Is surgery preferred for the diabetic with multivessel disease?

Surgery Is Preferred for the Diabetic With Multivessel Disease
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When angioplasty was first introduced by Andreas Gruentzig in 1977, it was envisioned as a treatment for angina pectoris refractory to medical therapy but applicable to patients who might otherwise have undergone bypass surgery. Assessment of patients before the intervention included exercise stress testing documenting ischemia, and the lesions selected for treatment were those that could be attempted using the primitive balloon angioplasty equipment that was available at that time. As the equipment for percutaneous coronary interventions (PCIs) improved, the technique was expanded to encompass a larger population of patients who otherwise would have been referred for bypass surgery. By 1990, the frequency of coronary angioplasty had increased to equal that of coronary bypass surgery. By the end of the decade, almost twice as many percutaneous interventions were being performed as coronary bypass surgical procedures. As angioplasty began to infringe on the domain of bypass surgery, there was a call for randomized control trials testing the comparative value of angioplasty in traditionally surgical applications. Andreas Gruentzig proposed such a trial when angioplasty had reached a degree of maturity 6 years after the first procedure was performed. National Heart, Lung, and Blood Institute (NHLBI) funding for the first comparison of bypass surgery and angioplasty was finally obtained, and the Emory Angioplasty versus Surgery Trial (EAST) was begun in 1987, 2 years after Gruentzig’s tragic death. A second multicenter randomized trial, the Bypass Angioplasty Revascularization Investigation (BARI), was also approved by the NHLBI and was begun 1 year after the initiation of the EAST trial. The outcomes of these trials confirmed the overall equivalence of angioplasty and bypass surgery for patients suitable for angioplasty and were consistent with other trials initiated in Europe and South America. However, when the 5-year outcome of the BARI trial was reported in 1996, a clear advantage for surgery was seen in the subset of patients with diabetes. Cardiac mortality at 5 years was 5.8% in the coronary artery bypass graft (CABG) group and 20.6% in the percutaneous transluminal coronary angioplasty (PTCA) group (P<0.0003). This report was accompanied by a clinical alert from the NHLBI pointing out the superiority of bypass surgery. A review of the long-term results of the EAST trial showed a similar trend.

A meta-analysis of the randomized controlled trials comparing CABG with PTCA was performed recently. The comparison was computed according to risk differences, which is the number of events per 100 patients treated in the group with the highest number of events minus the number of events per 100 patients in the comparative group. In the trials of multivessel disease with 5-year follow-up (n=3427), the risk difference for death was 2.3% (P=0.025), or, in other words, 2.3 fewer deaths in the surgery group than in the interventional group at 5 years. At 8 years, the risk difference was 3.4 fewer deaths in the surgery group per 100 patients treated. When observing the trials that can be evaluated from 1 to 8 years,
it is apparent that this difference in survival does not become established until after the 3-year follow-up. In this meta-analysis, there were 3 trials available in patients with the diabetic population identified. Those trials were the EAST, Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI), and BARI studies. At 4 years, the risk difference favoring surgery was 8.6 fewer deaths per 100 patients treated (P<0.01).

Since these early experiences, there have been dramatic changes in the practice of interventional cardiology as well as surgery. In addition, important advances in the medical management of patients with diabetes has occurred, and therefore, the question of whether surgery is still the preferred revascularization strategy for patients with diabetes and multivessel disease remains an important one.

Increased Risk in Patients With Diabetes

The cardiovascular risk in diabetic patients has been evaluated in a large population-based study. The long-term incidence of death or myocardial infarction was 20% in the diabetic patients but only 3.5% for patients without diabetes. Such observations led the National Cholesterol Education Program’s Adult Treatment Panel 3 to classify diabetes as a risk equivalent to established coronary artery disease. In patients with established coronary artery disease, the presence of diabetes increased the 5-year mortality rate to more than double that seen for nondiabetic patients. The long-term outcome of patients with diabetes after revascularization is also adverse. Although our group found no difference in the acute outcomes of angioplasty in diabetic and nondiabetic patients, the long-term outcome was clearly worse for the diabetic group. The NHLBI PTCA Registry documented increased post-procedure mortality for angioplasty patients with diabetes (3.2% versus 0.5%). Diabetes also confers a worse long-term outcome in patients undergoing bypass surgery. The Society of Thoracic Surgery database showed that surgical risk for diabetic patients is greater than for nondiabetic patients: 3.7% versus 2.7%, with greater risk for those requiring insulin.

Diabetes imparts a number of metabolic derangements that result in progression of atherosclerosis and the occurrence of cardiac events. The presence of hyperglycemia, abnormal lipid metabolism, and insulin resistance, coupled with frequently occurring hypertension, all result in acceleration of the atherosclerotic process. Hyperglycemia results in altered endothelial cell function by blocking the production of nitric oxide and leads to the production of increased oxidative stress. The presence of insulin resistance also results in liberation of free fatty acids from adipose tissue and leads to a cascade resulting in enhanced oxidative stress and reduction in nitric oxide production. Diabetic patients also have increased production of endothelin, which results in vasoconstriction. The presence of diabetes has many other effects on the vascular wall, including a decreased synthesis of collagen and increased production of matrix metalloproteinases. Platelet function is also altered in diabetes. Elevated blood glucose levels produce activation of protein kinase C and increased formation of oxidative species. Diabetic patients also have increased platelet activation and decreased inhibitors of platelet activity. The glycoprotein IIb/IIIa receptors are upregulated, leading to platelet aggregation. Diabetic patients also have decreased fibrinolytic activity.

The Society of Thoracic Surgery database showed that the surgical patients who had follow-up angiography and those operated on, regardless of their diabetic status, is inconsistent with the outcome of diabetic patients treated medically or with PCI. This may be indirect evidence of a protective effect of surgery.

What Could Have Been the Explanation for Superior Outcomes in Surgical Patients in the Surgery Versus Balloon Angioplasty Trials?

