

Percutaneous Coronary Interventions in the Diabetic Patient Where Do We Stand?

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Clinical observations made during the past 20 years have suggested that patients with diabetes mellitus (DM) have suboptimal outcomes after percutaneous coronary interventions (PCIs).¹⁻⁴ During the same time period, mechanistic studies have provided insights into the cardiovascular risk of DM. In this report, we attempt to synthesize observations made in the experimental laboratory with those made in the clinical setting to identify how diabetic traits may compromise the success of PCI (Figure 1).

Pathogenetic Mechanisms of Diabetic Traits That May Compromise PCI Success

The hallmarks of DM are hyperglycemia, insulin resistance or an absolute lack of endogenous insulin, and hyperinsulinemia. These metabolic derangements may lead to premature atherosclerosis, cardiomyocyte dysfunction, and renal failure through several mechanisms.

Diabetic Arteriopathy

In an early stage of atherogenesis, the presence of cholesterol crystals may induce the formation of small hydroxyapatite mineral clefts, which are also called microcalcifications, in the intima or media.⁵ In DM, medial calcification develops independently of hypercholesterolemia and may cause sheet-like calcific deposits that reduce vascular compliance.⁶ In the presence of hyperglycemia, medial calcification may be mediated by a glycosylation process, in which N-acetylglucosamine (O-GlcNAc) binds to serine and threonine residues of vascular proteins.⁷ In a drug-induced mouse model of type 1 DM, Heath et al⁶ found a strong increase in vascular O-GlcNAcylation after the onset of increased blood glucose levels, along with a significant increase in aortic calcium content and vascular stiffness. The connection between O-GlcNAcylation and the development of a mineralized matrix was confirmed in an experimental model of vascular smooth muscle cells cultured in osteogenic differentiation media along with an inhibitor of N-acetylglucosaminidase.⁶

The formation of vulnerable atherosclerotic lesions may be related to hyperglycemia⁸ or insulin resistance.⁹ Kuroda et al⁸ observed that daily glucose fluctuations, measured as the mean amplitude of glycemic excursion, correlated with the volume percentage of necrotic core within 165 lesions,

as assessed by virtual histology intravascular ultrasound. In the analysis, the investigators observed that mean amplitude of glycemic excursion was the only independent predictor for the development of thin-cap fibroatheromas,⁸ which have been associated with spontaneous plaque rupture and ischemic clinical events.¹⁰ The role of mean amplitude of glycemic excursion in causing restenosis or neoatherosclerosis within stented segments remains unknown.

Myocardial Dysfunction

Emerging evidence has identified a potential molecular link between insulin resistance and cardiomyopathy. The FoxO group of transcription factors that regulate cell size, viability, and metabolism are targets of insulin and growth factor signaling.¹¹ In a state of insulin resistance induced either genetically or by means of a high-fat diet in mice, the FoxO proteins are activated in cardiomyocytes and linked to the development of cardiomyopathy.¹¹ Cardiomyocyte-specific deletions of FoxO1 are associated with improvements in cardiac function when compared with native controls fed a high-fat diet.¹¹ Although the findings suggested that FoxO activation is an important factor in the pathogenesis of diabetic cardiomyopathy in the absence of coronary artery disease (CAD), a similar mechanism may contribute to ventricular dysfunction in the presence of obstructive CAD as well.

Chronic Kidney Disease

Hyperglycemia contributes to diabetic nephropathy, a microvascular complication of DM, initially by causing glomerulomegaly and later by inducing mesangial expansion, glomerular basement membrane thickening, and glomerular sclerosis.¹² Like DM, chronic kidney disease is associated with the macrovascular complication of medial calcification. The process may be triggered by hyperphosphatemia and involve the formation of macrophage-derived matrix vesicles.⁵ In an experimental model, New et al⁵ observed that complexes containing phosphatidylserine, annexin V, and S100 calcium-binding protein A9 are formed in the presence of calcium and phosphate within macrophage-derived matrix vesicles and facilitate hydroxyapatite nucleation, contributing to vascular microcalcification.

