EDITORIAL COMMENT

Coronary Artery Bypass Graft or Percutaneous Coronary Interventions in Patients With Diabetes: Another Nail in the Coffin or “Too Close to Call?”*

Spencer B. King, III, MD, MACC
Atlanta, Georgia

Percutaneous coronary intervention (PCI) was introduced by Gruentzig as an alternative to bypass surgery and was originally applied for symptomatic patients with single-vessel disease. As technology advanced, angioplasty became a therapy for the more usual forms of multivessel disease. Randomized trials have justified the use of angioplasty in selected patients with multivessel disease with one glaring exception—diabetics.

In the six years since the National Heart, Lung and Blood Institute (NHLBI) issued its clinical alert regarding the Bypass Angioplasty Revascularization Investigation (BARI) data, which showed superior five-year survival for coronary artery bypass graft (CABG) compared to angioplasty (1), interventional cardiologists have been hoping for a “recount.” Was there something unique about the population?

See page 1008

Did the findings apply to only a subset of patients with diabetes? Most have accepted the BARI findings and some have modified their approach to patients with diabetes. However, physicians continue to look for explanations for the difference, for other experiences that could clarify which patients are at greatest risk for angioplasty and reassurance that new technology has improved the outcomes for patients having interventions.

The report in this issue of the Journal describes a carefully collected experience among patients with diabetes undergoing revascularization in the mid-1990s (2). This study from the Northern New England group is important because, unlike a randomized trial or a large single-center experience, it captures the practice of an entire, albeit small, region. Prospective data collection identified the population by certain demographic, clinical and angiographic characteristics. Although not as detailed as would be found in a prospective randomized trial, this method is far superior to retrospective data collection methods. The practice of revascularization therapy reflects the standard of care delivered during the time of the study, and follow-up vital status was obtained from the National Death Registry.

Among 7,159 patients with diabetes undergoing PCI in the years 1992 to 1996, some 2,766 were similar in baseline features to patients in the BARI trial and registry. That is, they had multivessel disease and lacked the BARI exclusions. Selection for revascularization by the physician caring for the patients resulted in 736 patients undergoing initial PCI and 2,030 having initial surgery. After adjustment for baseline characteristics, the PCI patients had a 1.5-times greater risk of dying than the patients having initial bypass surgery (hazard ratio [HR] 1.49, p = 0.037). The BARI hazard ratio was 1.78 favoring surgery (3).

A search for other experiences has not produced important changes in the vote count favoring surgery. The largest reported single-center registry of patients with diabetes was from Emory University and confirmed a high mortality for diabetics treated with surgery or angioplasty (4). The surgery group of diabetics on insulin had a significantly better adjusted survival rate than the PCI group. Long-term follow-up of the Emory Angioplasty vs. Surgery Trial (EAST) also showed a trend favoring surgery in the patients with diabetes similar to BARI (5). Eight-year survival was 75.5% in the CABG group and 60.1% in the percutaneous transluminal coronary angioplasty (PTCA) group. This compares to seven-year survival of 76.4% and 55.7% for BARI (6). As the investigators (2) of the current study point out, other registries and randomized trials also trend toward better survival with surgery.

Three important questions are raised by the prior experiences and the current observation: 1) What are the explanations for surgical superiority? 2) Will new developments significantly improve the long-term survival for patients treated with PCI? 3) Is bypass surgery protective in patients with diabetes?

WHY HAS SURGERY BEEN SUPERIOR?

Examination of surgical curves from the BARI and EAST studies and from the current registry showed that the difference in long-term survival was not driven by operative mortality but by late events. Incomplete revascularization, restenosis and progression of disease may all be responsible. The EAST trial included follow-up angiography at one and three years. Although most surgical patients had complete revascularization, the number of narrowed segments that were open in the angioplasty group proved significantly less. At one year, the percent of revascularized segments in the angioplasty group was 59% versus 88% for surgery and by three years 70% versus 87% due to repeat revascularization in the angioplasty group (7). Systematic follow-up angiography was not performed in other studies, but a similar superiority for surgical revascularization would be expected.