Long-term survival in the BARI and EAST trials was not driven by excess operative mortality but rather by events occurring in the follow-up period. The differences in completeness of revascularization, reocclusion of dilated arteries, or progression of disease may all have contributed to the superiority of surgery. The EAST trial mandated 1- and 3-year angiographic follow-up and proved instructive regarding completeness of revascularization. At the 1-year angiographic follow-up, the percentage of revascularized segments was 59% in the angioplasty cohort versus 88% in the surgery group. By 3 years, the numbers were 70% for angioplasty and 87% for surgery. Disease progression in segments that were not treated is greater in patients with diabetes and, when combined with restenosis, results in much more jeopardized myocardium than is seen with bypass surgery. Examination of the patients receiving bypass surgery in the BARI randomized trial combined with the eligible but not randomized registry patients having surgery shows significantly greater mortality at 5 years for the patients with diabetes. However, the difference in cardiac mortality at 5 years was not significant (5.8% for diabetic patients versus 4.7% for nondiabetic patients). The significantly increased mortality was primarily a result of excess noncardiac mortality (12.2% versus 4.8%). The similar cardiac mortality in patients operated on, regardless of their diabetic status, is inconsistent with the outcome of diabetic patients treated medically or with PCI. This may be indirect evidence of a protective effect of surgery.

The BARI surgical patients who had follow-up angiography were also examined for graft patency. The average interval between surgery and follow-up angiography was 3.9 years. Surprisingly, there was no difference in patency of the internal mammary artery grafts (89% among patients with diabetes versus 85% among patients without diabetes) or for
vein grafts (71% for patients with diabetes versus 75% for patients without diabetes). This similarity of graft patency between diabetic and nondiabetic patients may partially explain the similar cardiac mortality seen in the BARI surgical patients.

The potential protective effect of bypass surgery among diabetic patients after myocardial infarction was evident from analysis of the BARI patients. All diabetic patients who were eligible for the trial and subsequently underwent revascularization were evaluated.24 Patients with diabetes (n=641) were compared with patients without diabetes (n=2962). Five-year mortality was 20% in the diabetic group and 8% in the nondiabetic group. After myocardial infarction, the patients who had undergone previous bypass surgery had a dramatically lower mortality rate than those treated with angioplasty (relative risk, 0.09; 95% CI, 0.03 to 0.29). This protective effect after myocardial infarction was much more dramatic than the effect in patients who did not have infarction. The risk ratio for diabetic surgical patients who did not suffer myocardial infarction was 0.65 compared with those undergoing percutaneous intervention. There was no protective effect of surgery compared with PTCA in patients who did not have diabetes. The completeness of revascularization may compensate for progression of disease. This was especially true in the BARI trial, in which the marked benefit seen in diabetic patients was limited to that large majority receiving internal mammary artery grafting to the anterior descending coronary artery. Because internal mammary artery grafts are patent in approximately 90% of the patients in late follow-up, they may serve as a protective conduit to the most important coronary artery should progression of disease occur in the anterior descending coronary artery.23,25 This protection would not be afforded in the angioplasty group even if restenosis did not occur because of potential progression of disease or plaque rupture in that proximal or mid anterior descending vessel.

Completeness of revascularization was also evaluated in a PCI study from Israel. The study included 352 patients with diabetes mellitus and multivessel disease. Revascularization was judged to be complete in 26.7% and incomplete in 73.3% of the patients. Five-year survival in the patients who had complete revascularization was 94.5%, compared with 83.0% for those with incomplete revascularization. Incomplete revascularization was the most powerful predictor of mortality.26

How Did Stenting Change the Results of Percutaneous Coronary Artery Intervention in Patients with Diabetes?

There have been significant improvements in the acute outcomes of patients undergoing PCIs, and the most important has been stenting. The patients with diabetes in the 1985–1986 NHLBI PTCA registry have been compared with the contemporary patients in the 1997–2001 NHLBI Dynamic Registry. Stenting was used in 87.5% of the latter registry and in none of the former. In the most recent registry, angiographic success was better (94.8% versus 78.1%), abrupt closure less (0.9% versus 2.2%), and the hard end points of death (1.9% versus 4.3%), myocardial infarction (1.0% versus 7.4%), and in-hospital CABG surgery (0.8% versus 6.2%) much improved.27 How have these improvements in technique and acute results translated into sustained benefit for multivessel-disease patients with diabetes?

There are no revascularization trials specific to diabetic patients with multivessel disease; however, 3 trials have evaluated revascularization strategies using stenting compared with coronary bypass surgery in patients with multivessel disease. They are the Arterial Revascularization Therapy Study (ARTS),28 the Stent or Surgery (SOS) trial,29 and the Argentina Randomized Trial of Angioplasty versus Surgery (ERACI II).30 Each of these was a strategy trial comparing bypass surgery with percutaneous intervention using stents. The ARTS trial was composed of 1205 patients with multivessel disease randomized to CABG or stenting and followed up for 3 years. Overall survival without stroke or myocardial infarction was 87.2% for PCI and 88.4% for CABG. Repeat revascularization was substantially less than previous balloon angioplasty trials for patients randomized to stenting (21.2% at 1 year and 26.7% at 3 years). In this trial, however, diabetes was a strong independent predictor of events at 3 years. Among the 208 patients with diabetes, 3-year mortality was 7.1% for those randomized to stenting, compared with 4.2% for CABG. Event-free survival for the stent and CABG groups was 52.7% versus 81.3%, largely driven by repeat interventions. When the ARTS trial is compared with the BARI trial for 1-year mortality, there is apparent improvement among diabetic patients treated currently. The 1-year mortality for diabetic patients in BARI randomized to surgery was 6.4%, compared with ARTS, 3.1%. Likewise, in the BARI PTCA group, the 1-year mortality in diabetic patients was 11.2%, compared with ARTS, 6.3%. Such improvement in outcomes may reflect selection differences between BARI and ARTS or may reflect improving medical management of diabetic patients in the current era.

The SOS trial was a multicenter trial evaluating 988 patients with multivessel coronary artery disease between CABG and stenting. Patients with diabetes represented only approximately 15% of this trial population and were not analyzed separately. Overall, 2-year mortality was 5% in the stent group and 2% in the surgery group. The ERACI II trial (n=230), comparing stenting and surgery, showed no difference in survival at follow-up (96.4% versus 95%).

