ISCHEMIA Trial Protocol

International **S**tudy of **C**omparative **H**ealth **E**ffectiveness with **M**edical and **I**nvasive **A**pproaches

Sponsor:	National Heart, Lung, and Blood Institute (NHLBI)
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Note: This version includes an appendix with CIAO-ISCHEMIA, an optional ancillary study for ~75 selected sites.

PROTOCOL VERSION AND AMENDMENT TRACKING

Version Number/Amendment	Approval Date
1.0	January 18, 2012
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Protocol Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulations and ICH guidelines.

Version Date: January 6, 2014

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Signature of Principal Investigator Date

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Printed Name of Principal Investigator

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Name of Facility

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Location of Facility (City, Country)

CLINICAL TRIAL SUMMARY

Title	**I**nternational **S**tudy of **C**omparative **H**ealth **E**ffectiveness with **M**edical and **I**nvasive **A**pproaches
Study Objectives	Primary objective is to determine whether an initial invasive (INV) strategy of cardiac catheterization and optimal revascularization, if feasible, in addition to optimal medical therapy (OMT) in patients with stable ischemic heart disease (SIHD) and at least moderate ischemia on ischemia testing reduces the incidence of the composite of cardiovascular death or nonfatal myocardial infarction compared with a conservative (CON) strategy of optimal medical therapy alone with cardiac catheterization and revascularization reserved for failure of OMT. Secondary objective is to determine whether an INV strategy is more effective than CON strategy in improving angina control, as assessed by the Seattle Angina Questionnaire (SAQ) Angina Frequency scale, and disease-specific quality of life, as assessed by the SAQ Quality of Life scale. Other secondary objectives include comparing the incidence of the composite of cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure; individual components of this endpoint; all-cause death; stroke; as well as comparing health resource utilization, cost, and cost-effectiveness between the two randomized strategies.
Study Design	ISCHEMIA is an international comparative effectiveness study. Participants will be recruited following clinically indicated ischemia testing and randomized in a 1:1 fashion to an INV or CON strategy.
Number of Participants	Approximately 8,000 participants randomized
Trial Location	Multinational: approximately 500 sites worldwide
Inclusion Criteria	• At least moderate ischemia on an ischemia test (see definitions in protocol appendix A) • Participant is willing to comply with all aspects of the protocol, including adherence to the assigned strategy, medical therapy and follow-up visits • Participant is willing to give written informed consent • Age ≥ 21 years

Exclusion Criteria	• LVEF < 35% • History of unprotected left main stenosis ≥50% on prior coronary computed tomography angiography (CCTA) or prior cardiac catheterization (if available) • Finding of "no obstructive CAD" (<50% stenosis in all major epicardial vessels) on prior CCTA or prior catheterization, performed within 12 months • Coronary anatomy unsuitable for either PCI or CABG • Unacceptable level of angina despite maximal medical therapy • Very dissatisfied with medical management of angina • History of noncompliance with medical therapy • Acute coronary syndrome within the previous 2 months • PCI within the previous 12 months • Stroke within the previous 6 months or spontaneous intracranial hemorrhage at any time • History of ventricular tachycardia requiring therapy for termination, or symptomatic sustained ventricular tachycardia not due to a transient reversible cause • NYHA class III-IV heart failure at entry or hospitalization for exacerbation of chronic heart failure within the previous 6 months • Non-ischemic dilated or hypertrophic cardiomyopathy • End stage renal disease on dialysis or estimated glomerular filtration rate (eGFR) <30mL/min (not an exclusion criterion for CKD ancillary trial, see CKD ancillary trial, Section 18) • Severe valvular disease or valvular disease likely to require surgery or percutaneous valve replacement during the trial • Allergy to radiographic contrast that cannot be adequately pre-medicated, or any prior anaphylaxis to radiographic contrast • Planned major surgery necessitating interruption of dual antiplatelet therapy (note that patients may be eligible after planned surgery) • Life expectancy less than the duration of the trial due to non-cardiovascular comorbidity • Pregnancy (known to be pregnant; to be confirmed before CCTA and/or randomization, if applicable) • Patient who, in the judgment of the patient's physician, is likely to have

	significant unprotected left main stenosis (Those who are able to undergo CCTA will have visual assessment of the left main coronary artery by the CCTA core lab) • Enrolled in a competing trial that involves a non-approved cardiac drug or device • Inability to comply with the protocol • Exceeds the weight or size limit for CCTA or cardiac catheterization at the site • Canadian Cardiovascular Society Class III angina of recent onset, OR angina of **any class** with a rapidly progressive or accelerating pattern • Canadian Cardiovascular Society Class IV angina, including unprovoked rest angina • High risk of bleeding which would contraindicate the use of dual antiplatelet therapy • Cardiac transplant recipient • Prior CABG, unless CABG was performed more than 12 months ago, and coronary anatomy has been demonstrated to be suitable for PCI or repeat CABG to accomplish complete revascularization of ischemic areas (CCC approval required)
Primary Endpoint	Time to first occurrence of cardiovascular death or nonfatal myocardial infarction.
Secondary Endpoints	• Angina control per SAQ Angina Frequency Scale • Disease-specific quality of life per SAQ Quality of Life Scale • Composite of cardiovascular death, nonfatal myocardial infarction, or stroke • Composite of cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure • All-cause death • Cardiovascular death • Nonfatal MI • Resuscitated cardiac arrest • Hospitalization for unstable angina • Hospitalization for heart failure

	• Stroke • Composite of cardiovascular death, nonfatal myocardial infarction, stroke, resuscitated cardiac arrest, hospitalization for unstable angina or heart failure. • Health resource utilization, costs, and cost-effectiveness
Assessment Schedule	Pre-eligibility screening, CCTA visit, randomization, 1.5 months, 3 months, 6 months, 12 months, and every 6 months thereafter.
Study Duration	Enrollment will occur over approximately 4 years with an expected minimum of 18-24 months follow-up and an average of approximately 4 years follow-up.
Clinical Event Adjudication Committee	The following events will be adjudicated by a blinded Clinical Event Adjudication Committee: death, myocardial infarction, resuscitated cardiac arrest, hospitalization for unstable angina, hospitalization for heart failure, and stroke.
Data and Safety Monitoring Board	An independent Data and Safety Monitoring Board will advise the NHLBI and study leadership on safety aspects and overall progress of the study.
Statistical Considerations	A sample size of approximately 8,000 randomized participants is expected to provide over 90% power to detect a 15% reduction in the primary composite event rate in participants randomized to INV as compared with CON strategy.
Ancillary Studies (optional)	1. ISCHEMIA-CKD ancillary trial Approximately 1000 additional patients with advanced CKD (estimated glomerular filtration rate [eGFR] <30 or on dialysis) with moderate to severe ischemia and who satisfy all other ISCHEMIA trial inclusion and exclusion criteria (other than the eGFR) will be included in the ISCHEMIA-CKD ancillary trial. The primary objective of the trial is to determine whether an invasive (INV) strategy reduces the incidence of the composite of death from any cause or nonfatal myocardial infarction compared with a conservative (CON) strategy of optimal medical therapy alone with cardiac catheterization and revascularization reserved for patients with refractory angina, acute coronary syndrome, acute ischemic heart failure or resuscitated cardiac arrest. The trial is designed to run seamlessly with the main trial but sites can opt out if they choose not to participate. See section 18 for more details. 2. CIAO-ISCHEMIA (Changes in Ischemia and Angina over One year among ISCHEMIA trial screen failures with no obstructive coronary

	artery disease on CT angiography). See appendix B 300 participants recruited from main trial screen failures enrolled using stress echo or CMR and excluded from the main trial due to absence of obstructive CAD on CCTA. Participants undergo symptom assessment and repeat stress imaging at one year.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS

ACC	American College of Cardiology
ACE-I	angiotensin converting enzyme inhibitor
ACS	acute coronary syndrome
AHA	American Heart Association
AST	aspartate aminotransferase
ALT	alanine aminotransferase
BARI 2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes trial
CABG	coronary artery bypass graft
CAD	coronary artery disease
Cath	cardiac catheterization
CCC	Clinical Coordinating Center
CCS	Canadian Cardiovascular Society
CCTA	coronary computed tomography angiography
CEC	clinical event adjudication committee
CI	confidence interval
CKD	Chronic kidney disease (defined as those with estimated glomerular filtration rate [eGFR] <30 or on dialysis)
CK-MB	creatinine kinase-MB
CIAO-ISCHEMIA	Ancillary study. Changes in Ischemia and Angina over One year among ISCHEMIA trial screen failures with no obstructive coronary artery disease on CT angiography.
CL	Core laboratory
CMR	cardiac magnetic resonance
CON	Conservative management strategy (initial management with OMT alone, with cath and revascularization reserved for refractory symptoms or acute ischemic events)

COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial
CV	Cardiovascular
DASI	Duke Activity Status Index
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
Echo	echocardiography
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
ERES	electronic signature
eGFR	estimated glomerular filtration rate
EQ-5D	self-reported generic preference-based measure of health, developed by the EuroQol Group
EQOL	economic and quality of life
EQOLCC	EQOL Coordinating Center
ESC	European Society of Cardiology
ETT	Exercise tolerance testing
EU Directive	European Union Directive on Data Privacy
FFR	fractional flow reserve
HbA1c	hemoglobin A1c
HDL	high density lipoprotein
HF	heart failure
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio

ICC	Ischemia Imaging Coordinating Center
ICH	International Conference on Harmonization
IEC	institutional ethics committee
INV	invasive management strategy (cath with intent to perform optimal revascularization plus optimal medical therapy)
IRB	Institutional Review Board
ISCHEMIA	International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial
IVRS	interactive voice response system
IVUS	intravascular ultrasound
IXRS	interactive web response system
LM CAD	left main coronary artery disease
LOT-R	Life Orientation Test – Revised
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MOE	margin of error
MOO	Manual of Operations
MPI	myocardial perfusion imaging
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NYHA	New York Heart Association
OMT	optimal medical therapy
ORT	optimal revascularization therapy
PACE	Patient-centered Assessment and Counseling for Exercise and nutrition
PCI	percutaneous coronary intervention

PET	positron emission tomography
PHI	protected health information
PHQ-8	Patient Health Questionnaire-8
PI	Principal Investigator
PIPEDA	Personal Information Protection and Electronic Documents Act
PSS	Perceived Stress Scale
REB	Research Ethics Board
RNA	ribonucleic acid
SAC	statistical analysis center
SAQ	Seattle Angina Questionnaire
SDCC	Statistical and Data Coordinating Center
SIHD	stable ischemic heart disease
SPECT	single photon emission computed tomography
WHF	World Heart Federation

2. BACKGROUND AND RATIONALE

Coronary artery disease (CAD) is the leading cause of death and disability worldwide and affects 17.6 million Americans, resulting in about 450,000 deaths in the United States annually.[1] Globally, 7.2 million deaths are caused by CAD each year.[2] An invasive approach to the evaluation and treatment of CAD is common, yet evidence that this approach to management favorably influences long-term clinical outcomes in patients with stable ischemic heart disease (SIHD) is outdated. In randomized clinical trials conducted in the 1970s, surgical revascularization (coronary artery bypass graft [CABG]) improved survival compared to medical therapy in SIHD patients.[3-6] The benefit was most apparent in subsets with high-risk anatomic features. The relevance of these studies to present-day patients with SIHD is unclear for many reasons. Most importantly, effective medical therapy proven in more recent trials to reduce clinical events was used minimally if at all. These therapies include aspirin, beta-blockers, statins, angiotensin-converting-enzyme (ACE) inhibitors, and lifestyle interventions.[7-17] High-dose statins, in particular, are disease and prognosis modifying agents. Moreover, in aggregate, these therapies could be expected to yield ~50% relative reduction in risk of clinical events.[9, 18-20] Thus, the continued relevance of findings from CABG vs. medicine trials conducted in an earlier era is, at best, speculative.

In the contemporary era, revascularization in addition to medical therapy vs. medical therapy alone has been studied in several patient populations. The Surgical Treatment for Ischemic Heart Failure (STICH) trial assessed all-cause mortality for CABG vs. medical therapy alone in a heart failure cohort at high risk of death: those with severe HF, an ejection fraction ≤35%, and coronary artery disease. These patients are excluded from the ISCHEMIA trial. STICH reported no significant difference in all-cause mortality (the primary end point) between the two treatment strategies (P = 0.12); CABG reduced the composite of CV death and hospitalization.[21] In a STICH substudy, myocardial viability did not identify patients with a differential treatment effect from CABG, as compared with medical therapy alone.[22]

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE)[23] and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D)[24] trials demonstrated that in patients with SIHD, predominantly without severe LV dysfunction, a management strategy of revascularization plus optimal medical therapy (OMT) did not reduce the risk of death or MI as compared with OMT alone. Importantly, both of these trials randomized patients after cardiac catheterization (cath). Cath is an invasive diagnostic test that typically triggers a therapeutic cascade involving revascularization.[25] This phenomenon is attributed, in part, to the common attitude among patients and physicians that visualized stenoses need to be “fixed” and that a revascularization procedure will prolong their lives and/or prevent MI, not just relieve angina.[26-28] Consequently, the decision to proceed with revascularization often hinges more on anatomic feasibility than on evidence that revascularization is clinically beneficial.[26, 28] The inherent assumption of this approach is that coronary revascularization of flow-limiting stenoses will prevent or reduce clinical events. This assumption is not warranted, based on the results of modern randomized trials.

FAME 2 was a trial of FFR-guided PCI with medical therapy vs. medical therapy alone in SIHD patients with at least 1 stenosis with FFR ≤0.80. Patients with recent ACS and stabilized class IV angina were included. FAME 2 was halted prematurely after only 54% of planned enrollment due to a statistically significant reduction in the primary endpoint (death, MI, urgent revascularization) in the PCI group at an average follow-up of only 7 months.[29] The difference in the primary endpoint was driven by a reduction in urgent revascularization, with no difference in death or MI between groups.[29] FAME 2 suffers from similar limitations of prior trials by randomizing all patients after cath, when physicians and patients knew anatomic and physiologic findings which could influence the decision to undergo urgent revascularization. If COURAGE and BARI 2D had included revascularization in the primary endpoint they would have had similar findings.

Moderate to severe ischemia has been considered a marker of increased risk for cardiovascular events.[30] It remains unclear whether a greater magnitude of ischemia may increase risk based on inherent adverse effects of ischemia, occlusion of severe stenoses that cause ischemia, or if more severe ischemia is simply a marker of more extensive atherosclerosis and more vulnerable plaques. Vulnerable plaques, which may not themselves be flow-limiting, are more commonly sites of plaque rupture and thrombosis and the cause of MI than severe stenoses.[31-34] However, individual plaques with severe stenoses are more likely to occlude than less severely stenotic plaques.[35] Notably, more recent studies call into question the association between presence and extent of ischemia and outcomes. The COURAGE baseline nuclear substudy found no relationship between the level of ischemia and risk.[36] In the Surgical Treatment for Ischemic Heart Failure (STICH) trial there were no differences in death or cardiovascular hospitalization rate between patients with or without ischemia in a cohort with ejection fraction of 35% or less and coronary artery disease amenable to CABG.[37] Moreover, ischemia was not a predictor of death among asymptomatic patients with previous revascularization and inducible ischemia on myocardial perfusion imaging (MPI).[38]

The power of the diagnostic-therapeutic cascade poses challenges for broad translation of COURAGE and BARI 2D results into practice. In both trials, randomization of all patients only after coronary anatomy had been visualized raises concerns that many patients with the most severe and treatable lesions may not have been enrolled but were instead revascularized preemptively while on the cath table, thus excluding an important high risk group from rigorous, prospective study. Although the finding that prompt revascularization in stable patients did not prevent death or MI suggests that cath may not be necessary in this cohort of patients, this conclusion is not valid due to the protocol design of these two landmark trials. Observational data suggest that early revascularization is associated with a lower likelihood of death and MI in patients with at least moderate ischemia on MPI,[39-41] but this concept has never been fully tested in a prospective, randomized clinical trial. Within a small (n=314) nuclear substudy of patients who had baseline and follow-up stress perfusion scans at 6-18 months in the COURAGE study, there were 105 patients with at least moderate ischemia at baseline, as measured by MPI in a core laboratory. Among these 105 patients, there was a significantly greater reduction in ischemia associated with PCI and OMT than OMT alone on follow-up MPI.[42] For PCI and OMT groups combined, the rate of death or MI over 3.6 years was 16% for those who experienced ischemia reduction compared with 34% for those without significant ischemia

reduction on follow-up MPI. In contrast, a newer, COURAGE analysis of outcomes *by treatment* in 468 patients with *site-determined* moderate or severe ischemia at baseline showed no difference in death or MI between PCI+OMT vs. OMT alone (P = 0.53).[36] The same lack of benefit for PCI was demonstrated in an unpublished analysis of 189 patients with at least moderate ischemia on baseline core lab-measured MPI among whom there was no reduction in death/MI (PCI and OMT vs. OMT 24% vs. 21%, respectivelyHR1.19, 95% CI0.65-2.18). Selection for repeat revascularization was not associated with lower mortality risk among patients with silent ischemia an average of 5 years after initial revascularization in an observational study.[38]

Data from 9 reports representing 5,833 patients suggest that only 35 to 65% of patients with moderate or severe ischemia on MPI are referred for cath, reflecting equipoise in the community.[43-51] It is presently unknown whether use rates for cath and revascularization are appropriate for optimal patient management. The results of COURAGE and BARI 2D are extremely valuable to physicians caring for patients with SIHD. However, a clinical trial to determine optimal management for SIHD patients uniformly at higher risk could not have been performed before the COURAGE and BARI 2D results were available. Moderate or severe ischemia is a marker for increased risk for death, but no well-designed clinical trial of patients with this degree of ischemia with or without definition of the coronary anatomy before randomization has studied whether an invasive strategy of prompt revascularization improves clinical outcomes and quality of life. 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. The results of ISCHEMIA will have profound implications for guidelines, health policy, and clinical practice.

