Benefit of Revascularization in Patients With Stable Ischemic Heart Disease Is Controversial; A Better Method for Patient Selection Is Needed

Over 30 years ago, a benefit of surgical revascularization was demonstrated in patients with stable ischemic heart disease (SIHD) but this was before most of our current disease-modifying medical therapies for coronary artery disease (CAD) were available. Analysis of these trials indicated that patients who derived the most benefit from surgery were those with more extensive CAD, particularly those with significant left main CAD or multivessel CAD, including proximal left anterior descending stenosis. After the introduction of percutaneous coronary intervention (PCI), studies were performed in the 1990s comparing PCI with contemporary medical therapy and found no benefit on death, myocardial infarction, or revascularization. It was at the time unclear whether this was because of the different revascularization technique or advances in medical therapy.

See Response by Hachamovitch

Subsequently, 2 large, randomized, multicenter trials were undertaken to determine whether revascularization offered an advantage over intensive medical therapy (optimal medical therapy). The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trials randomized patients with SIHD to a strategy of routine revascularization in addition to optimal medical therapy or to a strategy of optimal medical therapy alone. The optimal medical therapy approach included statin-based lipid-lowering therapy with a target low-density lipoprotein 60 to 85 mg/dL, anti-ischemic medications alone or in combination, and angiotensin-converting enzyme inhibition or angiotensin receptor blockade. The COURAGE trial included 2287 patients and used PCI as the revascularization technique. There was no benefit on the primary end point of death or myocardial infarction (MI) for the routine PCI strategy over a median 4.6 years of follow-up and there was also no difference between groups in survival. The BARI-2D trial included 2368 patients with diabetes mellitus and both PCI and surgery were used for revascularization. Randomization was stratified based on declared physician preference for PCI or coronary artery bypass graft surgery (CABG) after review of the coronary anatomy. Again, there were no benefits of the routine revascularization strategy for either the PCI stratum or the CABG stratum on survival over an average
Ischemia burden has repeatedly been identified as a powerful prognostic factor among patients referred for stress testing using nuclear imaging, echocardiography, and more recently, cardiac MRI (CMR). This is notable that both COURAGE and BARI-2D entry criteria were limited as exercise electrocardiographic changes, a limited and more recently required evidence that both COURAGE and BARI-2D were not performed.

Ischemia burden has repeatedly been identified as a powerful prognostic factor among patients referred for stress testing using nuclear imaging, echocardiography, and more recently, cardiac MRI (CMR). This is notable that both COURAGE and BARI-2D entry criteria were limited as exercise electrocardiographic changes, a limited and more recently required evidence that both COURAGE and BARI-2D were not performed.

Table 1. Summary of Large Randomized Trials Investigating the Role of Revascularization in Patients With Stable Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Year of Publication</th>
<th>Study</th>
<th>n</th>
<th>Ischemia-Based Entry Criteria</th>
<th>Revascularization Strategy</th>
<th>Medical Therapy</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Ischemia Testing in Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>Meta-analysis of randomized trials, CASS Trialists Collaboration</td>
<td>2649</td>
<td>Angina (not required for all trials in meta-analysis)</td>
<td>CABG</td>
<td>Aspirin, nitrates (not for all trials)</td>
<td>All-cause mortality, lower in CABG group at 1 to 5 years</td>
<td>Angina relief better in CABG arms (CASS) through 5 years</td>
<td>Not performed</td>
</tr>
<tr>
<td>2007</td>
<td>COURAGE randomized trial</td>
<td>2287</td>
<td>Site-determined abnormal stress test+70% stenosis or angina+80% stenosis</td>
<td>PCI</td>
<td>Aspirin, statin with target LDL&lt;70, ACE inhibitor or ARB, antianginals</td>
<td>All-cause mortality or nonfatal MI, no difference between treatment groups at 3-6 years</td>
<td>Angina relief modestly better in PCI arm through year 3</td>
<td>PCI reduced ischemia better than medical therapy but no interaction between baseline ischemia severity and treatment effect</td>
</tr>
<tr>
<td>2009</td>
<td>BARI-2D randomized trial</td>
<td>2368</td>
<td>Site-determined abnormal stress test or angina+70% stenosis</td>
<td>CABG or PCI</td>
<td>Aspirin, statin with target LDL&lt;100, antihypertensives for BP target&lt;130/80; diabetes management also tested in this trial</td>
<td>All-cause mortality, no difference between revascularization and medical therapy arms, no difference between CABG and medical therapy or PCI and medical therapy (stratified randomization) at 5.3 years</td>
<td>Composite of death, MI, stroke lower with revascularization in CABG stratum (n=763)</td>
<td>Revascularization reduced ischemia better than medical therapy</td>
</tr>
<tr>
<td>2014</td>
<td>FAME-2 randomized trial</td>
<td>888</td>
<td>FFR&lt;0.8 in at least one vessel</td>
<td>FFR-guided PCI</td>
<td>Aspirin, statin with target LDL&lt;70, β-blocker, ACE inhibitor or ARB</td>
<td>All-cause mortality, nonfatal MI or urgent revascularization, lower in FFR-guided PCI group at 2 years</td>
<td>No difference between treatment groups in death or MI</td>
<td>Not performed</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CASS, Coronary Artery Surgery Study; CABG, coronary artery bypass graft surgery; FAME-2, Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease; FFR, fractional flow reserve; LDL, low-density lipoprotein; MI, myocardial infarction; and PCI, percutaneous coronary intervention.
perfusion defect or a stenosis of ≥70% to 80% plus classic angina. Among the 60% of patients enrolled in COURAGE after nuclear stress imaging, most had less than moderate ischemia. It has been suggested that this could have contributed to the neutral overall results of the trial.

