Medical therapies and revascularization play complementary roles in the treatment of patients with coronary atherosclerosis. In general, the degree of clinical benefit from percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or medical therapy is proportional to the acuity of the clinical syndrome being treated. PCI for ST-segment elevation myocardial infarction and early angiography and revascularization for non–ST-segment elevation ACS have been demonstrated to improve survival and reduce myocardial infarction (MI) compared with medical therapy alone. Conversely, PCI in patients with stable coronary artery disease (CAD) has been proven to reduce symptoms and improve quality of life but has not been shown to prevent death or MI. Clinical trials and observational registries have demonstrated that objective evidence of myocardial ischemia is both qualitatively and quantitatively related to the subsequent risk of death and MI, and that greater reduction of ischemia with revascularization compared with medical therapy alone may correlate with improved event-free survival. This report examines the links between ischemia and prognosis, between revascularization and ischemia reduction, and therefore the likely relationship between revascularization and freedom from death/MI in patients with stable CAD.

Link Between Ischemia and Clinical Outcomes
Ischemia documented by single photon emission computed tomography (SPECT) myocardial perfusion scanning (MPS) has been quantitatively correlated with the occurrence of cardiac death/MI. Among 10,627 consecutive patients evaluated for CAD by SPECT MPS, quantitative ischemia was directly proportional to 2-year mortality in medically treated patients, and the relative survival advantage provided by coronary revascularization (versus medical therapy alone) was directly related to the magnitude of ischemic burden (Figure 1). The observation that revascularization above a quantitative ischemic threshold involving 10% of the left ventricle (LV) may be associated with an incremental survival advantage has gained acceptance. A graded relationship between SPECT quantified ischemic burden and adverse outcomes (death/MI) has also been suggested by the nuclear imaging substudy from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial (Figure 2). Moreover, an ischemic burden reduction of ≥5% on serial SPECT MPS imaging in patients with stable CAD in COURAGE was a powerful correlate of less death or MI in follow-up. Ischemia-guided revascularization using SPECT MPS has been shown to reduce the subsequent risk of major adverse outcomes.
cardiac and cerebrovascular events (MACCE) in patients with multivessel disease. \[^{10}\] Importantly, the data correlating SPECT MPS ischemia and revascularization with clinical outcomes are derived from observational studies, whereas the COURAGE trial nuclear substudy lacks power for definitive conclusions to be made. Finally, the relationship between ischemia and adverse clinical outcomes is evident regardless of the methodology used to demonstrate ischemia. The reliance on any single technique to quantify ischemia is limited by a lack of concordance between methodologies. For example, although ambulatory electrocardiographic monitoring demonstrated a strong relationship between ischemia and subsequent death, nonfatal MI, or hospitalization among asymptomatic patients enrolled in the Asymptomatic Cardiac Ischemia Pilot (ACIP) study, there was poor concordance between ambulatory electrocardiographic and SPECT MPS for demonstrating myocardial ischemia. \[^{11}\] A relationship between coronary lesion functional assessment by fractional flow reserve (FFR) and clinical outcomes has also been demonstrated, even in patients with normal regional perfusion by MPS and noncritical angiographic stenoses. \[^{12}\]

