Cardiovascular disease is the leading cause of morbidity and mortality for patients with type 2 diabetes mellitus (T2DM), accounting for two thirds of patient deaths. In addition to traditional cardiovascular risk factors, hyperglycemia and multiple other factors associated with T2DM such as obesity, insulin resistance, and inflammation play significant roles in cardiovascular disease risk. Patients with diabetes mellitus have derived less benefit from multiple preventive and interventional advances. Indeed, in the Bypass Angioplasty Revascularization Investigation (BARI) trial, angioplasty appeared to provide very little benefit for patients with diabetes mellitus, a finding supported by a meta-analysis of randomized interventional trials, although modern revascularization techniques with the use of drug-eluting stents were not yet widely utilized.

Therefore, the questions addressed in the BARI 2 Diabetes (BARI 2D) trial are of particular importance in determining optimal treatments to prevent mortality and major cardiovascular events in patients with T2DM and stable ischemic heart disease. Both prompt revascularization compared with intensive medical therapy alone or with delayed revascularization, and insulin-sensitization compared with insulin-provisional therapeutic strategies were evaluated in 2368 patients over 5 years with the use of a 2×2 randomized factorial trial design. With recognition of the cardiovascular benefits of optimal management of diabetes mellitus and cardiovascular risk factors in patients with diabetes mellitus, the BARI 2D study was performed with guideline-driven targets for lipids, blood pressure, and aspirin use.

Medical Therapy Compared With Prompt Revascularization
First, in a comparison of prompt revascularization with intensive medical therapy alone or with delayed revascularization, similar survival (88.3% versus 87.8%; \( P=0.97 \)) and freedom from cardiovascular event rates (77.2% versus 75.9%; \( P=0.70 \)) were demonstrated. However, a high proportion (42%) of subjects initially randomized to medical intervention received delayed revascularization. These findings extend those of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, in which an initial management strategy of percutaneous coronary intervention (PCI) when added to optimal medical therapy did not reduce mortality or cardiovascular event rates, although only approximately one third of patients in this trial had diabetes mellitus. Taken together, these trials support the use of optimal medical therapy for those with diabetes mellitus and stable coronary artery disease who prefer not to have an invasive procedure. Furthermore, because the treating cardiologist a priori selected the revascularization method, either coronary artery bypass grafting (CABG) or PCI, on the basis of clinical and angiographic factors, patients randomized to CABG compared with PCI more frequently had 3-vessel disease and proximal left anterior descending artery lesions and had more total occlusions and higher myocardial jeopardy scores. Thus, the BARI 2D trial does not directly compare CABG and PCI interventions. Notably, in subgroup analysis, among higher-risk patients with diabetes mellitus selected for CABG, prompt revascularization was shown to reduce major cardiovascular event rates compared with delayed or no revascularization (freedom from cardiovascular disease event, 77.6% versus 69.5%; \( P=0.01 \)), whereas among lower-risk patients selected for PCI, prompt revascularization compared with delayed or no revascularization had similar major cardiovascular event rates.

Insulin-Provisional Compared With Insulin-Sensitization Therapeutic Strategies
The second major aim of the BARI 2D study addressed the question of whether insulin provision (through either replacement or secretagogues) is associated with worse cardiovascular outcomes compared with insulin-sensitization strategies. Optimal therapeutic strategies to lower blood sugars and glycemic targets to improve cardiovascular outcomes have been under investigation for more than a half century, originating with the University Group Diabetes Program study. The University Group Diabetes Program evaluated mortality in T2DM patients randomized to tolbutamide, fixed...
or variable insulin-dosing regimens, or placebo. Surprisingly, mortality and death attributed to cardiovascular causes were 1.7 to 2.9 times higher in the tolbutamide-treated group and were equivalent, but not lower, in either insulin-treated group compared with placebo. These unexpected findings first fueled the controversy about whether insulin provision itself was associated with adverse cardiac risk. Subsequently, the finding of highest mortality in the tolbutamide-treated group was attributed to reduced ischemic preconditioning seen predominantly, but not exclusively, with first-generation sulfonylureas.

Increased plasma insulin concentrations have been associated with adverse cardiovascular outcomes, regardless of whether the insulin source is exogenous (ie, administered therapeutically) or endogenous in origin. On the other hand, insulin treatment in both type 1 and type 2 diabetes mellitus has been associated with improved outcomes over the long term. However, if a patient requires more insulin to maintain glycemia, then the patient is more resistant to insulin, and higher insulin concentrations without hypoglycemia define insulin resistance. Insulin resistance per se has been associated with incident diabetes mellitus, hypertension, dyslipidemia, and atherosclerosis and with participating in the pathogenesis of these components of the metabolic syndrome. Thus, it remains difficult to distinguish whether higher insulin concentrations themselves or insulin resistance and associated metabolic abnormalities account for the increased cardiovascular risk, although, in all likelihood, the high fasting insulin concentrations (particularly in people without diabetes mellitus) reflect underlying insulin resistance and thereby effects on cardiovascular risk.

In the BARI 2D trial, in patients with T2DM and documented ischemia and stable coronary artery disease, neither mortality nor cardiovascular event rates differed according to either insulin-sensitization or insulin-provisional strategies (survival, 88% versus 88% [P=0.89]; freedom from cardiovascular disease event, 78% versus 75% [P=0.13]). Of note, in secondary analysis, insulin-sensitization therapies appeared to enhance the benefit of revascularization in the higher-risk subgroup of patients selected for CABG. Additionally, insulin sensitization was associated with lower body mass index, higher high-density lipoprotein cholesterol level, and lower rates of severe hypoglycemia.

