

Role of Multivessel Intervention in Diabetes Mellitus

Advances in interventional procedures and medical therapy offer promising treatment options for the diabetic patient population.

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Diabetes has established itself as the pandemic of the 21st century. In 1985, an estimated 30 million people worldwide had diabetes; by 2003, it was estimated that there were approximately 194 million people with diabetes, with this figure expected to rise to almost 350 million by 2025.¹ There are several pathophysiological mechanisms in diabetes that contribute to increased morbidity and mortality rates. The underlying defect of insulin resistance seen in >90% of type 2 diabetic patients is associated with hyperglycemia, dyslipidemia, inflammation, and hypercoagulability. Eighty percent of all deaths among diabetic patients are due to atherosclerosis, compared with approximately 30% among nondiabetic persons. The nature and distribution of atherosclerosis in diabetes also portends a poorer prognosis and response to revascularization. Diabetic patients have a larger burden of disease, a greater proportion of lipid- and macrophage-rich plaques, more fissured plaque, and more intra-coronary thrombi. Multivessel disease (MVD), left main involvement, chronic total occlusions, and diffuse disease are seen frequently. Diabetic patients have an impaired ability to develop collaterals in response to atherosclerosis.²

MULTIVESSEL INTERVENTION

Almost 15% to 20% of patients undergoing revascularization procedures are diabetics. Simultaneously, approximately two thirds of patients who undergo revascularization procedures have MVD (Figure 1).³ Patients requiring multivessel intervention have a less favorable long-term outcome, increased procedural risk, and increased procedural complexity. They are more likely to have multiple risk factors, including diabetes, other comorbidities, and previous myocardial infarctions with reduced ventricular function. Unfavorable anatomy, such as chronic total occlusions, calcified bifurcation lesions, and diffuse small vessel disease, only adds to the complexity. Although considerations of safety and procedural success are paramount, the decision to choose percutaneous coronary intervention

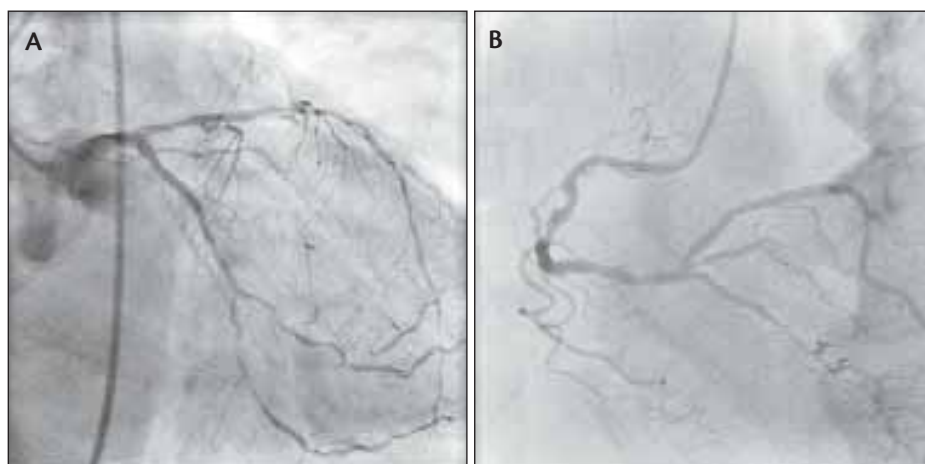


Figure 1. Multivessel disease in a diabetic patient (90%–95% stenosis of mid-left anterior descending artery (LAD) and 80%–90% stenosis of distal LAD; 70%–80% left circumflex coronary artery bifurcation; multiple 70%–80% lesions in the right coronary artery) with severe diffuse right posterior descending artery disease.

(PCI) as a revascularization strategy should be based on the morbidity and mortality risk when compared to the alternative of medical or surgical treatment.

