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Rationale and Design of the Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Noninvasive Examinations (RESCUE) Trial

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Abstract

RESCUE is a phase III, randomized, controlled, multicenter, comparative efficacy study, designed to compare two diagnostic imaging/treatment paradigms that use coronary computed tomography angiography (CCTA) or single photon emission computed tomography myocardial perfusion imaging (SPECT MPI) for assisting in the diagnosis of ischemic heart disease in patients with stable angina symptoms, and guiding subsequent treatment. The study is based on the hypothesis that CCTA as a diagnostic tool is associated with no increase in cardiac risk, decreased cost, and reduced radiation exposure compared with SPECT MPI. The RESCUE trial was funded by the Agency for Healthcare Research and Quality (AHRQ) and the American College of Radiology Imaging Network (ACRIN) Fund for Imaging Innovation, began in 2011, and completed in 2014.

Background

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial showed that there was no significant difference in death, myocardial infarction or stroke for patients with stable angina treated with optimal medical therapy (OMT) alone or in combination with percutaneous coronary intervention.¹ The results of the

COURAGE trial led to our hypothesis that it may be unnecessary to perform invasive coronary angiography (ICA) if a patient can be adequately diagnosed with ischemic heart disease (IHD) non-invasively and subsequently treated with OMT alone. Such an approach could provide substantial cost savings, particularly if noninvasive imaging could easily and safely identify a large group of patients for whom revascularization need not be performed. The Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Noninvasive Examinations (RESCUE) trial is a randomized, controlled, diagnostic, multicenter, phase III comparative efficacy trial designed to answer this question.

There are a number of imaging tests that may be used to diagnose IHD. Single Photon Emission Computed Tomography (SPECT) myocardial perfusion imaging (MPI) with stress is commonly performed for this purpose. The diagnostic accuracy for SPECT-MPI to identify obstructive coronary artery disease (CAD) appears to be modest² but the test has superior specificity and inferior sensitivity compared with CCTA.³ Both SPECT-MPI⁴ and CCTA⁵ have demonstrated prognostic value for predicting major adverse cardiovascular events (MACE) including death. However, both SPECT-MPI and CCTA demonstrated only modest impact on short-term ICA rates or medication changes in the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease (SPARC).⁶ In SPARC, there was relatively more ICA performed following CCTA likely secondary to its greater sensitivity but lower specificity.

While CCTA may have reduced specificity for detection of hemodynamically significant stenoses compared with ICA combined with fractional flow reserve or positron emission tomography, it does have high sensitivity and specificity for the presence of atherosclerosis.⁷ The linkage of imaging findings to treatment choices makes it possible to study integrated strategies of care. The comparison of alternative strategies provides an efficient approach to the assessment of outcomes from the use of diagnostic tests. It is with these thoughts in mind that we designed the RESCUE trial. We herein report the objectives, methods, and rationale for this study.

Overview of study design

The RESCUE trial assessed two strategies involving imaging technologies--CCTA and SPECT MPI for diagnosing and directing the treatment of CAD in patients with symptoms of stable angina or angina equivalent. Participants with positive cardiac findings on diagnosis (≥ 50% luminal stenosis by CCTA or ≥ 10% reversible defect by SPECT) were directed to OMT only or ICA and possible revascularization, depending on extent and location of disease (Fig. 1). Patients who at their physician's determination were sent directly to revascularization and whose physicians did not adhere to the study design were classified as a protocol deviation, but were still followed for MACE for this trial with an intention to treat analysis.

Participants were followed for at least 12 months. The RESCUE trial was performed in 44 investigative sites in the United States and Germany and the Netherlands.

Participant cohort, enrollment procedure and inclusion/exclusion criteria

Eligible participants included patients who were 40 years or older presenting with symptoms of stable angina or angina equivalent, with or without known CAD, with planned non-invasive imaging for diagnosis (Table 1). Stable angina was defined as having Class I or II angina by the Canadian Cardiovascular Society (CCS).⁸ Angina equivalent is defined as any symptom of finding or constellation of symptoms or findings that the referring physician feels is concerning for obstructive CAD. In conformance with the NIH Revitalization Act of 1993, both men and women and members of all ethnic groups were eligible for the RESCUE trial.

