In Mildly Symptomatic Patients, Should an Invasive Strategy with Catheterization and Revascularization Be Routinely Undertaken?

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Patients with mild, exertional angina and their physicians routinely face the decision of whether to pursue a conservative strategy of guideline-directed medical therapy (GDMT) versus an invasive strategy of diagnostic cardiac catheterization (cath) and revascularization plus GDMT. Recent randomized clinical trials with stable ischemic heart disease (SIHD) patients comparing a conservative versus revascularization strategy have demonstrated no difference in major clinical events, but these trials randomized patients after performing cath and knowing coronary anatomy.

This issue of Controversies in Interventional Cardiology addresses the following statement: “In mildly symptomatic patients, should an invasive strategy with catheterization and revascularization be routinely undertaken?” The authors presenting the pro and con positions have agreed on the following assumptions: (1) the patient has been diagnosed recently with SIHD on the basis of a stress test performed for typical symptoms; (2) the stress test did not demonstrate high-risk features to suggest significant left main disease; (3) the diagnosis of coronary artery disease (CAD) is not in question; (4) the symptoms are mild and do not interfere significantly with quality of life; and (5) medical therapy has not been optimized. In this discussion, GDMT will refer to lifestyle and pharmacological therapy for secondary prevention and for treatment of angina. For this clinical scenario, we recommend an approach using patient-centered shared decision-making (SDM) to enable clinicians and patients to discuss treatment options and decide whether to pursue a conservative or invasive strategy, rather than a routine invasive strategy with cath and revascularization for all such patients (Figure 1).

Eighty percent of percutaneous coronary intervention (PCI) is performed ad hoc, which means that diagnostic cath and PCI are performed at the same setting without temporal pause to assess alternative treatment options and patient preferences once the coronary anatomy is known. Patient preferences and values are paramount when alternative treatments confer equivalent clinical outcomes, as is the case in comparative effectiveness trials to date for SIHD patients with mild symptoms.

Review of Evidence for GDMT Versus Revascularization+GDMT

Evidence supporting a routine invasive strategy of cath and revascularization for patients with SIHD is outdated. In randomized controlled trials conducted in the 1970s involving ≈2600 patients with SIHD, coronary artery bypass grafting (CABG) improved survival as compared with medical therapy in patients with high-risk anatomy, specifically left main and 3-vessel disease. The relevance of these studies today is speculative because they compared CABG with minimal, if any, medical therapy, and medical therapy has since
improved significantly. In aggregate, contemporary GDMT can be expected to yield $\approx 50\%$ relative risk reduction, reducing and potentially eclipsing any benefit from revascularization.$^{6-9}$ Subsequent trials compared PCI with medical therapy and found no reduction in death or myocardial infarction (MI) from PCI.$^{10}$

**Recent Trials Comparing Revascularization and Medical Therapy**

**Impact on Death or Myocardial Infarction**

In the current era of GDMT, the 2 largest comparative effectiveness trials of coronary revascularization versus medical therapy in patients with SIHD—COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes)—enrolled patients with angiographically proven CAD with typical angina or objective evidence of ischemia.$^{11,12}$ These differed from all previous trials in that medical therapy was comprehensive, intensive, and applied equally to both treatment groups. COURAGE and BARI 2D found that an invasive strategy of revascularization (in COURAGE, PCI only) plus optimal medical therapy (OMT) did not reduce the rate of death/MI or death, respectively, as compared with OMT alone. The Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial compared fractional flow reserve–guided PCI plus GDMT (PCI group) with GDMT alone (medical-therapy group) in patients with stable CAD.$^{13}$ The primary end point was a composite of death, MI, or urgent revascularization. Recruitment was halted prematurely after 888 subjects were randomized with a mean follow-up of 7 months because of a significant between-group difference in the primary end point. Although fractional flow reserve–guided PCI did not reduce the risk of death or MI, it did reduce the rate of urgent revascularization ($1.6\%$ versus $11.1\%$; hazard ratio [HR], $0.13; 95\%$ confidence interval [CI], $0.06-0.30; P<0.001$).

