

Treatment for Type 2 Diabetes Mellitus and Stable Ischemic Heart Disease

by Michael Pazirandeh, PharmD Candidate 2011 and
Craig Stern, PharmD, MBA, FASHP. Special thanks to our Guest Editors
from Delfini Group, LLC, Michael E. Stuart, MD and Sheri A. Strite



Introduction

The BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) study was a randomized, multinational, multi-center, partially blinded (core laboratory staff and committee members adjudicating diagnosis of myocardial infarction, stroke and death were blinded), controlled trial. It was designed to determine the optimal treatment strategy for patients with diabetes and coronary artery disease.

The overall purpose and design of this study is unique due to the lack of other large, randomized trials that address the optimal treatment for patients with diabetes and

stable ischemic heart disease. The trial had two treatment regimens in a 2-by-2 factorial design. The first strategy divided patients by prompt coronary revascularization or medical therapy.

The second strategy divided patients by insulin-sensitization therapy (e.g. metformin and thiazolidinediones) or insulin-provision therapy (e.g. sulfonylureas and insulin). The target goal for the glycated hemoglobin level was less than 7.0%. Patients were also stratified to the method of revascularization: coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI). However, the intent of this study was not to compare the differences between CABG and PCI but rather compare the outcomes between immediate revascularization and medical therapy and the outcomes between insulin-sensitization and insulin-provision medications. The primary outcome was death from any cause, and the secondary outcome included death, myocardial infarction, or stroke.

Element	Criteria	Comments
Study Design Assessment	<p>Is the design appropriate to the research question? Is the research question useful?</p> <ul style="list-style-type: none"> <input type="checkbox"/> For efficacy, use of experimental study design (meaning study subjects and others were not allowed choice in determining interventions) <input type="checkbox"/> Clinically significant area for study (morbidity, mortality, symptom relief, functioning and health-related quality of life) and reasonable definitions for clinical outcome such as response, treatment success or failure <input type="checkbox"/> If composite endpoints used, reasonable combination used and used for safety if used for efficacy 	<p>BARI 2D was an open label randomized controlled trial to assess the optimal treatment strategy for patients with both type 2 diabetes and stable ischemic heart disease. Even though a double blinded design is considered the gold standard, it would be impossible to blind for patients who received immediate revascularization and those that received insulin therapy. The study had reasonable outcomes and endpoints.</p>
Internal Validity Assessment	<p>Can bias, confounding or chance explain the study results?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Ensure prespecified and appropriate 1) research questions, 2) populations to analyze, 3) outcomes, 4) group assignment methods, 5) study conduct methods, 6) analysis methods, and 7) level for statistical significance 	<p>Even though the arms were randomized between revascularization and medical therapy, the healthier patients were placed in the PCI stratum whereas the sicker patients were in the CABG stratum.</p> <p>THREAT: The authors explain that the purpose of the study was not to compare patients in the CABG vs. PCI stratum; however patients in the CABG stratum were more likely to experience fewer cardiovascular events if they underwent immediate revascularization. Since patients in the CABG stratum were sicker, an immediate revascularization would clinically make sense and therefore result in more favorable outcomes.</p>
Selection Bias	<ul style="list-style-type: none"> <input type="checkbox"/> Groups are appropriate for study, of appropriate size, concurrent and similar in prognostic variables <input type="checkbox"/> Methods for generating the group assignment sequence are truly random, sequencing avoids potential for anyone affecting assignment to a study arm and randomization remains intact <input type="checkbox"/> Concealment of allocation strategies are employed to prevent anyone affecting assignment to a study arm 	<p>The participants were patients at 49 clinical sites in the United States, Canada, Brazil, Mexico, Czech Republic, and Austria. The baseline characteristics were well balanced among each treatment group.</p> <p>THREAT: The authors never mention how the patients were randomized into the different groups (e.g. computer generated random numbers or codes) or the concealment of allocation strategies.</p>
Performance Bias	<ul style="list-style-type: none"> <input type="checkbox"/> Double-blinding methods employed (i.e., subject and all working with the subject or subject's data) and achieved <input type="checkbox"/> Reasonable intervention and reasonable comparator used (e.g., placebo) <input type="checkbox"/> No bias or difference, except for what is under study, between groups during course of study (e.g., intervention design and execution, co-interventions, concomitant medication use, adherence, inappropriate exposure or migration, cross-over threats, protocol deviations, measurement methods, study duration, etc.) 	<p>THREAT: The study was not double-blinded.</p> <p>THREAT: Though patients underwent treatment specific to their random assignment, there could be cross over in treatment if deemed necessary by the provider. At 5 years, 42.1% of patients in the medical therapy group underwent revascularization. In addition, 43.8% of the insulin-sensitization patients and 11.8% of the insulin-provision patients received medications from the other class. These were patients who could not maintain an HBA1C below 8.0%.</p>

