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Revascularization vs. Medical Therapy in Stable Ischemic Heart Disease

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Abstract

The keynote COURAGE and BARI-2D trials changed the way the interventional community selects patients for revascularization. What we now consider appropriate, especially for percutaneous coronary intervention, has narrowed significantly in scope compared to previous practice a decade ago. Medical therapy has been shown to be both safe and effective as a primary treatment modality for patients with stable ischemic heart disease on the whole. However, it appears that patients with a heavy ischemic burden may benefit from revascularization, although investigation of this is ongoing. Evidence preliminarily supports this practice with coronary artery bypass grafting, and possibly in specific populations undergoing multivessel intervention with functional assessment of lesion severity during PCI.

Keywords

Stable ischemic heart disease; Optimal medical therapy; Percutaneous coronary intervention

The world of interventional cardiology has seen major growth in the last two decades. With this, the world saw ever increasing revascularization of coronary stenoses in patients ranging from those with asymptomatic lesions to those suffering an acute myocardial infarction (MI). Although it would seem intuitive that revascularization of any significantly stenotic coronary lesions would result in improved hard clinical outcomes, the evidence has not uniformly supported this outside of the acute setting, and in fact significant benefit can be garnered from medications alone. It is with this in mind that we turn to the subject of revascularization versus medical therapy in stable ischemic heart disease (SIHD).

In the years preceding the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, a routine invasive strategy for SIHD was the default. This was despite guideline recommendations for a strategy of optimal medical therapy (OMT) with intensive anti-anginal medication utilization, lifestyle modifications, and risk factor reduction.¹ In 2004, >1 million stent procedures were performed in the US,² with data showing that 85% of percutaneous coronary interventions (PCI) were performed in patients with SIHD.³ It was assumed that revascularization of a symptomatic coronary stenosis

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would lead to not only improvement in angina, but also a reduction in hard cardiovascular (CV) outcomes. Yet, this was never proven. An early meta-analysis of 6 randomized controlled trials in patient with SIHD demonstrated a significant improvement in anginal symptoms and exercise capacity with PCI over medical therapy, but was limited in its ability to demonstrate improvements in MI or death due to the small number of these events during follow up.⁴⁻⁷ In 2005, Katritsis and colleagues published a larger meta-analysis including 11 randomized trials and 2950 patients that failed to demonstrate a significant reduction in death, MI, or need for subsequent revascularization with PCI in this population.⁸ It was unclear if this was a true effect or secondary to the relatively small patient numbers underpowering these studies to detect such differences, or because of what is now considered obsolete PCI therapy.

The COURAGE trial was designed to determine if initial modern PCI with OMT was superior to OMT alone in patients with SIHD, including those with now stabilized Canadian Cardiovascular Society (CCS) class IV angina.⁹ A total of 2287 patients were randomized, both receiving OMT which included aggressive risk factor modification: smoking cessation counseling, reduction in dietary fat and cholesterol intake, reduction in blood low-density lipoprotein cholesterol (LDL-C) levels to <85 mg/dL (achieved in approximately 70%), blood pressure control (achieved in 65%), control of hemoglobin A1C (achieved in 45% of patients with diabetes mellitus [DM]), and encouragement of moderate physical activity most days of the week. The majority of participants were white men, average age 62 years. Most had hypertension and approximately 1/3 had a history of DM or MI. Just over half the participants had manifest CCS class 2–3 angina, with 42% no or only mild (CCS class 0 or 1) angina at the start of the study. Eighty-five percent of the participants had undergone a stress evaluation with 2/3 of the nuclear studies demonstrating multiple perfusion abnormalities. Nearly 70% of participants had multi-vessel disease on angiography with >30% having involvement of the proximal left anterior descending artery. After an average of 4.6 years follow-up, there was no statistically significant difference in the primary endpoint of death or nonfatal MI between groups (HR 1.05, 95% CI 0.87–1.27, $p = 0.62$), Fig 1. In the PCI group, 21.1% required a repeat revascularization compared to 32.6% in the OMT group (HR 0.6, 95% CI 0.51–0.71, $p < 0.001$), owing to angina unresponsive to medical treatment or evidence of worsening ischemia on non-invasive testing. However, the initial evaluation demonstrated no significant difference in freedom from angina between groups at 5 years, with >70% being symptom free regardless of initial treatment strategy. A subsequent evaluation of quality of life measures demonstrated that although the PCI group had a significant improvement in health status initially, this incremental benefit disappeared by 36 months.¹⁰

