The Effects of Diabetes Mellitus on Coronary Artery Bypass Graft Surgery

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Coronary artery bypass graft (CABG) surgery has been a mainstay in the treatment of coronary artery disease. Diabetes is prevalent in these patients and has significant effects in the operative period as well as in long-term survival. Diabetes is a risk factor in increased incidence of mortality as well as deep sternal wound infection after CABG surgery. Long-term survival is also significantly affected by diabetes. Clinicians who treat diabetic patients with coronary artery disease should be aware of the effects this condition has on the outcomes of CABG surgery.

Introduction

Diabetes mellitus (DM) is a risk factor for the development of coronary artery disease (CAD). Since the 1960s, coronary artery bypass graft (CABG) surgery has been a mainstay in the treatment of CAD. Percutaneous coronary interventions such as balloon angioplasty and coronary artery stenting are also used to treat patients with CAD. The choice of which revascularization method to use with diabetic patients is discussed in this article.

It is also well known that diabetes can adversely affect the outcomes of any surgery, especially in the incidence of complications such as wound infections. Also, DM has a significant effect on long-term survival of these patients. Both short- and long-term outcomes of patients with DM undergoing CABG surgery are described in this article.

Prevalence

At the end of 2006 it was estimated that 500,000 patients in the United States will undergo CABG surgery in 2007 [1]. There are an estimated 25 million people in the United States that have DM [2]. The incidence of DM in patients undergoing CABG surgery is between 18% and 38% [3–5,6••]. Therefore, it is estimated that 210,000 diabetic patients will undergo CABG surgery in 2005. Diabetes plays a significant role in the treatment of these patients as well as their short- and long-term outcomes.

Perioperative Complications

In 1988, Lilienfeld et al. [7] conclusively showed that DM is a risk factor for the development of infections after cardiac surgery. The Northern New England Cardiovascular Disease Study Group (NNE) has been prospectively collecting data on cardiac surgical patients in Vermont, New Hampshire, and Maine since 1987. All patients in these three states who have undergone CABG surgery are in the NNE registry. Braxton et al. [8] documented that DM is an independent risk factor for the development of mediastinitis. Loop et al. [9] and Grossi et al. [10] both showed that the use of bilateral internal mammary artery (IMA) bypass grafts among diabetic patients having CABG surgery has been associated with an increased risk of deep sternal wound infection (DSWI). Since the paper by Loop et al. [9], it has been an accepted practice by most cardiac surgeons to not use bilateral IMA grafts in patients with DM. Most commonly, the IMA has been taken as a muscular pedicle. Recent early reports of using bilateral skeletonized IMAs in patients with DM has been shown to not increase the risk of DSWI [11].

The Society of Thoracic Surgeons (STS) created a national voluntary database involving patients undergoing cardiac surgery. This database is the largest cardiac surgical database in the United States. In 1997, Edwards et al. [12] used logistic regression analysis to determine the odds ratio for mortality in patients undergoing CABG surgery. This risk model was developed using the STS National Cardiac Surgical Database. Diabetes had an odds ratio for mortality of 1.3. Clough et al. [13] showed that DM is an independent predictor of in-hospital mortality in patients undergoing CABG surgery. The odds ratio for death for mortality in diabetic patients was 1.19 (95% CI, 1.01 to 1.40; $P = 0.03$).

Choice of Revascularization

Since the development of percutaneous coronary interventions (PCIs), clinicians are now faced with a markedly different choice in regard to revascularization. There have