Chart continued on page 48

Element	Criteria	Comments
Attrition Bias	<input type="checkbox"/> Zero or minimal missing data points or loss from randomization (e.g., approximately 5% with differential loss, or approximately 10% without differential loss) unless good ITT analysis (see ITT below)	The results after the five year trial do not account for the number of patients who dropped out during the study. THREAT: There is a possible threat because in each of the arms about 5-10% of the patients dropped of the study. However, there was no differential loss among the arms and so the number of drop outs may not be significant.
Assessment Bias	<input type="checkbox"/> Assessors are blinded <input type="checkbox"/> Low likelihood of findings due to chance, false positive and false negative outcomes (judgment call on statistical significance, including confidence intervals) <input type="checkbox"/> Non-significant findings are reported, but the confidence intervals include clinically meaningful differences <input type="checkbox"/> Intention-to-Treat Analysis (ITT) performed (all people are analyzed as randomized + reasonable method for imputing missing values which puts the intervention through a challenging trial or reasonable sensitivity analysis) <input type="checkbox"/> Use of modeling only with use of reasonable assumptions	The study fails to mention if the assessors are blinded. Due to the lack of validity in the study, it is difficult to assess whether the findings are due to chance; however, the study does contain statistical significance, power analysis, and intention-to-treat analysis. Researchers compared rates of death and major cardiovascular events using Kaplan–Meier survival curves. The researchers did not disclose the assumptions for the modeling.
Usefulness Assessment	<input type="checkbox"/> Clinically significant area + sufficient benefit size = meaningful clinical benefit (consider efficacy vs effectiveness)	THREAT: Due to the high amount of cross over between the treatment arms, one is unable to determine whether the results of the study are valid and clinically significant.
External Validity	How likely are research results to be realized in the real world considering population and circumstances for care? <input type="checkbox"/> Review n, inclusions, exclusions, baseline characteristics and intervention methods. This is a judgment call .	THREAT: The types of patients in this study represent a minority of patients with diabetes and ischemic heart disease. Since everyone in the study received an angiogram, the sickest patients, who would benefit from immediate revascularization, were excluded from the study. THREAT: Due to the amount of treatment crossover, it is hard to assess how effective each arm is individually. It is also difficult to assess the difference between the groups and the reported results.
Patient Perspective	<input type="checkbox"/> Consider benefits, harms, risks, costs, uncertainties, alternatives, applicability to which patients, adherence issues, potential for abuse, dependency issues and patient satisfaction	Since that the results of the study are not valid, a patient has the opportunity to choose whatever treatment he or she wants. Benefits and risks for patients cannot be adequately assessed because the study is not valid. From the patient's and payer's perspective, revascularization and medical therapy would cost more than medical therapy alone.
Provider Perspective	<input type="checkbox"/> Satisfaction, acceptability, likely appropriate application and actionability (e.g., FDA approval, affordability, external relevance, circumstances of care, able to apply, tools available)	All treatments and strategies are FDA approved. Since the results do not favor one strategy over another, a healthcare provider should be willing to accept any of these treatments.