In this regard, concordance between MPS and FFR documented ischemia has been poor on either a per patient or per lesion basis, particularly in patients with multivessel CAD. Indeed, MPS underestimated ischemic zones in 36% and overestimated in 22% of patients with multivessel CAD. \[^{13}\] Adverse clinical outcomes have been shown to be infrequent when PCI is deferred in stenoses with FFR >0.75 (6 studies) or >0.80 (1 study). \[^{14}\] In a randomized trial of FFR versus angiographically guided PCI, among 513 stenoses that were deferred for FFR >0.80, only 1 MI (0.2%) and 16 repeat revascularizations (3.2%) were observed through 2 years of follow-up. \[^{15}\] PCI deferred based on FFR >0.80 seems to be safe even for patients with a proximal left anterior descending stenosis. \[^{16}\] The advantages of revascularization of ischemia-producing lesions for patients with chronic stable CAD were recently demonstrated in the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial. In FAME 2, stable patients scheduled for PCI with second generation drug-eluting stent (DES) underwent FFR in all prospective target lesions. Patients in whom all lesions had FFR >0.80 were followed in an optimal medical therapy (OMT)-only registry, whereas 888 patients with ≥1 target stenosis with FFR ≤0.80 were randomized to receive PCI of those lesions plus OMT vs. OMT alone. The primary end point was the composite of death, MI, or unplanned hospitalization with urgent revascularization. Enrollment was halted before study completion by the independent data and safety monitoring board because of a marked between-group difference in the primary end point (4.3% PCI plus OMT versus 12.7% OMT alone; hazard ratio [HR], 0.32; 95% confidence interval, 0.19–0.53; P < 0.001). This difference was driven by a lower rate of urgent revascularization in the PCI group (0.7% versus 9.5% OMT alone; HR, 0.07; 95% confidence interval, 0.02–0.22; P < 0.001). Importantly, in patients randomly assigned to PCI, significantly fewer revascularizations were triggered by a confirmed MI or unstable angina with ECG changes. Furthermore, the need for any revascularization during follow-up was similar between the PCI plus OMT randomized patients (3.1%) and OMT registry patients (3.6%), but was significantly less than observed in patients assigned to OMT alone (19.5%, P < 0.001). Finally, the CCS Class II to IV angina was markedly less frequent with PCI plus OMT compared with OMT alone. Thus, in patients with stable CAD and ≥1 hemodynamically significant stenosis (FFR ≤0.80), PCI plus OMT (as compared with OMT alone) significantly improved clinical outcomes, although the trial was underpowered to show a difference in death/MI between the 2 strategies. \[^{16}\] These observations have spawned the concept of appropriate functional revascularization for symptomatic (and possibly even asymptomatic) patients with significant objective ischemia, which integrates FFR into the clinical decision-making path for performance of optimal PCI (Figure 3). \[^{14}\] Reliance on anginal symptoms to prompt revascularization in patients with objectively documented reversible ischemia may not be appropriate. In 1042 asymptomatic patients with objective reversible ischemia from 3 randomized

Figure 1. Top, Rate of cardiac death stratified by myocardial perfusion SPECT quantification of ischemia (% myocardium) and treatment modality in 10,627 consecutive patients followed for 1.9 years ± 0.6 years. Bottom, Change (reduction) in ischemic defect stratified by size (quantitative ischemia %) of baseline ischemic defect and treatment modality. \(^{*}P<0.05\). Adapted with permission from Berman DS, et al \[^{6}\] copyright © 2001 The American Heart Association.

Figure 2. Incidence of death or myocardial infarction (MI) stratified by the degree of residual myocardial ischemia present on the 6-month to 18-month myocardial perfusion scan. The composite occurrence of death or MI is proportional to the degree of residual myocardial ischemia. Adapted with permission from Shaw LJ, et al. \[^{8}\]
trials of PCI plus OMT versus OMT, significant reductions in both death and death/MI were evident with revascularization.17 These data should be viewed as hypothesis-generating and not conclusive. Nonetheless, long-term freedom from ischemia after PCI is increasingly achievable. More durable clinical and angiographic coronary patency and relief of objective ischemia by serial SPECT MPS have been demonstrated after PCI with DES versus bare metal stent (BMS).18

**Reality of Optimal Medical Therapy**

Although the COURAGE trial achieved exemplary compliance with OMT, similar benchmarks may be difficult to achieve in clinical practice.19 The ≥90% compliance through 3 years with aspirin, beta-blockers, and statins achieved in COURAGE20 stands in stark contrast with contemporary registry experiences.21,22 Possible explanations for this discrepancy include (1) use in COURAGE of clinical research nurse case managers, and (2) free medications in the trial. Until nurse case management and free pharmaceuticals become available in routine clinical practice, it will be difficult to recreate the apparent success of COURAGE OMT. Indeed, an American College of Cardiology/National Cardiovascular Data Registry analysis showed no difference in the use of guideline-based medical therapies in the 4 years after compared with before the COURAGE publication.23

