This supplement contains the following items for: Douglas PS, Nanna MG, Kelsey MD, et al. Comparison of an Initial Risk-Based Testing Strategy vs Usual Testing in Stable Symptomatic Patients With Suspected Coronary Artery Disease: The PRECISE Randomized Trial:

Original protocol, final protocol, and summary of amendments

Table of Contents

The **PRECISE** Protocol

Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization

Study Objective	The primary objective of the PRECISE trial is to assess clinical outcomes, decision making regarding noninvasive testing and invasive angiography, and costs using a precision evaluation strategy as compared to a usual care strategy in participants with stable symptoms suggestive of coronary artery disease. The precision evaluation strategy will be based on a pre-test risk assessment and will incorporate cCTA with selective FFR_{CT} and guideline-recommended care with symptom and risk factor management and no immediately planned testing.
Study Design	The study will be a prospective, pragmatic, randomized clinical trial of the comparative effectiveness of diagnostic evaluation strategies for stable CAD, to be performed in outpatient settings, including primary care and cardiology practices. Qualifying patients presenting with new symptoms suspicious for clinically significant CAD (and without known CAD), who are recommended for diagnostic testing and did not receive any cardiovascular testing within the past 12 months, will be randomized to an initial strategy of either precision care or usual care. All subsequent decisions in the usual care arm regarding additional testing, medications, and/or procedures will be at the discretion of the responsible clinical care team.
Study Principal Investigator	Pamela S. Douglas, MD Duke University Durham, NC 27701 USA
Sponsor	HeartFlow, Inc. 1400 Seaport Blvd., Building B Redwood City, CA 94063 Campbell Rogers, MD Chief Medical Officer

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 assigned physicians, nurses, and other professional personnel who will participate in the study and will be responsible for their compliance and adherence to the study protocol. 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 HeartFlow and may be utilized by HeartFlow 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 HeartFlow monitors and auditors and their designees full access to all medical records at the research facility for participants screened or randomized in the study. I agree to provide all participants with informed consent forms and will ensure adequate informed consent is obtained, as required by government regulations and International Conference on Harmonization guidelines.

Version Date: Jun 29, 2018

Site Name	**Site Number**
Principal Investigator (print name)	**Date**
DocuSigned by: Pamela S. Douglas, MD CE9FFC194FCE439..	6/30/2018
Pamela Douglas, MD, Trial PI	Date
DocuSigned by: 9DD0E3E5B72A4F2...	7/2/2018
Campbell Rogers, MD, HeartFlow CMO	Date

Protocol Version and Amendment Tracking

Version Number/Amendment	Approval Date
1.0	Jun-29, 2018

TABLE OF CONTENTS

TABLE OF ABBREVIATIONS

ACC	American College of Cardiology
AHA	American Heart Association
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CV	cardiovascular
CCC	Clinical Coordinating Center
CI	confidence interval
CK-MB	creatinine kinase-myocardial band
CMS	Centers for Medicare & Medicaid Services
COCATS	Core Cardiology Training Symposium
cCTA	coronary computed tomographic angiography
DCRI	Duke Clinical Research Institute
DECISION	Decisive Evaluation of Cardiac Ischemia, Symptoms and Revascularization
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
Echo	echocardiogram
EDC	electronic data capture
EQ-5D-5L	A standardized instrument developed by the *EuroQol* Group as a measure of health-related quality of life.
eCRF	electronic case report form
FFR	fractional flow reserve
FS	Finkelstein and Schoenfeld statistical method
FFR_{CT}	non-invasive technique using cCTA to determine FFR
g/L	grams per liter
HDL	high-density lipoprotein

ICA	invasive coronary angiography
IRB	institutional review board
IVUS	intravascular ultrasound
IXRS	interactive voice/web response system
LDL	low-density lipoprotein
LV	left ventricular
MACE	major adverse cardiovascular event
MAR	missing at random
MDCT	multidetector computed tomography
MI	myocardial infarction
MOP	manual of procedures
mSv	milliSievert
NICE	National Institute for Health and Care Excellence (In the United Kingdom's National Health Service)
NHPR	non hyperemic pressure ratio
PAD	peripheral arterial disease
PCI	percutaneous coronary intervention
PI	principal investigator
PLATFORM	Prospective LongitudinAl Trial of FFR_{CT}: Outcome and Resource Impacts study
PRECISE	Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization
PROMISE	PROspective Multicenter Imaging Study for Evaluation of Chest Pain randomized clinical trial
QoL	quality of life
ROC	receiver operating characteristic
SAQ	Seattle Angina Questionnaire
SCOT-HEART	Scottish Computed Tomography of the HEART randomized clinical trial
ULN	upper limit of normal

I. STUDY SYNOPSIS

Protocol Title	**PRECISE:** Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization
Investigational Strategy	Precision diagnostic evaluation as the initial strategy for suspected CAD in patients with stable symptoms
Study Principal Investigator	Pamela S Douglas, MD Duke Clinical Research Institute, Duke University, Durham NC
Academic Research Organizations	Duke Clinical Research Institute (DCRI), Durham, NC, USA Cardiovascular Research Foundation (CRF), New York, NY, USA
Clinical Research Organization	Medpace Research, Inc.
Sponsor	HeartFlow Inc. 1400 Seaport Blvd Redwood City, CA 94063
Participants and Study Centers	Approximately 2100 participants randomized at approximately 100 outpatient sites in the US and outside of the US
Planned Study Duration	Approximately 48 months
Primary Study Objective	To assess clinical outcomes, decision making regarding noninvasive testing and invasive angiography, and costs using a precision evaluation strategy as compared to a usual care strategy in participants with stable symptoms suggestive of coronary artery disease. The precision evaluation strategy will be based on a pre-test risk assessment, and will incorporate cCTA with selective FFR_{CT} and guideline-recommended care with symptom and risk factor management and no immediately planned testing.
Primary Hypotheses	In stable participants with a clinical recommendation for testing to evaluate suspected coronary artery disease (CAD) a precision evaluation strategy, incorporating a risk-based assignment to guideline recommended medical management without planned testing for selected low risk participants and cCTA with selective FFR_{CT} in elevated risk participants, will result in improved clinical outcomes of death/MI and a lower rate of catheterization without obstructive CAD as compared to usual care strategy.
Population	Stable patients who have a clinical recommendation for testing (noninvasive or invasive) for suspected coronary artery disease
Study Design and Methods	Prospective, pragmatic, randomized clinical trial of diagnostic evaluation strategies for stable CAD, to be performed in outpatient settings, including primary care and cardiology practices. Qualifying patients presenting with new symptoms suspicious for clinically significant CAD (and without known CAD), who are recommended for diagnostic testing and did not receive any cardiovascular testing within the past 12 months, will be randomized to an initial strategy of either precision care or usual care of the site's choosing. All subsequent decisions in the usual care arm regarding additional testing, medications, and/or procedures will be at the discretion of the responsible clinical care team; the use of cCTA as the initial diagnostic strategy is not allowed in the usual care arm.