The BARI-2D trial, published 2 years after COURAGE, specifically evaluated a higher risk population of patients with SIHD, specifically those with DM.¹¹ This study randomly assigned 2368 patients with SIHD and a history of DM to either revascularization with either PCI or coronary artery bypass grafting (CABG) and OMT versus OMT alone. Similar to the findings of COURAGE, there was no difference in survival (88.3% revascularization vs. 87.8 OMT, $p = 0.97$) or freedom from death, MI, or stroke (77.2% vs. 75.9%, $p = 0.70$). Interestingly, when outcomes were analyzed based on intended treatment arm, those assigned to PCI did not see an advantage to revascularization by way of survival or major

adverse CV events (MACE), consistent with the overall study findings. However, those assigned to CABG, while not demonstrating a survival advantage, did see a significantly reduced MACE rate (77.6% CABG vs. 69.5 OMT, $p = 0.01$), primarily driven by a nearly 50% reduction in the rate of nonfatal MI (14.2% vs. 7.4%), Fig 2. The interaction between study group assignment and intended method of revascularization was statistically significant ($p = 0.002$).

The findings of COURAGE and BARI-2D demonstrated more clearly than ever before that knee-jerk revascularization of all coronary stenoses was likely not warranted. More importantly, these studies demonstrated that in the majority of patients, it was *safe* to defer revascularization, which proved to be quite a cultural change in the interventional community. The improvement in outcomes of patients that underwent surgical revascularization in BARI-2D (i.e. those that by necessity had greater burden of disease), however, did raise an interesting perspective of extent of disease as a predictor of outcomes with revascularization. It appeared that those with a heavy atherosclerotic burden could be a specific subset of SIHD patients that were set apart from the findings in COURAGE.

Mancini et al. evaluated the angiographic data from COURAGE by quantitative coronary angiography (QCA) and found that event rates were higher among those with higher QCA jeopardy scores (used to estimate the amount of myocardium at risk on the basis of assessment of both the severity of the coronary artery lesion and the volume of myocardium it supplies).¹² This is further consistent with our understanding that the extent of atherosclerosis is predictive of future CV events. For instance, it is known that the presence of more diffuse atherosclerotic disease such as the presence of peripheral vascular disease is associated with a 20% risk of coronary events at 10 years.^{13–17} It follows, then, that a larger burden of atherosclerosis localized to the coronary bed as would be seen with great QCA jeopardy scores would be at greater risk for CV events. By corollary, one would expect that if extent of atherosclerosis is predictive of events, the degree of resulting ischemia should follow and help to stratify risk.

One signal of such a finding came from the COURAGE nuclear substudy. Previous studies had suggested that myocardial perfusion imaging (MPI) could provide an accurate assessment of the risk of MACE, with higher risk of MI and CV death with increasing stratus of ischemia quantification.^{18,19} Further, the Asymptomatic Cardiac Ischemia Pilot (ACIP) trial suggested that patients with both active angina and objective evidence of ischemia benefited significantly from revascularization, while there was a signal toward harm with PCI if no objective evidence of ischemia was quantified.^{20,21} The COURAGE nuclear substudy performed a pre-treatment MPI followed by a repeat MPI 6–18 months after enrollment.²² A total of 314 (13%) nonrandomized patients from COURAGE were enrolled. A core lab evaluation defined 10% ischemic myocardium as moderate to severe ischemia and <5% as mild, with the 10% value being defined as an inflection point above which one meets with increased mortality.²¹ The primary outcome, achievement of 5% ischemia reduction at study end, was significantly more likely in the group undergoing PCI with OMT versus OMT alone (33.3 vs. 19.8%, $p = 0.004$).²² Further, compared to those without a significant reduction in ischemia, those that achieved 5% ischemic reduction saw an unadjusted mortality benefit (event-free survival 86.6 vs. 75.3% in patients with or

