Does Ischemia Burden in Stable Coronary Artery Disease Effectively Identify Revascularization Candidates?

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Given the enormous economic and human consequences of ischemic heart disease (IHD), it is not unanticipated that IHD has been the central clinical focus of the cardiology community for many years. The primary question that generations of cardiologists have faced, and we continue to face, is how do we optimally manage these patients? Fundamentally, it is a strategy of revascularization with adjunct medical therapy superior to medical therapy alone for optimal survival in patients with IHD? Addressing this question has been an iterative process as pharmacotherapy and interventions have evolved over time. The importance of the answer, however, seems to increase as issues of healthcare costs face us today.

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Given the spectrum of IHD, an important component of this question is defining patient subgroups, in which different treatment strategies may be advantageous. In large part, physicians have defined these subgroups the way they have defined IHD, by using anatomic criteria—1 vessel, 2 vessel, multivessel, etc. Alternatively, patients with IHD can also be considered on the basis of whether their obstructive disease is flow limiting, as would be determined by direct assessment of the flow reserve of the individual lesions, or by assessment of the amount of ischemic myocardium by noninvasive myocardial perfusion imaging (MPI) using single photon emission computed tomography (SPECT) or positron emission computed tomography (PET) techniques. As we will see, the perceived therapeutic benefit of a treatment strategy can differ on the basis of how IHD is defined and which criteria are used for patient selection.

The early, original randomized clinical trials (RCT; pre-1990) comparing strategies of medical therapy versus revascularization with medical therapy were interpreted as suggesting a survival advantage for a revascularization strategy in the setting of more advanced, higher risk, IHD (left main, 3-vessel coronary artery disease [CAD]) but not in patients with more limited, relatively lower risk, IHD (1 vessel, limited 2 vessel CAD).1,2 Despite the results of these and other trials, a new era in clinical reasoning was introduced by the results of 2 major modern trials. The results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trials support the concept that the impact of aggressively applied modern medical therapy on patient survival and patient-reported outcomes is not further improved with the addition of percutaneous intervention.3-5 Generalizing these results to clinical practice would call into question much of how cardiology is practiced today, potentially reducing the use of catheterization, revascularization, and cardiovascular imaging. When considering these trials, however, it is important to keep in mind that while they addressed the same question posed by the previous trials to date—the efficacy of revascularization versus medical therapy for IHD—they also...
defined their patient cohort on the basis of the same metric as well, that is, the presence of CAD as defined by coronary anatomy. Whether identifying a study cohort for this type of trial on the basis of anatomic information, a commonly used approach, will yield an optimal therapeutic answer is unclear.

**Shifting the Paradigm From Anatomy to Physiology: Physiology-Based Identification of Revascularization Candidates**

A second line of investigation of IHD management addressed the more basic question of whether anatomy or physiology was a superior approach to defining the optimal revascularization candidate. In a trial of 325 stable patients in whom ischemia had not been documented but percutaneous intervention was planned, those patients with fractional flow reserve (FFR) >0.75 were randomized to performance versus deferral of their intervention. Patients having abnormal FFR were assigned to a reference group. Event-free survival was superior in patients whose intervention was deferred compared with the intervention and reference groups, suggesting the possibility that a physiology-based approach would be a superior means to identify percutaneous coronary intervention (PCI) candidates in certain situations.

These initial results were extended by the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial, in which patients with multivessel CAD were randomized to an angiography-guided strategy versus a FFR-guided strategy. The latter group, in whom PCI was performed only if the FFR was found to be <0.80, had superior survival compared with performance of PCI. Event-free survival was superior in patients whose intervention was deferred compared with the intervention and reference groups, suggesting the possibility that a physiology-based approach would be a superior means to identify percutaneous coronary intervention (PCI) candidates in certain situations.

Interestingly, despite this difference in survival, no difference in medication use, symptoms, freedom from angina, or perceived wellbeing were present between these groups. The authors also reported improved survival free of death or MI (not a prespecified end point), but the study was not powered to detect differences with respect to the individual components of the primary end point. The differences in the primary end point persisted at 2 years of follow-up, further confirming the superiority of a physiology-based approach for an anatomy-based approach for the selection of the revascularization candidate.

