The choice of which coronary revascularization strategy is best for diabetic patients with multivessel coronary disease has always been complex. The presence of diabetes, especially insulin-requiring diabetes, has been associated with higher rates of acute and late-term adverse events for both PTCA and bypass surgery, making either approach seemingly suboptimal. The results of the Bypass Angioplasty Revascularization Investigation (BARI) trial, however, strongly suggest that bypass surgery is the treatment of choice over PTCA. High restenosis rates, inability to fully revascularize all ischemic territories, and progression of atherosclerosis are generally cited as the major problems that limit the effectiveness of percutaneous coronary revascularization (PCR) in diabetic patients. But in everyday practice when patients are found to have clinical ischemia and multivessel disease at coronary angiography, the choice of revascularization approach is often based largely on the feasibility of PCR, with little regard for the presence or absence of diabetes. Is this decision-making process wrong? Lack of finding a detrimental PTCA treatment effect for diabetics in other randomized trials or large clinical databases, limited clinical follow-up (≤6 years) that cannot measure the impact of probable late-term bypass vein graft failure in patients who receive initial bypass surgery, and lack of outcomes reflecting coronary stenting are generally cited as the major factors that limit the notion that surgery is the treatment of choice. Moreover, initial experiences with radiation therapy and the glycoprotein IIb/IIIa receptor blocker abciximab have shown promising reduction in late loss within stents of diabetic patients and further support the hope for a PCR solution in some subsets of diabetic patients with multivessel disease.

Presently, pending the 10-year follow-up results of the BARI trial and the results of 2 ongoing coronary-stent versus bypass-surgery trials (Arterial Revascularization Therapy Study [ARTS] and the Stent Or Surgery trial [SOS]), surgical bypass has become the accepted treatment for nonselected diabetic patients with multivessel disease. Exactly why bypass surgery appears to be superior to PCR and whether selected diabetic patients with multivessel disease may benefit from PCR both now and in the future may be better understood if one focuses on the impact of atherosclerosis progression after successful coronary revascularization and examines the comparison of the BARI randomized trial and its parallel registry.

PTCA and Risk of Atherosclerosis Progression

Any coronary revascularization strategy must be evaluated in terms of 2 treatment goals: to provide a safe and durable treatment of flow-limiting epicardial coronary obstructions and to prevent future morbidity and mortality arising from ongoing coronary atherosclerosis in nontreated coronary segments. Historically, however, percutaneous revascularization techniques have been generally evaluated in terms of short-term and midterm procedural success alone, without much consideration toward their role in atherosclerosis prevention. From the outset, PTCA was intended to provide “spot” treatment of the flow-limiting discrete coronary stenosis for limited coronary artery disease. For patients with mild coronary disease, any remaining potential for new, clinically important atherosclerotic lesions has been considered to be small, and the prevention of such low-probability atherosclerosis progression was delegated to risk factor reduction through medical treatment or behavioral modification.

Consequently, once a given target lesion was safely treated, whereby the atherosclerotic segment was converted to a vascular scar virtually incapable of future renarowing via atherosclerosis, long-term patency could be practically guaranteed after the 6-month vascular repair period was reached without significant renarrowing. Thus, PCR has been viewed almost as a “cure” for obstructive coronary disease provided the offending lesion remained patent after 6 months of follow-up. In the prototypical coronary device trial designed for Food and Drug Administration approval, in which multivessel disease is usually excluded, these assumptions may be fair over the observed midterm (<1 year) follow-up. In fact, the 6- to 12-month target lesion revascularization rate (which measures restenosis) has been very similar to the 6- to 12-month target vessel failure rate (which measures target-vessel revascularization plus atherosclerosis-driven recurrent fatal and nonfatal myocardial infarction) in the coronary device trials to date. Thus, the overall potential for clinically important atherosclerosis progression in such populations has been observed to be small.

