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# Ischemia Burden in Stable Coronary Artery Disease Does Not Effectively Identify Revascularization Candidates

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## The benefit of revascularization in stable ischemic heart disease patients is controversial; a better method for patient selection is needed

Over thirty 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.[1] 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 to contemporary medical therapy and found no benefit on death, myocardial infarction or revascularization[2]. It was at the time unclear whether this was due to the different revascularization technique or advances in medical therapy.

Subsequently, two large, randomized, multi-center trials were undertaken to determine whether revascularization offered an advantage over intensive medical therapy ("optimal medical therapy", OMT). The COURAGE and BARI-2D trials randomized patients with stable ischemic heart disease to a strategy of routine revascularization in addition to OMT or to a strategy of OMT alone.[3, 4] The OMT approach included statin-based lipid lowering therapy with a target LDL 60–85 mg/dl, anti-ischemic medications alone or in combination and angiotensin converting enzyme inhibition or angiotensin receptor blockade. The COURAGE trial included 2,287 patients and utilized PCI as the revascularization technique. There was no benefit on the primary endpoint 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 2,368 patients with diabetes and both PCI and surgery were used for revascularization. Randomization was stratified based

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on declared physician preference for PCI or 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 follow up of 5.3 years. Both studies found an early, significant benefit of revascularization on angina relief but by 1–2 years of follow up, the majority of patients were asymptomatic regardless of treatment assignment and the duration of benefit of revascularization on angina was limited to 1–3 years.[5, 6] Details of these studies are summarized in Table 1.

In contrast to the older randomized trials of CABG, analysis of COURAGE and BARI-2D did not identify a subgroup that benefitted from PCI based on number of vessels diseased, presence of proximal LAD disease or clinical characteristics. [3, 4, 8, 9] Therefore, after these studies, selection for revascularization based on coronary anatomic features other than left main CAD, which was an exclusion criterion for both, appears to be inappropriate.

Still some physicians continue to believe that there are stable ischemic heart disease patients other than those with refractory symptoms or left main disease who may benefit from a routine revascularization strategy. Because COURAGE and BARI-2D randomized patients after angiography, selection bias based on anatomic and clinical features of the screened patients was likely in some cases. This post-cath enrollment approach, while absolutely necessary at the time, does limit the implementation of the guideline-determined medical therapy alone strategy and also may limit insight into the relationship between anatomic features and outcomes by treatment assignment. Strict interpretation of the findings would indicate they only apply to patients for whom a physician had equipoise about revascularization after viewing the coronary anatomy. Patient beliefs about the benefits of revascularization once they have been told about coronary stenosis may limit physician ability to implement guideline-determined medical therapy.[10, 11]

Mortality risk among patients enrolled in COURAGE and BARI-2D was relatively low and it remains unknown whether results would have been different if the trials had been carried out in cohorts at higher risk. Angina was not a marker of risk in BARI-2D.[12] If revascularization is effective at improving survival and reducing events in any patients with SIHD, many people believe that it is likely those patients at higher risk will receive the most benefit. However, the same argument was put forward regarding diabetes and risk before the publication of BARI-2D. Therefore the challenge is to identify a clinical characteristic that will help physicians select those patients who would have lower risk of death or myocardial infarction with a routine revascularization approach.

## Why has ischemia burden been suggested as a method of targeting revascularization?

Ischemic burden has repeatedly been identified as a powerful prognostic factor among patients referred for stress testing using nuclear imaging[13–20] echocardiography[21–24] and, more recently, cardiac MRI (CMR).[25–27]

It is notable that both COURAGE and BARI-2D entry criteria required evidence of ischemia, but the evidence could be as limited as exercise electrocardiographic changes, a

limited perfusion defect or a stenosis of ≥70–80% plus classic angina.[3, 4] Among the 60% of patients enrolled in COURAGE after nuclear stress imaging, most had less than moderate ischemia.[28] It has been suggested 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[20] suggest that selection for revascularization based on ischemia burden may be a reasonable approach. In this study including over 10,000 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 percent 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 while the opposite relationship was observed for patients with greater than 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. Though 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 multi-center SPARC 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.[29] Lastly, 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 quite severe, with an average wall motion score index indicating >8 segments ischemic.[30] Therefore this study, while also large (including over 3,000 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[31] 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, though 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 SPECT. [32]

