR (glomerular filtration rate) estimated from serum creatinine by abbreviated Modification of Diet in Real Disease Study equation based on age, sex, race, and calibration for serum creatinine. For stages 1 and 2, kidney damage was assessed by spot albumin-to-creatinine ratio > 17 mg/g (men) or 25 mg/g (women) on 2 measurements. Adapted with permission from the National Kidney Foundation.[37]

and coronary interventions have stage 3 or higher CKD and are at higher risk for complications. All patients admitted to the hospital with CVD should have their renal function estimated, either by the Cockroft-Gault equation or by the Abbreviated MDRD (Modification of Diet in Renal Disease) study equation, which are the 2 primary calculations for glomerular filtration rate (GFR) (Table 6).[39]

Patients with both CKD and CVD are at very high risk for adverse outcomes, but in a pooled analysis of 4 community-based longitudinal studies, even patients with CKD and no overt CVD were found to have an increased risk for all-cause mortality, fatal coronary heart disease, MI, and fatal and nonfatal stroke compared with patients without CKD (30.1% vs 13.2%, respectively).[40] Although CKD is associated with a constellation of traditional cardiovascular risk factors—including diabetes; hypertension; low high-density lipoprotein (HDL)-C; small, dense, low-density lipoprotein (LDL)-C; and hyperfibrinogenemia—as well as with nontraditional risk factors such as proteinuria, homocystinemia, and anemia, it nevertheless represents an independent predictor of risk. A variety of potential mechanisms to explain the predisposition of CKD for accelerated atherogenesis has been suggested (Table 7).[41]

Not only does CKD predispose to the presence of atherosclerosis, it also adds to the mortality and morbidity risk for a variety of cardiovascular conditions, and for patients undergoing PCI. Important insights are obtained from the GRACE (Global Registry of Acute Coronary Events) analysis of 11,774 patients hospitalized for a full spectrum of ACS conditions, including ST-segment elevation MI (STEMI), non-ST-segment elevation MI (NSTEMI), and UA.[42] The mortality rate doubled in patients with moderate CKD (creatinine clearance [CrCl] 30-60 mL/min) and increased 4-fold in those with severe CKD (CrCl < 30 mL/min), compared with patients with normal kidney function (defined as CrCl > 60 mL/min). When comparing the treatments provided for these hospitalized patients across the spectrum of renal function, one is struck by the reduced utilization of proven therapies such as the use of antiplatelet agents, angiotensin converting enzyme inhibitors, beta-blockers, statins, and GP IIb/IIIa inhibitors, as well as a relatively marked

Table 5
Serum Creatinine Corresponding to an eGFR of 60 mL/min/1.73 m^2

	European American		African American	
Age (y)	Men	Women	Men	Women
30	1.47	1.13	1.73	1.34
40	1.39	1.08	1.65	1.27
50	1.34	1.03	1.58	1.22
60	1.30	1.00	1.53	1.18
70	1.26	0.97	1.49	1.15
80	1.23	0.95	1.46	1.12

Calculations in this table assume a weight of 72 kg and body surface of 1.73 m^2. Units for serum creatinine are mg/dL (multiply by 88.4 μmol/L = 1 mg/dL). eGFR, estimated glomerular filtration rate. Adapted with permission from the National Kidney Foundation.[37]

Table 6
Equations to Predict Glomerular Filtration Rate (GFR) Based on Serum Creatinine

Cockcroft-Gault equation	$\text{CrCl (mL/min)} = \frac{(140 - \text{Age}) \times \text{Weight}}{72 \times \text{SCr}} \times (0.85 \text{ if female})$
Abbreviated MDRD study equation	$\text{GFR (mL/min/1.73 m}^2) = 186 \times (\text{SCr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$

CrCl, creatinine clearance; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine in mg/dL. Age is given in years and weight in kilograms. Adapted from Best PJ et al. with permission from Elsevier.[39]

reduction of in-hospital interventions, including PCI and CABG (Table 8). Patients with CKD are less likely to receive appropriate therapies compliant with American College of Cardiology/American Heart Association (ACC/AHA) guidelines. Clinical outcomes (death, stroke, major bleeding) are directly correlated with the severity of renal dysfunction (Table 9). Other large databases confirm the relationship between progressive CKD and less frequent use of cardiovascular medications.[43]

Unfortunately, patients with CKD who survive the acute MI remain at an increased risk of death following discharge—an increase ranging from 2-fold for those with mild to severe renal dysfunction to more than 5-fold for those with end-stage renal disease (Table 10).[44]