	Precision evaluation: Participants randomized to a precision strategy will be assigned to either guideline-recommended care without immediately planned testing (low risk) or cCTA with selective FFR_{CT} (elevated risk) using a risk tool based on pre-test clinical characteristics derived from the PROMISE trial and validated in SCOT-HEART trial. Participants assigned to guideline-recommended care without planned testing will be treated with preventive and antianginal medical treatment per guideline recommendations and clinical judgment and followed without testing. Participants and their providers will be provided informational resources explaining the safety and rationale of this strategy based on pre-test probabilities and the PROMISE Minimal Risk Score. Participants with documented intractable symptoms despite maximal medical management may undergo cCTA with selective FFR_{CT} at the participant's or site clinician's discretion. **Usual Care:** For participants randomized to usual care, the participant's care team will select the specific noninvasive stress test (exercise electrocardiogram, stress nuclear imaging [including PET], stress MR, or stress echocardiogram); OR invasive test: (direct to diagnostic catheterization). The use of cCTA as the initial diagnostic strategy is explicitly excluded in this arm. In both arms, the participant's care team will be provided with physician and patient informational resources summarizing current recommendations for test interpretation and preventive care. Optimal medical management will be recommended but not mandated in either arm.
Randomization and Stratification	Participants will be randomized using a 1:1 randomization scheme via an interactive web or voice-based system (IXRS). Randomization will be stratified by intended first test if randomized to usual care, low vs. elevated pre-test risk, and site. Enrollment in the strata of intended noninvasive test first (vs. intended invasive angiography first) will be capped at 90%.
Primary Endpoint	Time to a composite of: MACE (all cause death, non-fatal MI) or invasive cardiac catheterization without obstructive CAD (obstructive CAD defined as diameter stenosis ≥50% according to clinical site interpretation, FFR≤0.80, or NHPR<0.90) at one year (intention to treat)
Secondary Effectiveness Endpoints	Endpoints will be assessed at 45 days, 6 months, 1 year, and 2 years. 1. Hierarchical analysis (Finkelstein and Schoenfeld (FS) or Pocock's win ratio) of primary endpoint 2. Resource use patterns (all patients) and medical costs (US patients) to 12 months 3. QoL: measured by the Seattle Angina Questionnaire (SAQ) to assess angina-specific Quality of Life and the EuroQoL 5D (EQ-5D-5L) survey to assess overall (generic) health status 4. Death: All-cause, cardiovascular, non-cardiovascular 5. Myocardial infarction: All, procedural, spontaneous MI

	6. Hospitalizations: All, cardiovascular, non-cardiovascular, and for progressive or unstable angina 7. Preventive medication use (ASA, statins) in participants with clinical indication for use: eg: hyperlipidemia, diabetes, documented CAD 8. Cumulative radiation exposure at 1 year 9. PRECISE primary endpoint at 24 months 10. MACE, defined as all-cause death myocardial infarction, or ischemia-driven revascularization at 24 months (DECISION co-primary end point) 11. All-cause death, MI, all follow-up unplanned revascularization procedures, cardiac catheterizations without actionable findings at 24 months (DECISION co-primary end point) 12. Proportion of invasive cardiac catheterization patients who undergo revascularization (PCI or CABG) within 6 months of enrollment
Pre-specified subgroup analyses	1. Low risk vs. elevated risk by PROMISE score 2. Intended initial test: functional stress test vs. invasive (direct to cath) 3. Clinical factors: Sex, age, diabetes 4. Presentation: Primary symptom (chest pain vs. other), SAQ angina frequency score
Inclusion Criteria	Inclusion criteria (all must be present): 1. Age ≥18 years 2. Stable typical or atypical symptoms suspicious for coronary artery disease with further non-emergent testing or elective catheterization recommended to evaluate the presence of suspected coronary artery disease 3. Safe performance of cCTA: • Creatinine clearance ≥45 ml/min • For a female participant of childbearing potential, a pregnancy test must be performed with negative results known within 7 days prior to randomization 4. Willingness to comply with all aspects of the protocol, including adherence to the assigned strategy and follow-up visits 5. Ability to provide written informed consent
Exclusion criteria	Exclusion criteria (all must be absent): 1. Acute chest pain 2. Unstable clinical status 3. Noninvasive or invasive CV testing for CAD within 1 year 4. Lifetime history of any obstructive CAD (no prior CABG or PCI, stenosis ≥50%), or known EF ≤40% or moderate to severe valvular or congenital cardiac disease 5. Contraindications to cCTA including but not limited to estimated creatinine clearance (GFR) <45 ml/min measured within 90 days 6. Exceeds local weight or size limit for cCTA or cardiac catheterization 7. Any condition leading to possible inability to comply with the protocol procedures or follow-up 8. Any condition that might interfere with the study procedures or follow-up

	9. Enrolled in an investigational trial that involves a non-approved cardiac drug or device which has not reached its primary endpoint 10. Life expectancy less than 2 years due to non-cardiovascular comorbidities
Study Follow-up	Participant follow-up will be done at 45 days, 6 months, 1 year, and 2 years.
Sample Size Considerations	Primary superiority testing hypothesis of all cause death/MI or invasive cardiac catheterization without obstructive CAD (diameter stenosis ≥50% or FFR≤0.80/ or NHPR<0.90) at one year (intention to treat, time to first event analysis): Assuming an 8% event rate at 1 year in the usual care group and 5% in the precision care group (3% absolute [37.5% relative] effect magnitude). Assumed rates are based on 30% assigned to guideline-recommended care with symptom management and no planned testing (within which 30% will cross over to cCTA with selective FFR_{CT}); and overall 10% will not receive assigned testing; enrolling 1050 participants per group (2100 total participants) would provide at least 90% power to demonstrate superiority accounting for 10% attrition rate.

II. INTRODUCTION

II.A. Primary Hypotheses

The overarching goal of the Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization (PRECISE) research program is to assess clinical outcomes, decision making regarding noninvasive testing and invasive angiography, and costs using a precision evaluation strategy as compared to a usual care strategy in participants with stable symptoms suggestive of coronary artery disease. The precision evaluation strategy will be based on a pre-test risk assessment, and will incorporate cCTA with selective FFR_{CT} and guideline-recommended care with symptom management and no planned testing.

The primary hypothesis of PRECISE is: in stable participants with a clinical recommendation for testing to evaluate suspected coronary artery disease (CAD) a precision evaluation strategy will result in improved clinical outcomes of death/MI and a lower rate of catheterization without obstructive CAD as compared to a usual care strategy.

An important secondary hypothesis is that the precision evaluation strategy will result in improved patient-reported outcomes, reflected in the SAQ angina frequency and quality of life scores. We also expect the precision strategy to result in reduced resource utilization and net cost savings compared to usual care evaluation.

The usual care arm participants will undergo either noninvasive stress testing, with the specific modality at the discretion of the participant's clinician, or invasive cardiac catheterization (ICA) as the initial test.

The precision evaluation arm starts with the use of the PROMISE Risk Tool to categorize patient risk for CAD and events. The PROMISE Risk Tool is a validated risk model that has been shown to accurately identify chest pain patients who are unlikely to benefit from non-invasive testing (i.e. have minimal or no atherosclerosis and likely to have no events within two years). The lowest risk group in the precision arm identified using this model will be assigned to guideline-recommended care focused on symptom and risk factor management without planned cardiac diagnostic testing. The remaining participants, who will be of elevated risk, will be initially evaluated with cCTA with selective FFR_{CT}.

