The **PROMISE** Trial FINAL Protocol

PROspective **M**ulticenter **I**maging **S**tudy for **E**valuation of Chest Pain

Sponsor: National Heart Lung and Blood Institute (NHLBI)

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Investigation of: Diagnostic testing strategies for suspected coronary artery disease (CAD), including use of coronary computed tomographic angiography (CTA)

FINAL Date: **April 12, 2010**
Amended: **February 22, 2011**
April 30, 2013

Investigator Protocol Signature Page

I have read and understand the protocol and agree that it contains all the ethical, legal, and scientific information necessary to conduct this study. I will personally conduct the study as described. I will provide copies of the protocol to all physicians, nurses, and other professional personnel responsible to me who will participate in the study. I am aware that this protocol must be approved by the Institutional Review Board or Ethics Committee. I agree to adhere strictly to the attached protocol. I agree that clinical data entered on case report forms by me and my staff will be supplied to the Duke Clinical Research Institute (DCRI) and may be utilized by the DCRI in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow DCRI monitors and auditors full access to all medical records at the research facility for subjects screened or randomized in the study. I agree to provide all subjects with informed consent forms, as required by government regulations and International Conference on Harmonisation guidelines.

Version Date: Amendment 2

Principal Investigator (print name)	**Site Name and Number**
Principal Investigator (signature)	**Date**

Protocol Version and Amendment Tracking

Version Number/Amendment	Approval Date
1.0	April 12, 2010
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Table of Revisions to NHLBI PROMISE Protocol, Version 2.0

Section	Original	Revision	Rationale
Throughout the document	Made grammatical and spelling corrections		Correctness
Title page; Investigator Protocol Signature Page; Protocol Version and Amendment Tracking page	version number: 1.0 date: February 22, 2011	version number: Amendment 2 date: April 30, 2013	Self-evident

Section	Original	Revision	Rationale
A1	**Secondary Endpoints** • Death or MI or unstable angina hospitalization • Death or MI • Major complications from cardiovascular procedures and testing (stroke, major bleeding, anaphylaxis, and renal failure) • Medical costs, resource use, and incremental cost effectiveness • Health-related quality of life	**Secondary Endpoints** • Death or MI or unstable angina hospitalization • Death or MI • Major complications from cardiovascular procedures and testing (stroke, major bleeding, anaphylaxis, and renal failure requiring dialysis) • Composite endpoint of the primary endpoint or invasive catheterization without obstructive CAD • Invasive catheterization without obstructive CAD (Defined as no stenosis >= 50% in any major epicardial vessel including side branches ≥ 2 mm in diameter, on the first cath performed <= 60 days after randomization)) • Medical costs, resource use, and incremental cost effectiveness • Health-related quality of life (QOL)	Addition of secondary endpoint
A1	The trial will have an approximate 42-month enrollment period and 2-year minimum follow-up period. All subjects will be followed from enrollment until either death or the end of the follow-up period.	The trial will have an approximate 36-month enrollment period and 1-year minimum follow-up period. All subjects will be followed from enrollment until either death or the end of the follow-up period.	Clarify study timeline and patient follow-up period.

Section	Original	Revision	Rationale
A1	**End-of-Study Definition** 2-year minimum follow-up of all patients, with expected 30-month average follow-up for clinical status assessment.	**End-of-Study Definition** 1-year minimum follow-up of all patients, with expected 24-month average follow-up for clinical status assessment.	Clarify study timeline and patient follow-up period.
A1	**Number of Subjects** Approximately 10,000 subjects will be enrolled, which is expected to provide 90% power to detect a 20% reduction in the primary composite event rate in the anatomic testing arm as compared with functional testing.	**Number of Subjects** Approximately 10,000 subjects will be enrolled.	Clarification
A1	**Number of Sites** **~200-250**	**Number of Sites** **~220**	Clarification

Section	Original	Revision	Rationale
1d	Therefore, in response to these needs, the PROMISE trial, a multicenter, randomized, pragmatic trial, is comparing 2 state-of-the-art diagnostic strategies in symptomatic subjects at clinically determined, low-intermediate risk for CAD who require nonurgent testing. The "anatomic" testing strategy uses coronary CTA (greater than or equal to 64-slice) as the initial test. The "functional" stress testing strategy uses physician-selected stress imaging (ECHO or nuclear) or exercise ECG as the initial test. Ten thousand subjects will be randomized over approximately 42 months and followed for a minimum of 2 years (average 2.5 years). All subsequent diagnostic and therapeutic management decisions will be based on the latest clinical practice guideline recommendations and will be at the discretion of the treating care team.	Therefore, in response to these needs, the PROMISE trial, a multicenter, randomized, pragmatic trial, is comparing 2 state-of-the-art diagnostic strategies in symptomatic subjects at clinically determined, low-intermediate risk for CAD who require nonurgent testing. The "anatomic" testing strategy uses coronary CTA (greater than or equal to 64-slice) as the initial test. The "functional" stress testing strategy uses physician-selected stress imaging (echo or nuclear) or exercise ECG as the initial test. Ten thousand subjects will be randomized over approximately 36 months and followed for a minimum of 1 year (average 2 years). All subsequent diagnostic and therapeutic management decisions will be based on the latest clinical practice guideline recommendations and will be at the discretion of the treating care team.	Clarify study timeline and patient follow-up period.
C1	Subjects will be randomized over approximately 42 months and followed for 24 to 48 months (or until the study ends) at 200 to 250 North American primary-care, cardiology, and acute-care practice sites, reflecting the physician specialties and community settings where the vast majority of chest-pain patients receive care.	Subjects will be randomized over approximately 36 months and followed for 12 to 36 months (or until the study ends) at 200 to 250 North American primary-care, cardiology, and acute-care practice sites, reflecting the physician specialties and community settings where the vast majority of chest-pain patients receive care.	Clarify study timeline and patient follow-up period.
C3	The secondary aims are to compare the following clinical and economic outcomes in subjects randomized to initial	The secondary aims are to compare the following clinical and economic outcomes in subjects randomized to initial	Addition of secondary endpoint

Section	Original	Revision	Rationale
	anatomic versus functional diagnostic testing: • Death or MI or unstable angina hospitalization • Death or MI • Major complications from cardiovascular procedures and testing (stroke, major bleeding, anaphylaxis, and renal failure requiring dialysis) • Medical costs, resource use, and incremental cost effectiveness • Health-related quality of life (QOL) In addition, cumulative radiation exposure will be assessed as a secondary safety endpoint.	anatomic versus functional diagnostic testing: • Death or MI or unstable angina hospitalization • Death or MI • Major complications from cardiovascular procedures and testing (stroke, major bleeding, anaphylaxis, and renal failure requiring dialysis) • Composite endpoint of the primary endpoint or invasive catheterization without obstructive CAD • Invasive catheterization without obstructive CAD (Defined as no stenosis >=_50% in any major epicardial vessel including side branches ≥ 2 mm in diameter, on the first cath performed <= 60 days after randomization)) • Medical costs, resource use, and incremental cost effectiveness • Health-related quality of life (QOL)	

Section	Original	Revision	Rationale
C4	The use of a composite clinical endpoint and a subject follow-up of at least 2 years are essential to testing PROMISE's hypothesis of clinical superiority of CTA.	The use of a composite clinical endpoint and a subject follow-up of at least 1 year are essential to testing PROMISE's hypothesis of clinical superiority of CTA.	Change in study timeline and patient follow-up period
D1		Figure 1 changed to incorporate changes to secondary endpoint.	Addition of secondary endpoint
E2		Table changed to reflect follow-up of no more than 36 months.	Change in study timeline and patient follow-up period.
E2	• QOL questionnaires will be completed at 6 months, and annually for a minimum of 12 and maximum of 24 months post-randomization (for patients enrolled in QOL).	• QOL questionnaires will be completed at 6 months, 12 months, and 24 months post-randomization (among patients followed for 24 months).	Change in study timeline and patient follow-up period
E4	***Myocardial Infarction*** Defined as either 1) an abnormal cardiac biomarker level (either troponin or CK-MB) greater than institutional upper limit of normal (ULN), and either ischemic discomfort lasting greater than 10 minutes or ECG changes indicative of ischemia or infarction, or 2) new abnormal Q waves consistent with infarction. Additionally *peri-procedural infarctions* are defined as greater than 3x ULN for serum CK-MB for PCI and greater than 5x ULN for CABG.	***Myocardial Infarction*** Defined as either 1) an abnormal cardiac biomarker level (either troponin or CK-MB) greater than institutional upper limit of normal (ULN), and either ischemic discomfort lasting greater than 10 minutes or ECG changes indicative of ischemia or infarction, or 2) new abnormal Q waves consistent with infarction. Additionally *peri-procedural infarctions* are defined as greater than 3x ULN for serum CK-MB for PCI and greater	Clarification

Section	Original	Revision	Rationale
		than 5x ULN for CABG. • an abnormal cardiac biomarker level > institutional ULN (either troponin or CK-MB), and either ischemic discomfort lasting > 10 minutes or ECG changes indicative of ischemia or infarction, *OR* • new abnormal Q waves consistent with infarction. Additionally *peri-procedural infarctions* are defined as >3x upper limit of normal for serum CK-MB for PCI and >5x upper limit of normal for CABG.	
E4	***Unstable Angina Hospitalization*** Defined as 1) ischemic discomfort or equivalent symptoms requiring hospitalization within 48 hours of symptoms, 2) lasting greater than or equal to 10 minutes at rest, or in an accelerating pattern, 3) accompanied by dynamic ST depression, ischemia on stress testing, or significant epicardial coronary artery stenosis, and 4) considered to be myocardial ischemia upon final diagnosis.	***Unstable Angina Hospitalization*** Defined as 1) ischemic discomfort or equivalent symptoms requiring hospitalization within 48 hours of symptoms, 2) lasting greater than or equal to 10 minutes at rest, or in an accelerating pattern, 3) accompanied by dynamic ST depression, ischemia on stress testing, or significant epicardial coronary artery stenosis, and 4) considered to be myocardial ischemia upon final diagnosis. Is defined as an event in which the final diagnosis is unstable angina or acute coronary syndrome	Clarification

Section	Original	Revision	Rationale
		due to myocardial ischemia and has the following criteria: • ischemic discomfort or equivalent symptoms requiring hospitalization within 48 hours of symptoms, lasting ≥ 10 minutes at rest • ***OR*** • ischemic discomfort or equivalent symptoms occurring in an accelerated pattern within 48 hours of hospitalization ***AND ANY OF THE FOLLOWING*** • accompanied by dynamic ST depression • ischemia on stress testing • significant epicardial coronary artery stenosis	
E4		***Addition*** ***Invasive catheterization without obstructive coronary artery disease*** Only the results of the initial (first) invasive cardiac catheterization that occurs within the first 60 days following randomization will be considered for the secondary endpoints which include invasive angiography without obstructive disease. The absence of obstructive disease is defined as no stenosis >= 50% in any	Addition of secondary endpoint

Section	Original	Revision	Rationale
		major epicardial vessel including side branches ≥ 2 mm in diameter.	
E5	An independent clinical event adjudication committee will review and adjudicate all primary endpoint events in a blinded fashion based on the definitions presented above. The clinical secondary endpoint events and cumulative radiation exposure will not be adjudicated.	An independent clinical event adjudication committee will review and adjudicate all primary endpoint events and the catheterization secondary endpoints in a blinded fashion based on the definitions presented above. If the invasive cardiac catheterization report is inconclusive, the CEC will review the catheterization films for a visual assessment of CAD. The other clinical secondary endpoint events and cumulative radiation exposure will not be adjudicated.	Addition of secondary endpoint
E6	Baseline QOL interviews will be administered to subjects by site personnel as soon as possible after consent, preferably before the subject's randomization. Completed questionnaires will be sent directly to the EQOL CC for data processing. Follow-up QOL questionnaires will be administered to subjects via structured telephone interview by DOFG trained and supervised interviewers at 6 and 12 months postrandomization and annually thereafter until the end of the study. Proxy QOL questionnaires will be used when a subject has died in the follow-up interval	Baseline QOL interviews will be administered to ~6000 subjects enrolled (prior to July 2012) by site personnel as soon as possible after consent, preferably before the subject's randomization. Completed questionnaires will be sent directly to the EQOL CC for data processing. Follow-up QOL questionnaires will be administered to via structured telephone interview by DOFG trained and supervised interviewers at at 6 months, 12 months, and 24 months post-	Change in study timeline.

Section	Original	Revision	Rationale
	or has become incapacitated; these questionnaires will include items that can be reliably obtained from a relative, caretaker, or medical record. Proxy questionnaires will be used if the subject is unable to participate in follow-ups via telephone interview.	randomization (among patients followed for 24 months). Proxy QOL questionnaires will be used when a subject has died in the follow-up interval or has become incapacitated; these questionnaires will include items that can be reliably obtained from a relative, caretaker, or medical record. Proxy questionnaires will be used if the subject is unable to participate in follow-ups via telephone interview.	
F2, 2c	Two important components of information from the diagnostic test QA activity will be analyzed by the SDCC. The DTCC will review every subjects' initial diagnostic test for technical quality	Two important components of information from the diagnostic test QA activity will be analyzed by the SDCC. The DTCC will review the first 8000 subjects' initial diagnostic test for technical quality.	Change in study timeline
F2, 2c	The second important component of information from the diagnostic test QA activity is the quality of test interpretations. Approximately 20% of tests will be overread by the DTCC using a categorical level of coronary disease risk.	The second important component of information from the diagnostic test QA activity is the quality of test interpretations. Approximately 10% of tests will be overread by the DTCC using a categorical level of coronary disease risk.	Change in study timeline
F3		References corrected	Correction
I3		Study Timeline figure adjusted	Change in study timeline and patient follow-up period.
J	93. GORDON LAN KK, DEMETS DL. Discrete	93. Lan GKK, DeMets DL. Discrete sequential	Correction

Section	Original	Revision	Rationale
	sequential boundaries for clinical trials. *Biometrika*. 1983;70(3):659 -663.	boundaries for clinical trials. *Biometrika*. 1983;70(3):659 -663.	

