Managing Stable Coronary Disease in Patients With Diabetes: The BARI 2D Trial

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STUDY

SUMMARY
Design. BARI 2D is a multicenter, randomized, controlled trial.

Subjects. A total of 2,368 adults (average age 62 years) with diabetes (average A1C 7.2%) and coronary artery disease (CAD; based on angiography with > 50% blockage in a major epicardial artery and a positive stress test, or > 70% blockage with anginal symptoms) participated. Patients who required immediate revascularization or had left main disease, a creatinine level > 2.0 mg/dl, an A1C level > 13%, class IV heart failure, liver dysfunction, or revascularization within the previous 12 months were excluded.

Methods. The BARI 2D trial was designed to test and compare benefits of coronary revascularization and medical therapy, as well as insulin sensitization versus insulin provisional therapy for CAD in patients with diabetes. Enrolled patients underwent categorization to coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) groups based on the clinical judgment of their treating physician.

Two independent randomizations then occurred, in a two-by-two factorial design. In both the CABG and PCI groups, patients were randomized to primary revascularization plus medical therapy versus medical therapy alone. Independent of these results, both groups were also randomized to insulin provisional therapy (insulin and sulfonylureas) or insulin sensitization therapy (mainly metformin and thiazolidinediones).

All patients had goals of A1C < 7%, LDL cholesterol < 100 mg/dl, blood pressure < 130/80 mmHg, counseling for tobacco cessation, weight loss, and exercise. Those assigned to the revascularization arm were sent for PCI or CABG within the first 4 weeks. PCI group members had an average of 1.5 stents placed (34% drug-eluting and the remainder bare metal).

The primary study end point was all-cause mortality. A secondary end point was a composite of mortality, myocardial infarction (MI), and stroke. MI was defined as doubling of cardiac enzymes and symptoms, electrocardiographic changes, or supportive imaging. Peri-procedure events were defined as a tripling of cardiac enzymes post-PCI or a ten-fold increase after CABG.

Outcome assessors for MI and stroke events were blinded to the study arm. Data were collected during 6 years until 2008, with an average length of follow-up of 1.5 years. Outcomes were analyzed on an intention-to-treat basis. There was considerable crossover between groups (42% of those in the medical therapy arm eventually underwent revascularization; 40% of those in the insulin sensitization arm and 11% of those in the insulin provision arm received medications from the other strategy).

Results. The CABG and PCI groups differed in several characteristics. Most importantly, triple-vessel disease was more common in the CABG group than in the PCI group (52 vs. 20%). For the CABG and PCI groups combined, there was no difference in survival between the revascularization arm and the medical therapy alone arm (87.8 vs. 88.3%, P = 0.97).

For secondary outcomes, patients within the CABG stratum who were assigned to revascularization had significantly fewer major cardiovascular events than those randomized to medical therapy (22.4 vs. 30.5%, P = 0.01). The largest difference was in nonfatal MIs (7.4 vs. 14.6%). In the PCI group, the chance of major cardiovascular events did not differ between revascularization or medical therapy arms (23.0 vs. 21.1%; P = 0.15).

No difference in mortality or incidence of major cardiovascular events was noted between provisional insulin and insulin sensitization therapy. However, insulin sensitization appeared to have fewer complications, such as hypoglycemic events and weight gain.

Conclusion. The addition of early revascularization does not appear to improve outcomes compared with medical therapy alone for those assigned clinically to PCI. For those assigned clinically to CABG, early
revascularization appears to reduce nonfatal MIs, but not all-cause mortality. Insulin sensitization and insulin provisional therapies appear equivalent in their outcomes, but sensitization-based therapy may decrease adverse effects.

COMMENTARY
The BARI 2D study suggests that revascularization in addition to medical therapy fails to improve outcomes over optimal medical therapy for those clinically assigned to receive PCI. Those clinically thought to be candidates for CABG appear to have a reduced risk of coronary heart disease events, mainly nonfatal MIs. However, patients were assigned to the PCI and CABG groups based on overall clinical impression, and it remains unclear which specific characteristics define those who will benefit from early revascularization with CABG. It is also unclear whether differences in clinical characteristics or differences in the revascularization procedure itself account for the differences in outcomes observed.

BARI 2D addressed several clinically relevant end points; however, some important outcomes were not addressed. One unmeasured and clinically significant end point is symptom improvement. Eighty-two percent of the randomized patients had symptomatic angina at the start of the trial, but the effect of interventions on this outcome was not reported. The cognitive effects of undergoing CABG and its effects on patients’ self-reports of quality of life were also not assessed. Other pertinent limitations to this study include lack of long-term follow-up and relatively wide confidence intervals. Both limit the sensitivity for detecting smaller but important treatment differences.

BARI 2D also examined the question of whether insulin provision or insulin sensitization was more effective. The trial was designed to test the theory that sensitization therapy could improve cardiovascular outcomes compared to provisional therapy, based on several observational studies showing a correlation between elevated blood insulin levels and cardiovascular events. However, the two strategies appeared equivalent in this study, despite the anticipated reduction in serum insulin levels in the primarily sensitization group. This aspect of the study was limited by extensive crossover between groups.

Although the question of serum insulin level importance is scientifically intriguing, its application to clinical medicine is likely to be limited. Groupings of medications with differing mechanisms of action (such as insulin and sulfonyureas or metformin and thiazolidinediones) allows for little control based on mechanism. It allows for no control of the various other effects of each medication or for specific medication use or order of application.

The results of BARI 2D are consistent with the main findings of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial, suggesting that no clinically significant benefit is observed when primary PCI is added to optimal medical therapy in patients with diabetes and stable coronary heart disease. Specifically, optimal medical therapy appears to be as effective or more effective than PCI added to medical therapy in patients without an indication for CABG, emergent revascularization, or refractory angina. PCI intervention may also expose patients to undue risk, given the need for long-term anti-platelet therapy, a factor not addressed or measured in this trial.

Given the lack of clear benefit from early PCI, the practice in most U.S. centers of linking a CAD diagnosis through coronary angiography to therapeutic PCI is potentially problematic. Current evidence does not support the routine early addition of primary PCI to optimal medical therapy. Therefore, cardiologists should consider stopping the practice of performing routine PCI after diagnostic angiography in patients who have not had the opportunity to receive a trial of optimal medical therapy. If PCI is performed in the non-acute setting, it is important for patients to understand that the goal of therapy is improved relief of angina and not a reduction in the risk of MI or death.

REFERENCES

Britni Hebert, MD, is a second-year resident and Andrew Sampson, MD, is a chief resident in the Department of Medicine at the University of North Carolina School of Medicine in Chapel Hill.