PCI VERSUS CABG

Angioplasty Era

Historically, trials of MVD evaluating revascularization strategies have included only a minority of diabetic patients, in the range of 6% to 19%. In the Bypass Angioplasty Revascularization Investigation (BARI) trial,

although there was no difference in mortality or Q-wave infarction between percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) in the study overall (1,829 subjects) at 5 years; in the diabetic patient subgroup (457 subjects), there was a striking mortality advantage in favor of CABG at 10 years (57.8% CABG and 45.5% PTCA; $P=.025$).⁴ The Emory Angioplasty versus Surgery Trial (EAST) and the Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI) trials went on to reaffirm that the CABG arm had

TABLE 1. REVASCLARIZATION STUDIES IN DIABETICS WITH MVD

Trial	Sample Size	Intervention	Outcome	Follow-Up (y)	Control Group (%)	Treatment Group (%)	Relative Risk Reduction (%)	P Value
BARI	457	CABG vs PTCA	Survival	10	57.8	45.5	21	.025
BARI-Registry	339	CABG vs PTCA	Survival	5	85	86	—	.86
EAST	59	CABG vs PTCA	Survival	8	76	60	21	.23
CABRI	125	CABG vs PTCA	Survival	4	88	77	12	NS
DUKE	770	CABG vs PTCA	Survival	5	74	76	—	.91
ARTS	208	CABG vs BMS	Survival	3	96	93	3	.39
SOS	148	CABG vs BMS	Survival	5	94.6	82.4	13	.15
ERACI II	77	CABG vs BMS	Survival	1	95	96.4	—	.98
AWESOME	144	CABG vs BMS	Survival	5	66	74	11	.27
NYS BMS	17,946	CABG vs BMS	Survival	3	—	—	31	Significant
NYS DES	6,098	CABG vs DES	Survival	1.5	91.5	93.2	-3	.75
BARI 2D	2,368	Revasn vs Medical Rx	Survival	5	Recruitment complete			
					Follow-up ongoing			
CARDIA	600	CABG vs DES	Cardiovascular death, MI, stroke	5	Recruitment complete			
					Follow-up ongoing			
SYNTAX	1,500	CABG vs DES	Cardiovascular death, MI, stroke	5	Recruitment complete			
					Follow-up ongoing			
FREEDOM	2,058	CABG vs DES	Cardiovascular death, MI, stroke	5	Ongoing			
VA-CARDS	790	CABG vs DES	Cardiovascular death, MI	5	Ongoing			

a survival advantage over PTCA.^{5,6} The BARI registry, however, did not reflect the superiority of the CABG strategy demonstrated in the trial.⁷ Large observational studies, such as the Duke Cohort, however, directly contrasted the findings from subset analyses from trials with a 74% survival rate for those undergoing CABG compared with 76% in the PTCA group over the 5 years of follow-up ($P=.91$).⁸ There was no mortality difference in the observational study versus that seen in the trials.

Bare-Metal Stenting Era

Multiple trials comparing stenting to CABG for MVD have been performed. Results from the Arterial Revascularization Study (ARTS), the Stent or Surgery (SOS) trial, the ERACI-II study, and the MASS-II study all showed that CABG was still superior to PCI with stenting in regard to the need for repeat revascularizations, with trends for better long-term survival with CABG.⁸⁻¹² A trend for mortality benefit with PCI over CABG was, however, seen in the AWESOME (Angina with Extremely Serious Operative Mortality Evaluation) trial.¹³ The New York State registry provided data from 37,212 patients (33.2% with diabetes) who underwent CABG and 22,102 patients (25.3% with diabetes) who underwent PCI with bare-metal stents for MVD. Patients with diabetes and three-vessel CAD, including proximal LAD, had fewer deaths with CABG (hazard ratio [HR], 0.66; confidence interval [CI]=0.53–0.81) at 3 years.¹⁴

The Drug-Eluting Stent Era

Drug-eluting stents (DESs) ushered in the next revolution in the field of revascularization. The superiority of DESs for the reduction of the need for repeat revascularizations was established early on. The challenge of the choice of DES in terms of better results (paclitaxel-eluting stents or sirolimus-eluting stents) has yet to be definitively resolved.

Recently, the New York State registry published results from 7,437 patients (38.2% with diabetes) who underwent CABG and 9,963 patients (32.7% with diabetes) who underwent PCI with DESs for MVD. At 18-month follow-up, the mortality advantage that CABG had shown over PCI in earlier eras was no longer significant (HR, 0.97; CI=0.77–1.2; $P=.75$).¹⁵

Future

Multiple randomized studies have been initiated around the world to investigate the role of multivessel stenting in diabetic patients with MVD. The results of these studies will be available 3 to 5 years from now. Table 1 demonstrates the studies evaluating revascularization strategies in the management of MVD in diabetic patients.