I.B. Significance of the Study

The goal of PRECISE is to define the optimal evaluation and management strategy of stable, symptomatic participants with suspected CAD. If the hypotheses of PRECISE are supported by the results of the trial, PRECISE will form the core of a compelling body of evidence supporting important changes in clinical practice guidelines and clinical care that will both improve outcomes for patients and reduce the use of unnecessary (low yield) testing and associated medical costs. Chest pain is one of the most common symptoms that bring patients into the health care system and one of the most difficult for providers to address confidently. The variability of current practice and the frequent overuse of testing derive from the lack of consensus among experts and among guidelines about how best to achieve a secure diagnosis and appropriate management plan. The results of PRECISE will have major implications for all health systems where stable chest pain is a common reason for subjects to seek care.

III. BACKGROUND AND STUDY RATIONALE

III.A. Prior Literature and Studies

Unmet need to develop novel approaches for the diagnostic evaluation in stable chest pain patients

Coronary artery disease is an extremely common diagnosis worldwide and results in significant morbidity and mortality[1, 2]. Among the common presentations, stable symptoms of chest pain or exertional dyspnea can be diagnostically puzzling and often require diagnostic testing or angiography to be certain of the diagnosis and treatment. Current US, EU and UK guidelines recommend risk stratification using presentation characteristics and risk factors to determine which patients require noninvasive testing or should be referred directly to invasive catheterization[3]. However, in the current era, the results of using these recommended strategies are unsatisfactory. The population undergoing noninvasive testing has a low rate of obstructive CAD (10-20%) and very low annual event rates (~1-2%/year) [4, 5], while patients undergoing invasive angiography frequently don't have actionable CAD[6]. These patterns of care have resulted in high costs without accompanying clinical benefit[7]. A new approach to the risk stratification and subsequent diagnostic evaluation and management of patients with stable symptoms suggestive of CAD is urgently needed.

Uncertainty Regarding the Optimal First Test for Detection and Exclusion of Coronary Artery Disease: Evidence For cCTA

While a number of functional and anatomic non-invasive tests are available for the evaluation of stable chest pain patients, the optimal evaluation strategy for patients with stable chest pain is uncertain, and recommendations in current guidelines differ markedly. In a recent attempt to address these issues systematically, two large multicenter, open-label, randomized controlled trials explored the diagnostic evaluation of patients with symptoms that may represent coronary artery disease. The SCOT-HEART (Scottish Computed Tomography of the HEART)[4] and PROMISE (PROspective Multicenter Imaging Study for Evaluation of chest pain)[5] trials sought to address evidence gaps in noninvasive testing in stable chest pain, an area in which few randomized trials had previously been conducted.

Key findings from SCOT-HEART and PROMISE: The overall results and important similarities and differences between the two trials have been recently described[8]. The SCOT-HEART study enrolled 4,146 patients with stable chest pain to cCTA in addition to usual care (which generally included electrocardiogram [ECG] stress testing) or to usual care alone. The trial used an upstream primary endpoint related to diagnostic thinking: managing clinician certainty of the diagnosis of angina secondary to CAD, which showed an increase in the cCTA group (RR: 1.79; 95% confidence interval [CI]: 1.62 to 1.96), as did the secondary endpoint of certainty of diagnosis of CAD (RR: 2.56; 95% CI: 2.33 to 2.79). The clinical outcomes-related secondary endpoint of the rate of cardiovascular death or nonfatal myocardial infarction (MI) appeared to be reduced in the cCTA group at 20 months (RR: 0.62, 95% CI: 0.38 to 1.01; p=0.0527), although the overall event rates were low in both arms, reflecting the inclusion of a large number of patients without

CAD. Of note, a landmark analysis excluding the 7 week delay to receiving a cCTA yielded a hazard ratio of 0.50 for CV death and MI[9].

The larger PROMISE trial randomly assigned 10,003 symptomatic, stable outpatients requiring evaluation for suspected CAD to either initial cCTA or functional stress testing (exercise treadmill testing [ETT], nuclear stress testing, or stress echocardiography), with a median follow-up of 25 months. The event related composite primary endpoint (death, MI, hospitalization for unstable angina, or major cardiovascular procedural complication) occurred at similar rates in the cCTA and functional testing groups (3.3% and 3.0%), which was lower than previously established historical rates. More patients in the cCTA group underwent cardiac catheterization within 90 days after randomization (12.2% vs. 8.1%), but the secondary endpoint of the frequency of catheterization showing no obstructive CAD was significantly lower in the cCTA group (3.4% vs. 4.3%, p=0.02) as was the rate of death and MI at 12 months (HR 0.66; p=0.049). Furthermore, among patients randomized to an intended nuclear testing strategy, the mean cumulative radiation exposure was lower in the cCTA group compared with the functional testing group (12.0 - 8.4 mSv vs. 14.1 - 7.6 mSv). This encompassed all downstream radiation within 90 days, including that associated with cardiac catheterization, and is particularly intriguing because more cCTA patients received cardiac catheterization.

In addition to improving triage to the cardiac catheterization lab and potentially reducing radiation exposure, mounting evidence has demonstrated that use of cCTA, compared to functional testing, yields improved preventive medical treatment and better prognostic information[4, 5, 10]. Patients in the PROMISE trial who underwent cCTA experienced greater uses of indicated cardio-protective medications such as aspirin and statins[10]. This increase is prognostically important, as data from the CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes International Multicenter) demonstrated that baseline statin therapy among patients with non-obstructive CAD[11] identified on cCTA was associated with a reduction in mortality compared to non-use[12], while statin therapy among patients with obstructive CAD identified on cCTA was associated with a reduction in MACE[13].

The identification of non-obstructive CAD with high risk plaque characteristics can only be accomplished non-invasively by cCTA and is an important prognostic indicator, with even mild abnormalities conferring nearly three times the risk of death, MI and unstable angina compared to patients with a normal study[14, 15]. Furthermore, cCTA leads to higher yield of positive results with actionable or obstructive CAD, among patients undergoing cardiac catheterization[5]. This is in line with data from the CONFIRM registry, where investigators demonstrated that cCTA could be used as an effective gatekeeper prior to invasive coronary angiography[16].

Most importantly, a recent meta-analysis largely based on PROMISE and SCOT-HEART data showed a clear benefit in ‘hard’ cardiovascular outcomes to a cCTA first strategy, with a 29% reduction in MI[17]. This was potentially driven by the increase in medication utilization in the cCTA arm of the study as well as more catheterization and revascularization[17].

To summarize, there are several practical and clinical implications of SCOT-HEART and PROMISE which inform the proposed design of PRECISE:

- Contemporary patients with stable chest pain are at low risk of clinical events. Therefore, a strategy to test only those with an elevated likelihood of having obstructive CAD or risk for events, while instituting optimal medical care including deferring testing in those unlikely to

benefit (i.e. using the PROMISE Risk Score), may be feasible, clinically important and efficient.

- cCTA is a reasonable first test for routine assessment of patients with stable chest pain, and when compared to functional testing, is associated with an increase in preventive medication use and a reduction in myocardial infarction.
- Future trials investigating the optimal evaluation of patients with stable chest pain should include the evaluation of clinical outcomes and other measures of testing efficiency (i.e., cardiac catheterization without obstructive CAD).

The Case for the Use of cCTA with selective FFR_{CT} as the Optimal First Test

The current noninvasive diagnostic testing strategies using functional testing have relatively poor accuracy given the low disease prevalence in this population, leading to high rates of false-positive results[18]. Specifically, current diagnostic strategies lead to high rates (~50%) of cardiac catheterization without significant obstructive disease or need for revascularization[5, 7]. As described above, incorporating cCTA into testing strategies can reduce the frequency of cardiac catheterization without obstructive disease but tends to increase rates of invasive angiography [4, 5].