## 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[33] and BARI-2D.[34] Among patients enrolled in the COURAGE ancillary study who underwent stress imaging both at baseline and again after 6–18 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.[33] Approximately one-third of participants in the ancillary study had moderate-severe ischemia at baseline based on core lab interpretation, among whom the routine PCI strategy also resulted in a greater likelihood of reduction in ischemia (78% vs. 52%, p=0.007). Similarly, patients assigned to medical therapy alone in BARI-2D were more likely to have moderate-severe ischemia on a one-year nuclear scan compared to 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. [34] 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, when all patients with baseline scans were included, regardless of whether they returned for a second test 6–18 months later (Figure 1).[28] 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 pre-specified 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.[35] 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.[36] Furthermore, a recent meta-analysis of randomized trials of PCI with medical therapy vs. 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 as compared to anatomic guidance of PCI in the FAME and DEFER randomized trials[38, 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 upon when a patient is judged to need revascularization on clinical grounds, e.g. 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 FAME 2 study support this notion.[7] Patients referred for PCI

and found to have at least one vessel with abnormal FFR were randomized in FAME 2 to FFR-guided PCI or medical therapy alone. While the FFR-guided PCI arm was favored on comparison of the primary endpoint 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, with the caveat that the study was terminated prematurely by the data and safety monitoring board for the composite endpoint. 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 as compared to medical therapy alone may be limited to reducing unplanned revascularization. If the primary endpoints of COURAGE and BARI 2D had included revascularization they too would have reported benefit for the prompt revascularization strategy.

In summary, though revascularization appears 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 stable ischemic heart disease have not demonstrated reductions in death or MI despite interventions that “fix” or bypass stenosis and relieve ischemia.

Excess risk associated with a greater burden of ischemia could be due to adverse effects of ischemia itself, perhaps in combination with an increased risk of arrhythmia, but could be due to other factors. It is possible that increased risk associated with a greater burden of ischemia is ultimately due to 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 while ischemia severity was not.[40] Atherosclerosis is a diffuse disease and medical therapy, particularly statin therapy, stabilizes plaques. Statins were not utilized in earlier randomized trials of CABG and the plaque stabilizing effects of medical therapy may be the primary reason 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.[7,41] In the PROSPECT study, severely stenotic lesions comprised only 5% of those lesions destined to cause acute coronary syndrome while 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] For this reason, it may be hypothesized that CABG would offer greater protection against MI and cardiac death as compared to 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 touchdown 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", i.e., 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 that may cause extensive ischemia, chronic total occlusions and distal disease. 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 lab interpretation. In the clinical trial setting, enrolling sites typically overestimate the ischemia severity as compared to 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 10,003 participants with recent onset symptoms to a strategy of initial stress testing or coronary CT angiography.[48] Downstream management was not specified by protocol in this NHLBI-funded, multi-center trial. There was no difference between randomized groups in the primary endpoint of death, MI, unstable angina or major complications from CV procedures or testing. However, the included patients were at low risk of events, approximately 3% over 2 years. Revascularization was more common in the CT-assigned group, 6.2% vs. 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 approximately 4,300 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 SPECT imaging arm. The primary endpoint 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 two 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 "the 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 being 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 cardiac MRI, 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 approximately 5% per year mortality, in alignment with the nuclear criterion.[32] 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.

A unique component of this trial is that the randomization occurs before cardiac catheterization, unlike all prior trials of revascularization. Many believe that once the patient is referred to angiography that 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 in order to exclude patients with significant left main disease and those patients without obstructive CAD. (See Figure 2) There is not currently equipoise in the community regarding 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 less than 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 CKD 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 endpoint 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 endpoint includes cardiovascular death rather than all-cause mortality because it is believed that the invasive strategy may not influence non-cardiac death. However, the definition of cardiovascular mortality is broad. The study definition of MI was designed to avoid counting of lower levels of peri-procedural troponin elevations which do not have prognostic significance. The universal definition of MI will also be assessed.

