Does revascularization work?

Mandeep S. Sidhu and William E. Boden, Albany Stratton VA Medical Center, Albany Medical Center, Albany Medical College, Albany, New York, USA

Correspondence: Dr William E. Boden, Samuel S. Stratton VA Medical Center,
113 Holland Street, Albany, NY 12208, USA
Tel: 518-626-6386, fax: 518-626-6511
e-mail: william.boden@va.gov

Abstract

It is well established and accepted, based on the results of multiple randomized controlled trials (RCTs), that myocardial revascularization in patients with acute ST-segment elevation myocardial infarction (MI) and other acute coronary syndromes (ACS) results in improved outcomes, both in terms of reduced short and long-term mortality as well as rates of subsequent MI. By contrast, it is less clear that myocardial revascularization in patients with stable ischemic heart disease (SIHD) is associated with an improvement in clinical outcomes when compared to optimal medical therapy. Several RCTs in SIHD patients over the past several years, including well-conducted meta-analyses of these clinical trials, have universally failed to show an improvement in death, MI, or other "hard" clinical outcomes. While clinical event reduction is certainly not the only goal of myocardial revascularization, its notable absence in SIHD, as compared with ACS patients certainly provides pause for thought when deciding on the initial treatment strategy for a given patient with chronic stable angina or SIHD.

Keywords: Coronary artery disease; myocardial revascularization; optimal medical therapy; stable ischemic heart disease

■ Heart Metab. (2013) 58:10–14

Main Clinical Article

The provocative question posed by the title of this paper forces us to confront critically the question of the patient and the circumstance in which revascularization improves outcomes. When clinicians are faced with this important question, two critical issues need to be considered and addressed: (1) will revascularization reduce rate of mortality and/or myocardial infarction (MI)?; (2) will revascularization improve angina and quality of life compared with medical therapy? In addressing these questions, physicians must also ask whether these goals can be achieved in all cardiac patients, or whether these therapeutic goals apply differentially to subpopulations of coronary artery disease (CAD) patients? In particular, when should revascularization be the initial management strategy and when should it be reserved for patients who cannot be managed with optimal medical therapy (OMT).

There is an abundance of evidence that revascularization is not only indicated but necessary to achieve optimal clinical outcomes in patients with acute coronary syndromes (ACS) such as ST-segment elevation myocardial infarction (STEMI) or high-risk non-STEMI, as outlined in the 2009 and 2013 American College of Cardiology/American Heart Association guidelines for the management of STEMI [1]. Furthermore, emergent/urgent percutaneous coronary intervention (PCI) has been shown to result in established clinical benefits in certain ACS patients [2, 3].

There is compelling scientific evidence that total or subtotal coronary occlusion immediately following plaque rupture or fissuring cannot be optimally managed with medical therapy alone. Therefore, in these clinical scenarios, it is clear that acute myocardial revascularization reduces mortality, the risk of recurrent MI, and preserves left ventricular function. In other words, revascularization in ACS patients is "disease modifying" and clearly "works" from the important perspective of cardiac event reduction, based on both short and long-term clinical benefit and prognostic improvement in these patient populations.

By contrast, the utilization of revascularization in the chronic angina or stable ischemic heart disease (SIHD) population raises a more complex and relevant question as to the optimal clinical decision-making. There is discordant evidence from clinical trials and observational studies in patients with SIHD, notably several randomized controlled trials (RCTs), such as the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial [4], the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) [5] and the Japan Stable Angina Pectoris (JSAP) study [6], as well as numerous meta-analyses of these RCTs, including a very recent meta analysis of stent trials in the era of modern medical therapy published in the *Archives of Internal Medicine* [7]. All these studies have failed to demonstrate any incremental clinical benefit for PCI above and beyond OMT alone for the reduction of death or nonfatal MI, hospitalization for ACS, the need for unplanned revascularization and a durable, sustained effect on angina relief – findings quite in contrast to those achieved with PCI in acute MI or ACS patients.

For patients with chronic stable angina and SIHD, the COURAGE trial [4] and the BARI-2D trial [5] both support the management of patients with an initial trial of optimal pharmacotherapy, lifestyle interventions focused on improving dietary consumption and increasing exercise, as well as secondary prevention instead of immediate revascularization as is commonly performed in these populations of chronic stable angina and SIHD. It is best to review the data from these individual trials in order to examine further this important question regarding the effectiveness of revascularization.