Exclusion criteria were as follows: Prior revascularization; not suitable to undergo CT with an iodinated contrast agent because of a known allergy-like reaction to contrast media as defined by the American College of Radiology, renal failure or insufficiency as determined by glomerular filtration rate (GFR) < 30 mL/min/1.73 m² based on a serum creatinine level obtained within 28 days prior to registration; atrial fibrillation or significant arrhythmia judged to potentially limit quality of CCTA; acute ischemia or acute myocardial infarction; severe myocardial ischemia defined by markedly positive exercise treadmill stress test (significant ST segment depressions or hypotensive response during stage I of the Bruce protocol); unable to suspend respiration for 15 seconds or to follow instructions to do so; unstable angina and symptoms refractory to maximal oral and intravenous medical therapy (persistent CCS Class IV); history of known left ventricular ejection fraction < 45%; pulmonary edema or heart failure unresponsive to standard medical therapy; pacemaker, due to potential beam-hardening artifacts; valvular heart disease likely to require surgery in the next 18 months; congenital heart disease or cardiomyopathy likely to affect prognosis during follow up; significant systemic hypertension (blood pressure > 200/100 mm Hg) unresponsive to medical therapy; severe non-cardiovascular comorbidity limiting survival (e.g., cancer or other life threatening illness for which the patient is expected to live less than 12 months); prior imaging evaluation for this episode of symptoms (e.g., SPECT MPI or CCTA within the previous 72 hours); BMI > 40 kg/m² because of likely limited examination quality; pregnancy or intent to become pregnant (if a female is of childbearing potential—defined as a premenopausal female capable of becoming pregnant).

Study participants were enrolled and randomized in equal proportions into the two study arms: Group A (CCTA) and Group B (SPECT MPI/ICA). Block randomization with a fixed block size of six, stratified by gender and participating institution was used. Participants with positive cardiac-related findings on their CCTA or SPECT/MPI were followed for a minimum of four time points (at 2 weeks and 2, 6, 12 months). Participants with negative findings on CCTA or SPECT MPI, were followed for a minimum of two time points (6 and 12 months).

Study organization

RESCUE (ClinicalTrials.gov NCT01262625) was funded through AHRQ (R01 HS019403-01) and the the American College of Radiology Imaging Network (ACRIN) Fund for Imaging Innovation, and was conducted by ACRIN (www.acrin.org). Day-to-day

management of the study (Appendix) was the responsibility of the RESCUE-ACRIN Executive Committee. The RESCUE Steering Committee provided ad hoc advice. Study progress was monitored by an independent Data and Safety Monitoring Board (DSMB), which met every 6 months. Reports to the DSMB were prepared by the ACRIN Biostatistics and Data Management Center. An independent Adjudication Committee reviewed abstracted medical records for AMI, revascularization and all deaths (to identify cardiac deaths).

Study objectives

RESCUE was designed to compare two non-invasive diagnostic-treatment paradigms that differed primarily on the first test performed namely; CCTA versus SPECT-MPI. The primary endpoint of the study was a combined endpoint of occurrence of major adverse cardiac events (MACE), comprising cardiac-related death or acute myocardial infarction (AMI), and revascularization (Table 2).

Primary aim

The primary aim was to compare the time to MACE or revascularization between the two arms from a non-inferiority perspective that CCTA in guiding treatment is not associated with a higher hazard to MACE or revascularization, compared with SPECT-MPI.

Secondary aims

Secondary aims of RESCUE were: 1) to evaluate the ability of available prognostic indices to predict revascularization or MACE using CCTA information; 2) to develop new predictive indices using the RESCUE trial data and, 3) to compare angina symptoms and self-reported health status of participants in the two arms.