In the case of choosing a revascularization approach for patients with multivessel disease, the medical decision-
making process that incorporates such a target-lesion perspective may be rather myopic. For patients with multivessel coronary disease, the threat of consequences from atherosclerosis cannot be ignored. The clinical utility of initial PCR for the treatment of multivessel disease should depend on some extent on the rate of atherosclerosis progression and its clinical manifestations. Beyond the conventional 6-month horizon used to contemplate PCR effectiveness for single-vessel disease, the consideration of PCR effectiveness for multivessel disease requires a longer (≥5 years) time horizon. The effect of progressive atherosclerosis on limiting the long-term efficacy of PCR has been pointed out by many investigators and is well understood by most cardiologists when they consider the high ratio of new lesion-to-target lesion restenosis for percutaneous vein graft treatment. If progressive atherosclerosis tends to manifests itself in any given patient as a new flow-limiting but treatable obstruction, the safety, quality of life due to recurrent symptoms, and cost of repeat PCR (or bypass surgery) must be incorporated into the decision-making process. The realization that percutaneous strategies for patients with multivessel disease are associated with the frequent need for repeat revascularization procedures has generated controversy regarding its effectiveness. If, on the other hand, progressive atherosclerosis tends to manifest itself by new unstable plaques and subsequent rupture, causing fatal or nonfatal myocardial infarction, which PCR cannot prevent, the prospect of left ventricular dysfunction or death must be incorporated into the decision.

Is the risk of future adverse outcomes from atherosclerosis progression clearly associated with the severity of coronary disease at the time of initial revascularization? The recurrent myocardial infarction rates seen in the BARI trial were higher for patients with 3-vessel coronary disease (20.2%) than for patients with 2-vessel coronary disease (15.1%). A similar higher risk of myocardial infarction or death based on extent of coronary disease at initial revascularization was also seen in other bypass surgery trials and in the NHLBI PTCA Registry. Trying to gauge the extent of atherosclerosis by angiography is difficult, however, because intravascular ultrasound often discloses extensive disease not seen by angiography. Moreover, the probability that patients with multivessel disease will develop a new clinically significant plaque is based not only on the extent of atherosclerosis already present (in terms of coronary plaque images, a history of myocardial infarction, or the presence of peripheral vascular disease) but also on the presence of untreated risk factors that are known to accelerate the atherosclerosis process, such as cigarette smoking, hypercholesterolemia, and diabetes.

**Surgical Bypass and Its Potential Protective Effect Against Atherosclerosis Progression**

Patients who undergo initial surgical bypass for multivessel coronary disease may be less vulnerable to the consequences of native coronary atherosclerosis progression than patients who undergo initial PCR. Progression of atherosclerosis leading to new plaque ruptures, located within the bypassed native coronary segment, is likely to be of little consequence because the distal myocardial territory is perfused via an alternate route. Compared with PCR, therefore, the benefit of surgical bypass might be proportional to the length of the atherosclerosis-prone coronary segment that is bypassed. In fact, most obstructive lesions or plaque ruptures occur within the proximal 6 cm of epicardial arteries, a distance that is usually “bypassed” by conventional graft surgery.

Although bypass surgery may confer protection against the progression of native coronary atherosclerosis, long-term protection is likely limited to internal mammary grafting. Vein graft conduits are associated with a late-term deterioration process that is somewhat similar to native coronary atherosclerosis, both in its pathophysiology and its clinical manifestation of chronic obstruction and thrombus-mediated abrupt vessel occlusion. The time course required for such a vein graft deterioration process to be fully realized, however, is beyond the current 3- to 6-year follow-up period available from the bypass surgery versus PTCA trials.

**Multivessel Disease, Diabetes, and the Choice of Revascularization Strategy**

At once, the shift of target population from single-vessel coronary disease (and its lower potential for atherosclerosis progression) to multivessel disease (with its higher potential) complicates the choice of revascularization strategy. As the focused “spot” treatment approach of PCR, with all its promising technical advances, enters the realm of multivessel disease previously reserved for the more “holistic” bypass surgical approach, the decision to use PCR must integrate the effectiveness of adjunct antiatherosclerosis therapy and the hope that any breakthrough atherosclerosis will not cause severe injury or death. Despite these potential PCR shortcomings, the multiple randomized trials and large-center experiences of bypass surgery versus PTCA have shown an overall parity between the 2 treatments in terms of midterm (3 to 6.5 years of follow-up) mortality.

The multicenter BARI trial demonstrated no significant difference in all-cause mortality rates or rates of mortality plus Q-wave myocardial infarction at 5.4-year follow-up in the 1829 patients with multivessel coronary disease randomized to PTCA or bypass surgery. When cardiac mortality was compared in the BARI trial, the 8.0% rate of death for patients assigned to PTCA was significantly ($P=0.022$) higher than the 4.9% rate seen in patients assigned to bypass surgery (relative risk $=1.55$), and this difference was due entirely to the diabetic patients.

