Outcomes in Diabetics Undergoing Revascularization

The Long and the Short of It*

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Diabetes mellitus, a major determinant of cardiovascular events, portends an adverse prognosis in patients with coronary artery disease regardless of treatment strategy. Among patients undergoing coronary revascularization procedures, the Bypass Angioplasty Revascularization Investigation (BARI) trial (1) demonstrated an unfavorable interaction between diabetes and an initial strategy of percutaneous transluminal coronary angioplasty (PTCA) in patients with multivessel disease requiring revascularization, with an increased all-cause mortality of 34.7% at five years in the PTCA group. However, even with coronary artery bypass graft surgery (CABG), mortality was 19.1% at five years, still greater than the 9.5% and 10.3% five-year mortality rates for PTCA and CABG, respectively, in nondiabetics. Although this finding of inferior outcome with PTCA compared to CABG is often extrapolated broadly, resulting in the perception that CABG is the default revascularization modality for all diabetics, there are some confounding issues. Other available evidence (2–4) demonstrates that diabetes is not an absolute contraindication to percutaneous coronary intervention (PCI), and careful patient selection for each revascularization modality can result in comparable outcomes (Table 1). The understanding of this concept may be enhanced by an examination of the factors that affect both short- and long-term outcomes among diabetics undergoing coronary revascularization.

CABG in Diabetics

In the BARI trial, CABG was found to provide superior long-term survival in diabetics with multivessel coronary disease compared to PTCA (1). Although this was not a prespecified analysis and was not reproduced in the other randomized trials of revascularization for multivessel disease, the finding seems valid based on the vascular biology of diabetes, which is associated with abnormalities of thrombosis/fibrinolysis and endothelial dysfunction (5). However, data from the BARI registry (2) and the Duke database (3) make it clear that careful clinical selection of patients for either revascularization strategy results in comparable outcomes, acknowledging that patients referred for CABG had more advanced atherosclerosis and reduced ventricular function compared to PCI patients.

Short-term outcome. Despite the demonstrated superiority of CABG over PTCA in the BARI randomized trial, CABG obviously is associated with operative risk. The reported influence of diabetes on operative risk is variable, with some studies reporting excess mortality in diabetics (6–8), and others reporting comparable short-term survival in nondiabetics (9,10), although the independent effect of diabetes on short-term survival is less clear. Several studies, however, demonstrate increased perioperative morbidity among diabetics, including neurologic complications (8), renal dysfunction (7) and wound infection (7,11), with sternal wound infection being of particular concern when both mammary arteries are utilized as conduits.

In the current issue of the Journal, Carson et al. (12) performed an analysis of 146,786 patients undergoing isolated CABG operations from the 1997 Society of Thoracic Surgeons Registry (41,663 diabetics and 105,123 nondiabetics) to determine the effect of diabetes on 30-day operative mortality. Absolute mortality rates were higher in diabetics (3.74% vs. 2.7%); when adjusting for multiple differences in baseline characteristics with models that included demographic, clinical, procedural and periprocedural treatment variables, diabetes was independently correlated with 30-day mortality (odds ratio [OR] 1.23; 95% confidence intervals [CI] 1.15 to 1.32), comparable to the excess mortality effect of female gender and peripheral arterial disease, but less than the effect of pre-existing renal failure, preoperative cardiogenic shock and redo surgery. The increased mortality effect was greatest among diabetics treated with insulin (OR 1.39; 95% CI 1.27 to 1.52) and less pronounced, but still significant, in patients treated with oral hypoglycemic agents (OR 1.13; 95% CI 1.04 to 1.23). Importantly, although death was attributable to cardiac causes (which generally includes ischemia due to graft failure, left ventricular failure and dysrhythmia) in approximately two-thirds of all patients, neurologic events led to 9.64% of nondiabetic perioperative deaths and 12.14% of diabetic perioperative deaths.