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Fuqua Heart Center, Atlanta Cardiovascular Research Institute and Emory University School of Medicine, Atlanta, Georgia.
In the present study, the surgery group had 3.8 distal anastomoses placed per patient, whereas 74% of the PCI patients had some vessel with significant obstruction not treated. One assumes that these were the less critical vessels, but it is evident that surgery produces more complete revascularization in most of these patients. The increased restenosis rate in patients with diabetes also adds to the surgical advantage in the first year postintervention. The survival curves in this study are less steep than previous randomized trials, suggesting careful patient selection for PCI patients. Nonetheless, the continuing late events suggest that progression of disease is a very important determinant of survival. Current recommendations for optimal glycemic control, blood pressure and lipid management may not have been optimally understood or practiced during the observation period of this as well as prior studies.

**WILL NEW DEVELOPMENTS IMPROVE SURVIVAL FOR DIABETICS UNDERGOING PCI?**

Stenting, performed in only 14% of this group, has been shown to reduce emergency surgery and restenosis rates. Despite this fact, stenting in patients with diabetes still carries a higher restenosis and reintervention risk than in nondiabetic patients. A registry from the Washington Hospital Center of 954 stented patients with diabetes showed that freedom from late events of death, myocardial infarction (MI) or revascularization was 60% in the insulin-treated patients, 70% in the non-insulin-treated diabetics, and 74% in the nondiabetic patients. Another study of stented patients with diabetes from Hamburg shed some light on why this occurs. Quantitative angiography showed that insulin-treated diabetics had smaller vessels (2.73 mm vs. 2.88 for nondiabetics) and had more in-stent proliferative tissue at follow-up, resulting in restenosis rates of 39.6% for insulin-treated, 32.8% for non-insulin-treated diabetics and 23.8% for nondiabetics. This smaller arterial size in diabetics has also been observed recently by Steve Nissen (personal communication) using intravascular ultrasound.

Emergency surgery rates have been reduced to <2% ever since stenting became a common practice. The 1999 NHLBI Dynamic Registry patients who had BARI characteristics were compared to the BARI randomized patients. Stenting was not used in BARI but was used in 86% of the recent registry patients. Emergency surgery following a PCI was reduced from 10.2% to 1.8% in the recent registry group (Detre KM, University of Pittsburgh Core Data Center).

Will survival be impacted by the use of stents? Diabetic patients treated in New York State between 1994 and 1996 had a better adjusted two-year survival following stent placement than following balloon angioplasty (HR = 1.46) (10). The only reported trials of surgery versus PCI using stents is the Artery Revascularization Therapy Study (ARTS). One-year results show that the reintervention rate has been reduced by approximately 50% compared to prior CABG versus balloon angioplasty trials (Serruys PW, personal communication, December 2000). The mortality for diabetic patients at one year is 3.1% for the surgery group and 6.4% for the stent group. This difference does not reach significance, and based on previous trials much longer follow-up is needed. Another revascularization trial using stents, termed Stent or Surgery (SOS), is to be reported in March 2001.

Antiplatelet therapy with glycoprotein IIb/IIIa receptor blockers has reduced periprocedural MI. Data from the EPISTENT (11) trial shows a lower in-stent restenosis rate and slightly improved survival for patients with diabetes treated with stents and abciximab. Additional information from the recently completed TARGET trial of tirofiban and abciximab will give additional insights into the value of these agents in preventing late events in patients with diabetes. The 30-day outcome showed no increase in early events of stented diabetic patients compared to stented nondiabetic patients treated with either glycoprotein IIb/IIIa receptor blocker (presented at American Heart Association meeting, November 2000).