BARI 2D. Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) studies patients with mild or asymptomatic diabetes. After a diagnostic angiography, patients are randomized to either initial invasive strategy (PCI or CABG) with aggressive medical therapy, or to aggressive medical therapy alone. The 2X2 factorial design of the study requires that, within each of those two arms, patients are further randomized to management of their diabetes with insulin-sensitizing or insulin-providing agents, with a target value for HbA1c of <7% for all patients.¹⁶ The trial completed enrollment in 2007.

SYNTAX. The diabetic subset of the SYNTAX study will also add valuable information to the management of multivessel disease in diabetic patients. The SYNTAX trial is designed to determine the best treatment for patients with complex multivessel coronary disease, including left main disease, by randomizing patients to receive either PCI with polymer-based, paclitaxel-eluting Taxus stents (Boston Scientific Corporation, Natick, MA) or to CABG. The primary outcome will be 12-month all-cause death, cerebrovascular event, documented myocardial infarction (MI), and repeat revascularization.¹⁷ The trial results will be presented at the European Society of Cardiology meeting in September 2008.

CARDia. The CARDia (Coronary Artery Revascularization in Diabetes) trial is a multicenter, prospective, randomized comparison of optimal coronary angioplasty with stents and abciximab versus up-to-date CABG in 600 diabetic patients with multivessel or complex single-vessel disease. The trial is taking place at 21 sites in the United Kingdom and Ireland, with the combined primary endpoint being death, MI, and stroke.¹⁸ The trial completed enrollment in 2007.

FREEDOM. The NHLBI-sponsored FREEDOM (Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) trial will enroll 2,058 patients with diabetes at 160 centers worldwide. Patients will be randomized to contemporary CABG or PCI with DES. The primary endpoints will be death, MI, or stroke at 3 years. Important secondary outcomes that will be measured include 1-year major adverse cardiac and cerebrovascular events; mortality at 1, 2, and 3 years; quality of life; a cost-benefit analysis; and neurocognitive function.¹⁹ The trial will complete enrollment in early 2009.

VA-CARDS. The hypothesis being tested in the VA-CARDS study is that a strategy of surgical revascularization is superior to PCI in preventing death or MI in diabetics with severe ischemic heart disease. VA-CARDS aims to recruit 790 patients at 15 sites within the US Veterans Administration hospital system. The primary outcome measure for this study will be the time to either death or nonfatal MI.²⁰

TECHNICAL ISSUES

Staging

In an effort to reduce duration of radiation exposure and complications, such as contrast-induced renal failure, interventions were routinely performed after diagnostic angiography, and complex multivessel interventions were performed previously in two or more stages.

Currently, however, it has

become increasingly common to perform an intervention during the same session as the diagnostic angiography, even in the setting of multivessel angioplasty because of logistic and patient-physician preference issues. Data from the National Heart, Lung, and Blood Institute PTCA dynamic registry from 1999 to 2001 show that 30% of patients are treated in a single session.²¹ Thus, situations that can favor planned or unplanned staged procedures include the desire to reduce the risk of the procedure, avoid excessive contrast use, and reduce patient discomfort and physician fatigue.

Degree of Revascularization: Complete/Incomplete

Although complete revascularization is the goal in most patients undergoing multivessel intervention, incomplete revascularization is frequent in clinical practice. In the BARI trial, 5-year survival was not different between the two groups, even though 91% of important lesions were bypassed, whereas only 51% of important lesions were successfully dilated.²² However, incomplete revascularization portended a poorer long-term survival for diabetic subjects. Notably, repeat revascularization procedures were mostly for restenosis rather than revascularization of previously untreated lesions. In diabetic subjects with MVD, complete revascularization is therefore recommended, without relying on recurrence of symptoms or ischemia on stress testing.