Although the FAME trial demonstrated the advantages of a physiology-based approach to the identification of revascularization candidates, whether this strategy was superior to a strategy of medical therapy alone remains unresolved. These investigators further examined the importance of the FFR-guided strategy by comparing PCI to medical therapy in stable patients with FFR-positive lesions in the FAME II trial, thus, addressing the question of “if an FFR-guided strategy identifies lesions that should be intervened on, is it superior to medical therapy alone.”

FAME II randomized stable patients scheduled for 1-, 2-, or 3-vessel drug eluting stenting to PCI and medical therapy versus medical therapy alone, using the composite of death, MI, or hospitalization for urgent revascularization as the primary end point. This trial was stopped after an interim analysis revealed a significantly reduced risk of unplanned hospitalization for urgent revascularization in the PCI arm. Although a significant difference was found between PCI and medical therapy versus medical therapy alone with respect to the primary end point (P<0.001), the rates of death and MI were low and did not differ between groups, thus, the trial results were driven by increased hospitalization and revascularization of patients initially randomized to medical therapy. Importantly, 52% of hospitalizations and revascularizations in this trial occurred in patients presenting with unstable angina, without ECG-documented ischemia or acute MI. However, the authors subsequently revealed that exclusion of these patients would still yield an 83% relative risk reduction (P<0.001) with the PCI strategy compared with medical therapy alone.

Thus, the use of a physiology-based approach, rather than a traditional anatomy-based approach, for the evaluation of patients with documented CAD permits the identification of those patients who may have improved outcomes with revascularization compared with medical therapy alone. This raises the question of whether the COURAGE and BARI 2D trials may have yielded different results if the inclusion criteria had included more rigorously mandated minimum thresholds of myocardium at risk (eg, extent and severity of ischemia) rather than the presence of findings suggestive of possible ischemia (combinations of ischemic changes on resting or stress ECG, anginal symptoms, a proximal obstructive coronary lesion). Generalizing these results, however, would necessitate initial identification of coronary anatomy and FFR in all patients. The potential of a physiology-based approach would be enhanced if the identification of flow-limiting lesions could be achieved noninvasively. The noninvasive option for physiological assessment of structural CAD is often stress SPECT MPI. FFR was first validated using SPECT as the “gold standard”. This approach has the advantage of being noninvasive and widely available, but has limitations, such as issues with identification of extensive CAD. Finally, like invasive angiographic-based procedures, SPECT and all radionuclide studies are associated with the risks inherent with exposure to ionizing radiation.

**Can Inducible Ischemia Serve as the Gatekeeper to Revascularization?**

A third line of clinical investigation has examined the question of whether the amount of inducible ischemia identified by MPI can identify, which patients may gain a relative survival benefit with revascularization versus medical therapy. Although an extensive literature exists examining the value of stress imaging for risk stratification, evidence supporting the potential of cardiovascular imaging to enhance the identification of patients with IHD who may benefit from revascularization is a recent development. This question was first posed in an observational series of 10627 patients without previous CAD who were followed-up after an index stress SPECT MPI study at Cedars-Sinai Medical Center, 671 of whom were treated with early revascularization. Risk-adjusted survival analysis, including a propensity score to adjust for nonrandomization of
Ischemia Identifies Revascularization Candidates

These results—the ability of inducible ischemia to identify, which patients may have enhanced survival with early revascularization versus medical therapy—were extended in a series of 826 asymptomatic diabetic patients without known CAD who had undergone stress SPECT MPI at the Mayo Clinic. Improved survival with revascularization during follow-up was limited to those patients with high-risk SPECT treated with coronary artery bypass graft surgery.14 Similarly, the ability of SPECT measured inducible ischemia was also found to identify optimal post-SPECT treatment in a cohort of elderly patients, again, with early revascularization having improved survival in the setting of extensive ischemia (>15% myocardium ischemia).15