without ischemia reduction, respectively, $p = 0.037$). Although these findings were attenuated after adjusted analysis in the whole population ($p = 0.26$), the mortality benefit more closely trended toward significance when the analysis was stratified according to pre-treatment ischemic burden. Specifically, those that started with moderate to severe ischemia and incurred a 5% ischemic reduction with PCI saw a general improvement in event-free survival of 83.8% compared to 66.0% in those that did not achieve a reduction in ischemic burden (unadjusted $p = 0.001$, adjusted $p = 0.082$). The findings suggested that a target of 5% ischemic reduction should be sought, especially in those that began with greater ischemic burden. However, the major criticism was that the study ultimately demonstrated no interaction between no/mild ischemia and moderate/severe ischemia in predicting events, possibly owing to the relatively small size of the study population.

In order to better define whether objective measures of significant ischemia could stratify SIHD into those that could benefit from revascularization, studies of fractional flow reserve (FFR) were undertaken; FFR measures pressure via a transducer wire distal to a stenosis compared to the more normal proximal segment. An FFR of 0.5 means a given stenosis causes a 50% drop in blood pressure downstream from the stenosis. Several studies have demonstrated that PCI can be safely deferred in patients with intermediate stenoses with non-ischemic FFR values (>0.75), as the rate of survival and MI are not increased by such a practice.^{23–27} This is true in both single vessel and multi-vessel diseases.^{24,28,29} The FAME trial sought to compare patient outcomes with PCI guided by angiography to PCI guided by FFR in multi-vessel coronary artery disease (CAD).²⁹ FAME evaluated all lesions $>50\%$ for which PCI was planned and only those with an FFR of <0.8 were intervened upon. Over 1000 patients were randomized to angiography-guided versus FFR-guided PCI. At 1 year, the primary endpoint of death, MI, or repeat revascularization was significantly reduced in the FFR group (18.3% angiography-guided vs. 13.2% FFR-guided, RR 0.72 [0.94–0.96], $p = 0.02$). Significantly fewer stents were used in the FFR group (2.7 angiography-guided versus 1.9 FFR guided, $p < 0.001$). Further, there was no demonstrated difference in freedom from angina between groups (77.9% angiography-guided versus 81.3% FFR-guided, $p = 0.20$) with equal antianginal medication use and equal quality of life (QoL) as measured by EQ-5D. This was better evidence that demonstration of ischemia and functional significance of a lesion was of clinical importance.

The subsequent FAME 2 trial sought to build upon the findings of FAME and reconcile them with COURAGE by determining if *FFR-guided* PCI with OMT compared to OMT alone could improve outcomes in patients with SIHD.³⁰ A total of 1220 patients with SIHD planned for single or multi-vessel drug-eluting stent (DES)-PCI were evaluated by FFR. These patients were referred for either symptoms or evidence of ischemia on non-invasive testing. Of the total, 73% had at least one significant lesion by FFR and were randomized to either FFR with OMT or OMT alone ($n = 888$) and followed up to 5 years. The remaining 27% with angiographically significant but all FFR-insignificant lesions were followed in a registry. The study was stopped prematurely because of a significant difference between groups in the primary endpoint. At 1 year, the composite endpoint of death, MI, or urgent revascularization was significant reduced by FFR-guided PCI with OMT versus OMT alone (4.3% versus 12.7%, respectively, HR 0.32 [0.19–0.53], $p < 0.001$), primarily driven by an 8-fold reduction in urgent revascularization for acute coronary syndrome (ACS) (1.6%

versus 11.1%, respectively, HR 0.13 [0.06–0.3], $p < 0.001$). Of those requiring urgent revascularization, just under half presented with significant evidence of ischemia—21.5% with troponin positivity and 26.8% with unstable angina and ischemic ECG changes. Relief from angina was also significantly improved with FFR-guided PCI over OMT alone at both 30 days and 6 months. These data suggested that the use of tools to assess degree of lesion-specific ischemic burden may help tailor treatment strategies to those with SIHD that could see outcome benefit from revascularization with PCI.