Restenosis and Stent Thrombosis

Restenosis has remained the Achilles' heel of PCI. Although bare-metal stents, followed by drug-eluting stents, have significantly reduced this problem through their effects on intimal remodeling, restenosis continues to be a sizeable issue for diabetic subjects with MVD. Restenosis tends to present with recurrence of angina rather than a catastrophic event. The need for multiple repeat procedures to deal with restenotic lesions is one of the major disadvantages that PCI faces in its battle against CABG as an optimal revascularization tool. On the other hand, stent thrombosis, whether acute (<48 hours), suba-

TABLE 2. RESTENOSIS AND STENT THROMBOSIS

Predictors of Restenosis	Predictors of Stent Thrombosis
Multivessel stenting	Multivessel stenting
Diabetes mellitus	Diabetes mellitus
Lesion length	Left ventricular dysfunction
Previous revascularization	Previous MI
Greater postintervention residual burden	Bifurcation stenting
Small vessel	Renal insufficiency
Reduced BMI	Discontinuation of antiplatelet therapy

cute (2–30 days), late (1–12 months), or very late (>12 months) presents with high rates of MI and mortality. Review of the literature regarding predictors of these phenomena reveals that besides operator technique issues, anatomical factors, such as lesion length, vessel size, total occlusions, and number of lesions, and patient factors, such as diabetes, renal insufficiency, previous MI, and systolic dysfunction, put patients at very high risk for restenosis and late stent thrombosis (Table 2). Detailed attention to technique and long-term adherence to dual-antiplatelet therapy with aspirin and clopidogrel are of critical importance in the avoidance of stent thrombosis. It may well be that bioabsorbable stents or using bone marrow progenitor cells to promote endothelialization might reduce the phenomenon of stent thrombosis.

Associated Complex Anatomy

Chronic total occlusions. In a registry of 8,004 patients presenting for diagnostic angiography, 52% of patients with a stenosis $\geq 70\%$ had a chronic total occlusion (CTO).²³ These lesions are a major hurdle in achieving complete revascularization during multivessel stenting in diabetic patients. In a center with limited experience, CABG is probably the better method of revascularizing these challenging lesions. However, skilled operators who take on these lesions must pay special attention to CTOs in conjunction with side branches, bridging collaterals, lack of tapered stump, lesion length, and severe calcification. The operator should pay great attention in selecting the guide catheters, support catheters, guidewires, newer technologies for crossing CTOs (such as the Crosser [FlowCardia, Sunnyvale, CA]), and the dilatation strategies to ensure success. Nonguidewire approaches, such as the Safe-Cross (Spectranetics Corporation, Colorado Springs, CO) and the Frontrunner (Cordis Corporation, Warren, NJ) catheters are newer options for approaching CTOs in the coronary arteries. Creative procedural techniques, such as the subintimal tracking technique, have significantly reduced the number of CTOs that would have previously been considered unapproachable. Interventionists should

also remember that beyond procedural success, the patients' risk factor profile should also figure into the decision to approach CTOs via percutaneous means.

Bifurcation lesions. Compared to nonbifurcation interventions, bifurcation interventions have a lower procedural success rate, higher costs, longer hospitalizations, and a higher rate of clinical and angiographic restenosis. Although the conventional approach involved stenting the main branch with provisional stenting of the side branch, multiple two-stent techniques, such as the "V," simultaneous kissing stents, modified simultaneous kissing stents, crush, reverse crush, "T," culottes and the "Y," have gained popularity recently.²⁴

ADJUNCTIVE THERAPIES

Adjunctive medical therapy during and after the procedure has improved long-term outcomes after percutaneous interventions.

Antiplatelet Therapy

ASA. A meta-analysis of 145 prospective controlled trials of antiplatelet therapy in adults after MI, stroke, transient ischemic attack, or positive cardiovascular history (vascular surgery, angioplasty, angina, etc.) reported by the Anti-Platelet Trialists (APT) estimated that 38 ± 12 vascular events per 1,000 diabetic patients would be prevented if they were treated with aspirin as a secondary prevention strategy.²⁵

Clopidogrel. The addition of clopidogrel to aspirin therapy has yielded a significant improvement in outcomes. The CREDO (Clopidogrel for the Reduction of Events During Observation) trial demonstrated that 12-month administration of clopidogrel was associated with an 11% relative reduction in the composite endpoint of death, MI, or stroke.²⁶ Further data from the CAPRIE, CURE, and MATCH studies have shown a trend for benefit with add-on clopidogrel therapy for reduction of vascular events in diabetic subjects over longer follow-up.²⁷⁻²⁹