TABLE OF ABBREVIATIONS

ABI	ankle brachial index
ACC	American College of Cardiology
ACRIN	American College of Radiology Imaging Network
ACS	acute coronary syndrome
AHA	American Heart Association
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCC	Clinical Coordinating Center
CD	compact disc
CI	confidence interval
CK-MB	creatine kinase-myocardial band
COCATS	Core Cardiology Training Symposium
CTA	coronary tomographic angiography
DASI	Duke Activity Status Index
DCRI	Duke Clinical Research Institute
DOFG	Duke Clinical Research Institute Outcomes and Follow-up Group
DSMB	Data and Safety Monitoring Board
DTCC	Diagnostic Testing Coordinating Center
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
EQOL CC	Economics and Quality of Life Coordinating Center
g/L	grams per liter
HDL	high-density lipoprotein
IEC	institutional ethics committee
IRB	institutional review board
IVRS	interactive voice response system
LDL	low-density lipoprotein
LV	left ventricular
MAR	missing at random
MI	myocardial infarction

MOP	manual of procedures
mSv	millisievert
NCDR	National Cardiovascular Data Registry
NHLBI	National Heart Lung and Blood Institute (U.S.)
PAD	peripheral arterial disease
PCI	percutaneous coronary intervention
PI	principal investigator
PROMISE	PROspective Multicenter Imaging Study for Evaluation of Chest Pain
QA	quality assurance
QOL	quality of life
ROC	receiver operating characteristic
SAQ	Seattle Angina Questionnaire
SDCC	Statistical and Data Coordinating Center
SF-12	Medical Outcomes Study Short Form
ULN	upper limit of normal

A Introduction

A1 *Study Synopsis*

Sponsor	National Heart Lung and Blood Institute (NHLBI)
Protocol Title	The PROMISE Trial - **PRO**spective **M**ulticenter **I**maging **S**tudy for **E**valuation of Chest Pain
Diagnosis and Main Criterion for Inclusion	Symptomatic subjects without known coronary artery disease (CAD) for whom a nonemergent, noninvasive cardiovascular diagnostic test for CAD is planned.
Primary Study Objective	To determine whether an initial noninvasive anatomic imaging strategy with coronary computed tomographic angiography (CTA) will improve clinical outcomes in subjects with symptoms concerning for CAD relative to an initial functional testing strategy.
Primary Endpoint	Time to first event using the composite of the following major cardiovascular events: • Death • Myocardial infarction (MI) • Major complications from cardiovascular procedures including testing (stroke, major bleeding, anaphylaxis and renal failure) • Unstable angina hospitalization
Secondary Endpoints	• Death or MI or unstable angina hospitalization • Death or MI • Major complications from cardiovascular procedures and testing (stroke, major bleeding, anaphylaxis, and renal failure requiring dialysis) • Composite endpoint of the primary endpoint or invasive catheterization without obstructive CAD • Invasive catheterization without obstructive CAD (Defined as no stenosis >= 50% in any major epicardial vessel including side branches ≥ 2 mm in diameter, on the first cath performed <= 60 days after randomization)) • Medical costs, resource use, and incremental cost effectiveness • Health-related quality of life (QOL)

Secondary Safety Endpoint	Cumulative radiation exposure
Primary Hypothesis	An initial anatomic testing strategy will provide information that will result in superior long-term health outcomes as compared with an initial functional testing strategy.
Study Design	Pragmatic randomized trial of clinical effectiveness of diagnostic testing strategies for CAD, to be performed in outpatient settings, including urgent care, primary care, and cardiology offices. Qualifying patients presenting with new or worsening symptoms suspicious for clinically significant CAD who require diagnostic testing and have not been previously evaluated for this episode of symptoms will be randomized to an initial strategy of either anatomic or functional testing. All subsequent decisions regarding additional testing, medications, and/or procedures will be at the discretion of the responsible clinical care team. Within the functional testing arm, the subject's care team will select the specific test to be performed (exercise electrocardiogram, stress nuclear imaging, or stress echocardiogram) consistent with "usual care" in that practice setting. The subject's care team will be provided with "Information sheets" summarizing current standards for test interpretation and preventive care, but specific medical treatment will not be mandated by the trial.
Duration of Study Participation	The trial will have an approximate 36-month enrollment period and 1-year minimum follow-up period. All subjects will be followed from enrollment until either death or the end of the follow-up period.
End-of-Study Definition	1-year minimum follow-up of all patients, with expected 24-month average follow-up for clinical status assessment.
Number of Subjects	Approximately 10,000 subjects will be enrolled.
Number of Sites	~220
Study Follow-up	The sites will conduct the initial study follow-up at 60 (+/-14) days. Follow-up contact at 6 months post-randomization and every 6 months thereafter will be conducted centrally by the Duke Clinical Research Institute or its designees.

A2 *Primary Hypothesis*

The PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) hypothesis is that an initial anatomic testing strategy utilizing 64-slice or better coronary computed tomographic angiography (CTA) technology in subjects with low-to-intermediate risk for coronary artery disease (CAD) will reduce the composite primary endpoint (all-cause death, myocardial infarction [MI], major peri-procedural

complications, and hospitalization for unstable angina) when compared with an initial functional testing strategy over an average of 2.5 years of follow-up.

A3 *Significance of the Study*

PROMISE is the first large randomized trial comparing the 2 major alternative noninvasive diagnostic strategies for the initial assessment of stable symptoms suspicious for possible CAD. Community-based practices are anticipated to contribute substantially to subject enrollment, which will enhance generalizability of findings in contrast to previous smaller studies that relied on “expert” centers staffed by cardiologists and radiologists. This trial will provide an unbiased comparison of usual-care testing strategies with new CTA technology that is expected to yield definitive and unique evidence regarding the benefits and risks of these alternative approaches, with the primary endpoint being superior health outcomes.

B Background

B1 *Prior Literature and Studies*

1.a Current Management of Patients with Chest Pain: Extent of the Problem

Chest pain is a common presentation, with ~4 million Americans newly diagnosed with angina[1] and more than 6 million presenting to emergency rooms with chest pain annually.[2] The annual incidence of new angina ranges from 1% in middle-aged women to nearly 4% in elderly men in the U.S.,[1] with rates in diabetics of up to 10%.[3] Overall mortality is doubled compared with the general population, and rates range from less than 1% per year for those ultimately diagnosed as "nonanginal" to almost 10% per year for those with CAD and an unfavorable clinical risk profile.[4-8] (See Table 1.) These data suggest that between 4 and 5 million Americans require noninvasive testing for chest-pain symptoms every year. The high event rates in unselected but symptomatic populations support performance of a randomized trial to define optimal testing strategies in this at-risk group and to guide care.

Table 1: Event Rates in Populations with New Onset Chest Pain

Study	Population	Endpoint	Lowest event rates	Highest event rates	Follow-up
Daly BMJ 2006[4]	3,031 (58%M)	Death, MI	2.3% overall	3.9% with angiographic CAD	1 year
Mudrick Circ 2009[8]	98,872	Death, MI, Stroke	1.07%	N/A	1 year
Sekhri Heart 2007[9]	8,762 (52%M)	Death, MI, Unstable angina hospitalization	0.83% noncardiac CP	8.62% angina	1 year
			2.73% noncardiac CP	16.52% angina	3 years
Sekhri BMJ 2008[5]	8,176 (53%M)	Coronary death, MI	3-9% nonspecific CP	16-19% typical CP	2.5 years
Clayton BMJ 2005[6]	7,311 (79%M)	Death, MI, stroke	4% lowest risk decile	35% highest risk decile	5 years

MI=myocardial infarction; CAD=coronary artery disease; N/A=not applicable; CP=chest pain

In patients presenting with symptoms suggestive of CAD, such as chest pain or exertional dyspnea, the clinical risk profile and presentation are often insufficient to definitively exclude CAD and/or are not sufficient to implement invasive evaluation or revascularization without additional information. Thus, noninvasive diagnostic testing is required in the majority of such patients. Consistent with these data, an exercise electrocardiogram (ECG) was performed in 65% of all British chest-pain patients,[7] rising to over 90% in those eventually diagnosed with angina. In the Euro Heart Survey of Chronic Stable Angina, 76% of patients received an exercise ECG, while 18% had a stress imaging study, and 64% had a resting echocardiogram. A coronary angiogram was performed or planned in 41%.[10]

1.b Current Diagnostic Strategies Using Functional Tests are Inadequate

American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines and current noninvasive diagnostic testing includes exercise ECG, stress echo and stress nuclear imaging, all of which are based on detecting stress-induced myocardial ischemia caused by obstructive CAD.[11-13] All are also associated with high rates of

false-positive and false-negative results in the detection of significant CAD (defined as a left main obstruction greater than or equal to 50% and/or any major epicardial vessel obstruction greater than or equal to 70%), limited prognostic discrimination, relatively short "warranty period" for a negative test, and an inability to detect possibly significant nonobstructive CAD. The literature regarding functional test characteristics is summarized below in Table 2, along with reports of clinical event rates after testing.

False-negative test results may delay needed treatments and lead to worse clinical outcomes, while false-positive test results may lead to unnecessary treatment and procedures. Evidence of the inadequacies of current diagnostic strategies includes the occurrence of undetected MI (2.1%) and unstable angina (2.3%) in patients with suspected acute coronary syndrome (ACS) who are discharged from the emergency room.[14] A missed diagnosis of MI was associated with a 9.8% 30-day mortality vs. only 5.7% in hospitalized patients, or a relative risk of 1.9. Other relevant evidence comes from an analysis of the large ACC National Cardiovascular Data Registry, which suggests that misdiagnosis of chest pain is common in community practice.[15] Of nearly 400,000 patients without known CAD who underwent elective diagnostic catheterization, 84% had prior noninvasive testing, which was positive in 82%. Nevertheless, only 38% of patients overall, and 41% of those with positive tests, had obstructive CAD (left main stenosis greater than or equal to 50%; major epicardial vessel greater than or equal to 70%). Thus current clinical practice, as guided by functional stress testing, results in a pattern of referral to invasive angiography, which does not lead to revascularization in the majority of patients, despite the inherent risks and expense of an invasive test.

1.c Computed Tomographic Angiography is Highly Accurate in Detecting and Excluding Obstructive and Nonobstructive Coronary Artery Disease

The recent technological advance of coronary CTA permits direct visualization of the coronary arteries, allowing noninvasive detection of significant stenoses and with great accuracy.[16-19] Computed tomographic angiography also extends the spectrum of disease by detecting nonobstructive lesions and visualizing coronary plaque, important prognostic predictors. Computed tomographic angiography test characteristics and associated event rates are shown in Table 2 below. The superior ability of CTA to detect obstructive CAD means that patients at greatest risk will be more accurately identified and treated with life-saving therapies proven to reduce death and MI by about 30%,[20] while those without disease will not be subjected to unnecessary additional, perhaps invasive, testing.

Table 2: Diagnostic Test Characteristics and Resulting Event Rates

	Stress Nuclear	Stress Echo	Exercise ECG	CTA
TEST CHARACTERISTICS (CAD with stenosis ≥ 70%; LM ≥ 50%)				
Sensitivity	76%–94%[21-24]	87%–88%[21-24]	52%[21]	85%–99%[25]
Specificity	62%-88%[21-24]	77%-84%[21-24]	71%[21]	82%–95%[25]

Event Rate after Negative Study (Prognostic Accuracy)	0.5%–2.0%/yr[26-30]	0.5%–2.0%/yr[26-30]	3%/yr[5]	< 0.3%–0.4%/yr without plaque; 1.1%without significant stenosis[31-33]
Event Rate after Positive Study (Prognostic Accuracy)				1.6%/yr with any plaque; 11.9% with any stenosis[31]
Detection of Nonobstructive CAD	N/A	N/A	N/A	Yes[31]
OVERALL EVENT RATES (1 yr; all patients)				
Death	0.45%–2.5%[34-37]	2.9%–6.6%[38-40]	0.5%–5.0%[41-43]	0.3%–2.2%[32,33,44-47]
Nonfatal MI	0.9%–1.3%[34-37]	0.9%–1.3%[38-40]	-	0.4%–0.6%[32,33,44-47]
Unstable Angina Hospitalization	3.8%	-	-	0.2&–4.2%

Echo=echocardiogram; ECG=electrocardiogram; CTA=computed tomographic angiography; CAD=coronary artery disease; LM=left main; yr=year; N/A=not applicable; MI=myocardial infarction

1.d Additional Important Considerations in Comparing Test Characteristics

Limited Evidence Base to Guide Diagnostic Testing

The majority of the studies discussed above were conducted in single academic centers and are plagued by numerous sources of bias (verification, selection, etc.), making evaluation of true accuracy very difficult.[48,49] Data from academic research settings provide only a rough indication of actual performance in the real world.[50-52] Even these data, however, are based on convenience samples of subjects already referred for a particular test rather than the true population of interest.[50] The absence of high-quality unbiased comparative data on test performance and outcomes has led to the unusual situation of conflicting ACC/AHA Guidelines, with each of these relevant documents recommending the initial use of a different test: treadmill ECG, stress echo, or stress perfusion imaging.[11-13,53,54] Further, very few studies have addressed Fryback and Thornberry's highest levels of evidence for assessing diagnostic testing: subject outcome efficacy and societal efficacy.[55] This situation has resulted in clinical confusion, performance of multiple tests, and marked variation in clinical practice that can only be addressed by high-quality effectiveness research based on improving patient outcomes.