3. STUDY OBJECTIVES

PRIMARY AIM

The primary aim of the ISCHEMIA trial is to determine whether an initial invasive strategy of cardiac catheterization and optimal revascularization, if feasible, in addition to OMT, will reduce the primary composite endpoint of cardiovascular death or nonfatal myocardial infarction in participants with SIHD and at least moderate ischemia over an average follow-up of approximately 4 years compared with an initial conservative strategy of OMT alone with catheterization reserved for failure of OMT.

SECONDARY AIMS

The secondary aims are to compare the following clinical and economic outcomes in participants randomized to INV or CON strategies:

- Angina control, as assessed by the Seattle Angina Questionnaire (SAQ) Angina Frequency scale
- Disease-specific quality of life, as assessed by the SAQ Quality of Life
- Composite of cardiovascular death, nonfatal myocardial infarction, or stroke
- Composite of cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure
- All-cause death
- Cardiovascular death
- Nonfatal MI
- Resuscitated cardiac arrest
- Hospitalization for unstable angina
- Hospitalization for heart failure
- Stroke
- Composite of cardiovascular death, nonfatal myocardial infarction, stroke, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure.
- Health resource utilization, costs, and cost-effectiveness

Please see section 18 for the primary and secondary aims of the ISCHEMIA-CKD ancillary trial.

4. STUDY DESIGN

The ISCHEMIA trial is an international, randomized, comparative effectiveness study. Approximately 8,000 participants at approximately 500 sites worldwide with SIHD and at least moderate ischemia on ischemia testing will be randomized in a 1:1 fashion to the INV or CON strategies in the main trial. In addition, approximately 1,000 participants with advanced CKD (defined as eGFR <30 or on dialysis) and at least moderate ischemia on ischemia testing will be randomized in a 1:1 fashion to the INV or CON strategies in an optional CKD ancillary trial (see section 18). Additionally, other optional ancillary studies will be conducted (see section 19).

4.1 Study Flow

See figure 1 for details. Patients with at least moderate ischemia (see section 1.1) will be identified and screened for clinical inclusion/exclusion criteria (see section 4.3). Patients who are suspected to be trial eligible may also be pre-screened , for example, prior to clinically indicated ischemia testing in clinical areas where SIHD patients are cared for. Patients who meet clinical and ischemia (site-interpreted) eligibility criteria and are interested in participating in the trial will be enrolled by signing an informed consent and receiving a study number via the interactive voice response system (IVRS) or interactive web response system (IXRS) (see section 5.3). Ischemia test data (e.g., images, ECG, report) will be transferred to the relevant core lab electronically for enrolled participants (see Figure 1).

CCTA step: Participants with eGFR ≥60 ml/min will undergo a blinded CCTA unless they had visualization of the coronary arteries by CCTA or invasive angiography within 12 months with a stable subsequent clinical course, or unless CCTA is deemed clinically unnecessary by the site based on an exception as indicated in the MOO and approved by the CCC. Such examples might include variation in eGFR calculation based on local lab policies, or local rules for performance of CCTA which vary from the study protocol. CCTA images will also be transferred electronically to the CCTA core lab for interpretation. Coronary CCTA images will not be interpreted at the sites unless: 1) the participant is excluded due to CCTA findings, including incidental findings. In the event of any of these exclusionary findings, the participant will not be eligible to continue in the study, and these results will be communicated to the site; 2) the participant is excluded from randomization for any other reason; 3) the participant undergoes protocol-assigned or non-protocol assigned catheterization and review of CCTA findings is desirable for planning of revascularization.

Sites may interpret non-coronary CT images locally to evaluate for any non-coronary incidental findings; this review will be encouraged if the core lab identifies an incidental finding on CCTA which does not disqualify the patient, e.g., smaller lung nodules. A list of incidental findings for which the CCTA core lab routinely screens may be found in the MOO.

All participants meeting CCTA eligibility criteria should then be randomized to the INV or CON strategy via the IVRS/IXRS system.

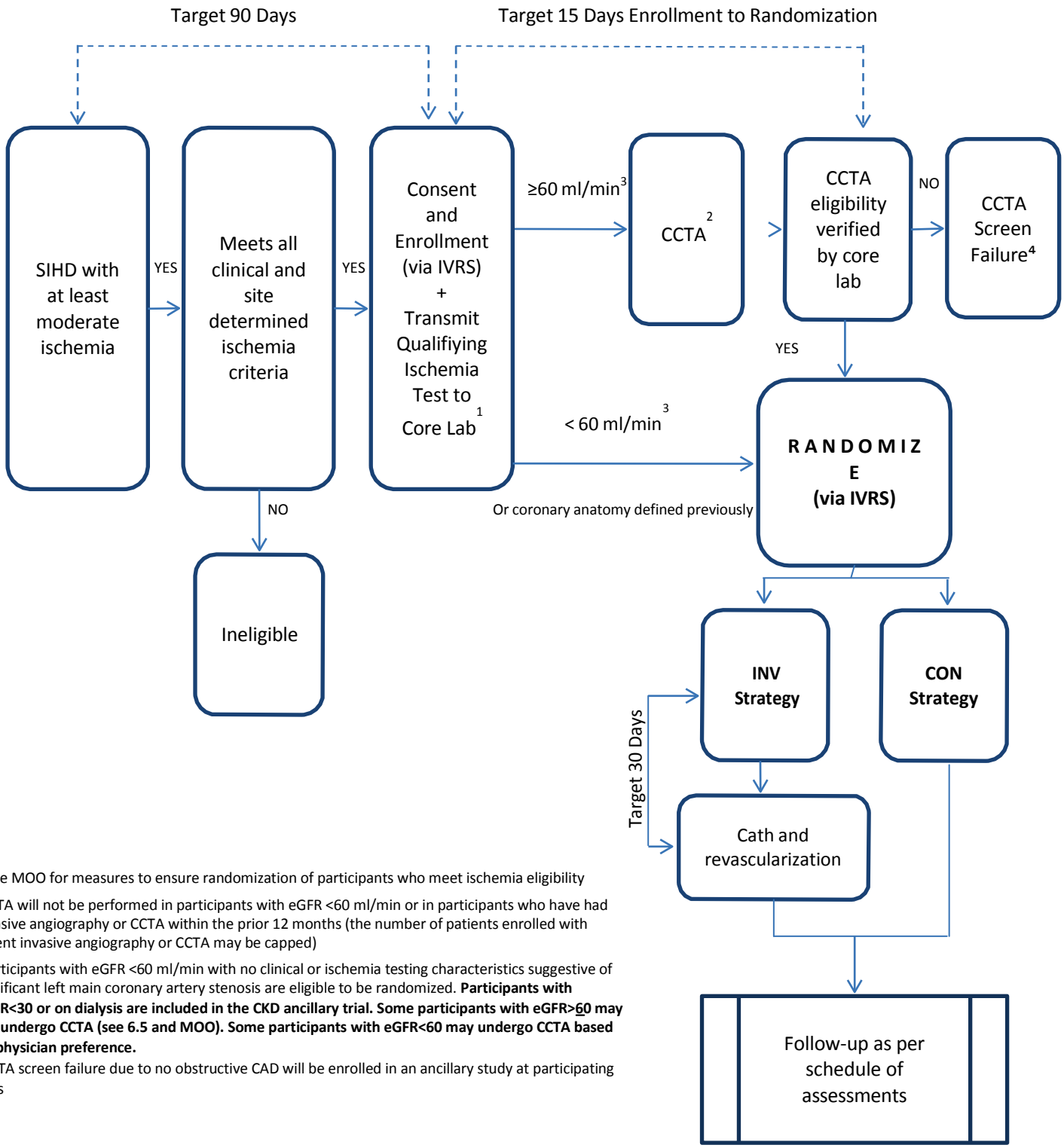
Participants with known or a high likelihood of unprotected left main stenosis ≥50% will be excluded before randomization. The primary method to identify such patients is CCTA.

Participants with eGFR <60 ml/min will not undergo a CCTA due to the increased risk of developing contrast-induced nephropathy, unless the site investigator and participant's personal physician believe the benefits outweigh the risks. Some participants with eGFR ≥ 60 may not undergo CCTA (see section 5.5 and MOO). Local practices vary regarding calculation of eGFR and cut points of eGFR used for performance of CCTA. Participants who do not undergo CCTA who, according to the participant's physician, are unlikely to have significant unprotected left main stenosis, will proceed directly to randomization.

Patients who qualify through exercise tolerance testing (ETT) alone without imaging (e.g. exercise treadmill and bicycle ergometer testing) will be required to be eligible for and to have a CCTA prior to randomization unless they meet a specified exception, e.g., patients who have had CCTA or invasive angiography within 12 months (see MOO for other exceptions).

Timing of Randomization: Participants determined to be eligible for randomization should be randomized within a target of 15 days of consent, and participants randomized to INV strategy should undergo catheterization within a target of 30 days after randomization, with optimal revascularization therapy (ORT) soon thereafter as appropriate. Participants will be enrolled over approximately 4 years. Randomized participants will be followed for an average of approximately 4 years. The minimum follow-up period for randomized participants will be approximately 18-24 months following randomization of the final participant. A schedule of assessments is provided in section 9.

Figure 1 Study Flow



[1] See MOO for measures to ensure randomization of participants who meet ischemia eligibility

[2] CCTA will not be performed in participants with eGFR <60 ml/min or in participants who have had invasive angiography or CCTA within the prior 12 months (the number of patients enrolled with recent invasive angiography or CCTA may be capped)

[3] Participants with eGFR <60 ml/min with no clinical or ischemia testing characteristics suggestive of significant left main coronary artery stenosis are eligible to be randomized. **Participants with eGFR<30 or on dialysis are included in the CKD ancillary trial. Some participants with eGFR>60 may not undergo CCTA (see 6.5 and MOO). Some participants with eGFR<60 may undergo CCTA based on physician preference.**

[4] CCTA screen failure due to no obstructive CAD will be enrolled in an ancillary study at participating sites

4.2 Study Population

Patients with SIHD and at least moderate ischemia. SIHD is synonymous with stable coronary artery disease, and refers to patients with coronary artery disease who are clinically stable (i.e., who are not in an unstable phase such as an acute coronary syndrome).

Enrollment within any subgroup, including by trial site or region, may be capped in order to ensure the trial population's representativeness.

4.3 Inclusion/Exclusion Criteria

Screening for inclusion/exclusion criteria will include assessment for clinical and ischemia criteria at the local site, ability and willingness to provide informed consent and the need for CCTA. Core labs will work with sites to ensure randomization of participants with at least moderate ischemia.

4.3.1 Criteria Prior to Informed Consent

Patients will be screened for the following inclusion and exclusion criteria:

Inclusion (pre informed consent)

1. At least moderate ischemia on qualifying ischemia test (See protocol appendix A)
2. Participant is willing to give informed consent
3. Age ≥ 21 years

Exclusion (pre informed consent)

1. LVEF <35%
2. History of unprotected left main stenosis ≥50% on prior coronary computed tomography angiography (CCTA) or prior cardiac catheterization (if available)
3. Finding of "no obstructive CAD" (<50% stenosis in all major epicardial vessels) on prior CCTA or prior catheterization, performed within 12 months
4. Coronary anatomy unsuitable for either PCI or CABG
5. Unacceptable level of angina despite maximal medical therapy
6. Very dissatisfied with medical management of angina
7. History of noncompliance with medical therapy
8. Acute coronary syndrome within the previous 2 months
9. PCI within the previous 12 months
10. Stroke within the previous 6 months or spontaneous intracranial hemorrhage at any time

11. History of ventricular tachycardia requiring therapy for termination, or symptomatic sustained ventricular tachycardia not due to a transient reversible cause
12. NYHA class III-IV heart failure at entry or hospitalization for exacerbation of chronic heart failure within the previous 6 months
13. Non-ischemic dilated or hypertrophic cardiomyopathy
14. End stage renal disease on dialysis or estimated glomerular filtration rate (eGFR) <30 ml/min (not an exclusion criterion for CKD ancillary trial, see CKD ancillary trial, section 18)
15. Severe valvular disease or valvular disease likely to require surgery or percutaneous valve replacement during the trial
16. Allergy to radiographic contrast that cannot be adequately pre-medicated, or any prior anaphylaxis to radiographic contrast
17. Planned major surgery necessitating interruption of dual antiplatelet therapy (note that patients may be eligible after planned surgery)
18. Life expectancy less than the duration of the trial due to non-cardiovascular comorbidity
19. Pregnancy (known to be pregnant; to be confirmed pre-CCTA and/or randomization, if applicable)
20. Patient who, in the judgment of the patient's physician, is likely to have significant unprotected left main stenosis (Those who are able to undergo CCTA will have visual assessment of the left main coronary artery by the CCTA core lab)
21. Enrolled in a competing trial that involves a non-approved cardiac drug or device
22. Inability to comply with the protocol
23. Exceeds the weight or size limit for CCTA or cardiac catheterization at the site
24. Canadian Cardiovascular Society Class III angina of recent onset, or angina of any class with a rapidly progressive or accelerating pattern
25. Canadian Cardiovascular Society Class IV angina, including unprovoked rest angina
26. High risk of bleeding which would contraindicate the use of dual antiplatelet therapy
27. Cardiac transplant recipient
28. Prior CABG, unless CABG was performed more than 12 months ago and coronary anatomy has been demonstrated to be suitable for PCI or CABG to accomplish complete revascularization of ischemic areas (CCC approval required)

4.3.2 Criteria After Enrollment (Informed Consent) and Prior to Randomization

Participants who provide informed consent and are clinically eligible will be registered via the IVRS/IXRS system. They are considered enrolled and will undergo assessment of ischemia by

the relevant core lab and may undergo a blinded CCTA (if eGFR ≥60 ml/min or as per the MOO). Participants meeting the following exclusion criteria will not be randomized.

Exclusion (after informed consent and before randomization)

1. Pregnant (negative pregnancy test before CCTA required for premenopausal females)
2. Left main stenosis ≥50% (unprotected) on CCTA
3. Finding of "no obstructive coronary artery disease" (<50% stenosis) in all major epicardial vessels on CCTA (participants excluded from randomization for this reason will be considered for CIAO-ISCHEMIA ancillary study; see appendix B)
4. Incidental findings on CCTA of clinical importance (e.g., lung mass suspicious for malignancy; see MOO for details)
5. Interval development of a clinical event e.g., a primary or secondary endpoint event or interval development or discovery of an exclusion criterion

5. STUDY PROCEDURES

5.1 Qualifying Ischemia Test

The criteria for at least moderate ischemia with each test modality and the rationale for their selection are described in protocol appendix A. Ischemia tests documenting eligibility may be performed before or after medical therapy for SIHD has been initiated and adjusted. Similarly, participants already taking medical therapy for SIHD may have been on or off medications on the day of the ischemia test documenting eligibility, consistent with customary clinical practice.[40, 41] A 24-hour, 7-day helpline will be available to sites for assistance with ascertainment of eligibility, enrollment, and adherence to protocol. Sites may send anonymized ischemia tests (images and/or ECG) for core lab verification of trial eligibility before trial enrollment, as permissible by local IRBs/ECs and privacy boards.

5.2 Informed Consent Process

The study will be reviewed with the prospective study participant by the investigator or his/her designee. This discussion is a critical component of the consent process and the prospective study participant will be given adequate time for this discussion and to read the written consent form. Two standard clinical care strategies are being compared in this study and clinicians should enroll patients for whom there is clinical equipoise regarding their management. Prevailing practice patterns vary widely within and between regions; the discussion with prospective participants should note these local patterns. The investigator or his/her designee will be available to answer questions about the study including procedures, risks, and alternatives. The informed consent form will be signed and dated by the patient as per local regulation.

In addition, prospective study participants will be requested to consent to a biorepository sample, and to allow use of the biorepository sample for biomarkers and/or genetic analysis (DNA) in this optional study component conducted at participating sites. Prospective study participants will be informed that declining participation in the biomarker or genetic analysis portion of the study does not preclude their participation in the main study. A copy of the signed consent form will be given to the participant and the original(s) will be kept securely with each participant's research records.

Specific consent will be obtained before any protocol-mandated procedure that requires consent (including CCTA) is performed. The consent will allow for protected health information (PHI) to be transferred to the Clinical Coordinating Center (CCC) and/or the Regional Research Organization that serves as the Coordinating Center in the country/region unless prohibited by regulations. This will make it possible for another site within that country or the CCC to follow participants if a site closes down or cannot continue follow-up for any reason, and to look up vital status. Privacy regulations in all countries will be followed, (e.g., Health Insurance Portability and Accountability Act [HIPAA] in the US; Personal Information Protection and Electronic Documents Act [PIPEDA] in Canada; European Union Directive on Data Privacy [EU Directive]). For North American participants only, PHI will also be sent to the EQOLCC.

5.3 Interactive Voice Response System (IVRS) and Interactive Web Response System (IXRS)

Enrollment and randomization will be accomplished by contact with the IVRS or IXRS. When a participant meeting site-determined clinical and ischemia test criteria has provided informed consent, the study coordinator or investigator at the site will call the IVRS or log on to the IXRS to receive a participant identification number. At this point the participant is registered as *enrolled*.

Several language options will be provided for international sites using IVRS/IXRS. To eliminate any manual transcription errors, IVRS/IXRS will be programmed to electronically transfer the participant data and study identification number to create the participant's case book within the electronic data capture (EDC) system.

In order to randomize the participant, the study coordinator or investigator will call IVRS or log in to IXRS a second time. Subjects meeting all clinical, site, and core lab inclusion/exclusion criteria will then be randomized to either the INV or CON strategy and will be registered as *randomized*. This information will be transmitted to the participant's electronic case book within the EDC system.

Detailed information on enrollment and randomization will be provided in the MOO and in specific IVRS/IXRS materials.

5.4 Core Lab Ischemia Verification

Ischemia test data (e.g., images, ECG, reports) will be transferred electronically to the appropriate core lab for enrolled participants. The core labs will review and interpret the degree of ischemia. Sites will wait for verification of ischemia before CCTA (or, for patients who will not undergo CCTA, before randomization) unless the CCC permits an exception.

