Implications of Contemporary Clinical Trials

General Cardiology Perspective: Decision Making Regarding Revascularization of Patients With Type 2 Diabetes Mellitus and Cardiovascular Disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial

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The interest in the diabetic population undergoing coronary revascularization began with the reporting of the Bypass Angioplasty Revascularization Investigation (BARI) trial in 1996.1 In patients with multivessel disease, a post hoc analysis demonstrated a significant survival advantage for patients in the coronary artery bypass grafting (CABG) arm compared with those undergoing balloon angioplasty. This striking finding sensitized the cardiovascular community to the unique nature of diabetic coronary disease. A comprehensive meta-analysis of percutaneous coronary intervention (PCI) versus CABG trials before the drug-eluting era has confirmed the BARI findings.2 Over the next decade, there were tremendous advances in medical risk factor modification, particularly the widespread use of statin drugs and improvements in therapies for glycemic control. The BARI 2 Diabetes (BARI 2D) investigators posed the next important question about optimal management of coronary disease in patients with less severe symptomatology than those enrolled in the multivessel PCI versus CABG trials.3 About 80% of patients were either asymptomatic or had stable class I/II Canadian Cardiovascular Society angina. In this trial, the comparison was now between prompt revascularization on top of optimal medical therapy (OMT) versus OMT alone. BARI 2D heralded in a new era in National Heart, Lung, and Blood Institute–sponsored trials by exclusively studying patients with type 2 diabetes mellitus. BARI 2D demonstrated no difference in 5-year mortality between the prompt revascularization and OMT alone arms (11.7% versus 12.2%; \( P=0.97 \)) as well as no difference in 5-year rates of the combined end point of death, myocardial infarction, and stroke (22.8% versus 24.1%; \( P=0.70 \)).

How Can the BARI 2D Findings Translate Into Recommendations for Clinical Practice?
The most efficient way to evaluate the impact of BARI 2D on practice is to evaluate the patients studied and the interventions that were applied.

The Patients
BARI 2D randomized patients with demonstrated ischemia who were either asymptomatic or who had mild to moderate symptoms. All patients had undergone a diagnostic angiogram. This puts into play 2 important variables: degree of ischemia based on symptoms and/or a functional study and the extent of coronary disease based on angiography. Before the impact of these 2 important determinants is evaluated, it is critical to evaluate the characteristics of the BARI 2D cohort.

One of the most impressive aspects of the BARI 2D trial was the generalizability of the cohort to a real-world cardiology practice. Approximately one third of patients had a prior myocardial infarction, and 20% had undergone PCI in the past. Recently, clinical trials have been heavily criticized for having to screen many more patients to recruit the study population. In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, >25 000 patients were screened to recruit 2287.4 By comparison, BARI 2D screened only 4623 patients to recruit 2368. Most impressively, 96% of the 2463 patients found to be meet eligibility criteria were eventually randomized into the trial.

Taking into account the extent of ischemia has important implications for how we translate the BARI 2D findings into practice. Because the BARI 2D trial reported results only a few months after the Detection of Ischemia in Asymptomatic Diabetics (DIAD) trial, it is important to place these 2 pivotal trials into context.5 DIAD arose because of a real-world question: What is the role of routine coronary ischemia screening of asymptomatic patients with type 2 diabetes mellitus? DIAD randomized >1000 patients with diabetes mellitus to either myocardial perfusion imaging or routine medical care and followed the patients for 5 years. The most striking finding was an exceedingly low yield of moderate to large perfusion defects in the screening arm (6%) and a very high adherence to an optimal medical risk factor program. At 5 years, there was no difference in the rates of cardiac death
and nonfatal myocardial infarction between the 2 groups. On the heels of DIAD, the evidence for routine screening of asymptomatic patients with type 2 diabetes mellitus in the era of OMT is nonexistent. On the other hand, selective screening of asymptomatic patients at highest risk is warranted given the moderate likelihood for ischemia on stress testing. It is important to note that about 20% of patients enrolled in BARI 2D were asymptomatic.

For patients with mild to moderate symptoms, what is the role for screening for coronary ischemia? With regard to extent of coronary artery disease (CAD), this cohort had predominantly stable multivessel CAD. Left main disease was excluded from the trial, but almost 40% of patients had 3-vessel CAD. Compared with the extent of ischemia, there was a wide variation in the extent of disease and the amount of myocardium at risk as measured by the myocardial jeopardy index. Overall, the mean myocardial jeopardy index was 46%. The best predictors of extensive CAD were hypertension, advanced age, low-density lipoprotein cholesterol levels, and a low ankle-brachial index ≤0.90.