Diagnostic procedures: CCTA and SPECT MPI

ECG-gated coronary CTA was performed on 64-slice or greater CT scanners and gated SPECT-MPI to fall within literature-based guidelines.^{9,10} CCTA guidelines for RESCUE sites were as follows: All image acquisitions were performed using a breath hold in inspiration during intravenous administration of 80 mL of iodinated contrast, on average, injected as a bolus at a rate of 5 mL/s to attenuate the lumen of the coronary arteries, the aorta, and the left ventricle. Appropriate timing of the contrast bolus was ensured by either the determination of the transit time or the bolus trigger technique. Using ECG gating, the tube current was reduced during systole according to each manufacturer's specific protocol to minimize radiation exposure. Sites were permitted to perform this with either prospective or retrospective ECG-gating. If retrospective gating was performed, the scan was required to be performed with radiation dose modulation or a minimum radiation dose protocol to reduce the tube current during systole. With the exception of sites with a dual-source CT (DSCT) scanner, all participants with a heart rate > 65 beats per minute received a heart-rate lowering drug (usually a beta blocker), intravenously or orally, to optimize image quality and sublingual nitroglycerin to maximally dilate the coronary arteries unless their systolic blood pressure was < 100 mm Hg or other contraindications were present. At sites with a DSCT scanner, due to the improved temporal resolution, heart-rate lowering drugs were not

required, with participants receiving only sublingual nitroglycerin if there were no contraindications. At least one data set that showed the least cardiac motion was reconstructed a minimum 0.8 mm thick axial images, with 50% overlap from the contrast-enhanced CCTA scan for the detection of coronary plaque and stenosis (pixel matrix: 512 x 512, FOV: 25 cm).

SPECT-MPI guidelines for the RESCUE trial were as follows: All site protocols were reviewed and approved by the ACRIN core lab prior to the enrollment period in order to ensure optimal imaging techniques. At minimum, SPECT-MPI data sets were to consist of the following: non attenuated-corrected AND attenuated-corrected raw rest and stress projection data; reconstructed files (short axis, vertical long axis, and horizontal short axis); screen capture of quantitative analysis results page displaying “% of LV ischemia or “% LV reversibility” from a commercial quantitative software program (i.e. Emory Cardiac Toolbox, 4D-MSPECT, QPS (Cedars Sinai); gated SPECT MPI data with Beat Length Histogram (if available). SPECT MPI image quality was evaluated to determine whether the entire left ventricle was in the Field of View; raw data projection images were of minimal motion and low levels of hepatic and bowel uptake; gated nuclear images were assessed to ensure optimal gating was achieved.

All CT and SPECT readers were required to have at least COCATS II level training or equivalent.

Optimal medical therapy

Individualized OMT regimen guidelines were determined by the treating cardiologist, but a standard guideline to achieve OMT was proposed¹ and adherence was monitored throughout the study follow up. The proposed protocol was based on the regimens used in the COURAGE trial¹ and lipid lowering targets were defined by the National Heart, Lung, and Blood Institute.¹¹ OMT guidelines were as follows: 1. An antiplatelet such as aspirin, 81 to 325 mg each day, and/or clopidogrel, 75 mg per day if participant was aspirin intolerant, or prasugrel. 2. A statin such as atorvastatin, pravastatin, or rosuvastatin with target LDL cholesterol of 70 mg/dL.⁴¹ 3. An anti-hypertensive/anti-anginal beta blocker, such as metoprolol, carvedilol, or atenolol, with a blood pressure goal of < 130/80 mm Hg and reduced CCS angina class. 4. An additional anti-hypertensive, such as amlodipine or an ACE-inhibitor, as needed. 5. An additional anti-anginal, such as amlodipine or long-acting nitrate, as needed. 6. An ACE-inhibitor (lisinopril) or angiotensin II receptor antagonist (Losartan) if ACE-inhibitor not tolerated, for all participants with left ventricular ejection fraction < 40%. 7. Attempt to raise HDL cholesterol, > 40 mg/dL in men and > 50 mg/dL in women, with exercise, extended release niacin, or fibrates alone or in combination once LDL level is at goal. 8. Medications for diabetes control, with target HbA1c < 7%. 9. Smoking cessation. 10. Exercise regimen appropriate to diagnosis. 11. Nutritional/dietary modification. Adherence to the OMT regimen was documented on CRFs during participant follow up (phone calls by the site coordinator at 6 and 12 months and documentation of targets achieved was verified when possible from medical record/chart abstraction, including records from referring physicians. Chart abstraction was made performed by healthcare

professionals who were career chart abstractors (Care Communications; <http://www.carecommunications.com/about-care>).

If a participant developed worsening or persistent angina after randomization, the following management guidelines were used:

- a. For all but CCS Class IV participants medical therapy (increase doses of anti-ischemic drugs and/or add additional agents as needed clinically); if the participant subsequently stabilizes to CCS Class I to II, continue medical therapy indefinitely;
- b. If symptoms did not stabilize, or worsen to CCS Class III after 4 to 6 weeks of maximum medical therapy, it was recommended that the participant should undergo ICA for evaluation for revascularization.