In COURAGE, 2287 patients with objective evidence of myocardial ischemia and significant coronary disease at coronary angiography were randomly assigned to PCI with OMT versus OMT alone. The rate of the primary endpoint (all-cause mortality or non-fatal MI) during follow-up which ranged from 2.5 to 7.0 years with a median of 4.6 years, and was similar between the PCI and OMT groups (with cumulative primary event rates of 19.0% and 18.5%, respectively, with a hazard ratio (HR) of 1.05 for the PCI group and a 95% CI of 0.87 to 1.27; $P = 0.62$). Therefore, as an initial management strategy in patients with stable CAD, PCI did not reduce the risk of death, MI, or other major cardiovascular events when added to OMT alone.

Subsequently, in 2009, the BARI-2D trial [5] enrolled 2368 patients with both type 2 diabetes and SIHD who were randomly assigned in a 2×2 factorial design to undergo either prompt revascularization with intensive medical therapy or intensive medical therapy alone, and to undergo either insulin sensitization or insulin provision therapy. The results demonstrated that, at a mean follow-up of 5 years, rates of survival (88.3% versus 87.8%; $P = 0.97$) and freedom from major cardiovascular events (77.2% versus 75.9%; $P = 0.70$) did not differ significantly between the revascularization group and the intensive medical therapy group. Importantly, however, although there was no significant difference in primary endpoints between the revascularization group and medical therapy group in the PCI stratum, the study findings did demonstrate that the coronary artery bypass grafting (CABG) stratum had a significantly lower rate of major cardiovascular events in the revascularization group (22.4%) than in the medical therapy group (30.5%), which was driven largely by a significant reduction in recurrent MI. Therefore, the CABG cohort, which included a higher-risk population of patients with more extensive multivessel coronary disease, did reveal a lower rate of the secondary endpoint of major cardiovascular events (death, MI, or stroke) compared with intensive medical therapy alone (22.4% versus 30.5%; $P = 0.01$). In essence, the results of the BARI-2D trial in CAD patients with diabetes replicated the principal findings of the COURAGE trial, and reaffirmed that survival rates did not differ with intensive or OMT compared with percutaneous revascularization.

In light of the BARI-2D trial, the role of CABG surgery as a strategy of revascularization was further evaluated in 1212 patients with CAD and heart failure in the

STICH trial [8], in which patients were randomly assigned to medical therapy alone or medical therapy plus CABG. There was no significant difference in the primary outcome of death from any cause that occurred in 244 patients (41%) in the medical therapy group and 218 (36%) in the CABG group (HR with CABG of 0.86, 95% CI 0.72 to 1.04; $P = 0.12$). However, death from any cause or hospitalization for cardiovascular causes occurred in 411 patients (68%) in the medical therapy group and 351 (58%) in the CABG group (HR with CABG 0.74; 95% CI 0.64 to 0.85; $P < 0.001$). Patients assigned to CABG had lower rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes. In summary, the STICH trial data further support similar outcomes derived from comparisons of PCI as a revascularization strategy to medical therapy (COURAGE) and PCI or CABG versus medical therapy (BARI-2D).

More recently, Hannan et al [9] published an analysis of long-term (2–4 years) comparative outcomes in patients with stable CAD who did and did not undergo PCI from the large, prospective New York State PCI registry. Overall, a total of 9586 patients was followed prospectively in this registry, of whom 89% received PCI, 2% underwent bypass surgery and only 11% received what the authors labeled as "routine medical therapy" (RMT). Outcomes of interest for this study were the composite of death or MI, death alone, MI alone and the rate of subsequent revascularization during follow-up (median 2.87 years). Because so few patients (n = 1100) received RMT alone, the propensity matching comprised only 933 matched pairs of patients (n = 1866), but the study did show that compared with those who received RMT alone, patients who received PCI plus RMT had a significantly lower rate of death or MI ($P = 0.003$), mortality ($P = 0.02$), MI ($P = 0.007$) and subsequent revascularization ($P = 0.005$).