However, there are major limitation and legitimate criticism of the above data. First, although the COURAGE nuclear substudy suggested that ischemia reduction was better achieved with PCI than medical therapy, the study failed to definitively show a benefit by way of reduction in death or MI. Further, the inclusion of urgent revascularization in FAME 2 resulted in the majority of the improved outcome with FFR-guided PCI but was met with some skepticism about its importance. Nearly half of those that underwent urgent revascularization did so for the purposes of non-ST elevation ACS (NSTEMI-ACS), which carries a higher risk of MACE compared to those without.^{31,32} By 6 months, NSTEMI-ACS mortality rates equal to or even exceed those of ST-segment elevation MI.³³ Some would still question whether this is clinically important, however, since the overall rate of MI was not affected by PCI. This was further supported by a recent meta-analysis of 5 trials of OMT versus revascularization, including COURAGE, BARI-2D, and FAME 2, which demonstrated only a trend toward reduction in urgent revascularization but no reduction in other clinically important hard outcomes despite evidence of inducible ischemia.³⁴ Although even this study is tempered by inclusion of data from the early 2000s and the lack of information regarding the degree of inducible ischemia, it remains questionable given the weight of evidence whether revascularization with PCI, even with functional assessment of lesion-specific ischemic impact, results in the kind of outcome benefit that warrants procedural risks over the proven benefit OMT provides. Even if one points to improvement in angina, it remains unclear if there is long-term and sustainable benefit from PCI as early benefit seems to equalize over time.

When one looks only at those with a heavy burden of ischemia, however, the data *do* support revascularization. BARI-2D did, in fact, demonstrate a reduced rate of MI in those requiring CABG. Further, evidence of significant reduction in ischemia burden by complete revascularization compared to incomplete revascularization has demonstrated hard outcome benefit in those with heavy burden of disease to start. In patients with multivessel diseases, two large meta-analyses demonstrated a significant reduction in mortality and MI with complete revascularization compared to incomplete revascularization,^{35,36} and complete revascularization was more readily achieved by CABG compared to PCI.³⁶ Further, analyses of the SYNTAX trial (study which evaluated PCI versus CABG in patients using a quantified anatomy-based risk score) looking specifically at residual SYNTAX score after revascularization has demonstrated that a score of >8 was associated with a significantly higher 5-year mortality compared to lower residual scores (35.3% mortality with a score >8 versus 8.7% with score 0–4 and 11.4% with score 4–8, $p < 0.001$).³⁷ Although troubled by the potential for bias, these data point to the fact that in those patients with a great burden of disease, lowering the degree of ischemia was beneficial and CABG appeared best able to accomplish this. It remains unclear if PCI would be able to accomplish the same as thus far

only FFR-based (i.e. lesion-specific) PCI trials have been performed. No study has successfully evaluated revascularization based on total cardiac ischemia. The currently-enrolling ISCHEMIA trial will aim to shed light on the subject in a randomized way.

