

The Impact of Diabetes on PCI Case Selection

An evaluation of the current therapeutic options for patients with diabetes mellitus and cardiovascular disease.

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Diabetes mellitus (DM) is a disease that affects people worldwide and is associated with coronary artery disease (CAD), stroke, peripheral artery disease, cardiomyopathy and congestive heart failure, and generally results in premature death. Patients with DM have twice the risk of myocardial infarction (MI) and stroke as that of the general population.¹

Cardiovascular complications² remain the leading cause of mortality among patients with type 2 DM. As many as 80% of them will develop, and possibly die of, macrovascular disease.¹ Clear clinical trial evidence published during the past decade³ suggests that broad-based treatment of dyslipidemia, hypertension, and hypercoagulability, as well as percutaneous coronary intervention (PCI) and cardiovascular surgery during acute coronary syndrome (ACS), can improve the event-free survival rate in patients with DM who already have clinical cardiovascular disease.¹

THE MAGNITUDE OF THE PROBLEM

Patients with DM comprise approximately 25% of the 1.5 million people undergoing coronary revascularizations annually in the United States, and it has been estimated that the global prevalence of DM among adults will be 7.7% (439 million individuals) in 2030.⁴ Approximately 8% of adults in developed countries have DM,² and its prevalence has increased by 42% in industrialized countries (51 million in 1995 and 72 million in 2005), whereas it has nearly tripled in developing countries (84 million in 1995 and 228 million in 2005) during the last decade.⁵

Diabetes magnifies the risk of cardiovascular morbidity and mortality. More than 75% of hospitalizations for diabetes are due to atherothrombosis, as there is a three-fold increased risk of CAD and, generally, a worse prognosis in diabetic compared with nondiabetic patients.^{6,7}

TABLE 1. CLINICAL CHARACTERISTICS OF DIABETIC PATIENTS POTENTIALLY LEADING TO POOR OUTCOMES

- Higher prevalence of extensive and complex CAD
- Higher rate of previous MI, congestive heart failure, and hypertension than nondiabetic patients
- More prevalence of left main and/or three-vessel disease
- Smaller vessel size in diabetic compared with nondiabetic patients
- Higher degree of restenosis, late luminal loss, and neointimal hyperplasia shown by angiography and intravascular ultrasound
- Higher rate of early stent thrombosis
- Higher prevalence of nonresponders to clopidogrel
- Increased platelet aggregability and procoagulopathy
- Greater degree of underlying vascular inflammation and of a prothrombotic milieu
- Negative remodeling, impaired endothelial function and endogenous fibrinolysis, and microvascular dysfunction

CURRENT THERAPEUTIC OPTIONS

PCI in Diabetic Versus Nondiabetic Patients

Diabetic patients who are treated for CAD with PCI appear to have a particularly unfavorable prognosis compared with nondiabetic patients (Table 1). Subgroup analysis of the BARI and other randomized trials have demonstrated that diabetic patients with multivessel CAD who are treated with PCI had a 5-year mortality rate of 35% compared with 9% for patients without diabetes.⁸⁻¹⁰ However, we must bear in mind that inhibitors of the platelet glycoprotein (GP) IIb/IIIa receptor were not available at the time of the BARI trial. Nevertheless, the availability of these agents and newer generations of stents may contribute to a reduction in the composite

TABLE 2. CLINICAL SCENARIOS AND PATIENT CHARACTERISTICS FAVORING DES OVER BMS

Scenarios Favoring DES Over BMS	Scenarios Without Sufficient Data
• Diabetic patients • Long lesions • Small vessels • Chronic total occlusions • In-stent restenosis • Unprotected left main artery disease	• Saphenous vein grafts • Large vessels • Short lesions • ST-segment elevation myocardial infarction (STEMI)

endpoint of mortality and MI after PCI^{11,12} and may promote a lower incidence of other major adverse cardiac and cerebral events in diabetics, despite a higher prevalence of diffuse and extensive CAD.¹³

PCI in Diabetic Patients With Stable Coronary Disease

From balloon angioplasty (BA) to bare-metal stents (BMS), drug-eluting stents (DES), and drug-eluting balloons, to the more recent bioresorbable vascular scaffolds, technological advances in the field of interventional cardiology have made a positive impact on the prognosis of diabetic patients with CAD. Breeman and colleagues demonstrated that in the setting of stable angina, treatment decisions regarding revascularization or the choice of coronary artery bypass grafting (CABG) versus PCI were not influenced by the presence of diabetes.¹³ Similarly, the BARI 2D trial¹⁴ pointed out that in DM patients with stable CAD, survival as well as major adverse cerebral and cardiovascular events did not differ between the revascularization group and the medical therapy only group.

