News and Views from the Literature

Stents

Revascularization in Diabetes: Have Stents Made a Difference?

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Diabetic patients with coronary artery disease are well recognized as having a significantly worse long-term outcome than nondiabetic patients with coronary disease. Long-term survival studies indicate a two-fold increase in mortality and excessive morbidity.[1] The reasons for this poor outcome are complex but relate in part to more extensive atherosclerosis and an increased risk of thrombosis, as well as more rapid progression of disease.[2] In addition, the outcome of diabetic patients following coronary revascularization procedures with either bypass surgery or percutaneous coronary intervention (PCI) has also been shown to be worse, with a one and one half to two-fold increase in mortality.[3]

The benefits of bypass surgery compared to angioplasty in such patients has been under intense study since the initial report from the Bypass Angioplasty Revascularization Investigation (BARI Trial), which demonstrated that in treated diabetic patients with symptomatic multi-vessel disease, coronary artery bypass graft (CABG) resulted in a significantly better outcome than PCI over 7 years.[4] The benefit is largely confined to patients with more severe multivessel disease and those receiving left internal mammary artery (LIMA) bypass grafts. Importantly, no benefit was seen in patients receiving only saphenous vein grafts. These findings have been confirmed in the 8-year follow-up of the Emory Angioplasty versus Surgery Trial (EAST Trial) and Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI Trial).[5,6] These findings have been criticized because the BARI Trial was

conducted prior to the introduction of coronary stenting and adjunctive therapy (such as glycoprotein IIb/IIIa drugs). The recent results of the Arterial Revascularization Therapy Study (ARTS Trial) is the first to specifically address the role of coronary stenting versus bypass surgery in diabetic patients with multivessel disease.

Clinical and Economic Impact of Diabetes Mellitus on Percutaneous and Surgical Treatment of Multivessel Coronary Disease Patients: Insights from the Arterial Revascularization Therapy Study (ARTS Trial)

Abizaid A, Costi M, Centereo M, et al.
Circulation. 2001;104:533–538.

In this study, 1205 patients with multivessel disease were randomized to either stent placement or bypass surgery in 67 centers. Of the 1205 patients, 208 had diabetes (defined as a history of diabetes mellitus on oral hypoglycemic agents or insulin) at entry. Both groups had an average of 2.7 lesions treated and 89% of the surgical patients received a LIMA graft. In-hospital events were similar between the groups; however, at 1 year the bypass surgery group had a trend toward lower death rate (3.1% vs 6.3%, $P = .40$) and lower myocardial infarction rate (3.1% vs 6.3%, $P = .40$), and a significantly lower repeat revascularization rate (3.1% vs 22%, $P < .001$). Overall event-free survival was 84.4% for the CABG group and 63.4% for the stent group ($P < .001$). The results from the diabetic subgroup were similar to the results of the overall trial. This study continues to emphasize the poor outcome of diabetic patients but also the value of bypass surgery with LIMA graft in patients with diabetes and multivessel disease.

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The study does not mean, however, that coronary stents in diabetics are not of clinical value. Numerous studies have shown that stents decreased restenosis in diabetics, as well as in nondiabetics.[7] It also should not be interpreted that patients with diabetes and multivessel disease should not undergo angioplasty. The BARI Registry included all BARI patients eligible for randomization, but who refused. This group was followed to the same extent as the BARI randomized patients. Within this group, the outcome of the treated diabetic patients receiving PCI was equivalent to those receiving bypass surgery.[8] Patients receiving bypass surgery had more extensive multivessel disease and more diffuse disease than the angioplasty patients, whereas the angioplasty patients had more discrete two-vessel disease. The decision to choose angioplasty or bypass surgery in the Registry was left entirely to treating physician discretion. For this reason, the recently begun BARI 2D Trial comparing revascularization or no revascularization in asymptomatic or mildly symptomatic patients with diabetes and coronary disease will allow either form of revascularization, because physician judgment appears to appropriately select patients for both revascularization procedures.