These studies consist, in large part, of patients without previous CAD, a study from the Cleveland Clinic examined 765 patients with chronic, severe IHD, and LVEF≤35% who underwent stress/rest Rb-82/F18-FDG viability PET. In this study, patients had improved survival with revascularization compared with medical therapy alone irrespective of the amount of jeopardized myocardium present (ischemic plus hibernating myocardium).16 These results are discordant to those of the previously mentioned studies, and suggest that the relationship between MPI-assessed jeopardized myocardium, post-MPI treatment, and downstream risk is modified by the presence of known CAD. Indeed, subsequent studies confirmed the amount of fixed defect, remodeling, and LV dysfunction to be a confounding factor in this relationship.

A subsequent study from these investigators examined this relationship in a large cohort of 13969 patients both with and without previous CAD who were followed-up for an average of 8.7 years. This study reported that inducible ischemia identified, which patients had improved survival with versus without early revascularization both among patients without previous CAD (n=8791), as well as in patients with previous CAD limited to revascularization (but without previous MI; n=1352), but this was not the case in patients with previous MI (Figure 2).17 However, when their analysis was limited to those patients with %myocardium fixed <10% (patients with little or no scar), the above described relationship between post-SPECT treatment and ischemia was present. Thus, the ability of MPI to identify revascularization candidates is not impacted as much by patient history of CAD as it is by the presence of significant myocardial scar. The left ventricular volumes probably play a role in this relationship, but it has yet to be defined (Figure 3).

A study from the Surgical Treatment for Ischemic Heart Failure (STICH) trial by Panza et al18 reported outcomes in a cohort of 399 patients with ejection fraction ≤35% (mean, 26±8%), 256 of whom underwent either a stress SPECT MPI or dobutamine stress echocardiogram study that was found to have ischemia. In this nonrandomized cohort from this RCT, there was no impact of ischemia on outcomes in either adjusted or unadjusted analyses. Similarly, there was no interaction found between ischemia and treatment on outcome. These results are consistent with those above by Hachamovitch et al17 and Tarakji et al16 in that ischemia or jeopardized myocardium did not identify a survival benefit in patients with extensive scar or LV dysfunction.

Hence, a series of observational studies suggest that the results of FAME—the superiority of a physiology-based strategy to identify revascularization candidates—may extend to the use of physiology assessment using noninvasive MPI. These results also suggest that in certain patients, assessment of scar and remodeling along with inducible ischemia may be necessary to identify optimal patient post-test management. It is important to note that the SPECT MPI studies reviewed above are entirely observational and based on single-site registries and databases.
Limitations of Observational Studies

Observational studies, such as those presented above, are fraught with limitations. The single-site design leads to issues of generalizability, and the limitations associated with multivariable techniques (including propensity scores) applied to observational data to adjust for potential confounding have been characterized. Even with these risk adjustments, the impact of selection biases, spurious observations, and unmeasured covariates cannot be ignored. Although, however, these studies are designed as effective studies in that the treatment received by patients was dictated by the clinical practice of their physicians, the underuse of medical therapy after MPI and other noninvasive testing has been well documented. The current use of postimaging therapeutics—catheterization referral and medical therapy—is far less than expected, and 30% to 45% of patients are not on guideline-indicated medications after significant MPI abnormalities are reported.

Thus, whether the observational studies presented above are representative of revascularization versus medical therapy or revascularization versus no revascularization—and the use of aggressive medical therapy would have yielded different results—is uncertain.

RCT Substudies

Although these observational studies suggest the possibility that MPI-identified inducible ischemia may identify, which patients have improved outcomes when treated with revascularization versus medical therapy, to date, no RCTs data exists supporting this hypothesis. The RCT data available thus far is limited to the results of substudies from two trials, COURAGE and BARI 2D.

The primary aim of the nuclear cardiology substudy of the COURAGE trial was to compare changes in ischemic burden after randomization to PCI plus optimal medical therapy (OMT) compared with OMT alone and to explore associations with patient outcome. The nuclear substudy revealed that the addition of PCI resulted in greater reduction in ischemia...
testing was not mandated in the main study protocol, and, as such, treatment comparisons may be the result of selection bias.