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Altered Antiplatelet Pharmacokinetics

Patients with DM have an impaired response to clopidogrel, but it has been unclear whether this is caused by altered metabolism or an upregulation of the platelet-membrane P2Y₁₂ receptor. Using a comprehensive pharmacokinetic and pharmacodynamic approach, Angiolillo et al¹³ observed that the active metabolites of clopidogrel were significantly lower in diabetic patients than in nondiabetic patients after a load of 600 mg. The findings suggested that the impaired responsiveness of diabetic patients to clopidogrel is caused by the pharmacokinetic profile of the drug and less so by an alteration in the functional status of the P2Y₁₂ signaling pathway.

Exogenous Insulin

Premature CAD is common in DM, but it has been difficult to identify a relationship between hyperinsulinemia and atherogenesis. Clinical studies have suggested that glucose control in type 1 DM often requires exogenous insulin in amounts far greater than that secreted by normal β -cells and that endogenous hyperinsulinemia of type 2 DM is associated with increased hepatic synthesis of cholesterol and triglycerides.¹⁴ Wang et al¹⁵ investigated the relationship between hyperinsulinemia and hepatic markers of atherogenesis in a mouse model of type 1 DM. Although they observed that insulin injection significantly raised the plasma levels of proprotein convertase subtilisin/kexin type 9, an enzyme that cleaves the low-density lipoprotein receptor and thus raises low-density lipoprotein, the rise in proprotein convertase subtilisin/kexin type 9 levels did not exceed that of nondiabetic mice with lower insulin levels. In contrast, insulin injection in diabetic mice appeared to trigger the release of the proinflammatory mediators, tumor necrosis factor- α and interleukin-1 β , from macrophages to levels higher than that seen in nondiabetic mice. The observations, which suggest that exogenous insulin promotes proinflammatory macrophage responses independent of markers of hepatic cholesterol processing,¹⁵ may help explain the earlier clinical finding that inflammatory markers are increased in coronary atherectomy specimens obtained from diabetic patients.¹⁶

Clinical Trial Results

The association between premature CAD and DM has been known for >35 years,¹⁷ and suboptimal outcomes after PCI for the diabetic population have been known for >20 years.^{1,2} Clinical trials completed during the past 20 years comprise an evidence base of comparisons of PCI with medical therapy (MT) or coronary artery bypass graft (CABG) surgery in patients with DM.

PCI Versus MT in Diabetic Patients With Stable Ischemic Heart Disease

In the diabetic subgroup of the COURAGE trial, which comprised 33% of all randomized patients, no advantage of PCI over MT was seen for the composite primary outcome of death from any cause or nonfatal myocardial infarction (MI) during 4.6 years of follow-up (hazard ratio [HR], 0.99; 95% confidence interval [CI], 0.73–1.32).¹⁸

In BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes),¹⁹ patients who underwent PCI had similar rates of major adverse cardiac events as those treated with MT, including nonfatal MIs (11.3% versus 10.2%). In a separate but higher risk stratum, patients treated with CABG had significantly fewer major cardiac events than those treated with MT, a finding that was driven mainly by a reduction in nonfatal MIs (7.4% versus 14.6%). BARI 2D was not designed to compare PCI with CABG.

Clinical Trials Comparing PCI With CABG

After the seminal report from the first Bypass Angioplasty Revascularization Investigation (BARI), which described a 3-fold higher mortality rate 5 years after percutaneous transluminal coronary angioplasty than after CABG (20.6% versus 5.8%; $P=0.0003$),³ several observational studies and randomized clinical trials (RCTs) have reported outcomes in diabetic subgroups. Although some studies suggested equivalent outcomes, none has suggested a survival advantage of PCI (Table).

The SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial reported no significant difference in mortality after PCI compared with

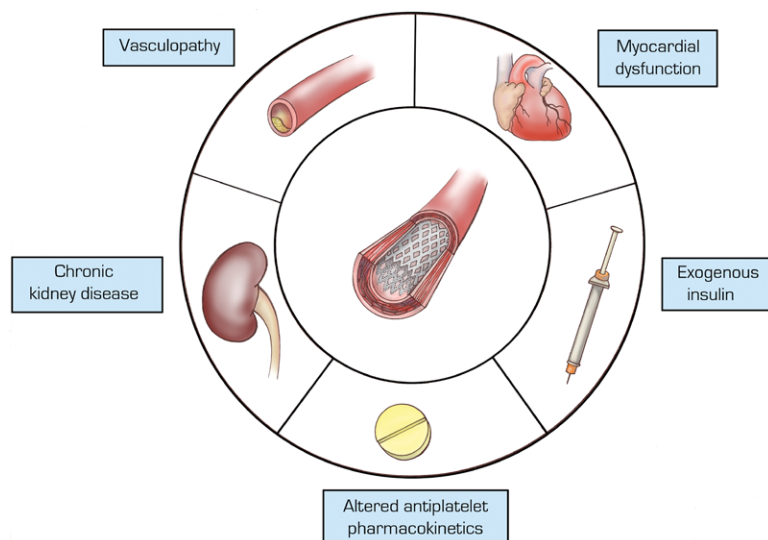


Figure 1. Diabetic traits potentially compromising the success of percutaneous coronary intervention.

CABG in the diabetic subgroup at 5 years (19.5% versus 12.9%; $P=0.065$).⁴³ The Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, a dedicated RCT of 1900 diabetic patients with multivessel CAD, reported a higher rate of the composite of all-cause death, MI, or stroke after PCI than after CABG (26.6% versus 18.7%; $P=0.005$), which was driven by higher rates of MI (13.9% versus 6.0%, $P<0.001$) and death from any cause at 5 years (16.3% versus 11.0%; $P=0.049$).⁴⁵

Clinical Guidelines

A systematic overview (Figure 2) suggests that diabetic patients with multivessel CAD enrolled in 9 RCTs have had higher mortality rates after PCI than after CABG at 5 years or the longest follow-up (odds ratio, 1.86; 95% CI, 1.32–2.63). Because only 3 of 9 RCTs reported mortality differences that were statistically significant (Figure 2)^{3,31,45} and because the mortality difference in FREEDOM was statistically borderline,⁴⁵ the treatment benefit of CABG over PCI has remained uncertain. A Bayesian approach (Figure 3)⁴⁸ can be used to update what was previously known in early trials (prior distribution) with what is learned from FREEDOM (likelihood) to produce a new inference (posterior distribution) that supports the Class I recommendation proposed by the major cardiac societies favoring CABG over PCI to improve survival in diabetics with multivessel CAD requiring revascularization.^{51,52}

Which Diabetic Patients Should Get PCI?

Survival is not the only important outcome; so, we must not hold PCI or CABG in diabetic patients to a higher standard than revascularization for other indications. Relief of ischemic symptoms is another important goal. For diabetic patients in current practice who remain symptomatic despite optimal MT or who have substantial ischemia and severe CAD, PCI may be appropriate. In particular, diabetic patients with stable ischemic heart disease, focal disease, and a low SYNTAX score of ≤ 22 can be offered PCI as an alternative to CABG,⁵² given

the favorable long-term outcomes reported for this subgroup treated with PCI⁴³ and a lower risk of stroke after PCI than after CABG (2.4% versus 5.2%, $P=0.03$).⁴⁵

Acute Coronary Syndromes

Neither BARI 2D¹⁹ nor COURAGE¹⁸ demonstrated a survival advantage of PCI over MT, but both studies enrolled low-risk patients. Diabetic patients with acute coronary syndrome and focal disease may benefit from early revascularization with PCI.⁵² Diabetic patients with multivessel CAD and acute coronary syndrome refractory to MT should probably have urgent or emergency PCI for the culprit lesion and a Heart Team consultation to discuss whether MT, PCI, or CABG would be most suitable for the remaining significant obstructive CAD.⁵¹ For most diabetic patients with extensive multivessel CAD, particularly if the proximal segment of the left anterior descending coronary artery is involved and a left internal mammary graft can be used, CABG is the preferred method of revascularization based on evidence from clinical studies (Table).^{51,52}