Non-invasive computationally-derived FFR_{CT} has been developed using resting coronary CT images without the administration of adenosine or change in underlying cCTA protocols[18-21]. The methodology has been previously described elsewhere. [22] In short, FFR_{CT} uses the accurate anatomical model of the coronary arteries and myocardium obtained with conventional cCTA and applies the physical laws that govern flow, microcirculatory resistance, coronary branching, and simulated hyperemia. The Navier-Stokes equations that solve for velocity, resistance and pressure for all Newtonian fluids are applied to provide a 3-dimensional pressure map across the coronary tree. This use of computational fluid dynamics generates FFR values from 0 to 1, with $\leq$0.80 considered hemodynamically significant. The values are congruent with invasive FFR, as shown in several prospective validation studies[18-20]. Finally, the anatomical modeling has been improved by the use of advanced deep and machine learning techniques applied to the large data sets acquired via central analysis.

The addition of FFR_{CT} may reduce a potential limitation of a cCTA-first approach, excess invasive angiography, by providing both functional and anatomic data. Specifically, FFR_{CT} markedly reduces in the false positive rate of cCTA alone vs. invasive FFR adjudicated ischemia with 68% of false positive CT interpretations in the NXT Trial reclassified as true negative. A retrospective analysis from the PROMISE trial in 181 patients with cCTA, cardiac catheterization and FFR_{CT} revealed that FFR_{CT} was a better predictor of revascularization and events than cCTA alone. Modelling of the incorporation of FFR_{CT} into catheterization decision making suggested a reduction in catheterization rate with cCTA from 12.2% to 7.8% while reducing the rate of catheterization without obstructive CAD from 27% to 15% and increasing the yield of catheterization leading to revascularization from 49% to 61%[23]. Given that PCI of lesions with negative FFR is associated with worse outcomes[24, 25], while treatment of FFR positive lesions with PCI vs. optimal medical therapy results in improved clinical outcomes, the potential clinical value of adding FFR_{CT} to a cCTA based diagnostic strategy is evident.

The safety and utility of a CT/ FFR_{CT} strategy were further tested in the PLATFORM Study (Prospective LongitudinAl Trial of FFR_{CT}: Outcome and Resource Impacts) which evaluated rates of invasive catheterization without obstructive CAD in patients undergoing invasive evaluation. Patients in 2 sequential non-overlapping cohorts of patients referred for ICA were assigned to either undergo ICA or cCTA/ FFR_{CT} with ICA use based on the results of the cCTA and FFR_{CT}. The cCTA/FFR_{CT} strategy resulted in a significant reduction in the rate of cath lab finding of no obstructive disease, from 73 to 12%[7]. Furthermore, ICA was deferred in 61% of cCTA/FFR_{CT} strategy patients. A follow-up at one year demonstrated that cCTA with selective FFR_{CT} strategy yielded similar clinical outcomes and quality of life, at a substantially reduced cost.

While much of the early focus has been on a reduction in referral for ICA in the absence of actionable CAD, more recently there has been growing interest in using FFR_{CT} to enhance catheterization lab efficiency by increasing the proportion of catheterizations that include revascularization (ICA/PCI ratio) and providing guidance regarding revascularization strategies before the invasive angiogram. Importantly, in this case FFR_{CT} is not being used only in a binary fashion but rather to provide a richer understanding of the pattern and degree of pressure loss across the epicardial coronary system and its connection to the extent of ischemia present.
The value of cCTA and FFR_{CT} has been recognized by The National Institute for Health and Care Excellence (NICE) in their advisory for stable chest pain (Clinical Guidance 95) and technical evaluation of FFR_{CT}, as well as by establishment of reimbursement standards by the Centers for Medicare and Medicaid Services (CMS) [26, 27]. The 2016 NICE guidance recognized the difficulties with risk stratification in an era of reduced obstructive CAD prevalence in the population undergoing evaluation and the importance of anatomical assessment of CAD[26, 27]. In response, it recommends coronary cCTA as the first-line investigation for patients presenting with new-onset chest pain felt to be due to CAD based on its superior clinical diagnostic utility and cost-effectiveness[26, 27]. Further, based on the results of the PLATFORM trial, the NHS recommends addition of FFR_{CT} to cCTA as a cost savings measure[26]. In the United States, CMS approved a New Technology Ambulatory Payment Classification (APC) for HeartFlow FFR_{CT} analysis on January 1, 2018[28]. The acknowledgement of FFR_{CT} by CMS is a critical step toward increasing the availability of the technology to patients who may benefit. However, other organizations' standards documents have not yet been revised to incorporate the emerging evidence base supporting CCTA and FFR_{CT}, indicating that there is still a need for additional evidence to support the routine use of FFR_{CT} in clinical practice.

<u>Rationale and Evidence for Incorporation of a Strategy of Guideline-recommended Care without Planned Testing in Low Risk patients</u>

Given the low prevalence of obstructive CAD (10-20%) and very low annual event rates (~1-2%/year) among stable chest pain patients undergoing non-invasive testing, combined with the high cost of testing[4, 5], prospective evaluation of the safety and efficacy of an approach of guideline-recommended care without planned testing has become a necessity. Although there are no data regarding outcomes and costs of a guideline-recommended care without planned testing in symptomatic patients, it is possible to define in principle a cohort in whom deferred testing might be the optimal strategy. The argument for testing this is further strengthened by the equivalence of medical and invasive strategies in preventing cardiovascular events in stable CAD, as several trials have shown no benefit of revascularization over optimal medical treatment [29, 30]. It is reasonable to hypothesize that this may be especially true for those at lowest risk, in whom noninvasive testing is even less likely to lead to outcomes-improving revascularization, thereby removing the need for testing as a gateway to the catheterization laboratory.

The COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) demonstrated no significant difference in a composite of death, myocardial infarction, and stroke between patients with objective evidence of myocardial ischemia and significant CAD on medical therapy vs. those undergoing PCI (19.5% vs. 20.0%, p=0.62)[29]. The more recent ORBITA trial (Percutaneous coronary intervention instable angina) randomized 200 patients with stable angina and a single-vessel stenosis to optimal medical therapy + PCI vs. optimal medical therapy plus a sham procedure, with a primary endpoint of difference in exercise time during a 6-week follow-up period[30]. The authors found no significant difference in improvement in exercise time (+28.4 seconds in PCI group vs. +11.8 seconds in sham group, p=0.2), nor any significant change in the secondary outcome of Seattle Angina Questionnaire (SAQ)-angina frequency from baseline (14.0 in PCI group vs. 9.6 in sham group, p=0.26)[30]. The ongoing improvements in medical management of CAD risk, angina and established coronary artery disease further emphasize the need for diagnostic strategies that minimize unnecessary invasive angiography and revascularization by emphasizing guideline-recommended care in patients at very low risk for obstructive disease.

These studies support the development of a patient-centric strategy to identify those who may derive minimal benefit from testing, a strategy which carries several desirable implications for patients, clinicians, and clinical practice in general. For patients, this process can mean a reduction in use of testing from which they would not benefit, thereby saving time, anxiety, and cost, as well as potential reductions in radiation exposure and false-positive test results that could lead to more invasive, unnecessary procedures. For clinicians, a tool identifying the lowest risk patients has the potential to help optimize office-based decision making. From a practice and societal perspective, in an era in which practitioners are increasingly held accountable for costs and quality, the ability to confidently identify patients highly unlikely to benefit from potentially expensive testing and who may therefore be managed conservatively has many potential economic and process-of-care advantages.