There are also other issues to consider about the study design. In order for the trial participants to have their ischemic burden tracked over time, they had to survive to the time of their follow-up study. We often do not have information about who in this substudy was lost to follow-up or did not return for a follow-up myocardial perfusion scintigraphy study—and whether the time to the follow-up myocardial perfusion scintigraphy was similar in both the intervention groups.

**Implications for Cardiovascular Imaging**
Outcome- or risk-based approaches are currently the accepted metric for patient assessment and management, as well as the evaluation of imaging modalities. In current guidelines, recommended actions at individual decision nodes within clinical algorithms are based on patient risk levels, as are recommendations for treatment strategies. At the core of this approach is the belief that if we can identify the vulnerable patient (based on risk parameters), we can address that risk via changes in patient management. Two important considerations emerge from re-examining this paradigm.

First, with this risk-based approach, there is no assurance that all patient risk can be reduced by our current interventions. Indeed, those patients identified by MPI as being at the greatest risk (eg, LV dysfunction, enlarged LV, and extensive scar) seem least likely to benefit from revascularization. Second, the historical development of MPI prognostic data focused on risk stratification, thus, the focus was on total defect size and LVEF rather than ischemia extent and severity. Despite our focus on risk stratification and estimation of patient risk, those metrics most predictive of patient risk (LVEF, LV volumes, and scar extent) neither predict post-test referral to catheterization or revascularization nor identify, which patients are most likely to benefit from a revascularization strategy. Conversely, both of these end points are best predicted by inducible ischemia. Thus, rather than a risk-based approach, we in effect practice a benefit- or value-based approach to patient care in that we use our testing to identify, which patients are most likely to benefit (rather than those at greatest risk) and preferentially intervene on those patients.

It is recognized that the use of imaging does not change patient outcomes, but that imaging results alter physicians’ management of patients, which, in turn, may alter patient outcomes. Hence, the value of imaging is in its ability to augment and enhance a patient treatment strategy. It follows that discussions of the role of cardiovascular imaging in patient management should refer to identifying, which therapeutic approach may yield a potential benefit or which patient is an optimal treatment candidate, rather than the results of risk stratification or estimation of patient risk. Also, within this context, evidence of incremental value, rather than being a statistical exercise in quantifying prognostication, would be the determination of whether the results of testing can identify, which therapeutic approach will result in maximal benefit for a particular patient given a specific test result.

Of note, although the focus of these studies has been on the identification of the optimal revascularization candidate, the

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**Figure 3.** Potential algorithm for selection of patients for revascularization after myocardial perfusion imaging (MPI). Of patients with abnormal MPI results (top), those with >10% myocardium ischemia (left) are candidates for early revascularization. However, left ventricular end-systolic volume index (LVESVI) may need to be assessed in some patients to determine whether it is excessive. Patients with not only 10% ischemia but also >10% myocardium fixed/scar (center) are probably not candidates for early revascularization, unless the amount of remodeling present is within limits (as defined by LVESVI). Finally, patients with <10% myocardium ischemia or >10% fixed defect (right) are probably best suited for medical therapy without initial revascularization. CAGB indicates coronary artery bypass graft surgery.

By comparing with the use of medical therapy alone. The rates of cardiac death and MI were not lower in patients with significant ischemia reduction compared with those without ischemia reduction (irrespective of how the ischemia reduction was achieved) after adjustment for underlying differences.

A second study from the COURAGE nuclear substudy examined 1381 randomized patients (OMT alone n=699 and PCI plus OMT n=682) who underwent a baseline stress MPI that was interpreted by site investigators. This interpretation was limited to a 6-segment scoring model considering only defect extent, not severity. Comparing patients with ≥3 segments demonstrating ischemia to those with <3 segments, the authors found no difference with respect to the rates of death and MI. Interestingly, in this study risk did not increase with worsening ischemia, suggesting a failure of this metric to risk stratify patients.