Randomization of 8,000 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. Firstly, higher risk patients will be enrolled. Secondly, the coronary anatomy will not be known before 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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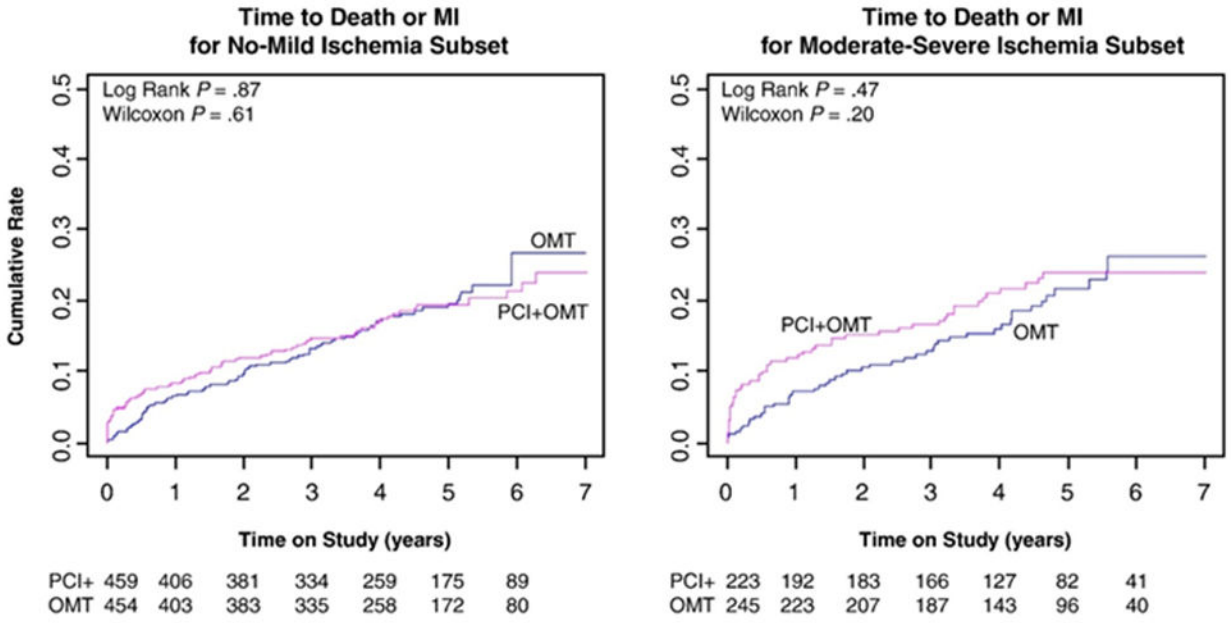


**Figure 1.**

Rates of death or myocardial infarction 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.

From[28]