The main confounder in the Hannan study is that this was an observational study in which treatment assignment (PCI or RMT) was not randomized but was rather left to the discretion of the treating cardiologist and, furthermore, the intensity or specifics of medical therapy were not collected to characterize the intensity of pharmacologic therapy. While it can be argued that this represents a more "real world" comparison of revascularization with medical therapy, there was a high likelihood of selection bias and other confounding factors that cannot be entirely eliminated with propensity matching. As such, these findings cannot be considered in any way definitive as the study related to purported significant improvements in clinical outcomes with PCI.

Finally, the effectiveness of revascularization in SIHD was most recently studied in the FAME 2 trial, which was published in 2012 following the original FAME 1 trial of 2009, which evaluated fractional flow reserve (FFR) versus angiography to guide PCI [10,11]. FAME 2 sought to determine whether PCI plus "best available medical therapy" (eg. evidence-based multifaceted medical therapy) would be superior to the best available medical therapy alone as a preferred initial treatment strategy for patients with chronic stable angina – a population very similar to that of COURAGE and BARI-2D. The trial used FFR measurements to evaluate all visually assessed coronary stensoses and, in patients whose FFR values were 0.8 or less, subjects were randomly assigned to an FFR-guided PCI strategy plus best available medical therapy or to a strategy of best available medical therapy alone. The trial was terminated prematurely, 17 months earlier than planned, after the enrollment of 1220 patients (only 888 patients from a projected sample size of 1632), who were randomly assigned to the two strategies, while those patients whose FFR values were greater than 0.8 (n = 332) were enrolled in a parallel registry. The primary outcome measure for FAME 2 was cardiovascular mortality, non-fatal MI, or hospitalization for unplanned revascularization for suspected ACS. There was a significant between-group difference in the percentage of patients who had a primary endpoint with PCI versus medical therapy (4.3% versus 12.7%, HR 0.32, 95% CI 0.19 to 0.53; $P < 0.002$), which was driven solely by a lower rate of urgent revascularization in the PCI group than in the medical therapy group (1.6% versus 11.1% with HR of 0.13 and 95% CI of 0.06 to 0.30; $P < 0.001$). Of note, there were only 33 "hard events", of which there were only four deaths (three in the OMT arm and one in the PCI arm) along with 29 MIs (14 in the OMT arm and 15 in the PCI arm). Most importantly, the urgent revascularization endpoint that was responsible for the overall primary endpoint was largely a clinical one, and did not mandate objective evidence of either electrocardiographic ischemia or elevated cardiac biomarkers in order to meet this endpoint. Approximately half of

the 56 unplanned hospitalizations, which led to urgent revascularization, were not accompanied by any objective findings of high-risk ischemia or positive biomarkers.

Therefore, because this was an unblinded trial, there was a potential for selection bias that could have created a lower threshold to admit a trial patient in the OMT arm who had recurrent angina and no objective evidence of ischemia, without first attempting to uptitrate or intensify medical therapy by either increasing the doses of existing medications or adding additional anti-anginal pharmacological agents to delay or obviate the potential need for revascularization. Finally, the FAME 2 trial study population was not particularly high risk as, according to the published baseline characteristics, 11% of patients were asymptomatic, 16% had silent ischemia and 66% has class 1 or 2 anginal symptoms, while only 3% of patients had three-vessel CAD by FFR, with a majority of patients having single-vessel CAD. In addition, the short follow-up period of approximately 7 months probably did not allow for restenosis to emerge in the PCI subset, which might have altered the rate of unplanned revascularization in the PCI arm had the study been continued to the planned end of follow-up. In summary, while FAME 2 did show that an FFR-guided PCI strategy resulted in a lower rate of unplanned revascularizations as compared with medical therapy alone, the notable limitations of the trial as highlighted above makes it difficult to justify or generalize the more widespread use of an FFR-guided revascularization approach in the management of SIHD patients.