**Improvements in Coronary Revascularization Technology and Decision-Making**

The principal argument for an OMT first strategy in patients with stable CAD is the lack of reduction in death/MI with PCI in the COURAGE trial. However, the past decade has witnessed an improved understanding of the relative benefits of CABG versus PCI in different patient cohorts, as well as improvement in both catheter-based technologies and adjunctive pharmacotherapies. PCI therapy as performed in the COURAGE trial is clearly suboptimal by contemporary standards.24 Of 1149 patients randomly assigned to PCI in COURAGE, 73 did not undergo the procedure because of refusal, unsuitable anatomy, or failure to cross the target lesion with a guidewire. Inexplicably, these 73 patients (6.4%) were not included in subsequent intention to treat analyses of procedural success. Thus, the 89% per patient and 93% per lesion procedural success rates cited in COURAGE are really 83% (intention to treat) or 87% (actual treatment received) on a per-patient basis and 89–91% on a per lesion basis.25 These measures of procedural success fall well below the 10th percentile of a contemporary ACC/NCDR catheterization PCI registry ranking.25 Importantly, only 2.7% of COURAGE trial patients were treated with a DES and 14% had balloon angioplasty alone. The relative benefit of DES compared with BMS for reducing clinically driven repeat revascularization (50–70% relative reduction) has been repeatedly demonstrated in randomized controlled clinical trials and clinical registries. Freedom from clinically driven repeat revascularization is a surrogate for freedom from angina, improved exercise tolerance, and enhanced quality of life. Finally, different DES may vary with regard to long-term safety and efficacy. Recent meta-analyses of DES versus DES as well as DES versus BMS randomized controlled clinical trials have demonstrated that the fluoropolymer-based everolimus-eluting stent (EES) is associated with a lower incidence of stent thrombosis and improved outcomes compared with both BMS and other DES types. In a pooled, patient-level analysis involving 6789 patients from 4 randomized trials that compared the EES versus the paclitaxel-eluting stent, EES was associated with significant reductions in target lesion revascularization, target vessel revascularization,
MI, and stent thrombosis through 2-year follow-up, particularly in those patients who required multivessel or multiless revascularization. Therefore, the results from studies of patients with stable CAD using BMS or even early DES cannot be generalized to contemporary outcomes with current generation DES, which are safer, more effective, and produce longer freedom from recurrent ischemia. Studies modeling these improvements in DES technology have suggested that superior clinical outcomes after PCI versus OMT or CABG (in patients with complex CAD) may have been observed had EES been used.

Despite the limitations of PCI as performed in the COURAGE trial, the strategy of PCI+OMT was nevertheless significantly more effective in reducing ischemia demonstrated on serial SPECT MPS than was OMT alone (Figure 4). Strikingly, despite the excellence of OMT in COURAGE, the amount of ischemia as objectively measured by SPECT MPS was not significantly reduced. Furthermore, the reduction in ischemia by PCI+OMT (versus OMT) was highly significant despite the fact that 15% of subjects assigned to OMT crossed-over to PCI as a result of refractory symptoms in follow-up.

New data from 2 landmark trials has provided important directions for triage of stable patients with CAD to PCI versus CABG. The SYNTAX trial prospectively validated the predictive utility of a 12-point angiographic lesion complexity score after random patient assignment of patients with left main or 3-vessel CAD to PCI (using paclitaxel-eluting stent) or CABG. Comparable rates of death, MI, or stroke were observed through 5 years follow-up after PCI or CABG in patients with low (0–22) complexity SYNTAX scores, although repeat revascularization was observed more frequently after PCI. However, patients with intermediate (23–32) SYNTAX scores (principally those with triple vessel disease) or high (≥33) SYNTAX scores (all enrolled groups) fared significantly better after CABG with lower rates of death, MI, and repeat revascularization. This observation is similar to that of a recent integrated ACC/NCDR, Society of Thoracic Surgeons, and Centers for Medicaid and Medicare Services database analysis, which demonstrated enhanced survival through 4-year follow-up after CABG (compared with PCI) revascularization of patients with multivessel CAD. New data have emerged as well regarding revascularization in the patient with diabetes mellitus. In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, although nonrandomized, the composite occurrence of death, nonfatal MI, or stroke was observed less frequently through 5-year follow-up after CABG compared with PCI in patients with diabetes.