Observational data from the Cedars-Sinai nuclear registry published by the author of the pro viewpoint in this debate suggest that selection for revascularization based on ischemia burden may be a reasonable approach. In this study including >10000 patients referred for stress perfusion imaging at a single center, there were nearly 150 cardiac deaths and nearly 500 acute coronary syndrome events over an average 2-year follow-up. The authors plotted the hazard ratio for cardiac death against the percentage total ischemic myocardium separately for patients who were selected for revascularization within 60 days of stress testing and patients who were treated with medical therapy alone. The curves cross such that below 10% ischemic myocardium, patients who were treated with medical therapy alone had better outcomes than those selected for revascularization, whereas the opposite relationship was observed for patients with >10% of the myocardium ischemic. The threshold of 10% ischemic myocardium is commonly used to denote moderate ischemia on nuclear imaging. However, the confidence intervals on these estimates are wide and confidence bounds overlap over the entire range of percent ischemic myocardium. Although these data lend themselves easily to translation into clinical practice, there is ample reason for caution. This was a single-center study conducted at a highly skilled nuclear imaging center. Although the authors included a propensity score for revascularization in their multivariate modeling, the fact that only 10% of the cohort overall and just 39% of the patients with >10% myocardium ischemic were selected by physicians for revascularization indicates that the decision to revascularize is, and likely should be, made based on more than the ischemic burden alone. Data from the multicenter SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease) registry showing that only 48% of patients with moderate–severe ischemia were referred for cardiac catheterization similarly suggest that multiple factors are taken into account when considering revascularization. Finally, medical treatment of the patients was not specified by a protocol and based on the years when the study was conducted, was unlikely to have included routine use of medical therapy now considered optimal, such as high intensity statins.

The study mentioned above is characteristically cited in articles referring to the potential benefit of revascularization based on ischemia severity. An observational study of ischemia severity by stress echo also found that selection for revascularization was associated with better outcome among those patients with the most severe ischemia. However, the degree of ischemia at which selection for revascularization was associated with improved outcomes was severe, with an average wall motion score index indicating >8 segments ischemic. Therefore, this study, while also large (including >3000 patients), has the same limitation of potential for bias in selection for revascularization as in the study by Hachamovitch et al. Another study comparing different stress echo techniques found no relationship between treatment with revascularization or ischemia severity and risk of death or MI but did not assess risk by the degree of ischemia and selection for revascularization. There is no similar analysis to our knowledge using stress CMR, although it is possible to identify stress echo and stress CMR criteria which result in approximately the same risk level as that associated with 10% left ventricular ischemia on single photon emission computed tomography.

Revascularization Appears to Reduce Ischemia but No Randomized Data Show a Favorable Impact on Hard Outcomes

The effects of medical therapy and revascularization on ischemic burden were evaluated in ancillary studies to COURAGE and BARI-2D. Among patients enrolled in the COURAGE ancillary study who underwent stress imaging both at baseline and again after 6 to 18 months, assignment to the routine PCI strategy was associated with a greater likelihood of reduction in the amount of ischemia by 5% of the myocardium. Approximately one third of participants in the ancillary study had moderate–severe ischemia at baseline based on core laboratory interpretation, among whom the routine PCI strategy also resulted in a greater likelihood of reduction in ischemia (78% versus 52%, P=0.007). Similarly, patients assigned to medical therapy alone in BARI-2D were more likely to have moderate–severe ischemia on a 1-year nuclear scan compared with either revascularization stratum.