The previously referenced meta-analysis8 examined the stent trials, but they were underpowered and of too limited duration to detect a difference between stenting and surgery for patients with diabetes and multivessel disease. In the
absence of such trials, it is important to examine the outcome of contemporary registries of patients undergoing stenting or surgery. Randomized trials have the advantage of eliminating bias in the selection process; however, registries facilitate inclusion of broader segments of the population that may not have been addressed in randomized trials and therefore more accurately reflect clinical practice.

The NHLBI Dynamic Registry is an investigation of contemporary patients undergoing PCI collected from participating hospitals over a defined time period. Multivessel-disease patients, including diabetics, treated in the stent era were compared with patients with multivessel disease treated in the BARI trial. The clinical features of the 857 BARI-eligible patients from the Dynamic Registry were compared with 904 patients who were randomized to angioplasty in the BARI trial. Stents were used in 76% of the Dynamic Registry patients and glycoprotein IIb/IIIa receptor antagonists in 24%. Fewer lesions were attempted in the contemporary group (1.53 versus 2.56). There has been a dramatic decrease in abrupt closure in contemporary angioplasty (1.5% versus 9.5% in BARI) and in in-hospital bypass graft surgery (1.9% versus 11.2% in BARI). There was no difference in hospital mortality. Among the diabetic patients in these 2 cohorts, 1-year survival for the BARI surgery patients was 93.6%, compared with BARI PTCA, 88.1%. The NHLBI Dynamic Registry patients with characteristics similar to those of the BARI patients had a 92.1% survival at 1 year. These are not concurrent patient groups and may reflect the significant differences between randomized and registry patients and improved medical management of patients in the current era. Nonetheless, the introduction of stenting has obviously had a dramatic impact on reducing the need for in-hospital surgery and the subsequent 1-year revascularization rates. A registry conducted by the Northern New England Cardiovascular Disease Study Group evaluated patients undergoing revascularization procedures in a large regional database linked to the national death index to evaluate 5-year mortality. A subset of 7159 patients with diabetes treated between 1992 and 1996 was examined. Of those, 2766 were similar to the patients with diabetes randomized in the BARI trial. The patients selected for percutaneous intervention (n=736) were compared with those selected for CABG surgery (n=2030). After risk adjustment, hazard ratios (HRs) were computed along with 95% CIs. After adjustment of the outcomes for the differences in the baseline characteristics, the patients treated with percutaneous intervention were seen to have higher mortality (HR=1.49; 95% CI, 1.02 to 2.17; \(P=0.037\)). Among the patients with 3-vessel disease, the HR was 2.02 (95% CI, 1.04 to 3.91; \(P=0.038\)). Among the patients with 2-vessel disease, the difference was less (HR=1.33; 95% CI, 0.84 to 2.1; \(P=0.21\)). Although there was a significant difference overall, it did not reach statistical significance for 2-vessel-disease patients.

Is Diabetes Still an Important Predictor of Outcome in the Contemporary Stenting Era?

In the stenting era, there is ample evidence that diabetes remains an important factor for patients undergoing revascularization. The NHLBI Dynamic Registry, a cooperative registry sponsored by the NHLBI, collects consecutive patient data over a defined time frame to get a snapshot of the practice of interventional cardiology. Phase 1 and phase 2 of the registry, extending from the years 1997 through 1999, included 3576 patients without diabetes and 1056 with diabetes. During this period, 73% of the patients received stents and 27% glycoprotein IIb/IIIa receptor blockers. Single-vessel disease was more common in the nondiabetic patients and triple-vessel disease in the diabetic patients (32% in the diabetic group and 23% in the nondiabetic group). Hospital outcomes were not significantly different, but there was a 1% higher mortality rate in the diabetic population (diabetic patients, 2.3%; nondiabetic patients, 1.3%). At 1 year, the diabetic patients had a significantly higher mortality (relative risk, 1.80; 95% CI, 1.35 to 2.41).

A recent registry of contemporary patients from the Hospital Corporation of America database was compiled. More than 3000 patients were enrolled, and although follow-up was incomplete, approximately 24% of the enrolled patients had diabetes mellitus. Acute outcomes between diabetic and nondiabetic patients in hospital were not different; however, the 1-year survey showed that the patients with diabetes had more target lesion revascularization (13.6% versus 8.9%) and were 1.8 times more likely to experience a major adverse cardiac event. Some other contemporary observations regarding stent implantation are available from the United States and from Europe. A trial from Scotland included 831 patients with diabetes. Follow-up over a period of 2.3 years showed that the diabetic patients, compared with nondiabetic patients, had a worse prognosis after both surgery (adjusted HR, 1.43) and percutaneous intervention (HR, 2.58). However, patients with diabetes and more severe disease fared better with surgery. Those diabetic patients with impaired left ventricular function and triple-vessel disease had an adjusted HR for death of 3.58. This registry supports the findings of the BARI trial even in the modern era with stenting. The registry from the Lenox Hill Hospital classified patients with no diabetes (n=501), diabetes mellitus treated with oral agents (n=102), and patients with diabetes mellitus treated with insulin (n=86). Survival was lower for those diabetic patients treated with either oral agents or insulin (85% and 86% compared with 95% for patients without diabetes).

The PRESTO trial was a large randomized trial evaluating the drug tranilast for restenotic events after stenting. There were 2694 diabetic patients in that trial and 8798 without diabetes. Diabetes was independently associated with death at 9 months, with a risk ratio of 1.87. Once again, it is apparent that diabetes carries an increased mortality risk in patients treated with percutaneous interventions. A recent report from
Italy included 133 patients with type 2 insulin-dependent diabetes who underwent stenting from 1992 to 2001.\textsuperscript{38} Seventy-six percent of these patients had multivessel disease. Clinical follow-up at 19.5 months revealed 18% mortality and a major adverse cardiac event rate of 40.5%. All of these patients were treated with stent implantation.