The use of DES in diabetic patients has reduced the risk of repeat revascularization when compared with BA (hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.29–0.58) or with BMS (HR, 0.55; 95% CI, 0.39–0.76) without significant statistical differences in the rates of death or MI.¹⁵ The SCORPIUS¹⁶ and DIABETES¹⁷ trials published similar results.

The most recent European Myocardial Revascularization Guidelines¹⁸ recommend revascularization in all stable DM patients with extensive CAD (class I, level of evidence A). In addition, in DM patients, the guidelines recommend CABG rather than PCI when the extent of the CAD justifies a surgical approach and the patient's risk profile is acceptable (class I, level of evidence B). The American Non-ST-Segment Elevation Acute Myocardial Infarction (NSTEMI) ACS guidelines¹⁹ advise that decision making with respect to stress testing, angiography, and revascularization should be similar in patients with and without DM, whereas the European guidelines recommend an early invasive strategy for all DM patients presenting with NSTEMI ACS (class I, level of evidence A).

PCI in Diabetic Patients With STEMI

Several studies have demonstrated the benefit of revascularization for DM patients with STEMI in terms of symptoms and survival.²⁰ The therapeutic advantage of primary PCI over thrombolysis appears particularly pronounced in diabetic patients, with respect to the value of GP IIb/IIIa inhibitors. In the ADMIRAL study,²¹ administration of abciximab in diabetics was associated with a significant reduction in the combined endpoint of death, reinfarction, or revascularization (7.4% vs 15.9%; $P = .02$; relative risk, 0.46; 95% CI, 0.22–0.93) compared to placebo at 6 months. At 3-year follow-up, there was a trend favoring the abciximab-treated group in the combined endpoint (13.8% vs 21.6%; $P = .07$), although it was not statistically significant.²² The American and European ACS guidelines recommend an early invasive strategy for all DM patients presenting with ACS.^{23,24}

PCI Versus CABG in Diabetic Patients With Unprotected Left Main and/or Multivessel CAD

Several studies^{25–27} have shown a significant and sustained survival benefit associated with CABG at 5 years in treated diabetic patients, mainly in those treated with unilateral or bilateral internal thoracic grafting.^{28–30} The BARI trial²⁹ showed similar mortality rates in the overall population (PCI, 13.7% vs CABG, 10.7%; $P = .19$) but decreased survival among diabetic patients ($n = 353$) treated with PCI (PCI [35.5%] vs CABG [19.4%]; $P = .003$)²⁹ at 5-year follow-up. Nevertheless, the survival benefit in favor of CABG was limited to patients who were revascularized by means of a left internal thoracic artery (LITA) graft (the 5-year mortality of diabetic patients treated with LITA was 2.9%), whereas mortality rates were similar among patients who were treated with a saphenous vein graft (18.2%) and BA.

Arterial revascularization with the use of both internal thoracic arteries (BITA) has been shown to decrease the risk of death (HR, 0.72; 95% CI, 0.57–0.91) and the need for reoperation (HR, 0.38; 95% CI, 0.19–0.77) in both diabetic and nondiabetic patients.²⁷ These findings are reflected in current guidelines, which favor CABG over

PCI in most diabetics with advanced multivessel CAD who require revascularization.^{23,24} Part of these results may be influenced by the low use of GP IIb/IIIa inhibitors, dual-antiplatelet treatments, and stents during that era. Recent studies have found comparable survival rates between diabetics treated with PCI or CABG.³¹

However, most of the evidence points in favor of surgery with regard to lower recurrence of unstable angina and repeat revascularization. With the development of more potent platelet inhibitors (such as prasugrel, ticagrelor, or cangrelor), bioresorbable polymers or polymer free DES platforms, and fully bioresorbable scaffold, these advances in therapies would be expected to narrow the difference in survival and repeat revascularization between diabetics with complex multivessel CAD treated by an initial strategy of CABG or PCI.