If PCI reduces adverse outcomes in patients with SIHD and moderate–severe ischemia, many would presume it does so via reduction in the amount of myocardial ischemia. In the BARI-2D nuclear ancillary study, severity of residual ischemia was not an independent predictor of outcome after adjustment for an array of clinical variables. The amount of scarred myocardium did remain a predictor of outcome after adjustment. Change in ischemia burden from baseline was not available. However, evaluation of outcomes by treatment assignment within the COURAGE nuclear ancillary study failed to show a benefit for PCI among those with moderate–severe ischemia at baseline in an analysis including all patients with baseline scans, regardless of whether they returned for a second test 6 to 18 months later (Figure 1). Furthermore, the degree of ischemia in that cohort was not associated with risk of events. It must be recognized that power was severely limited in this analysis, which was not prespecified and may have been affected by selection bias. However, consistent with this analysis, a recent study including patients with ischemia late after revascularization by the author of the pro viewpoint demonstrated similar outcomes for those selected to undergo repeat revascularization or medical therapy alone. In addition, there was no interaction between ischemia at baseline and treatment assignment on outcome, as well as no independent relationship between baseline ischemia and outcome, in
the randomized Surgical Treatment for Ischemic Heart Failure (STICH) trial. Furthermore, a recent meta-analysis of randomized trials of PCI with medical therapy versus medical therapy in patients with ischemia based on stress testing or fractional flow reserve (FFR) found no benefit with PCI on mortality and a trend toward higher rates of nonfatal MI in those assigned to PCI.37

Finally, it has been suggested that the improved outcomes observed with the use of FFR-directed PCI when compared with anatomic guidance of PCI in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) and Deferral of Percutaneous Coronary Intervention (DEFER) randomized trials38,39 indicate that ischemia as defined by low FFR identifies candidates for revascularization. Neither of these studies included a control group treated with medical therapy alone. We agree that FFR is an important consideration when evaluating which lesions should be intervened on when a patient is judged to need revascularization on clinical grounds, for example, symptoms. However, just as is the case for stress test abnormalities, patients should not be selected for revascularization solely on the basis of abnormal FFR. The results of the multicenter Fractional Flow Reserve–guided PCI Versus Medical Therapy in Stable Coronary Disease (FAME 2) study support this notion.7

Patients referred for PCI and found to have at least 1 vessel with abnormal FFR were randomized in FAME 2 to FFR-guided PCI or medical therapy alone. Although the FFR-guided PCI arm was favored on comparison of the primary end point of death, MI, and target vessel revascularization, this finding was driven by urgent target vessel revascularization. There was no difference in the rate of death or MI between the randomized treatment arm or between either arm and a registry of patients who had been referred for PCI but had normal FFR.7 The indication for PCI in follow-up was unstable angina without ECG changes in over half of patients who crossed over to PCI in this study and this rate of PCI must be considered in the context of physician and patient awareness of anatomic details and FFR results in an unblinded study. Thus, the value of ischemia burden by FFR when compared with medical therapy alone may be limited to reducing unplanned revascularization. If the primary end points of COURAGE and BARI 2D had included revascularization, they too would have reported benefit for the prompt revascularization strategy.

In summary, although revascularization seems to reduce ischemic burden, randomized trial data have not demonstrated that this translates into improvement of hard outcomes.

### How Can We Reconcile the Prognostic Impact of Ischemia Burden and a Greater Reduction in Ischemia Burden After Revascularization With the Overall Neutral Results of COURAGE and BARI-2D?

It is to a certain extent counterintuitive that randomized trials of a routine revascularization strategy for SIHD have not demonstrated reductions in death or MI, despite interventions that relieve or bypass stenosis and relieve ischemia.