**Impact on Quality of Life**

The Coronary Artery Surgery Study demonstrated that CABG was superior to medical therapy for long-term quality of life.$^{14}$ At 1 and 5 years after entry, the frequency of angina-free patients was $66\%$ and $63\%$ in the surgical group and $30\%$ and $38\%$ in the medical group. In COURAGE, patients with angina at baseline had an incremental benefit from PCI for 6 to 24 months (Figure 2A); patients with more severe angina had a greater benefit from PCI.$^{15}$ By 3 years the frequency of angina-free patients was $59\%$ in the PCI+OMT group and $56\%$ in the OMT group ($P=0.30$). There was no significant difference between treatment groups in mean quality of life score after 12 months for the entire COURAGE cohort (Figure 2B). Among patients with mild-to-moderate angina at baseline, there was no significant difference between treatment groups in quality of life after 6 months (Figure 2C). In BARI 2D, patients in the CABG stratum randomized to revascularization had a higher rate of freedom from angina throughout the 5-year follow-up compared with patients randomized to medical therapy. The quality of life benefit from PCI in BARI 2D was less durable; freedom from angina was significantly higher in the PCI group compared with the medical therapy group only in the first year of follow-up.$^{16}$
Limitations of Previous Trials

All patients who participated in COURAGE and BARI 2D underwent cath to define coronary anatomy before randomization. Strict interpretation of these and all previous SIHD strategy trials is that the results apply only to patients when coronary anatomy is known. No adequately powered strategy trials have randomized patients before cath, highlighting the lack of evidence to support a strategy of GDMT without knowledge of coronary anatomy, even among SIHD patients with mild symptoms. However, there is also no evidence from randomized controlled trials that performing cath and revascularization in patients with SIHD reduces major cardiovascular events. Another limitation is that the majority of PCI procedures performed in COURAGE and BARI 2D used bare metal stents because drug-eluting stents had not been routinely available. Yet current evidence does not demonstrate that drug-eluting stents reduce death or MI compared with bare metal stents.10 Furthermore, fractional flow reserve–guided PCI was not performed in COURAGE or BARI 2D. Lastly, COURAGE and BARI 2D had low enrolled-to-screened patient ratios, calling into question their generalizability. However, a low enrolled-to-screened ratio was also observed for the BARI (Bypass Angioplasty Revascularization Investigation) trial, a landmark study that compared CABG with PCI in SIHD patients with multivessel CAD and helped to justify PCI as a comparable alternative to CABG.17

High-Risk Subgroups That Might Benefit From Routine Revascularization in the GDMT Era

It is unclear whether the lack of superiority of PCI compared with contemporary GDMT to reduce adverse cardiovascular events in patients with SIHD is attributable to improvements in medical therapy, less complete revascularization with PCI as compared with CABG, patient selection (ie, high-risk patients were not enrolled), or other unknown reasons. If there is a benefit from revascularization in SIHD compared with GDMT alone, it should be most evident among the highest risk patients.

High-Risk Anatomic Features

COURAGE and BARI 2D included modest numbers of patients with high-risk anatomic features, and secondary analyses were performed to elucidate the role of revascularization in such patients. In COURAGE, there was no significant benefit from PCI in patients with 3-vessel CAD and EF <50%, but the sample size was small (n=126, P=0.26).18 Among 406 patients with EF<50% (18% of the sample), the hazard ratio for PCI+OMT versus OMT was 1.14 (95% CI 0.77–1.70).11 There was no anatomic feature that defined a subset that benefited from PCI, including proximal left anterior descending artery stenosis which was present in 25% of patients.19 In contrast, among patients in BARI 2D for whom CABG was determined to be the most appropriate method of revascularization, the 5-year rate of the secondary end point (death, MI, or stroke) was lower (driven by MI events) in the subset assigned to CABG (n=378) versus those assigned to GDMT (n=385, 22.4% versus 30.5% [79 versus 115 events], P=0.01).12 This was a post hoc analysis of a secondary end point in the CABG stratum.
High-Risk Clinical Features
COURAGE investigators performed a post hoc analysis of high-risk patients defined as onset of Canadian Cardiovascular Society (CCS) Class III angina within 2 months or stabilized acute coronary syndrome within 2 weeks of enrollment. They found an initial strategy of OMT alone for these patients did not result in increased death or MI at 4.6 years or worse angina at 1 year, but it was associated with a high rate of crossover to PCI in the first year (30%), whereas the overall crossover rate was 16%. Courage patients with mild angina had fewer events than more symptomatic patients and experienced no reduction in events from routine PCI. This suggests there should be equipoise between GDMT versus PCI+GDMT in patients with mild angina.