These registries continue to point to excess mortality in diabetic patients treated with stenting. Registries comparing the revascularization methods show superior outcomes for patients with diabetes and multivessel disease who undergo bypass surgery compared with those who undergo percutaneous intervention. Even with the advent of stenting and other adjunctive therapies, surgery continues to be the more successful therapy in this cohort.

Should Drug-Eluting Stents Change the Selection for Revascularization in Diabetic Patients With Multivessel Disease?

Because the opportunity for altering the outcome for patients undergoing percutaneous intervention by use of drug-eluting stents is related to the ability to reduce restenosis, we should first understand the magnitude of restenosis reduction that is being achieved. It is also important to understand how a reduction in restenosis will affect the hard end points of death and myocardial infarction in such patients. In the controlled randomized trials, the reduction in reintervention was very large. In the SIRIUS trial of sirolimus-eluting stents, 279 patients with diabetes mellitus were randomized. At 9 months, target lesion revascularization was reduced from 22.3% with bare-metal stents to 6.9% with drug-eluting stents, and major adverse cardiac events were reduced from 25% to 9.2%.\textsuperscript{39} However, one must remember that these trials mandated an angiographic follow-up, and therefore, revascularization was driven not only by clinical necessity but also by the angiographic appearance of narrowing within the treated segment even in patients who did not have documented ischemia. Registries of the broad population of patients who have received bare-metal stenting outside of clinical trials have shown very different results. Among patients not having routine angiographic follow-up, the reduction in reintervention is much less. The RESEARCH Registry conducted in Rotterdam evaluated the first 6 months of drug-eluting stent use and compared that result with bare-metal stent use the year before drug-eluting stents were available. In patients followed up for 6 months, reintervention occurred in only 2.7% of the drug-eluting stent group, compared with 7.1% in the bare-metal stent group. By 1 year, that 4.4% difference had widened to slightly more than 6 procedures avoided per 100 patients treated.\textsuperscript{40}

There is other evidence that the reintervention rate in patients treated with bare-metal stents may not have been as high as perceived from the randomized trials. A review of the NHLBI PTCA registry collected in the third wave in 2001 and 2002 showed that among 1631 patients, the 1-year reintervention rate was 210 (13.1%). However, when considering which patients had reintervention on the treated segment, it was found that the potentially reducible 1-year target segment revascularization rate was between 7.9% and 9.4%.\textsuperscript{41} Examination of a large database, the Goodroe Data Warehouse (Goodroe Healthcare Solutions, Norcross, Georgia), which was composed of a consecutive series of 14 075 patients treated between December 1998 and September 2002, reveals the limits of clinical restenosis reduction. The overall repeat revascularization rate at 1 year was 12.6%; however, only 56% of these patients had revascularization to the same target segment as originally treated, and 64% of the patients who underwent target segment revascularization also had revascularization to treat other disease.\textsuperscript{42} Another pre–drug-eluting stent observation showed that among 3177 consecutive patients, the 1-year total reintervention rate was 9.7%.\textsuperscript{43} One can see that the reduction in restenosis in “real-world” patients depends on the reintervention risk that was present before the introduction of drug-eluting stents, as well as the ability of drug-eluting stents to obviate the need for reintervention. It is likely that this single-digit opportunity to avoid a reintervention will be higher in diabetic patients, but with longer follow-up and progression of disease, we will not see the kind of reductions in reinterventions that were suggested by the randomized trials.

A temptation that must be avoided is broadening the selection of intervention patients to such a degree that increased acute complication rates are accepted so as to take advantage of the availability of drug-eluting stents and the perception of decreased restenosis. A population-based survey of CABG surgery patients was reviewed at the Mayo Clinic.\textsuperscript{44} Only 6% of these patients had lesions that matched the inclusion criteria for drug-eluting stents in trials, 40% had lesions that could be stented but were not in the initial trials, and 17% had lesions considered technically difficult for stent placement. Thirty-seven percent had lesions clearly unsuitable for percutaneous intervention. An aggressive application of drug-eluting stents would be possible in almost one half of the coronary surgery patients, but it is unclear what the clinical outcome of such a strategy would be. It should be remembered that restenosis is not fatal but that complications can be.

The other question to be considered is whether a reduction in restenosis will result in improvement in the hard end points of myocardial infarction and death. The observation from the previously mentioned RESEARCH Registry in Rotterdam showed that 1-year mortality was virtually identical during the pre–drug-eluting stent era and after the routine use of sirolimus-eluting stents. The largest evaluation of the impact of restenosis in more than 3000 patients showed that patients with and without restenosis had no difference in 6-year survival.\textsuperscript{45} Even when the randomized trials are examined, there is no apparent impact on death or myocardial infarction.
A meta-analysis of 10 randomized drug-eluting stent trials involving 5066 patients with 6- to 12-month follow-up showed that sirolimus- and paclitaxel-eluting stents had mortality and myocardial infarction risks during the first year of follow-up equivalent to those of the bare-metal stent cohorts in those trials.\textsuperscript{46}

Long-term cardiovascular events are often caused by disease progression at sites not treated with stents. Progression of disease was highlighted in the experience of the group from Toulouse, France. Ninety-nine diabetic patients with multivessel disease were treated with stenting. Fifty-six percent of these patients had 3-vessel disease, and 2.3 stents were implanted per patient. At 14 months of follow-up, there were 4 deaths and 21 repeat revascularizations. Of those, 9 were because of restenosis only, whereas 9 others were because of restenosis plus new progressive disease and 3 were for progressive disease independent of the originally treated segment.\textsuperscript{47}

A recent pooled analysis of individual patient level data from 4 second-generation stent trials also points to the impact of progression of disease. Although not specific for diabetic patients, 5-year follow-up documented that twice as many late cardiac events occurred because of progression of disease as occurred because of restenosis at the originally treated site.\textsuperscript{48} Events caused by the treated lesion occurred in 20.3% of the patients, most of them in the first year as result of restenosis. There were very few target lesion–specific events after the first year. Conversely, events related to untreated segments of the coronary tree continued and affected 37.9% of the patients by 5 years. At the end of 5 years, only 8.9% of patients had events limited to restenosis of the target lesion originally treated, whereas 37.9% had events that included nonrestenotic segments.