Excess risk associated with a greater burden of ischemia could be because of adverse effects of ischemia itself, perhaps in combination with an increased risk of arrhythmia, but could be because of other factors. It is possible that increased risk associated with a greater burden of ischemia is ultimately because of a greater burden of atherosclerosis in patients with more ischemia. A subset analysis of COURAGE found that extent of disease was a predictor of outcome in COURAGE, whereas ischemia severity was not.40 Atherosclerosis is a diffuse disease and medical therapy, particularly statin therapy, stabilizes plaques. Statins were not used in earlier randomized trials of CABG. The plaque stabilizing effects of medical therapy may be the primary factor underlying differences between these older trials and the more recent trial results, particularly considering that in both COURAGE and BARI-2D, there was no anatomic subset identified with a benefit from routine PCI.41 In the Prospective Natural-history Study of Coronary Atherosclerosis (PROSPECT) study, severely stenotic lesions comprised only 5% of those lesions destined to cause acute coronary syndrome, whereas approximately two thirds of future culprit lesions were of mild degree at baseline.42 Several previous angiographic studies also showed that the majority of culprit lesions for MI were mild plaques before the event.43-47

![Figure 1. Rates of death or myocardial infarction (MI) among patients with core laboratory interpretation of baseline stress nuclear imaging in COURAGE, by ischemia severity. Note that patients who did not return for follow-up imaging were included in this analysis. OMT indicates optimal medical therapy; and PCI, percutaneous coronary intervention. Reprinted with permission from Shaw et al.28 Copyright © 2012, Elsevier.](http://circimaging.ahajournals.org/doi/fig/10.1161/CIRCIMAGING.117.009532)
For this reason, it may be hypothesized that CABG would offer greater protection against MI and cardiac death when compared with PCI, because a bypass graft could potentially protect the patient from the ischemia caused by rupture of a vulnerable plaques located proximal to a patent graft touch-down site. In contrast, PCI is not directed at mild plaques and treats a smaller segment of the vessel. Thus, in addition to myocardial ischemia burden, factors such as extent and distribution of vulnerable plaque, the progressive nature of the atherosclerotic disease process, extent of myocardial scar, ventricular function, and improvements in medical therapy play a role in determining outcome. In addition, as mentioned earlier, most patients enrolled in these trials did not have moderate–severe ischemia.

The relatively high proportion of participants in the COURAGE and BARI-2D ancillary studies with residual moderate–severe ischemia after revascularization could be taken to indicate that the revascularization approach may not have been complete, that is, not all ischemia-producing arterial segments may have been adequately treated. Some would suggest this could have contributed to neutral results. However, it must be noted that not all CAD is amenable to revascularization, particularly diffuse disease, chronic total occlusions, and distal disease, all of which may cause extensive ischemia. In addition, restenosis, stent thrombosis, and graft occlusion contribute to residual ischemia during follow-up.

**Variability in Ischemia Interpretation**

The determination of ischemia severity by individual site stress imaging laboratories may not correspond perfectly to core laboratory interpretation. In the clinical trial setting, enrolling sites typically overestimate the ischemia severity when compared with a core laboratory. This may relate to core laboratory review of images in the absence of information about symptoms and for exercise tests, exercise duration, and ECG results. Thus, a test showing mild ischemia by perfusion criteria in isolation may be interpreted as high risk after synthesis of imaging results with additional risk parameters. This may explain the relatively low prevalence of moderate–severe ischemia in trials such as COURAGE and BARI-2D.

**Trials Addressing This and Related Questions**

**PROMISE and RESCUE Trials**

The PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial randomized 10003 participants with recent onset symptoms to a strategy of initial stress testing or coronary computed tomography (CT) angiography. Downstream management was not specified by protocol in this National Heart, Lung, and Blood Institute (NHLBI)-funded, multi-center trial. There was no difference between randomized groups in the primary end point of death, MI, unstable angina, or major complications from cardiovascular procedures or testing. However, the included patients were at low risk of events, ~3% over 2 years. Revascularization was more common in the CT-assigned group, 6.2% versus 3.2%; severity of ischemia in the stress testing group has not yet been reported.

The Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Diagnostic Examination (RESCUE) trial will randomize ~4300 participants to an initial diagnostic strategy of coronary CT angiography or stress nuclear imaging. (ClinicalTrials.gov NCT01262625) Unlike PROMISE, the RESCUE protocol specifies criteria for invasive coronary angiography in the single photon emission computed tomography imaging arm. The primary end point is major adverse cardiac events.

PROMISE and RESCUE are novel and important for clinicians in that clinical outcomes are assessed according to a randomized imaging strategy. The 2 studies will provide complementary information because they use different types of stress testing, and use of invasive angiography and revascularization varies from clinician directed to protocol-directed.