Obstructive CAD Relatively Uncommon; Nonobstructive CAD Common, Clinically Important, and Difficult to Detect with Functional Tests

The National Cardiovascular Data Registry (NCDR) analysis shows that the absence of significant obstructive disease is common in patients undergoing diagnostic

catheterization. Of the 62% of patients without significant CAD, two-thirds had nonobstructive CAD (20%-70% epicardial and less than 50% left main) and one-third had no CAD (defined as stenosis less than 20%).[15] A similar pattern has been noted by others: in 400 patients at low-intermediate risk for CAD undergoing CTA, 47% had nonobstructive CAD, 13% had obstructive stenoses, and 27% had no disease, with 13% of scans being inconclusive.[45] These data are similar to Ostrom et al[33] and the Michigan Advanced Cardiovascular Imaging Consortium findings. In this registry of over 4000 subjects very similar to PROMISE's target population, it was noted by the investigators that 40% had nonobstructive disease, 41% had normal anatomy, and only 14% had lesions greater than or equal to 70% (written communication from Gil Raff, 2008). Finally, only 14% of the subjects in a multicenter CTA study, Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography (ACCURACY), had obstructive disease (defined as stenosis greater than or equal to 70%) on catheterization.[16] Thus, current clinical data suggest that nonobstructive CAD will be frequent and obstructive CAD relatively uncommon in the PROMISE cohort.

Long-term outcomes in subjects with nonobstructive disease on angiography, such as was found in 39% of the NCDR cohort,[15] have been found to be intermediate between subjects with obstructive CAD or with no disease.[56,57] This is consistent with the known prognostic power of coronary calcium scoring,[56] and an observed 2x increase in death in patients with nonobstructive disease compared with those with normal coronary anatomy on CTA.[33,45] The knowledge that most MIs arise from nonobstructive lesions[58,59] provides biologic plausibility to these observed differences in outcomes. Since functional testing relies upon inducing ischemia due to limited coronary flow reserve in the presence of obstructive lesions, it cannot detect potentially important nonobstructive disease. Patients receiving these tests will have undetected nonobstructive disease. In contrast, nonobstructive disease is routinely detected by CTA, yielding information that may be important for properly adjusting the intensity of preventive therapy to reflect the presence of coronary plaque.

Therefore, in response to these needs, the PROMISE trial, a multicenter, randomized, pragmatic trial, is comparing 2 state-of-the-art diagnostic strategies in symptomatic subjects at clinically determined, low-intermediate risk for CAD who require nonurgent testing. The "anatomic" testing strategy uses coronary CTA (greater than or equal to 64-slice) as the initial test. The "functional" stress testing strategy uses physician-selected stress imaging (echo or nuclear) or exercise ECG as the initial test. Ten thousand subjects will be randomized over approximately 36 months and followed for a minimum of 1 year (average approximately 2 years). All subsequent diagnostic and therapeutic management decisions will be based on the latest clinical practice guideline recommendations and will be at the discretion of the treating care team.

B2 *Rationale: The Urgent Need for a Randomized Trial of Diagnostic Strategies in Subjects with Suspected Coronary Artery Disease*

Millions of patients undergo different diagnostic testing for suspected CAD in the U.S. every year despite little or no evidence that it will improve their outcomes. The remarkable imprecision and inefficiency of current evaluation strategies is perhaps best documented by the high rate (up to 60%) of invasive coronary angiograms in which no

significant CAD is detected,[15] while the U.S. economic burden of caring for patients with chest pain exceeds $75 billion/year.[60] Limitations of current tests, an inadequate evidence base, and escalating costs have led all major professional societies, Centers for Medicare and Medicaid Services, and National Institutes of Health to publicly demand the development of new evidence to optimize the clinical use of diagnostic testing, reduce unnecessary invasive procedures and control costs. Further, all stakeholders have called for further investigation of the appropriate role of coronary CTA, a novel diagnostic imaging technology that may potentially change the standard of care in this common but challenging situation.[48,52,61-63]

The problem at hand must be addressed by an effectiveness trial, as examination of efficacy only (i.e., optimal performance at expert sites) would fail to capture the actual performance of diagnostic strategies in the community where the vast majority of these tests are performed and where future clinical decisions based on trial results will impact patient outcomes. The concept of a pragmatic clinical trial, as proposed by Tunis et l,[64] is an ideal format to acquire the quality of evidence required to address the needs of clinical decision makers. The PROMISE study embodies all the characteristics of such a trial, including (1) incorporation of clinically relevant alternatives, including usual clinical testing and usual clinical care; (2) a diverse study population; (3) heterogeneous practice settings; and (4) use of a broad range of health outcomes rather than focusing solely on cost. Each of these features is essential to establish an evidence-based standard of care for the large number of patients who require diagnostic testing for symptoms of CAD.

Thus, the ideal approach to addressing these problems is a randomized trial of different testing strategies that is adequately powered to demonstrate superior clinical outcomes, as only improved patient health would be sufficiently motivating to change practice and justify the routine use and reimbursement of a new technology. Because test-reimbursement policies can be expected to evolve and change in response to many nonmedical forces in the economy, conclusions based primarily on the differential costs of alternative testing strategies are unstable over the long term. The ideal trial must also directly target the clinical outcomes that are most relevant to assessing value. Finally, the ideal trial must ensure the broadest possible applicability of its results by demonstrating real-world effectiveness across the appropriate spectrum of tests, practice settings, and caregiver specialties and expertise, which are pertinent to the clinical decisions needed to care for the vast majority of chest-pain patients nationwide. The PROMISE trial design has been shaped by these objectives.

C Study Overview and Objectives

C1 *Overview of the PROMISE Trial*

PROMISE is a multicenter, randomized, pragmatic trial comparing 2 state-of-the-art diagnostic strategies in approximately 10,000 symptomatic, low-to-intermediate–risk subjects with suspected CAD who require nonurgent testing. One testing arm will use an “anatomic” testing strategy with coronary CTA (greater than or equal to 64-slice) as the initial test. The other arm, or “functional” testing strategy, will use either stress imaging (echo or nuclear) or exercise ECG as the initial test. All subsequent diagnostic and therapeutic management will be at the discretion of the treating care team. The trial will encourage adherence to evidence-based practice and document actual therapies used, but will not mandate specific care plans, which will be left to the discretion of the clinical

care team. Subjects will be randomized over approximately 36 months and followed for 12 to 36 months (or until the study ends) at 200 to 250 North American primary-care, cardiology, and acute-care practice sites, reflecting the physician specialties and community settings where the vast majority of chest-pain patients receive care.

C2 *Primary Aim*

The primary aim of PROMISE is to determine if an initial anatomic testing strategy with CTA (greater than or equal to 64-slice; anatomic care) in symptomatic subjects with low-to-intermediate risk for CAD will reduce the composite primary endpoint (all-cause death, MI, major peri-procedural complications, and hospitalization for unstable angina) when compared with an initial functional testing strategy (stress echo, stress nuclear, or exercise ECG), over an average of 2.5 years of follow-up (range approximately 2–4 years, or until the end of the study).

The primary endpoint is time to the first event in a composite of major cardiovascular events including:

- Death
- MI
- Major complications from cardiovascular procedures and testing (stroke, major bleeding, anaphylaxis, and renal failure requiring dialysis)
- Unstable angina hospitalization

C3 *Secondary Aims*

The secondary aims are to compare the following clinical and economic outcomes in subjects randomized to initial anatomic versus functional diagnostic testing:

- Death or MI or unstable angina hospitalization
- Death or MI
- Major complications from cardiovascular procedures and testing (stroke, major bleeding, anaphylaxis, and renal failure requiring dialysis)
- Composite endpoint of the primary endpoint or invasive catheterization without obstructive CAD
- Invasive catheterization without obstructive CAD (Defined as no stenosis >= 50% in any major epicardial vessel including side branches ≥ 2 mm in diameter, on the first cath performed <= 60 days after randomization))
- Medical costs, resource use, and incremental cost effectiveness
- Health-related quality of life (QOL)

In addition, cumulative radiation exposure will be assessed as a secondary safety endpoint.

C4 *Rationale for the Selection of Outcome Measures*

Rationale for Clinical Assessments

Because patients with CAD remain at risk for major adverse events related to their disease over their lifetimes, consideration of long-term outcomes is essential to exploring the impact of test selection on health outcomes and costs. The endpoints of all-cause death, nonfatal MI, major complications related to cardiovascular procedures, and unstable angina hospitalizations are clinically relevant and together reflect the success or failure of the diagnostic testing strategy to accurately detect or exclude disease, guide procedural care, and provide useful long-term prognostic information with high confidence. Any event that could potentially be influenced by the anatomic information provided by CTA, such as percutaneous coronary intervention (PCI), is excluded as an endpoint regardless of when during the follow-up period it occurred. Conversely, major peri-procedural complications are included, as these are a potentially important cause of harm resulting from a need for an invasive study due to inaccurate initial diagnostic tests. The use of a composite clinical endpoint and a subject follow-up of at least 1 year are essential to testing PROMISE's hypothesis of clinical superiority of CTA.

Rationale for Economic and QOL Assessments

The use of noninvasive diagnostic testing for the assessment of CAD has grown at a far faster rate than other medical care, including related procedures such as cardiac catheterization or revascularization.[65] Cardiac diagnostic testing now costs over $4 billion annually for Medicare Part B alone.[66] Although these unsustainable testing costs mandate the development of better evidence, recent efforts by payers to reduce costs have largely addressed the number of tests performed, or payment per test, rather than the value derived for guiding patient care. Thus testing is increasingly driven by onerous administrative practices such as prior authorization designed to discourage physicians from providing indicated care[67] or drastic reductions in reimbursement. This default approach is not in the best interests of either patients or our increasingly dysfunctional health care system.

The studies that have examined the costs and cost effectiveness of functional vs. anatomic testing strategies to date are limited by the lack of reliable long-term effectiveness and cost data.[24,44,68,69] Thus, a formal examination of the incremental cost of testing and its value for patients is urgently needed and is an essential part of the PROMISE trial.

C5 *Rationale for Selection of Testing in Each Experimental Arm*

Functional Testing Arm: Stress Nuclear, Stress Echo, and Exercise ECG

Each of these procedures is a well-established and accepted strategy to diagnose CAD. Each has also been in routine clinical use for over 20 years and is well supported by class I, level of evidence B ACC/AHA practice guideline recommendations for use in suspected CAD. The guidelines further document specific indications as well as diagnostic and prognostic performance. (See also Table 2.) A national claims database (United HealthCare) documenting contemporary U.S. testing patterns shows that stress

nuclear exams constitute 61% of tests, with stress echo at 18% and exercise ECG at 21%. Computed tomographic angiography and stress magnetic resonance imaging comprised less than 1% each. Seventy-nine percent of tests were performed with exercise stress.[8] The lack of a single dominant diagnostic strategy for current practice, even in this insured population, highlights the essential need for flexibility and breadth in the choice of functional tests to fully reflect real-world diagnostic practices and maximize generalizability and clinical impact. Thus it is essential that exercise ECG, stress echo, and stress nuclear imaging are all included in the functional testing arm.