The need to focus on more aggressive long-term prevention was highlighted by a recent study from Denmark. A multipronged approach to prevention of vascular disease progression has gained traction in recent years. A small multifactorial intervention study in patients with type 2 diabetes illustrates this point.\textsuperscript{49} Patients were randomized to a conventional treatment according to national guidelines of Denmark or to receive intensive behavioral modification and pharmacological therapy targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria in addition to aspirin therapy. Hemoglobin A\textsubscript{1c} values were improved in patients with the intensive therapy, and the end points of cardiovascular death, nonfatal infarction, stroke, revascularization, and amputation were reduced more than 50% (HR, 0.47; 95% CI, 0.24 to 0.73).

Some have suggested that more extensive use of drug-eluting stents to include non–flow-limiting lesions and angiographically uninvolved segments may reduce future clinical events. Such strategies must undergo rigorous clinical trials to prove that they do not incur increased risks of thrombosis, impaired side-branch perfusion, or very late unknown complications of the “full metal jacket.”

The practice of interventional cardiology continues to make significant strides in technical performance. Expansion of selection from single-vessel, highly symptomatic patients with ischemia to broader inclusion of patients with diffuse coronary artery disease has occurred. Whereas most patients with multivessel disease have had outcomes comparable to those of surgical patients, those patients with more extensive multivessel disease, and especially the diabetic population, have fared better with surgery throughout the era of balloon angioplasty and stenting. As yet, there is no evidence that the hard end points of death and myocardial infarction will be dramatically altered by the use of drug-eluting stenting, and this is a question that desperately needs answers.

To that end, a new trial is beginning. This trial, FREEDOM (Future Revascularization Evaluation in patients with Diabetes Mellitus: Optimal Management of Multivessel disease), is designed to evaluate whether PCI with drug-eluting stenting is more or less effective than the coronary artery bypass surgery. In this study, sponsored by the NHLBI, 2400 patients with diabetes and multivessel disease will be randomized on a 1:1 basis to PCI or CABG. The study duration will be 5 years, and the primary end point will be all-cause mortality, nonfatal myocardial infarction, and stroke. Longer-term observation of these patients will also be important, because meta-analysis of the existing trials of multivessel disease showed a significant difference favoring surgery only after the 3-year time point. Two other trials are in the preimplementation phase. The SYNTAX trial compares the Taxus stent with bypass surgery in patients with multivessel disease, including 3-vessel and left main disease. There will be a diabetic subset. The Veterans Administration system is planning another trial specific for diabetic patients with multivessel disease randomized to drug-eluting stenting or surgery. While awaiting the outcome of these trials, it will be important for physicians to carefully weigh the previous evidence favoring bypass surgery for patients with diabetics and extensive multivessel disease before concluding that drug-eluting stenting has completely altered the prudent choice.

References


The choice of revascularization in diabetic patients with multivessel coronary artery disease is a critical issue in cardiovascular therapy. Diabetes mellitus is an emerging epidemic in the United States, with almost 16 million confirmed cases and an additional 20 million patients with impaired glucose tolerance, most destined to progress to diabetes. Moreover, in the 20-year interval from 1979 to 1999, the mortality rate in the United States from diabetes has risen more than 30%. Diabetes mellitus, either type 1 or type 2, is a very strong risk factor for the development of coronary artery disease and stroke; 80% of all deaths among diabetic patients are attributed to atherosclerosis, compared with approximately 30% among nondiabetic patients.

Pathogenesis of Diabetic Cardiac Morbidity and Mortality

Diabetic patients are at particularly high risk for acute and long-term complications in the presence of atherosclerosis because of the problems with hyperinsulinemia, hyperglycemia, dyslipidemia, and hypercoagulability. In addition to the global effects of these factors, the associated obesity, endothelial dysfunction, and increased inflammatory markers make these patients complex and challenging. Diabetes mellitus accelerates the natural course of atherosclerosis in all groups of patients and involves a greater number of coronary vessels with more diffuse atherosclerotic lesions. Coronary angiographic studies in diabetic patients have shown significantly more severe proximal and distal atherosclerosis. In addition, rates of plaque ulceration and thrombosis have been found to be significantly higher in diabetic patients. A complex interaction may exist between diabetes and inflammation that may propagate coronary atherosclerosis and endovascular thrombosis. Coronary atheroma of diabetic patients has been found to be more lipid-rich and to contain a greater quantity of macrophages than that of nondiabetic patients. Blood from diabetic patients with coronary artery disease has been found to have higher concentrations of several inflammatory proteins, including C-reactive protein, tumor necrosis factor-alpha, platelet-derived soluble CD40 ligand, and enhanced expression of adhesion molecules such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1. All of these factors can be accentuated by unstable coronary artery disease, but they may in turn signal the development of such cardiac complications.

Finally, in the face of percutaneous coronary interventions (PCIs), it is unknown whether increased restenosis or generalized coronary instability in areas remote to those in which intervention took place bears more impact on long-term patient outcome after multivessel PCI. However, it is clear that this issue is clinically most important in the diabetic population.

Debate on Revascularization Strategy for Diabetic Patients With Multivessel Coronary Artery Disease

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Randomized Trials of Angioplasty Versus Surgery

The most consistent finding in studies comparing PCI and coronary artery bypass graft surgery (CABG) has been the essentially identical mortality and myocardial infarction (MI) rates between the two treatment strategies at follow-up, the only significant difference being the rate of repeat revascularization during the first year, which favored coronary bypass surgery. Thus, when choosing a revascularization strategy in nondiabetic patients, the only issue is merely that of repeat PCI, an issue that is minimized with drug-eluting stent implantation.

Outcomes in the diabetic subgroups of these trials have been intriguing. Although the outcomes between PCI and CABG in diabetics have not generally differed, the long-term outcomes of the Bypass Angioplasty Revascularization Investigation (BARI) indicated that the diabetic subgroup had significantly higher mortality with PCI than with CABG. This has been verified in the 8-year follow-up of the Emory Angioplasty versus Surgery Trial (EAST) and further supported by several large-scale registries, principally the Northern New England Cooperative trial.