Which Type of Stent? The Advantages of DES Over BMS

The advent of DES has challenged the supremacy of CABG and has become a valuable alternative to surgery. One of the main advantages of DES over BMS is the lower rates of restenosis in different scenarios (Table 2).^{32,33} In diabetic patients, DES improve vessel patency as measured by either late loss or the need for target vessel revascularization and have an acceptable safety profile. There does not seem to be an increased risk of either death or MI among diabetic patients that is related to DES treatment.^{34,35}

Differences Between Insulin-Dependent and Noninsulin-Dependent DM

DES are associated with a lower risk of repeat revascularization compared with BMS for treating CAD among patients with either insulin- or noninsulin-treated diabetes. In addition, DES use is not associated with any significant increased safety risk compared with BMS.³⁴ Mulukutla and colleagues³⁴ found that in more than 2,500 diabetic patients, the use of DES compared with BMS was associated with a lower risk of repeat revascularization for both noninsulin-treated patients (adjusted HR, 0.59; 95% CI, 0.45–0.76) and insulin-treated patients (adjusted HR, 0.63; 95% CI, 0.44–0.9). With respect to safety in the overall diabetic population, DES use was associated with a reduction in death or MI (adjusted HR, 0.75; 95% CI, 0.58–0.96).

Similar results have been published in other trials¹⁷; however, this benefit was confined to the population of noninsulin-treated patients (adjusted HR, 0.57; 95% CI, 0.41–0.81). Among insulin-treated patients, there was no difference in death or MI risk between DES- and BMS-treated patients³⁴ (adjusted HR, 0.95; 95% CI, 0.65–1.39). Restenosis rates and mortality after PCI are higher among insulin-treated patients than among noninsulin-treated

diabetic patients.³⁴ The higher rate of mortality among insulin-treated patients is consistent with other studies showing a higher mortality risk among insulin-dependent patients.^{33,36} These findings suggest that DES should be the preferred strategy for diabetic patients, but among insulin-treated diabetic patients, the benefit could be minor.

Potential Mechanisms for the Increased Risk of Restenosis and Thrombosis in Diabetic Patients

Diabetic patients have higher restenosis rates in comparison to nondiabetic patients due to a multifactorial etiology.^{37–41} Diabetes increases the risk of developing cardiovascular disease and is a consistent predictor of mortality, MI, and restenosis after BA and BMS.⁴² Incomplete endothelialization of strut surfaces is a recognized pathologic substrate for late stent thrombosis, but there are several other factors, including stent malapposition and/or underexpansion, number of implanted stents, stent length, persistent slow coronary blood flow, residual dissections, patient and lesion characteristics, stent design, and discontinuation of antiplatelet drugs. Late stent thrombosis is an infrequent but severe complication with life-threatening consequences.^{43–48}

ANTIPLATELET THERAPY IN DM

Platelets of patients with DM have been proven to be hyperreactive with intensified adhesion, activation, and aggregation.^{49–54} Multiple mechanisms contributing to this increased platelet reactivity have been proposed including hyperglycemia, insulin resistance, associated metabolic conditions that may have an impact on platelet function (including obesity, dyslipidemia, and enhanced systemic inflammation), and other cellular abnormalities (dysregulation of calcium metabolism, augmented oxidative stress, and reduced platelet antioxidant levels).⁴⁹

Several studies support the use of low-dose aspirin (75–162 mg/d) for secondary prevention, and these studies have been extended to patients with DM.^{55,56} The benefit of aspirin therapy in the early management of ACS patients has been demonstrated repeatedly and consistently in earlier trials including those evaluating unstable angina/NSTEMI^{57–59} and STEMI.^{60,61} The lack of benefit and the potential for increased bleeding complications of high-dose (300–325 mg) versus low-dose (75–100 mg) aspirin was recently demonstrated in the CURRENT/OASIS7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions) trial, but no data on patients with DM are available.⁶²

Thienopyridines (ie, ticlopidine, clopidogrel, and prasugrel) are nondirect (ie, metabolism required), orally

administered, and irreversible platelet P2Y₁₂ receptor inhibitors. Currently, clopidogrel is the most used thienopyridine because it has an equal efficacy to that of ticlopidine, a favorable safety profile, and a faster onset of action upon administration of the loading dose.⁶³

The CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial evaluated the efficacy of clopidogrel (75 mg/d) versus aspirin (325 mg/d) and showed a significantly lower annual rate of the composite endpoint (ischemic stroke, MI, or vascular death) with clopidogrel (5.32% vs 5.83%; $P = .043$).⁶⁴ The benefit of clopidogrel therapy was higher in the DM subgroup (15.6% vs 17.7%; $P = .042$), leading to 21 vascular events that were prevented for every 1,000 patients with DM treated (38 among insulin-treated patients).⁶⁵ The current recommended dose of clopidogrel is a 300-mg loading dose (up to 600 mg in the setting of PCI) followed by a maintenance dose of 75 mg daily. The OPTIMUS study pointed out that the use of the high maintenance dose was associated with a marked improvement in platelet inhibition, although a significant number of patients had remaining elevated platelet reactivity.⁶⁶