In the BARI 2D nuclear substudy, in which nuclear studies were repeated at 1 year after enrollment in 1505 patients, both total defect size and %myocardium ischemia were reduced in patients treated with revascularization compared with those randomized to medical therapy alone. Furthermore, 59% of revascularization-treated patients had no inducible ischemia at 1-year compared with 49% of medical therapy patients (P<0.001). Interestingly, at 1-year, more extensive and severe stress MPI abnormalities were associated with greater 5-year rates of death and combined cardiac death/MI rates. However, as in the COURAGE substudy, event reduction with a revascularization strategy compared with a strategy of medical therapy alone was not ascertained.

**Limitations of These RCT Substudies**
The most important limitation of these substudies is their limited statistical power. Although patients in the main trial were randomized, results from these substudies are nonrandom comparisons by treatment. Substudy patients may have differed from their counterparts in the main trial who did not undergo additional noninvasive testing. Myocardial perfusion scintigraphy ischemia compared with respect to the rates of death and MI. Interestingly, in this substudy was lost to follow-up or did not return for a follow-up myocardial perfusion scintigraphy study—and whether the time to the follow-up myocardial perfusion scintigraphy was similar in both the intervention groups.

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majority of patients in these studies would have greater benefit from an initial approach of medical therapy. Aggressive risk factor modification in these patients, many of whom may well be in a relatively early phase of atherosclerotic disease, is an important consideration. Finally, it must be kept in mind that ischemia assessment is an approach for patients with advanced IHD, many patients referred to MPI may have been better served by an initial test of atherosclerosis.

Implications for the Design of RCTs Examining the Role of Cardiovascular Imaging

The data supporting a role for MPI-identified inducible ischemia in the identification of the revascularization candidate is based on observational data; RCTs thus far have not supported this concept and future RCT validation of this hypothesis will be necessary. To this end, consideration must be given to the methodological implications of examining this question. The value of cardiovascular imaging can be assessed by various RCT designs. The test result can be an inclusion criterion (eg, a minimum threshold of inducible ischemia present). The limitations of this approach would include the need to successfully identify an ischemia threshold at which therapeutic superiority of 1 arm can be detected, as well as the restriction of the therapeutic question to those patients above this threshold (but not the relative value of treatments below the threshold). It has yet to be shown whether this threshold exists for all modalities. Furthermore, it seems that this threshold varies between modalities.

A recent multicenter study followed 15,207 intermediate-risk patients without known CAD who underwent coronary computed tomography angiography invasive angiography during 2.3±1.2 years.27 Patients were followed for subsequent revascularization and all-cause mortality. Invasive angiography rates for patients with coronary computed tomography angiography-defined no CAD and mild CAD were low (2.5% and 8.3%), and these patients had similarly low rates of revascularization (0.3% and 2.5%). An exploratory analysis was included in this article, which compared invasive coronary angiography (ICA) to no ICA and revascularization to no revascularization in patients with mild CAD and with obstructive CAD. In patients with mild CAD (n=5380) the use of ICA was associated with worsened survival compared with no ICA (hazard ratio: 2.25 [1.16-4.39]), whereas in patients with obstructive CAD (n=2799) the use of ICA was associated with improved survival (hazard ratio: 0.61 [0.38-0.99]). The use of revascularization did not improve outcomes in either patient group. Importantly, as in the previously mentioned imaging studies, patients with obstructive CAD were not randomized. In this study, unlike the previous studies, the analysis of survival as a function of treatment and imaging result was not a primary analysis and did not include a propensity score.

Taqueti et al28 in a preliminary report on 2223 patients without previous coronary artery bypass graft surgery, LVEF >40%, and <10% scar undergoing stress PET at Brigham and Women’s Hospital, found that equipoise between revascularization and medical therapy occurred at 8% myocardium ischemia (compared with 10% to 15% with SPECT MPI in other studies). This difference is probably because of the enhanced resolution of PET and also serves as warning against assuming a standard level of equipoise across all modalities.

