

## Executive Summary of the ISCHEMIA/ISCHEMIA-CKD Trials

### International Study of Comparative Health Effectiveness with Medical and Invasive Approaches

#### Background and Rationale

The COURAGE and BARI 2D trials demonstrated that an initial management strategy of revascularization + optimal medical therapy (OMT) did not reduce the risk of death or MI in stable ischemic heart disease (SIHD) patients compared with OMT alone. This raised two important questions: 1) Were enough high risk patients enrolled in those trials to adequately test the hypothesis that a strategy of prompt revascularization reduces events? and 2) Do SIHD patients need to undergo coronary angiography prior to a trial of OMT?

Two lines of evidence suggest that revascularization may improve outcomes of SIHD patients with moderate or severe ischemia on myocardial perfusion imaging (MPI). First, in an observational study from Cedars-Sinai, 10,627 consecutive patients who underwent MPI were followed for 2 years. When at least moderate ischemia (>10%) was present, patients undergoing revascularization had fewer cardiac deaths than patients who were not revascularized. Second, among 105 patients with  $\geq 10\%$  ischemia who had follow-up scans 1 year later in the COURAGE nuclear substudy, PCI more frequently led to significant ischemia reduction than OMT alone (78% versus 52%;  $P=0.007$ ). Compared to those with persistent or worsening ischemia, patients with ischemia reduction by whatever means (i.e., PCI or OMT) had lower unadjusted risk for death or MI. However, a subsequent COURAGE analysis of outcomes by treatment group in 468 patients with at least moderate ischemia on baseline MPI, showed no reduction in death or MI from PCI.

*Evidence of Equipoise:* Data from 9 reports representing 5,833 patients indicate that only 35 to 65% of patients with moderate or severe ischemia on MPI are referred for cath, reflecting equipoise in the medical community. It is presently unknown whether use rates for cath and revascularization are appropriate for optimal patient management. Hence, there remains an important gap in our knowledge regarding the need for an invasive strategy and the value of revascularization in stable patients with moderate or severe ischemia. Given the potential clinical benefit from revascularization on the one hand, and the significant expense of an invasive strategy on the other, this is a critically important issue to resolve. In addition, patients with advanced chronic kidney disease (eGFR <30 or dialysis) have been routinely excluded from cardiovascular trials, including COURAGE and BARI 2D, even though cardiovascular disease is the leading cause of death in these patients and the optimal management strategy is unknown.

