Diabetes with Coronary Disease — A Moving Target amid Evolving Therapies?

William E. Boden, M.D., and David P. Taggart, M.D., Ph.D.

The prevalence of diabetes mellitus is rising at an alarming rate and is projected to more than double by 2030. The disease currently affects 171 million people worldwide, with 23.6 million in the United States. The adverse microvascular and macrovascular consequences of diabetes are well recognized, as is the accompanying accelerated rate of atherosclerosis that predisposes patients to coronary artery disease and to higher rates of myocardial infarction and death. Treatment strategies that are aimed at reducing these events have embraced both optimal medical therapy (lifestyle intervention, vigilant glycemic control, and aggressive secondary prevention) and interventional management (catheter-based and surgical revascularization).

In a previous study, investigators in the Bypass Angioplasty Revascularization Investigation (BARI) trial (ClinicalTrials.gov number, NCT00000462), who compared percutaneous coronary intervention (PCI) using balloon angioplasty with coronary-artery bypass grafting (CABG) in patients with coronary disease, reported no overall difference in long-term rates of death and myocardial infarction. However, their initial study also showed that patients with diabetes had significantly better survival after CABG than after PCI. Confusion ensued when subsequent analyses of smaller randomized trials and larger clinical registries did not replicate these findings, whereas many observers suggested that the advent of bare-metal stenting had made these earlier results obsolete.

More recently, two new pieces of data have emerged regarding revascularization in patients with diabetes. First, the BARI investigators reported that the survival benefit of CABG persisted at 10 years. Second, in a collaborative meta-analysis of 10 studies involving 7812 patients who had undergone either PCI or CABG, there was a significant 30% reduction in total mortality among patients with diabetes who had undergone CABG — a finding that persisted even after the BARI trial was excluded.

In this issue of the Journal, Frye and colleagues report the findings of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial (NCT00006305), which involved 2368 patients with both diabetes and coronary disease. The investigators simultaneously addressed two parallel strategies and hypotheses for reducing long-term rates of death and cardiovascular events: first, that prompt revascularization (with either PCI or CABG) would be superior to optimal medical therapy alone; and second, that insulin sensitization (with a target glycated hemoglobin level of less than 7.0%) would be superior to insulin provision. Notably, the use of either PCI or CABG was prespecified before randomization, with patients who had more severe coronary disease typically undergoing CABG.

Although both hypotheses were negative for the primary end point of death from any cause, two prespecified analyses of a secondary composite end point (death, myocardial infarction, or stroke) provided potentially important scientific and clinical insights. First, insulin-sensitizing therapy was associated with fewer secondary end points than the use of insulin, especially among patients undergoing CABG. Second, as compared with optimal medical therapy, patients who underwent CABG (but not PCI) had significantly fewer major cardiac events, an important finding that was driven mainly by a reduction in non-fatal myocardial infarction. Although it is essen-
tial to stress that BARI 2D was not designed to directly compare long-term outcomes between PCI and CABG, the differences in secondary end points render indirect comparisons likely.

What limitations might affect the generalizability of these results to all patients with both diabetes and coronary disease? No data are provided regarding the proportion of eligible patients who were screened or excluded. The enrolled patients were generally at relatively low risk for major cardiovascular events on the basis of baseline angina symptoms, the extent of coronary artery disease, and ventricular function. The trial may have lacked adequate statistical power for the analyses of both primary and secondary end points, since neither the original target number of patients nor the estimated rate of events was achieved. The rates of use of both drug-eluting stents (35%) and thienopyridines (21%) were very low by contemporary treatment standards. Indeed, in a recent analysis of more than 2.6 million patients who underwent PCI from 2005 through 2007 at 968 U.S. sites, 58% of PCI procedures were performed electively in patients with stable coronary disease, of whom 35% had diabetes; the rates of use of drug-eluting stents in patients with diabetes and in those without diabetes were virtually identical (78%). However, since several randomized trials and meta-analyses have shown no significant reduction in rates of death and myocardial infarction with drug-eluting stents, as compared with bare-metal stents, it seems unlikely that greater use of drug-eluting stents would have altered the overall trial results. Finally, in both the glycemic control and revascularization strata, rates of concomitant, alternative therapy and crossover were high, with 42% of patients in the medical-therapy group requiring subsequent revascularization. Of these procedures, almost half occurred during the first year of follow-up.

In any clinical trial that does not meet its primary end point, the potential medical relevance of secondary outcomes must be interpreted with considerable caution and in the context of what has already been established. Accordingly, several points merit consideration. The BARI 2D results replicate the principal finding of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial (NCT00007657) — that an initial strategy of PCI provides no incremental clinical benefit over intensive medical therapy, including in patients with both diabetes and coronary disease. Among patients who remain symptomatic despite intensive medical therapy or who have substantial ischemia or extensive coronary artery disease, revascularization is appropriate, and either PCI or CABG is a reasonable choice, depending on the anatomical complexity of disease. If a further goal of revascularization is to reduce long-term events (especially myocardial infarction), BARI 2D reinforces other current scientific evidence supporting the benefits of CABG over PCI, especially in patients with diabetes and those with multivessel coronary artery disease. The cardioprotective superiority of CABG is postulated to result from bypass grafts to the midcoronary vessels that not only treat culprit lesions (even anatomically complex ones) but also afford prophylaxis against new proximal disease, whereas stents treat only suitable stenotic segments with no benefit against native coronary disease progression.

Finally, the BARI 2D investigators found that as compared with insulin provision, insulin-sensitization therapy significantly improved several metabolic and clinical measures, including plasma insulin levels, glycated hemoglobin control, levels of high-density-lipoprotein cholesterol, weight gain, and severe hypoglycemia — particularly in the CABG cohort.

BARI 2D further underscores how major advances in PCI, CABG, and optimal medical therapy have created a constantly moving target against which the comparative effectiveness of rapidly evolving treatments must be repeatedly assessed. Will the results of BARI 2D change clinical practice? In the United States, the use of PCI, particularly with drug-eluting stents, remains high (1.2 million procedures per year). Yet, as health care costs continue to spiral upward, physicians, payers, and health economists need to make informed, evidence-based treatment decisions that improve both symptoms and clinical outcomes. BARI 2D shows that for many patients with both diabetes and coronary disease, optimal medical therapy rather than any intervention is an excellent first-line strategy, particularly for those with less severe disease. When revascularization is indicated, both BARI 2D and other studies support the use of CABG as the preferred approach, unless or until future studies indicate otherwise. Finally, although the results of any randomized trial must be individualized for specific patients,
a “multidisciplinary team approach” to clinical decision making, as originally advocated by Simoons\textsuperscript{13} and used successfully in a recent trial,\textsuperscript{10} can ensure that all therapeutic options (optimal medical therapy, PCI, and CABG) are fully and transparently discussed so that patients are offered the most appropriate, evidence-based treatment recommendations.

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From the Department of Medicine, State University of New York at Buffalo Schools of Medicine and Public Health, Buffalo (W.E.B.); and Nuffield Department of Surgery, Oxford University, John Radcliffe Hospital, Oxford, United Kingdom (D.P.T.).


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