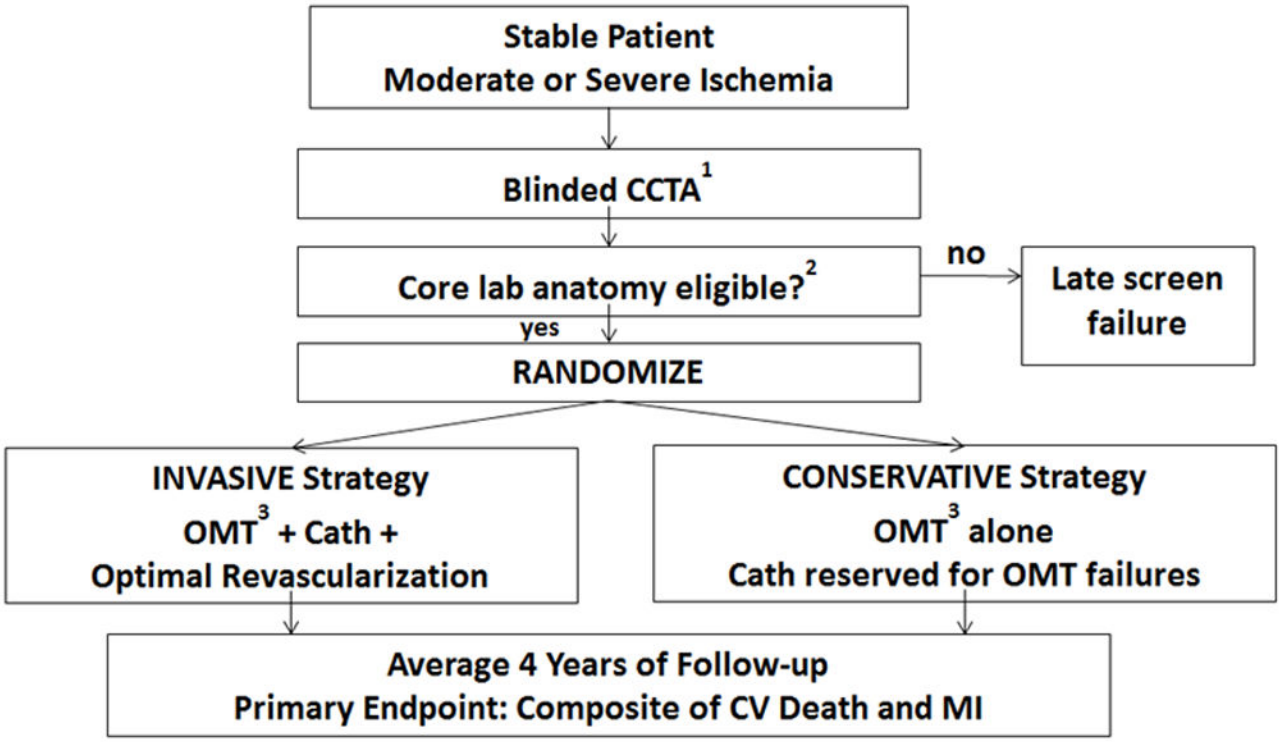


**Figure 2.**

ISCHEMIA trial design schematic

[1]CCTA will be performed in most patients with eGFR >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=Optimal medical therapy

**Table 1**

Summary of large randomized trials investigating the role of revascualrization in pateints with stable ischemic heart disease

| Year of publication | Study | N | Ischemia-based entry criteria | Revascularization strategy | Medical therapy | Primary outcome | Secondary outcomes | Ischemia testing in follow up |
|---|---|---|---|---|---|---|---|---|
| 1994 | Meta-analysis of randomized trials, CABG Trialists Collaboration[1] | 2649 | Angina (not required for all trials in meta-analysis) | CABG | Aspirin, nitrates (not for all trials) | All-cause mortality, lower in CABG group at 5–10 years | Angina relief better in CABG arms (CASS) through 5 years | Not performed |
| 2007 | COURAGE randomized trial[3] | 2287 | Site-determined abnormal stress test + 70% stenosis or angina + 80% stenosis | PCI | Aspirin, statin with target LDL<70, ACE inhibitor or ARB, anti-anginals | All-cause mortality or nonfatal MI, no difference between treatment groups | Angina relief modestly better in PCI arm through year 3 | PCI reduced ischemia better than medical therapy but no interaction between baseline ischemia severity and treatment effect |
| 2009 | BARI-2D randomized trial[4] | 2368 | Site-determined abnormal stress test or angina + 70% stenosis | CABG or PCI | Aspirin, statin with target LDL <100, antihypertensives for BP target <130/80; diabetes management also tested in this trial | 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) | Composite of death, MI, stroke lower with revascularization in CABG stratum (n=763). Angina relief modestly better with revascularization in PCI stratum through year 1, CABG stratum through year 5 | Revascularization reduced ischemia better than medical therapy |
| 2014 | FAME-2 randomized trial[7] | 888 | FFR ≤0.8 in at least one vessel | FFR-guided PCI | Aspirin, statin with target LDL<70, beta blocker, ACE inhibitor or ARB | All-cause mortality, nonfatal MI or urgent revascularization, lower in FFR-guided PCI group at 7 months. | No difference between treatment groups in death or MI | Not performed |

**Table 2**

Ischemia-based entry criteria for the ISCHEMIA trial

| Test Modality | Diagnostic criterion[1] |
|---|---|
| Nuclear perfusion via SPECT or PET | ≥10% myocardium ischemic |
| Echo | ≥3/16 segments with stress-induced severe hypokinesis or akinesis |
| CMR | perfusion: ≥12% myocardium ischemic<br>and/or<br>wall motion: ≥3/16 segments with stress-induced severe hypokinesis or akinesis |
| Exercise Test without Imaging (Criteria 1–4 must all be met) | **1** Clinical history of typical angina or typical angina during the exercise test<br>**2** Absence of resting ST segment depression ≥1.0 mm or confounders that render exercise ECG non-interpretable (LBBB, LVH with repolarization, pacemaker, etc.)<br>**3** As compared to 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 non-infarct territory. Both the J-point and the ST segment at 80 msec. need to meet criteria. When the HR is >130/min, the ST segment at 60 msec. may be used if the segment at 80 msec. cannot be determined.<br>**4** Either of the following:<br>**a.** 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<br>**b.** ST segment criteria are met at <75% of the maximum predicted HR |

SPECT=single photon emission computed tomography, PET=positron emission tomography; Echo= echocardiography; CMR=cardiac magnetic resonance

[1] Additional criteria must be met for confirmation of obstructive coronary artery disease, depending on eGFR and type of ischemia test.