5.5 Coronary Computed Tomography Angiography (CCTA)

In general coronary computed tomography angiography (CCTA) will be performed in participants with eGFR ≥60ml/min to identify and exclude participants with significant left main stenosis (defined as ≥50% unprotected stenosis) and participants without obstructive coronary stenoses (with <50% stenosis in all epicardial coronary vessels). Participants with eGFR <60 ml/min will in general not undergo a CCTA due to the risk of developing contrast-induced nephropathy and trial eligibility will be based on physician determination of the likelihood of significant left main stenosis. In this subpopulation, participants can be randomized if the treating physician does not suspect significant unprotected left main stenosis based on the results of the stress test, including the imaging portion, where applicable. However, if a significant left main stenosis is suspected, these participants will not be enrolled into the study. There will be additional exceptions to eGFR-based determination of use of CCTA (see section 4.1 and the MOO). If local calculation of eGFR is different from the IXRS-generated eGFR, the site investigator must follow local practices regarding patient eligibility for CCTA (i.e., site may use local eGFR calculation to decide whether the participant is CCTA eligible or not). Participants qualifying via non-imaging exercise tolerance testing (ETT) will undergo CCTA prior to randomization unless they have a specified exception, e.g., patients who have had CCTA or invasive angiography within 12 months (see MOO for other exceptions).

Radiation reduction techniques will be used. We will suggest standardized patient-specific image acquisition protocols that permit high quality CCTA with low dose radiation. Radiation reduction methods will include ECG dose modulation, weight-based tube voltage, minimization of Z-axis

coverage, limiting the field of view, and automatic exposure control. Importantly, all of these dose reduction techniques are additive, can be programmed into a single default protocol, and are available in all ≥64-detector row CT scanners. The investigative group has evaluated the efficacy of combined dose reduction techniques and found a >90% reduction in biological radiation dose (1-2 mSv) without compromise of image quality or diagnostic accuracy.[52-56] Each site will be provided with a concise, easy-to-read manual and an instructional video, prepared for this trial, on how to obtain high quality CCTA images with low radiation dose. For newer scanners, we will employ further dose reduction algorithms including prospective ECG triggering, minimization of padding, and iterative reconstruction techniques.

The CCTA core laboratory will interpret the images and sites will be notified if the participant is or is not eligible because of significant unprotected left main coronary artery stenosis, absence of obstructive stenosis or incidental findings. Further definition of the anatomy will not be disclosed to the participant, treating physicians, or the site except as in section 4.1. The interpretation of the CT, including coronary anatomy, will be made available to the treating physicians for participants excluded based on CCTA findings (see section 4.1 and MOO for details). In addition, there may be findings on CT of potential clinical significance that will not exclude patients from the study, such as lung nodules. The interpretation of these trial-specified incidental findings by the core lab will be made available to the treating physicians who are expected to request local clinical review and reporting of the incidental findings and to remain blinded to coronary findings (see MOO).

If a trial-consented participant is not randomized after CCTA, despite being confirmed eligible by the CCTA core laboratory, maintenance of investigator blinding will be investigated.

Participants meeting the clinical, ischemia, and CCTA eligibility (or physician judgment for participants who will not undergo CCTA) will be randomized to the INV or CON strategy via the IVRS/IXRS system. The targeted time to randomize a participant after consent is obtained is 15 days (see Figure 1).

6. MANAGEMENT STRATEGIES

Table 1. Components of CON and INV management strategies

CON (Section 6.1)	**INV** (Section 6.2)
• Optimal medical therapy (OMT; includes angina management) (Section 6.3) • Provisional cardiac catheterization (Section 6.6)	• Optimal medical therapy (OMT; includes angina management) (Section 6.3) • Cardiac catheterization • Optimal revascularization therapy (ORT) (Section 6.4)

6.1 Conservative (CON) Strategy

In participants randomized to the CON strategy, initial management with **OMT alone will be employed** (described below). A fundamental principle of the CON strategy is to restrict cath to participants who fail OMT, i.e., those who experience an acute coronary syndrome, acute ischemic heart failure or resuscitated cardiac arrest or who have angina that is refractory to maximal medical therapy. In such participants who require cath during follow-up, revascularization should be performed using the principles of optimal revascularization therapy as outlined below.

6.2 Invasive (INV) Strategy

In participants randomized to INV strategy, **initial management with cath will be performed, with subsequent revascularization**, as appropriate, based upon coronary anatomy and other clinical considerations. The principles of optimal revascularization therapy will be followed (described below). In addition, **all INV participants will receive OMT as outlined below.**

6.3 Optimal Medical Therapy (OMT)

OMT will consist of intensive, comprehensive secondary prevention with lifestyle and pharmacologic intervention applied equally to both treatment groups using individualized treatment regimens based on treat-to-target algorithms under supervision by the site PI and in conjunction with the participant's primary care physician and/or cardiologist. The research team in collaboration with the participant's treating physicians will implement changes in medical therapy in keeping with guideline recommendations. The research team will obtain results of routine laboratory tests that reflect secondary prevention targets performed by the participant's physician and provide the results of any tests obtained by the study to the participant's physician. Behavioral interventions will focus on smoking cessation, nutrition, physical activity, weight control, and medication adherence. Pharmacologic interventions will include anti-atherothrombotic and anti-ischemic medications. The

minimum goals of OMT will be those recommended for SIHD patients by national/international organizations (e.g., the National Cholesterol Education Program, American College of Cardiology, American Heart Association, European Society of Cardiology, and World Health Organization). Details of this strategy are provided in the MOO and will be updated, as needed, over the course of the trial.

6.3.1 Management of Angina in CON Participants

Medical management of angina in CON participants will be intensified according to the ISCHEMIA angina treatment algorithm (see MOO). The goal for all CON participants is to control angina such that participants report a good angina-related quality of life. If the level of angina is unacceptable to the participant despite maximal medical therapy, then cath and possible revascularization is recommended, consistent with good medical care.

6.3.2 Management of Angina in INV Participants

Participants randomized to the INV strategy who experience angina following revascularization may be treated medically, as per the ISCHEMIA angina treatment algorithm (see MOO). The goal for all INV participants is to control angina such that participants report a good angina-related quality of life. Unlike the approach to CON participants with angina, repeat cath and revascularization may be performed without first maximizing medical therapy in INV participants.

6.4 Optimal Revascularization Therapy (ORT)

Optimal revascularization therapy will be performed based on findings from the diagnostic catheterization and relevant clinical information. While the selection of PCI vs. CABG (or medical therapy only in cases of normal coronary arteries, diffuse small vessel disease, etc.) will be left to the discretion of the treating team per local standards and expertise, several general principles should be followed:

- The revascularization modality selected should have the highest likelihood to safely and effectively relieve significant ischemia in all viable myocardial territories of at least moderate size.
- Decisions regarding viability testing and revascularization decisions based on such testing should be based on routine clinical practice.
- Revascularization should be performed with a goal of relieving all areas of significant ischemia, i.e., ischemia that would be detected by non-invasive imaging or FFR.
- Prior to selection of the revascularization modality, ischemic territories should be identified based on the results of noninvasive tests, angiography and, in selected cases, FFR (as outlined in the MOO).

Details of ORT are provided in the MOO and will be updated, as needed, over the course of the trial.

6.4.1 Criteria to Select PCI vs. CABG

In general, the decision between PCI and CABG will be determined according to local hospital standards and practices. Guidelines from professional societies and appropriateness criteria should be incorporated into the decision process. It is desirable for the study Heart Team (interventional cardiologist and cardiac surgeon) to discuss each case after diagnostic angiogram to reach a consensus as to the best revascularization technique.

It is recognized, however, that in some cases of non-complex coronary artery disease the performance of “ad hoc” PCI after diagnostic angiography may be preferred by participants and physicians. Whenever possible, the Heart Team should record an opinion on each participant regarding the best mode of revascularization, reaching consensus where possible and recording disagreement if not possible.

Details are provided in the MOO.

6.4.2 Guidelines for Optimal Percutaneous Coronary Intervention

PCI should be performed in a manner considered optimal by contemporary standards and guidelines. Procedural strategy, device selection, adjunctive medical therapy, pre-procedural preparation, post-procedural care and supportive services, and clinical site and operator experience are each areas where optimal performance is required. Details of this are provided in the MOO and will be updated as needed over the course of the trial.

6.4.3 Guidelines for Optimal Surgical Revascularization

The term optimal CABG is reserved for a comprehensive approach towards surgical revascularization that minimizes periprocedural risk and optimizes short- and long-term outcomes with regard to the progressive nature of atherosclerotic heart disease. This goes well beyond the intraoperative technical aspects of surgical revascularization.

The principles for optimal CABG include:

- Accurate assessment and evaluation of potential CABG participants
- Complete revascularization (anatomic and physiologic criteria)
- Optimize intraoperative management, including myocardial protection
- Minimize associated organ and system injury
- Maximize opportunity for long-term graft patency
- Optimize secondary prevention of atherosclerotic heart disease following CABG

Details of this are provided in the MOO.

6.5 Maximizing Adherence to CON Strategy

Adherence to the CON strategy means that all CON participants receive OMT and that none undergo cath or revascularization after randomization unless they 1) have an acute coronary syndrome, resuscitated cardiac arrest, or acute ischemic heart failure or 2) have unacceptable angina refractory to maximal medical therapy (see MOO for definition and recommended

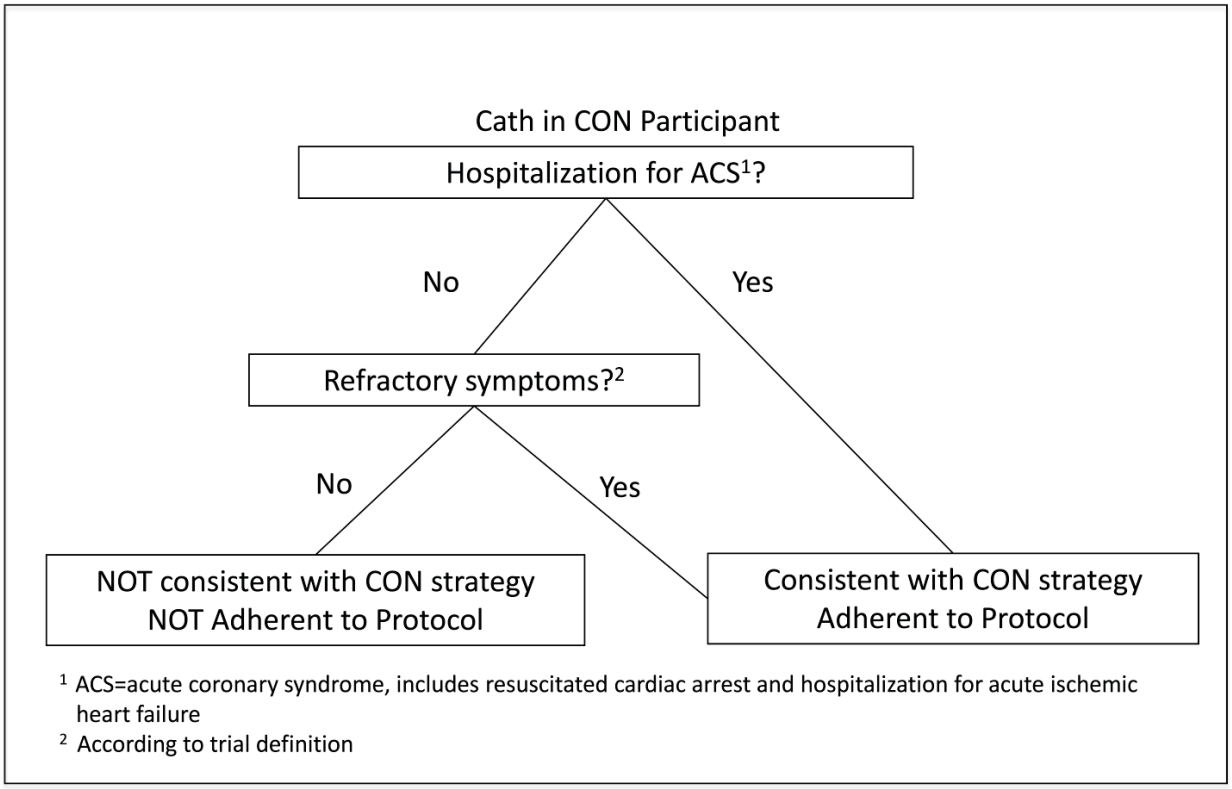
management of refractory angina). Cath performed for any other reason, including changing physician or participant preferences, is not adherent to the CON strategy and is considered a protocol violation. All protocol violations will be reported according to the guidelines provided in the MOO and may require notification of the local IRB as required by local regulations.

Investigators are discouraged from performing stress tests for the purpose of monitoring participants who are clinically stable. Guidelines for avoidance of crossover in participants with worsening symptoms in the absence of ACS may be found in the MOO. In brief, if angina worsens, medical therapy will be intensified. If symptoms are refractory to maximum medical therapy, or become unstable, participants should undergo cath. Site investigators must provide documentation, including current intensity of medical therapy, heart rate, blood pressure, and a repeat SAQ to document the appropriateness of cath. Sites are instructed to call the 24-hour helpline when elective cath is being considered, and they must complete a checklist.

6.6 Cath in Participants Randomized to CON Strategy

Cath and/or revascularization for an acute coronary syndrome, resuscitated cardiac arrest, or acute ischemic heart failure is consistent with the CON strategy. Similarly, cath for refractory symptoms (according to the trial definition) is also consistent with CON strategy. Figure 2 describes cath in participants randomized to CON and the definitions of protocol adherence and non-adherence as it relates to this. Once the decision has been made that the performance of cath in a CON participant is consistent with the CON strategy, the same principles described for optimal revascularization (6.4) apply.

Figure 2 Cath in Participants Randomized to CON Strategy



[1] ACS=acute coronary syndrome, includes resuscitated cardiac arrest and hospitalization for acute ischemic heart failure

[2] According to trial definition

7. AUXILLIARY SCREENING LOG AND SURVEY

7.1 Screening Log

During the study enrollment period, sites will maintain a de-identified, written screening log of patients with site-determined moderate or severe ischemia who have undergone testing at the site's designated primary laboratory. Patient characteristics (age [recorded for patients <90 years of age, recorded as 90 if ≥90 years of age], sex, and, if excluded, reason(s) for exclusion will be recorded) and intended management strategy for patients who are eligible but not enrolled, if known.

The screening log will be sent to the CCC on a regular basis, where it will help identify the major reasons why patients are not enrolled, thus allowing CCC staff to develop corrective action plans for sites that are not meeting target enrollment. Depending on the site's enrollment rate over time, the CCC may decide that a given site no longer needs to submit its screening log, although the site should continue to maintain the log through the end of enrollment. In the event of poor enrollment, sites may be asked to provide comparable information about patients referred to cath without prior ischemia testing.

7.2 Screening Survey

For brief designated periods, sites will collect de-identified data on all patients with at least moderate ischemia who are screened but not enrolled by the study team. The goal of this effort will be to describe the characteristics of patients who are screened but not enrolled and to document the major reasons for exclusion. This screening survey will include the site's primary laboratory and any other screening and referral sources. Data will be entered via a web-based EDC system which will not include patient identifiers and will be separate from the main trial EDC system. For analysis, we will compare baseline characteristics and treatment plan of patients who were screened and met inclusion criteria but were not randomized with those who were randomized. This information will provide insight into any potential bias in trial enrollment. Examples of data elements to be collected, when available, include:

- Age (excluding any age ≥90)
- Sex
- Race/ethnicity
- LVEF
- Results of the ischemia test (ischemia severity and location, where applicable)
- Basic medical history from ischemia test report (if available)
- Presence or absence of LM stenosis ≥50% on previous CCTA or cardiac catheterization
- History of ACS within the last 2 months
- History of PCI or CABG within the last 12 months
- History of stroke within the last 6 months or intracranial hemorrhage at any time
- End stage renal disease or eGFR 15-29 mL/min

- History of NYHA III/IV heart failure or admission to hospital in the last 6 months
- Planned non cardiac surgery within the next 12 months
- Severity of angina symptoms
- Current anti-angina medications
- Willingness to take medications
- Plan for treatment (e.g., cardiac catheterization, mode of revascularization if applicable)
- Actual treatment received (e.g., cardiac catheterization, mode of revascularization if applicable)
- Reason for not participating in the trial

Only de-identified health information will be recorded. An informed consent waiver will be obtained where applicable. There will be no follow-up of these screening survey patients.

8. Study Assessments

8.1 Creatinine and Pregnancy Test

At the screening visit a serum creatinine test must be drawn if one is not available within the previous 90 days. In addition, a pregnancy test is required if the participant is pre-menopausal.

8.2 Standard Blood Tests

In this population with established coronary disease, as part of standard practice the following tests will typically be obtained by the participant's treating physician: complete blood count, electrolytes, creatinine, glucose, liver transaminases, lipid profile, and HbA1c. If HbA1c results are available for nondiabetics they will be recorded. If these test results are not available within specified time windows around the randomization visit (see MOO), then the following should be obtained: complete blood count, lipid profile, and HbA1c (for diabetics only). Liver transaminases should only be obtained if not available before starting statin therapy. An attempt will be made to coordinate participant follow-up visits so that they occur close in time to routine follow-up visits with their physicians when routine blood tests are performed. At 6 month follow-up visits, if lipid tests (and HbA1c at annual visits for diabetics) are not available within specified time windows they will be obtained by the study coordinator or participants will be referred to their treating physicians for the tests. Creatinine values obtained clinically for participants with eGFR <60 at the three month follow-up visit and annually will also be recorded.

8.3 Endpoint Assessments

At every visit after randomization, the study coordinator will ask participants if they have had any symptoms or a report from a healthcare provider consistent with an endpoint event since the last study visit. See MOO for detailed instructions on collection of source documents.