#### Study Overview

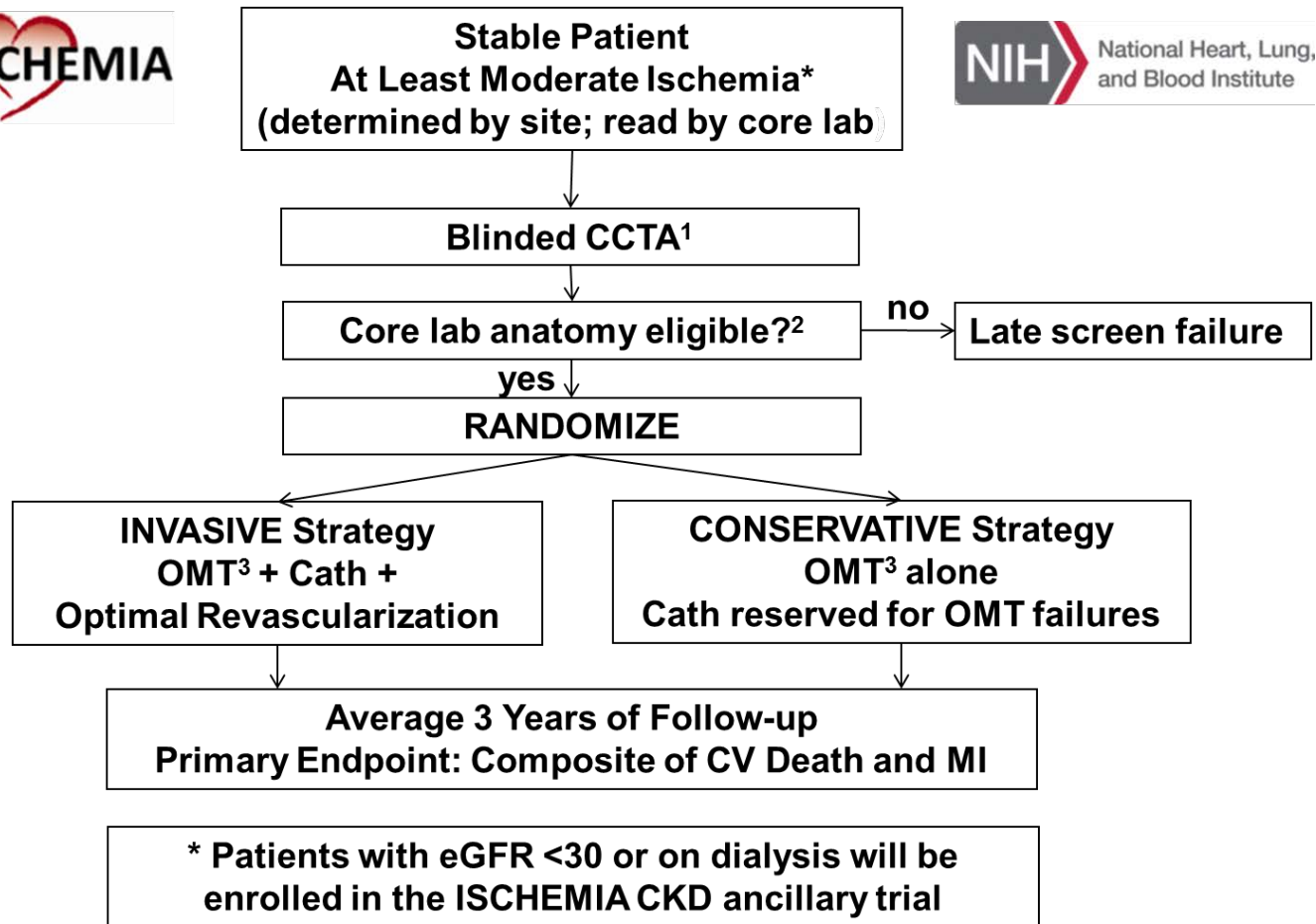
ISCHEMIA is an NHLBI-funded international randomized controlled trial comparing the effectiveness of two initial management strategies in 5,000 to 6,000 patients with at least moderate ischemia on stress testing: an invasive strategy with cardiac catheterization and optimal revascularization plus OMT versus a conservative strategy with OMT alone and cath reserved for patients who fail medical therapy. An additional 500-700 patients with advanced chronic kidney disease (eGFR <30 or dialysis) will be randomized in the NHLBI-funded ISCHEMIA-CKD ancillary trial. The primary aim of the ISCHEMIA trial is to determine whether the invasive strategy will reduce cardiovascular death or nonfatal myocardial infarction as compared with the conservative strategy. Patients who qualify on the basis of ischemia and have normal renal function will undergo blinded coronary CT angiography (CCTA) to exclude left main disease and to confirm the presence of obstructive coronary artery disease prior to randomization. Eligible patients are then randomized to the invasive or conservative strategy. Individuals with no obstructive disease on CCTA may qualify for an ancillary study of patients with angina, at least moderate ischemia, and no obstructive disease.

Accrual is projected to last 5.5 years with a minimum 1 year and maximum 6.5 years of follow-up. Patients randomized to the invasive group will undergo optimal revascularization—PCI or CABG—as recommended by the local interventional cardiologist and cardiovascular surgeon based on protocol recommendations. Patients randomized to the conservative strategy will be permitted to undergo invasive management as needed for refractory angina or acute coronary syndrome. The protocol is designed to minimize unnecessary cath in patients randomized to the conservative strategy. The primary outcome measure is time to cardiovascular death or nonfatal MI. Secondary outcome measures will include quality of life, cost-effectiveness, and cardiovascular hospitalizations. Enrollment began in late 2012.

#### Study Organization

The ISCHEMIA Leadership Committee includes Judith Hochman (Study Chair), David Maron (Study Co-Chair/PI), and co-PIs William Boden, Bruce Ferguson, Robert Harrington, Gregg Stone, and David Williams. The ISCHEMIA-CKD trial is led by Sripal Bangalore. The Clinical Coordinating Center is at NYU with regional/country site management coordinating centers and the Statistical and Data Coordinating Center is at Duke Clinical Research Institute. There are a number of core labs (e.g., angiography, nuclear, echo, cardiac MR, CCTA, ETT, ECG, biorepository), an Ischemia Imaging Coordinating Center, and an Economics and Quality of Life Coordinating Center. Committees include Executive, Steering, Biostatistics, OMT, Optimal Revascularization (PCI and CABG), Recruitment and Retention of Women and Minorities, Biorepository, and Clinical Event Adjudication.

# ISCHEMIA Enrollment and Randomization



<sup>1</sup>CCTA may not be performed in participants with eGFR <60 mL/min

<sup>2</sup>Exclude participants with LM disease or no obstructive disease

<sup>3</sup>OMT=optimal medical therapy