In addition to phone calls by site coordinators, RESCUE trial patients were encouraged to adhere to lifestyle modifications via access to a website that contained suggestions for lifestyle modification with links to sites to assist with smoking cessation (www.RESCUEtrial.org)

Quality assurance

All CCTA and SPECT MPI were performed on ACRIN qualified scanners. All readers were required to be at least COCATS level II¹³ trained or have ACR CCTA minimum proficiency as defined by the ACR CCTA Practice Guidelines.

ACRIN imaging research personnel performed ongoing technical quality control (QC) review of all imaging tests in RESCUE for quality and completeness of the diagnostic test dataset, adequate test protocol, proper data/image reconstruction for CCTA and SPECT MPI, and minimal radiation exposure for CCTA. For participant safety, the ACRIN Core Lab conducted a 100% QC of radiation exposure for CCTA. Sites with CCTA radiation dose with a last 5 case mean of 15 mSv or greater were contacted by the QC monitors at ACRIN and a telephone call scheduled with site principal investigators to discuss parameter adjustment. The CCTA and SPECT MPI core labs performed expert central reads (blinded to the local interpretations) and reviewed overall image quality in 10% of participant cases. To ensure protocol compliance early on and to account for sites with low accrual, the first two studies and a random sample of 10% of the remaining studies from each site were read in each modality to assess quality of local reads. These 10% were selected by block randomization stratified by testing site and test modality.

Self-reported health status and quality of life assessment

Angina symptoms were monitored using the Seattle Angina Questionnaire (SAQ)^{13,14} and global health-related quality of life (HRQoL) using the Short Form-36(SF-36).^{15,16} The SAQ Physical Limitation, Anginal Stability, Angina Frequency, Treatment Satisfaction and Quality of Life scores have been shown to be sensitive to improvement in angina symptoms following treatment with percutaneous coronary intervention (PCI) and OMT.^{17,18}

The SAQ and the SF-36 were administered at baseline and 12-months post-test. Administration was done at the recruiting sites at the time of the baseline examination. Administration at approximately 12-months post-test was coordinated by the ACRIN Outcomes and Economics Unit (OEAU) located within the ACRIN Biostatistics Center at the Brown University Center for Statistical Sciences, Providence, RI and was limited to patients from those sites that agreed to provide participant contact information to the OEAU.

The SAQ was used to assess whether participants were angina-free at 12 months, as well as to determine whether participants reported a clinically meaningful improvement in any of the SAQ scales between the baseline and 12-months assessments. Participants were classified as angina-free if their SAQ score was 100, indicating no angina symptoms.

The Short Form (SF-36) was used to derive eight profiles of functional health and well-being. We compared change in each of these subscales between the baseline and the 12-month assessments for participants in each arm of the study.

Statistical hypotheses and sample size determination

Primary Aim

Comparison of time to MACE or revascularization between the two arms from a non-inferiority perspective—Participants were enrolled in the study between May, 2011 and June, 2013 (24 months) and were randomized to the two study arms in equal proportions. Randomization was stratified by gender and participating institution. Participants declared positive for disease by imaging were followed at 2 weeks and at 2, 6, and 12 months, while those declared negative for disease by imaging were followed at 6 and 12 months until the end of the trial for a minimum of 12 months. Time to the primary endpoint was measured from randomization to the first occurrence of any of the component events (Table 2).

The choice of CCTA non-inferiority in the formulation of the primary aim reflects clinical judgment about the expected advantages of the CCTA strategy in terms of patient burden and resource utilization. These advantages would result from the ability of CCTA to direct patients without left main disease to a trial of OMT without first performing ICA, as would be necessary in patients who underwent SPECT as their first method of imaging diagnosis.

The primary analysis will be conducted from an intent-to-treat perspective and will compare time to endpoint event between the two arms using Kaplan-Meier curves and a logrank test for testing the hypothesis of non-inferiority of the CCTA arm.^{19,20} Further, we will use Cox regression models to adjust for the effect of patient characteristics, including gender, age, and major comorbidities. Of primary interest in this regression analysis will be the coefficient of study arm indicator, and the interaction of patient covariates with the study arm indicator.