The cardiac mortality rate for the 353 diabetic patients (the largest reported randomized subset and 19% of the overall BARI trial) currently stands at 23.4% for PTCA compared with 8.2% for bypass surgery ($P=0.0002$, relative risk $=3.10$). The benefit of bypass surgery, however, was mainly seen in those who received 1 or 2 internal mammary artery (IMA) grafts (cardiac mortality was 2.9% for IMA grafts versus 18.2% for vein grafts only) and was more apparent in those diabetic patients who used insulin. The 18.2% cardiac mortality rate for diabetic patients who received vein grafts only was similar to the 20.6% cardiac mortality rate for diabetic patients who received PTCA. Because there was no difference in mortality between nondiabetic patients stratified by IMA grafting, vein grafting, or PTCA, one may speculate that diabetes had similar profound effects on atherosclerosis progression within native coronaries and vein grafts of diabetic patients.
Although the occurrence of new coronary narrowings after PTCA in the BARI trial has been shown to be due in part to target-vessel instrumentation, the risk of diabetes causing widespread atherosclerosis progression makes sense from a biological and epidemiological perspective. Similar to smoking and hypercholesterolemia, diabetes is an independent risk factor that confers cardiovascular death through atherosclerosis, and its effect is potentiated by hyperglycemia, hyperinsulinemia, and lipid abnormalities. In diabetic patients without coronary disease, the risk of death has been shown to be equivalent to that of nondiabetic patients with prior myocardial infarction.

Unlike the randomized BARI results, however, the RITA-I investigators, who have the second largest reported series of randomized diabetic patients, have shown no detrimental diabetes-PTCA interaction in their 1011-patient randomized trial of bypass surgery versus PTCA. Forty-five percent of patients enrolled in RITA-I had single-vessel coronary disease, and the diabetic subset was only 62 patients, compared with 353 in the BARI trial. Nevertheless, there was a trend (P=0.09) for lower mortality in the PTCA group than in the surgical group. BarNESS et al showed no significant detrimental effect of PTCA on diabetic patients from the Duke database, whereas the Emory database reported by Weintraub et al showed a mild effect that was only apparent after adjustment for predictors of long-term mortality.

Understanding the BARI Trial PTCA-Diabetes Interaction

Could the harmful effect of PTCA for diabetic patients with multivessel disease detected in the BARI trial have been overestimated or possibly have been due to chance? Although the magnitude of the effect was large, it is important to point out a few features that may aid in the interpretation of these results. First, there were 4 a priori protocol-specified analyses in the BARI trial: analyses stratified by severity of angina, number of diseased vessels, left ventricular function, and complexity of the lesions. A diabetes-subset analysis was not prespecified and was only added at the request of the safety and data monitoring group in 1992 on the basis of poor outcomes in diabetic patients from the published Thrombolysis In Myocardial Infarction (TIMI) 2 trial, presumably without knowledge of the primary end-point results of the BARI trial. Nevertheless, the BARI study group required the analysis of the diabetic subgroup to show an a-error of <0.005 to 0.01 (which the diabetic subanalysis met) to help correct for the play of chance that was possible with 5 comparisons.

Second, examination of the treatment interaction between PTCA and diabetes (not reported) would have been a reasonable alternative to comparing the main effect of PTCA versus bypass surgery within the subset of diabetic patients (reported). Such main-effect analysis within the subset does not adjust for any potential main-effect tendencies already present between the 2 randomized treatments. Given the magnitude of the difference in outcomes from the subgroup analysis, however, the treatment interaction was probably highly statistically significant. Third, there is a statistical proclivity to overestimate an effect observed from any positive subgroup analysis that becomes “hypothesis generating,” with a tendency to observe less effect in subsequent trials due to a random-chance process very similar to regression to the mean seen with screening for outlier values.

Comparing the BARI Trial and Registry

In this light, we should now evaluate the comparison of the BARI randomized trial with the parallel observational registry, in which 339 patients (17% of the overall registry) who met eligibility criteria for the randomized trial were not randomized but underwent PTCA or bypass surgery by choice. Parallel registries are often used to test for the consistency of any treatment effect observed in the randomized trial. Because a parallel observational registry sample is generally more heterogeneous than a randomized sample, in the sense that patients selected for randomization are restricted by “randomizable” patient characteristics (such as unmeasured factors that make some patients more suitable than others for both randomized treatments), there is a notion of “real world” testing that makes the analysis of registry results appealing. In observational registries, however, the potential for confounding by selection bias is great, and thus the randomized trial should always be considered as the primary clinical test.