Conversely, these results have not been duplicated in the BARI registry (constituted of those patients eligible but not randomized), which demonstrated similar outcomes between diabetic patients treated with PCI and CABG. This could reflect a clinically significant case-selection bias by either physician or patient preference as practices in the BARI registry that may be able to minimize the handicap of multivessel balloon angioplasty compared with CABG in the BARI randomized trial (Figure 1).

Three randomized trials have compared CABG with implantation of tubular slotted metallic stents for multivessel disease: the Arterial Revascularization Therapies Study (ARTS), the Stent or Surgery trial (SOS), and Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). In all three trials, the main difference between the two strategies was the greater need for repeat revascularization because of restenosis after stenting.

The ARTS trial reported specifically on diabetic patients. The inclusion of stroke as part of the combined end point allowed the identification of diabetic patients as a particularly high-risk group for periprocedural stroke after CABG. ARTS again documented that CABG was associated with less need for repeat revascularization procedures than metal stent implantation. At 3-year follow-up of the entire ARTS study population, the composite end point of death, nonfatal MI, or stroke was similar between the two treatment strategies (Figure 2), again isolating the restenosis-related target lesion revascularization events as the driving force of the superiority of CABG.

The AWESOME trial randomized high-risk patients (predominantly with previous bypass surgery) to percutaneous intervention and CABG and observed no differences in survival between the stent group and the bypass group at 3 years. The study has not observed differences in the survival between these two strategies and the diabetic or even other high-risk populations. Therefore, the results of the BARI randomized trial have not been duplicated in any other clinical setting thus far. If one combines this fact with the continuing evolution in technique and equipment for PCI, then it is understandable why the suggestions drawn on the basis of the diabetic subgroup analysis of BARI were not adopted by the medical community, as recently reported.

Causes of Differences in Mortality Noted in the BARI Trial

An important observation in the BARI trial was that approximately 50% of the survival benefit conferred by CABG was the result of an 8-fold decrease in mortality in diabetics.
treated with CABG with Q-wave MIs compared with the PCI group. The coronary bypass group with Q-wave MIs and diabetes had the same survival as the nondiabetic CABG group. Moreover, any survival advantage in the diabetic CABG group was conferred strictly upon those who had a left internal mammary artery bypass graft to the left anterior descending coronary artery (LAD). Patients who did not have that graft or who had a vein graft to the LAD had mortality rates identical to those of the percutaneous intervention group.

Therefore, one may deduce that increased restenosis in diabetics is only one issue that needs to be addressed in optimizing percutaneous intervention in diabetic subjects. Complete vessel occlusion is a major technical problem, and the potential protective effect of the left internal mammary artery graft needs to be accounted for as well. In addition, the different character of restenosis in diabetes with coronary angioplasty compared with nondiabetics is important in attempts to unravel the causes of the differential mortality in these trials. Studies have demonstrated that the rate of occlusive restenosis with balloon angioplasty in diabetics is substantially higher than in nondiabetics. Importantly, the prognosis of occlusive restenosis is markedly worse than nonocclusive restenosis. Thus, one can infer that any technique that reduces occlusive restenosis in diabetics may contribute to a subsequent reduction in mortality. In addition, strategies to arrest disease progression and subsequent MIs over the ensuing years could also help redress the mortality imbalance observed in the BARI and EAST trials.

One important retrospective study compared a diabetic group treated with PTCA to stenting with systematic follow-up and indicated that stents have a major impact not only on reducing restenosis in diabetics but also, importantly, on reducing occlusive restenosis (from 13% to 4%), translated into a reduced late mortality rate (Figure 3).

Another important observation of the BARI trial was that the predominant benefit of bypass surgery was in insulin-treated diabetes. This is in keeping with the observation that insulin-requiring diabetics have much higher rates of restenosis after balloon angioplasty than those treated with oral agents or diet, and, in addition, they have an increased rate of disease progression. In a recent large-scale database analysis in a population treated with metallic stenting for multivessel disease, we found no difference between insulin-treated and non–insulin-treated diabetics with respect to target lesion revascularization. Because diabetics are characterized by a different arterial remodeling process, the routine use of intravascular ultrasound–guided stenting may have accounted for this elimination of difference between insulin-dependent and non–insulin-dependent diabetics in this study.

None of the randomized trials discussed thus far have used what one would consider contemporary therapies for reducing adverse ischemic events in diabetics: adjunctive pharmacology and drug-eluting stents.

Impact of Adjunctive Pharmacology
A large body of evidence from prospective, randomized, double-blind clinical trials supports the use of platelet glycoprotein IIb/IIIa inhibitors during PCI, derived primarily from the abciximab clinical trials. A prespecified analysis of clinical outcomes in diabetics was included in the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT) trial (20% of total cohort, or 491 patients with diabetes). Patients were assigned to a strategy of stent implantation plus placebo, stent implantation plus abciximab, or angioplasty plus abciximab. For diabetic patients receiving a stent and abciximab, compared with stent alone, there was a 50% reduction in death, nonfatal MI, or urgent revascularization rate at 6-month follow-up. In addition, diabetics were less likely to require repeat target-vessel revascularization if they were treated with stent plus abciximab compared with either stent plus placebo (16.6%, P=0.02) or angioplasty plus abciximab.
abciximab (18.4%, \(P=0.008\)). Thus, it appears that the benefit of abciximab is additive to the benefit of stent implantation in diabetics. One-year mortality was also marginally lower with stent plus abciximab versus stent plus placebo (1.2% versus 4.1%, \(P=0.11\)).

Moreover, a meta-analysis of the 3 abciximab trials (encompassing both PTCA and stenting) revealed a significant (50%) reduction in 1-year mortality. In another trial, which compared Integritin with placebo in coronary stenting in diabetics, a similar 50% reduction in 1-year mortality was observed with the glycoprotein IIb/IIIa inhibitors.43

The ISAR-SWEET (Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics) is the latest trial44 that investigated the role of abciximab in the clinical and angiographic outcome of diabetic patients undergoing bare-metal stenting and receiving 600 mg of clopidogrel loading before PCI. Although abciximab therapy had no impact on death or MI rates (8.3% versus 8.6%), it reduced significantly the rates of angiographic restenosis (29% versus 38%) and target lesion revascularization (23% versus 30%). These results suggest that aggressive oral antiplatelet therapy before PCI optimizes acute outcomes and that abciximab may render a restenosis benefit in diabetic patients receiving bare-metal stents.