It is interesting to speculate on the reasons why insulin-sensitization compared with insulin-provisional strategies were not more favorable, as hypothesized, despite statistically significant changes in insulin concentration (median, 6.3 versus 10.0 μU/mL; P<0.001). There are multiple potential reasons. First, there was substantial crossover between treatment groups, so that at the end of the intervention period, 92% of those randomized to insulin-provisional regimens were receiving the assigned treatment, but 18% were receiving insulin-sensitization agents; however, although 80% of those randomized to insulin-sensitization regimens were receiving the assigned treatment, fully 54% were also receiving insulin-provisional agents. Crossover would attenuate the ability to identify potential differences between treatment strategies. Second, although an association with cardiovascular risk is demonstrated across the entire spectrum of insulin resistance in a population of patients with T2DM and advanced cardiovascular disease, the magnitude and duration of change in insulin resistance may not have been sufficient to demonstrate clear clinical differences. Alternatively, increased insulin concentrations or insulin resistance per se may be a biomarker for atherosclerosis but not directly associated with worse cardiovascular outcomes, such that altering insulin concentration or insulin sensitivity may not directly alter the outcome of interest. Overall, these results are compatible with the “mixed” results of the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial, in which, despite some benefits of pioglitazone on the primary composite cardiovascular event end point was not reduced significantly.

In the BARI 2D trial, individual drugs were not tested, and the outcomes result from mixed benefits and unintended adverse effects for multiple drugs used in either stratum. As mentioned above, both insulin and sulfonylureas have been implicated to have potential adverse cardiovascular consequence, yet the insulin sensitizer rosiglitazone has also been suggested to increase the risk of myocardial infarction and death from cardiovascular causes. BARI 2D assessed therapeutic strategies rather than any specific drug. Although no mortality benefit was realized for insulin-sensitization strategies, no safety concerns were seen for the insulin-sensitizing group, in which >60% received thiazolidinediones, predominantly rosiglitazone (55%). The BARI 2D findings with regard to rosiglitazone use are consistent with the recently reported findings of the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) multicenter, randomized, open-label trial. Indeed, the data are even more reassuring because BARI 2D included patients at particularly high risk for cardiovascular events. Notably, although peripheral edema was more frequent with insulin sensitization, congestive heart failure was not. The latter finding contrasts with several trials with thiazolidinediones and may represent optimal management of fluid retention by the BARI 2D investigators. Overall, the trial provides considerable reassurance to clinicians with regard to the use of whatever diabetes mellitus medication they choose for individual patients and should help to dispel the myths that diabetes mellitus medications cause cardiovascular events.

T2DM is widely recognized to be a progressive disease in which it is increasingly difficult to manage hemoglobin A1c over time, as shown by mean hemoglobin A1c levels of >8.1% 10 years after diagnosis of diabetes mellitus despite concerted attempts for intensive management and of 8.7% in the standard of care arm within the United Kingdom Prospective Diabetes Study (UKPDS). Nevertheless, in the BARI 2D study of patients with mean duration of diabetes mellitus of 10 years and established cardiovascular disease at enrollment, mean hemoglobin A1c concentrations at the end of study were 7.2% and 7.5% in the insulin-sensitization and insulin-provisional groups, respectively. These findings demonstrate the substantial improvements in management of glycemia over the last decade.
Conclusions
In conclusion, initial multifactorial medical management is a good option for BARI 2D eligible patients, particularly those at lower risk, with CABG being appropriate for those at highest risk. Insulin-sensitization and insulin-provisional approaches both appear appropriate, although insulin-sensitization regimens have some demonstrated benefits, enhancing the benefit of revascularization particularly among those selected for CABG, resulting in higher high-density lipoprotein cholesterol levels, less weight gain, less frequent severe hypoglycemia, and lower hemoglobin A1c levels. Advances in diabetes mellitus are occurring at a rapid rate, and emerging therapies, including incretin modulators, were not assessed. It is hoped that ongoing advances in diabetes mellitus and cardiovascular therapies will continue to lead to better health for patients with diabetes mellitus, with the ultimate goal to reduce disparity in results of interventions such that patients with diabetes mellitus have outcomes that are at least as good as those without the disease.

Disclosures
Dr Goldfine has received grants from the American Diabetes Association and National Institutes of Health, with additional research support for National Institutes of Health sponsored trials from Caraco Pharmaceuticals; Lifescan, a Division of Johnson and Johnson; Mercodia; and Medtronic. Dr Goldfine also received honoraria for consulting from Daiichi Sanyko, Tethys Bioscience, Merck, CV Therapeutics, and NovoNordisk. Dr Fonseca has received research support grants (to Tulane University Health Sciences Center) from GlaxoSmithKline, Novartis, Novo Nordisk, Takeda, AstraZeneca, Sanofi-Aventis, Eli Lilly, Daiichi Sanyko, National Institutes of Health, and the American Diabetes Association. Dr Fonseca has also received honoraria for consulting and lectures from GlaxoSmithKline, Novartis, Takeda, Novo Nordisk, Sanofi-Aventis, Eli Lilly, and Daiichi Sanyko.

References

Key Words: coronary disease, diabetes mellitus, insulin, revascularization
Management of Diabetes Mellitus in Patients With Cardiovascular Disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial

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_Circulation._ 2010;121:2447-2449
doi: 10.1161/CIRCULATIONAHA.109.925883

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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