8.4 Blood Biomarkers and Genomics Biorepository

Randomized participants will be invited to participate in the biorepository protocol, unless precluded by local regulations. Participants who give informed consent will be asked to allow storage of samples of their blood in two biorepository protocols, one for biomarkers and one for genetic analysis. Participants who decline participation in one or both of the biorepository protocols are still eligible to participate in the main trial. The biorepositories will serve as resources for future analyses. Although no specific scientific proposals are put forth in the present protocol, we anticipate a wealth of opportunities for ancillary studies and sharing of resources with other investigators. Participants will be asked to separately consent for use of their blood samples for the biomarker biorepository and the genetic (DNA) biorepository. If a site is unable to process blood samples they may still participate in the genetic biorepository; in this case saliva samples may be collected from participants.

Blood will be drawn for the biorepository at the time of randomization, and may be drawn after 3 months of follow-up. At the time of randomization, up to a maximum of 49 mL of whole blood will be collected, which will be processed and stored as serum, plasma, RNA and, where allowable,

DNA. At the 3 month follow-up visit, up to 49 mL of blood may be drawn. (If needed, specimen collection for genetic analysis may be collected at any point during the trial.)

Measures will be taken to protect the identity of the blood sample donor by de-identifying the biospecimen samples at the enrollment site. The link between the participant's name and the numeric code will not be available to staff managing samples at the biorepository, or any investigative personnel requesting samples. Strict confidentiality and maintenance of the chain of custody will be observed in the collection and storage of biospecimens. Complete details of the biorepository protocol are provided in the MOO.

8.5 Medication Adherence

To assess medication adherence, a 4-item modified Morisky adherence survey (Likert scale responses to 4 questions)[57-60] will be completed at the randomization visit, 6 month visit, and all subsequent visits.

8.6 Lifestyle Assessment

To assess each participant's readiness to change health-related behaviors, study coordinators will use questionnaires developed by the Patient-centered Assessment and Counseling for Exercise and nutrition (PACE) program. Responses to these brief surveys will be used to tailor counseling for lifestyle change. These assessments will occur at randomization, 3 months, 12 months, annually, and at the closeout visit.

8.7 Quality of Life Assessment

To quantify the full spectrum of patient-reported quality of life outcomes in ISCHEMIA, a battery of validated instruments will be used. Angina-related quality of life will be measured by the Seattle Angina Questionnaire (SAQ); dyspnea symptoms from the Rose Dyspnea scale; physical function by the disease-specific Duke Activity Status Index (DASI) and angina-specific SAQ physical limitations sub-scale; a Rand general health rating; psychological well-being and depression screening symptoms by the Perceived Stress Scale (PSS) and Patient Health Questionnaire-8 (PHQ-8); a measure of optimism about the future from the Life Orientation Test-Revised (LOT-R); the EQ-5D as a measure of overall, generic health status; and demographic items (e.g., marital status, education, perceived income). We will use these data to analyze the health status of participants in both groups over time to quantify both the magnitude and trajectory of health status recovery as a function of randomized management strategy.

8.8 Economics Assessment

As a measure of medical utilization, resource utilization data, including hospitalizations, emergency department visits, and selected cardiac procedures and tests will be collected by the Site Coordinators at each ISCHEMIA study visit or contact and entered into the main study EDC database. These data, in conjunction with billing data (collected for the US study participants only by the EQOLCC economic team and entered into a database separate from the main EDC study database), will be used to estimate and compare medical care costs from the perspective of the US healthcare system for both management strategy groups. They will also be used, along with the

clinical endpoints and quality of life data, to calculate the net incremental cost and quality-adjusted life expectancy associated with the invasive strategy and the resulting within-trial incremental cost-effectiveness ratio. Details are provided in the MOO.

9. SCHEDULE OF ASSESSMENTS

Overview of Visits

All participants will undergo eligibility screening, informed consent and randomization procedures. Participants will undergo CCTA according to criteria in section 5.5 and the MOO.

Follow-up in randomized participants will occur at 1.5, 3, 6, and 12 months following randomization during the first year and every 6 months thereafter, with clinic visits, phone follow-up, and other testing as described below (See Table 2 for complete assessment schedule). The schedule of assessments (Table 2) specifies the preferred method of contact for each visit. Six-month visits may be via telephone or email, depending on participant stability, risk factor control, and the participant's distance from the clinic ("geography") (see Table 2). In the event that a scheduled clinic visit is not possible, to ensure participant follow-up other forms of contact should be used, such as telephone, email, communication from a personal physician, other allied health professional, or family member, or review of electronic health record or public records. After the first year, participants will be followed every 6 months until the end of the trial, at which time sites will be notified to perform a closeout visit.

Dependent on additional funding, telephone or email follow-up every 6 months or ascertainment of database information on vital status may continue after all clinic visits have been completed, unless prohibited by local regulations. At these long-term follow-up contacts, information on current health and medications, and interval hospitalizations will be collected.

Dependent on additional funding, telephone, in-person and/or email follow up may occur for participants who are enrolled and subsequently excluded from randomization due to CCTA findings of no obstructive or LM CAD. It may include up to 5 visits over the first 18 months and up to 2 visits per year thereafter until the study ends. All participants, including those excluded based on CCTA or ischemia test findings will be asked to provide consent for future contact for research purposes.

Withdrawal from the Study: Complete and accurate follow-up is extremely important for the duration of the study**.** The participant, however, may decline to continue with their assigned management strategy at any time. This does not constitute withdrawal from the study. Participants will continue to be followed per the assessment schedule. If at any time the subject refuses to continue with study visits, every attempt will be made to continue contact by telephone, written communication, email, by proxy contact with family, friends, or allied health care providers, or record review to determine if outcome events have occurred, unless the subject specifically refuses such follow-up. National databases that record deaths will be used to ascertain vital status, unless prohibited by local regulations. The reason for (and the level of) withdrawal will be documented for all subjects withdrawn from the study or for those having limited follow-up. The subject must specify in writing what follow-up (s)he will allow, if any, at the time of withdrawal discussion.

Quality of Life (QOL) and Economics Overview

Collection of economic and QOL data, including the follow-up Full QOL Questionnaire validated scales will be repeated at 3, 12, 24 and 36 months from randomization and at the final ISCHEMIA visit by trained telephone interviewer staff from the EQOL Coordinating Center (EQOLCC) for participants enrolled in North America and by the site coordinator in sites outside North America. A Proxy QOL questionnaire obtained from a relative, caretaker, or medical record will be used when a participant has died in the follow-up interval, is too ill, otherwise incapacitated, or unable to participate. Lastly, a brief set of items capturing selected interval angina and dyspnea symptoms QOL (Brief/Symptom/QOL) will be collected by the site coordinator and entered into the EDC study database at every study visit through 36 months and then each 6 months until the final closeout ISCHEMIA visit. For the ISCHEMIA-CKD ancillary trial, only the Brief/Symptom/QOL questionnaire is required, the Full QOL questionnaire will not be collected. All symptom and QOL data will be data processed and analyzed by the EQOLCC quality of life team. A Hospitalization assessment as part of the main study EDC database will be collected on all randomized ISCHEMIA participants at each follow-up study interval throughout the trial to provide a measure of resource utilization.

Additionally, as part of the economic data in ISCHEMIA, medical bills for participants enrolled at US sites only will be collected throughout the trial by the EQOLCC economic team from this Hospitalization assessment. The medical billing data will be obtained, extracted, data processed and analyzed by the EQOLCC (not applicable to the ISCHEMIA-CKD ancillary trial).

Collection of economic and QOL data may be capped within any subgroup or overall if needed based on achieved power and operational needs.

Table 2 Schedule of Study Assessments and Procedures (see Manual of Operations for visit windows)

	Screening visit	CCTA visit	Randomization visit (Baseline Visit)	Catheterization & PCI or CABG	Follow up								
					1.5m[A] Visit 1	3m[A] Visit 2	6m[B] Visit 3	12m[A] Visit 4	18m[B] Visit 5	24m Visit 6	30m[B] Visit 7	36m[C] Visit 8	Frequency beyond 36 months
Eligibility screen	X												
Informed consent (including biorepository consent if applicable)	X												
Creatinine and pregnancy test[D]	X												
Medical History/Medical Status	X		X		X	X	X	X	X	X	X	X	Q6m
Cardiovascular medications	X		X		X	X	X	X	X	X	X	X	Q6m
Transmit Stress Test to Core Lab[E]	X												
NYHA* and CCS class**	X		X		X	X	X	X	X	X	X	X	Q6m
Release for medical records signed			X					X		X		X	Q12m
Coronary CT Angiography (CCTA)		X[F]											
Safety assessment[G]		X		X									
Vital signs, weight, height[H]			X		X	X	X	X	X	X	X	X	Q12m
Standard lab results[I]			X[J]			X	X	X	X	X	X	X	Q12m
Biorepository blood draw			X			X[K]							
Cardiac biomarkers[L]				X									
Electrocardiogram (ECG)[M]			X	X[N]				X		X			@ closeout
Lifestyle Assessment (PACE)***			X			X		X		X		X	Q12m
Lifestyle Counseling (PACE)***			X		X	X	X	X	X	X	X	X	Q6m
Modified Morisky Medication Adherence Survey			X				X	X	X	X	X	X	Q6m
Full Quality of Life (QOL) assessment[O]			X			X		X		X		X	@ closeout
Brief symptoms/QOL assessment[P]			X		X	X	X	X	X	X	X	X	Q6m
Initiate Optimal Medical Therapy (OMT)			X										
Medical Therapy Evaluation and Optimization[Q]					X	X	X	X	X	X	X	X	Q6m
Schedule catheterization for INV participants[R]			X										
Hospitalization assessment					X	X	X	X	X	X	X	X	Q6m
Endpoint assessment				X	X	X	X	X	X	X	X	X	Q6m

Follow-up visits will be scheduled based on time since the date of randomization (baseline).

*****NYHA- New York Heart Association **CCS- Canadian Cardiovascular Society ***PACE-** Patient-centered Assessment and Counseling for Exercise and nutrition (PACE) assessment and counseling

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[A] 1.5, 3, and 12 month visits should be in clinic visits, depending on participant stability, risk factor control, and geography.

[B] 6, 18, and 30 month visits may be via telephone, email, or in clinic depending on participant stability, risk factor control, and geography.

[C] Following the 36 month visit, follow-up visits should be in clinic visits at least every 12 months. Clinic visits can be replaced by email or phone depending on participant stability, risk factor control, and geography.

[D] Creatinine if not done within 90 days and pregnancy test if premenopausal.

[E] Send ischemia test images (immediately following enrollment and before randomization), technical worksheets, and site interpretations/local reports from qualifying ischemia tests to core labs.

[F] CCTA not performed if estimated glomerular filtration rate < 60ml/min (unless requested by the treating physician) and not performed in other selected participants (see sections 4.1 and 5.5 and MOO); Blinded CCTA images and technical worksheets will be transferred to CCTA core lab for interpretation.

[G] Safety Assessment (refer to section 13.4).

[H] Height is only needed at randomization, assessments only required if visit is completed in clinic.

[I] Required labs include: lipids (preferably fasting) at 3 month visit then semiannually only, and HbA1c (at visit 4, 6, 8 and annually thereafter for diabetic participants. These lab results will be requested from the participant's physician. If these results are not available they should be obtained by either the participant's treating physician or study staff. Creatinine values obtained clinically for participants with eGFR <60 at the three month follow-up visit and annually will also be recorded.

[J] Additional lab required at randomization includes complete blood count Request from participant's physician, since it is expected that routine blood work will have been done within the last 6 months

[K] May be requested.

[L] For participants undergoing PCI: troponin and CK-MB pre-procedure and at 8-16 ± 2 hours post-PCI or at hospital discharge, whichever comes earlier. For participants undergoing CABG: troponin and CK-MB pre-procedure and at 18 ± 6 hours post-CABG. All biomarker measurements should be recorded on eCRF. A biomarker measurement should be obtained before and after all PCI and CABG procedures, whenever possible.

[M] Send to ECG core lab; ECG required for all cardiac admissions and revascularizations; year 1 ECG optional (filed on site) and closeout.

[N] ECG done following procedure (60±30 mins post-PCI, 3 days post-CABG).

[O] Seattle Angina Questionnaire/Duke Activity Status Index/Rand general health status item/Perceived Stress Scale/Patient Health Questionnaire/Life Orientation Test – Revised/EQ-5D/Demographic characteristics. Not required for the ISCHEMIA CKD ancillary trial.

[P] Selected Seattle Angina Questionnaire/Rose dyspnea scale/EQ-5D.

[Q] At every follow-up visit the research team, in collaboration with the treating physician(s), will evaluate effectiveness of medical therapy and optimize as needed according to guideline recommendations and study algorithms.

[R] Planned cath and revascularization only in the INV group. See MOO for time windows for performing cath and revascularization after randomization. Catheterization and optimal revascularization treatment should be targeted within 30 days after randomization in the Invasive strategy group. In the Conservative group, catheterization and optimal revascularization is reserved for participants with refractory angina symptoms or acute ischemic events.

Screening visit

- Patients with at least moderate ischemia (see protocol appendix A) will be assessed as potential study candidates
- General medical and cardiac history will be reviewed for eligibility according to the inclusion/exclusion criteria in section 4.3
- Willingness of both the prospective participant and their physician for participation throughout the study will be confirmed
- All screened prospective participants will be recorded in the paper screening log
- Prospective participants meeting clinical and site-based ischemia inclusion and exclusion criteria and interested in participating in the study will be consented for the study
- Consented participants will receive a study ID number via IVRS/IXRS. These participants are considered "enrolled" (not randomized).
- Creatinine testing if it has not been done within the last 90 days
- Pregnancy test if premenopausal
- For enrolled participants ischemia tests will be transferred electronically to the appropriate core laboratory. (see section 5.4)

CCTA visit

- For participants with eGFR ≥60ml/min and selected participants with lower eGFR, blinded CCTA will be performed (exceptions apply, see sections 4.1 and 5.5 and MOO)
- Blinded CCTA images will be transferred to CCTA core lab for interpretation
- Participants with eGFR <60 ml/min do not require CCTA before randomization (exceptions apply, see sections 4.1 and 5.5 and MOO)
- Assessment for safety (e.g., complications of CCTA)
- Participants excluded due to no obstructive CAD on CCTA will be considered for CIAO-ISCHEMIA ancillary study at participating sites (see appendix B)

Randomization visit (Baseline Visit) (targeted within 15 days of participant's consent)

- Confirm ischemia and CCTA eligibility
- Medical history including CV medications will be documented

- NYHA and CCS class (see MOO)
- Brief symptoms/QOL assessment will be collected (prior to actual randomization)
- Full QOL assessment will be collected (prior to actual randomization)(not applicable to the ISCHEMIA-CKD ancillary trial)
- Modified Morisky medication adherence survey (see MOO)
- Vital signs, height and weight will be measured
- 12 lead ECG will be performed and sent to ECG core lab; stress ECG, and symptom, and hemodynamic results will be sent to ECG core lab
- Results of routine laboratory tests performed within 6 months of visit will be recorded, including HbA1c for diabetic participants. If these test results are not available a blood draw for routine laboratory tests will be done at this visit (see MOO)
- Baseline blood draw for biomarker/genetics biorepositories
- Eligible participants will be randomized to INV or CON strategies via the IVRS/IXRS system. (These participants are considered randomized)
- Participants randomized to INV strategy should target to undergo catheterization, with optimal revascularization to be completed within a target of 30 days from randomization
- PACE will be implemented for all participants
- Initiate OMT in all randomized participants according to guideline recommendations and study algorithms

Cath and Revascularization for participants randomized to INV strategy (protocol assigned); also applies to all revascularization procedures for participants in both management strategies

- For protocol assigned cardiac cath and revascularization (INV strategy participants), target completion within 30 days of randomization
- Revascularization to be performed as per Optimal Revascularization Therapy (ORT) (refer to MOO)
- For participants undergoing PCI
  - 12 lead ECG to be performed post-PCI at 60 ± 30 minutes, and as needed for chest pain
  - Blood draw for both CK-MB and troponin before PCI, and at 8-16 ± 2 hours post-PCI or at hospital discharge, whichever comes earlier, whenever possible
  - All pre- and post-procedure biomarker measurements that are obtained should be recorded on eCRF

- For participants undergoing CABG
  - 12 lead ECG to be performed on day 3 post-CABG or at hospital discharge whichever comes earlier, and as needed for chest pain
  - All pre- and post-procedure operative biomarker measurements that are obtained should be recorded on eCRF

1.5 month (6 week) visit (Visit 1)

- Medical status assessment
- NYHA and CCS class (see MOO)
- Vital signs and weight will be measured
- Lifestyle counseling as per PACE will be performed
- Brief symptoms/QOL assessment will be collected
- Hospitalization assessment will be collected
- Endpoints will be assessed
- The study team, in collaboration with the treating physician(s), will evaluate effectiveness of medical therapy and optimize as needed according to guideline recommendations and study algorithms

3 month visit (Visit 2)

- Medical status assessment
- NYHA and CCS class (see MOO)
- Vital signs and weight will be measured
- Lifestyle assessment and counseling as per PACE will be performed
- Brief symptoms/QOL assessment will be collected
- Full QOL assessment will be collected (not applicable to the ISCHEMIA-CKD ancillary trial)
- Hospitalization assessment will be collected
- Biorepository blood draw may be performed if additional funding is obtained
- Endpoints will be assessed

- Obtain lab results from participant's treating physician for lipids (preferably fasting). If not available these tests should be obtained by the participant's treating physician or the study staff. Creatinine values obtained clinically for participants with eGFR <60 will be recorded.
- The study team, in collaboration with the treating physician(s), will evaluate effectiveness of medical therapy and optimize as needed according to guideline recommendations and study algorithms

6/18/30 month visits (Visits 3, 5, 7 respectively)

- Medical status assessment
- NYHA and CCS class (see MOO)
- Vital signs and weight will be measured (only if clinic visit)
- Modified Morisky medication adherence survey (see MOO)
- Lifestyle counseling as per PACE will be performed
- Brief symptoms/QOL assessment will be collected
- Hospitalization assessment will be collected
- Endpoints will be assessed
- Obtain lab results from participant's treating physician for lipids (preferably fasting). If not available lipid tests should be obtained by the participant's treating physician or the study staff.
- The study team, in collaboration with the treating physician(s), will evaluate effectiveness of medical therapy and optimize as needed according to guideline recommendations and study algorithms

12/24/36 month visits (Visits 4, 6, 8 respectively)

- Medical status assessment
- NYHA and CCS class (see MOO)
- Vital signs and weight will be measured
- 12 lead ECG will be performed and submitted to core lab only at 24 month visit. Optional ECG to be retained at site at 12 months
- Modified Morisky medication adherence survey (see MOO)

- Lifestyle assessment and counseling as per PACE will be performed
- Brief symptoms/QOL assessment will be collected
- Full QOL assessment will be collected (until 36 months) (not applicable to the ISCHEMIA-CKD ancillary trial)
- Hospitalization assessment will be collected
- Endpoints will be assessed
- Obtain lab results from participant's treating physician for lipids (preferably fasting) and HbA1c for diabetic participants. If not available lipid tests should be obtained by the participant's treating physician or the study staff. Creatinine values obtained clinically for participants with eGFR <60 will also be recorded.
- The study team, in collaboration with the treating physician(s), will evaluate effectiveness of medical therapy and optimize as needed according to guideline recommendations and study algorithms

Continuing Follow-Up Visits (every 6 months following the 36 month visit until close out)

- Medical status assessment
- NYHA and CCS class (see MOO)
- Vital signs, and weight (only at every 12 month clinic visit)
- Modified Morisky medication adherence survey
- Lifestyle assessment as per PACE (only at every 12 month visit)
- Lifestyle counseling as per PACE
- Brief symptoms/QOL assessment will be collected
- Hospitalization assessment will be collected
- Endpoint will be assessed
- Obtain lab results from participant's treating physician for lipids (preferably fasting). If not available lipid tests should be obtained by the participant's treating physician or the study staff.
- The study team, in collaboration with the treating physician(s), will evaluate effectiveness of medical therapy and optimize as needed according to guideline recommendations and study algorithms

Close out visit (in addition to all assessments for the regularly scheduled visit)

- 12 lead ECG will be performed and submitted to core lab
- Full QOL assessment will be collected (not applicable to the ISCHEMIA CKD ancillary trial)
- Obtain lab results from participant's treating physician for lipids (preferably fasting) and HbA1c for diabetic participants. If not available from the participant's treating physician these tests should be obtained by the participant's treating physician or the study staff.