Interestingly, preliminary observations indicate that insulin sensitizers such as the glitazones can impart a significant reduction in intimal hyperplasia in stented diabetes.45 It is possible that the anti-inflammatory effects of these drugs may contribute to this observation, as well as its ability to reduce hyperinsulinemia and insulin resistance with their independent growth factor potential, which may contribute to both restenosis after PCI and atherosclerosis. In a balloon angioplasty study,46 angiographic restenosis indeed correlated with higher insulin levels during an oral glucose tolerance test. Hyperinsulinemia has also been associated with greater levels of proatherogenic small dense LDL particles.47 In a cohort study, diabetic patients with low hemoglobin A1C had 1-year cardiac event rates similar to those of nondiabetics, as opposed to diabetics with poor glycemic control, who had significantly worse major adverse cardiac event rates (26%, 24%, and 37%, respectively).48

The increasing use of insulin-sensitizing agents for long-term glycemic control in diabetics is therefore likely to also affect cardiovascular outcomes after coronary artery stenting in future trials.

### Impact of Drug-Eluting Stents

The most profound impact on restenosis has been obtained with the use of drug-eluting stents. Data for both the TAXUS II trial49 and the TAXUS IV trial50 using paclitaxel and the SIRIUS trial using sirolimus have yielded encouraging results in diabetic subgroups.31,50

In the SIRIUS trial, 27% of the 1048 patients were diabetic. This group of patients had an approximately 75% reduction in both restenosis and target vascular revascularization with sirolimus-eluting stents compared with bare metal stenting. Although glycoprotein IIb/IIIa inhibitors were used in 60% of the patients, this reduction was seen in all subgroups irrespective of IIb/IIIa inhibitors.50

Being the first large drug-eluting stent study, SIRIUS led to the identification of an imperfect drug-eluting stent implantation technique, namely, the mismatch between balloon-injured and stent-covered vessel segments leading to a relative excess of margin restenosis, particularly in diabetics. This was improved in subsequent studies that modified the technique of implantation of drug-eluting stents. We believe that this can explain the suppression of persistent restenosis in subsequent drug-eluting stent trials with the same or other stents.32,51,52

Drug-eluting stents have demonstrated a profound reduction of restenosis in diabetics (Figure 4). We can therefore conclude that short-term outcomes, 1-year mortality, and restenosis can potentially be markedly improved with contemporary techniques by use of both drug-eluting stents and IIb/IIIa inhibitors.

### Can We Slow the Progression of Coronary Disease in Diabetics?

The profound importance of slowing disease progression, as noted in the above discussion, is also highlighted by the fact that attempts at secondary prevention efforts in past randomized trials were substandard when judged by contemporary best practice. The average LDL levels in patients on entry to the BARI trial were virtually identical to those at the end of 5 years: 143 mg% at the beginning and 141 mg% at the end.26 Although there is no evidence in the BARI trial that there is a specific difference in outcomes between groups who had their lipoprotein profiles improved and those who did not, the above finding is certainly proof that secondary prevention did not approximate the more rigorous clinical standards of contemporary practice.

Today, pharmacological antiatherosclerotic intervention in diabetics is directed toward the hyperinsulinemia, hyperglycemia, hypertension, hyperlipidemia, and hypercoagulability that accompany diabetes. In addition, the Heart Outcomes Prevention Evaluation (HOPE)53 revealed that ACE inhibitors can specifically improve vascular outcomes independently of their effect on blood pressure in the diabetic subgroup. Although the United Kingdom diabetes study, UKDG, indicated that aggressive glycemic control per se did not reduce large-vessel vascular events in that population,54 there are other lines of evidence to indicate that aggressive risk factor control directed toward lipids can have positive effects on long-term outcomes. Importantly, in the Scandinavian Simvastatin Survival Study (4S), diabetics who were placed on statins had atherosclerotic event rates comparable to those of the treated nondiabetic group: a 30% to 40% reduction compared with placebo.55 This evidence supports the hypothesis that aggressive risk factor control will favorably influence the long-term outcomes in the diabetic popu-
lation and assist in eliminating the gap between PCI and CABG patients. In addition, other treatments, including long-term dual antiplatelet therapy with aspirin and clopidogrel, show promise in minimizing atherothrombotic events in the diabetic population. Although they have not been specifically studied in the context of diabetes and multivessel coronary artery disease, they also hold the potential to minimize long-term events after successful revascularization.56,57

What Should the Current Recommendations Be in the Treatment of Diabetics With Multivessel Disease?

With contemporary treatment, non–insulin-requiring diabetic patients treated with oral hypoglycemic agents or dietary therapy can fare as well with percutaneous intervention and stenting as with bypass surgery. The remaining advantage of bypass surgery in this group is in terms of the excess target-vessel revascularization rates in the PCI with balloon angioplasty or bare-metal stent groups. In the era of drug-eluting stents, the issue of repeat revascularization because of restenosis in these patients does not seem to be problematic, because it has been <5%.32,50 Patients with diffuse disease and insulin-requiring diabetes still require a cautious approach, but these constitute a distinct minority of diabetic patients. The angiographic distribution of coronary artery disease plays an important role in case selection.

Future Directions

Two major trials are under way to address the remaining issues in this field: the BARI 2D and FREEDOM trials. The BARI 2D trial is a 2800-patient trial randomizing a 2×2 design between insulin-sensitizing versus hyperglycemic therapy along with a second arm of revascularization versus medical therapy.58 The second trial, FREEDOM (Figure 5), will directly compare multivessel bypass surgery with multivessel stenting with drug-eluting stents plus abciximab in 2300 diabetic patients with 3-year follow-up for death, nonfatal MI, or stroke and will have a parallel registry of 2000 patients.