Alternatively, patients can be randomized to alternative strategies with versus without the use of an imaging modality (noninvasive test versus conventional care or no imaging) or strategies with 1 test versus another (noninvasive test of imaging versus one of anatomy; randomization to the use of MPI versus PET). An important consideration in this design is the need to couple the test result with post-test physician decision-making. The PET and Recovery Following Revascularization (PARR) trial,29 a prospective RCT comparing clinical outcomes after patient management strategies with versus without FDG PET in patients with severe LV dysfunction, serves as an example of the potential adverse consequences of this study design. The results of this trial were negative—outcomes were not different whether patients were randomized to receive viability imaging.30 However, many physicians did not act on the results of the F18-FDG PET that was performed, and others ordered an F18-FDG PET, despite their patients’ randomization to the standard care arm. A sub-study reanalysis of the results revealed that a significant interaction between PET mismatch and protocol revascularization was present such that the use of revascularization in the setting of greater amounts of mismatch was associated with fewer primary outcome events.30 Hence, an RCT randomizing patients to alternative imaging modalities, or a modality versus standard care, must either dictate post-test patient management or account for variability in treatment within its analyses. Without this condition, it would not be possible to distinguish whether a trial result is because of the ability of a modality to aid in patient care or to differences in physician action. Thus, because imaging does not directly impact outcomes, the design of trials to assess the value of imaging must address issues and challenges that therapeutic trials do not.

The ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial is designed to test the hypothesis that patients with moderate amounts of inducible ischemia as determined by stress testing will have superior outcomes (cardiovascular death or nonfatal MI) with a strategy of initial catheterization and optimal revascularization compared with OMT alone (Figure 4). The trial has a target enrollment of ≈8000 patients with a 4-year mean follow-up scheduled. Patients can meet enrollment criteria by either moderate amounts of ischemia by stress imaging (>10% of the myocardium) or by prespecified nonimaging exercise testing criteria. This trial excludes patients with reduced left ventricular function (<35% ejection fraction), patients with unprotected left main disease, CAD that cannot be revascularized, or the presence of nonobstructive CAD (by blinded coronary computed tomography angiography). When completed, this trial will hopefully address the questions left unanswered by the COURAGE and BARI 2D trials.

Conclusions

With respect to patients with known or suspected IHD, RCT evidence to date suggests that physiology-based approaches (eg, FFR), but not anatomy-based approaches, can identify
which patients have improved outcomes with revascularization and medical therapy versus medical therapy alone. To date, a series of observational studies extending this physiological concept to the use of MPI-identified ischemic myocardium suggest that ischemic burden in stable IHD effectively identifies revascularization candidates. If further, directly validated by RCT, this finding suggests that a value- or benefit-based paradigm may enhance the application of cardiovascular imaging.

Disclosures

None.

References


Response to Hachamovitch

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Dr Hachamovitch rightly acknowledges the limitations of the observational data, which suggest that a larger ischemia burden may be associated with reduced risk of events with a strategy of revascularization. It is critical when reviewing the observational studies to consider that physician selection for revascularization versus medical therapy in these cohorts was not random and incorporated clinical judgment specific to each case. Propensity score adjustment does not completely remove the effect of confounders. We differ from Dr Hachamovitch on the value of fractional flow reserve for selection of patients who may benefit from revascularization as opposed to medical therapy. The value of fractional flow reserve for guidance of PCI in patients already selected for PCI is clear but there was no benefit of fractional flow reserve–guided PCI for medical therapy on death and myocardial infarction in the FAME-2 trial.

Observational data and logical reasoning have led the cardiology community to conclusions, which have not stood the test of randomized trial evidence on previous occasions, such as hormone therapy for postmenopausal women and antiarrhythmic drugs for ventricular ectopy after myocardial infarction.

The idea that revascularization should reduce events in patients with moderate–severe ischemia seems logical; however, if ischemia will also be considered logical and in alignment with existing evidence. As Dr Hachamovitch notes, characteristics which place patients at higher risk, such as ejection fraction, do not necessarily predict which patients may benefit from revascularization. We eagerly await the completion and reporting of the ISCHEMIA trial.
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