10. ADJUDICATION OF CLINICAL EVENTS

An independent clinical event adjudication committee (CEC) will review and adjudicate all primary endpoint events and selected secondary endpoints in a blinded fashion based on study definitions. Endpoints to be adjudicated include death (including cause), myocardial infarction, resuscitated cardiac arrest, hospitalization for unstable angina, hospitalization for heart failure, and stroke. Because the trial is not blinded, to mitigate bias in the ascertainment of events, several strategies will be used to identify ("trigger") all suspected endpoints in all participants including carefully constructed data collection tools that focus sites on key endpoint events, screening of ECG core lab data, site investigator and coordinator education about CEC procedures, and processing of events found by physicians during review of source documents pertaining to already identified endpoints. Care will be taken to blind reviewers to any information that could identify the participant or could reveal the randomized management strategy assignment. CEC members do not have access to management strategy assignment in order to avoid bias, which is an important process issue in this unblinded trial.

11. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

11.1 Sample Size Determination and Statistical Power

11.1.1 Considerations and Assumptions

The sample size of approximately 8,000 randomized participants was selected to yield high power for testing the primary superiority hypothesis under reasonable assumptions about the frequency of the primary composite endpoint, the magnitude of the difference in event rates for INV vs. CON strategies, and the pattern of accrual and dropout. Based on the distribution of coronary disease expected in this population (core-lab documentation of at least moderate ischemia; CCTA documentation of obstructive CAD) and based on unpublished data from the COURAGE trial and several observational stress imaging registries, the percent of participants experiencing the primary composite endpoint within 4 years of randomization in the CON group was projected to be 20% (range 15%-25%). In addition to the CON event rate, an additional key driver of the required sample size is the magnitude of benefit that can reasonably be expected to be achieved with the INV strategy. This determination was based on multiple factors including (i) effect size estimates from related studies; (ii) anticipated increase in effect size by using CCTA to exclude non-obstructive CAD, (iii) potential for CON participants to receive catheterization in violation of the protocol; and (iv) the investigators' assessment of the minimum effect size needed to be impactful and clinically relevant. After careful consideration of these and other factors, the sample size was formulated to provide high power to detect a 15% relative reduction (i.e., from 20% to 17% at 4 years) in the 4-year rate of the primary composite endpoint for participants randomized to INV versus CON (See Table 3 footnote for other assumptions.) Recognizing that event rates and outcome differences in ISCHEMIA may differ somewhat from these assumptions, the required sample size was also calculated for several different plausible combinations of parameter values. The final sample size was chosen to provide adequate power, even if our current assumptions prove to be optimistic. Loss of power due to protocol non-adherence was reflected in the sample size analysis by computing power with a relatively modest assumed treatment effect (20% vs.17%). Ideally, with perfect protocol adherence, a larger treatment effect would be plausible. Although the study objectives are worded in terms of testing a hypothesis (i.e. that the INV strategy is superior), another important objective is to estimate the magnitude of difference in outcomes (to within an acceptable level of statistical precision), regardless of which strategy (if either) is proven superior. Thus, the study is powered for precise parameter estimation (i.e. narrow confidence intervals) as well as hypothesis testing power.

11.1.2 Summary of Power and Precision

As shown in Tables 3 and 4 below, the planned sample size of approximately 8,000 randomized participants will result in an estimate of the hazard ratio that differs from the true hazard ratio by no more than a factor of 1.11 with probability 95% and will yield power ≥90% for comparing the primary composite endpoint across the two randomized groups assuming the 4-year cumulative rate of the primary composite endpoint is 20% in participants randomized to CON strategy and is less by a factor of 15% (i.e. is reduced from 20% to 17%) in participants randomized to INV

strategy. Power will be ≥80% if the 4-year event rate of the primary composite endpoint is reduced by 13% instead of 15%, still assuming the 4-year rate is 20% in the CON strategy. Thus we have excellent power even with a more conservative effect size projection. Finally, power will be ≥80% if the 4-year cumulative rate of the primary composite endpoint is 15% instead of 20% in the CON strategy group, and is reduced by a factor of 15% in the INV strategy group. Thus, we have excellent power even with a more conservative estimate of the incidence of the primary endpoint. Power and precision under other assumptions are summarized in Table 3 and Table 4 below.

Table 3. Estimated Power as a Function of the Anticipated 4-Year Cumulative Event Rate in CON and the 4-Year Cumulative Risk Reduction in INV (Δ)

CON anticipated 4-year event rate	Estimated Power		
Event %	Δ = 0.13	Δ = 0.15	Δ = 0.17
10%	48%	60%	72%
15%	67%	80%	89%
20%	82%	92%	97%
25%	92%	97%	99%
30%	97%	99%	≥99%

NOTE: Δ denotes relative reduction in 4-year event rate in INV vs. CON groups. **Assumptions:** Two-sided log-rank test with alpha = 0.05; 4000 participants per group; average follow-up 3.7 years; loss-to-follow-up 0.85% per year; survival times follow exponential distribution.

Table 4. Range of Estimated Precision (Margin of Error) as a Function of the Anticipated 4-Year Cumulative Event Rate in CON and the 4-Year Cumulative Risk Reduction in INV (Δ)

CON anticipated 4-year event rate	Margin of Error (MOE)		
Event %	Δ = 0.13	Δ = 0.15	Δ = 0.17
10%	1.16	1.16	1.16
15%	1.13	1.13	1.13
20%	1.11	1.11	1.11
25%	1.10	1.10	1.10
30%	1.09	1.09	1.09

NOTE: MOE is the anti-log of the expected half-width of the 95% confidence interval for the log-hazard ratio. **Assumptions:** Based on a univariable Cox model with a binary treatment indicator and Wald-type 95% confidence intervals. See Table 3 for additional assumptions.

11.2 Statistical Analysis Plan

All major treatment comparisons between the randomized groups will be performed according to the principle of "intent-to-treat;" that is, participants will be analyzed (and endpoints attributed) according to the randomized strategy, regardless of subsequent invasive testing or treatment. Statistical comparisons will be performed using two-sided significance tests. A statistical analysis plan will be finalized before trial completion and data analysis.

11.2.1 Analysis of the Primary Endpoint

The statistical comparison of the two randomized groups with respect to the primary composite endpoint will be a “time-to-event” analysis, and will therefore be based on the time from randomization to the first occurrence of any of the components of the primary composite endpoint (CV death or nonfatal MI). The Cox proportional hazards will be the primary analytic tool for assessing outcome differences between the two randomized groups. To preserve power in the face of participant heterogeneity, the overall comparison may be adjusted for a selected set of prognostically important baseline covariates that will be carefully defined and pre-specified in the statistical analysis plan. The level of significance for the assessment of the primary endpoint will be $\alpha=0.05$. In addition to Cox regression, event-free survival probabilities will be estimated as a function of follow-up time in each treatment group using the Kaplan-Meier method and presented with point wise 95% confidence intervals. If the data provide evidence of an overall difference in outcome between management strategy groups, we will further examine whether the therapeutic effect is similar for all participants, or whether it varies according to specific participant characteristics, which will be pre-specified in the statistical analysis plan.

11.2.2 Analysis of the Secondary Endpoints

Secondary endpoints that will be evaluated include: (1) quality of life as measured by the SAQ Angina Frequency Scale and SAQ Quality of Life Scale; (2) composite of cardiovascular death, nonfatal myocardial infarction, or stroke; (3) composite of cardiovascular death, nonfatal MI, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure; (4) all-cause death; (5) CV death (6) MI; (7) resuscitated cardiac arrest; (8) hospitalization for unstable angina; (9) hospitalization for heart failure; (10) stroke; (11) composite of cardiovascular death, nonfatal MI, stroke, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure; and (12) health resource utilization, cost, and cost effectiveness. Plans for the analysis of the quality of life and economic endpoints are addressed below in Sections 11.2.4 and 11.2.5. For other secondary endpoints, analysis will be similar to the primary endpoint, using time from randomization until the first occurrence of the specific secondary endpoint as the response variable.

Unambiguous operational definitions of each study endpoint will be documented in the Clinical Event Committee Charter and statistical analysis plan before performing unblinded analysis. For MI we will specify a primary definition (adapted from the universal definition of MI[61]; to be used in the primary analysis of the primary and secondary endpoints). Other definitions (to be used in secondary analyses) will include the universal definition of MI and criteria to categorize large

infarctions. Data collection instruments and the adjudication process will allow construction of alternative endpoint MI definitions.

11.2.3 Contingency Plan For Insufficient Primary Endpoint Events

The projected event rate of 20% at 4 years for the primary composite endpoint in CON participants was based on multiple data sources including the COURAGE nuclear substudy and several stress imaging registries. Although we believe the projected rate is reasonably conservative, an acceptably precise estimate of the true event rate of the primary endpoint will not be known until substantial participant recruitment and follow-up have been accrued. To ensure that the primary analysis is well-powered and useful, a prospective plan to allow extending follow-up and/or changing the primary endpoint based on aggregate event rate data will be established prior to the first review of unblinded trial data. At a designated time during the trial, an analysis will be conducted to estimate the overall aggregate primary endpoint event rate and project the final number of observed events. If the estimated unconditional power (i.e. based on aggregate event rate data; not by treatment group) is less than the originally targeted 90%, then one or more of the following options will be considered:

1. Extend follow-up to allow more events to accrue.
2. Change the primary endpoint to one that occurs more frequently.
    - The current primary endpoint would become a secondary endpoint
    - The proposed new primary endpoint would be the composite of CV death, MI, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure.
3. Follow the recommendation of an independent advisory panel.

An independent advisory panel, separate from the DSMB, will be convened for the purpose of reviewing unconditional power estimates and making a recommendation to the NHLBI Director. Members of this panel will not have access to unblinded data by treatment group or other data that may bias their recommendation.[62, 63] Additional details will be finalized in cooperation with the DSMB and recorded in the statistical analysis plan before the first unblinded interim analysis.

11.2.4 Quality of Life (QOL) Analysis

All QOL comparisons will adhere to the intention-to-treat principle. For each QOL measure examined in this study, data analysis will proceed in several stages. First, we will provide simple descriptive and comparative analyses by intention-to-treat. Statistical power estimates for this part of our analysis, based on data collected in the COURAGE trial, show that we should have in excess of 99% power to detect ¼ SD differences in our 3 principal QOL measures. Second, we will examine changes over time from baseline and identify the major determinants of those changes using regression analysis. Since there is currently no consensus in the statistical literature about the best way to deal with the multiple comparisons problem arising from testing each individual scale separately, we propose two complementary approaches. First, we will pre-

specify the angina frequency and QOL scales from the SAQ as the CAD-specific measures of primary interest and assign all other comparisons to a secondary (descriptive) status. Second, we will employ a mixed model methodology that makes use of all available QOL data at each study assessment point to model the time profile (fixed effect). Using the fitted model, we can estimate the overall difference in the QOL measures as well as test the global hypothesis of no difference over time. We can also estimate the difference in the areas under the two QOL treatment curves (and test the hypothesis of no difference, on average). In addition, we can estimate differences in QOL at the end of the study or at intermediate points. Lastly, to address the possibility that international differences in QOL exist despite our use of extensively culturally validated instruments, we will examine interactions between key QOL outcomes, treatment, and geographic region.

11.2.5 Health Economics Analysis

The health economic analyses for ISCHEMIA will consist of two major parts, an empirical intention-to-treat cost comparison and a cost-effectiveness analysis. Primary statistical comparisons between the two treatment groups of empirical costs will be performed by intention-to-treat. The participants enrolled outside the United States will be excluded from the primary cost intention-to-treat analyses. Confidence limits around the observed cost differences will be constructed using bootstrap methods.

The cost-effectiveness analyses will estimate the incremental cost required to add an extra life year with the INV strategy group relative to CON strategy group. In secondary analyses, we will incorporate utility weights to estimate the incremental cost per quality adjusted life year gained with the INV strategy relative to CON strategy. These analyses will be conducted from a societal perspective and will use a lifetime horizon so that the estimated incremental cost-effectiveness and cost-utility ratios can be compared with societal benchmarks. We will also calculate within-trial cost-effectiveness/cost-utility ratios, although these ratios are limited in their value due to their failure to account for long-term benefits and costs and the absence of comparative benchmarks. Cost will be adjusted for inflation, and both costs and life expectancy will be discounted to present value at a 3% annual discount rate. Plots of cost-effectiveness acceptability curves indicating the probability that the intervention is cost-effective for a range of willingness-to-pay thresholds will be done. Extensive sensitivity analyses will be performed.

11.2.6 Interim Analysis

For ethical reasons, interim examination of clinical endpoints and key safety events will be performed at regular intervals during the course of the trial. An independent Data and Safety Monitoring Board (DSMB) appointed by the NHLBI will monitor participant safety and to review performance of the trial (see 13.1). The primary objective of these interim analyses is to ensure the safety of the participants enrolled in the trial and evaluate the accumulating endpoint data by treatment group to test for possible differences favoring either of the two randomized management strategies. In addition, interim monitoring will involve a review of participant recruitment, compliance with the study protocol, status of data collection, an assessment of whether control group event rates are consistent with the rates hypothesized in the sample size calculations, and other factors which reflect the overall progress and integrity of the study.

Because interim analyses may occur when adjudication of an event is in progress, the interim analyses will be based primarily on adjudicated events and secondarily on all best available events, i.e., as adjudicated by CEC if present or as eCRF/Investigator defined if the event has not yet been adjudicated by CEC. The results of the interim analyses and status reports will be carefully and confidentially reviewed by the DSMB. Detailed plans for interim monitoring will be documented in a separate DSMB analysis plan.

Interim comparisons by management strategy will focus on all-cause mortality and the primary composite endpoint (cardiovascular death and MI). Cox-proportional hazard models with treatment as the covariate will be used for the analysis. Estimates of hazard ratios and 95% confidence intervals comparing the INV and CON strategies will be reported. To account for repeated significance testing of the accumulating data, the group sequential method of Lan and DeMets[64] will be used as a guide for interpreting these interim analyses. Monitoring boundaries for each endpoint will be based on a two-sided symmetric O'Brien-Fleming type spending function with an overall two-sided significance level of $\alpha = 0.05$. The O'Brien-Fleming approach requires large critical values early in the study but relaxes (i.e., decreases) the critical value as the trial progresses.[65] These proposed monitoring boundaries are intended as a guide for interpreting the interim analyses and not as a rule for early termination.

An additional key parameter for interim monitoring will be the frequency of early catheterization among participants randomized to the CON strategy. Such catheterizations will be classified according to (1) whether the catheterization was allowed by the protocol (e.g. for documented refractory symptoms) and (2) whether the catheterization was preceded by a nonfatal primary endpoint event (i.e., MI). A pattern of frequent early catheterization in CON participants without prior endpoint events would suggest that the study may have difficulty achieving high statistical power. Moreover, if this was due to frequent protocol violations, then a finding of no treatment effect may be challenging to interpret. To address these concerns, rates of early catheterization in the CON group will be analyzed and reported, with a focus on estimating the probability that a CON participant will undergo catheterization within a specified time interval and before an endpoint event. To obtain this probability, the distribution of "time from randomization to catheterization" for CON participants will be estimated using the cumulative incidence function method for competing risks.[66] For this latter analysis participant follow-up will be censored at the last contact date or terminated after the participant's first primary endpoint event, whichever occurs first.