Sample size and power considerations

Sample size computations for the primary outcomes were conducted based on a log-rank test for non-inferiority.¹⁹ Design parameters (listed in the Appendix) were determined by reported data from the COURAGE study combined with data from our clinical experience.

For the primary aim, we assumed that about 1% of participants would experience MACE within 12 months from study entry and that an additional 5% would undergo revascularization within the same period. Thus we assumed a combined rate of 6% within 12 months for the primary endpoint (hazard rate=0.0052, assuming an exponential survival distribution). We also assumed that about 5% of participants would drop out during a 12 month period from each arm and about 1% will switch from each arm to the other. The accrual time was set at 18 months and the additional follow-up time at 12 months for the last enrolled participant. The following table shows the power of a test of non-inferiority for a test at level 0.05 and the indicated non-inferiority hazard ratio.

Power	Total sample size	Margin of hazard ratio for non-inferiority
.74	4300	1.25
.85	4300	1.30
.93	4300	1.35
.97	4300	1.40

The choice of non-inferiority margin reflects an implicit tradeoff between expected advantages and possible decrement in performance as measured by the primary metric (time to MACE or revascularization)

The above power computations were performed under the assumption that the actual hazard rates are identical in the two arms. The table indicates that if the hazard ratio for non-inferiority is 1.3 and above, a total sample size of 4300 would provide adequate power under the above assumptions about the 12 month rate for the combined primary event rate, drop out, drop in and non-compliance. If the 12 month rate of MACE or revascularization is higher than 6%, the power would increase. For example, if the 12 month event rate was 7% and all other assumptions were kept unchanged, the power is about 90% for hazard ratio equal to 1.3 and is about 80% for hazard ratio equal to 1.25. All computations were performed using the subroutine for logrank test for non-inferiority in the software package PASS.²¹

Secondary Aims

I. Evaluation of the ability of available prognostic indices to predict revascularization or MACE using CCTA information—In this aim, we will first evaluate a modified Duke Prognostic Index to predict MACE or revascularization for participants in the CCTA arm within 12 months from randomization. Its predictive performance will be evaluated using receiver operating characteristic curve (ROC).

We will also develop other modifications of the Duke index adapted to the context of predicting MACE or revascularization using CCTA. In particular, multivariate binary regression modeling will be used to examine the relation between the binary responses to the multidimensional vector of predictors used in a modified Duke index. We will use cross-validation to limit the potential for overfitting and to derive realistic estimates of the predictive performance of the model.²³ We also will consider using approaches such as Ridge regressions to reduce the impact of collinearity in the predictors. The cross-validated area under the ROC curve for the new index will be compared to the area under the curve estimated earlier for a modified Duke index. A non-parametric approach will be taken to the analysis of these ROCs.²⁴ We will estimate and compare the areas under the curves using bootstrap methods, in order to account for the correlation in the index values arising from the fact that the indices will be evaluated on the same participants.

II. Development of new predictive CCTA indices using the RESCUE trial data—

In this aim we will use the CCTA assessments of the American Heart Association model of the coronary arteries to develop a new index for the prediction of revascularization or MACE. First, we will develop an index using the information of the maximum degree of stenosis (grade: none 0%, very mild 1–29%, mild 30–49%, moderate 50–69%, severe 70%) in each segment, as listed on the CRFs provided by each site. The analytic approach will be based on multivariable binary regression modeling as described above and will also incorporate clinical input and judgment for defining predictor variables. The cross-validated area under the ROC curve for the new index will be compared to the areas under the curve for the other modified Duke indices discussed earlier in this section. We will also estimate measures of predictive performance based on reclassification.²⁴

The predictive index for SPECT MPI will be the measurement of size of the reversible perfusion defect on SPECT MPI. We will estimate an ROC curve for this index and use it to obtain threshold values of the index that achieves a desired trade-off between sensitivity and specificity. We also will compare the areas under the ROC curves across the two arms using methods appropriate for independent curve comparisons.

To compute the statistical power for the comparison of areas under the ROC curves envisioned in this aim we assumed that about 6% (or approximately 129 participants) would have MACE or undergo revascularization with 12 months in each arm and the correlation between index values will be about 0.5. The projected sample size of N=4300 provides power between 81% and 99% to detect a difference of 0.07 to 0.1, using a test of level 0.05, if the lower area is 0.8.