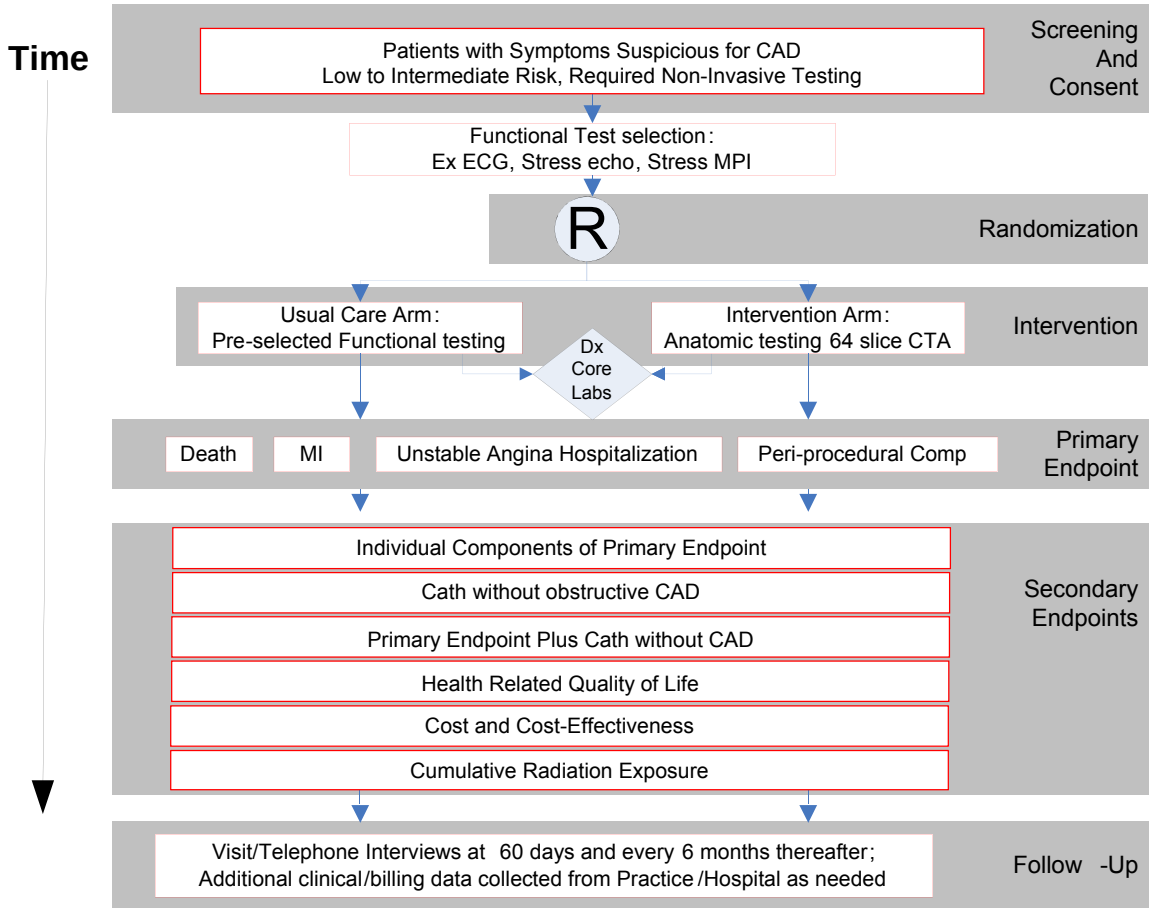
Anatomic Testing Arm: CTA

Because CTA is quick, robust, readily available, and accurate, it may lead to a major practice shift in the evaluation of chest pain where a strategy of imaging coronary anatomy is preferred over the current practice of first searching for inducible ischemia using functional testing. In this sense its widespread adoption would represent substantial change, as it may improve diagnostic testing in an unexpected way (through anatomic rather than functional information) and may alter the indications for testing, thereby expanding the patient population being tested. Further, there is evidence of increasing physician confidence over time,[70] a hallmark of an improved diagnostic testing strategy.[71] This growing experience indicates that the greatest strength of CTA may lie in excluding obstructive CAD in lower-prevalence cohorts—exactly the symptomatic population being studied in PROMISE.[72] Finally, because of its visual strength, CTA has an inherent important motivational ability that has been shown to improve prescription and adherence to effective preventive strategies, an important goal of any testing strategy.[73] On the other hand, CTA cannot be performed in all patients, as calcified lesions and temporal and spatial resolution can be limiting. However, evidence suggests that CTA is superior to functional testing in reducing false-positive and false-negative test results, identifying nonobstructive disease, improving the prognostic accuracy of a negative test, and extending the “warranty period” of test results, all of which strongly suggest clinical superiority over functional testing.

D Investigational Plan

D1 *Overview of Trial Design*

PROMISE is a multicenter, randomized, pragmatic trial comparing 2 state-of-the-art diagnostic strategies in approximately 10,000 symptomatic, low-to-intermediate CAD-risk subjects with suspected CAD who require nonurgent testing. The following discussion includes trial assessments, outcomes, substudies, organization and operations, sites and site management, timeline, and potential criticisms. See the figure below for a schematic summary of the trial design.



D2 *Subject Population*

To optimize the generalizability of the study results and reflect current patterns of care, subjects considered for enrollment into PROMISE will be outpatients without known CAD who are symptomatic, and whose physician has decided that the subject requires nonurgent, noninvasive cardiovascular testing to further evaluate suspected CAD. This population is purposefully and carefully chosen to be directly reflective of the population in which elective noninvasive cardiac diagnostic testing is currently being used.

PROMISE's inclusion criteria stipulate that all subjects will be symptomatic and will, in the judgment of the physician caring for the subject, require an elective noninvasive test

for symptoms suspicious for CAD. Thus, whether or not the subject chooses to participate in the trial, he or she will likely undergo testing. All of the modalities in PROMISE are clinically well established and performed routinely and safely across the U.S. No experimental treatment or testing is involved, and there should be equipoise about the feasibility to perform either functional OR anatomic testing. **The trial intervention is simply the random assignment of the initial test.**

Justification of Population

Since subjects are symptomatic and have already been determined to require outpatient noninvasive testing, this is an ideal population in which to compare the results of different testing strategies. We include subjects presenting in primary care offices, cardiology offices, and urgent care settings without suspected ACS to ensure inclusion of all subject profiles; however, patients undergoing testing as part of a rule-out-ACS protocol are not eligible. To ensure broad generalizability, we are using a patient-centric design and not limiting enrollment to a single care setting or single type of provider (cardiology). PROMISE reflects the care settings, patient groups, and providers who will eventually apply its results.

2.a Inclusion Criteria

1. New or worsening chest-pain syndrome or equivalent symptoms suspicious for clinically significant CAD
2. No prior cardiac evaluation for this episode of symptoms
3. Planned noninvasive testing for diagnosis
4. Men age greater than or equal to 55 years and women age greater than or equal to 65 years
5. If age in men 45–54 years or women 50–64 years, then must have increased probability of CAD due to 1 or more of the following risk factors:
    - Diabetes mellitus requiring medical treatment
    - Peripheral arterial disease (PAD), defined as documented peripheral arterial stenosis greater than or equal to 50%, treated medically or invasively
    - Cerebrovascular disease (stroke), defined as documented carotid stenosis greater than or equal to 50%, treated medically or invasively
    - Ongoing tobacco use
    - Hypertension
    - Abnormal ankle-brachial index (ABI), defined as less than 0.9
    - Dyslipidemia
6. Serum creatinine less than or equal to 1.5 mg/dL within the past 90 days
7. Negative urine/serum pregnancy test for female subjects of childbearing potential

2.b Exclusion Criteria

1. Diagnosed or suspected ACS requiring hospitalization or urgent or emergent testing; elevated troponin or creatine kinase-myocardial band (CK-MB);

outpatients who have completed a rule-out ACS protocol are eligible provided they have negative biomarkers x 2 and a nondiagnostic or normal ECG.

2. Hemodynamically or clinically unstable condition (systolic blood pressure [BP] less than 90 mm Hg, severe atrial or ventricular arrhythmias, or persistent resting chest pain felt to be ischemic despite adequate therapy)
3. Known CAD with prior clinical history of MI, PCI, coronary artery bypass graft (CABG) or any angiographic evidence of CAD greater than or equal to 50% lesion in a major epicardial vessel
4. Any invasive coronary angiography or noninvasive anatomic or functional cardiovascular test for detection of CAD, including CTA and exercise ECG, within the previous 12 months (+/- 30 days); prior resting ECG and/or resting echo do not constitute an exclusion to participation
5. Known significant congenital, valvular (greater than or equal to moderate) or cardiomyopathic process (hypertrophic cardiomyopathy or reduced systolic left ventricular [LV] function [LV ejection fraction less than 40%]) that could explain cardiac symptoms
6. Contraindication to a CTA, including, but not limited to:
    a. Allergy to iodinated contrast agent
    b. Pregnancy
7. Any other contraindications that would preclude performing a CTA per local site practice, such as 1 or more of the following:
    a. Inability to receive beta blockers if heart rate is greater than 65 beats per minute
    b. Agatston score greater than 800
    c. Body mass index (BMI) greater than 40
    d. Cardiac arrhythmia
8. Life expectancy less than 2 years
9. Unable to provide written informed consent or participate in long-term–follow-up

2.c Ethical Considerations

Human Subjects' Involvement and Characteristics

All human adult subjects who meet inclusion criteria and who do not meet any of the exclusion criteria will be considered eligible for this trial. Subjects who are within vulnerable populations will be included at the discretion of the site institutional review boards (IRBs).

2.d Subject Recruitment Plans and Consent Process

Diagnostic testing for the assessment of CAD symptoms is ordered by physicians of all specialties; is performed in multiple settings, including physician offices, hospital outpatient departments, and diagnostic testing facilities; and is interpreted by physicians of multiple specialties, including primary care physicians, cardiologists, and radiologists. Therefore, subjects will be recruited from multiple clinical settings, including outpatient

clinics, urgent care centers, and testing facilities. Sites that do not perform the full range of diagnostic testing, including CTA, will be paired with regional referral centers for echo, nuclear, and/or CTA testing where subjects may undergo the necessary testing. Existing clinical referral and research networks will be used to identify and enroll subjects.

Subjects will be recruited from 200 to 250 clinical sites. All potential PROMISE sites will obtain IRB/Institutional Ethics Committee (IEC) approval of the protocol and the associated consent form and any recruitment tools. Written informed consent will be obtained from each subject before to any study procedures are performed. Assessment of CAD risk will begin during screening to ensure eligibility. It will include medical history and physical exam and laboratory testing for the presence/absence of major cardiac risk factors, including BP/hypertension, diabetes, cholesterol (low-density lipoprotein [LDL], high-density lipoprotein [HDL]), smoking, family history, sedentary life style, obesity, cerebrovascular and PAD history, and ABI.

Subjects will be identified and enrolled in a step-wise process as follows:

1. All subjects being considered for outpatient noninvasive testing for the initial evaluation of symptoms suspicious for clinically significant obstructive CAD will be screened.
2. Subjects meeting inclusion criteria and not having any of the exclusion criteria will be approached to participate in the study and have the study explained to them.
3. Subjects agreeing to participate after having all their questions answered will be asked to document their agreement on the study-specific IRB-approved consent form with a signature.

2.e Subject Randomization

Eligible subjects who have given written informed consent and meet all inclusion and no exclusion criteria will be randomly assigned in equal proportions (1:1) to either the anatomic or functional diagnostic testing arm of the trial. A computer-generated permuted block randomization schedule with stratification by clinical site will be used in the trial. Before randomization, the managing caregiver, site investigator, or authorized designee will be asked to indicate the functional test he or she would plan to use if the subject were randomized to the functional testing arm. This information will be tracked and used as another stratification factor in the randomization scheme to facilitate comparisons of anatomic vs. functional testing according to the type of functional test. Subject randomization will be accomplished by telephone through a centralized toll-free interactive voice response system (IVRS).

If a subject is randomized but does not undergo the planned initial diagnostic test within 30 days of randomization, that subject will still be followed and included in the intention-to-treat statistical comparisons according to his or her randomized treatment assignment.

2.f Risks and Benefits

Potential Risks

Protocol-specific risks associated with the PROMISE trial are minimal. All PROMISE enrolled subjects will, by inclusion criteria, require noninvasive testing for their symptoms. Thus all subjects will have compelling medical reasons for performance of

the noninvasive test arm to which they are randomized. All care in PROMISE is part of routine clinical practice and, because the only intervention being performed in PROMISE is the random assignment of initial diagnostic test, safety considerations and adverse events are limited to complications arising from initial testing. Reporting of these safety events will be the responsibility of the site investigator.

Drawing Blood

Risks associated with drawing blood include momentary discomfort and/or bruising, infection, excess bleeding, clotting, or fainting.

Potential Loss of Confidentiality

In any clinical trial, there is a possible risk to subjects as to the potential loss of confidentiality. To prevent this from occurring, the Clinical Coordinating Center (CCC) and the Statistical and Data Coordinating Center (SDCC) at the Duke Clinical Research Institute (DCRI) have strict procedures in place to ensure that all study data are confidential and anonymized except as required for data collection by the Economics and Quality of Life Coordinating Center (EQOL CC) and the DCRI Outcomes and Follow-up Group (DOFG). For all data received by DCRI, subjects will be identified only by unique code numbers. The link to these codes will be maintained at the SDCC. Trial records that identify subjects will be kept secure and confidential as required by law. Federal privacy regulations provide safeguards for privacy, security, and authorized access.

If the DOFG finds that a subject has undergone diagnostic testing or a diagnostic or therapeutic procedure or has been hospitalized, the DOFG will obtain the subject's test results or discharge summary, and the EQOL CC will obtain relevant medical billing information on behalf of the trial. Once received at the SDCC, these documents will be anonymized, removing the subject's name, personal identifiers, and local physician's name and will be identified by unique study enrollment numbers.

Potential Benefits

The PROMISE trial results should improve the care of future subjects requiring diagnostic testing for suspected CAD. In addition, the trial will deliver high-quality data on radiation exposure, incidental findings, and other clinically important "side effects" of the testing strategies that will be examined in a large real-world experience.

D3 *Diagnostic Testing*

3.a Approach to Diagnostic Testing

An important goal of PROMISE is the broadest possible applicability of its results. Therefore, all commonly used tests are included in the functional testing arm, a designation that generally implies a multiplicity of approaches. This inclusiveness will facilitate enrollment by ensuring that all eligible subjects will have ready access to high-quality testing in both arms. Because the preferred type of functional test will be recorded by the IVRS before randomization, the trial subjects, each of whom has been selected by his or her managing clinician to undergo a different form of functional testing, can later be divided into 3 cohorts for prespecified subgroup analyses. In each cohort, half will be randomized to undergo that prespecified functional test, while the other half

will be randomized to undergo CTA, forming paired CTA-functional test subgroups for each functional test type.

We will ensure that the standard of care of testing and imaging performance and interpretation consistent with good medical practice is maintained throughout the trial by requiring that sites have expertise and qualify in all modalities, by providing recommended imaging protocols and by providing timely quality feedback and expert overreading in a subset of studies, again for all modalities.

3.b Description of Testing To Be Performed

Subjects will initially be evaluated according to their physicians' specific protocols for management of subjects with an indication for nonurgent, noninvasive cardiovascular testing. Typically, the standard evaluation will include the relevant past and current medical history, a physical examination, and a resting 12-lead ECG and may include cardiac biomarkers (troponin and/or CK-MB) as well as other routinely obtained blood testing. Subjects who meet eligibility criteria will have their physicians' preferred functional tests designated as part of the stratification requirements for randomization.