High-Risk Ischemia
Although severity of ischemia is correlated with risk of death, it is unknown whether revascularization to reduce ischemia improves prognosis. It is not known whether the increased risk of death from ischemia is attributable to inherent adverse effects of ischemia (eg, arrhythmias), occlusion of severe stenoses, or whether severe ischemia is simply a marker of a larger number of nonflow-limiting vulnerable plaques prone to rupture. Observational data suggest that revascularization is associated with lower cardiac mortality in patients with >10% ischemia. Using paired core laboratory-measured myocardial perfusion imaging studies, the COURAGE serial nuclear substudy found that PCI+OMT was superior to OMT alone in reducing ischemia. For both treatment groups combined, ischemia reduction was associated with a lower rate of death or MI for 3.6 years: 16% for those with significant ischemia reduction compared with 34% for those without (adjusted multivariate P=0.08). A subsequent COURAGE analysis of outcomes by treatment strategy in 468 patients with moderate or severe ischemia on baseline myocardial perfusion imaging showed no reduction in death or MI from PCI+OMT for 4.6 years (PCI+OMT 22% versus OMT 19%, HR 1.08, 95% CI 0.71,1.65). Therefore, it is not known whether PCI+OMT reduces death or MI as compared with OMT even among the subset of patients with moderate to severe ischemia.

Practice Guidelines and Appropriate Use Criteria for Managing Patients With SIHD
The purpose of an invasive strategy for patients with SIDH is to improve survival or relieve symptoms. The American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) 2011 guidelines for revascularization provide three Class I recommendations for CABG in SIHD to improve survival (all based on the outdated CABG versus medical therapy studies): unprotected left main, 3-vessel disease with or without proximal left anterior descending artery disease, and 2-vessel disease with proximal left anterior descending artery disease. There is one Class I recommendation for PCI or CABG to relieve symptoms: patients with ≥1 significant stenoses amenable to revascularization and unacceptable angina despite guideline-directed medical therapy. SIHD guidelines recommend cath when (1) noninvasive testing suggests high-risk coronary lesion(s), or (2) unacceptable symptoms persist despite an adequate trial of guideline-directed medical therapy, and (3) revascularization is consistent with patient preferences. This recommendation is not based on clinical trial evidence.

Appropriate use criteria were developed by ACCF in collaboration with other societies to provide practice standards in use of cath and PCI, and to mitigate over- and underuse. The 2012 appropriate use criteria for cath indicate that it is appropriate to perform cath when a patient with suspected CAD has symptoms associated with intermediate- or high-risk features on noninvasive testing, or high-risk findings on noninvasive testing regardless of symptom severity. The 2012 appropriate use criteria for revascularization prioritized the following factors to determine the appropriateness of revascularization: (1) clinical presentation (acute coronary syndrome or stable angina); (2) severity of angina (asymptomatic, CCS Class I, II, III, or IV); (3) severity of ischemia on noninvasive testing; (4) intensity of medical therapy; and (5) extent of anatomic disease (1-, 2-, 3-vessel disease, with or without proximal left anterior descending artery or left main coronary disease). For patients with CCS Class I or II angina, Figure 3 indicates whether revascularization is appropriate (A), inappropriate (I), or uncertain (U) as modified by severity of ischemia, intensity of medical therapy, and extent of anatomic disease. Maximal medical therapy is defined as the use of ≥2 classes of agents to reduce angina. Low-risk stress test findings are associated with cardiac mortality <1% per year; intermediate-risk with 1% to 3% per year; and high-risk with >3% per year. Figure 3 shows that revascularization is appropriate for patients with mild angina who are on maximal medical therapy and have a high-risk stress test, whereas revascularization is either inappropriate or uncertain (as modified by extent of anatomic disease) for patients with mild angina who are not on maximal medical therapy and have a low-risk stress test.