III: Comparison of angina symptoms and self-reported health status of participants in the two arms—Measures of health status as measured by SAQ and SF-36 will be computed for each participant at baseline and 12 months. We will use regression modeling for longitudinal data to compare the two arms.²⁵ In addition to the overall comparison between the arms, the interactions of covariates with indicator of study arm also will be of primary interest. The regression analysis will be used to examine potential effects of patient characteristics such as gender, race, and co-morbidity. We will use pattern mixture models to address patient drop out and missing assessments. The clinical

implications of potential effects identified in the analysis of the scale measures computed from SAQ and SF-36 will be examined using published guidelines.²⁷

We used data from the OMT arm of the COURAGE study¹⁸ to guide us in the choice of assumptions needed in the power computations for this aim. For the quality of life score from the SAQ, we assumed that the standard deviation at each time point is about 25 and the average, within arm, change between baseline and 12 months is about 20. We also assumed a correlation of 0.5 for the repeated measurements. Under these assumptions, the projected sample size will provide 83% and 99% power if the difference in average means between the arms is respectively 2 and 3 units and a two-sided test of level 0.05 is used. Overall, the proposed design can provide adequate power to compare quality of life changes in the two arms.

Study Monitoring

In consultation with the DSMB, a strategy to monitor the primary endpoint of the study for efficacy and safety was put into effect for the RESCUE. Formal interim reports on monitoring of safety were presented to the DSMB at 12, 18 and 24 months after the beginning of participant enrollment.

Enrollment Demographics

The study opened to enrollment in May, 2011 and was closed to enrollment in June, 2013 due to resource limitations. A total of 1050 participants were enrolled and randomized to the two arms of the study. The flow of patients is presented via a CONSORT diagram in Figure 2. Participant demographics and risk factors are presented in Table 3.

Conclusion

The RESCUE trial is a phase 3 randomized controlled comparative efficacy trial of two diagnostic imaging/treatment strategies for patients with symptoms of stable angina or angina equivalent. RESCUE was primarily supported via ARRA funding, which necessitated a narrow timeframe for completing enrollment and follow-up. Thus, our original projections about the timeline for accrual did not materialize and enrollment had to be suspended. The decision to stop the study was not related to study outcomes and the early termination does not affect the validity of the intention to treat analysis or bias the comparison between the arms; however, as discussed in the statistical methods above, the smaller sample size provides markedly reduced power for the primary comparison.

The Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial – in a patient population similar to RESCUE – symptomatic patients with suspected CAD – compared patient outcomes in a strategy of initial CCTA, as compared with functional testing and showed no improvement in clinical outcomes over a median follow-up of 2 years.²⁷ Unlike the COURAGE and RESCUE trials, in PROMISE no attempt was made to direct physician treatment based on imaging results.

Guidelines based on available literature are developed with the hopes that physicians will follow them – but there is no guarantee that they will. Although the COURAGE trial showed that there was no significant difference in death, myocardial infarction or stroke for patients with stable angina treated with optimal medical therapy (OMT) alone or in combination with percutaneous coronary intervention¹, the RESCUE trial met with difficulty in convincing sites to participate in a study that might direct a patient with CAD other than left main disease to a trial of OMT. To date no published prospective trial assessing noninvasive imaging outcomes has attempted to directly link imaging results to guidelines for therapy, although the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial²⁸ is such a trial linking results of invasive and non-invasive imaging that is on-going. ISCHEMIA is an international trial that compares two initial strategies for treating patients with stable obstructive coronary heart disease and at least moderate ischemia on cardiac stress testing: one arm is an invasive management strategy (INV), consisting of early routine cardiac catheterization followed by optimal revascularization therapy plus optimal medical therapy (OMT), and one arm, as in RESCUE, is conservative management – OMT alone with catheterization and revascularization if the participant does not respond to therapy. Notably, to achieve recruitment goals, a significant number of ISCHEMIA sites are outside of the United States. While ideal, trials with imaging results directing care are ultimately difficult to recruit for and to successfully complete especially if one arm provides a treatment algorithm contrary to the prevailing culture, even if literature suggests that the treatments within each arm are - at the very least - at equipoise.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