The PROMISE Risk Tool was expressly developed to identify low-risk patients with stable chest pain who are unlikely to benefit from non-invasive testing, and for whom guideline-recommended medical management alone may be safe. Current guidelines recommend using a version of the Diamond and Forrester risk score for pretest likelihood of obstructive CAD, but multiple investigators have found that this tool grossly over estimates actual presence of disease[5, 31, 32]. The consequence is an imprecise evaluation strategy for millions of patients, resulting in unhelpful testing of lower risk individuals. For a significant portion of these, a false positive functional testing leads them to have invasive cardiac catheterizations to rule out the disease they do not have. The Risk Tool developed using the PROMISE cohort employs 10 readily available clinical variables and has been validated in the SCOT-HEART population[33, 34]. This risk tool identifies patients with stable chest pain who have no coronary plaque or calcification by cCTA and no cardiac events over 2 years, and who therefore would be predicted to derive minimal or no value from noninvasive testing[33, 34]. Testing whether this risk tool can be employed prospectively to safely and effectively risk stratify low risk patients into a strategy of guideline-recommended care with symptom and risk factor management and without diagnostic testing is one of the core secondary objectives of the PRECISE research program.

III.B. Rationale for the Current Study: A Precision Approach to Chest Pain Evaluation

Despite the high-burden of stable chest pain in the U.S., and the enormous research literature reporting on the comparative effectiveness of different options, no single diagnostic strategy has emerged with a broad consensus of support. Each testing community continues to favor its own technology and the clinicians who must select the testing approach to use for their patients are caught in the middle, unable to resolve the controversies that have characterized this area of cardiovascular medicine for decades. The situation is complicated by the heterogeneity of the current population's burden of disease. More than a quarter (27%) of the PROMISE cohort had no coronary plaque whatsoever, while high-risk CAD, defined as left main stenosis (≥50% stenosis) or either (a) ≥50% stenosis '[50]' or (b) ≥70% stenosis '[70]' of 3 vessels or 2-vessel CAD involving the proximal left anterior descending artery was identified in 6.6% [50] and 2.4% [70] of patients. Thus, the first goal of any optimal management strategy for stable symptoms in patients with suspected CAD is determination of an individual patient's risk. Using the PROMISE Risk Tool to accurately assess patient risk[33, 34], we will prospectively test the hypothesis that low risk patients can be correctly identified with only baseline clinical data and that emphasizing guideline-recommended care while deferring testing in these patients improves chest pain decision making by reducing unnecessary invasive angiography without leading to an increase in MACE, and by reducing cost.

Among patients in whom contemporary risk evaluation suggests an elevated risk for obstructive CAD, the observational data suggest that cCTA with selective FFR_{CT} may improve appropriate triage to invasive angiography[5, 23], while reducing cost[9].

Thus, the case for an adequately powered randomized clinical trial with a pragmatic design, comparing clinical outcomes following testing strategies regularly used in current clinical practice to a precision evaluation strategy is compelling. PRECISE is designed to be that trial

If the findings of PRECISE are positive as hypothesized, it is expected that the trial will lead to updates in appropriate use criteria, clinical practice guidelines, and payer policies such that cCTA with selective FFR_{CT} receives a class IA recommendation for stable chest pain patients to improve outcomes and reduce costs. PRECISE will identify those chest pain patients for whom non-invasive testing may be safely deferred and simultaneously improve the efficiency of testing for elevated risk patients. The results of this study will shift the paradigm of clinical thinking in this area from the current approach of identifying a single best test for all, to incorporating a patient-centric risk-based evaluation and management strategy for stable chest pain patients.

IV. STUDY OVERVIEW AND OBJECTIVES

IV.A. Overview of PRECISE

PRECISE is a multicenter, randomized, trial that will enroll approximately 2100 participants in a comparison of a risk-based precision evaluation strategy of guideline-recommended medical management without planned testing (in minimal risk participants) and cCTA with selective FFR_{CT} (in elevated risk participants) with usual care in stable symptomatic patients with suspected CAD.

Location

Participants will be enrolled at approximately 100 outpatient sites in the US and outside of the US. No center may enroll more than 315 (15%) participants in the trial.

Participant Population and Selection

Participants will be symptomatic patients with suspected CAD and a stable clinical course who are recommended by their managing clinician to have a non-invasive diagnostic test or ICA. Subjects will be excluded if they have any history of documented CAD (including revascularization, myocardial infarction or any degree of CAD proven by imaging) or have had diagnostic cardiovascular testing for suspected CAD within the last year. Subjects will also be excluded if their symptoms are not clearly stable or if their managing clinician feels testing is needed on an urgent or emergent basis.

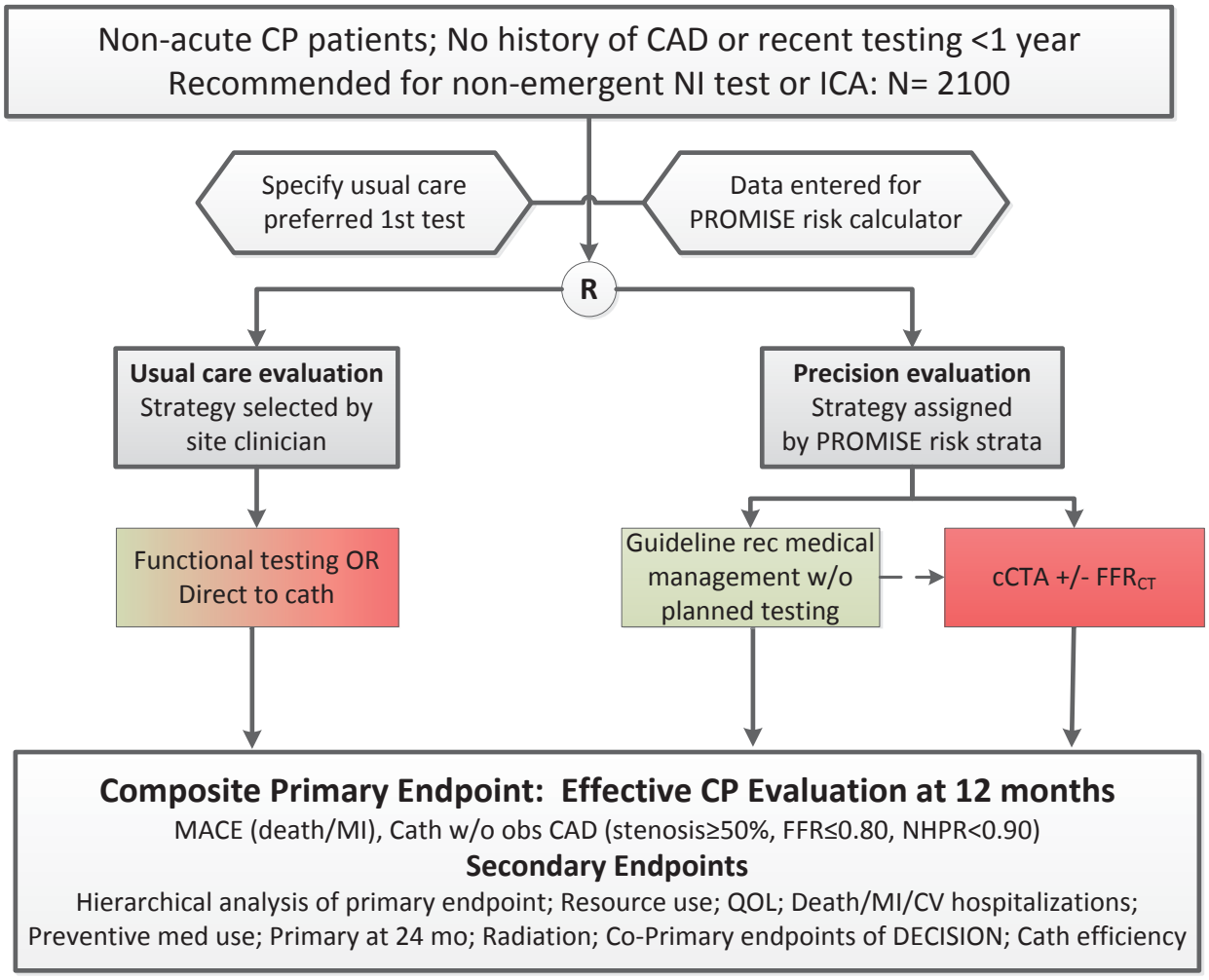
Diagnostic testing for the assessment of CAD symptoms is ordered by physicians and other clinicians from many specialties and is performed in multiple settings, including physician offices, hospital outpatient departments, and diagnostic testing facilities. A trial, such as PRECISE, that seeks to improve the management of non-acute chest pain must incorporate this diversity in order to be broadly relevant to the target population under study. PRECISE site selection will seek to encompass this diversity.

