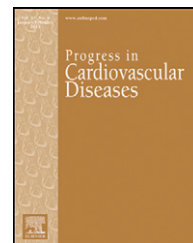


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# Revascularization vs. Medical Therapy in Stable Ischemic Heart Disease

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## ARTICLE INFO

### Keywords:

Stable ischemic heart disease

Optimal medical therapy

Percutaneous coronary intervention

## 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.

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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.<sup>1</sup> In 2004, >1 million stent procedures were performed

in the US,<sup>2</sup> with data showing that 85% of percutaneous coronary interventions (PCI) were performed in patients with SIHD.<sup>3</sup> It was assumed that revascularization of a symptomatic coronary stenosis 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.<sup>4–7</sup> 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.<sup>8</sup> 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.

Statement of Conflict of Interest: see page 304.

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<http://dx.doi.org/10.1016/j.pcad.2015.07.005>

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### 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

ly 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.<sup>10</sup>

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.<sup>9</sup> 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 approximate-

The BARI-2D trial, published 2 years after COURAGE, specifically evaluated a higher risk population of patients with SIHD, specifically those with DM.<sup>11</sup> 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).<sup>12</sup> 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.<sup>13–17</sup> 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.<sup>18,19</sup> Further, the Asymptomatic Cardiac Ischemia Pilot (ACIP) trial suggested that patients with both active angina and objective evidence of ischemia benefited significantly from revascularization,

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