Published in final edited form as:

Coron Artery Dis. 2010 November ; 21(7): 383–385. doi:10.1097/MCA.0b013e32833d014a.

Clinical Implications of the BARI 2D and COURAGE Trials:

Overview

Maria Mori Brooks, PhD¹, William E. Boden, MD², and Robert L. Frye, MD³

¹ Department of Epidemiology and Biostatistics, University of Pittsburgh, Pittsburgh, PA

² Division of Cardiovascular Medicine, University at Buffalo Schools of Medicine & Public Health, Buffalo, NY

³ Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN

Introduction

The principal goals of myocardial revascularization in patients with coronary artery disease (CAD) are to decrease mortality and myocardial infarction (MI), and to improve angina and quality of life. Compared to medical therapy, percutaneous coronary intervention (PCI) has been associated with lower mortality or MI rates in patients with ST-segment elevation myocardial infarction and in high-risk patients with acute coronary syndromes, and coronary artery bypass graft (CABG) surgery has been associated with lower mortality or MI rates in patients with left mainstem coronary disease and in those with multivessel coronary disease and impaired left ventricular systolic function. By contrast, the effectiveness of coronary revascularization for relieving angina has been widely recognized in both patients with acute coronary syndromes and stable ischemic heart disease, yet its benefit in reducing subsequent mortality and MI risk has not been demonstrated in patients with stable CAD. Indeed, among 11 randomized clinical trials comparing PCI with medical therapy published between 1992 and 2005, involving fewer than 3,000 subjects, no differences in death, MI, or need for subsequent revascularization were demonstrable between groups, although almost all studies were underpowered for “hard” clinical outcomes.¹

In 2007, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial established that for patients with stable CAD, an initial management strategy of PCI plus optimal medical therapy did not reduce the long term rates of death, MI, or other cardiovascular events as compared with optimal medical therapy alone.² The investigators pre-specified 8 subgroups, including age, sex, prior MI, diabetes, extent and severity of angiographic CAD, and ejection fraction < 50%, but there was no significant interaction between treatment and any subgroup variable. These results garnered wide attention from practicing physicians, clinical researchers and health policy decision makers. Two years later, the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial reported that a strategy of prompt coronary revascularization and intensive medical therapy did not reduce all-cause mortality or the composite of death, myocardial infarction or stroke compared with intensive medical therapy alone; however, in the group of patients appropriate for coronary artery bypass graft surgery (CABG), prompt revascularization with CABG resulted in significantly lower rates of major cardiovascular events, specifically myocardial infarction, than intensive medical therapy alone.³ This trial focused on patients with type 2 diabetes

Address for correspondence: Maria Mori Brooks, PhD, Department of Epidemiology, University of Pittsburgh, GSPH, 130 DeSoto Street/A530 Crabtree Hall, Pittsburgh, PA 15261, Telephone: (412) 624-1618, FAX: (412) 383-8690, mbrooks@pitt.edu.

mellitus in whom outcomes for any treatment for CAD is worse compared to those without diabetes. The BARI 2D trial demonstrated that insulin sensitization and insulin provision glycemic treatment strategies, both with a target HbA1c < 7%, yielded similar outcomes over five years of follow-up, and there was a suggestion that insulin sensitization therapy might be advantageous among patients undergoing revascularization. The evidence from these two large multicenter clinical trials has led the medical community to reevaluate the way we approach and treat patients with CAD and stable ischemic symptoms. In this special issue, experts from several disciplines discuss how the COURAGE and BARI 2D results have affected clinical practice and highlight the key questions that remain unanswered.

Evaluation of patients with suspected coronary artery disease

Dr. Menees and Dr. Bates carefully review the current guidelines on patient diagnosis, clinical factors that are critical for risk stratification, and the process of selecting an appropriate treatment strategy. Following the ACC/AHA recommendations for evaluating chest pain in patients with stable coronary disease, chest pain history, risk factor status and noninvasive stress test results are used to classify patients. This information allows the physician to determine what additional tests should be ordered, administer medical therapy at an appropriate level, and possibly refer patients for coronary angiography.

COURAGE and BARI 2D evaluated the benefit of immediate revascularization beyond optimal medical therapy for patients who had gone through a diagnostic and prognostic evaluation. The trial participants were referred for coronary angiography and were deemed appropriate for treatment with either initial medical therapy or revascularization. A large proportion of patients referred for coronary angiography are similar to those in COURAGE and BARI 2D with clinical co-morbidities, significant inducible ischemia, and multivessel coronary disease. However, based upon the risk stratification scheme described in this paper, patients with the highest risk (e.g. left main disease) were excluded from these trials and referred for revascularization and those with the lowest risk profile were excluded and referred for medical therapy. Consequently, the results from COURAGE and BARI 2D do not change the standard of care for diagnosing coronary artery disease, since in both studies, coronary anatomy was defined by trial design and was a potential factor in defining which patients were included or excluded from enrollment. Information from future studies is needed to further refine the diagnostic process and to determine if all such patients require diagnostic coronary angiography or if non-invasive testing alone is useful for risk stratifying patients and for defining when revascularization is warranted.