The Interventions
BARI 2D not only involved the question of prompt versus deferred revascularization but also emphasized OMT in all participants. The majority of resources in BARI 2D were devoted to the intensive medical surveillance of study subjects.

Selection of Revascularization Strategy
In BARI 2D, the decision about whether the patient was enrolled in the CABG versus OMT stratum or the PCI versus OMT stratum was left up to the discretion of the attending physician. There was wide regional variability in the selection of strata that reflected the differences in interventional practice. For the most part, patients selected for the CABG stratum were higher-risk patients and were more likely to have more extensive CAD and a higher myocardial jeopardy index compared with the PCI stratum. This higher risk is reaffirmed in the clinical outcome findings, whereby 30.5% of patients in the OMT arm of the CABG stratum experienced a major adverse cardiac event by 5 years compared with only 21% in the OMT arm of the PCI stratum. Because of this higher baseline risk, the CABG stratum had greater power to show a difference between prompt revascularization and OMT. The observation that CABG was more effective than OMT in preventing 5-year major adverse cardiac events (22.4% versus 30.5%; \(P=0.01\)), whereas no difference was observed between PCI and OMT in the PCI strata, has led some to conclude that CABG is superior to PCI in BARI 2D. However, any comparison between CABG and PCI is highly problematic and without solid methodological grounds. This finding is interesting only in that there was a clear subpopulation in BARI 2D that benefited from CABG. This is consistent with our understanding of the benefits of surgical revascularization in patients with diabetes mellitus with more extensive CAD. This is also consistent with the Synergy Approach to patients with type 2 diabetes mellitus with stable CAD. LDL indicates low-density lipoprotein.
Between PCI With Taxus and Cardiac Surgery (SYNTAX) score demonstrated that patients with a high score based on angiographic features had a greater benefit from CABG over PCI.8

**Crossover**

Because BARI 2D compared a strategy of prompt versus “deferred” revascularization, it is critical to acknowledge that by 5 years, ≈ 40% of patients randomized to OMT alone eventually underwent a subsequent revascularization. This highlights the fact that even committing to an OMT strategy upfront will not prevent a substantial number of future revascularization procedures.

**Optimal Medical Management**

The American Diabetes Association and the American Heart Association have progressively advocated for more aggressive targets for key medical risk factors, including low-density lipoprotein <100 mg/dL, blood pressure <130/80 mm Hg, and hemoglobin A1C <7.0%. The BARI 2D investigators followed subjects every 3 months for the duration of the trial, and the results are impressive. Over a 3-year follow-up, a majority of patients had achieved optimal goals for low-density lipoprotein cholesterol (83%) and blood pressure (71%). As in the COURAGE trial, this is testimony for low-density lipoprotein cholesterol (83%) and blood pressure (71%). As in the COURAGE trial, this is testimony that OMT can be achieved in the setting of a clinical trial far more effectively than in routine clinical practice. This may be the major message of BARI 2D: Can your patient achieve the aggressive targets set by the national guidelines?

**Clinical Decision Making**

In proposing a clinical decision-making strategy, it is clear that 3 variables will influence the decision of whether or not to revascularize a patient with type 2 diabetes mellitus patient presenting to the general cardiologist: (1) the extent of ischemia; (2) the extent of CAD with emphasis on the presence or absence of multivessel disease, the SYNTAX score, and the myocardial jeopardy index; and (3) the potential to achieve optimal risk factor modification in a real-world setting. The Figure outlines a strategy to approach patients with type 2 diabetes mellitus at risk for coronary disease. The ongoing Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial will help clarify this figure more precisely.9

**Conclusions**

The evaluation and management of diabetic patients with stable CAD has been significantly affected by the findings of the BARI 2D trial. With a goal of background OMT in all patients, the approach to revascularization is ultimately individualized. The willingness of clinicians to defer revascularization in light of BARI 2D will require a comprehensive follow-up plan in concert with our colleagues in primary care.

**Disclosures**

None.

**References**


**Key Words:** coronary artery disease ■ diabetes mellitus ■ disease management
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