Prasugrel. The TRITON-TIMI 38 study randomly assigned 13,608 patients with moderate- to high-risk acute coronary syndromes with scheduled PCI to receive prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) or clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose) for 6 to 15 months.³⁰ Overall, the study showed a significant reduction in the primary efficacy endpoint of death from cardiovascular causes, nonfatal MI, or nonfatal stroke with prasugrel over clopidogrel (HR, 0.81; $P < .001$). The benefit tended to be greater among the 3,146 patients with diabetes (HR, 0.7; $P < .001$) than among the 10,462 patients without diabetes (HR, 0.86; $P = .02$). However, prasugrel suffered from a statistically higher incidence of life-threatening bleeding.

Glycoprotein IIb/IIIa inhibitors. Routine use of glycoprotein IIb/IIIa inhibitors has improved outcomes after coronary intervention. A meta-analysis of the 1-year data from the EPIC, EPILOG, and EPISTENT trials showed a significant effect of abciximab on the 1,462 diabetic patients whose mortality decreased from 4.5% to 2.5% ($P = .031$).³¹ The effect was even more magnified in diabetic patients with multivessel disease (7.7%–0.9%; $P = .018$). A combined analysis of eight trials with more than 5,154 patients showed that there was an absolute mortality benefit associated with the usage of abciximab at 6 months and 3 years (0.74% [$P = .04$] and 0.94% [$P = .031$], respectively).³² Other glycoprotein IIb/IIIa inhibitors, such as eptifibatide, lamifiban, and tirofiban, have also shown benefit in coronary interventions. A pooled analysis of six major trials of glycoprotein IIb/IIIa inhibitors in 6,458 diabetic patients with non-ST-segment elevation myocardial infarcts (NSTEMI) showed a 30-day mortality rate was lower in the IIb/IIIa group compared to control (6.2%–4.6%; $P = .007$). Diabetic patients undergoing PCI derived an even greater mortality benefit (4%–1.2%; $P = .002$).³³

Bivalirudin. The REPLACE-2 trial enrolled 1,624 diabetic patients and 4,368 nondiabetic patients undergoing elective or urgent PCI and randomized them to routine glycoprotein IIb/IIIa inhibitor plus heparin therapy versus bivalirudin plus provisional glycoprotein IIb/IIIa inhibitor therapy. Both arms were equivalent for short- or long-term ischemic events among the diabetic patients.³⁴

MEDICAL THERAPY

Aggressive risk factor modification has become the main focus in the management of cardiovascular disease in diabetic patients. Therapeutic lifestyle modification involving weight loss, regular exercise, smoking cessation, and a healthy diet form the keystone of risk factor management. In the past decade, goals of therapy for glycemia, lipids, and blood pressure have become increasingly rigorous. Despite accumulating data in favor of effectiveness of medical therapies, data from the National Health and Nutritional Evaluation Survey (1999–2004) showed that only 13.2% of adults with diabetes attained the recommended goals of HbA1c level $< 7\%$, blood pressure $< 130/80$ mm Hg, and total cholesterol level < 200 mg/dL (5.18 mmol/L).³⁵ There clearly remains a lot of room for improvement in effectively delivering evidence-based therapies.

CONCLUSION

With the increasing burden of atherosclerosis, there is an ominous need for us to obtain data that helps clinicians make the right decisions regarding optimal management in diabetic patients. The advances that have been made in interventional cardiology with the introduction of

DESs and in the field of medical therapies with the widespread use of statins, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and newer antiplatelet therapies, have raised the possibility that we might be able to control, if not cure, this pandemic. Until the results of important trials such as FREEDOM, BARI-2D, CARDia, SYNTAX, VA-CARDS, AIM-HIGH, ACCORD, and ADVANCE are presented during the next 5 years, there will still be uncertainty about the best approach to treating individual diabetic patients who have multivessel disease. By designing trials powered to study outcome differences exclusively in diabetic patients, we have at least graduated to recognizing the uniqueness of their coronary disease. ■

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