ST-Segment–Elevation MI

Diabetic patients presenting with ST-segment–elevation MI and suitable anatomy should have PCI of the culprit lesion. If multivessel CAD is present, culprit-lesion PCI should be performed, followed by a Heart Team consultation to discuss whether MT, PCI, or CABG would be most suitable for remaining significant obstructive CAD.⁵² If cardiogenic shock complicates ST-segment–elevation MI, multivessel PCI with or without hemodynamic support may be considered as an option to hemodynamic support and emergency CABG.⁵³

Specific Challenges in Diabetic Patients Who Need Revascularization

Although RCTs are helpful for making broad treatment recommendations, they cannot identify fine mechanistic details. A discussion of trial results, viewed against a background of

Table. Evidence for Survival Benefit in Diabetic Patients With Stable Ischemic Heart Disease Who Are Receiving MT and Are Suitable Candidates for Revascularization With Either CABG Surgery or PCI

Evidence Supporting CABG for Survival Over MT	Evidence Supporting PCI for Survival Over MT	Evidence Supporting Superiority of Either CABG or PCI for Survival	Evidence Supporting Equivalence of CABG and PCI for Survival
For: Sorajja et al ^{20*}	For: none	CABG better: BARI ^{3,21†} ; Bair et al ²² unadjusted*; Brenner et al ^{23*} ; Deb et al ²⁴ for SYNTAX score >22 ; Hlatky et al ^{25†} ; Javaid et al ^{26*} ; Malenka et al ^{27*} ; Niles et al ^{28*} ; Pell et al ²⁹ for 3-V CAD*; SoS ^{30†} ; VA CARDS ^{31†} ; Verma et al ^{4†} ; and Weintraub et al ^{32†}	ARTS ^{33†} ; ARTS II ^{34*} ; Bair et al ²² adjusted*; Bangalore et al ^{35†} ; Barsness et al ^{36*} ; Bravata et al ^{37†} ; CARDia ^{38†} ; Daemen et al ^{39†} ; Deb et al ²⁴ for SYNTAX score ≤ 22 †; Dzavik et al ^{40*} ; MASS II ^{41†} ; Pell et al ²⁹ for 2-V CAD*; and SYNTAX ^{42,43†}
No benefit: BARI 2D ^{19†}	No benefit: BARI 2D ^{19†}	PCI better: none	

2-V CAD indicates 2-vessel coronary artery disease; 3-V CAD, 3-vessel coronary artery disease; ARTS, Arterial Revascularization Therapies Study; BARI, Bypass Angioplasty Revascularization Investigation; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CABG, coronary artery bypass graft; CARDia, Coronary Artery Revascularization in Diabetes; DM, diabetes mellitus; ERACI II, Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease II; MASS II, Medicine, Angioplasty, or Surgery Study Part II; MT, medical therapy; PCI, percutaneous coronary intervention; SoS, Stent or Surgery; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; and VA CARDS, Veterans Administration Coronary Artery Revascularization in Diabetes. Reprinted from Levine et al⁴⁴ with permission of the publisher. Copyright ©2011, American College of Cardiology Foundation/American Heart Association.

*Observational studies.

†Randomized controlled trials.

‡Meta-analyses.