Functional Testing Arm

For subjects randomized to usual care, the preselected functional test will be performed as the initial test. This includes stress nuclear imaging, stress echo, or exercise ECG.

Anatomic Testing Arm

In subjects randomized to the anatomic testing arm, a contrast-enhanced coronary CTA will be performed as the initial test.

Subsequent Care

The results of all tests will be provided to the care team in the usual manner for that testing laboratory, and, depending on the results, subjects may or may not undergo medical treatment and/or additional noninvasive functional, anatomic, or invasive testing (coronary angiography), and/or coronary revascularization, at the care team's discretion. It is assumed that patient management will be additionally informed and guided by the test findings. The local physician will resume care of the subject and make all subsequent clinical decisions (e.g., need for further evaluation or admission) based upon his or her cumulative clinical assessment of the subject, including findings revealed on the noninvasive testing.

3.c Functional and Anatomic Testing and Cardiac Catheterization

Equipment and Protocols

Criteria for qualification of participating sites or referral laboratories will include use of standard equipment for usual-care testing (stress echo, stress nuclear, and exercise ECG) as defined in current practice guidelines, and greater than or equal to 64-slice MDCT technology for coronary CTA.[12,74-77]Similarly, all test acquisition protocols will adhere to best-practice standards as defined in current national practice guidelines.[12,74-77] Sites will be allowed to use their own standard acquisition protocols as long as they

fall within the standard-of-care guidelines. Sample protocols are provided in the Manual of Operations and Procedures (MOP).

Interpretation

All studies will be interpreted by qualified physicians who have at least ACC COCATS (Core Cardiology Training Symposium) level 2 training[78] or equivalent. For nuclear studies, certification by the Certification Board of Nuclear Cardiology or Board Certification in nuclear medicine or radiology is also sufficient to qualify as a reader. Coronary CTA will be interpreted by physicians trained at least COCATS level 2 or equivalent, either Society of Cardiovascular Computed Tomography level 2 or the Certification Board of Computed Cardiovascular Tomography. However, because coronary CTA is a relatively new technology, and practice requirements and expertise may not have evolved to the same level as other diagnostic tests, reader qualification may include online review and evaluation of clinical cases consisting of paired coronary CTA and invasive angiography datasets.

All diagnostic tests will be interpreted and reported by diagnosticians at the sites in real time according to current guidelines to ensure timely availability of results for patient management. The diagnostic test reports will capture the major findings, including:

1. Presence and extent of CAD (CTA).
2. Resting LV function and perfusion (echo and nuclear scans) as either: normal, global dysfunction, regional dysfunction/scar, both, or not interpretable. Ejection fraction will be quantified. This information will be optionally gathered for CTA.
3. Functional capacity determined for exercise ECG, stress echo, or stress nuclear.

3.d Test Transfer and Storage

Test transfer will be accomplished by transmission of paper recordings for stress ECGs and the ECG component of echo and nuclear studies. For digital images including invasive coronary angiography, transmission may be accomplished by compact disc (CD) or over the Web. For Web transmission, an image-transfer system will be deployed at the site. The data-transfer software will provide encryption, lossless compression, and transmission capabilities for the submission of deidentified data sets via the Web to the central Test Data Repository hosted by the American College of Radiology Imaging Network (ACRIN) in Philadelphia.

Upon arrival in the central data repository, datasets will be processed as needed: paper ECGs converted to PDFs; CDs uploaded; and Web images decompressed, deencrypted and imported into the central imaging database, a networked long-term image-archiving and storage system. This will ensure maximal site flexibility as well as seamless and efficient transfer of imaging data from sites into a central data repository and will allow real-time quality control and feedback.

3.e Quality Assurance of Diagnostic Testing

Before beginning enrollment, eligible sites and readers will be qualified by the Diagnostic Testing Coordinating Center (DTCC) based on site and reader surveys, on successful transfer of 1 or more complete data sets with sufficient image quality and completeness for each modality, and participation in the CTA case review. Site qualification will be issued by the DTCC for each modality before subject enrollment.

During the study, technical quality assessment of image and test acquisition will be accomplished on all studies by central repository research technicians trained by the DTCC or by the CCC for invasive coronary angiography. This ongoing review will ensure the adequate quality and completeness of data sets (see details and definitions in the MOP) and will monitor radiation exposure in the CTA arm throughout the trial.

Expert overreading of the initial, randomized, noninvasive tests and first invasive angiogram within 60 days of randomization will be performed in approximately 10% of subjects by modality experts in the DTCC and CCC. To ensure protocol compliance early on and to account for low-accrual sites, the first 2 studies and ~10% of the remaining studies from each site will be overread in each modality. These will be selected by block randomization stratified by testing site and test modality.

In addition, to strengthen the link between site investigator reported invasive catheterization without obstructive disease and angiographic findings, a sample of invasive angiograms determined by site investigators to be without obstructive disease will undergo core lab QCA and the results compared.

Feedback to Clinical Sites, Remediation, and Disqualification

Sites whose performance does not consistently meet the quality criteria for both quality assurance (QA) and radiation exposure will be asked to undergo protocol review and retraining up until March 31, 2013. Sites that fail to improve may be recommended for discontinuation of enrollment.

3.f Subsequent Medical Care

Care following the imaging studies will be provided by the local care physicians at their discretion. However, they will be encouraged to follow established guidelines for the management of CAD or for primary prevention. To this end, test-information sheets specific to each modality will be created and supplied to each enrolling site and physician and to relevant imaging site staff. These will consist of a brief literature review of diagnostic and prognostic indications of various test results.

In addition, primary and secondary prevention information sheets will be created and provided to each enrolling site and physician at the beginning of the trial. These will consist of brief summaries of relevant ACC/AHA Guidelines and will be referenced to the test-information sheets' results.

3.g Testing Risk and Benefits

To be eligible for entry into the study, each subject and his or her health care provider will have considered the risks and benefits of noninvasive testing and will have determined that the incremental information gained outweighs the potential risks. For example, although diagnostic testing provides important diagnostic and prognostic information and is noninvasive, it cannot be used indiscriminately. Associated risks include maximal exercise testing, use of pharmacologic stress and contrast agents, and radiation exposure on the order of 7 to 17 mSv for stress nuclear and CTA (although aggressive dose-reduction strategies can reduce this to ~2–6 mSv in CTA). Computed tomographic angiography also often involves the use of beta blockers to lower heart rate and an angiographic contrast agent.[79-81] **(**For comparison, the radiation exposure from a single-view chest x-ray is about 0.03 mSv).

Because the long-term risks and benefits of one form of testing vs. another are unknown, the PROMISE trial is collecting all relevant information to address these knowledge deficiencies, including test complications and estimated total biological radiation exposure for cardiovascular procedures during the duration of the trial. For radiation, doses will be estimated whenever possible using the site's specific scanning protocols for diagnostic testing and fluoroscopic time for invasive procedures. However, if these are unavailable or deemed unreliable, modeled estimates from the sites with such data or from the relevant literature will be used. We will also record the presence of incidental findings as reported on all initial tests and follow-up procedures (including surgical procedures) or testing performed to further evaluate any resulting new diagnoses of significant noncardiac disease.

E Study Procedures

E1 *Screening for Eligibility*

Screening of subjects for this trial will be conducted by the site investigator (or authorized designees) at each participating site. Written, informed-consent documentation will be obtained from each prospective trial subject once study eligibility is confirmed and before the first study procedure.

E2 *Schedule of Assessments*

Subjects will be screened and randomized at or before time of enrollment. Baseline medical history, blood work, and QOL will be assessed. Subsequently, subjects will have either a telephone call or clinic visit at 60 (+/- 14) days for outcome evaluation and recording of any test complications. After that, subjects will be contacted under DOFG supervision by either DOFG or its trained designees at 6 months postrandomization and at 6-month intervals for subsequent follow-up assessments until death, withdrawal, or the end of the trial.

Screening assessments are described below.

TABLE OF ASSESSMENTS	Screening/ Day 1	Day 1-30	Day 60[1]	6 mos	12 mos	18 mos	24 mos	30 mos	36 mos
Informed Consent	X								
Confidential Patient Information Form	X								
Medical History	X		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Concomitant Medications	X		X	X	X	X	X	X	X
CV Risk	X			X	X	X	X	X	X
Pregnancy Test[3]	X								
Creatinine[4]	X								
Resting 12-lead ECG[5]	X								
Quality of Life[6]	X			X	X		X		
Economics	X			X	X	X	X	X	X
Biomarker Banking	X								
Randomization	X								
Initial Diagnostic Test		X							
Clinical Assessment			X	X	X	X	X	X	X
Endpoint Assessments			X	X	X	X	X	X	X
Test Safety Assessment			X						

mos=months; CV=cardiovascular; ECG=electrocardiogram

[1] +/- 14 days

[2] During medical history review, if subjects have received an additional diagnostic test, a cardiovascular procedure or have been hospitalized since the last visit, additional data will be collected from the practice or institution with subject consent

[3] Pregnancy test required only for female subjects of childbearing potential

[4] Creatinine blood draw required only for subjects without a recent normal value (within previous 90 days)

[5] Resting 12-lead ECG required if none available within past 30 days

[6] Quality of Life assessments will be performed in ~ 6000 subjects enrolled (prior to July 2012).

Day 0/1 Screening/Randomization:

- The subject's relevant medical history (including concomitant medications) will be obtained.
- Coronary arterial disease risk factors will be assessed, including BP/hypertension, PAD (ratio of arm to leg systolic BPs or formal ABI), cerebrovascular disease (carotid bruits), diabetes, cholesterol (LDL, HDL), smoking, family history, sedentary life style, obesity.
- Factors increasing probability of CAD (including diabetes, PVD, and/or other CAD risk factors) will be documented.
- Cardiac symptoms and chest pain descriptors will be assessed.
- Eligible subjects will be asked to give consent for study participation.
- If the subject is of childbearing potential, a pregnancy test will be performed.
- Creatinine blood draw will be done if there is no creatinine measurement within the previous 90 days.

- Subjects will receive a 12-lead resting ECG unless one obtained within the past 30 days is available.
- Subjects will be administered baseline QOL questionnaires at the time of randomization.
- A blood sample will be drawn on subjects participating in biomarker and/or genomic banking (See Section E8).
- The subject will be randomized to the functional test of investigator or care provider choice or CTA. (*Note: functional test of choice must be selected and documented before placing the call to randomize the subject.)*

Days 1-30:

- The functional diagnostic test or CTA will be performed according to the randomized assignment.

Day 60 (+/- 14 days) Postrandomization Follow-up Assessment—site clinic visit or telephone call:

- Relevant interval medical history (including symptoms and concomitant medications) since last assessment will be obtained, including death, MI, major complications from cardiovascular procedure or testing (stroke, major bleeding, anaphylaxis, renal failure), unstable angina hospitalization.
- Test images and stress ECGs from the first test (and the randomized test, if different) will be uploaded to the DTCC. If applicable, the subject's first invasive coronary angiography report and images will be uploaded to the DTCC. All clinical test reports will be sent to the CCC at the DCRI.
- The results of any additional noninvasive tests or invasive catheterizations performed within the first 60 days will be collected.
- Radiation exposure will be assessed.
- Interval resource consumption, including hospitalizations, will be assessed.
- Patient satisfaction will be assessed.

Follow-up at 6 months postrandomization and every 6 months thereafter will be conducted by DOFG staff or its trained designees:

- Relevant interval medical history (including symptoms and concomitant medications) since last assessment will be obtained, including death, MI, major complications from study-related cardiovascular procedures (e.g. catheterization, PCI, CABG, CTA, stress echo, stress nuclear) or testing (stroke, major bleeding, anaphylaxis, renal failure), unstable angina hospitalization.
- Interval radiation exposure will be assessed.
- Interval resource consumption, including hospitalizations, will be assessed.
- Cardiovascular risk modification will be recorded.
- QOL questionnaires will be completed at 6 months, 12 months, and 24 months post-randomization (among patients followed for 24 months).

E3 *Safety*

3.a Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be appointed by the National Heart Lung and Blood Institute (NHLBI) to monitor subject safety and to review performance of the protocol. 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 at the initial meeting of the DSMB. Reports will be prepared regularly by the DCRI as requested by the DSMB chair. Depending upon the operational plan established by the DSMB, the report might include recruitment and retention rates, interim analyses, primary and secondary endpoints, 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.

3.b Study Coordinating Center or Food and Drug Administration Notification by Investigator

No reporting (other than through the InFORM system) is required.

3.c Definitions of Safety Events and Reporting

Because the only intervention in the trial is the randomized assignment of the initial test to be performed in a symptomatic subject with clinically indicated testing, the only safety events arising from the study are related to the initial test. Mild safety events are considered related to testing only up to 24 hours after the initial randomized test and will be collected and reported by site personnel. The site investigator/designee will document the safety events listed below occurring within 24 hours of initial testing and report them in the InFORM system.

In contrast, those severe events/complications related to cardiovascular testing or cardiovascular procedures that are also trial endpoints (e.g. peri-procedural MI, major bleeding, renal failure, and anaphylaxis requiring circulatory or respiratory support) will be collected throughout the duration of the trial and will be considered to be related to testing or a procedure if occurring within 72 hours.