Current Practice
Registry data show that among patients with suspected CAD who have moderately or severely abnormal noninvasive tests, 38% to 61% are not referred to cath. The appropriate cath referral rate after an abnormal stress test is unknown. An adequate trial of guideline-directed medical therapy should be undertaken before revascularization is contemplated. Unfortunately, among patients with the most abnormal noninvasive tests, 24% do not receive aspirin and 23% do not receive a lipid-lowering agent at 90 days after the index test, as recommended by guidelines. Revascularization rates vary widely and are related closely to rates of cath, varying by region from 16 to 77 per 1000 among Medicare beneficiaries. The relationship between cath and PCI is strong (R²=0.78), whereas the association with CABG is modest (R²=0.41). The tighter relationship between cath and PCI may be explained by the common practice of ad hoc PCI,
which is based more on visual estimation of stenosis and technical feasibility than on evidence that revascularization reduces events.34–37 The diagnostic-therapeutic cascade may explain why GDMT is not maximized before PCI, even after publication of COURAGE.38 If a routine cath is performed before optimizing medical therapy, ad hoc PCI is likely to be performed, potentially distracting attention away from medications with proven benefit to decrease events. On the other hand, the diagnostic cascade assumes noninvasive testing accurately identifies obstructive CAD when 59% of the time it does not.39

There are multiple forces that favor performing ad hoc PCI when a significant stenosis is detected at diagnostic cath.36,37,40,41 They include referring physician and patient expectations, incremental burden and costs to the patient and practice to schedule a second procedure, ability to improve ischemia and angina burden quickly, avoidance of vascular access and bleeding complications, avoidance of regret from a perceived error of omission (ie, regretting inaction if the patient has a bad outcome), fear of malpractice litigation, and reimbursement policies. Unfortunately, ad hoc PCI involves proceeding directly from a diagnostic test (cath) to a therapeutic procedure (PCI) when the patient is sedated and has not been fully informed about the potential risks, benefits, and alternative treatment options.

Even before sedation, however, there is evidence that patients are not aware of the benefits and harms of alternative treatments for SIHD. In a survey of 153 patients with SIHD undergoing elective cath with possible PCI, 88% believed that PCI would reduce their risk for MI and 82% believed that PCI would reduce their risk for death.42 In contrast, patients’ cardiologists (n=27) believed that PCI would prevent MI in 17% of the cases and reduce mortality in 15% of the cases. This discordance highlights the need to improve patients’ knowledge of the expected benefit of alternative treatments as well as enhancing patients’ involvement in making decisions aligned with their preferences, values, and goals.

Shared Decision-Making

Patient-centered SDM is an approach to improve patient knowledge and involvement in medical decisions, particularly when alternative treatments have comparable clinical outcomes. SDM is not appropriate for decisions when benefits clearly outweigh risks (such as resuscitation for cardiac arrest) and technical decisions (such as PCI coronary guide catheter selection). In the SDM model, patient involvement begins with the development of a partnership between clinician and patient, and includes participation in information exchange, deliberation, and decision-taking.43 Decision aids are tools to facilitate information exchange, as well as integration and understanding of the information.44 A systematic review of 55 randomized clinical trials involving decision aids found that compared with usual care, the use of decision aids is associated with greater patient knowledge, more realistic expectations, lower decisional conflict, and increased proportion of patients actively engaged in decision-making.45

For patients with SIHD, SDM aims to help clinicians and patients choose between an initial strategy of GDMT alone versus GDMT+cath±revascularization (Figure 1).46 An older randomized trial compared SDM with an interactive video presenting benefits and risks of medical therapy, PCI, and CABG versus usual care. SDM significantly improved patient knowledge, and fewer patients in the SDM arm decided to have revascularization (58%) as compared with usual care (75%).47 Ting and colleagues are conducting a randomized trial using a decision aid for patients with SIHD considering GDMT versus PCI+GDMT.48 (Figure 4 shows the personalized decision aid for patients with CCS Class I/II angina).