been several randomized trials studying CABG surgery versus percutaneous transluminal coronary angioplasty (PTCA) for patients with ischemic CAD needing revascularization. The BARI (Bypass Angioplasty Revascularization Investigation) study has published several papers on the differences in outcomes of patients with DM enrolled in this national trial [4,14,15]. In 1997, BARI [4] investigators first published data that clearly showed that patients with DM who had three-vessel CAD had improved 5-year survival with CABG surgery compared with PTCA. The mortality at 5 years was 5.8% in the CABG surgery group and 20.6% in the PTCA group. The benefit was seen in patients who received at least one IMA graft. In 2000, Detre et al. [15] documented that patients with DM treated initially by CABG surgery in the BARI trial had improved survival with a subsequent acute myocardial infarction compared with patients randomized to receive PTCA. Their conclusions were that this study should influence the choice of revascularization in patients with DM needing revascularization. In 2001, Niles et al. [16] published a paper on series of patients similar to the BARI study [16]. Only 14% of the PCI patients had stents in this study. In the BARI study, all patients underwent PTCA in the PCI group. Niles et al. [16] found similar results to the BARI study, in that the 5-year survival of PCI patients was significantly less that the CABG surgery group. In the EAST (Emory Angioplasty versus Surgery Trial) trial, insulin-requiring diabetic patients had improved 5- and 10-year survival in the CABG surgery cohort compared with patients initially receiving PTCA as a revascularization strategy [17]. In one of the only studies that used stenting as an arm in a randomized trial comparing PCI with CABG surgery, surgery was again significantly associated with an improved 1-year survival [18]. One can conclude that in diabetic patients with three-vessel CAD, CABG surgery has a survival advantage over PTCA in regard to choice of revascularization treatment for ischemic CAD. However, most of these studies were done prior to the use of drug-eluting stents as well as the use of platelet IIb/IIIa inhibitors. To date, there have been no published randomized trials comparing drug-eluting stents and/or platelet IIb/IIIa inhibitors in patients with DM undergoing revascularization treatment for ischemic CAD. Flaherty and Davidson [19•] nicely summarized the issues of the choice of revascularization in patients with DM.

Improvements in Glucose Control

Insulin has been the mainstay of the acute treatment of hyperglycemia in patients with DM undergoing surgery. Until recently, most clinicians used subcutaneous insulin to control blood glucose levels. In 1997, Zerr et al. [20] showed that blood glucose levels of greater than 200 mg/dL on the first and second postoperative day after CABG surgery were associated with an increase in DSWIs. They also showed that improved glucose control lowers the risk of wound infections after heart surgery.

Furnary et al. [21] have dramatically changed the process of controlling postoperative serum glucose levels in diabetic patients undergoing CABG surgery. They developed a continuous insulin infusion practice that is now known as the Portland Protocol. This protocol was published in 1999 in the *Annals of Thoracic Surgery* [21]. This protocol was published in addition to the prospective study of 2467 diabetic patients undergoing open heart surgery between 1987 and 1997. Patients were classified into two groups: 1) 968 patients with intermittent sliding scale subcutaneous insulin (SQI); and 2) 1499 patients who were treated with a continuous insulin infusion (CII) to maintain a blood glucose level of less than 200 mg/dL. Blood glucose levels (mg/dL) were significantly lower in the CII group compared with the SQI patients (day of surgery, 199 vs 241; postoperative day [POD] #1, 176 vs 206; POD #2, 181 vs 195; and POD #3, 179 vs 188). There was a 2.5-fold reduction in incidence of DSWIs in the CII group compared with the SQI control group (0.8% vs 2.0%, $P = 0.001$). Obesity and the use of an internal thoracic artery pedicle also increased the incidence of DSWIs. The published Portland Protocol in 1999 used a continuous intravenous insulin infusion through a piggyback pump. Blood glucose monitoring was either by fingerstick blood sample or arterial line drop sample. Insulin was started up to 3 units per hour. Blood glucose testing was done at every 1-hour interval until the glucose was between 150 and 200 mg/dL; then it was measured every 2 hours. Changes in the insulin infusion rate are then determined by a scale that uses the last blood glucose level. The insulin infusion was carried out until POD #3 when the patient had started oral intake of nutrition and the preadmission glycemic control medications were restarted. In patients with previously undiagnosed DM, an endocrinology consult was ordered. The Portland Protocol for continuous insulin infusion in patients undergoing cardiac surgery is available online at http://www.providence.org/oregon/programs_and_services/heart/portlandprotocol/default.htm.

In 2003, Furnary et al. [22] published a second paper that studied mortality in the same two groups of patients. They compared two cohorts of patients: 1) 942 patients in the SQI group (1987 through 1991); and 2) 2612 patients in the CII group (1991 through 2001). The mortality rate in the SQI group was 5.4% compared with a mortality of 2.5% in the CII group. Multivariate analysis showed that CII was protective (odds ratio for mortality 0.50, $P = 0.005$). A major limitation of this study is the fact that the two cohorts were from significantly different time frames. Mortality rates in many regions have decreased significantly during that time frame and the cause of that decrease is multifactorial [23].