Judgment concerning the continuation of the study will involve not only the magnitude of observed differences between randomized strategies and degree of statistical significance, but also careful consideration of many other important factors including the need for precise parameter estimation, the overall progress and integrity of the trial (including the frequency of catheterization in the CON group, as discussed above), and information available from other studies at the time of DSMB deliberations. If a stopping boundary is crossed early in the trial, this result should be tempered by the knowledge that revascularization may result in early hazard, but long-term benefit. Although we hypothesize that outcomes will be improved by the INV strategy, it should be emphasized that a small treatment effect for the primary endpoint is not necessarily a negative result for the study. Indeed, evidence suggesting absence of a large

benefit from the invasive strategy would be highly important to future guidelines and clinical practice. However, a large sample size is required in order to derive such evidence. If the study were to be stopped early with less than the full sample size, the lack of statistically significant difference may be accompanied by wide confidence intervals and no clear conclusion might be possible. The DSMB will incorporate this perspective along with other considerations when making recommendations about continuation.

12. DATA HANDLING AND RECORD KEEPING

12.1 Electronic Data Capture (EDC) System

The full study dataset will be collected for participants who enter the randomized phase of the study. The primary data collection system for ISCHEMIA will use a web-based electronic data capture (EDC) system, a validated Electronic Record, Electronic Signatures (ERES) compliant platform (21 CFR Part 11). All these data collected at any point in the trial except the economic and quality of life information, are entered into this EDC system.

12.2 Data Management and Quality

Any out-of-range values and missing or inconsistent key variables will be flagged and addressed at the site in real time during the data entry process. When a query is generated on a particular variable, a flag will be set in a field in the database enabling the system to track the queries and produce reports of outstanding queries. Queries can also be generated from manual review of the data forms. These queries will be entered into the database and tracked in the same manner as the computer-generated queries. At regular intervals, all data will be transferred from the EDC database to SAS for statistical summarization, data description, and data analysis. Further cross-checking of the data will be performed in SAS, and discrepant observations flagged and appropriately resolved through a data query system. The Statistical and Data Coordinating Center (SDCC) will perform internal database quality-control checks, and data audits throughout the course of the trial.

12.3 Data Confidentiality and Security

Computerized data will be accessible only by password, and a centralized monitoring system will record and report all access to data. The DCRI computer network is protected by a firewall. Electronic CRFs (eCRFs) will be identified by study number only, to ensure participant anonymity. No participant identifiers will be used in the presentation of data. Study records that might identify participants will be kept confidential as required by law. Except when required by law, participants will not be identified by name, personal identification number (e.g. social security number, social insurance number), address, telephone number, or any other direct personal identifier in study records. This information will be retained by each individual center and will not be disclosed to the Coordinating Center except as needed for centralized clinical, quality of life and economic follow-up of the participants. Participants will be informed that the study physician and his/her study team will report the results of study-related tests to the Coordinating Center and to the NIH. Participants will be informed that their records may be reviewed in order to meet federal, state or regional/local regulations. Reviewers may include the CCC/SDCC monitors, IRBs/ECs, the NIH, other government regulators as dictated by local law, or their delegates.

Ischemia tests will be stripped of identifiers during the upload process, with the exception of date of study in DICOM headers, by a vendor which will be responsible for ischemia test transfer and storage for this trial.

12.4 Training

All investigational site and core lab staff authorized to enter ISCHEMIA study data will receive training on the EDC system. Training records will be retained by the EDC Helpdesk at the SDCC.

12.5 Records Retention

Study records will be maintained by the site investigators for a period of three (3) years following the expiration of the grant or length of time as required by local regulations, whichever is longer.

12.6 Management of Economic and Quality of Life (EQOL) Data

The economic and quality of life studies will be fully integrated into the clinical trial and will be covered by the main trial Informed Consent Form. Interviewers will be blinded to the study group. Data processing, quality control, and analysis of EQOL data will be performed by the EQOLCCs. Although the EQOL computer network is not a regulated environment as are the clinical databases, EQOL follows the same network security protocols including password protection, expiring logons, and restricted access. Participant information records will be kept confidential in a separate, secured SQL Server database, and the participant's name will never be released. Even though the interviewers must be unblinded to participant identity in order to collect the EQOL data, unblinded information is locked with restricted access, and none of the electronic databases or analysis files include direct participant identifiers. The electronic databases have (coded) study identifiers. In addition to participant identifiers never being linked to the clinical database, they are never passed on to the sponsor or third party. The interviewers obtain an approved Duke University IRB required consent from the participant on the telephone before a questionnaire may be administered. All of the EQOL data are analyzed in aggregate with only coded study identifiers (no direct participant identifiers), and no individual data/participant identifier will ever be presented in any oral or written form. No name or other identifiable information ever appears on the data or reports about the study.

13. SAFETY MONITORING PLAN

13.1 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be appointed by the NHLBI to monitor participant safety and to review performance of the trial. A DSMB charter that outlines the operating guidelines for the committee and the procedures for the interim evaluations of study data will be developed by the NHLBI and agreed upon by the DSMB. Reports will be prepared regularly by the SDCC in accordance with the plan outlined in the charter and as requested by the DSMB chair, and will include interim analyses of primary and secondary endpoints; additional safety events; and other information as requested by the committee. After each meeting, the DSMB will make recommendations to the NHLBI and the trial leadership about the continuation of the study. After approval by the NHLBI director, a summary of the DSMB report and recommendations will be forwarded by the CCC to investigators for submission to their local, regional and national IRB/Ethics Committees, as applicable. DSMB reports will be the primary mechanism for reporting safety concerns to NIH and IRBs.

13.2 Risks and Benefits

All procedures and tests performed in this study are commonly performed in clinical practice and have well defined safety profiles. Furthermore, all procedures performed in this study, except CCTA, are commonly performed for the patient population enrolled in the study, i.e., those with SIHD and at least moderate ischemia. The only procedure being done for study purposes is CCTA. Although CCTA has increasingly been used to evaluate the presence and extent of coronary artery disease, it is not considered standard of care when used in the testing sequence in the trial. The risk of cath and revascularization will be minimized by the selection of experienced operators who meet study certification criteria. These risks are justified by the potential benefit (long-term reduction in events resulting from revascularization, as discussed in the background section).

Risks:

CCTA Risks: The primary risk is an increased exposure to radiation from the CCTA scan. On average, the estimated total radiation dose from this study (one CCTA scan) will range from 4-8 mSv. In comparison, other estimated doses of medical radiation include: chest X-ray (0.05 mSv); invasive cardiac catheterization (5-7 mSv); PCI (10-16 mSv); nuclear stress test (12-30 mSv). In 1 year a person living at sea level is exposed to natural radiation of about 3 mSv, so the expected radiation dose from CCTA is around 1-3 times that amount.

Other known risks of CCTA include allergy. Participants with known contrast allergy will be premedicated and participants with prior anaphylaxis to contrast will not be included in the study. As noted above participants with eGFR <60 ml/min will not undergo CCTA to minimize risk from this procedure in the trial, except as noted in sections 4.1, 5.5 and the MOO. Beta blockade, which is routinely used during CCTA, may cause bradycardia, hypotension or bronchospasm, and nitroglycerin can lower blood pressure and may cause headache.

Participants will be monitored throughout the procedure for these effects and treated if necessary.

It is recognized that CCTA, as a 3-dimensional imaging modality, does not correlate perfectly with and may be more accurate for localization of a stenosis to a particular arterial segment than 2-dimensional invasive angiography. Therefore CCTA may rarely be interpreted as showing no significant left main stenosis when invasive angiography shows left main stenosis ≥50%.

All females who are premenopausal must have a negative pregnancy test documented before undergoing the CCTA or being placed into either of the two study groups.

Cath/PCI/CABG Risks: Each of these procedures is commonly performed in clinical practice for patients who meet eligibility criteria for the study. The major risks of these procedures include death, myocardial infarction and stroke. Other risks of catheterization and PCI include severe contrast reaction such as anaphylaxis, emergency CABG, bleeding, need for blood transfusion, contrast-induced nephropathy and vascular access site complications including pseudoaneurysm, AV fistula, retroperitoneal bleed or infection. Other risks of CABG include return to operating room for bleeding, need for blood transfusion, infection, prolonged intubation, mediastinitis and atrial fibrillation. Risks of these procedures vary in likelihood based on the patient's risk profile.

Risk Lowering Measures:

Study procedures are designed to manage and minimize risks through careful selection of the patients who participate in the trial. Participants will be monitored closely through the trial at many time points to check on their health. In addition, an independent DSMB will monitor safety of the participants throughout the study (see section 13.1)

Benefits:

The ISCHEMIA trial results should provide evidence based data to support management of patients with SIHD.

There may be benefit from participation in this study by receiving the medications and lifestyle counseling that are proven to improve outcomes in patients as well as involvement of an additional team following the participants' health status. Participants may receive some medications and stents free of cost, as available. It is hoped the knowledge gained will be of benefit to others with a similar medical condition in the future.

13.3 Safety Monitoring Objectives and Rationale

The main safety objectives in ISCHEMIA are to characterize the risk profiles of the two randomized management strategies and to monitor for unanticipated risks to study participants. All medications and procedures to be used/performed in this study are commonly used/performed for clinical indications as part of standard of care and have well-defined safety profiles. Because no investigational device, drug, diagnostic test or therapeutic intervention is being tested in this comparative effectiveness trial, reporting is primarily governed by the

Common Rule (45 CFR Part 46, Subpart A), as well as ICH Guidelines, IRBs and local regulations.

13.4 Adverse Events Reporting by Investigators

Data for monitoring participants' safety will be captured within the EDC database as part of the required study data. There are no additional study-specific reporting requirements. Site investigators should follow usual clinical practices at their institutions for reporting serious, unexpected events related to standard of care medications and devices to regulatory agencies.

13.5 Events to be Monitored

Safety monitoring in ISCHEMIA will be concerned with estimating event rates for the following types of clinical events:

1. Complications of cardiovascular tests (e.g. CT coronary angiogram, cardiac catheterization) and therapeutic procedures (e.g. PCI, CABG)
2. Events occurring in the time period between consenting to participate in the trial and being randomized.
3. Study endpoints.

1. Complications of cardiovascular tests and therapeutic procedures
All drugs, diagnostic tests and therapeutic procedures to be used in this trial have been extensively evaluated previously, have established safety profiles with known risks and benefits and are routinely used in clinical practice. Events listed below occurring within 72 hours of the procedure will be considered as a complication of the procedure. Some safety events related to specific tests and procedures captured within EDC, in addition to death and MI, include:

CT coronary angiography:

1. Severe contrast reaction such as anaphylaxis
2. Hemodynamic instability, including symptomatic bradycardia or hypotension, due to the beta blockade or nitrates given for the CCTA scan acquisition
3. Acute bronchospasm due to the beta blockade given for the CCTA scan
4. Contrast induced nephropathy/dialysis
5. Radiation dose exposure

In addition the incidence of finding significant LM stenosis ($\geq$50%) on cardiac catheterization not reported on CT coronary angiogram will be monitored and reported to the DSMB. Incidental findings on CCTA will be reported to the site according to the list specified in the MOO. The participant may be excluded from the study based on certain incidental findings (e.g., large aortic aneurysm or neoplasm).

Cardiac catheterization and PCI:

1. Severe contrast reaction such as anaphylaxis
2. Periprocedural stroke

3. Emergency CABG
4. Contrast-induced nephropathy/dialysis
5. Vascular access site complications including pseudoaneurysm, AV fistula, retroperitoneal bleed

CABG:

1. Return to operating room for bleeding
2. Prolonged intubation
3. Mediastinitis
4. Atrial fibrillation

2. Events occurring in the time period between consent and randomization

In general, eligibility for randomization will not be known at the time of enrollment but will need to be confirmed after performing additional screening procedures (e.g. pregnancy test and blinded CCTA). As a result, several days may elapse before the participant is randomized. Frequency of clinical events (e.g. death, MI) occurring during this time period, prior to randomization, will be monitored and reported to the DSMB.

3. Events that are trial endpoints

Selected trial endpoints (e.g. all-cause mortality) will be monitored at regular intervals during the course of the trial for the purpose of protecting participants' safety. Event rates in each treatment group will be confidentially reviewed by the DSMB. These analyses will inform the DSMB's recommendation to stop or continue the study or modify the protocol (see **section 11.2.6**).

14. ETHICAL CONSIDERATIONS

14.1 Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the international conference on harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 45 and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

14.2 Informed Consent Process

Investigators must ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every participant or, in those situations where consent cannot be given by participants, their legally acceptable representative, prior to clinical study participation, including informed consent for study CCTA. The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society. Women of child bearing potential will be informed that there may be unknown risks to the fetus if pregnancy were to occur during the study and they were exposed to radiation (e.g. CCTA and cardiac catheterization and revascularization if randomized to the INV strategy group) and agree that in order to participate in the study they must adhere to the contraception requirement during this period of the study. If there is any question that the prospective participant will not reliably comply with study procedures and/or follow-up, they should not be entered in the study.

14.3 Responsibilities of the Investigator and IRB/IEC/REB

The protocol and the proposed informed consent forms (main consent form and genetics testing consent form) will be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) at each site. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB is required before site initiation. A separate IRB/IEC/REB waiver of consent may also be required for the screening survey, according to local regulations. Prior to study start, the site principal investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to monitors, auditors, Clinical Quality Assurance representatives, designated agents of CCC, IRBs/IECs/REBs, and regulatory authorities as required. Investigators must agree to apply due diligence to avoid protocol deviations.

14.4 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by CCC, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for participant safety may be implemented prior to IRB/IEC/REB

approval. As soon as possible, the implemented deviation or change, the reasons for it and, if appropriate, the proposed protocol amendment(s) will be submitted: (a) to the IRB/IEC/REB for review and approval/favorable opinion; (b) to the sponsor, NIH/NHLBI for agreement; and, if required, (c) to the regulatory authority(ies). Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, CCC should be notified of this action and the IRB/IEC/REB at the study site should be informed.

14.5 Early Termination of the Study

The CCC and NHLBI retain the right to terminate the study, a study site or an investigator at any time. The CCC will monitor the progress of the study. If warranted, the study may be suspended or discontinued early if there is an observation of safety concerns posing an unreasonable risk to the study population. If the study is terminated early, the CCC will provide a written statement to the site Principal Investigators to enable notification to site IRBs/IECs/REBs and study participants. The CCC will also inform the appropriate Competent Authorities. The CCC may terminate enrollment activity at a site, or participation in the study by the investigator and site if there is evidence of an investigator's failure to maintain adequate clinical standards or failure to comply with the protocol. Notification of enrollment suspension or termination of the study or study site/investigator will be sent to the investigator and the IRBs/IECs/REBs.

15. STUDY ORGANIZATION

ISCHEMIA is sponsored by the US National Heart, Lung, and Blood Institute (NHLBI). The Clinical Coordinating Center (CCC), Study Chair, and Study Co-Chair maintain responsibility for the overall conduct of the study, including site management and site monitoring in participating countries, analysis and reporting. The Statistical and Data Coordinating Center (SDCC) is responsible for the treatment allocations of eligible participants, receipt and processing of data collected by the clinical sites, core laboratories and coordinating centers, quality control programs, and statistical analysis and reporting. The Ischemia Imaging Coordinating Center (ICC) will organize and oversee the stress imaging core laboratories, coordinate and implement educational systems for sites and monitor site stress imaging performance. The Economics and Quality of Life Coordinating Center (EQOLCC) is responsible for the conduct of the quality of life and the economics and cost effectiveness portions of this study. The Computed Tomography Coronary Angiography Core Laboratory (CCTA CL) will interpret all CCTA scans and will provide technical support. The angiographic core laboratories (ACL) will characterize coronary anatomy for participants undergoing coronary angiography and procedural outcomes for those undergoing PCI. Members of the NHLBI will participate in the study leadership. Details regarding the Cores and Coordinating Centers may be found in the MOO.

Details of the Committees, their charge and membership may be found in the MOO. These Committees include Leadership, Executive and Steering Committees, optimal medical therapy and optimal revascularization committees, committee on recruitment of women and minorities, biorepository, statistics, ancillary studies and publications committees.

16. DATA ACCESS AND SHARING

The Publication Committee will authorize access to study data and biospecimens (in conjunction with the Biorepository Committee). Investigators must submit a proposal requesting approval to access ISCHEMIA trial data/specimens. The ISCHEMIA trial will participate in the NHLBI Central Repository for study data and specimens.

All data access will follow guidelines described in the NHLBI Limited Access Data Policy (www.nhlbi.nih.gov/resources/deca/policy_new.htm), the NIH Data Sharing Policy (http://grants.nih.gov/grants/gwas/index.htm), and the Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS) http://grants.nih.gov/grants/gwas/index.htm) with regard to documentation, content, storage and timing.

17. PUBLICATIONS POLICY: OVERVIEW

Primary and secondary reports of study findings will be published in peer-reviewed journals. Proposals for presentations and publications incorporating data obtained from participants involved in the ISCHEMIA trial must be submitted for review by the publications committee. The primary publication will be authored by the trial's writing committee. No site is permitted to present or publish data obtained during the conduct of this trial without prior approval from the publications committee. Authorship for ISCHEMIA-related publications will be determined by the publications committee taking into account contribution to the trial and the relevant analyses. The full publications policy may be found in the MOO.

18. ISCHEMIA-CKD Ancillary Trial

The ISCHEMIA-CKD ancillary trial will enroll 1000 additional patients with advanced CKD (defined as those with estimated glomerular filtration rate [eGFR] <30 or on dialysis) with moderate to severe ischemia randomized to invasive (INV) strategy versus a conservative (CON) strategy. The design of the trial to randomize patients upstream of cath is advantageous as it will expose only 50% of participants (enrolled to INV) to contrast agent and will be the largest treatment strategy trial in advanced CKD patients with SIHD.

The trial is designed to run seamlessly with that of the main trial but sites can opt out if they choose not to participate.