For CTA:

1. Mild contrast reaction such as rash and hives (severe reactions including anaphylaxis or death are part of the primary endpoint)
2. Extravasation of contrast into the surrounding tissue of the extremity where the intravenous line was placed and contrast administered
3. Hemodynamic instability, including symptomatic bradycardia or hypotension, due to the beta blockade or nitrates given for the CTA scan acquisition
4. Acute bronchospasm due to the beta blockade given for the CTA scan

For exercise testing during exercise ECG, stress echo, or stress nuclear:

1. Exercise-induced hypotension with systolic BP fall greater than 20 mm Hg
2. Stress-induced symptoms that do not resolve within 20 minutes
3. Rapid atrial fibrillation that does not slow or convert with treatment

4. Ventricular tachycardia
5. Hemodynamic instability, defined as systolic BP less than 80 mm Hg
6. Hospital admission not otherwise captured by the primary endpoint, including that precipitated by any symptomatic event (chest pain, dyspnea, etc.), persistent or worsening ischemic ECG changes, any bradycardic or tachycardic arrhythmia, or any hemodynamic changes (hypertension or hypotension)

For stress nuclear:

1. The above events for exercise testing
2. Any events potentially related to the use of vasodilators such as dipyridamole or adenosine, including an anaphylactic reaction to contrast agent not requiring circulatory or respiratory support

For stress echo:

1. The above events for exercise testing
2. Stress-induced wall motion abnormality that does not resolve within 20 minutes (despite treatment)
3. Any anaphylactic reaction to contrast agent not requiring circulatory or respiratory support

E4 *Study Outcome Measurements and Ascertainment*

All-cause Mortality

All-cause mortality is used rather than cardiac mortality to eliminate the need for possibly difficult adjudication of causes of death, especially given the relatively low mortality expected.

Myocardial Infarction

Defined as either 1) an abnormal cardiac biomarker level (either troponin or CK-MB) greater than institutional upper limit of normal (ULN), and either ischemic discomfort lasting greater than 10 minutes or ECG changes indicative of ischemia or infarction, or 2) new abnormal Q waves consistent with infarction. Additionally *peri-procedural infarctions* are defined as greater than 3x ULN for serum CK-MB for PCI and greater than 5x ULN for CABG.

- an abnormal cardiac biomarker level > institutional ULN (either troponin or CK-MB), and either ischemic discomfort lasting > 10 minutes or ECG changes indicative of ischemia or infarction,

OR

- new abnormal Q waves consistent with infarction.

Additionally *peri-procedural infarctions* are defined as >3x upper limit of normal for serum CK-MB for PCI and >5x upper limit of normal for CABG.

Unstable Angina Hospitalization

Defined as 1) ischemic discomfort or equivalent symptoms requiring hospitalization within 48 hours of symptoms, 2) lasting greater than or equal to 10 minutes at rest, or in an accelerating pattern, 3) accompanied by dynamic ST depression, ischemia on stress testing, or significant epicardial coronary artery stenosis, and 4) considered to be myocardial ischemia upon final diagnosis.

Is defined as an event in which the final diagnosis is unstable angina or acute coronary syndrome due to myocardial ischemia and has the following criteria:

- ischemic discomfort or equivalent symptoms requiring hospitalization within 48 hours of symptoms, lasting ≥ 10 minutes at rest

OR

- ischemic discomfort or equivalent symptoms occurring in an accelerated pattern within 48 hours of hospitalization

AND ANY OF THE FOLLOWING

- accompanied by dynamic ST depression
- ischemia on stress testing
- significant epicardial coronary artery stenosis

Major Complications From Cardiovascular Procedures and Diagnostic Testing That Occur Within 72 Hours

Defined as:

- Stroke is defined as an acute focal neurological deficit of sudden onset, not reversible within 24 hours, or that resolves in less than 24 hours with clear evidence of a new stroke on cerebral imaging.

- Bleeding is defined as major based on 1 or more of the following:
    - Transfusion of greater than or equal to 2 units heterologous packed red blood cells or whole blood
    - Decrease in hemoglobin level by greater than or equal to 2.0 g/L
    - Need for reoperation or invasive intervention (*e.g.* evacuation of wound hematoma)
    - Bleeding at a critical anatomic site (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome)
- Renal Failure is defined as new requirement for renal replacement therapy.

- Anaphylaxis is defined as a severe contrast reaction requiring emergency respiratory and/or circulatory support.

Invasive catheterization without obstructive coronary artery disease

Only the results of the initial (first) invasive cardiac catheterization that occurs within the first 60 days following randomization will be considered for the secondary endpoints which include invasive angiography without obstructive disease. The absence of obstructive disease is defined as no stenosis >= 50% in any major epicardial vessel including side branches ≥ 2 mm in diameter.

Radiation Exposure Safety Endpoint

Cumulative radiation exposure will be collected as follows:

- CTA: the actual administered dose (computed tomography dose index volume and dose length product for CTA) will be recorded by sites and confirmed by extracting information directly from the images.
- Nuclear imaging: the injected/administered contrast agent dose will be recorded and standard tables used to convert into equivalent doses for appropriate comparison with CTA.
- Invasive coronary angiography and intervention: the actual administered radiation dose or fluoroscopy time will be recorded by sites and standard tables used to convert into equivalent doses for appropriate comparison with CT.

These measures will ensure accurate calculation of the actual cumulative radiation exposure in each arm for tests performed for the diagnostic work-up during the 60 days following enrolment. In addition, we will capture all cardiac diagnostic testing involving radiation performed during the entire follow-up period (CTA, nuclear cardiology, catheterization) and will estimate cumulative radiation exposure over the entire trial using our original data collection (average dose per test for each site) to extrapolate radiation exposure during follow-up.

E5 *Independent Clinical Event Adjudication Committee*

An independent clinical event adjudication committee will review and adjudicate all primary endpoint events and the catheterization secondary endpoints in a blinded fashion based on the definitions presented above. If the invasive cardiac catheterization report is inconclusive, the CEC will review the catheterization films for a visual assessment of CAD. The other clinical secondary endpoint events and cumulative radiation exposure will not be adjudicated.

Primary outcome events will be documented through 60 (+/- 14) days after randomization by the site Investigator or authorized designees. After that, the DOFG or its designees will be responsible for documenting study events from 6 months until the end of the study.

E6 *Quality-of-life Assessments*

Baseline QOL interviews will be administered to ~6000 subjects enrolled (prior to July 2012) by site personnel as soon as possible after consent, preferably before the subject's randomization. Completed questionnaires will be sent directly to the EQOL CC for data processing. Follow-up QOL questionnaires will be administered via structured telephone interview by DOFG trained and supervised interviewers at 6 months, 12 months, and 24 months post-randomization (among patients followed for 24 months). Proxy QOL questionnaires will be used when a subject has died in the follow-up interval or has become incapacitated; these questionnaires will include items that can be reliably obtained from a relative, caretaker, or medical record. Proxy questionnaires will be used if the subject is unable to participate in follow-ups via telephone interview.

Content of Health-related Quality-of-life Questionnaires

A battery of validated instruments will be used that build on a disease-specific core supplemented with generic measures to provide a comprehensive but brief assessment of health-related QOL.

Chest-pain–specific symptoms will be measured using the **Seattle Angina Questionnaire (SAQ)**, a 19-item instrument that assesses 5 dimensions of the impact of chest pain on QOL: physical limitations, angina stability, angina frequency, treatment satisfaction, and disease perception. The **Duke Activity Status Index (DASI)**, a 12-item scale that has been validated in cardiac patients against maximal oxygen uptake measured at exercise (VO_2 max), will be used as a disease-specific functional status assessment. The 4-item **Rose Dyspnea Scale** will be used to assess patients' levels of dyspnea with common activities.

The generic core instrument to be used is the **Medical Outcomes Study Short Form (SF-12)**. The SF-12 is composed of 8 scales (physical function, role function–physical, role function–emotional, general health, bodily pain, social function, psychological well-being/mental health, and vitality), a health transitions item, and 2 summary scores. Additionally, the entire scales for general health, psychological well-being, vitality, and social functioning from the SF-36 health survey will be used to provide better resolution of any treatment differences in these domains.

To assess effects of the 2 diagnostic strategies on the prevalence of depression, we will employ the **Patient Health Questionnaire (PHQ)**, a 9-item depression scale that has demonstrated good agreement with the clinical diagnosis of depression.

Patient-specific utilities will be assessed using the **EuroQoL-5D (EQ-5D)**, a standardized generic health-status measure that links specific health states to general population-based utilities. The EQ-5D consists of a 5-dimension health-state assessment, which allows for definition of 243 discrete health states that can be mapped to population utility weights and a self-rating (0-100) "thermometer" of current health-related QOL. The EQ-5D will be collected as part of all QOL questionnaires.

Employment/productivity will include time lost from work and reduced productivity while at work as measured by the 6-item **Stanford Presenteeism Scale** and questions adapted from the NHLBI Bypass Angioplasty Revascularization Investigation Substudy in Economics and Quality of Life.

E7 *Economic Assessments*

Resource-use data to be collected on the study case report form (CRF) will include hospitalizations, emergency department visits, selected cardiac procedures, and tests. Hospital bills (detailed, summary ledger, and UB 04) will be collected by the EQOL CC at the DCRI for all hospitalizations identified throughout the length of the study. They will include care at clinical sites and at institutions not participating in PROMISE. In addition, cost-to-charge ratios will be obtained from each hospital where a PROMISE follow-up hospitalization is reported.

E8 *PROMISE Biorepositories*

8.a Imaging and Electrocardiograms

Since future developments in image interpretation and integration with clinical data will remain important in the diagnosis and management of chronic diseases of CAD, PROMISE will create a unique anonymized “Image and ECG Data Warehouse” with all initial noninvasive test images, stress ECGs, and initial catheterization films, which will be linked to clinical information. Collection and release of data and images will be at the discretion of the study team including NHLBI and is included as part of the subjects’ initial consent.

8.b Blood Biomarkers and Genomics

The PROMISE investigators also believe that an integrated approach to disease characterization and therapeutic responses will play an increasingly important role in the diagnosis and management of chronic diseases such as CAD. Accordingly, subjects will be asked to provide a blood sample for deposit into a biomarker repository at the time of randomization for future assessment of advanced molecular biomarkers (plasma, serum) such as troponin and high-sensitivity C-reactive protein relevant to disease characterization, risk stratification, characterization of treatment response, and adverse effects. In addition, subjects will be requested to separately consent to allow use of the biorepository sample for genetic testing (DNA).

F Statistical Plan

F1 *Sample Size Determination and Statistical Power*

Several design factors and research objectives were considered in selecting the target sample size for the study. First, the number of subjects was determined so there would be a sufficient number of endpoints to provide a high degree of power (greater than or equal to 90%) for testing the primary superiority hypothesis. Second, the statistical power for secondary endpoints was considered, including the composite clinical endpoints and the economic and QOL endpoints. Third, it was considered important for the sample size to be large enough to permit a prudent examination of diagnostic testing effects in selected subgroups of subjects where anatomic testing might be particularly advantageous or where the question of a benefit from CTA is particularly relevant.

Important prespecified subgroups of interest in this study include those defined by age, sex, race, comorbidity, cardiovascular risk factors, the prerandomization choice of functional test, and characteristics of the precipitating symptoms. Fourth, the sample size was selected to provide a reasonable level of confidence for detecting clinically important outcome differences between the anatomic and functional testing strategies even if current projections of event rates and the hypothesized differences in clinical outcomes between the 2 arms prove to be optimistic. A fifth consideration was the adequacy of the sample size for assessing noninferiority of anatomic testing compared with functional testing in the event that the anatomic testing strategy is not demonstrated to be statistically superior to functional testing. Finally, although the study objectives are expressed in terms of testing specific hypotheses (i.e., that the anatomic testing strategy is superior [and if not superior, then noninferior]) to functional testing, another important objective of the trial is to estimate the magnitude of the difference in outcomes to within an acceptable level of statistical precision, regardless of whether either testing strategy is proven to be superior. Thus, the precision of the estimated difference in outcomes between the 2 arms of the trial (i.e., width of the confidence interval [CI]) has been considered in addition to the statistical power for the hypothesis tests.

Based on the distribution of coronary disease expected in this patient population (approximately 15% obstructive disease [i.e., greater than or equal to 50% stenosis of the left main coronary artery or greater than or equal to 70% stenosis of 1 or more of the other major epicardial coronary arteries], 40% nonobstructive disease, and 45% normal coronary arteries) and based on national claims data or published information from other databases, the event rate at 2.5 years (the average length of follow-up in PROMISE) for the primary composite endpoint in subjects randomized to the functional testing strategy was projected to be approximately 9%.

With this event-rate projection in the functional testing arm, a key driver of the sample size is the magnitude of benefit that can reasonably be expected to be achieved with the anatomic testing strategy. This determination requires careful consideration of multiple characteristics of CTA, including its likely incremental diagnostic and prognostic accuracy and its ability to more effectively detect nonobstructive CAD. A careful assessment of the impact of the advantages of CTA with respect to these test characteristics translates to a projection (hypothesis) that CTA will reduce the primary composite endpoint by 20% (from 9% to 7.2% at 2.5 years).

Based on the event rates for each arm discussed above, sample-size requirements were formulated to provide high power for detecting the postulated 20% relative risk reduction. Recognizing, however, that the actual event rates and the outcome differences between the 2 testing strategies in PROMISE may vary somewhat from these estimates, sample-size requirements were calculated for several different combinations of event rates, effect sizes, and power levels in order to examine the sensitivity of the sample size to different event rates and outcome scenarios that might conceivably arise in this trial.