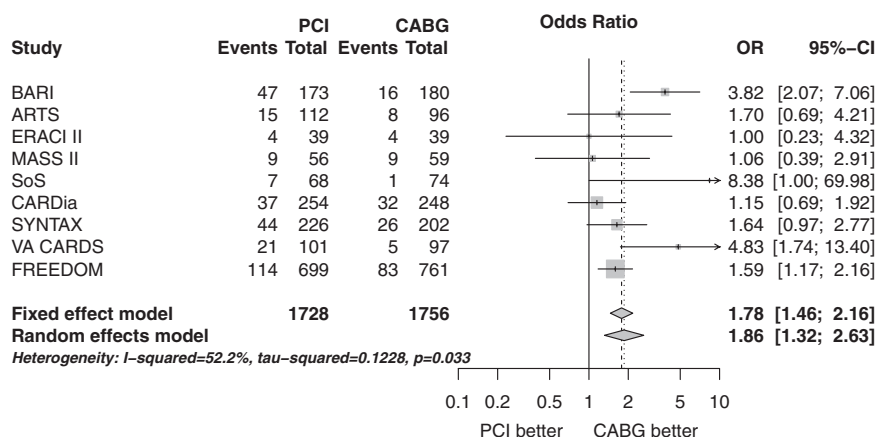


Figure 2. Forest plot of mortality risk after coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) in diabetic patients with multivessel coronary artery disease. Original analyses were created with [R] 3.0.2,⁴⁶ using library package “meta” 3.8-0.⁴⁷ BARI indicates Bypass Angioplasty Revascularization Investigation; CARDia, Coronary Artery Revascularization in Diabetes; CI, confidence interval; ERACI II, Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease II; FREEDOM, Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease; MASS II, Medicine, Angioplasty, or Surgery Study Part II; OR, odds ratio; SoS, Stent or Surgery; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; and VA CARDS, Veterans Administration Coronary Artery Revascularization in Diabetes.

known pathogenetic mechanisms (Figure 1), may explain some of the limitations of PCI and identify approaches to improve outcomes in diabetic patients who need revascularization.

Diabetic Arteriopathy and PCI Outcomes

Two factors that compromise long-term success after PCI are high rates of restenosis and the development of vulnerable plaques outside stented segments. Almost all trials enrolling diabetic patients, including FREEDOM at 1 year (12.6% versus 4.8%; $P<0.001$),⁴⁵ have reported higher rates of repeat revascularization after PCI than after CABG. Likewise, as in FREEDOM (13.9% versus 6.0%; $P<0.001$),⁴⁵ most studies of diabetic patients have reported higher rates of MI after PCI than after CABG. These findings suggest that bypass conduits in diabetic patients provide better protection against the future development of clinically important lesions in longer segments of the coronary tree than does spot treatment with stents, despite the theoretical drawback of anastomosing bypass conduits to poor targets in small diabetic vessels.⁵⁴

A hallmark of diabetic arteriopathy is medial calcification. Although it is difficult to quantify angiographically,⁵⁵ coronary calcification may be associated with suboptimal outcomes after PCI. A recent study suggested, however, that DM itself (HR, 2.10; 95% CI, 1.56–2.83) was a stronger independent predictor of all-cause mortality 1 year after PCI than was lesion calcification (HR, 1.10; 95% CI, 0.81–1.48).⁵⁶ The use of adjunctive ablative therapies for diabetic patients with calcified lesions has undergone limited investigation. In an uncontrolled trial of orbital atherectomy for patients with severely calcified lesions, 36.1% had DM and appeared to have acceptable procedural success rates,⁵⁷ but an earlier overview of randomized trials suggested that the routine use of ablative therapies does not improve long-term outcomes compared with standard approaches during PCI.⁵⁸ Additional studies are needed to compare ablative therapies with standard approaches for diabetic patients with calcified lesions.

A major advance in interventional cardiology has been the development of drug-eluting stents. Bangalore et al⁵⁵ reported that survival after implantation of platinum–chromium everolimus-eluting stents might be no different from that after CABG in diabetic patients with multivessel disease. It is important to recognize, however, in the absence of a survival advantage with each successive improvement in stent design in the general population of patients undergoing PCI,^{59,60} that survival after spot treatment with everolimus-eluting stents would be unlikely to match the survival rate after CABG in diabetic patients in a prospectively designed randomized trial.