The clinical implications of not finding a consistent main-effect result between the registry and the randomized trial (such as an overall equivalency in mortality between PTCA and bypass surgery) must be interpreted cautiously. Moreover, the importance of showing similar subgroup effects (such as the same differential mortality outcome in the diabetic subset) to reinforce or extend clinical inference is possibly overreaching. Nonetheless, if a conservative approach in the interpretation of the results is used so that the inference is not overextended, careful analysis of parallel registries can provide some value in evaluating the confidence of an unexpected finding seen in the randomized trial.

Although the main randomized BARI trial showed a significant mortality risk for diabetic patients randomized to PTCA compared with bypass surgery, the BARI registry showed no significant difference (cardiac mortality for PTCA was 7.5% compared with 6.0% for surgery; P=0.73). Unlike the randomized trial, there was no significant reduction in 5-year cumulative survival for patients using insulin who received PTCA. After adjustment was made for the differences in clinical and angiographic factors, the relative risk in predicted mortality was more exaggerated but not statistically different for PTCA compared with bypass surgery (the relative risk of cardiac death for PTCA increased from 1.07 to 1.35 after adjustment for angiographic and clinical variables).

The authors offered several explanations as to why the registry results did not show the same degree of harmful effect of PTCA seen in the BARI randomized trial. Patient characteristics were different between the registry group and the randomized trial. On average, registry patients had attained a higher educational level, were more physically active, were less likely to smoke, and had indicated on self-evaluated questionnaires a higher level of quality of life. These factors could be related loosely to better diabetes control for the registry group than for the randomized group, and thus the registry patients might have had less diabetes-induced progression of atherosclerosis than the randomized...
patients. Diabetes control was not measured in the BARI randomized trial or registry. Whether diabetes or its control had additional plaque effects for any given measurable level of atherosclerosis (such as number of vessels diseased) cannot be known. However, atherosclerotic plaque constituency and presumably its natural history do vary among individuals with different risk factors.29

What is more likely to explain the differences in outcomes of diabetic patients between the BARI randomized trial and its registry is the difference in baseline measures of atherosclerosis between the PTCA and surgical groups within the registry. In the registry, unlike the randomized trial, which successfully balanced atherosclerosis severity, there were profound differences due to nonrandom treatment assignment. The incidence of 3-vessel coronary disease in the surgical group, for example, was almost twice that in the PTCA group. When this observation is combined with the results of the randomized trial, the incidence of 3-vessel coronary disease was 35% for the PTCA registry group, 45% for the randomized trial group (the PTCA and bypass surgery groups are assumed to be the same via randomization), and 60% for the bypass surgery registry group. Although the incidence of 3-vessel coronary disease is a crude measure of overall atherosclerosis tendency for each group, the severity of atherosclerosis was likely highest in the bypass-surgery registry group and lowest in the PTCA registry group. Indeed, it would appear that diabetic patients with multivessel disease who were eligible for enrollment into the BARI trial were subject to certain routing tendencies based on atherosclerosis severity: those with limited atherosclerosis were likely to be considered only for PTCA, those with moderate atherosclerosis were likely to be randomized in the BARI trial, and those with severe atherosclerosis were likely to be considered only for surgery.

In this context, comparison of outcomes between the PTCA and surgery groups within the registry was likely confounded by the most important determinant of late mortality, the degree of atherosclerosis. The modest increase in relative risk, from 1.07 to 1.35, seen after clinical and angiographic factor adjustment may not reflect the true difference in risk for PTCA compared with bypass surgery. The similarity in unadjusted 5-year mortality rates between PTCA and bypass surgery seen in the BARI registry could be conjectured to be the result of comparing patients who possessed a low risk of atherosclerosis progression and were treated by PTCA with patients who possessed a high risk and were treated, but also protected against atherosclerosis progression, by surgery. Moreover, the difference in the extent of atherosclerosis between the 2 nonrandomized groups may not have been fully revealed by the incidence of 3-vessel disease (or number of significant lesions), because there are likely other, nonmeasurable clinical and angiographic cues of atherosclerosis severity that are used by cardiologists and cardiac surgeons to determine revascularization strategy.