**ISCHEMIA Trial**

In recognition of the lack of conclusive evidence supporting ischemia-guided revascularization, current ACCF/AHA/SCAI PCI guidelines indicate that

> [t]he PCI and CABG guideline writing committees endorse the performance of the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, which will provide contemporary data on the optimal management strategy (medical therapy or revascularization with CABG or PCI) of patients with SIHD, including multivessel CAD, and moderate to severe ischemia.49

Patients are selected for this randomized, international trial primarily based on the presence of moderate–severe ischemia on stress testing at baseline, whether based on stress nuclear imaging, stress echocardiography stress CMR, or exercise tolerance testing alone (Table 2; ClinicalTrials.gov NCT01471522). Ischemia testing methods other than nuclear imaging were included to improve generalizability of trial results. Moderate ischemia criteria for the echo and CMR stress modalities were based on published studies that identified findings that were associated with an ~5% per year mortality, in alignment with the nuclear criterion. Ischemia tests are interpreted by central core laboratories. Participants are randomized to an invasive or conservative strategy. Both treatment groups receive intensive, goal-directed medical therapy, as well as lifestyle counseling. The invasive strategy includes routine cardiac catheterization followed by revascularization, the mode of which (percutaneous or surgical) is selected according to ability to achieve relief of ischemia in all territories and suitability of the anatomy. The conservative strategy targets medical management alone, with cardiac catheterization reserved for participants with acute ischemic events or symptoms refractory to medical therapy.
Ischemia Does Not Identify Revascularization Candidates

A unique component of this trial is the randomization, which occurs before cardiac catheterization, unlike all prior trials of revascularization. Many think that once the patient is referred to angiography, the decision to undergo PCI or CABG is a foregone conclusion and that knowledge of coronary anatomy in COURAGE, BARI-2D, and FAME 2 biased enrollment and therefore results. In ISCHEMIA, blinded coronary CT angiography is performed before randomization to exclude patients with significant left main disease and those patients without obstructive CAD (Figure 2). There is not currently equipoise in the community about revascularization of patients with significant left main disease and patients without obstructive CAD would not be expected to benefit from a revascularization strategy. Patients with chronic kidney disease (estimated glomerular filtration rate <60 mL/min) are permitted to participate without a coronary CT angiogram if the treating physician does not suspect left main disease. Patients on dialysis and with advanced chronic kidney disease are eligible. Those with an unacceptable degree of angina after treatment with medical therapy will be excluded from participation, as will patients with EF<35%.

The aim of the trial is to determine whether the invasive strategy will be superior to the conservative strategy for the end point of cardiovascular death or MI over an average follow-up of 4 years in this subset of SIHD patients with moderate–severe inducible ischemia. The study is powered for narrow confidence intervals, as well as hypothesis testing, reflecting equipoise. The primary end point includes cardiovascular death rather than all-cause mortality because it is thought that the invasive strategy may not influence noncardiac death. However, the definition of cardiovascular mortality is broad. The study definition of MI was designed to avoid counting of lower levels of periprocedural troponin elevations which do not have prognostic significance. The universal definition of MI will also be assessed.

Enrollment of approximately 8000 patients will take place at a projected 400 sites globally. The trial has been designed in an effort to build on the prior SIHD trials. First, higher risk patients will be enrolled. Second, randomization will occur after coronary computed tomography angiography, rather than catheterization, in the large majority of participants so the coronary anatomy will not be known prior to randomization in either group and will remain blinded in the conservative group. Finally, revascularization will incorporate the modality judged to be most likely to relieve all ischemia, including hybrid procedures if needed.

It is hoped that this trial will determine whether ischemia burden effectively identifies patients who will have a lower risk of death or MI if subjected to a routine strategy of revascularization. At present, the answer is unknown.