Taken together, the COURAGE, BARI-2D, STICH and FAME 2 randomized trials, along with other observational analyses and meta-analyses, have challenged the notion that revascularization is superior to OMT, and clearly more prospectively acquired data are necessary to elucidate further what role revascularization should play in this chronic stable angina population. The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial (ISCHEMIA; ClinicalTrials.gov, NCT 01471522), funded by the US National Institutes of Health, is currently underway and is designed and powered to evaluate the long-term superiority of revascularization of choice combined with OMT versus OMT alone, with respect to cardiovascular death or MI (combined primary endpoint) in patients with stable CAD and moderate to severe myocardial ischemia as assessed by non-invasive stress imaging studies (myocardial perfusion imaging, stress echocardiography, or magnetic resonance imaging). The study is projected to enroll 8000 patients from among 400 sites worldwide, with a planned average follow-up period of 4 years [12].

In summary, clinical trials data firmly support the premise that "revascularization works" in high-risk patients, and is currently the preferred treatment approach (with a class I recommendation) in both STEMI and ACS patients to improve both short and long-term clinical benefit as well as prognostic improvement. The role of PCI and/or CABG surgery is established to lower both incident MI and death rates in these patient populations. The more difficult question of whether "revascularization works" in patients with chronic stable angina and SIHD, based on the clinical trials reviewed above, suggest that OMT should be considered as an initial approach in these patients compared with a "PCI first" treatment strategy. Clearly, further study is warranted to clarify whether patients with moderate to severe pre-treatment myocardial ischemia may fare better with myocardial revascularization compared with OMT alone, as is being tested actively in the ongoing ISCHEMIA trial. Until the results of this large-scale trial are available, we should utilize a judicious and selective approach to decision-making.

Clearly, revascularization is of clinical benefit in selected patient populations when there is a reduction in mortality and/or an improvement in quality of life via a reduction in angina, and should therefore be regarded as the initial management strategy in STEMI and high-risk ACS populations. By contrast, in SIHD patients, evidence derived from multiple, prospective RCTs comparing PCI with OMT shows no incremental benefit on clinical event reduction compared with OMT alone. For this reason, OMT should be considered the foundation of treatment and first-line therapy, unless the severity of anginal symptoms limits the effectiveness of medical therapy or the patient's quality of life is sufficiently compromised that revascularization should be considered. •

References

1. O'Gara PT, Kushner FG, Ascheim DD, et al (2013) 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task

Force on Practice Guidelines *Circulation. 2013; 127: e362–e425*
2. Cannon CP, Weintraub WS, Demopoulos LA, et al (2001) Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 344:1879–1887
3. Mehta SR, Cannon CP, Fox KAA, et al (2005) Routine versus selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. JAMA 293:2908–2917
4. Boden WE, O'Rourke RA, Teo KK, et al (2007) Optimal medical therapy with or without PCI in stable coronary disease. N Engl J Med 35:1503–1516
5. The BARI-2D Study Group (2009) BARI-2D: a randomized clinical trial of treatment strategies for type 2 diabetes and coronary artery disease. N Engl J Med 360:2503-2515
6. Nishigaki K, Yamazaki T, Kitabatake A, et al (2008) Percutaneous coronary intervention plus medical therapy reduces the incidence of acute coronary syndrome more effectively than initial medical therapy only among patients with low-risk coronary artery disease; a randomized, comparative multicenter study. J Am Coll Cardiol Intv 1:469–479
7. Stergiopoulos K, Brown DL (2012) Initial coronary stent implantation with medical therapy versus medical therapy alone for stable coronary artery disease: meta-analysis of randomized controlled trials. Arch Intern Med 172:312–319
8. Vlaszquez EJ, Lee KL, Deja MA, et al (2011) Coronary-artery bypass surgery in patients with left ventricular dysfunction (STICH trial). N Engl J Med 364:1607–1616
9. Hannan EL, Samadashvili Z, Cozzens K, et al (2012) Comparative outcomes for patients who do and do not undergo percutaneous coronary intervention for stable coronary artery disease in New York. Circulation 125:1870–1879
10. Tonino PAL, DeBruyne B, Pijls NHJ, et al (2009) Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 360:213–224
11. De Bruyne B, Pijls NHJ, Kalesan B, et al (2012) Fractional flow reserve-guided PCI versus medical therapy in stable coronary artery disease N Engl J Med 367:991–1001
12. Boden WE (2012) Mounting evidence for the lack of PCI benefit in stable ischemic heart disease: what more will it take to turn the tide of treatment? Comment on "initial coronary stent implantation with medical therapy vs. medical therapy alone for stable coronary artery disease". Arch Intern Med 172:319–321