In the TRITON-TIMI 38 trial, prasugrel (60-mg loading dose followed by 10 mg/d) versus standard clopidogrel therapy (300-mg loading dose followed by 75-mg/d maintenance dose)^{67,68} showed a significant reduction in the rate of the primary endpoint (composite of cardiovascular death, nonfatal MI, or nonfatal stroke) favoring prasugrel (9.9% vs 12.1%; HR, 0.81; $P = .001$), as well as a reduction in the rate of stent thrombosis.⁶⁹ Importantly, there were no differences in major bleeding among DM patients who were treated with prasugrel compared with clopidogrel (2.6% vs 2.5%; HR, 1.06; $P = .81$). The primary endpoint was reduced significantly with use of prasugrel in subjects with DM (12.2% vs 17%; HR, 0.7; $P = .001$), and this benefit was consistent in patients with (14.3% vs 22.2%; HR, 0.63; $P = .009$) and without (11.5% vs 15.3%; HR, 0.74; $P = .009$) insulin treatment. Prasugrel also improved the risk of stent thrombosis in the DM subgroup (overall DM cohort, 2% vs 3.6%; HR, 0.52; $P = .007$; insulin-dependent patients, 1.8% vs 5.7%; HR, 0.31; $P = .008$).⁷⁰

The PLATO trial showed that ticagrelor compared with clopidogrel (300–600 mg) loading significantly reduced the rate of the primary ischemic endpoint of death from vascular causes, MI, or stroke at 12 months (10.2% vs 12.3%; HR, 0.84; $P = .0001$) in ACS patients ($n = 18,624$) who were treated either medically or with revascularization (percutaneous or surgical),^{71,72} maintaining the same benefits in the subgroup of diabetic patients.⁷³

The CHAMPION PLATFORM trial failed to show superiority in reducing the primary endpoint (composite of death from any cause, MI, or ischemia-driven revascular-

ization at 48 h) of cangrelor over 600 mg of clopidogrel administered 30 minutes before PCI (7.5% vs 7.1%; odds ratio [OR], 1.05; 95% CI, 0.88–1.24; $P = .56$) in CHAMPION PCI⁷⁴ and in patients who had not been treated with clopidogrel and received either cangrelor or placebo at the time of PCI, followed by 600 mg of clopidogrel (7% vs 8%; OR, 0.87; 95% CI, 0.71–1.07; $P = .17$) in CHAMPION PLATFORM.⁷⁵ A subgroup analysis of more than 2,700 patients performed in CHAMPION PCI showed that results were consistent among the cohort of DM patients (OR, 1.08; 95% CI, 0.8–1.46).

FUTURE DIRECTIONS

The future will likely include newer DES platforms and pharmacologic agents. Among the list of pharmacologic agents stands the “triple therapy” of adding cilostazol to dual-antiplatelet therapy, oral thrombin receptor antagonists^{76,77} that block the platelet protease-activated receptor-1 subtype (of note, thrombin generation processes are enhanced in patients with DM), thromboxane receptor inhibitors (ramatroban and terutroban), the combined TXA2 synthase inhibitors and thromboxane receptor blockers picotamide and ridogrel, and NCX 4016, a nitric oxide–releasing aspirin derivative. There are also new oral anticoagulants, including antifactor IIa (eg, dabigatran) and antifactor Xa (eg, rivaroxaban and apixaban), that are currently in different stages of clinical development and are being tested for long-term use in ACS populations as an adjunct to dual-antiplatelet therapy, in which, DM patients represent a cohort of particular interest.

CONCLUSION

Despite advances in medical and interventional therapies during the last decade, patients with DM continue to experience high rates of adverse cardiovascular events and worse clinical outcomes after revascularization procedures compared with nondiabetic patients. Choosing the best revascularization strategy is a challenge, and the options continue to evolve due to the advent of new technologies, attempting to improve the periprocedural and long-term outcome with PCI. In the acute setting, including STEMI and NSTEMI, PCI appears to be the preferable treatment. In patients with stable CAD, the extent of disease and noncardiac morbidity require more customized evaluation.

Although clinical outcomes after surgical revascularization are worse in diabetic patients as opposed to nondiabetic patients, CABG appears to be more effective in terms of repeat revascularization procedures in patients with advanced and diffuse multivessel disease. PCI with the use of DES and optimal adjunctive pharmacological treatment, including thienopyridines and glycoprotein

IIb/IIIa antagonists, is a valuable alternative to surgery in patients with less-extensive disease.

The safety and efficacy of newer generations of DES with innovative stent designs and platforms for the treatment of patients with diabetes and multivessel disease are currently under investigation in several ongoing randomized controlled trials, and the forthcoming results seem promising. ■

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