Similarly, although the presence of diabetes adversely influenced clinical outcomes after both CABG and PCI in the SYNTAX trial, the net effect favored CABG in diabetic patients with left main or triple vessel CAD. These findings have now been confirmed in the FREEDOM trial, which demonstrated a 30% relative reduction in the composite end point of death, MI, or stroke through 5-year follow-up among 1900 diabetic subjects randomized to CABG versus PCI (18.7% versus 26.6%; P = 0.005). Notably, 85% of these subjects had 3-vessel disease; only first generation DES were used for PCI; and ischemia guidance of PCI was not performed. Moreover, the rate of stroke was significantly less with PCI than CABG (2.4% versus 5.2%; P = 0.03), and the primary end point event curves were nearly superimposable in patients with a low SYNTAX score. Thus FREEDOM has essentially confirmed the results from SYNTAX in multivessel disease patients with complex anatomy for PCI. Although PCI outcomes in both SYNTAX and FREEDOM would have undoubtedly been better with EES, improved pharmacotherapy, and other best current practices, the observation that coronary anatomic complexity is a key determinant of both the relative efficacy and safety of PCI (versus CABG) is important and will help guide patient selection for revascularization in the future.

Lessons Learned From COURAGE and FAME 2

Both COURAGE and FAME 2 demonstrated improved angina-free status and a reduction in subsequent revascularization in patients with stable CAD who are initially treated with PCI+OMT compared with OMT alone. COURAGE also documented improved quality of life and less requirement for antianginal medications after PCI, especially in those with at least moderate angina at baseline. The objective benefits of newer

![Figure 4. Baseline (pretreatment) and follow-up (6–18 months) single photon emission computed tomography (SPECT) myocardial perfusion scanning (MPS) results by randomly assigned treatment strategy in the COURAGE trial nuclear substudy. The strategy of percutaneous coronary intervention (PCI) plus optimal medical therapy (OMT) was more effective in reducing myocardial ischemia than initial OMT. Modified with permission from Shaw LJ, et al.](image-url)
generation DES, coupled with ischemia-guided complete revascularization, would have further enhanced the magnitude and durability of the PCI strategy (vs. OMT alone). Importantly, enrollment into COURAGE (and FAME 2) occurred only after coronary angiography, and patients with clear indications for revascularization were not enrolled. In COURAGE, >10,000 patients were excluded after diagnostic angiography, including 947 with significant (>50%) left main stenosis. Thus, coronary angiography contributes valuable incremental information for risk stratification and therapeutic triage, and all patients with stable CAD should undergo angiography to inform appropriate decision-making. To date, no study has demonstrated that medical management of patients with stable CAD and ischemia without coronary angiography is safe.

Approach to the Patient With Stable Ischemic Heart Disease

In patients with objectively documented myocardial ischemia or evidence of previous MI, coronary angiography should be performed to define the coronary anatomy and inform appropriate therapeutic triage (OMT alone versus revascularization [PCI or CABG] plus OMT). At the time of coronary angiography, stenoses of intermediate severity should undergo functional assessment (FFR) if not previously demonstrated to be associated with objective evidence of myocardial ischemia. Current evidence is inadequate to justify the designation of a quantitative ischemic threshold above which coronary angiography should be performed or below which a noninvasive medical treatment strategy is preferred. If a revascularization strategy is chosen in cases with left main or multivessel CAD, the decision to choose PCI versus CABG is based on coronary anatomic, functional, and clinical risk stratification, and should be made by a cooperating heart team. In general, patients with more complex coronary anatomy, particularly in the presence of diabetes mellitus, have better long-term outcomes after surgical revascularization. If PCI is elected, ischemia guidance of revascularization using FFR or SPECT MPS has been demonstrated to improve safety and efficacy outcomes.45,46