Several additional findings support the importance of considering atherosclerosis progression when choosing a revascularization strategy for diabetic patients. The mortality outcomes for PTCA were dramatically different between the registry and randomized trials: 14.4% for the registry arm, with its mild-to-moderate degree of atherosclerosis, and 34.5% for the randomized arm, with its moderate degree of atherosclerosis. Interestingly, there were no significant differences in all-cause mortality between the surgical groups: 19.4% for the randomized arm with its moderate degree of atherosclerosis and 14.9% for the registry with its severe degree of atherosclerosis. Furthermore, the slight reduction in mortality for the registry surgical group compared with the randomized surgical group may have been due in part to a trend toward more frequent IMA usage (87% for the registry versus 81% for the randomized trial; \(P = 0.15\)). These results, on the whole, support the notion that the effectiveness of PCR in diabetics with multivessel disease is highly sensitive to the level of severity of atherosclerosis present at initial therapy, whereas the effectiveness of bypass surgery, with its conduit bypass protective effect, is less sensitive to such variations in atherosclerosis severity.

**Making the Hard Call**

In choosing the best treatment for both diabetic and nondiabetic patients, one must consider the force of atherosclerosis progression that may cause future clinically important coronary narrowings and plaque ruptures. The clues that can be used to predict high-probability atherosclerosis progression are not exact and include the extent of disease, seen by coronary angiography or intravascular ultrasound, and the patient’s risk factor profile, including the presence of diabetes mellitus. The diagnostic coronary angiogram and intravascular ultrasound, therefore, give a snapshot of the magnitude of coronary atherosclerosis, which must be factored in with the slope of expected atherosclerotic progression, which is steep in diabetic patients. If the potential for progression is deemed to be great, PCR, even when combined with antiatherosclerosis medical therapy, is not very protective of the consequences of atherosclerosis, which include fatal myocardial infarction. Despite the fact that coronary stents, radiation therapy, the glycoprotein IIb/IIIa receptor blockers, or other advances may substantially reduce the high incidence of diabetic restenosis for discrete lesions, the remaining untreated coronary vessel is vulnerable to catastrophic events. Bypass surgery, on the other hand, appears to offer some protection from atherosclerosis progression, simply by providing a bypass conduit beyond the epicardial coronary segment most vulnerable to future plaque development. When the replacement conduit is a vein graft, however, one may be providing only a reprieve from atherosclerotic events in the native coronaries, because the graft itself may undergo degeneration and cause obstruction or occlusion at a later date. The importance of using IMA grafting for diabetic patients referred for surgery, therefore, cannot be overstated.

For patients with diabetes mellitus and clinically important multivessel coronary disease, the revascularization decision remains complex. The BARI study group should be congratulated for providing the data needed to help answer this important revascularization question. The results of the comparison of the BARI randomized trial and its registry suggest that patients with advanced 3-vessel coronary disease who are insulin-requiring diabetics should be revascularized by use of bypass surgery. Further interpretation of the comparison of the BARI trials and the results of RITA-P and EAST10 suggests that diabetic patients...
(especially those taking oral hypoglycemic agents) with minimally apparent multivessel disease (2-vessel disease) could be considered for PCR. Those diabetic patients with a moderate degree of atherosclerosis, especially those requiring insulin, should probably be considered for surgery until the results of longer follow-up of existing trials and future trials are completed, such as the 10-year BARI follow-up and the coronary- stent–bypass-surgery trials (ARTS and SOS). The importance of research in atherosclerosis prevention and its reversal could not be greater than for diabetic patients. There is also a need for better quantitative scales of coronary atherosclerosis severity (possibly intravascular ultrasound) and longitudinal correlation with adverse events if we are to accurately predict the consequences of atherosclerosis and make better decisions. Needless to say, the most important planned study to determine the optimum revascularization approach for diabetic patients is the BARI-II randomized trial, which aims to broaden the inclusion criteria of BARI-I, include coronary stents, and reinforce and measure glucose and lipid control, which have been shown to affect future cardiovascular events.

References

Key Words: Editorial ▪ revascularization ▪ diabetes mellitus ▪ bypass ▪ angioplasty.

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