Although the investigators hypothesize that volume/electrolyte shifts, perioperative hyperglycemia and the potentially negative inotropic and arrhythmogenic effects of free fatty acids may help to explain the excess mortality in diabetics, these factors would in general be expected to affect cardiac mortality, which somewhat surprisingly in this study (12) was lower in diabetics than in nondiabetics (65.8% vs. 68.3%). This suggests that the excess short-term mortality in diabetics undergoing CABG is largely due to increased noncardiac mortality, including neurologic, renal, infectious

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and perhaps other causes. Whether heightened vigilance and awareness of these issues in the perioperative period can reduce morbidity and mortality in diabetics is not clear. Although the use of off-pump techniques has been suggested to reduce the neurologic sequelae of extracorporeal circulatory assist devices, the benefits in this regard may disappear during long-term follow-up (13). As the morbidity and mortality rates appear highest in insulin-treated patients, this group may warrant the highest level of attention.

Long-term outcome. Among patients undergoing CABG, diabetics have worse long-term survival than nondiabetics. The observation that insulin-requiring patients fare worse than oral-agent–treated patients is also apparent in the long-term outcome (all-cause mortality) of diabetics undergoing CABG in the BARI randomized trial (2), but this may signify that insulin treatment is a marker of more advanced state and/or longer duration of diabetes, resulting in more advanced atherosclerosis, rather than an independent effect of insulin therapy. Other factors also influence long-term event-free survival in diabetics undergoing CABG. Importantly, the survival advantage of CABG over PCI in BARI diabetics was exclusively in those patients who received an internal mammary arterial graft; those who only received vein grafts had outcomes similar to PTCA patients (1). Although BARI demonstrated improved long-term survival in diabetics undergoing CABG rather than PTCA, in the more recent Arterial Revascularization Therapies Study (14), which compared stent implantation (with a low rate of glycoprotein IIB/IIIA antagonist use) to CABG for multivessel disease, mortality of patients undergoing CABG was similar to that observed in PCI patients, although only one-year mortality has been reported thus far.

### PCI in Diabetics

**Short-term outcome.** Although comparing short-term outcome (in-hospital or 30 day) after PCI in diabetics versus nondiabetics has not been a primary focus of coronary interventional studies, the majority of available evidence would suggest that periprocedural mortality rates are comparable (1,15,16), although diabetes increases the likelihood of postprocedural renal dysfunction including hemodialysis (17,18), and it may increase the occurrence of stroke (17).

**Long-term outcome.** In contrast to short-term events, long-term outcome after PCI in diabetics has consistently been shown to be worse than in nondiabetics. The higher rate of restenosis in diabetics compared to nondiabetics is due to an exaggerated neointimal response after PCI (19), greater negative vessel remodeling (20), increased platelet aggregability and reduced fibrinolytic mechanisms (5). Although the use of intracoronary stents has been reported to negate the adverse effect of diabetes on restenosis (20), most series report that diabetics have an increased likelihood of repeat revascularization even when utilizing stents (21,22), underscoring the influence of exaggerated neointimal hyperplasia in this population.

The increased risk of restenosis after PCI in diabetics, including a higher rate of occlusive restenosis (23), translates into increased rates of target lesion-related ischemic events. In diabetics undergoing PTCA, restenosis manifesting as total vessel occlusion occurred in 13% of treated lesions and was associated with both a reduction in left ventricular ejection fraction at six-month follow-up (23) and with reduced long-term survival compared to patients with no restenosis or nonocclusive restenosis (24). This link between increased vessel reocclusion and reduction in left ventricular function, and the correlation with long-term mortality, may...
in part explain the poor outcome observed in diabetics after PTCA alone.

All is not lost, however, with respect to diabetics and PCI. In this issue of the Journal, Van Belle et al. (25) demonstrate a highly beneficial, durable effect of stent implantation compared to PTCA in diabetics. By matching 157 diabetics and 157 nondiabetics for gender, diabetes treatment regimen (insulin or oral agent), stenosis location, reference diameter and minimal lumen diameter, with other baseline characteristics being similar between the two groups, the investigators demonstrated that six-month restenosis and vessel occlusion was significantly reduced by utilizing stents (27% vs. 62%, \( p < 0.0001 \) and 4% vs. 13%, \( p < 0.005 \)). The PTCA patients in this cohort had a significant reduction in ejection fraction at six months (\(-2.4 \pm 10.9\%\), \( p = 0.02 \)), whereas stent patients did not, presumably owing to the importance of occlusive restenosis previously documented by these investigators (23). Stent implantation was also associated with reduced death/myocardial infarction (14.8% vs. 26%, \( p = 0.02 \)) and need for target lesion revascularization (TLR) (21% vs. 40.6%, \( p = 0.0002 \)).