*Chart taken from the Delfini Group, LLC. Short Critical Appraisal Checklist: Updated 02/19/08
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It is important to note that symptoms of angina are subjective from the patient's perspective and this has the potential of skewing the results even more.

Authors' Results and Conclusions:

Mean follow-up time was 5.3 years and 2,194 patients (92.7%) completed the trial. Overall, there were no statistically significant (e.g. $p < 0.05$) differences between the survival rates in any of the arms. The survival rates between the revascularization and medical therapy groups were 88.3% and 87.8% respectively ($p = 0.97$), and the rates between the insulin sensitization and insulin provision groups were 88.2% and 87.9% respectively ($p = 0.89$). With regards to freedom from major cardiovascular events, the rates were 77.2% and 75.9% ($P = 0.70$) in the revascularization and medical therapy respectively and 77.7% and 75.4% ($p = 0.13$) in the insulin sensitization and insulin provision therapy respectively. The only significant data was found in freedom from major cardiovascular events in patients who underwent CABG. The rates for revascularization and medical therapy were 77.6% and 69.5% respectively ($p = 0.01$). Authors of the study concluded that there was no significant difference in the rates of death between the patients receiving prompt revascularization and those receiving medical therapy or between the patients receiving insulin-sensitization and insulin-provision therapies. However, there was a significant difference in the CABG stratum with a decrease in major cardiovascular events in patients who received prompt revascularization compared to those in the medical therapy group ($p = 0.002$).

Reviewers' Conclusion:

A major limitation in this study is the amount of cross over between the different treatment arms. At year 3, 43.4% of patients

in the insulin-sensitization group and 11.8% of patients in the insulin-provision group were receiving medications from the alternative class (at year 5 the numbers increased to 54% and 18%). Patients were able to switch groups if they were unable to maintain a hemoglobin level below 8.0%. Also, patients in the medical group were able to receive revascularization if there was progression of angina or the development of an acute coronary syndrome. It is important to note that symptoms of angina are subjective from the patient's perspective and this has the potential of skewing the results even more. Even though the authors conclude that there is no difference between the difference medication strategies, it is hard to determine whether or not the insulin-sensitization patients would have had such favorable data if such a large number had not used insulin-provision medications. In addition, at year 5, 42.1% of patients in the medical-therapy group underwent revascularization. For the same reason, it is hard to determine whether or not the medical-therapy group is as good as the revascularization group since a large number of medical-therapy patients underwent revascularization.

The authors mention that among the different treatments for patients in the CABG stratum, the lowest rate of cardiovascular events was seen in patients who received immediate revascularization and insulin-sensitization medications. However, they are comparing this data with patients who are receiving only insulin-sensitization medications (18.7% vs. 32.0% $p = 0.002$). When compared to patients that underwent immediate revascularization and received insulin-provision medications, there is no statistical

significance ($p = 0.066$). Also, there may be statistical significance in the CABG spectrum for cardiovascular events due to the fact that patients indicated for CABG over PCI have more extensive coronary disease, and revascularization is more imperative in these patients.

Overall, due to the lack of treatment consistency in each of the arms, it is hard to determine whether or not the results are clinically meaningful. Other studies are necessary in order to determine the effects of each strategy individually in the treatment of patients with type 2 diabetes mellitus and ischemic heart disease.

Overall Grade: U = Uncertain validity

Delfini Comments: We agree with the reviewer's assessment of this study. Because of the major threats to validity described above we would not use the results of this study to inform health care decisions. Only when studies are found to be valid (grade B-U or higher) do we use them to inform clinical and other health care decisions. 🗣️

About the Authors & Guest Editor

Michael Pazirandeh is a 2011 PharmD Candidate at the University of Southern California and a student representative on the CPbA Editorial Review Committee (ERC). Craig Stern, PharmD, MBA is president of ProPharma Pharmaceutical Consultants, Inc and chair of the CPbA ERC.

Dr. Michael E. Stuart and Sheri A. Strite of Delfini Group are experts at systematic literature reviews. The chart template is adapted from "Delfini Group, LLC. Short Critical Appraisal Checklist: U