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Appendix: RESCUE Trial Governance

Executive Committee

Mehdi Adineh, MD
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 Constantine Gatsonis, PhD
 Udo Hoffmann MD, MPH
 João A C Lima, MD
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 Matthew J Budoff, MD
 Ralph J Damiano, MD
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 Jon F Merz, JD, PhD

Adjudication Committee

Bernard R Chaitman, MD
 Thomas C Gerber MD, PhD
 Benico Barzilai, MD

Fig. 1.
RESCUE schema

Figure 2.
CONSORT diagram for RESCUE TRIAL

Table 1

Entry Criteria for RESCUE

<ul style="list-style-type: none">• Willing and able to provide a written informed consent• 40 years or older• Presentation with symptoms of stable angina (CCS Class I to III) or angina equivalent with or without known CAD• Planned non-invasive imaging for CAD diagnosis• Able to tolerate CCTA or SPECT MPI per randomization as required by protocol, to performed at an ACRIN-qualified facility with a RESCUE-qualified scanner

Table 2

Definition of Primary Endpoint

Primary endpoint will have been reached if either (a) or (b) occurs		Definition
(a) MACE	Cardiac-related death	Any sudden cardiac death, death due to AMI, and death to heart failure/ cardiogenic shock. Death without a clear non-cardiovascular cause or death without known cause will be presumed cardiovascular death.
	AMI	Myocardial necrosis/loss of viable myocardium in a clinical setting consistent with MI.
(b) Revascularization		An attempted CABG and PCI (whether the procedure is successful or not) to include plain balloon angioplasty, stent placement, brachytherapy, atherectomy, laser, or rotational ablations. Coronary revascularization procedures for restenosis or as a part of staged PCI will be considered a subcategory of coronary revascularization.

Table 3

Participant Demographics and Risk Factors.

Category	Value	CCTA - Enrolled	%	SPECT - Enrolled	%
<i>Number of participants</i>		518	100.0	532	100.0
<i>Age</i>	<i>Mean</i>	57.4		532.0	
	<i>Median</i>	58.0		57.7	
	<i>Minimum</i>	40.0		58.0	
	<i>Maximum</i>	85.0		40.0	
<i>BM²**</i>	<i>Mean</i>	29.7		86.0	
	<i>Median</i>	29.5		29.4	
	<i>Minimum</i>	16.2		29.1	
	<i>Maximum</i>	41.3		16.7	
<i>Race</i>	<i>American indian or native Alaskan</i>	9	1.7	7	1.3
	<i>Asian</i>	11	2.1	14	2.6
	<i>Black or African American</i>	73	14.1	78	14.7
	<i>Native Hawaiian or other</i>	2	0.4	1	0.2
	<i>White</i>	401	77.4	415	78.0
	<i>Multiple race endorsement</i>	10	1.9	5	0.9
	<i>Unknown</i>	12	2.3	12	2.3
<i>Ethnicity</i>	<i>Hispanic or Latino</i>	46	8.9	58	10.9
	<i>Not Hispanic or Latino</i>	469	90.5	469	88.2
	<i>Unknown</i>	3	0.6	5	0.9
<i>Gender</i>	<i>Female</i>	235	45.4	245	46.1
	<i>Male</i>	283	54.6	287	53.9
<i>CCS angina scale**</i>	<i>Class I</i>	297	57.3	305	57.3
	<i>Class II</i>	185	35.7	181	34.0
	<i>Class III</i>	33	6.4	35	6.6
<i>Cardiac risk factors</i>	<i>CAD, ACS OR AMI, female <65 years of age</i>	73	14.1	74	13.9
	<i>Diabetes mellitus</i>	105	20.3	114	21.4
	<i>CAD, ACS OR AMI, male <55 years of age</i>	137	26.4	125	23.5

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Category	Value	CCTA - Enrolled	%	SPECT - Enrolled	%
	Dyspnea	258	49.8	258	48.5
	Cigarette smoking (any) in the past 30 days	75	14.5	87	16.4
	Hypercholesterolemia/Hyperlipidemia	326	62.9	313	58.8
	Hypertension	319	61.6	317	59.6
	Prior history of CAD	58	11.2	55	10.3
	Triglyceridemia	114	22.0	121	22.7