The ISCHEMIA trial (NCT01471522), sponsored by the National Heart, Lung, and Blood Institute will enroll 8000 patients with moderate to severe ischemia to either PCI plus OMT versus OMT alone. ISCHEMIA's primary end point is time to CV death, MI, or hospitalization for unstable angina, resuscitated cardiac arrest, or heart failure. The secondary end points include angina-related QoL and cost-effectiveness. The motivation for this study largely comes from the key criticisms of the preceding COURAGE and BARI-2D trials. First, the preceding trials randomized patients *after* angiography, potentially adding an element of selection bias as the patients with the most severe disease were not enrolled. This was supported by the fact that although 85% of the patients in COURAGE had some form of ischemic evaluation, only 1/3 of patients had >10% ischemia on noninvasive evaluation. ISCHEMIA aims to eliminate this potential confounder by randomizing prior to angiography. Second, of the 1149 patients randomized to PCI in COURAGE, 14% received balloon angioplasty alone, 86% received angioplasty with stent implantation, and 97% of the stents implanted were bare metal stents (BMS); DES, where used, were first generation. Considering the use of DES in numerous randomized trials and registries reduced the rate of target lesion revascularization by 50–70% compared to BMS, the widespread use of BMS in COURAGE is of some concern as restenosis may have accounted for a significant portion of repeat revascularizations in the PCI group.^{38–41} ISCHEMIA will allow for more contemporary practice where DES use will be largely encouraged.

However, limitations remain to truly answering the question of whether there is a role for revascularization in SIHD. First, although the ISCHEMIA trial asks the extremely important question of whether significant ischemia warrants more than just medical therapy, the trial is slow to enroll, in large part because physicians are reluctant to randomize those with significant ischemia to OMT. Further, although atherosclerotic disease is often tackled medically because mechanical therapy treats only a small portion of a larger problem, a major hurdle to medical therapy continues to be the degree of medical compliance. At COURAGE study entry, 51% of patient in the PCI and in the OMT groups were on a combination of aspirin, lipid-lowering therapy, and beta-blockers. Impressively, by 5-years compliance with this regimen rose to 79% and 80%, respectively.⁴² However, 1-year medication compliance in the real-world CRUSADE registry fared far worse. Aspirin compliance fell to 71%, lipid-lowering therapy 43%, and combination aspirin, lipid-lowering therapy, and beta-blockade only 21%.⁴³ Importantly, nonadherence to medications, especially beta-blockers and statins, is associated with increased risk of CV mortality.⁴⁴

In summary, COURAGE and BARI-2D changed the way we view selection of patients for revascularization and what we now consider appropriate, especially for PCI, has narrowed significantly in scope. Compared to our practice in the early part of this century, we are better able to protect patients from procedural risks that may be of limited benefit in the face of safe and effective medical therapy in SIHD. It appears that patients with a heavy ischemic burden may benefit from revascularization, although investigation of this is ongoing. Evidence preliminarily supports this practice with CABG, and possibly in specific

populations undergoing multivessel intervention with functional assessment of lesion severity during PCI. The bottom line, however, is that SIHD can and likely should be managed conservatively in the majority of patients.

Abbreviations and Acronyms

ACS	acute coronary syndrome
BMS	bare-metal stent
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society
DES	drug-eluting stent
DM	diabetes mellitus
FFR	fractional flow reserve
LDL-C	low density lipoprotein c
MACE	major adverse cardiovascular event
MI	myocardial infarction
MPI	myocardial perfusion imaging
NSTE-ACS	non ST-elevation acute coronary syndrome
OMT	optimal medical therapy
PCI	percutaneous coronary intervention
QCA	quantitative coronary angiography
QoL	quality of life
SIHD	stable ischemic heart disease

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Fig 1.

Kaplan Meier survival curves of OMT alone vs. PCI plus OMT. From New England Journal of Medicine, Boden WE, O'Rourke RA, Teo KK, et al. Optimal Medical Therapy with or without PCI for Stable Coronary Disease, Volume 356, Page 1503. Copyright © 2007 Massachusetts Medical Society. Reprinted with permission. <http://www.nejm.org/doi/full/10.1056/NEJMoa070829>.

Fig 2.

Rates of survival and freedom from MACE, stratified by PCI and CABG. From New England Journal of Medicine, Bari-2D Study Group, A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease, Volume 360, page 2503. Copyright © 2009 Massachusetts Medical Society. Reprinted with permission. <http://www.nejm.org/doi/full/10.1056/NEJMoa0805796>.