The results of drug-eluting stent studies may also reopen the issue of bypass surgery versus PCI therapy in diabetic patients.

The ARTS Trial could be criticized, however, because the majority of patients did not receive glycoprotein IIb/IIIa drugs, and the results of the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibition for Stenting) Trial suggests that diabetic patients receiving stents benefit not only in recurrent events but also in reduced mortality when abciximab, a IIb/IIIa agent, is used.[9]

Very recently, the results of drug-eluting stent studies may also reopen the issue of bypass surgery versus PCI therapy in diabetic patients. The recent report from the RAVEL Trial, presented at the European Congress of Cardiology Meeting in Stockholm this past September, suggests that drug-eluting stents are a powerful factor in reducing restenosis. In this study, 238 patients were randomized in 19 centers.[10] Event-free survival at 210 days in the group receiving the drug-eluting stent coated with rapamycin (sirolumus) was 97% as compared to 73% in the control stent group. The restenosis rate (>50% at follow-up) was 0% for the stent group and 26% for the control group. Although the numbers were not reported in this initial presentation, the authors indicate that similar results were seen in diabetic patients who were randomized. Although a significant proportion of adverse events in diabetics is related to restenosis, recent studies suggest that it is also due to more rapid progression of coronary

disease. This could impact the PCI group as compared to the bypass surgery group, which would have vascular conduits bypassing large areas of potentially obstructable diseased coronary arteries.[11] This suggests that drug-eluting stents alone may not be sufficient in reducing events during follow-up.

Revascularization with either bypass surgery or angioplasty in diabetic patients is associated with a less favorable outcome. Whether early intervention would be of value will be assessed in the ongoing BARI 2D Trial. However, it remains to be determined whether the widespread use of glycoprotein IIb/IIIa drugs in diabetic patients receiving stents and possibly drug-eluting stents will significantly alter results so that outcomes become similar to those receiving bypass surgery. For the present, it seems prudent not only to consider bypass surgery with LIMA grafting in diabetic patients with severe multivessel disease, but also to consider angioplasty in selected patients who have more discrete and less severe disease. ■

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Angina

Folate Treatment to Prevent Nitrate Tolerance

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Long-acting nitrates have been used for the treatment of angina and congestive heart failure for decades. Clinicians are well aware that the major limitation of long-term therapy using nitroglycerin is nitrate tolerance. Nitrate tolerance is defined as the tachyphylactic response when nitrate is used in a chronic fashion without a nitrate-free period. This tolerance is manifested as the loss of the blood pressure–lowering effect as well as the heart rate–raising response. Systemic venous vasodilatory effect is attenuated markedly after 48 hours of continuous nitrate infusion. It has been well demonstrated that after prolonged continuous nitrate use, the clinical effectiveness against angina pectoris is lost.

To avoid nitrate tolerance, patients are instructed to build in a nitrate-free period during their chronic therapy. Long-acting mononitrates are given in a once-a-day or in an asymmetric b.i.d. fashion; nitrate patch is applied to the skin for 12 hours and then removed for 12 hours. The provision of this nitrate-free interval seems to attenuate the nitrate tolerance. Other methods for reducing nitrate tolerance include the use of diuretics or angiotensin-converting enzyme inhibitors to counter fluid retention and depletion of thiols (-SH) groups. Often nitrate dosage has to be increased over time, especially when nitrate is given in a continuous intravenous fashion. However, despite these maneuvers nitrate tolerance continues to counter the actions of the organic nitrates and reduce the efficacy and compliance of this class of drug.

The mechanisms of nitrate tolerance have been studied by a variety of investigators for some time and include the depletion of thiols, an increase in venous blood volume limiting vasodilator response, and increased generation of reactive oxygen species. Evidence is mounting that nitrate tolerance is associated with an increase in production of superoxide anion in the vascular wall. The sources of these superoxides include membrane-bound nicotinamide adenine dinucleotide phosphate (NADPH) oxidase as well