18.1 Background

Among patients with advanced CKD, cardiovascular disease is the leading cause of death,[67, 68] 15-30 times higher than the age-adjusted cardiovascular mortality rate in the general population.[69, 70] The projected 4-year mortality is >50% in patients with advanced CKD [71-75] and is worse than that for patients in the general population who have cancers, heart failure, stroke or MI.[76] Participants with advanced CKD are 5-10 times more likely to die than to reach end stage renal disease (ESRD).[77] Despite this, ~80% of contemporary coronary artery disease (CAD) trials exclude participants with advanced CKD. [78] Most of the treatments aimed at reducing cardiovascular events in advanced CKD are therefore extrapolated from cohorts without advanced CKD. Participants with advanced CKD and cardiovascular disease are undertreated with less frequent use of statins and revascularization therapies, and the optimal management approach to these patients is unknown. Participants with advanced CKD are notably underrepresented in contemporary trials comparing revascularization with medical therapy in SIHD patients, such as the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial[24] or the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial,[79] making any assessment about the efficacy of revascularization plus medical therapy vs. initial medical therapy alone in this cohort problematic.

Participants with advanced CKD are at increased risk for complications of the assigned invasive procedure, specifically contrast-induced acute kidney injury (AKI), [80, 81] dialysis, major bleeding and short-term risk of death. However, there is controversy in the medical literature regarding the incidence (<1% to >30%), effective treatment (saline hydration, N-acetyl cysteine, or sodium bicarbonate) and prognosis of contrast induced AKI (<0.5% to >5% requiring dialysis).[82-85] In addition although contrast induced AKI have been associated with increase in short-term mortality residual confounding in these studies makes interpretation difficult. Moreover it is unknown if these short-term increased risks are offset by long-term benefits. Limited observational study in the CKD cohort suggests a survival benefit of revascularization when compared with medical therapy alone long-term, [86-89] despite increase in short-term risks. However, the medical therapy in these trials was not optimized, drug eluting stents were rarely used and there is undoubtedly inherent selection and ascertainment bias with observational studies. The above has resulted in **substantial clinical equipoise in the management of**

these patients with the rates of revascularization of only around 10-45%.[86, 88, 90] The results of ISCHEMIA-CKD will have profound implications for guidelines, health policy, and clinical practice.

18.2 Objectives

The primary objective for the chronic kidney disease (CKD) ancillary trial is to determine whether the INV strategy reduces the incidence of death or nonfatal myocardial infarction compared with CON in participants with advanced CKD.

The Secondary objective is to determine whether an INV strategy is more effective than CON strategy in improving angina control, as assessed by the Seattle Angina Questionnaire (SAQ) Angina Frequency scale, and disease-specific quality of life, as assessed by the SAQ Quality of Life scale.

Other secondary objectives include comparing the incidence of the composite of cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure; composite of cardiovascular death or nonfatal myocardial infarction; individual components of this endpoint; all-cause death; stroke; as well as comparing health resource utilization, cost, and cost-effectiveness between the two randomized strategies.

18.3 Study Design

The study design for the CKD ancillary trial is similar to that of the main trial participants with eGFR 30-59, with requirement of at least moderate ischemia on ischemia testing and no requirement for CCTA. Participants who otherwise meet ISCHEMIA trial eligibility but with advanced CKD will be randomized after a qualifying ischemia test to INV vs. CON. The study procedure (Section 5) and management strategies (Section 6) will be similar to that of the main trial. Strategies to minimize the volume of contrast used and reduce the risk of contrast induced AKI are outlined in the MOO. The follow-up and study assessments (Section 9) are similar to that of the main trial. The similarities and differences in processes between the main trial and the CKD ancillary trial are outlined in the MOO.

18.4 Statistical Consideration and Power

As shown in Tables 5 and 6 below, for participants in the CKD ancillary trial, the planned sample size of approximately 1,000 randomized participants will result in an estimate of the hazard ratio that differs from the true hazard ratio by no more than a factor of 1.19 with 95% probability and will yield power ≥80-95% for comparing the primary composite endpoint across the two randomized groups assuming the 4-year cumulative rate of the primary composite endpoint is 60% in participants randomized to CON strategy and is less by a factor of 15% to 19% (relative reduction) in participants randomized to INV strategy. Power and precision under other assumptions are summarized in Table 5 and Table 6 below.

Table 5. Estimated Power as a Function of the Anticipated Cumulative Event Rate in CON and the Cumulative Risk Reduction in INV (Δ)			
CON anticipated 4-year event rate	**Power**		
Event %	Δ = 0.15	Δ = 0.17	Δ = 0.19
45%	56	67	76
50%	64	75	84
55%	73	83	90
60%	81	90	95
65%	88	95	98
70%	94	98	99

NOTE: Δ denotes relative reduction in 4-year event rate in INV vs. CON groups. **Assumptions:** Two-sided log-rank test with alpha = 0.05; 500 participants per group; average follow-up 3.7 years; loss-to-follow-up 1% per year; survival times follow exponential distribution.

Table 6. Range of Estimated Precision (Margin of Error) as a Function of the Anticipated Cumulative Event Rate in CON and the Cumulative Risk Reduction in INV (Δ)			
CON anticipated 4-year event rate	**Margin of Error (MOE)**		
Event %	Δ = 0.15	Δ = 0.17	Δ = 0.19
45%	1.22	1.22	1.23
50%	1.21	1.21	1.21
55%	1.20	1.20	1.20
60%	1.19	1.19	1.19
65%	1.18	1.18	1.18
70%	1.17	1.18	1.18

NOTE: Margin of Error is the anti-log of the expected half-width of the 95% confidence interval for the log-hazard ratio. Assumptions: Based on a univariable Cox model with a binary treatment indicator and Wald-type 95% confidence intervals.

Other aspects of the statistical consideration including contingency plan for insufficient primary endpoint events, QOL analysis and health economic analysis are detailed in Section 11.2

18.5 Safety Monitoring Plan

18.5.1 Data and Safety Monitoring Board

As reported in **section 13**, a Data and Safety Monitoring Board (DSMB) will be appointed by the NHLBI to monitor participant safety and to review performance of the trial. The main trial DSMB with a nephrologist added to the roster will serve as the DSMB for the CKD ancillary trial. A DSMB charter that outlines the operating guidelines for the committee and the procedures for the interim evaluations of study data will be developed by the NHLBI and agreed upon by the DSMB. After each meeting, the DSMB will make recommendations to the NHLBI and the trial leadership about the continuation of the study. DSMB reports will be the primary mechanism for reporting safety concerns to NIH and IRBs.

18.5.2 Risks and Benefits

All procedures and tests performed in this study are commonly performed in clinical practice and have well defined safety profiles. The risks and benefits are described in more detail in section 13.2. The risks and benefits pertaining to the CKD cohort are described below.

Risks:

Cath/PCI/CABG Risks: Each of these procedures is performed in clinical practice for patients who meet eligibility criteria for the CKD trial. The major risks of these procedures include death, myocardial infarction and stroke. Other risks of catheterization and PCI include severe contrast reaction such as anaphylaxis, emergency CABG, bleeding, need for blood transfusion, contrast-induced AKI, AKI requiring dialysis and vascular access site complications including pseudoaneurysm, AV fistula, retroperitoneal bleed or infection. Other risks of CABG include return to operating room for bleeding, need for blood transfusion, infection, prolonged intubation, mediastinitis, AKI, AKI requiring dialysis and atrial fibrillation. Risks of these procedures vary in likelihood based on the patient's risk profile and are generally higher in the CKD cohort than in participants without CKD.

Risk Lowering Measures:

The risk of cath and revascularization will be minimized by the selection of experienced operators who meet study certification criteria. Strategies to minimize the volume of contrast used and reduce the risk of contrast-induced AKI are outlined in the MOO. These risks are justified by the potential benefit (long-term reduction in events resulting from revascularization, as discussed in the background section). Moreover, a nephrologist will be involved in the care of the participants.

Study procedures are designed to manage and minimize risks through careful selection of the patients who participate in the trial. Participants will be monitored closely through the trial at many time points to check on their health. In addition, an independent DSMB will monitor safety of the participants throughout the study (see section 13.1)

Benefits:

The ISCHEMIA-CKD trial results should provide evidence based data to support management of participants with CKD and SIHD. It is hoped the knowledge gained will be of benefit to others with a similar medical condition in the future.

18.5.3 Adverse Events Reporting by Investigators

Data for monitoring participants' safety will be captured within the EDC database as part of the required study data. There are no additional study-specific reporting requirements. Site investigators should follow usual clinical practices at their institutions for reporting serious, unexpected events related to standard of care medications and devices to regulatory agencies.

18.5.4 Events to be Monitored

Safety monitoring for the CKD ancillary trial will be similar to ISCHEMIA and will be concerned with estimating event rates for the following types of clinical events:

1. Complications of cardiovascular tests (e.g. cardiac catheterization) and therapeutic procedures (e.g. PCI, CABG)
2. Events occurring in the time period between consenting to participate in the trial and being randomized.
3. Study endpoints.

Details of the events to be monitored are outlined in section 13.5. The events to be monitored which are of special interest for the CKD ancillary trial are described below.

Complications of cardiovascular therapeutic procedures

All therapeutic procedures to be used in this trial have been extensively evaluated previously, have established safety profiles with known risks and benefits and are used in clinical practice. Events listed below occurring within 72 hours of the procedure will be considered as a complication of the procedure. Some safety events related to specific tests and procedures captured within EDC, in addition to death and MI, include:

Cardiac catheterization and PCI:

1. Severe contrast reaction such as anaphylaxis
2. Periprocedural stroke
3. Emergency CABG
4. AKI
5. AKI requiring dialysis
6. Vascular access site complications including pseudoaneurysm, AV fistula, retroperitoneal bleed

CABG:

1. Return to operating room for bleeding
2. Prolonged intubation
3. Mediastinitis
4. Atrial fibrillation
5. AKI requiring dialysis

In addition the incidence of finding significant LM stenosis (≥50%) on cardiac catheterization will be monitored and reported to the DSMB.

18.6 Adjudication of Clinical Events (See Section 10)

18.7 Data Handling and Record Keeping (See Section 12)

18.8 Ethical Consideration (See Section 14)

18.9 Study Organization (See Section 15)

18.10 Data Access and Sharing (See Section 16)

18.11 Publication Policy (See Section 17)

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20. APPENDIX A

Ischemia Test Eligibility Criteria

Specific criteria for each modality were developed and refined based on data indicating that the risk of cardiovascular events based on inducible ischemia is consistent with that targeted in this trial. Criteria were harmonized across modalities in order to yield a similar risk of cardiovascular death or MI regardless of the type of stress test performed.[1]

Table: Criteria for at least Moderate Ischemia by Stress Test Modality[2]

Test Modality	Diagnostic criterion
Nuclear perfusion via SPECT or PET[3]	≥10% myocardium ischemic
Echo[3]	≥3/16 segments with stress-induced severe hypokinesis or akinesis
CMR[3]	Perfusion: ≥12% myocardium ischemic and/or 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 2. Absence of resting ST segment depression ≥1.0 mm or confounders that render exercise ECG non-interpretable (LBBB, LVH with repolarization, pacemaker, etc.) 3. As compared to the baseline tracing, additional exercise-induced horizontal or downsloping ST segment depression ≥1.5 mm in 2 leads *or* ≥2.0 mm in any lead; ST segment elevation ≥1mm 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. 4. Either of the following: a. Peak workload not to exceed completion of stage 2 of a standard Bruce protocol or ≤7 METS if a non-Bruce protocol is used *or* 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] Shaw L, Berman D, Stone G, Picard M, Friedrich M, Kwong R, et al. Comparative definitions for moderate-severe ischemia in stress nuclear, echocardiography, and magnetic resonance imaging. JACC Cardiovasc Imaging (in press).

[2]Additional criteria may be required for confirmation of obstructive coronary artery disease, depending on eGFR and type of ischemia test. See Section 5.5.

[3]Ancillary findings may also be included in the core lab determination of severity of ischemia by imaging (see MOO).

Note the exclusion criterion: Patient who, in the judgment of the patient's physician, is likely to have significant unprotected left main stenosis will be excluded (see Section 4.3.1).

21. APPENDIX B CIAO-ISCHEMIA Ancillary Study

21.1 Background

The relationship between ischemia, symptoms and atherosclerosis in patients without angiographically obstructive CAD remains to be fully elucidated. It is not known whether persistent chest pain represents ongoing ischemia, nor to what extent subgroups of patients with persistent chest pain, ischemia on imaging and greater atherosclerotic burden overlap.

Angina and ischemia may not be correlated. Angina frequency and duration are similar among patients with and without ischemia on noninvasive testing.[1] Small treatment trials have been undertaken showing improvement of angina that was not reflected in objective measurement of ischemia, though these studies were markedly underpowered for that comparison.[2,3] Treatment for patients with symptoms and/or ischemia without obstructive CAD is highly variable in clinical practice.[4] Guidelines focus on symptom management.

21.2 Objectives

This ancillary study will investigate the association between changes in ischemia over one year and changes in angina over one year in participants excluded from the main ISCHEMIA study based on the absence of obstructive CAD on the study CCTA. If the study finds that angina and ischemia vary together over time, symptoms in these patients are likely due to ischemia and not, for example, altered pain sensitivity. Alternatively, the study may find the trajectories of angina and ischemia are not associated and in this case, therapy might be better targeted to relief of ischemia than symptoms in these patients. Further, in this case it would be concluded that symptoms were not due to ischemia in some or all patients and ischemia was either silent or represented a false positive finding.

21.2.1 Primary Specific Aim

The primary aim of the CIAO-ISCHEMIA ancillary study is to investigate the association between change in angina severity and change in ischemia severity on stress wall motion imaging over one year in female and male patients with an initial finding of moderate-severe ischemia and with no obstructive CAD on CCTA. Severity of angina will be characterized by the Seattle Angina Questionnaire and severity of ischemia by the number of ischemic segments on stress wall motion imaging. Changes in angina severity and stability of the finding of moderate-severe ischemia over one year will be described. Correlates of change in angina over time will be identified. Selection of core-lab confirmed moderate-severe ischemia is expected to reduce the likelihood of including patients with false positive tests

21.2.2 Other Specific Aims

- To determine the effect of medication classes selected by treating physicians on angina and change in ischemia over one year in this cohort
- To assess the relationship between change in ischemia and change in angina in selected subgroups (by sex, age, presence/severity of atherosclerosis)
- To assess the relationship between severity of non-obstructive atherosclerosis and ischemia at baseline

- To assess the relationship between severity of non-obstructive atherosclerosis and angina at baseline
- To assess the relationship between severity of ischemia and angina at baseline.

In addition the association of severity of ischemia with cardiovascular events over one year (death, MI, stroke, CV hospitalization/ER visits) will be assessed.

21.3 Study Design and Procedures

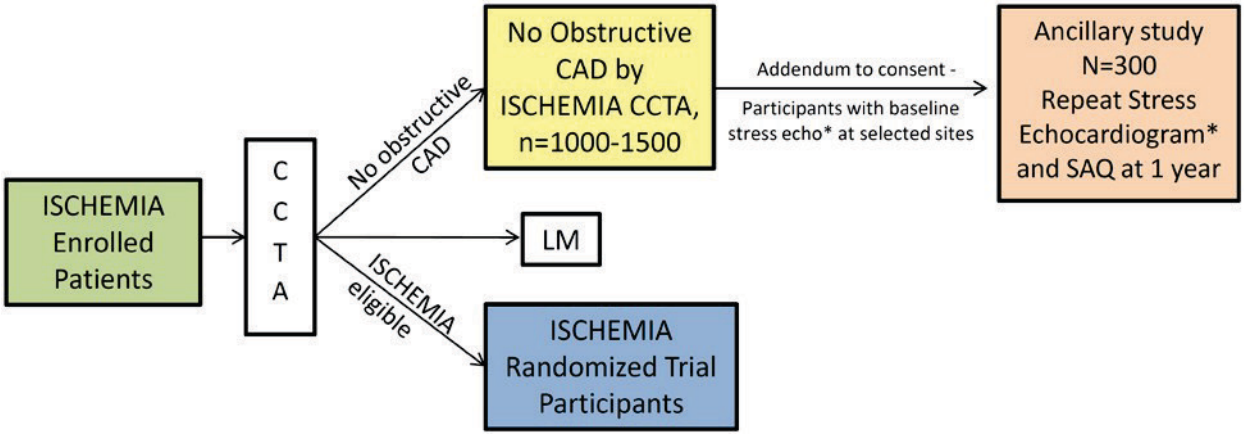
21.3.1 Study Population and Eligibility Criteria

Refer to section 4.3 of the main ISCHEMIA protocol for all inclusion and exclusion criteria for the main study. Participants to be considered for this ancillary study will already have met ischemia (stress echo*) and coronary anatomic (CCTA) entry criteria for the main ISCHEMIA study and will be interested in participating in research as demonstrated by consent to the main study. This approach will maximize enrollment in the ancillary study.

Only participants enrolled after stress echocardiography in the main ISCHEMIA study at participating sites, and who are not randomized due to the absence of obstructive CAD on CCTA will be considered for this ancillary study (see Figure 3)*. Participants enrolled in the CIAO-ISCHEMIA ancillary study are also required to have ischemic symptoms (chest pain or other potential ischemic equivalent).

A total of 300 participants will be enrolled.

Figure 3. Flow of participants into the CIAO-ISCHEMIA ancillary study



* The study may be expanded to include stress CMR wall motion imaging based on enrollment; see MOO for details.

21.3.2 Informed Consent Process

ISCHEMIA anatomic screen failure patients due to non obstructive CAD will be approached for inclusion in this ancillary study. These patients will be presented with an informed consent form which describes in detail the CIAO-ISCHEMIA ancillary study and what participating in the study means. The informed consent form will be signed by those patients who agree to participate in this ancillary study.

21.3.3 Study Flow

Repeat stress wall motion imaging will be performed at one year. Symptoms will be assessed using the SAQ at 6 months and one year. Participants will be routinely treated for their condition according to standard of care guidelines and in accordance with local practice. Medical therapy will not be specified by this ancillary study. Events will be collected and monitored, including hospitalization for angina, hospitalization for heart failure, death, MI, stroke/TIA.

21.3.4 Schedule of Study Assessments

Data collected during screening for the main ISCHEMIA study will be used by the CIAO-ISCHEMIA ancillary study. This data includes general medical and cardiac history which was collected to determine eligibility for the main ISCHEMIA study. The stress imaging study that was used to determine eligibility for the main ISCHEMIA study, and transmitted to the Stress Core Laboratory, will also be used for the CIAO-ISCHEMIA ancillary study.