Heart Failure

Many diabetic patients have heart failure, with or without systolic dysfunction. The presence of systolic dysfunction and multivessel CAD generally favors a recommendation of CABG over PCI to improve survival,^{44,61} but the disadvantage of PCI in this setting has not been fully understood. A recent study suggested that a left ventricular ejection fraction of $<40\%$ is a risk factor for ST (adjusted odds ratio, 2.25; 95% CI, 1.09–4.70).⁶²

Chronic Kidney Disease

Patients with chronic kidney disease have been under-represented in clinical trials. In BARI 2D and FREEDOM, patients were excluded if serum creatinine exceeded 2 mg/dL.^{19,45} Like DM,⁶ chronic kidney disease is associated both with medial calcification and suboptimal outcomes after PCI.⁶³ In patients with advanced renal failure with or without DM, a recent study found that CABG was associated with a 2- to 3-fold higher risk of causing acute kidney injury in the short term than was PCI,⁶⁴ but other studies have found that CABG was associated with a greater survival benefit in the long term.⁶³ Although current data might be more robust for CABG than for PCI in observational studies of patients with chronic kidney disease and multivessel CAD,⁴⁴ no dedicated RCTs have been completed in this patient population.

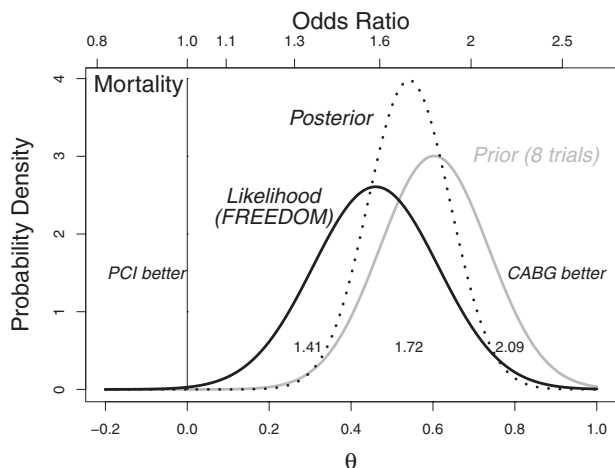


Figure 3. Bayesian triplot of mortality risk after percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery in diabetic patients with multivessel coronary artery disease. The figure, which illustrates the way that Bayesian methods combine information from various sources, contains 3 plots on the familiar odds ratio (OR) scale as well as on the θ , or $\log_e(\text{OR})$, scale. The prior distribution (gray), which is represented by a bell-shaped curve to show the distribution of all possible ORs based on evidence from 8 older trials,^{3,30,31,33,38,41,43,49} strongly favors CABG. The likelihood (solid black), which represents the OR obtained from Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM),⁴⁵ still favors CABG but less so than the prior. Bayesian methods combine the likelihood with the prior in a type of meta-analysis to produce the posterior distribution (dotted black). The resulting bell-shaped curve is not twice the height of the prior or the likelihood because precision represented by probability density is additive. The most obvious difference between traditional frequentist and Bayesian methods is that frequentist statistics uses only the likelihood, whereas Bayesian statistics uses both the likelihood and the prior information. The posterior distribution (dotted black) confirms that there is a 95% probability that the mortality risk is 1.41 to 2.09 \times higher after PCI than after CABG, with a mode at 1.72 (data labels). Original analyses were created with [R] 3.0.2,⁴⁶ using a normal conjugate model.^{48,50} All curves are normalized to 1.

Altered Pharmacokinetics

Given the impaired metabolism of clopidogrel in diabetic patients, many investigators have performed subgroup analyses of RCTs to evaluate alternative P2Y12 inhibitors. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON TIMI 38),⁶⁵ lower rates of cardiovascular death, nonfatal MI, or nonfatal stroke were seen with prasugrel than with clopidogrel in patients with DM (12.2% versus 17.0%), without DM (9.2% versus 10.6%), and without increased major bleeding (2.6% versus 2.5%).