Treatment of Patients With CKD and Obstructive Coronary Artery Disease

Once we appreciate the complexity of the renal dysmetabolic syndrome and the close association with cardiovascular disease and its complications, we must take this into account in the decision process when developing a therapeutic plan for these patients. In 2002, an analysis of 5327 patients undergoing PCI at the Mayo Clinic revealed that even mild CKD was associated with a lower procedural success rate and increased in-hospital complications.[45] For those patients whose procedure was successful, 1-year mortality rates were related to the degree of CKD. Patients with CrCl ≥ 70 mL/min had a 1-year mortality rate of 1.5%, whereas those with CrCl of 50-69, 30-49, and ≤ 30 mL/min had mortality rates of 3.5%, 7.8%, and 18.3%, respectively. CKD also predisposes to complications following CABG, including mortality, longer postoperative ventilation time, and higher postoperative bleeding rates.[46]

In an analysis of outcomes from BARI, the presence of CKD even in its mildest form was associated with an increased risk of recurrent angina, recurrent hospitalization, subsequent CABG surgery, and mortality among patients who underwent revascularization with either PCI or CABG.[47] At 7 years post revascularization, the presence of CKD was associated with a more than 2-fold increment in all-cause and cardiac mortality rates. The risk associated with CKD was independent of and additive to that of diabetes.

In a substudy of the PRESTO (Prevention of Restenosis with Tranilast and Its Outcomes) trial, which evaluated 11,184 patients who had undergone a *successful* PCI,

Table 7
Potential Mechanisms for Enhanced Atherogenesis in Patients With Chronic Kidney Disease (CKD)

Lipid abnormalities	↑ apolipoprotein (a); ↓ HDL; ↑ triglycerides
Hypertension	↑ prevalence; ↑ in ESRD due to volume overload
Diabetes	↑ Prevalence
Inflammation and oxidative stress	↑ in ESRD (mechanism unknown); ↑ monocyte activation; ↑ cytokines (due to inflammation); ↑ oxidative stress; ↑ C-reactive protein; ↑ oxidative stress → ↑ LDL oxidation + ↓ nitric oxide bioavailability → endothelial dysfunction
Hyperhomocysteinemia	↑ due to ↓ serum folate and ↓ B vitamin intake; ↓ renal clearance of homocysteine; ↑ oxidative stress → ↑ free apolipoprotein (a), ↓ fibrinolysis, ↑ platelet adhesion = endothelial dysfunction
Fibrinogen	↑ by CKD; predicts coronary artery disease in CKD patients; ↑ fibrinogen → platelet aggregation = procoaguable state
Nitric oxide	bioavailability is impaired in CKD, which leads to endothelial dysfunction and promotes atherogenesis.

ESRD, end-stage renal disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Adapted from Best PJ et al. with permission from Elsevier.[39]

Table 8
Medication Use and In-Hospital Interventions for the Study Population

	ACS			STEMI			NSTEMI/UA		
Renal function	Severe dysfunction (n = 786)	Moderate dysfunction (n = 3397)	Normal/ minimally impaired (n = 7591)	Severe dysfunction (n = 301)	Moderate dysfunction (n = 1347)	Normal/ minimally impaired (n = 3068)	Severe dysfunction (n = 485)	Moderate dysfunction (n = 2050)	Normal/ minimally impaired (n = 4523)
Medications before admission (%)									
Aspirin	46.8	47.1	39.6*	38.0	34.6	24.4*	52.3	55.3	50.0†
Ticlopidine/ clopidogrel	5.2	4.4	3.1†	4.4	2.7	1.8†	5.6	5.5	4.1†
ACE inhibitors	34.3	32.4	22.3*	32.6	28.9	16.7*	35.4	34.8	26.2*
ARBs	5.9	3.6	2.4*	4.1	2.6	2.1	7.0	4.2	2.6*
β-Blockers	34.5	31.8	29.0†	27.4	23.1	18.1*	38.9	37.6	36.4
Diuretics	38.4	25.4	11.9*	37.0	21.7	8.6*	39.3	27.9	14.2*
Statins	19.5	20.9	21.8	14.3	16.0	13.7	22.7	24.2	27.3†
In-hospital medications (%)									
Aspirin	91.1	92.0	94.0*	92.7	93.0	95.3†	90.1	91.3	93.1†
Ticlopidine/ clopidogrel	23.9	29.0	36.3*	27.4	32.6	42.7*	21.8	26.6	32.0*
ACE inhibitors	55.7	61.6	55.7*	62.1	69.3	65.6†	51.8	56.4	49.0*
ARBs	6.4	3.8	2.5*	3.8	2.9	2.3	8.0	4.4	2.6*
β-Blockers	69.3	74.3	83.8*	64.9	73.8	86.2*	72.0	74.6	82.2*
Diuretics	61.6	47.0	25.2*	62.0	50.8	25.5*	61.3	44.6	25.0*
Statins	33.4	42.0	53.3*	31.6	41.1	54.3*	34.5	42.7	52.6*
LMWH	46.7	49.4	50.1	47.3	46.6	45.7	46.4	51.2	53.1†
Thrombolytics	7.2	13.3	19.5*	15.0	30.1	44.4*	2.3	2.3	2.7
GP IIb/IIIa	11.3	16.0	22.0*	14.6	20.6	28.1*	9.3	13.0	17.9*
In-hospital interventions									
PCI or CABG	22.6	30.3	39.8*	27.3	36.4	47.1*	19.7	26.3	34.8*