### Table 2. Ischemia-Based Entry Criteria for the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) Trial

<table>
<thead>
<tr>
<th>Test Modality</th>
<th>Diagnostic Criterion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear perfusion via SPECT or PET</td>
<td>≥10% myocardium ischemic</td>
</tr>
<tr>
<td>Echo</td>
<td>≥3/16 segments with stress-induced severe hypokinesis or akinesis</td>
</tr>
<tr>
<td>CMR</td>
<td>Perfusion: ≥12% myocardium ischemic or wall motion: ≥3/16 segments with stress-induced severe hypokinesis or akinesis</td>
</tr>
<tr>
<td>Exercise test without imaging (Criteria 1–4 must all be met)</td>
<td>Clinical history of typical angina or typical angina during the exercise test</td>
</tr>
<tr>
<td></td>
<td>Absence of resting ST segment depression ≥1.0 mm or confounders that render exercise ECG noninterpretable (LBBB, LVH with repolarization, pacemaker, etc)</td>
</tr>
<tr>
<td></td>
<td>As compared with the baseline tracing, exercise-induced horizontal or downsloping ST segment depression ≥1.5 mm in 2 leads or ≥2.0 mm in any lead; ST segment elevation ≥1 mm in a noninfarct territory. Both the J-point and the ST segment at 80 ms need to meet criteria. When the HR is &gt;130 per min, the ST segment at 60 ms may be used if the segment at 80 ms cannot be determined Either of the following: (1) Workload at which ST segment criteria are met is not to exceed completion of stage 2 of a standard Bruce protocol or 7 METS if a non-Bruce protocol is used or (2) ST segment criteria are met at &lt;75% of the maximum predicted HR</td>
</tr>
</tbody>
</table>

**CMR** indicates cardiac magnetic resonance; **Echo**, echocardiography; **HR**, heart rate; **LBBB**, left bundle branch block; **LVH**, left ventricular hypertrophy; **METS**, metabolic equivalents; **PET**, positron emission tomography; and **SPECT**, single photon emission computed tomography.

*Additional criteria must be met for confirmation of obstructive coronary artery disease, depending on estimated glomerular filtration rate and type of ischemia test.

---

Figure 2. Schematic flowchart of International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial design. (1) Coronary computed tomographic angiography (CCTA) will be performed in most patients with estimated glomerular filtration rate >60 mL/min. (2) Exclude patients with LM disease or no obstructive disease. Those with no obstructive disease are considered for an ancillary study investigating the relationship between symptoms and ischemia over time. (3) OMT indicates optimal medical therapy.
Sources of Funding
This article refers to work supported by National Institutes of Health grants SU01HL105907-03 and SU01HL105561-03.

Disclosures
Dr Hochman discloses the following consultant/advisory relationship: Entity: Glaxo Smith Kline, Role: National Coordinator for STABILITY Trial & Steering Committee Member for SOLID-TIMI 52 Study. The other authors report no conflicts.

References

Response to Reynolds et al

Rory Hachamovitch, MD, MSc

I agree with the arguments eloquently put forward by Reynolds et al that the assessment of myocardium at risk is central in assessing the value of a revascularization strategy in patients with stable ischemic heart disease. However, as is said, the devil is in the details. The design of trials addressing these questions is problematic. First, what is the appropriate ischemia threshold—10% myocardium at risk? 12.5%? 15%? The larger studies suggest that the latter are more likely to demonstrate revascularization benefit but result in greater recruitment challenges. This question has not been addressed using all modalities. Threshold selection is also complicated by insufficient studies using certain modalities. Determining these thresholds indirectly by equating test results from different modalities on the basis of associated risk although convenient is inadequate. As previously discussed, high risk imaging results (low left ventricular ejection fraction, scar, and increased left ventricular volumes) do not identify which patients may benefit from revascularization. Also, as mentioned previously, the threshold for a benefit with revascularization will likely vary with which modality is used—one size does not fit all. Finally, an additional study design challenge involves interfacing the results of imaging with patient treatment allocation. If post randomization patient treatment is not mandated, or at least adjusted for in the analytic design, discerning whether changes in outcomes between treatment arms is because of testing results versus the care plan pursued by the referring physician is problematic. The issue of post-testing patient management has been demonstrated by the results of the SPARC study. Thus, understanding the results of a study such as PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) is more challenging than interpreting a study design such as International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA). The results of PROMISE and, in the near future, ISCHEMIA and Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Diagnostic Examination (RESCUE), will hopefully yield insight into these important therapeutic questions. However, their interpretation and application will need to be carefully tempered by the methodological challenges they faced.
Does Ischemia Burden in Stable Coronary Artery Disease Effectively Identify Revascularization Candidates?: Ischemia Burden in Stable Coronary Artery Disease Does Not Effectively Identify Revascularization Candidates
Harmony R. Reynolds, Michael H. Picard and Judith S. Hochman

Circ Cardiovasc Imaging. 2015;8:
doi: 10.1161/CIRCIMAGING.113.000362
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/8/5/e000362

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/