Conclusions

Although earlier data from randomized trials and registries indicated an advantage of CABG, this has not been translated
to clinical practice because the major advances in technique and equipment of PCI, with a major focus on the introduction of drug-eluting stents and the implementation of more aggressive adjunctive pharmacology during and after PCI, have substantially improved clinical outcomes. Therefore, for diabetic patients with an anatomy suitable for drug-eluting stents combined with glycoprotein IIb/IIIa inhibitors and aggressive risk factor control (targeting glycemic control and lipids abnormalities), percutaneous intervention is a safe alternative with the promise of excellent long-term outcomes.

References


Response to Dangas and Moses
Spencer B. King III, MD

I completely agree that there have been important advances in the medical, surgical, and interventional care of patients with diabetes and multivessel disease. Drug-eluting stents will reduce restenosis, but there is no evidence as yet that they will improve survival. Cardiac events caused by progression of disease are twice as common over a 5-year follow-up period as are restenotic events with the use of bare-metal stents.

Speculation about how recent changes will enable percutaneous coronary intervention (PCI) to equal surgery in this difficult group of patients, of course, reflects what we all hope for. The weight of evidence from trials and matched controlled registries, however, tells another story. “Shoulda, woulda, coulda” is not good enough. I have several explanations why the Atlanta Falcons should have defeated the Philadelphia Eagles in the National Football League playoff game, but when I look objectively at the score, I remain disappointed.

I am also disappointed that we have not shown equivalent survival for multivessel diabetic patients with PCI compared with surgery. Reduction in restenosis will be an important step, but equivalent survival is what must be demonstrated. I hope the speculations about future outcomes of such patients treated with PCI will come true and allow better survival. The FREEDOM trial and the Veterans Administration trial, which is in the planning stages, are designed to answer this question. We anxiously await the results, and I hope for a tie at least. Meanwhile, the evidence and good clinical judgment should continue to guide revascularization choices.

Response to King
George Dangas, MD; Jeffrey W. Moses, MD

The practical approach of the majority of patients and physicians to opt for the less-invasive techniques whenever possible drives the quest to determine whether the results of multivessel revascularization with drug-eluting stents can be at least equivalent to those of bypass surgery with the FREEDOM trial. This trial is currently enrolling and is not anticipated to yield final results for at least 5 years.

In the meantime, we have to interpret and frequently are also forced to extrapolate the best possible and most current data available that are relevant to this subject. The recently presented 6-month results of the Arterial Revascularization Trial part II (ARTS-II) address many of the outstanding issues and will be discussed below (Patrick W. Serruys, MD, PhD, oral presentation at the Transcatheter Cardiovascular Therapeutics Conference, Washington, DC, September 2005).

The ARTS-II trial enrolled 607 patients with multivessel disease treated with the sirolimus-eluting stent, and the results were compared with those of the bypass surgery arm (n=605) and the bare metal stent arm (n=600) of the earlier, randomized ARTS trial; the inclusion and exclusion criteria of the two trials were identical. ARTS-II enrolled a higher percentage of patients with diabetes (26% versus 16% in ARTS-CABG and 19% in ARTS-Stent), hyperlipidemia (74% versus 58% in ARTS), and hypertension (67% versus 45% in ARTS). Lesions were also more frequently type C by the American College of Cardiology/American Heart Association classification in ARTS II (13% versus 8% in ARTS-CABG and moderately/severely calcified (31% versus 15% in ARTS-CABG and 18% in ATRS-Stent). In addition, the percentage of patients with triple-vessel revascularization was higher in
ARTS II (54% versus 28% to 30% in ARTS) and the mean number of lesions treated, 3.2 ± 1.1 versus 2.5 ± 1.0 in ARTS. Finally, the number of stents implanted was higher (3.7 ± 1.5 versus 2.8 ± 1.3) and the total stent length longer (73 ± 32 versus 48 ± 22 mm).

We itemized all these important details of the ARTS-II trial in comparison with ARTS to point out that the ARTS-II population appears to consist of higher-risk patients with more complex lesions that were treated with a greater number of as well as longer stents and with achievement of more extensive revascularization. Therefore, this documents the paradigm shift in “real-world” coronary stent implantation because of the advent of drug-eluting stents, and the inclusion of a greater number of diabetic patients in ARTS-II is of particular interest to this article.

The short-term results indicated an increase in periprocedural cardiac enzyme elevation to more than 5 times the upper normal value of 1.5% in ARTS-II versus 12.7% in ARTS-CABG and 6.2% in ARTS-Stent; the evolution of technique and equipment as well as usage of glycoprotein IIb/IIIa inhibitors in 32% of ARTS-II patients versus 0 in ARTS can explain these results. The 30-day composite end point of major cardiac and cerebrovascular events (MACCE) was 2.8% in ARTS-II, versus 6.3% in ARTS-CABG and 9.2% in ARTS-Stent (P < 0.01 for both comparisons). The subacute thrombosis rate in ARTS-II was 0.8%, which is lower than the 2.8% documented in the bare-metal stent arm of ARTS.

The 6-month MACCE rate was 6.4% in ARTS-II versus 9.0% in ARTS-CABG and 20% in ARTS-Stent; event-free survival curves are shown in the Figure.

Therefore, we can deduce that the application of this interventional approach in the ARTS-II population seems to have fulfilled our expectations: (1) higher-risk patients were treated, (2) more complex lesions were targeted, (3) more complete revascularization was achieved, (4) a greater number of and longer stents were used, (5) the subacute thrombosis rate was lower than with bare-metal stents, (6) periprocedural enzyme elevation was also suppressed, (7) repeat revascularization was profoundly suppressed, and (8) the 6-month MACCE rate was lower than in both the CABG and bare-metal stent arms of the earlier ARTS trial.

One-year results and specific subset analysis of the diabetic patients are anticipated and will further enlighten our understanding of multivessel revascularization with drug-eluting stents. These will be an adequate prelude to the 3-year data of the FREEDOM trial, which is comprehensively assessing this question in the diabetic population.
Surgery Is Preferred for the Diabetic With Multivessel Disease
Spencer B. King III

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