In 2004, Lazar et al. [24] studied 141 diabetic patients undergoing CABG surgery and prospectively randomized

the patients into two groups based on method of treating hyperglycemia. One group received standard subcutaneous insulin for 12 hours after arrival in the intensive care unit and the other group received a continuous infusion of glucose, insulin, and potassium (GIK) for a similar time. After the study period ended, the patients were placed back on their preoperative diabetic medical regimen. Patients in the GIK group had a significantly lower blood glucose (138 vs 260 mg/dL), shorter length of stay (6.5 vs 9.2 days), and lower incidence of atrial fibrillation (16.6% vs 42%). Two-year survival was improved in the GIK group. In addition, there were less postoperative infections in the GIK group compared with the subcutaneous insulin group (1% vs 10%, $P = 0.03$).

Graft Patency

There are few studies looking at graft patency in patients with DM. In 2002, Schwartz et al. [14] published CABG surgery patency in patients involved in the BARI trial. There were 1526 patients who had CABG surgery in the BARI study, and 292 had DM. Thirty-four percent of the DM patients and 38% of the non-DM patients had angiography at a mean of 3.9 years. There were 3.0 grafts per CABG surgery patient in the DM group and 2.9 grafts per patient in the non-DM group. Only one third of the patients in both groups received an IMA graft. This percentage of IMA grafts is significantly lower than is currently being used [25]. Patients with DM had smaller and poorer quality vessels; however, the patency was similar in the two groups. IMA patency at 3.9 years was 89% in the DM group compared with 85% in the non-DM group. Vein graft patency was 71% versus 75% in the non-DM group.

Long-term Survival

In 1997, Barsness et al. [26] studied the relationship between DM and long-term survival after CABG surgery and PTCA. The study included 3220 patients undergoing CABG surgery or PTCA from 1984 through 1990. Twenty-four percent had DM. Both adjusted (89% vs 93%) and crude (74% vs 86%) 5-year survival rates for DM patients undergoing CABG surgery were significantly worse compared to patients without DM. There was no significant difference in the survival of PTCA versus CABG surgery patient in this study, which was a different finding compared with many other studies comparing CABG surgery to PCI in patients with DM [4,16,17,27].

In 1999, Thourani et al. [28] looked at the influence of DM on early and late outcomes after CABG surgery. There were 12,198 patients operated on between 1978 and 1993. Nineteen percent had DM (2278 patients). There were a greater percentage of significant comorbidities (hypertension, chronic heart failure, previous myocardial infarction, left main stenosis, and lower ejection fraction) in this group compared to those patients without DM. Patients with DM had a higher postoperative mortality (3.9% vs 1.6%) and stroke (2.9% vs 1.4%) compared to those patients without DM. Five-year survival (78% vs 88%) and 10-year survival (50% vs 71%) were significantly lower in the DM group compared with the non-DM group. Patients requiring insulin for treatment of their DM had a worse 5- and 10-year survival compared with noninsulin-treated diabetic patients. They postulated that the requirement of insulin treatment might reflect a greater severity of the diabetic disease process, and therefore contribute to greater complications that affect long-term survival.

In 2000, Whang and Bigger [3] reported the effect that DM has on the outcomes of patients with severe left ventricular function (ejection fraction < 36%) undergoing CABG surgery in the CAGB Patch Trial database. There were 342 patients with DM followed up for 48 months. There was no difference in survival in these patients compared to those without DM (74% vs 76%).

Colleagues from the NNE and I recently reported the effects of DM and associated medical conditions on long-term survival after CABG surgery [6••]. There were 36,641 consecutive, isolated CABG surgery procedures performed in Vermont, Maine, and New Hampshire from 1992 through 2001. Thirty-one percent of our patients had DM. Our database was linked to the National Death Index to assess long-term mortality. Survival was stratified into three categories: no diabetes; diabetes without renal failure and peripheral vascular disease; and diabetes with peripheral vascular disease and/or renal failure. The reason to examine the subgroup of diabetic patients with the comorbid conditions of renal failure and/or peripheral vascular disease was to see if these conditions affected long-term survival in patients with DM compared to those diabetic patients without those conditions. The annual incidence of death (AIOD; death per 100 person years) was 3.1 in the non-DM group and 5.5 in the DM group. The AIOD in patients with diabetes alone was 4.4. In the group with DM and peripheral vascular disease, the AIOD was 8.4. DM and renal failure had an AIOD of 16.3. Finally, the AIOD of diabetic patients with both renal failure and peripheral vascular disease was 26.3. Log-rank test comparing each of these groups to the nondiabetic group was statistically significant (log-rank test, $P < 0.001$). Figure 1 plots the Kaplan-Meier survival curves of three groups of patients. DM and the comorbidities of renal failure and/or peripheral vascular disease have a significant affect on long-term survival. It is interesting to note that patients with DM who do not have renal failure and/or peripheral vascular disease have 10-year survival slightly less than those patients undergoing CABG surgery without DM. Figure 2 depicts the Kaplan-Meier survival curves for all five groups. One can see the significant effect that DM with renal failure and peripheral vascular disease has on long-term survival. The clinical implication of our study was to provide the surgi-

