PERCUTANEOUS CORONARY INTERVENTION AND OPTIMAL MEDICAL THERAPY AT THE CROSSROADS IN STABLE CAD MANAGEMENT

Will the ISCHEMIA trial define a clear path forward?

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Patients with obstructive CAD represent a clinical continuum that ranges from subjects who may be asymptomatic (including those with or without ischemia) to those with well-recognized chronic exertional angina, to those who exhibit profound angina symptoms at rest (consistent with acute coronary syndromes), including those with STEMI or NSTEMI. It is now widely accepted that all patients with established CAD should be prescribed multifaceted, pharmacologic secondary prevention therapies, including intensive lifestyle intervention. In the aggregate, this is often referred to as "optimal medical therapy," a term that came into widespread usage as a result of the COURAGE trial.[1] Such robust therapy has been shown to mitigate progression of atherosclerosis and to prevent MI and cardiovascular death in both nondiabetic and diabetic patients.[1,2]

While there is little controversy regarding the clinical benefit and utility of revascularization in patients with acute coronary syndromes (particularly primary PCI in patients with STEMI and expedited PCI in patients with NSTEMI or unstable angina),[3-5] there is a paucity of scientific evidence to support the clinical benefit of PCI in patients with stable CAD. Over the past decade, landmark randomized clinical trials and meta-analyses comparing initial management strategies in patients with stable CAD have demonstrated no significant reduction in "hard" clinical end points (all-cause mortality, cardiac death, or MI) among patients treated with PCI vs optimal medical therapy.[1,2,6-9] One possibility for this discrepancy of PCI benefit in patients with acute coronary syndromes, as compared with patients who have stable CAD, is that the former group may have more ischemic myocardium at risk of necrosis, whereas patients with stable CAD may have less ischemic myocardium and hence may be at a lower risk—thus making it difficult to discern an advantage of PCI on clinical event reduction. Moreover, the main advantage derived from early revascularization is improved short-term angina relief and improved quality of

life, and often a reduction in myocardial ischemia, though these putative benefits have been challenged recently.[10]

Thus, important questions remain regarding how best to approach the initial management of patients with stable CAD, such as whether one or more high-risk subgroups (defined by either coronary anatomy or functional ischemic burden) could be identified who would benefit from early revascularization and whether PCI for symptom relief alone in patients with stable CAD is justified. The focus of this paper will be to address the role of PCI and optimal medical therapy, particularly in the management of patients with stable CAD with a moderate-to-high risk, and to marshal available scientific evidence from clinical trials to clarify whether greater usage of optimal medical therapy in the setting of PCI may have additive benefits to improve clinical outcomes.

REVIEW OF CLINICAL TRIALS OF OPTIMAL MEDICAL THERAPY WITH OR WITHOUT PCI IN PATIENTS WITH STABLE CAD

Two major randomized clinical trials during the past 15 years (COURAGE and BARI 2D)[1,2] showed no reduction in death or the composite end points of death/MI or death/MI/stroke with PCI during periods of follow-up ranging from 5 to 7 years. Both studies provided a compelling rationale for deferred revascularization and an upfront trial of optimal medical therapy, including intensive pharmacotherapy and lifestyle intervention as secondary prevention. Moreover, these findings of strategic equivalence between PCI and optimal medical therapy have now been observed to persist for up to 15 years.[11] In addition, the more recent FAME 2 trial[6] showed that, among patients with stable CAD randomized to fractional flow reserve (FFR)-guided PCI plus medical therapy or to medical therapy alone, there was no overall difference in the end points of cardiac mortality, the composite of cardiac mortality or nonfatal MI, or in all-cause mortality; although, for the primary composite end point of death, MI, or urgent revascularization, there was a significantly lower rate in the PCI group (4.3%) vs the medical therapy alone group (12.7%; $P<0.001$). This difference, however, was driven solely by a lower rate of urgent revascularizations in patients assigned to PCI vs medical therapy (1.6% vs 11.1%; $P<0.001$) during a relatively limited (mean 7-month) follow-up.[11] Moreover, an extended follow-up of the FAME-2 trial to both 2 and 5 years failed to show a durable benefit of FFR-guided PCI on the clinical outcomes of death and/or MI.[12,13]

UNRESOLVED ISSUES IN THE CONTROVERSY OF PCI VS OPTIMAL MEDICAL THERAPY IN STABLE CAD MANAGEMENT

However, it remains unclear whether the extent and magnitude of myocardial ischemia in the setting of obstructive CAD is the principal driver of subsequent cardiac events—notably spontaneous (type 1) MI and the composite of MI and car-

diovascular death. Both the COURAGE[1] and BARI-2D trials[2] did not explicitly require that all enrolled patients demonstrate moderate-to-severe ischemia on noninvasive testing and, while all patients in COURAGE did have objective evidence of baseline myocardial ischemia, most of these randomized patients appeared to have mild-to-moderate ischemia. In addition, all prior contemporary "strategy trials"[1,2,6,12,13] comparing optimal medical therapy with or without PCI were uniformly undertaken after the results of coronary angiography were known to the study investigators, which introduced the possibility that bias may have led to the investigators' decision not to randomize patients to optimal medical therapy or PCI once the coronary anatomic results were apparent. Thus, we have not yet addressed (nor answered) the pivotal question of whether timely revascularization may improve clinical outcomes in patients with stable CAD with flow-limiting CAD and moderate-to-severe baseline ischemia.