Since the primary treatment comparisons in this study will be based on time-to-event methodology using the log-rank test[82]or equivalently, the Cox proportional hazards model,[83] the approach used for calculating sample-size requirements for PROMISE was based on the sample-size methodology for the proportional hazards regression model outlined in Schoenfeld.[84]

To provide an adequate number of subjects for the trial that will be relatively robust in providing (1) excellent statistical power under various assumptions about the event rates in the functional testing arm and the magnitude of the benefit of anatomic testing compared with functional testing for reducing the primary endpoint, (2) adequate power

for selected secondary endpoints, (3) adequate power for assessing noninferiority in the event that superiority is not demonstrated, and (4) a relatively high degree of precision for estimating the true effect of an anatomic vs. functional testing strategy regardless of whether the final result has a *P* value that is statistically significant, the study will enroll 10,000 subjects (5,000 per arm). This number will provide greater than 90% power for detecting a 20% reduction in the primary clinical endpoint if the 2.5-year event rate in the functional testing arm is 8% or higher and 80% power if the event rate is as low as 6%. This number of patients will also provide adequate power for detecting a smaller (16%–17%) reduction if the event rate in the functional testing arm is 8% to 9% or higher and acceptable power for selected secondary endpoints, allowing for up to a 3% loss to follow-up. Ten thousand patients will also provide 90% power for testing noninferiority with a margin of 1.10 (expressed as a hazard ratio of CTA vs. functional testing) if the functional testing arm event rate is 9%, 86% power if the event rate is 8%, and 81% power if the event rate is 7%, assuming that anatomic testing is only better than functional testing by 10%, an assumption that was felt to be reasonable for the noninferiority assessment. That is, we will have excellent power for demonstrating that anatomic testing is not worse than functional testing by more than 10% under these various assumptions.

In summary, 10,000 patients will provide excellent and robust statistical power for assessing clinically relevant and realistic outcome differences between the 2 testing strategies being studied in this trial.

F2 *Statistical Analysis Plan*

Statistical analysis will be performed at the PROMISE SDCC at DCRI. All major treatment comparisons between the randomized groups will be performed according to the principle of "intention-to-treat"; that is, subjects will be analyzed (and endpoints attributed) according to the diagnostic testing strategy to which subjects were randomized, regardless of subsequent additional testing or postrandomization treatment and medical care. Statistical comparisons will be performed using 2-sided significance tests. Additional perspective regarding the interpretation of the data will be provided through extensive use of CIs[85] and graphical displays.

2.a **Analysis for the Primary Endpoint**

The statistical comparison of the 2 randomized arms (anatomic vs. functional diagnostic testing) with respect to the primary composite endpoint (death, MI, major peri-procedural complications, or hospitalization for unstable angina) will be a “time-to event” analysis and therefore will be based on the time from randomization to the first occurrence of any of the components of the primary composite endpoint. The Cox proportional hazards model will be the primary analytic tool for assessing outcome differences between the 2 randomized arms.[83] To appropriately account for heterogeneity among the subjects, the overall comparison will be adjusted for a selected set of prognostically important baseline covariates that will be carefully defined and prespecified in the statistical analysis plan. The level of significance for the assessment of the primary endpoint will be α=0.05.

In addition to the statistical hypothesis testing, Kaplan-Meier “survival” (or event-free) estimates[86] will be calculated for each randomized arm as a function of follow-up time to display the event rates graphically. A hazard ratio and 95% CI for descriptively

summarizing the difference in outcome between the 2 study arms will be computed using the Cox model.[83]

If the data provide evidence of an overall difference in outcome between the randomized arms, an assessment will be made of whether the effect is similar for all patients or whether it varies according to specific patient characteristics. In particular, this analysis will focus on whether the relative benefit differs according to subject age, sex, race, comorbidity, selected risk factors, characteristics of the precipitating symptoms, and the prerandomization specification of the functional test that would be used if the subject was randomized to the functional testing arm. This latter factor is built into the randomization scheme. For subjects for whom the prerandomization choice for functional testing (if the subject was assigned to the functional testing arm) was stress nuclear imaging (for example), the outcomes of these subjects in the CTA arm will be compared to the outcomes of corresponding subjects randomized to functional testing. In this way, CTA can be compared with stress nuclear imaging, as well as with each of the other functional testing modalities with the benefits of randomization in each comparison maintained by virtue of the stratified randomization scheme. These analyses will utilize the Cox model by testing for interactions between the randomized testing strategy and these specific baseline variables. In addition to the formal assessment of testing strategy by covariate interactions, effects of the diagnostic testing strategy characterized by a hazard ratio and 95% CI will be calculated and displayed for prospectively defined subgroups of subjects defined by the variables listed above. These descriptive hazard ratios will be carefully interpreted in conjunction with the formal interaction tests.

If the data do not provide statistical evidence that the CTA testing strategy is superior to functional testing with respect to the primary endpoint, a test for noninferiority of the anatomic testing strategy will be performed. This assessment will be based on a noninferiority margin of 1.10 (expressed as a hazard ratio for CTA vs. functional testing). The noninferiority assessment will be performed by comparing the upper limit of the 95% CI for the hazard ratio with the noninferiority margin. If the upper limit of the CI falls below 1.10, noninferiority will have been demonstrated. We emphasize that the superiority hypothesis will be assessed first, and if significant, the noninferiority assessment will not be performed. Only if superiority is not demonstrated will the noninferiority analysis then be performed.

2.b Analysis of Secondary Endpoints

Secondary endpoints that will be evaluated include (1) a composite endpoint consisting of death, MI, or hospitalization for unstable angina; (2) death or MI; (3) major peri-procedural complications (stroke, major bleeding, renal failure, anaphylaxis); (4) a composite of the primary endpoint or invasive catheterization without obstructive CAD, (5) invasive catheterization without obstructive CAD, (6) resource-use patterns, medical care costs and incremental cost effectiveness; and (7) QOL. In addition, major adverse cardiac events (events other than the endpoints listed above) will be monitored and reported.

The analysis of secondary endpoints 1 through 4 will be similar to that outlined for the superiority assessment of the primary endpoint, using time from randomization until the first occurrence of any component of the specific secondary endpoint (or censoring) as the response variable, and assessing group differences using the Cox proportional hazards model. The effect of the diagnostic testing strategy on these secondary clinical endpoints will be descriptively summarized using hazard ratios (with associated CIs)

computed from the Cox model. Kaplan-Meier curves will be computed to graphically display the cumulative event rates of the 2 randomized arms as a function of time from randomization. We note that the analysis of secondary endpoint (3) above (major peri-procedural complications) will have to be interpreted cautiously, particularly if there should be a higher death rate in one arm compared with the other. To deal with this complexity and clarify and enhance the interpretation of this comparison, the analysis of this endpoint will be supplemented with further analyses by considering major peri-procedural complications and death as a combined endpoint.

Plans for the analysis of the QOL and economic endpoints are addressed below in Sections F2.g and F2.h.

2.c Analysis of Diagnostic Testing Core Data

The DTCC will implement robust QA programs to ensure uniformity and high-quality testing in support of the primary aims of PROMISE.

Two important components of information from the diagnostic test QA activity will be analyzed by the SDCC. The DTCC will review the first 8000 subjects' initial diagnostic test for technical quality, and each test will be assigned a quality assessment using an ordinal categorical scale (for example, excellent, good, fair, poor, uninterpretable). Using simple frequency counts, the SDCC will tabulate a description of the distribution of this scale on an ongoing basis by type of test and by testing site in order to provide feedback to the sites on their performance, to inform the study leadership and the DSMB as to the quality of the diagnostic testing, and to flag potential problem areas, whether by testing site or across a given testing modality, for remedial attention. This quality measure will be compared among the different testing modalities using rank-based tests (e.g., Kruskal-Wallis nonparametric analysis of variance) and ordinal logistic regression to characterize, describe, and assess any differences in overall quality among the various testing modalities. In particular, the technical quality of the anatomic (CTA) tests will be compared with the quality of the functional tests. This comparison may be helpful in interpreting the comparisons of the 2 randomized arms with respect to the clinical outcomes.

The second important component of information from the diagnostic test QA activity is the quality of test interpretations. Approximately 10% of tests will be overread by the DTCC using a categorical level of coronary disease risk. The site interpretation of level of risk will be compared with the level of risk using the same scale assessed by the core lab's overread of the test, and overall summary statistics of the agreement between the site and core lab assessments will be computed. Raw proportions of agreement (perfect agreement, and agreement differing by less than or equal to 1 category of risk) will be tabulated, and Kappa statistics will be used to characterize the level of agreement. The Kappa statistics are "chance corrected" (i.e., adjusted for agreement due to chance), and both unweighted and weighted Kappa statistics will be used in these analyses since more substantial disagreements in the assessment of risk for a given subject would be more serious than small disagreements. These agreement statistics will then be compared across the different testing modalities to determine whether the level of agreement between the site readings and the core lab readings varies with the type of test.

Another important component of information to characterize data quality for the secondary endpoints that involve non-obstructive CAD will be the review of selected

coronary angiograms to determine the degree to which site-reported assessments of non-obstructive coronary disease are concordant with carefully-performed core lab QCA. The same type of agreement statistics as described above, including raw proportions of agreement and chance-corrected Kappa statistics, will be used to describe and characterize the accuracy of the site-reported assessments of non-obstructive CAD.

Analysis of Diagnostic Accuracy

Although PROMISE is designed with the primary objective of evaluating initial anatomic vs. functional testing strategies with respect to clinical outcomes and thus represents a different paradigm than the traditional design to assess diagnostic accuracy, performance of supplementary analyses of diagnostic accuracy are prespecified. This cannot be done in a conventional manner as not all subjects will undergo invasive angiography (the "gold standard"), and those who do will not undergo angiography by random selection. Instead, the decision to verify disease will be based on test results and other characteristics of the subject. This nonrandom selection process will likely result in a strong verification bias,[87] often characterized by higher than true sensitivity and lower than true specificity results. (Of note, the trial cannot require angiography in a subset of subjects for purposes of determining testing accuracy, as this would provide additional information to these subjects' physicians and care givers above and beyond that provided by the randomized testing strategy, and therefore invalidate the trial results.) Correction of the verification bias is possible if the process leading to verification with angiography is known. However, this is rarely achievable, but the process can be modeled under the missing at random (MAR) assumption,[88] namely that disease status affects referral to angiography only through measured covariates and not the disease status itself. In view of the inherent limitations, the following steps will be taken with respect to evaluating diagnostic accuracy.

Accuracy rates will be assessed using conventional measures (sensitivity, specificity, and receiver operating characteristic [ROC] curves) in subjects undergoing cardiac catheterization, bringing to bear where applicable the latest statistical methods for dealing with verification bias. The probability of verification will be modeled with a logistic regression model using covariates that are predictors of referral to angiography. Corrected values of sensitivity, specificity, and the ROC curve will be estimated.[88,89] Assessment of the impact of potential departures from the MAR assumption on sensitivity and specificity will utilize the "test ignorance region" approach.[88] Alternatively, we will use the clinical outcome (rather than coronary angiography) as the "gold standard," such that measures of diagnostic accuracy, including time-dependent ROC curves, will be computed to describe and statistically compare the 2 arms of the trial with respect to these measures. A subgroup analysis of diagnostic accuracy will be performed comparing results at sites with high volume and extensive experience or expertise in diagnostic testing with results in less-experienced or lower-volume sites.

Imaging prognostic performance will also be evaluated by comparing the association of test results with subsequent clinical events, including the primary endpoint of the trial. Finally, as described in Section F2.c above, concordance between the site interpretations of studies and core lab interpretations will be assessed.

We emphasize that all of these analyses of diagnostic accuracy will be strictly supplementary to the analysis of the primary and secondary clinical endpoints outlined in Sections F2.a and F2.b above.

2.d Analysis of Safety Events, Morbidity, Radiation Dose, and Incidental Findings

The frequency with which major safety cardiac events occur (events other than the primary and secondary endpoints) will be carefully tabulated and descriptively summarized. Statistical comparisons of the randomized arms with respect to these events will use chi-square or other appropriate 2-sample methods, depending on the nature of the event, interpreting such comparisons in the context of differences between the 2 randomized arms in the primary and major secondary clinical endpoints and bringing to bear clinical judgment as to the relative seriousness of these events.

Of particular interest in this trial is the amount of radiation exposure to which subjects are subjected in each of the randomized arms of the trial. Radiation exposure for the various tests will be collected as elements of the electronic CRF (eCRF) and through the documentation of radiation exposure submitted to the DTCC. All cardiac diagnostic testing involving radiation exposure (e.g., CTA, stress nuclear, cardiac catheterization) performed during the entire follow-up period will be captured so that cumulative radiation exposure for each patient can be calculated. The distribution of radiation exposure in each arm will be summarized (using medians and percentiles) and compared between the randomized arms and different testing modalities using the Wilcoxon rank-sum test.

Incidental findings (e.g., such things as lung nodules) that may be discovered with the anatomic (CTA) testing strategy in contrast to the functional testing modalities will be captured as part of the data collection and tabulated descriptively.

2.e Assessment of Prognostic Factors

With the large database of information that will be collected on the 10,000 subjects enrolled in this study, extensive regression modeling analyses will be performed, using primarily the Cox regression model, to identify and assess the factors (predictors) that are associated with the clinical outcomes of these subjects. These analyses will comprehensively evaluate the strength and shape of the relationships of numerous clinical factors with the clinical outcomes. While these analyses are more exploratory than the rigorous prespecified primary and secondary comparisons of the randomized arms of the trial, they will nonetheless be helpful in elucidating relationships and identifying the key factors that impact patient outcomes and any observed differences in outcomes between the diagnostic testing arms.