In the Platelet Inhibition and Patient Outcomes (PLATO) trial,⁶⁶ lower rates of all-cause mortality (HR, 0.82; 95% CI, 0.66–1.01) and stent thrombosis (HR, 0.65; 95% CI, 0.36–1.17) were seen with ticagrelor than with clopidogrel, without increased major bleeding (HR, 0.95; 95% CI, 0.81–1.12). In this study, the absence of P2Y12 blocker therapy was the strongest predictor of ST, and the presence of DM itself was a major risk factor for ST (adjusted odds ratio, 1.82; 95% CI, 1.02–3.24).⁶²

Although the 2011 PCI guideline did not specify a preference of one P2Y12 agent over another,⁴⁴ the more potent

agents might be considered in diabetic patients undergoing PCI. Clinicians should recognize, however, that the potent P2Y12 receptor antagonists are not a panacea without complications, contraindications, or cost.⁶⁷ Patients with DM will continue to have a higher risk of ischemic events than patients without DM, apart from the P2Y12 antagonist used.^{65,66}

Glycemic Control

Several analyses have related poor outcomes after revascularization with the use of exogenous insulin.^{43,68} Using data from the FREEDOM trial, Dangas et al⁴⁵ observed that the composite rate of death, MI, or stroke was higher in insulin-treated patients than in diabetic patients not treated with insulin. Moreover, the comparative advantage of CABG over PCI in lowering the primary end point was seen both in insulin-treated patients (24.3% versus 32.2%) and in diabetic patients not requiring insulin (15.6% versus 23.2%).⁶⁸ A time-to-event analysis suggested that cardiovascular risk was related to the duration of DM, with event rates being higher in patients with DM of duration ≥ 9 years than in those with DM of duration < 9 years.⁶⁸ These results suggest, but do not prove, that CABG is favored over PCI for insulin-dependent or long-term diabetics.^{43,68} On the other hand, an analysis of the survival curves suggests that PCI is favored over CABG for patients with a limited prognosis of < 3 years because the event curves in the FREEDOM trial did not begin to separate and favor CABG over PCI until 2 to 4 years after revascularization.⁴⁵

In several studies of MT with or without revascularization, tight glycemic control was unhelpful or associated with increased cardiovascular events.^{69–71} In the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE), there was no significant effect of the type of glucose control on major macrovascular events (HR, 0.94; 95% CI, 0.84–1.06), death from cardiovascular causes (HR, 0.88; 95% CI, 0.74–1.04), or death from any cause (HR, 0.93; 95% CI, 0.83–1.06).⁷²

Insulin Sensitization

Insulin sensitization, as tested in BARI 2D most frequently with metformin (74.6%) or a thiazolidinedione (62.1%), did not improve the primary end point of freedom from major cardiovascular events (77.7% in the insulin sensitization group versus 75.4% in the insulin provision group; $P=0.13$).¹⁹ However, on the basis of results from the earlier UK Prospective Diabetes Study, metformin continues to be favored over the sulfonylureas to reduce cardiovascular complications in patients with DM.⁷³

Conclusions

Interventional cardiologists currently have a different perspective about treating diabetic patients with PCI than they had in 1997 when the BARI substudy was published.³ Current evidence suggests that the development of vulnerable lesions, impaired left ventricle function, altered thienopyridine metabolism, renal failure, and the use of exogenous insulin impair the response to PCI. To optimize outcomes after

PCI or CABG in diabetic patients, physicians recognize that a revascularization procedure is one component of a comprehensive strategy involving cardiac rehabilitation, blood pressure control, smoking cessation, statins for lipid lowering, and angiotensin-converting enzyme inhibitors to prevent renal failure; but many challenges remain. Using PCI to treat patients with DM will become better understood and develop into a logical science if additional research can elucidate the molecular links between the metabolic derangements and the clinical manifestations of DM and if dedicated clinical trials continue to inform best practices.

Disclosures

None.

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