Clinical Implications of BARI 2D and COURAGE on optimal medical therapy for coronary artery disease

Dr. Lewis Kuller summarizes what we have learned from the COURAGE and BARI 2D trials about medical therapy in patients with coronary artery disease and poses provocative questions to ponder. The COURAGE and BARI 2D trials provide confirmation that lipid lowering therapy and antihypertensive therapy are tremendously beneficial for patients with coronary artery disease. These studies do not resolve whether there are advantages associated with lowering HbA1c below 7% or with the use of specific diabetes drug classes. Since myocardial ischemia is present in many asymptomatic patients with type 2 diabetes, the evidence that intensive medical therapy slows the progression of atherosclerosis signifies that we should consider shifting the treatment objective in these patients from the prevention of microvascular disease to include the prevention of macrovascular disease. Dr. Kuller suggests that imaging for atherosclerosis and atherosclerotic plaque might be used to predict myocardial infarction or sudden death and that tools besides the current inflammatory measures such as CRP are needed to identify a hypercoagulable state, or to better identify the soft, inflamed

atherosclerotic plaques that are vulnerable to acute rupture, fissure, or erosion. Furthermore, we need new drugs to reduce risk of arterial thrombosis without increasing bleeding as a side effect. He concludes that COURAGE and BARI 2D prove that intensive medical therapy is feasible and effective in clinical trials, but it is difficult to translate this to community practice because preventive health care is underemphasized in the current health system. The existing “fee for service” or “pay for performance” reimbursement models that characterize existing healthcare policy do not reward physicians economically for achieving prevention goals and treatment targets. We should focus our attention on preventive care including exercise and smoking cessation in order to improve the health of patients.

The evolving role of percutaneous coronary intervention (PCI)

Dr. Holper and Dr. Addo define the patient population, the clinical circumstances, and the aspects of PCI that make it a critical component for managing coronary artery disease. In the COURAGE and BARI 2D trials, patients in low to moderate risk categories and stable symptoms derived no reduction of cardiovascular events with the addition of PCI. Yet, it is important for clinicians to recognize that patients assigned to an initial strategy of optimal medical care had the availability and the benefit of subsequent revascularization if clinically indicated. The medical groups in these trials did well because they could have a procedure when needed. The authors recommend that PCI be used for markedly limiting symptoms or unstable symptoms that require urgent intervention. They emphasize that the ease, safety and efficiency of PCI at the time of angiography make it an attractive tool, and the convenience continues to improve with advances like the use of radial arteries for access. PCI relieves symptoms, enhances patient quality of life, and reduces subsequent clinic visit for angina. Current PCI techniques allow the cardiologist to take on more complicated cases like total occlusions, diffuse lesions and small vessels. The primary lesson from COURAGE and BARI 2D is that optimal medical therapy should be provided to all patients with coronary artery disease as the foundation upon which all other treatments are configured, and for many patients, revascularization can be deferred until symptoms or the anatomy dictate. On the other hand, these trials also illustrate the importance of carefully following coronary patients who are being treated with medical therapy and that PCI plays a key role under many circumstances.

Coronary Artery Bypass Graft Surgery (CABG) for patients with diabetes and multi-vessel coronary artery disease: identifying patients who would benefit with CABG and understanding the potential mechanisms involved

Dr. Greason and Dr. Schaff present a thorough review of the studies that have compared CABG to medical therapy and have compared CABG to PCI for treating patients with coronary artery disease. BARI 2D provides evidence that patients with type 2 diabetes and moderate CAD can be treated safely with medical therapy but with careful followup and subsequent revascularization if needed. However, if ischemic symptoms persist or if severe multivessel disease is present, CABG has been shown to be the most effective treatment in terms of myocardial infarction, cardiac death and the need for repeat procedures. Indeed, BARI 2D showed that CABG (but not PCI) patients had significantly fewer major cardiac events driven mainly by a reduction in MI than patients assigned to medical therapy. This is an important and novel finding not previously demonstrated in clinical trials and may be due to the higher risk patients selected for CABG. The authors propose that outcomes will continue to improve in this high risk group of patients with recent advances in surgical techniques and the development of anti-platelet therapies. The BARI 2D data suggest that the combination of insulin sensitization and revascularization may provide further benefits for reducing the risk of myocardial infarction. The results from these trials indicate that anatomic risk stratification may be useful for identifying high risk patients with extensive anatomic CAD who would

benefit from CABG. However, there is considerable controversy in the literature about screening patients with diabetes for coronary disease since the DIAD study has shown that screening asymptomatic patients has a very low yield.⁴ The challenge is to determine how to best identify patients with severe anatomical coronary disease so that they can be referred for CABG.

Summary

The COURAGE and BARI 2D trial results have important implications for the way cardiologists approach clinical decision-making and practice. Evaluation of symptoms, risk factors and test results are first used to risk stratify patients. In patients with stable or no symptoms with documented ischemia, the results from COURAGE and BARI 2D provide a rationale for intensive medical therapy and lifestyle intervention, and a strong justification for delaying revascularization in patients with the characteristics of those enrolled in the trials. Intensive medical therapy aimed at treating dyslipidemia, hypertension and glycemia must be available for all patients. Achieving and maintaining optimal treatment targets are essential to lowering the risk for subsequent events. Preventive care that facilitates a healthy lifestyle should also be routine. These studies indicate that PCI is vital when symptoms become unstable and may be useful to relieve burdensome symptoms in other situations. BARI 2D provides important new evidence that CABG is preferred over medical therapy alone for patients with diabetes and severe coronary disease not only for symptom relief but also for reducing the rate myocardial infarction. Practitioners must carefully consider generalization of trial results to individual patients, and in the case of CABG and BARI 2D risk stratification, knowledge of the patient's coronary anatomy is essential before applying the results to individual patients. In patients who are appropriate candidates for revascularization, a thoughtful and transparent discussion between the cardiologist, surgeon, and patient should be undertaken to ensure that the goals of therapy are aligned with the scientific evidence that supports it, and that the decision to proceed with PCI or CABG is individualized in the interests of what is best for the patient.

References

1. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. *Circulation* 2005;111:2906–12. [PubMed: 15927966]
2. The BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360:2503–2515. [PubMed: 19502645]
3. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503–16. [PubMed: 17387127]
4. Wackers FJ, Young LH, Inzucchi SE, et al. Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care* 2004;27:1954–1961. [PubMed: 15277423]