Study duration

The anticipated total duration of the PRECISE study will be approximately 48 months for start-up, enrollment, follow up, and close out. Participants will be followed for 24 months after enrollment.

Study design

The figure below represents a diagrammatic representation of the trial design.



IV.B. Primary Objective and Endpoints

The primary objective of the PRECISE study is to assess clinical outcomes, patient-reported outcomes, decision making regarding noninvasive testing and invasive angiography, and costs using a precision evaluation strategy as compared to a usual care strategy in participants with stable symptoms suggestive of coronary artery disease. The precision evaluation strategy will be based on a pre-test risk assessment and will incorporate cCTA with selective FFR_{CT} and guideline-recommended care with symptom and risk factor management and no immediately planned testing. We hypothesize that in stable patients with a clinical recommendation for testing to evaluate suspected CAD the proposed precision evaluation strategy will improve outcomes and reduce costs compared to usual care evaluation.

The primary endpoint is a composite of: MACE (all cause death and non-fatal MI) or invasive cardiac catheterization without CAD (no coronary stenosis ≥50%, or with FFR≤0.80, or non-hyperemic pressure ratio (NHPR) <0.90). The primary study hypothesis will be tested at one year using an intention to treat analysis.

IV.C. Secondary Endpoints

Endpoints will be assessed at 45 days, 6 months, 1 year, and 2 years. Secondary endpoints include:

1. Hierarchical analysis (Finkelstein and Schoenfeld (FS) or Pocock's win ratio) of primary endpoint (gives priority to clinical importance of the components of the composite outcome rather than time to event)
2. Resource use patterns (all participants) and medical costs (US participants): resources to be assessed include index testing, follow up testing, diagnostic and other cardiac procedures and hospitalizations. Primary comparisons will be made at 12 months.
3. QoL: the Seattle Angina Questionnaire (SAQ) will be used to assess angina-specific Quality of Life; the EuroQoL 5D (EQ-5D-5L) survey will be used for a brief assessment of overall (generic) health status; patient satisfaction with diagnostic process will be assessed once at 45 days using a 4-item instrument created for this trial.
4. Death: All-cause, cardiovascular, non-cardiovascular
5. Myocardial infarction: All, procedural, spontaneous MI
6. Hospitalizations: All, cardiovascular, non-cardiovascular, and for progressive or unstable angina
7. Rates of preventive medication use (ASA, statins) in participants with clinical indication for use: hyperlipidemia, diabetes, documented CAD
8. Cumulative radiation exposure at 1 year
9. PRECISE primary endpoint at 24 months
10. MACE, defined as all-cause death myocardial infarction, or ischemia-driven revascularization at 24 months (DECISION co-primary end point)
11. All-cause death, MI, all follow-up unplanned revascularization procedures, cardiac catheterizations without actionable findings at 24 months (DECISION co-primary end point)
12. Proportion of invasive cardiac catheterization patients who undergo revascularization (PCI or CABG) within 6 months of enrollment (catheterization efficiency)

IV.D. Rationale for the Selection of Outcome Measures

Rationale for Clinical Assessments

Major adverse cardiovascular events (MACE) are a primary concern for clinicians and patients presenting with stable chest pain. The primary composite endpoint of MACE at 12 months (all cause death, non-fatal MI), invasive cardiac catheterization without obstructive CAD (diameter stenosis ≥50%, FFR≤0.80 or NHPR<0.90)) is clinically relevant and, the components taken together, represent a sound measure of an effective diagnostic chest pain evaluation[4, 5, 35, 36]. The selection of 12 months is based on the rationale that the longer the duration between the evaluation strategy and an eventual outcome, the less likely it is that the evaluation strategy is directly related to the outcome of interest. In PROMISE, there was a significant reduction in death and MI in the cCTA arm compared to the usual care arm at 12 months, which was no longer significant after a median 25 months of follow-up[5]. The use of this composite clinical endpoint will be critical to assessing the PRECISE hypothesis that a precision evaluation strategy with cCTA and selective FFR_{CT} and guideline-recommended medical management without planned testing will yield superior outcomes at lower cost compared with a usual care testing strategy.

Rationale for Economic and Quality of Life (QoL) Assessments in PRECISE

Non-invasive diagnostic testing for the evaluation of stable chest pain represents a significant cost to the U.S. and other healthcare systems. In the past when payers in the US have attempted to control costs by reducing the reimbursements provided for diagnostic testing, clinicians responded by increasing the number of tests obtained. An emphasis on generating evidence for cost-savings via a safer and more efficient approach is critical in enhancing value while reducing the financial burden on patients, providers, and the system alike. In addition, this precision-based approach to diagnostic evaluations in CAD participants may result in improvements in the quality of care of our participants. Further, since there has been no prospective trial of guideline-recommended care without planned testing, the ability of such an approach to provide equivalent symptom relief compared with usual care is of great importance and critical to the evaluation of this approach. For these reasons, the potential impact of a precision-based approach on resource use and QoL must be evaluated in PRECISE.

IV.E. Rationale for Selection of Testing in Each Arm

Usual Care Arm

Functional stress testing with stress nuclear, stress echocardiography, and exercise ECG for the diagnosis of CAD is well-established in clinical practice (ACC/AHA 2012 Stable Ischemic Heart Disease guidelines, class I, Level of Evidence (LOE) B)[37]. While stress CMR is less commonly used, it also receives a class IIa, LOE B recommendation in patients who are unable to exercise[37] and is used in some centers. In contrast, it is common for patients to be referred direct to diagnostic angiography without undergoing a functional test. This group represents up to 50% of elective catheterization populations and is thus an important usual care approach to suspected CAD[35, 38, 39]. In order to accurately capture the wide variety of testing strategies available to and used by community clinicians and real-world practice patterns, a usual care strategy arm with site clinician decision-making should include all of the above options. This will improve the generalizability of the trial while accurately capturing the potential impact of the implementation of a precision approach. Use of cCTA as the initial diagnostic strategy is specifically excluded in the usual care strategy arm.