Recent advances in medical therapy of diabetic patients may modify the late-event rate for patients undergoing both PCI and surgery. The UK Prospective Diabetes Study (UKPDS) showed a reduction in microvascular complications and suggested a benefit in reducing heart attacks by tighter glycemic control (12). The Heart Outcomes Prevention Evaluation (HOPE) trial (13) showed a reduction in ischemic events in the diabetics treated with angiotensin-converting enzyme (ACE) inhibitors. Guidelines based on the Scandinavian Simvastatin Survival Study (4S) trial (14) and other secondary prevention trials have resulted in lower targets for low density lipoprotein (LDL) cholesterol in diabetics. Angiographic progression in the EAST trial was found to be associated with LDL levels, the cholesterol to high density lipoprotein (HDL) ratio and recently with the small, dense LDL pattern suggesting further therapeutic options for these patients (15).

**IS BYPASS SURGERY PROTECTIVE?**

In the current study, the surgery group may have benefited from the frequent use of the internal mammary artery graft. This conduit is commonly used to bypass the left anterior descending (LAD) coronary artery and has been shown to have superior long-term patency compared to saphenous vein grafts. An interesting observation is that 81% of the diabetic patients in BARI received internal mammary artery grafts. It is also worth noting that the survival benefit seen in the diabetic group was driven by a difference in cardiac survival (cardiac mortality at five years was 5.8% for surgery and 20.6% for PTCA). How did the use of the internal mammary artery graft influence the outcomes? Obviously there were anatomic factors driving the use of the internal mammary artery, but the seven-year survival for surgery patients with an internal mammary artery was 83.2%; for
surgery patients with saphenous vein grafts it was only 54.5%; and for PTCA patients it was 55.5%. Nondiabetic patients had approximately 86% survival at five years in all three groups.

How could the use of the internal mammary artery graft protect the patient with diabetes? It is possible that a graft with excellent longevity placed distal in the most critical artery (the LAD) could remain viable even if coronary events (plaque rupture) occurred in the proximal and mid-segments of the vessel due to disease progression over many years of follow-up. A proximally performed balloon angioplasty or stent placement could not solve the problem of more distal plaque rupture.

One other bit of evidence from the BARI study may be instructive. All BARI randomized and registry patients were separated into those who received surgery at any time and those who remained surgery free. Spontaneous Q-wave MI occurred in 8% of the diabetic patients during follow-up. The mortality risk following an MI was 10 times greater for those diabetics who had not undergone prior surgery compared to those who had (HR for surgery patients 0.09) (16). This did not hold for the nondiabetic patients. Could the use of the internal mammary artery (91%) in the current study have protected the surgery group from a fatal MI? There is not sufficient data to be sure.

**HOW SHOULD THE FINDINGS OF THIS STUDY AND THE OTHERS HELP INFLUENCE PRACTICE?**

Overall, the vote is in and the winner has been declared. Surgery with at least one internal mammary artery graft is superior to angioplasty in the broad population of patients with diabetes and multivessel disease. All patients, however, do not fit the mean. In this study, the patients with two-vessel disease did not have a significantly worse outcome with PCI. There are probably some two-vessel patients who will do equally as well and some who will not. That discrimination is beyond the capability of this registry as it would require a careful angiographic core laboratory evaluation.

Because PCI has undergone significant changes and is still widely applied in diabetic patients, it would be helpful to follow the investigators’ advice and perform future registries. The NHLBI Dynamic Registry is such an effort, and others limited to patients with diabetes may also be instructive. The pending BARI 2-D study, which will evaluate revascularization versus medical therapy in patients with diabetes, will follow guidelines based on the previously developed evidence from trials and registries.

In the meantime, the present study provides supporting evidence that the most prudent selection for PCI in diabetic patients with multivessel disease will be those patients who require interventions and have favorable features, such as predominantly two-vessel disease, absence of proximal LAD disease, discrete lesions favoring PCI therapy, and those patients with a reasonable opportunity to provide nearly complete functional revascularization. Vigorous secondary prevention must be provided. The accepted treatment guidelines being applied in the BARI 2-D trial (i.e., tight glycemic control, LDL cholesterol <100 mg/dl, and blood pressure <135/85 mm Hg) should be the goals. In addition, heightened surveillance of all diabetic patients who have had PCI should be practiced. Finally, a recount will be required as new technology and medical therapies emerge.

**REFERENCES**