It seems both logical and intuitive that targeting revascularization to lesions causing substantial ischemia may further improve outcomes. Many myocardial perfusion imaging studies have demonstrated a strong relationship between the extent of underlying baseline myocardial ischemia and prognosis. In one study of 1137 patients with chest pain and suspected CAD in whom thallium imaging was performed, a strong graded association was present between the number of abnormal ischemic segments and the 6-year rate of cardiac death and MI.[14] In another study of 205 patients with angiographic CAD, there was a greater reduction in cardiac death or MI at 10 years in patients with a normal vs abnormal thallium scan (83% vs 58%; P=0.005).[15] In addition, in a large study of 10 627 patients in whom stress myocardial perfusion imaging was performed (671 of whom were treated with early revascularization), the mean 1.9-year rate of cardiac mortality in nonrevascularized patients increased from 0.7% in those with no ischemia to 6.7% in those with >20% ischemia.[16] Finally, in a substudy of 314 COURAGE trial patients who underwent serial rest/stress myocardial perfusion imaging before and after randomization to PCI plus optimal medical therapy vs optimal medical therapy alone at 6 to 18 months (mean 374±50 days),[17] there was a graded relationship between the amount of residual ischemia on the repeat myocardial perfusion imaging scan and subsequent death or MI; although, after adjustment for baseline variables and treatment, this was not significant (P=0.09). However, only ≈33% of these patients had at least moderate (≥10%) ischemia at baseline.[17] Thus, it remains unclear whether the extent and magnitude of myocardial ischemia in the setting of obstructive CAD in patients with stable CAD is the principal driver of subsequent cardiac events—notably spontaneous (type 1) MI and the composite of MI and cardiovascular death.

WILL THE RESULTS OF THE ISCHEMIA TRIAL SETTLE THIS UNCERTAINTY OF POTENTIAL PCI BENEFIT?

The primary objective of the ISCHEMIA trial (ClinicalTrials.gov Identifier: NCT01471522) is to determine whether an initial invasive strategy of cardiac catheterization and optimal revascularization (with PCI or coronary artery bypass surgery as determined by the local heart team) plus optimal medical therapy will reduce the primary composite end point of cardiovascular death, nonfatal MI, resuscitated sudden cardiac death, or hospitalization for unstable angina or heart failure, in a time-to-first event analysis, during an average 3.5-year follow-up in patients with stable CAD with moderate or severe ischemia and medically controllable or absent symptoms vs an initial conservative strategy of optimal medical therapy alone (with catheterization reserved for failure of optimal medical therapy).[18] The major secondary end points are the composite end point of cardiovascular death or MI and angina-related quality of life. The trial is sponsored by the U.S. National Heart, Lung, and Blood Institute. Blinded coronary computed tomographic angiography is performed prior to randomization to exclude those with significant left main CAD and no obstructive CAD. Enrollment began in late 2012 and 5179 patients have been successfully randomized as of January 2018[19]; the trial is projected to conclude on June 30, 2019. ISCHEMIA thus aims to address limitations of previous strategy trials by: (i) enrolling patients before catheterization, so that anatomically high-risk patients are not excluded; (ii) enrolling a higher risk group with at least moderate ischemia; (iii) minimizing crossovers; (iv) using contemporary drug-eluting stents and physiologic-guided decision-making (FFR) to achieve complete ischemic (rather than anatomic) revascularization; and (v) being adequately powered to demonstrate whether routine revascularization improves a prognostically important composite clinical outcome in patients with stable CAD with at least moderate ischemia.

CONCLUSION

In summary, while PCI has been shown to reduce death or MI in patients with STEMI and in many high-risk patients with NSTEMI, definitive data are lacking at present to validate whether clinical event reduction with PCI can be achieved in higher risk patients with stable CAD who have significant ischemia at baseline. It is anticipated that the results of the ISCHEMIA trial can define a clear path forward in terms of providing more enlightened decision-making in an important population of patients whose optimal management remains uncertain for clinicians. For these reasons, the ISCHEMIA trial findings will very likely have important implications regarding global clinical practice guidelines for years to come. ■

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