Evidence Gap in Support of an Invasive Practice Paradigm for SIHD: Ongoing Research

Results from COURAGE and BARI 2D underscore the need to define the appropriate role of revascularization for SIHD in the era of GDMT. Because these trials showed no reduction in their primary end points from revascularization, which patients with SIHD, if any, benefit from an invasive strategy in terms of clinical events? This is the primary question asked by the National Heart, Lung, and Blood Institute–sponsored ISCHEMIA (International Study of Comparative Health Effectiveness
with Medical and Invasive Approaches) trial (ClinicalTrials.gov Identifier NCT01471522), which will determine whether an invasive strategy of routine cath and revascularization plus GDMT in SIHD patients with at least moderate ischemia reduces cardiovascular death or MI compared with a conservative strategy of GDMT alone, with cath reserved for patients who fail GDMT. In contrast with COURAGE and BARI 2D, randomization of patients will occur before cath, avoiding potential selection bias that would exclude higher-risk patients by knowing their coronary anatomy. The feasibility of patient recruitment is supported by multiple imaging registries showing the rate of referral to cath for patients with at least moderate ischemia is only 35% to 65%. In further support that sufficient equipoise exists to study the initial management of patients with SIHD, a survey of 500 cardiologists found that 80% were willing to enroll SIHD patients with at least moderate ischemia into a trial with an initial noninvasive strategy arm. The ACCF/AHA CABG and PCI guideline writing committees endorse the performance of theISCHEMIA trial, “which will provide contemporary data on the optimal management strategy (medical therapy or revascularization with CABG or PCI) of patients with SIHD.”

**Conclusion**

In patients with mild angina (CCS Class I/II) and no high-risk findings on stress testing, GDMT should be initiated routinely for secondary prevention and symptom control. The weight of evidence indicates that revascularization does not reduce adverse events in SIHD when added to GDMT but does improve symptoms more rapidly than GDMT alone (the benefit from PCI is transient, the benefit from CABG more durable). Based on this evidence, we do not recommend a routine invasive strategy in patients with mild symptoms. Rather, we recommend routine patient-centered SDM to enable the clinician and patient to decide on a treatment that is most aligned with the patient’s preferences, values, and goals—be it conservative or invasive.

All patients in randomized controlled strategy trials to date underwent cath before randomization, leading to possible selection bias by excluding higher-risk patients after knowing the coronary anatomy. This leaves cardiologists with a knowledge gap regarding the need to perform cath in patients with SIHD, recognizing that once cath is performed, ad hoc PCI is likely to follow. The ISCHEMIA trial results are expected to fill this gap. Meanwhile, in the absence of evidence that an invasive strategy is superior to a conservative strategy, informed and knowledgeable clinician–patient dyads should jointly choose an initial treatment strategy.

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**References**


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Response to Maron and Ting
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Although shared decision-making between patients and physicians is essential, relying on studies such as COURAGE in which substantial ischemia was uncommon, mortality was low, and contemporary technologies weren’t used under-estimates the potential benefits of modern revascularization. In a recent study from Ontario, Canada, adjusted 3-year rates of death or ACS were 64% and 75% higher if revascularization was not performed in patients with Appropriate or Uncertain disease. Invasive Strategy Should Not Be Routine.

Best-in-class DES are associated with lower rates of stent thrombosis, MI, recurrent ischemia, unplanned revascularization and improved quality of life. By the time large-scale studies such as COURAGE and BARI 2D are completed, the therapies tested are often out of date. The FAME-2 study demonstrated a 58% reduction in death and spontaneous MI with PCI compared to medical therapy alone in hemodynamically significant lesions. Even when including peri-procedural MIs (which have little or no prognostic significance), the hazard ratio for death and MI was 0.61 favoring PCI, a benefit not reaching statistical significance (P=0.22) as the trial was stopped early given the benefit of PCI for preventing unplanned urgent revascularization.

Drs. Maron and Ting state that “GDMT can be expected to yield ~50% relative risk reduction, reducing and potentially eclipsing any benefit from revascularization.” The benefits of GDMT apply to patients undergoing PCI as well. PCI and GDMT are complementary in that PCI relieves ischemia whereas GDMT may not, as seen in the COURAGE nuclear sub-study. Conversely, GDMT prevents progression of atherosclerosis and vulnerable plaque rupture from lesions which are mostly non-ischemia-producing. Thus, pending results of the ISCHEMIA trial, revascularization is appropriate in most patients with mild symptoms and at least moderate ischemia.
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