2.f Quality-of-life Analyses

For each of the QOL measures, data analysis will proceed in several stages. We will start by providing simple descriptive and comparative analyses by intention-to-treat. A nonparametric bootstrap will be used to estimate treatment differences with 95% CIs and *P* values. Because 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 at each time point separately, we propose 2 complementary approaches. First, we will prespecify the angina frequency and disease perception/QOL scales from the SAQ as the CAD-specific measures of primary interest, since these measures most directly quantify the therapeutic goal of coronary diagnosis and therapy: to minimize symptoms and optimize patients' QOL. We will also specify cardiac functional status measured with the DASI as a primary outcome measure of interest. Other disease-specific and generic QOL measures will be assigned to a secondary

(descriptive) status in our analyses. Second, we will fit a mixed effect longitudinal proportional odds model[90] that makes use of all available QOL data at each study assessment point to model the time profile (fixed effect) using a restricted cubic spline function. 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 2 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 such as at 1 year. Statistical power estimates for this part of our analysis show that we should have in excess of 90% power to detect ¼ standard deviation differences in the 3 principal QOL endpoints.

2.g **Economic Analyses**

The health economic analyses for PROMISE will consist of 2 major parts, namely an empirical intention-to-treat cost comparison and a cost-effectiveness analysis. Primary statistical comparisons between the 2 treatment arms of empirical costs will be performed by intention-to-treat analysis. 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 investigational anatomic arm relative to the control functional testing arm. In secondary analyses, we will incorporate utility weights to estimate the incremental cost per quality-adjusted life year gained with the CTA anatomic strategy, relative to the functional testing strategy. These analyses will be conducted from a societal perspective and will use a lifetime time 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. Costs will be adjusted for inflation, and both costs and life expectancy will be discounted to present value at a 3% annual discount rate. Adjustments for censored data due to staggered entry will be made following the approach of Bang and Tsiatis.[91] Extensive sensitivity analyses will be performed.

F3 ***Interim Analyses***

For safety and ethical reasons, interim examinations of key safety and endpoint data will be performed at regular intervals during the course of the trial. The primary objective of these analyses will be to evaluate the accumulating data for an unacceptably high frequency of negative clinical outcomes in either of the 2 randomized arms. In addition, the interim monitoring will also involve a review of subject recruitment, compliance with the study protocol, status of data collection, and other factors that reflect the overall progress and integrity of the study. The results of the interim analyses and status reports will be carefully and confidentially reviewed by the NHLBI-appointed DSMB. The DSMB will meet at approximately 6-month intervals to review the accumulating data.

To properly account for the repeated interim testing in PROMISE, a group sequential method similar to that proposed by O'Brien and Fleming[92] will be used as a guide for interpreting the interim analyses. This procedure requires large critical values early in the study, but relaxes (i.e., decreases) the critical value as the trial progresses. Because of the conservatism early in the trial, the critical value at the final analysis is near the

"nominal" critical value. The actual method for this interim monitoring that will be employed in PROMISE is the “spending function” approach to group sequential testing developed by Lan and DeMets.[93] The Lan-DeMets approach only requires specification of the rate at which the Type I error (which in this trial will be α=0.05 for the primary endpoint) will be "spent." This procedure allows "spending" a portion of α at each interim analysis in such a way that at the end of the study, the total Type I error does not exceed 0.05. One such spending function generates boundaries that are nearly identical to the O'Brien-Fleming[92] boundaries. It is this approach that will be used in PROMISE, namely 2-sided, symmetric O'Brien-Fleming type boundaries generated using the flexible Lan-DeMets[93] approach to group sequential testing. Since the number of looks and the increments between looks need not be predetermined, it allows considerable flexibility in the monitoring process for accommodating additional comparative examinations of the data in response to concerns of the DSMB that may arise during the course of the trial.

The analytic approach that will be used at the interim analyses for assessing outcome differences between the randomized arms will be the time-to-event analysis methods described previously, except that interpretation of statistical significance will be guided using the group sequential monitoring boundaries outlined above. At each interim analysis, the monitoring boundaries will be calculated using the fraction of the total number of primary events expected by the end of the trial.

Judgment concerning the continuation or termination of the study will involve not only the degree of statistical significance observed at the interim analyses, but also careful consideration of many other factors reflecting the progress and integrity of the trial, including how well event rates in the functional testing arm are tracking with the rates considered in the power calculations. It should be emphasized that regardless of whether CTA demonstrates a statistically significant benefit compared with functional testing, the results of the study will be important to future clinical practice. Indeed, a non-statistically significant effect for the primary endpoint is not necessarily a negative result in this study. The range of experience and expertise of the DSMB will enable them to put all important considerations into proper perspective, including the precision of estimates of clinical outcome differences between the testing strategies, and make well-reasoned recommendations to the NHLBI regarding continuation of the study.

G Data Handling and Record Keeping

Study Data Collection—All Subjects

The full study dataset will be collected for subjects who enter the randomized phase of the study. The primary data collection system for PROMISE will use the electronic data capture system InForm™.

Data Management and Quality

Any out-of-range values and missing or inconsistent key variables are flagged and addressed/answered at the site in real time during the data entry process. When a query is generated on a particular variable, a flag is 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 InForm™ 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 SDCC will perform internal database quality-control checks and data audits throughout the course of the trial.

G1 *Confidentiality and Security*

All study data will be stored in locked, secure locations. Computerized data are accessible only by password, and a centralized monitoring system records and reports all access to data. The DCRI computer network is protected by a firewall. Electronic CRFs will be identified by study number only, to ensure subject anonymity. No subject identifiers will be used in the presentation of data. Study records that might identify subjects will be kept confidential as required by law. Except when required by law, subjects will not be identified by name, social security 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 DCRI centralized clinical, QOL, and economic follow-up of the subjects. Subjects will be informed that the study physician and his or her study team will report the results of study-related tests to the Coordinating Center and to the National Institutes of Health (NIH). Subjects will be informed that their records may be reviewed in order to meet federal or state regulations. Reviewers may include the Food and Drug Administration, IRBs/IECs, or the NIH. Subjects will be informed that if their research record is reviewed, their entire medical record may also need to be reviewed. If an adverse event occurs, management of the event and subsequent care will be according to appropriate care practices at that site and will be implemented under the direction of the treating physician. All of the tests used in this study currently represent a reasonable standard of care for the subject population as demonstrated by ACC/AHA practice standards.

G2 *Training*

All investigator staff authorized to enter PROMISE Study data will receive training on the InForm™ system.

G3 *Electronic Case Report Form*

This study will use Web-based e-CRFs developed through a validated, Electronic Record, Electronic Signatures-compliant platform (21 CFR Part 11). Data will be entered into the InForm™ eCRF by authorized Investigator personnel, ACRIN, and the diagnostic testing core labs.

G4 *Records Retention*

Study records will be maintained by the site investigators for a period of 6 years following the expiration of the grant or length of time as required by local regulations.

H Study Monitoring, Auditing, and Inspecting

H1 *Study Monitoring Plan*

See E3.a

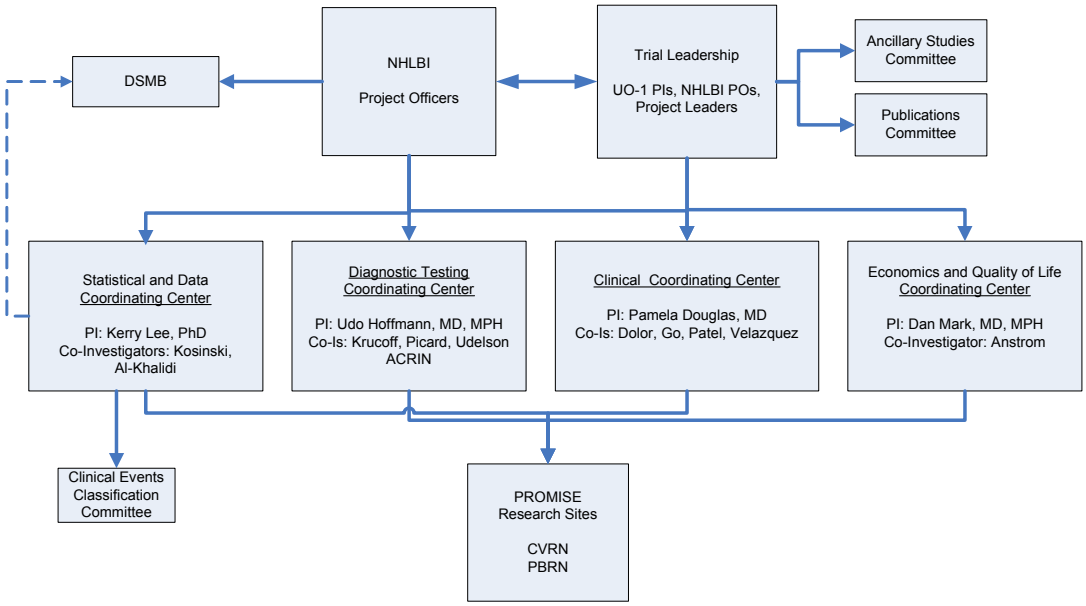
H2 *Auditing and Inspecting*

National Heart Lung and Blood Institute personnel or their designees may perform an audit at any time during or after completion of this study. All original study-related documentation will be made available to the designated auditor as required. A representative of the NIH or other government agency may choose to inspect a study center at any time before, during, or after completion of the clinical study. All pertinent original study data will be made available to responsible regulatory authorities for verification, audit, or inspection purposes.

I Study Administration

I1 *Organization and Participating Centers*

The PROMISE trial will be conducted under the following principal investigator (PI) leadership: Dr. Pamela Douglas as the overall and CCC PI, Dr. Kerry Lee as the SDCC PI, Dr. Daniel Mark as the EQOL CC PI, and Dr. Udo Hoffmann at Massachusetts General Hospital as the DTCC PI. The organization of the **PROMISE** trial and interrelationships between the NHLBI, the CCC, the SDCC, the various committees, and the clinical sites are outlined in the figure below.

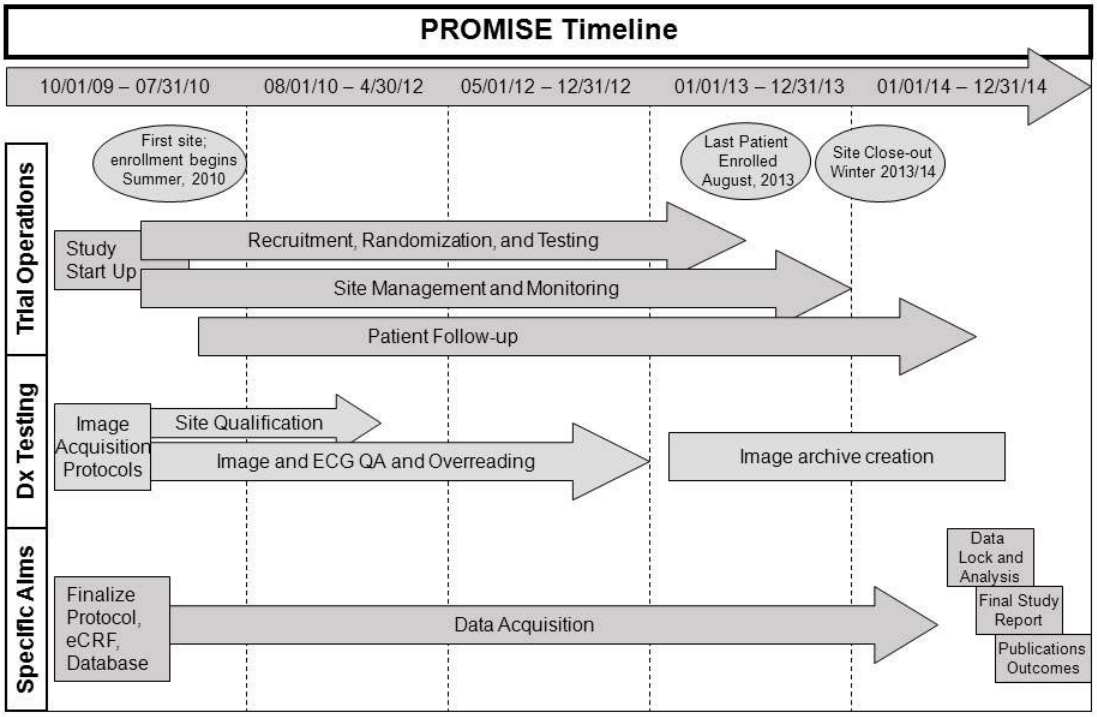


I2 *Funding Source*

The PROMISE trial is funded by the National Heart Lung and Blood Institute, National Institutes of Health.

I3 *Study Timetable*

The PROMISE timeline includes a 9-month start-up period, followed by approximately 36 months of enrollment, approximately 12 months of follow-up after the last subject is enrolled, and 3 months of closeout and data analysis.


PROMISE Timeline
10/01/09 – 07/31/10
08/01/10 – 4/30/12
05/01/12 – 12/31/12
01/01/13 – 12/31/13
01/01/14 – 12/31/14
First site; enrollment begins Summer, 2010
Last Patient Enrolled August, 2013
Site Close-out Winter 2013/14
Trial Operations
Study Start Up
Recruitment, Randomization, and Testing
Site Management and Monitoring
Patient Follow-up
Dx Testing
Image Acquisition Protocols
Site Qualification
Image and ECG QA and Overreading
Image archive creation
Specific Aims
Finalize Protocol, eCRF, Database
Data Acquisition
Data Lock and Analysis
Final Study Report
Publications Outcomes

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