*$P < .05$ across all categories of renal function within ACS, STEMI, or NSTEMI/UA subgroups; †$P < .0001$ across all categories of renal function within ACS, STEMI, and NSTEMI subgroups. ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; NSTEMI/UA, non-ST-segment elevation myocardial infarction/unstable angina; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GP, glycoprotein; LMWH, low-molecular-weight heparin. Adapted with permission from Santopinto JJ et al.[42]

there was no difference in the composite 30-day endpoint of death, MI, or TVR in patients with relatively mild CKD (SCr < 1.8 mg/dL) compared with those with normal renal function.[48] However, there was a doubling of the 9-month mortality rate in patients with CrCl < 60 mL/min compared with those with CrCl > 89 mL/min.

The ARTS study randomized 1205 participants with and without CKD to CABG versus multivessel stenting in the pre-drug-eluting stent era.[49] There was no significant difference in the primary composite endpoint of death, MI, or stroke. Allocation to CABG was associated with a decrease in subsequent revascularization rates. The investigators concluded that multivessel stenting is an acceptable and less invasive alternative to CABG.

With the advent of drug-eluting stents, it is now possible to markedly reduce the rate of TVR. A subgroup analysis of the TAXUS-IV trial provides insight into the impact of CKD on restenosis and adverse clinical events.[50] This trial excluded patients with SCr > 2.0 mg/dL and does not provide guidance for patients with more severe CKD. Compared with the bare metal Express stent, the TAXUS stent reduced the 9-month angiographic restenosis rate from 20.5% to 2.1% ($P < .001$), with no difference in the 1-year rates of the composite of death, MI, and stent thrombosis.

Safety and efficacy data are available on the medical treatment of

Table 9
Odds Ratios (OR) for In-Hospital Outcomes for the Study Population

Outcome	Creatinine clearance* (mL/min)	Crude OR (95% CI)	Adjusted OR (95% CI)
Death	< 30	9.92 (7.43-13.24)	3.71 (2.57-5.37)
	30-60	4.17 (3.27-5.32)	2.09 (1.55-2.81)
Stroke	< 30	1.94 (0.98-3.84)	1.21 (0.56-2.60)
	30-60	2.03 (1.35-3.04)	1.42 (0.87-2.32)
Major bleeding	< 30	3.70 (2.74-4.98)	2.78 (1.96-3.94)
	30-60	1.87 (1.49-2.34)	1.52 (1.17-1.99)

Referent group is creatinine clearance > 60 mL/min. CI, confidence interval. Adapted with permission from Santopinto JJ et al.[42]

patients with CVD and CKD. Because of the differences in pathophysiology of atherosclerotic disease, differences in the uremic milieu that contributes to the hypercoagulable state, and marked differences in the way these medical therapies are metabolized by the patient with CKD, there is a knowledge gap about what constitutes an optimal approach for these patients. An example of this biological variability can be seen with aspirin therapy: a dose of 100 mg/m^2 leads to an increase in the bleeding time for patients with CKD but not for patients with normal renal function.[51] Most clinicians are unaware that unfractionated heparin, a drug that is ubiquitous in the catheterization laboratory, depends not only on a saturable clearance mechanism of binding to endothelial cells and macrophages but also on renal clearance mechanisms, which become important when higher heparin doses are used. Under certain circumstances, this biphasic kinetic pattern of elimination leads to a higher bleeding potential.[52] In the case of low-molecular-weight heparin therapy, there are no published clinical trials evaluating the accumulation of anticoagulant activity in patients with severe CKD, but empirical dose-reduction algorithms based on renal function are available.