Precision Evaluation Arm

PRECISE will evaluate whether a precision evaluation strategy that combines contemporary risk stratification using the PROMISE Risk Tool with functional and anatomic non-invasive evaluation with cCTA with selective FFR_{CT} can improve outcomes over usual care in stable chest pain patients while safely deferring further testing in low-risk patients and reducing cost overall. While current guidelines recommend the non-invasive and invasive initial testing approaches for patients with stable chest pain[37], current practice is known to lead to high rates of ICA without obstructive CAD[6, 40]. Further, although guidelines also recommend no testing in the lowest risk groups (pre-test probability of obstructive CAD <10 or 15%), currently available risk tools result in many clinicians appearing to ignore this recommendation: current patterns of care using available risk stratification tools results in testing populations with a prevalence of obstructive CAD of only 10-20%, and a prevalence of no coronary plaque of >25%[4, 5]. The intervention in PRECISE will triage patients into two risk groups who will be assigned to receive either guideline-recommended medical management without planned testing or cCTA with selective FFR_{CT}. The PROMISE Risk

Tool can identify low-risk patients with stable chest pain that would be expected to derive minimal value from noninvasive testing and is superior to either Framingham Risk Score or Diamond and Forrester assessments[33, 34]. cCTA with selective FFR_{CT} represents a combined functional and anatomic testing modality that can lower the frequency of finding no obstructive CAD at catheterization and thus reduce costs[7, 41].

IV.F. Randomization Method

Participants who meet all inclusion criteria and none of the exclusion criteria will be randomized in a ratio of 1:1 within a clinical center to either a precision evaluation strategy or usual care using an interactive web or voice-based system (IXRS). Randomization will be stratified by intended first test if randomized to usual care and by classification as minimal vs. elevated risk by the minimal risk model. The randomization scheme within a clinical center will be carried out by the method of random permuted block design with variable block size.

Enrollment in the randomization strata of intended first test being noninvasive (vs. direct to catheterization) will be capped at 90% of the sample size.

Risk will be classified by a risk tool using pre-test clinical characteristics derived in the PROMISE trial and validated in SCOT-HEART. Participants randomized to follow a precision strategy group will be assigned to either guideline-recommended care with symptom and risk factor management and no immediately planned testing (low risk group) or cCTA with selective FFR_{CT} (elevated risk of obstructive coronary disease and/or events). Participants randomized to precision evaluation and risk stratified into the low risk group and their providers will be provided informational materials explaining the rationale for this decision and the safety of this strategy based on outcomes of similar participants in the PROMISE trial.

Participants randomized to usual care will undergo either noninvasive stress testing or invasive testing (direct to diagnostic catheterization), as recommended by their managing clinician and agreed to by the participant. Acceptable noninvasive testing options will include exercise electrocardiogram, stress nuclear imaging (including PET), stress MR or stress echocardiogram. The use of cCTA is explicitly excluded as the initial diagnostic strategy in this arm.

In both arms, all subsequent decisions regarding additional testing, medications, and/or procedures will be at the discretion of the responsible clinical care team. Each care team will be provided with informational materials summarizing current standards for test interpretation and preventive care. However, specific medical treatment will not be mandated by the study.

IV.G. Diagnostic Evaluations and Subsequent Care

<u>Description of Evaluations to be performed</u>

Participants will be assessed per the individual clinicians' routine approach to patients presenting with stable chest pain. Initial evaluation will include an appropriate medical history, physical examination, resting 12-lead ECG, and other routine blood work. A pregnancy test will be required for female participants of childbearing potential, and a creatinine blood test will be required for participants without a recent normal value (within previous 90 days).

At the time of randomization, the site clinician will specify the preferred first diagnostic strategy (noninvasive stress test vs. direct to catheterization) if randomized to the usual care arm and this choice will be used to stratify randomization. Also part of the randomization process, every participant will undergo risk stratification with the PROMISE risk calculator although sites will be blinded to results. Participants randomized to the precision evaluation arm, will be assigned to either no planned testing vs cCTA/FFR_{CT} based on results.

Sites will be provided with informational materials outlining standards of care for all noninvasive test interpretation and guideline recommendations for care and symptom and risk factor management. Participant-friendly versions of these material will also be provided to sites, and may be used as handouts.

Symptoms and Quality of Life (QoL) will be assessed by the EuroQoL 5D (EQ-5D-5L) survey to assess overall (generic) health status and the Seattle Angina Questionnaire (SAQ) to assess angina-specific Quality of Life.

Equipment, Protocols & Interpretation

All participating sites will use standard equipment and procedures for usual care testing, including diagnostic angiography, stress echocardiography, stress nuclear perfusion imaging, stress CMR, and exercise ECG as defined by current practice guidelines[42-49]. Sites must also use at least 64-slice temulti-detector computed tomography (MDCT) for coronary cCTA[49, 50]. All testing protocols will be in accordance with current best-practice standards[42-48, 50].

Interpretation

The interpretation of all diagnostic tests will be performed in a timely fashion and will capture the presence and extent of findings including diagnosing or excluding CAD (diagnostic angiography), fixed or inducible LV perfusion and wall motion abnormalities (stress echo, cMR and stress nuclear), and functional capacity (in the case of exercise ECG, exercise echo and exercise nuclear). The site interpretation and clinical report of all diagnostic tests, including noninvasive stress testing, cCTA and invasive angiography, will be uploaded through the EDC.

cCTA study interpretation will be carried out by physicians with at least ACC COCATS (Core Cardiology Training Symposium) level 2 training, Society of Cardiovascular Computed Tomography level 2, recognized by the Certification Board of Computed Cardiovascular Tomography, or equivalent[50]. Certification by the Certification Board of Nuclear Cardiology or Board Certification in nuclear medicine or radiology will be considered satisfactory for interpretation of stress nuclear imaging studies. Stress echo and cMR readers also be at least COCATS level 2 trained or equivalent. Prior to being opened to participant enrollment, sites will be certified to ensure that quality cCTA images can be obtained.

Referral of precision evaluation cCTA participants for FFR_{CT} determinations

Participants randomized to the precision evaluation arm who are determined to be at elevated risk will undergo cCTA as the initial diagnostic strategy according to current best practice standards. Image sets showing at least one 30-90% stenosis in epicardial vessels of 2mm diameter or greater will be promptly sent to HeartFlow for analysis of FFR_{CT}. Results will be returned to sites in < 24 hours to enable rapid incorporation into clinical decision making,

Subsequent Care

Subsequent care will be provided by the individual site clinicians at their own discretion, with encouragement to follow guideline-based approaches. Information will be provided to the individual sites on diagnostic test interpretation and subsequent management approaches for the various imaging modalities, including relevant guideline recommendations for primary and secondary prevention.

Need for testing in low risk participants randomized to the precision care arm

Participants randomized to the precision evaluation arm and determined to be at low risk will be treated for symptoms and risk factor management according to current guideline recommendations. While it is expected that this will resolve symptoms in nearly all cases it is recognized that chest pain will persist in some despite medical treatment. In some cases, additional non-cardiac diagnostic testing may be pursued. In other cases, the site clinician may decide that further cardiac testing is warranted, in which case a cCTA followed by selective FFR_{CT} should be performed. Details regarding such decision making will be captured in the case report form.