Although the need for any repeat revascularization was reduced with stents (35.4% vs. 52.1%, \( p = 0.001 \)), the difference between these figures and the rates of TLR approximates the need for nontarget lesion revascularization during the course of follow-up, and it serves as a reminder of the systemic, ubiquitous nature of atherosclerosis. Indeed, it has been demonstrated that diabetics are more likely to develop new coronary lesions at untreated sites after PTCA (26), particularly in instrumented vessels. It has also been demonstrated that the appearance of new coronary lesions correlates with worse long-term mortality among BARI PTCA patients (relative risk 1.27 for every new lesion found on five-year protocol angiography) (27). Furthermore, patients with diabetes undergoing PTCA in BARI had a significantly greater myocardial jeopardy index at five-year protocol or nonprotocol angiography, a finding not observed in CABG patients (28).

It seems unlikely, therefore, that optimizing only the target lesion utilizing stents, glycoprotein IIB/III A antagonists (29), or even drug-coated stents (30) will alone eliminate the excess risk associated with diabetes in coronary disease patients; although these measures appear effective in reducing TLR and target lesion-related adverse events, persistent long-term efforts at optimizing the patient with strict glycemic control, treatment of concomitant cardiovascular risk factors including aggressive lipid-lowering with statins, and long-term antiplatelet therapies seem prudent (though yet unproven) to complement periprocedural measures.

The impact of diabetes treatment also bears consideration. The adverse effect of sulfonylureas on outcomes after myocardial infarction has been documented (31,32), as well as the potential for an adverse long-term effect of insulin treatment after PCI (16,33), although it is possible that requiring insulin may be merely a marker of more advanced diabetes rather than an independent adverse effect of treatment. The potential antirestenotic effect of the newer insulin-sensitizing agents such as troglitazone is of interest (34) and merits further clinical investigation. Whether treatment of diabetes with an insulin-sensitizing regimen or an insulin-providing regimen is preferred will be further elucidated in the BARI 2D study.

In addition, BARI 2D will also address the question of whether revascularization in diabetics carries any advantage over medical therapy, an issue that has not been explicitly demonstrated. However, the use of an early invasive strategy in diabetic patients with non–ST-elevation acute coronary syndromes appears to be superior than an early noninvasive strategy as demonstrated in the Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (35) and Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction 18 (36) trials, allaying some of the concern of perceived excess risk associated with an invasive approach in diabetics.

**REVASCULARIZATION IN DIABETICS: WHAT TO DO NOW?**

Despite the realization that diabetes is associated with greater adverse events than nondiabetes regardless of revascularization strategy, it is clear that diabetics will continue to require coronary revascularization; while ongoing and future studies may help clarify the role of revascularization and optimize the short- and long-term outcome of diabetics undergoing revascularization, how should these patients be managed at present? In diabetic patients with single-vessel disease, the use of revascularization should be considered for relief of ischemia, treatment of angina pectoris, and improvement in quality of life, just as in nondiabetic patients. The optimal strategy for diabetics with single-vessel disease requiring revascularization has not been specifically studied, although PCI would seem reasonable as an initial strategy if medically feasible. In multivessel disease, careful patient selection for one revascularization strategy versus the other is essential; patients with more extensive atherosclerosis (many lesions, diffuse multivessel disease, chronic occlusions, multiple complex lesions) are better suited for CABG. The presence of multivessel disease does not preclude PCI, particularly when lesions are discrete and approachable with a high likelihood of success and not associated with excessive likelihood of restenosis.

In borderline situations, or situations where the perceived advantage of CABG over PCI is less compelling, other comorbidities should also be taken into account; for example, in patients with a history of stroke or other evidence of significant cerebrovascular disease, PCI may hold an advantage over CABG. Regardless, if PCI is the chosen therapy, optimizing angiographic results, and the use of stents and glycoprotein IIB/III A antagonists should be strongly con-
REFERENCES