Baseline Visit

- Patients who have not been randomized to the main ISCHEMIA study will be assessed as potential CIAO-ISCHEMIA ancillary study candidates
- General medical and cardiac history will be reviewed for eligibility according to the eligibility criteria described above
- Informed consent will be obtained from patients who are willing to participate in this ancillary study.
- If Stress Core Lab interpretation has not already been done (by the time of exclusion from the main ISCHEMIA study) it will be done at this time.
- Coronary non-obstructive plaque scoring will be performed based on the CCTA interpretation provided by the CCTA Core Lab for the main ISCHEMIA study
- Physical exam
- Concomitant medications will be reviewed and recorded including use of beta-blockers, calcium channel blockers, long-acting nitrates, ranolazine, ivabrandine/other anti-anginals, statins, other lipid-lowering agents, aspirin, other anti-platelets
- Symptom assessment including the SAQ and CCS Class
- Event assessment and ascertainment including: death, myocardial infarction, unstable angina, stroke, cardiovascular hospitalizations, cardiac catheterization, and coronary revascularization procedures (PCI or CABG)

Visit 2 (6 month follow-up)

- Concomitant medications will be reviewed and recorded including use of beta-blockers, calcium channel blockers, long-acting nitrates, ranolazine, ivabrandine/other anti-anginals, statins, other lipid-lowering agents, aspirin, other anti-platelets
- Symptom assessment including the SAQ and CCS Class
- Event assessment and ascertainment including: death, myocardial infarction, unstable angina, stroke, cardiovascular hospitalizations, cardiac catheterization, and coronary revascularization procedures (PCI or CABG)

End of Study (1 year follow-up)

- Repeat stress echocardiogram (or CMR if the study is expanded to include CMR; see MOO)

- Transmittal to and interpretation by the Stress Core Lab of the repeat stress imaging test
- General medical and cardiac history
- Physical exam
- Concomitant medications will be reviewed and recorded including use of beta-blockers, calcium channel blockers, long-acting nitrates, ranolazine, ivabrandine/other anti-anginals, statins, other lipid-lowering agents, aspirin, other anti-platelets
- Symptom assessment including the SAQ and CCS Class
- Event assessment and ascertainment including: death, myocardial infarction, unstable angina, stroke, cardiovascular hospitalizations, cardiac catheterization, and coronary revascularization procedures (PCI or CABG)

Figure 4: Schedule of Assessments for CIAO-ISCHEMIA ancillary study

	Main Trial	Ancillary Study Baseline Visit	6 month follow up[3]	1 year follow up
Main Trial Consent	X			
Ancillary Study Consent	X	X[1]		
Inclusion/exclusion Criteria assessment	X	X		
Stress Echocardiogram[2]				
Acquisition	X			X
Transmittal to core lab	X			X
Core lab interpretation	X	X		X
Coronary CTA showing no obstructive CAD (core lab interpretation)	X			
Coronary non-obstructive plaque scoring based on core lab interpretation		X		
History and physical		X		X
Concomitant medications		X	X	X
Symptom assessment (including SAQ and CCS class)		X	X	X
Event ascertainment		X	X	X

[1]If not done with main study consent. [2]Or stress CMR, if permitted per the MOO.[3]May be conducted in person or by telephone per participant preference.

See MOO for acquisition of 1-year stress imaging test. Data will be collected in InForm, using the same participant number which was assigned at the time of enrollment in the main study.

21.4 Statistical Considerations

21.4.1 Analysis of the Primary Specific Aim

Primary Analysis

The primary goal of this study is to examine the association between change in angina severity as measured by the SAQ (continuous scale) and change in severity of ischemia as estimated by stress wall motion imaging and quantified by the number of ischemic segments (nIS; ordinal categorical scale) from baseline to one year. It is hypothesized that changes in ischemia and angina over time will be associated, because angina is hypothesized to be due to ischemia in these patients. Alternatively, if ischemia resolves as symptoms continue (including symptoms

which may be considered refractory to medical therapy), we will conclude that symptoms are not due to ischemia. If symptoms resolve but ischemia continues, then either a partial response occurred or symptoms were not due to ischemia. All participants will have nIS ≥3 at baseline due to selection criteria. For primary analysis, ischemia at one year will be categorized as improved (nIS at baseline minus nIS at 1 year is >1) or not improved (nIS at baseline minus nIS at 1 year is ≤1) for all participants with paired data available. This cutpoint of 2 segments with resolution of inducible severe hypokinesis or akinesis was selected to minimize the potential effects of intra/interobserver variability.

Secondary Analyses

Secondary analyses will be performed using change in ischemia (nIS at one year minus nIS at baseline) as an ordinal categorical variable. The association between change in ischemia and change in angina will be examined based on a one-way analysis-of-variance (ANOVA)[7] model, a regression model (e.g., the proportional odds model) and/or logistic regression to estimate the probability of at least moderate angina improvement across categories of ischemia improvement. Sensitivity analysis will be used to assess the validity of study results. Best-case and worst-case scenarios will be considered for imputing the missing values for both nIS and SAQ, resulting in a range of estimates for the association. Given a consistent range of the estimates, the study results will be considered reliable and unaffected by the missing data. The CCC will work with sites to minimize loss to follow up. The 1-year mortality rate is expected to be very low (e.g., 0-2 participants). Predictors of death and loss to follow up will be analyzed.

Sample Size and Power

Sample size calculations are based on the primary analysis, taking into account the likelihood that severity of ischemia at baseline will not be normally distributed based on selection criteria (at least 3 segments with ischemia) and early trial data showing that ~40% of patients are likely to have moderate (as opposed to severe) ischemia on the baseline stress imaging test. Participants will be categorized based on 1-year improvement in ischemia or no improvement, as discussed. Taking into consideration 10% estimated dropout or death rate, use of the two-sided Mann-Whitney test, equal groups and a projected standard deviation of the change in SAQ score of 21 based on prior literature, the sample size of 300 participants will provide 80% power to detect a difference of 7.3 in SAQ score between those with and without improvement in ischemia over one year, at the 0.05 significance level. This difference size is less than the previously described clinically meaningful effect size of 8-10 for the SAQ physical limitation score and 10-20 for the angina frequency score. In the same setting, the study has 90% power to detect an 8.4 difference in SAQ score between those with and without improvement in ischemia at one year with a sample size of 300 and 80% power to detect a difference of 8.5 with a sample size of 220.

Additional Analysis

To determine the stability of ischemia over one year, we will calculate the proportion of patients whose ischemia has resolved (nIS at one year is zero), improved (nIS at baseline minus nIS at 1 year is >1), or did not improve (nIS at baseline minus nIS at 1 year is ≤1). Results will be expressed as percentages and reported with 95% binomial confidence intervals.

To assess angina severity at baseline and over one year, descriptive statistics at baseline and at 1 year will be presented using appropriate measures of center (mean or median) and

variability (standard deviation or interquartile range) overall and with stratification by sex. Changes in angina will be examined using paired t-test or a non-parametric alternative (Wilcoxon signed rank test[10]) depending on whether angina severity measures have normal distribution. Changes of angina severity on categorical scale will be examined using chi-square tests and exact tests of proportions (such as Binomial or Fisher's exact test). [11]

21.4.2 Analysis of Other Specific Aims

Effect of medication classes on angina and change in ischemia
Summary statistics will be used to present frequency of medication use by type of medication and/or by change in angina and change in ischemia. Medications will be classified as anti-anginal (beta blockers, calcium channel blockers, long-acting nitrates, ranolazine, ivabradine, other anti-anginals) or anti-atherosclerotic (aspirin or statin). To explore the impact of medication, we will first examine association between change in angina and change in ischemia in subgroups of patients defined based on whether or not any medication in the grouping (anti-anginal or anti-atherosclerotic) was reported by the patient during follow up. Follow up medications will be used rather than baseline medications based on prior research showing that physicians frequently stop medications after learning of the absence of obstructive CAD.[4,12] It is hypothesized that anti-anginal, but not anti-atherosclerotic, medications will lead to less angina and less ischemia. Next, we will examine whether medication groups modify the relationship between change in angina and change in ischemia based on ANOVA[10]. In this analysis, change in angina is a response variable. Additional analyses will be performed to examine the main, additive, and interactive effects of medication and change in ischemia. In investigating these effects, our analysis may focus on the one most frequently used medication, to improve power. Multivariate adjustments for clinically important variables (e.g., age, sex, characteristics of initial test) will be considered.

Relationship between change in angina and change in ischemia in subgroups
This association will be examined in subgroups of participants categorized by sex, age, presence or absence of atherosclerosis on CCTA performed for the main study, and characteristics of the initial stress test (e.g., use of exercise or dobutamine during stress testing). This may provide insight into the reasons for an association between change in angina and change in ischemia if it is present, or may identify a subgroup in whom the two are associated if the primary analysis does not identify a significant association between these two change variables.

Baseline relationship between severity of non-obstructive atherosclerosis and severity of ischemia
Non-obstructive atherosclerosis severity in each vessel is defined on a categorical scale with three levels based on CCTA core lab interpretation according to guidelines (i.e., 0 stenosis, 1-24% stenosis, 25-49% stenosis). From this information, a composite score representing severity of non-obstructive atherosclerosis throughout the coronary tree will be calculated according to the methods of Lin et al.[13]: each of 16 coronary segments will be assigned a score of 0 for no atherosclerosis or 1 for 1-49% stenosis in the segment. The sum of the segment scores will be the global atherosclerosis score, which varies from 0-16. Although the sensitivity of CCTA for "significant" plaque vs. no significant plaque is lower in distal segments, the ability of CCTA to distinguish between the absence of plaque and the presence of non-obstructive plaque is excellent, ~97%.[14]

Descriptive analysis will be used to present location of ischemia and severity of non-obstructive atherosclerosis at baseline. For this descriptive analysis, atherosclerosis severity will be

presented by vessel (using categories as above) and based on the global atherosclerosis score. The relationship between atherosclerosis severity and ischemia severity will be examined using tests of proportions, such as chi-square tests and exact tests.[11] In addition, the relationship between the global atherosclerosis score and severity of ischemia will be examined using ANOVA and multinomial logistic model, proportional odds model or cumulative logits model. Alternatively, multinomial logistic model may elucidate an effect of the global atherosclerosis score on ischemia severity. Similarly, tests of proportions will be used to examine whether the ischemic segments on the stress imaging study correspond to the artery with the worst stenosis (e.g. test if the proportion of correspondences is significantly different from zero).

For this analysis, we will not attempt to match location of ischemia to location of non-obstructive atherosclerosis. Although this analysis would be of interest, it is quite complicated. In the simple case of anterior wall ischemia and atherosclerosis in the LAD alone, it would be clear that location of atherosclerosis and ischemia matched. However, ischemia may be identified in multiple coronary territories, and atherosclerosis is frequently present in multiple vessels. We considered matching location based on the most severe non-obstructive stenosis, but it is likely that multiple vessels will be categorized as having 25-49% stenosis in some patients in whom only one coronary territory is ischemic, and in that case it would be unclear whether location of ischemia matched the vessel with the greatest degree of atherosclerosis. Based on these and other permutations, we elected not to examine this association in this proposal.

Relationship between severity of non-obstructive atherosclerosis and severity of angina at baseline
The relationship between severity of non-obstructive atherosclerosis on a continuous scale (global score) and severity of angina at baseline (SAQ score) will be explored using linear regression models. Nonparametric alternatives and appropriate transformations will be considered. Next, multivariate linear regression model will be used to examine the relationship between location & severity of non-obstructive atherosclerosis and severity of angina (response variable). Multivariate adjustments for clinically important variables will also be considered.

Relationship between severity of ischemia and severity of angina at baseline
This analysis will follow schemes described above.

21.4.3 Analysis of Events

We will explore the association of severity of angina, ischemia and atherosclerosis with cardiovascular events over 1 year. This analysis will be based on a composite outcome: death, MI, stroke, CV hospitalizations/ER visits. The projected composite event rate is projected to be 10% over one year. Events will be ascertained by sites according to definitions specified in the manual of operations. CV hospitalization and ER visits are expected to be the most common events. Regardless of any independent confirmation, if patients present to hospitals with chest pain/ischemic symptoms, this is an important outcome to the health care system. Summary of mortality predictors: Depending on the number of events, we will consider examining the association with other components of this composite outcome (e.g., death). Descriptive analysis will be used to present baseline severity of angina, ischemia and atherosclerosis in subgroups defined based on the occurrence of cardiovascular events over one year. Appropriate tests of means (two independent samples t-test or Wilcoxon test) and proportions (Chi-square or Fisher's exact) will be used to examine differences. Univariate logistic regression models will be used to study main effects of severity of angina, ischemia and atherosclerosis on the occurrence of the composite cardiovascular event. Additive and interactive effects of these

factors will be studied based on multivariate logistic regression model. Some covariates, such as chest pain, will be included in the model as time-dependent covariates. Adjustments for clinically important variables will also be considered.

Power for analysis of events

Considering two groups of patients (based on severity of ischemia) and estimating that the event rate in one group is 10%, with 150 participants in each group, the two-sided two sample Fisher's exact test will have 62% power to detect an absolute increase in the composite event rate of 10% in patients with more severe ischemia, at the 0.05 significance level.[15] Due to low power, these analyses are considered exploratory and hypothesis-generating. Precision for the event rate is estimated as follows: the projected 95% CI for a projected event rate of 10% with 300 patients would be 0.068, 0.140.

21.4.4 Descriptive Analysis

Characteristics of study participants will be summarized overall and within important subgroups (e.g. by sex). Differences across subgroups will be assessed using T-tests/F-tests for continuous variables (e.g. age) and chi-square tests for categorical variables.[11] The frequency of missing data will be summarized for baseline and follow-up data. Missing data will be investigated by inferring a relationship between baseline characteristics and a 0-1 indicator that defines whether a measurement is observed. The analysis may help identify factors likely to cause measurements to be missing. These analyses will be based on logistic regression model. Baseline characteristics will be summarized as percentages for categorical variables and appropriate measures of center (mean or median) and variability (standard deviation, 25th and 75th percentiles (interquartile range) for continuous variables. In all of the proposed analyses, assumptions will be checked, and non-parametric approaches will be used if assumptions are violated. Multiple comparisons will be addressed by pre-specifying a single primary endpoint for each aim, and other comparisons will be given a secondary status.

21.5 Data and Safety Monitoring Plan

21.5.1 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be appointed by the NHLBI to monitor participant safety and to review performance of the study. Any serious, study related, and unexpected events will be reported to the NIH and the DSMB in an expedited fashion.

21.5.2 Risks and Benefits

Risks

All procedures and tests performed in this ancillary study are commonly performed in clinical practice and have well defined safety profiles. Furthermore, all procedures performed in this study are commonly performed for the patient population enrolled in the study.
The main potential risk in this study is risk of stress imaging. Each participant will already have undergone stress wall motion testing safely at baseline before main study inclusion. Local investigators will assess participants for safety to undergo stress imaging before scheduling the procedure. A very rare but major risk is myocardial infarction and death which happens in less

than 1 in 10,000 procedures. Other side effects during the procedure are chest pain, irregular heartbeat, dizziness and nausea. Per clinical routine, a physician and/or cardiac nurse will supervise the stress test at sites, including monitoring of hemodynamics and symptoms during the test.

Risk Lowering Measures:

Study procedures are designed to manage and minimize risks through careful selection of the patients who participate in the study. Participants will be monitored closely through the study to check on their health. In addition, an independent DSMB will monitor safety of the participants throughout the study (see section 13.1 of the main ISCHEMIA protocol). There is no radiation exposure based on this protocol.

Benefits

The CIAO-ISCHEMIA ancillary study results should provide evidence based data to support management of patients with symptoms and/or ischemia without obstructive CAD.

The one year stress imaging test will be made available for clinical care and may prove useful for risk stratification for future events.[16]

Adverse Event Monitoring

Study-related serious adverse events (SAEs) will be collected on an eCRF which will be part of the overall study's InForm™ database and will ultimately be reviewed by the DSMB. The DSMB will report on all serious and unexpected adverse events or other unanticipated problems that involve risk to study participants or others at any site, and whether these appear to be related to the study-based interventions or research assessment protocols.

21.6 Data Handling and Record Keeping

21.6.1 Data Collection, Management and Security

The same data handling principles apply to the CIAO-ISCHEMIA ancillary study as were described in the main ISCHEMIA protocol (see section 12 of the main ISCHEMIA protocol for complete details). The same web-based EDC system as in the main ISCHEMIA study, InForm, will be used for this ancillary study

Also, the same unique patient identification number assigned by the interactive voice-response system (see section 5.3 of the main ISCHEMIA protocol) at the time of main ISCHEMIA study enrollment will be used for the CIAO-ISCHEMIA ancillary study database to reduce the potential for error and facilitate use of data from the main ISCHEMIA study database to reduce workload.

The CIAO-ISCHEMIA eCRF will record relevant history, symptoms, physical exam, stress imaging studies, vital signs, and clinically ordered laboratory results. Instructions regarding collection of these data elements will mirror those in the main ISCHEMIA study; all of the data elements to be collected are also collected in the main ISCHEMIA study.

Imaging studies will be uploaded by the site using a commercially available internet-based secure server with a software package that de-identifies the DICOM header for the study and

assigns the unique study identifier. Images will be distributed from this server to the stress imaging core lab for interpretation, as is done in the main ISCHEMIA study.
Follow-up visits will be made in person or by telephone to determine symptom status, any re-hospitalizations or ER visits. Attempts to collect follow-up data will be made for all except those who specifically withdraw consent for release of such information.

Hospitalization records will be obtained, and extracted, by site staff for completion of subsequent hospitalization report form (eCRF).

21.7 Ethical Considerations

The CIAO-ISCHEMIA ancillary study will uphold the same ethical and regulatory conditions as the main ISCHEMIA study (see section 14 of the main ISCHEMIA protocol).

21.8 References

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