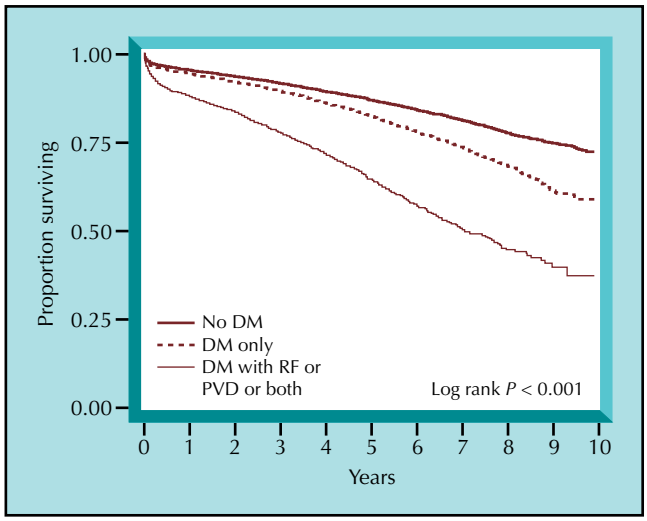

Figure 1. Kaplan-Meier survival curves of three groups of patients with CABG surgery. DM—diabetes mellitus; PVD—peripheral vascular disease; RF—renal failure. (*From* Leavitt et al. [6••]; with permission.)

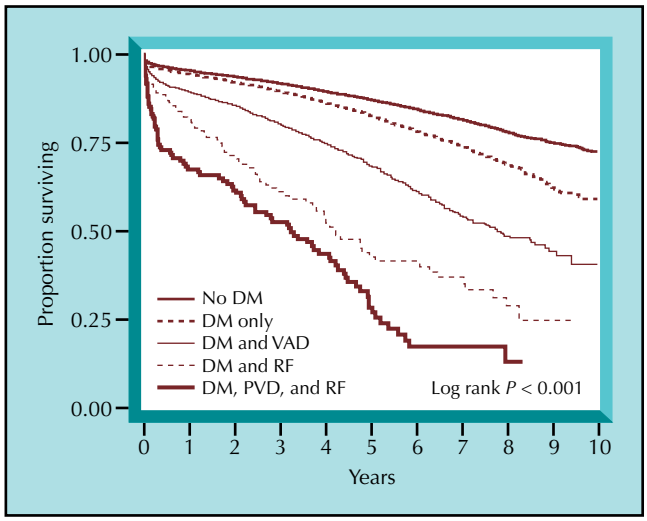

Figure 2. Kaplan-Meier survival curves of five groups of patients with CABG surgery. DM—diabetes mellitus; PVD—peripheral vascular disease; RF—renal failure; VAD—vascular disease. (*From* Leavitt et al. [6••]; with permission.)

cal clinician with documented and accurate information on mortality rates and long-term survival in patients with DM and/or the comorbidities of renal failure and peripheral vascular disease.

Conclusions

DM is a risk factor for the development of CAD. Patients with diabetes comprise nearly one third of patients undergoing CABG surgery for ischemic CAD. Patients with diabetes have better long-term survival rates with CABG surgery than those who undergo PTCA. Aggressive glucose control with continuous insulin infusion reduces the mortality and infectious morbidity associated with CABG surgery. Long-term survival in diabetic patients is lower than those patients without diabetes. The additional comorbidities of renal failure and/or peripheral vascular disease in diabetic patients significantly contribute to poor long-term survival.

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