Role of Patient Preference

Although a definitive randomized trial demonstrating a benefit of revascularization in reducing death or MI in patients with stable CAD has not been performed, meta-analyses have clearly shown that PCI (and CABG) compared with OMT reduces angina and anginal equivalent symptoms such as dyspnea and fatigue, and improves exercise tolerance and quality of life.44 Furthermore, no randomized trial has shown harm of PCI (versus OMT) for important end points (death, MI, or stroke). Despite this favorable risk-benefit ratio, current guidelines recommend that revascularization in stable CAD be reserved for unacceptable angina symptoms on 2 or more chronic oral antianginal medications.45 Even when achievable, medical angina relief often requires foregoing activities such as active exercise, sex, and work (to avoid stress), and antianginal drugs may result in fatigue, impotence, and other side-effects. The decision to accept a diminished life-style should be based on patient preference and may be valid for specific individuals. Similarly, patients should not be denied the option of early revascularization to relieve ischemia, minimize chronic medication use, and optimize physical activity. This is especially relevant for the patient with at least moderate ischemia in whom revascularization may prevent subsequent death/MI, although definitive correlation awaits conclusion of the National Heart, Lung and Blood–funded ISCHEMIA trial in 7–10 years. As recently emphasized, the practice of medicine should be patient-oriented, with patient preference based on a thorough understanding of the risks and benefits of reasonable alternative therapies (including quality of life issues) assuming priority in dictating healthcare decisions.42,46

Conclusions

Medical therapies and revascularization play complementary and synergistic roles in the management of patients with cardiovascular disease. The therapeutic approach for each individual patient must be made based on coronary anatomic suitability and in the context of the patient’s lifestyle, functional capacity, level of symptom limitation, and their ability (physically, emotionally, and financially) to be adherent with prescribed treatments. If revascularization is performed, the procedure should use the most contemporary and effective tools available, and should always be in addition to (rather than in place of) OMT to reduce plaque progression and thrombosis. In patients with objective signs or symptoms of myocardial ischemia, coronary angiography should be performed and provides incremental information to inform choice of therapeutic strategy. Coronary stenosis functional assessment (FFR) should be done at the time of diagnostic angiography to determine the functional significance of intermediate stenoses in the absence of previously documented ischemia or unstable clinical presentation, as well as to guide the performance of multivessel PCI.

In patients with chronic stable CAD, early revascularization rather than initial OMT provides more effective and durable relief of angina, improved quality of life, reduction in antianginal medications (and their side-effects), and fewer late unplanned revascularization procedures. Revascularization plus OMT (versus OMT alone) provides a greater reduction in both objective and subjective measures of ischemia.44

Based on clinical, anatomic, and functional data, the optimal revascularization choice may be clear for selected patients with stable CAD. For many others, several alternatives may be reasonable. This reality mandates an individualized approach and must consider regional expertise and performance outcome measures. Therapeutic decision-making should be made at the point of care by a heart team using all pertinent data, and absent definitive evidence of different rates in survival or MI between an initial revascularization versus OMT approach, must strongly take into account the informed patient’s preference.
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References
In their excellent review Drs. Kereiakes and Stone do not focus on mildly symptomatic patients for whom they advocate a routine invasive strategy with cath and revascularization. Instead they examine the links between ischemia and prognosis, between revascularization and ischemia reduction, and the available evidence regarding revascularization and risk of death or MI in patients with stable ischemic heart disease (SIHD). While their position is focused on the critical role of the magnitude of ischemia, they later argue that “all patients with stable CAD should undergo coronary angiography” and there is no “ischemic threshold...below which a non-invasive medical treatment strategy is preferred.” In contrast, we endorse an invasive strategy for informed patients who prefer this approach (shared decision-making) or when symptoms refractory to medical therapy reduce quality of life. We and the writing committee of the 2012 ACCF/AHA/SCAI SIHD management guidelines disagree with their position that all patients with SIHD—including mildly symptomatic patients—should undergo cath. There is no evidence that routine cath to define coronary anatomy in patients with mild symptoms is beneficial. Evidence, guidelines, and appropriate use criteria argue that until results from the ISCHEMIA Trial demonstrate which SIHD patients, if any, have fewer clinical events with an invasive strategy, patients with mild symptoms should be educated about treatment options and reach an informed decision with their physician aligned with their preferences, goals, and values.
In Mildly Symptomatic Patients, Should an Invasive Strategy with Catheterization and Revascularization Be Routinely Undertaken?: In Mildly Symptomatic Patients, an Invasive Strategy With Catheterization and Revascularization Should Be Routinely Undertaken

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