Direct thrombin inhibitors are an alternative to heparin therapy. Argatroban, which is primarily metabolized by the liver, has not been assessed in a large PCI or ACS trial. In a meta-analysis of clinical trials with bivalirudin versus unfractionated heparin (UFH) in PCI, bivalirudin was found to be superior in terms of both ischemic and bleeding events (efficacy and safety).[53] The absolute benefit of bivalirudin (vs UFH) increased as renal function worsened.

Clinical data support the use of GP IIb/IIIa inhibitors for patients with CKD who are undergoing PCI. Abciximab is the only GP IIb/IIIa inhibitor approved for use in patients with severe CKD, and it has been shown not to increase bleeding events for patients with CKD more than for those with normal renal function.[54] In addition, GP IIb/IIIa inhibition was shown to reduce in-hospital mortality in patients with ACS and CKD.[55] Based on the results of available clinical data, GP IIb/IIIa inhibition with abciximab should be considered for use in patients with CKD if there is no contraindication.

To further optimize the care of patients with CKD, it will be important for clinicians to identify these high-risk patients and, in the absence of specific clinical data, to apply recommended primary and secondary prevention strategies. More clinical trial data specific to this patient population are needed, because it is clear that the clinical course for these patients differs from that of patients with normal renal function. Based

Table 10
Chronic Renal Disease Increases Risk of Death Post-Myocardial Infarction

Degree of renal impairment	In-hospital mortality (%)	Adjusted hazard ratio for post-discharge death	*P*
Normal kidney function (n = 1320)	2	—	—
Mild renal failure (n = 860)	6	2.4	< 0.001
Moderate renal failure (n = 491)	14	2.2	< 0.001
Severe renal insufficiency (n = 391)	21	1.9	< 0.006
End-stage renal disease (n = 44)	30	5.4	< 0.001

Adapted with permission from Wright RS et al.[44]

on current clinical trial data, patients with CKD are at higher risk of cardiovascular disease and its complications, and at higher risk of complications from coronary interventions. Patients with CKD benefit from revascularization strategies when indicated. CABG has been associated with greater benefit than PCI, due to a reduced rate of repeat revascularization. However, the use of drug-eluting stents may negate this relative benefit of CABG and make PCI even more attractive. Concomitant therapy with GP IIb/IIIa inhibitors has been shown to improve clinical outcomes (survival) in patients with CKD, and abciximab is the only agent indicated for all grades of CKD.

Summary

Optimizing the care of patients with diabetes or chronic kidney disease who have obstructive coronary artery disease remains a challenge. This article presents an overview of the clinical trial data that deal with these patient populations. In the absence of specific clinical data for these conditions, the 2005 ACC/AHA/SCAI PCI guidelines[56] on the use of GP IIb/IIIa inhibitors for all patients undergoing PCI are recommended:

Class I: In patients with UA/NSTEMI undergoing PCI without clopidogrel, a GP IIb/IIIa inhibitor should be administered

Class IIa:

A. In patients with UA/NSTEMI undergoing PCI with clopidogrel administration, it is reasonable to administer a GP IIb/IIIa inhibitor
B. In patients with STEMI undergoing PCI, it is reasonable to administer abciximab as early as possible
C. In patients undergoing elective PCI with stent placement, it is reasonable to administer a GP IIb/IIIa inhibitor ■

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Main Points

- A significant proportion of patients undergoing coronary angiography and coronary interventions (such as percutaneous coronary intervention [PCI]) in the United States have abnormalities of glucose metabolism or stage 3 or higher chronic kidney disease.
- The prothrombotic state found in many diabetic patients may promote atherogenesis and, following coronary plaque rupture, propagation of thrombi; also, chronic hyperglycemia increases the inflammatory response to vascular injury and increases smooth muscle cell proliferation.
- Optimal glycemic control has been associated with a lower rate of target vessel revascularization (TVR).
- Clinical outcomes (death, stroke, major bleeding) are directly correlated with severity of renal dysfunction, but patients with chronic kidney disease are less likely to receive appropriate therapies compliant with American College of Cardiology/American Heart Association guidelines.
- The use of drug-eluting stents markedly reduces the rate of percutaneous-coronary-intervention-related restenosis and TVR in patients with diabetes or CKD.
- Abciximab is the only glycoprotein IIb/IIIa inhibitor approved for use in patients with severe CKD, and it has been shown not to increase bleeding events for patients with CKD more than for those with normal renal function.

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