V. STUDY PROCEDURES

V.A. Patient Screening for Eligibility

Patients will be screened by site personnel for eligibility and provided information about the study. Patients not meeting inclusion and or having exclusion criteria will be documented as being excluded. Patients meeting inclusion and not meeting any exclusion criteria will be provided an informed consent form to review and sign prior to being randomized into the study.

Screening visit (in-person)

At the screening visit, patients will undergo the following:

- Review consent form and have all questions appropriately answered.
- Provide consent by signing the Informed Consent Form
- Review of medical history
- Review of concomitant medications
- Pregnancy test (for females of child-bearing potential)
- Creatinine test (if not done in last 90 days)
- Resting 12-lead ECG (optional, clinical care only)

Inclusion Criteria

1. Age ≥18 years
2. Stable typical or atypical symptoms suggesting possible coronary artery disease (CAD) with further non-emergent testing or elective catheterization recommended to evaluate the presence of suspected CAD
3. Safe performance of cCTA:
    a. Creatinine clearance ≥45 ml/min
    b. For a female participant of childbearing potential, a pregnancy test must be performed with negative results known within 7 days prior to randomization

4. Willingness to comply with all aspects of the protocol, including adherence to the assigned strategy and follow-up visits
5. Ability to provide written informed consent

Exclusion Criteria

1. Acute chest pain
2. Unstable clinical status
3. Noninvasive CV testing within 1 year (for suspected CAD)
4. History of known obstructive CAD (prior myocardial infarction, CABG or PCI, stenosis ≥50%), known EF≤40% or other moderate to severe valvular or congenital disease
5. Contraindications to cCTA including but not limited to estimated creatinine clearance (GFR) <45 ml/min
6. Any condition leading to possible inability to comply with the protocol
7. Exceeds the weight or size limit for cCTA or cardiac catheterization at the site
8. Life expectancy less than 2 years due to non-cardiovascular comorbidities
9. Enrolled in an investigational trial that involves a non-approved cardiac drug or device which has not reached its primary endpoint
10. Any condition that might interfere with the study procedures or follow-up

Assessment of CAD risk will be performed during screening to ensure eligibility. It will include:

- General medical history
- Cardiovascular risk factors and comorbidities as well as prior testing or events
- Physical exam
- Laboratory testing

The following major cardiac risk factors will be assessed:

- Age
- Sex
- BP/hypertension
- Diabetes
- Cholesterol (including low-density lipoprotein [LDL], high-density lipoprotein [HDL]), if available
- Smoking status
- Family history
- Sedentary life style
- Obesity (BMI, waist hip ratio)
- Cerebrovascular and peripheral arterial disease (PAD)
- Ankle brachial index (ABI)

V.B. Randomization and Enrollment

Once a participant has consented to participate in the trial, participant information will be entered into the database. If a patient is a screen failure, the data that has been collected up until this point for the patient for screening purposes will be entered into the case report forms (CRF) in the electronic data capture (EDC) system. No additional information will be collected after this point for such a patient.

For eligible participants, medical history data will be captured in the EDC. In addition, sites will need to specify the intended first test which would be performed if the participant is randomized to the usual care arm. The participant will then be randomized to either the usual care arm or the precision evaluation arm. Once randomization occurs, the participant is considered enrolled in the study. If randomized to the precision evaluation arm, participants will be further assigned to guideline-recommended without planned testing or cCTA with selective FFR_{CT}.

V.C. Participant Cohort Assignment

Participant will be randomized to either the usual care arm or the precision evaluation arm within 14 days of screening.

Usual Care Arm
Participants randomized to the usual care arm will undergo either noninvasive stress testing (exercise electrocardiogram, stress nuclear imaging including PET, stress MR, or stress echocardiogram), with the specific modality at the discretion of the participant's clinician, or invasive catheterization. Performance of cCTA as the initial test is excluded in this arm.

Precision Evaluation Arm
Participants randomized to the precision evaluation arm will be assigned a management approach based on their PROMISE Risk Score, a risk model based on pre-test clinical characteristics derived from the PROMISE trial and validated in SCOT-HEART[34]. Participants will be assigned to either guideline-recommended medical management without planned testing (low risk) or cCTA with selective FFR_{CT} (elevated risk). Participants assigned to the strategy of guideline-recommended medical management without planned testing will be treated with risk-appropriate preventive care and symptom control (including therapeutic trials of anti-anginal medications). Participants and their providers will be provided informational materials demonstrating the safety of this strategy based on pre-test probabilities and the PROMISE Risk Score. Participants with intractable symptoms despite maximal medical management whose clinicians opt for further testing (crossovers) will undergo cCTA with selective $FFR_{CT.}$

Participants undergoing cCTA as the initial test (both assigned or crossover) should have FFR_{CT} analysis ordered if cCTA shows at least one 30-90% stenosis in epicardial vessels of 2mm diameter or greater. Image sets will be sent promptly to HeartFlow for analysis and results will be returned to sites in < 24 hours to enable rapid incorporation into clinical decision making.

V.D. Participant Follow-Up

Participants will be followed up at 45 (+/-14) days and at 6, 12, and 24 months (+/- 30 days) after enrollment. For North American participants, follow-up after the 45 day visit will be done by phone interviews conducted by the DCRI Outcomes Call Center. For participants outside North America, follow-up will be conducted by the site coordinators.

Activities to be conducted at each follow up contact are described below and in the Schedule of Events.

45(+/-14) day follow-up visit (in-person)

At the 45-day follow-up visit, participants will be asked the following:

- Assessment if any MACE has occurred since enrollment
- CV Update: Review and documentation of any cardiovascular diagnostic test, cardiovascular procedure, or hospitalizations/clinic visits due to cardiovascular symptoms and complications since enrollment
- Review and documentation of concomitant medication changes since enrollment
- Complete the following 3 questionnaires:
    - Seattle Angina Questionnaire
    - EQ-5D-5L Questionnaire
    - Participant Satisfaction Questionnaire
- Collection of
    - Any cardiovascular test – both written report and test output
    - Any cardiovascular imaging – both written report and image file

6 months (+/-30 days) follow-up contact

At the 6-month follow-up contact, participants will be asked the following:

- Assessment if any MACE has occurred since the 45-day visit
- CV Update: Review and documentation of any cardiovascular diagnostic test, cardiovascular procedure, or hospitalizations/clinic visits due to cardiovascular symptoms and complications since last visit
- Review and documentation of concomitant medication changes since enrollment
- Complete the following 2 questionnaires:
    - Seattle Angina Questionnaire
    - EQ-5D-5L Questionnaire
- Collection of (may also be done centrally)
    - Any cardiovascular test – both written report and test output
    - Any cardiovascular imaging – both written report and image file

12 months (+/-30 days) follow-up contact

At the 12-month follow-up visit, participants will be asked the following:

- Assessment if any MACE has occurred since the 6-month visit/phone call
- CV Update: Review and documentation of any cardiovascular diagnostic test, cardiovascular procedure, or hospitalizations/clinic visits due to cardiovascular symptoms and complications since last visit
- Review and documentation of concomitant medication changes since enrollment
- Complete the following 2 questionnaires:
    - Seattle Angina Questionnaire
    - EQ-5D-5L Questionnaire
- Collection of (may also be done centrally)
    - Any cardiovascular test – both written report and test output
    - Any cardiovascular imaging – both written report and image file

24 months (+/-30 days) follow-up contact

At the 24-month follow-up visit, participants will be asked to report the following:

- Assessment if any MACE has occurred since the last visit/phone call
- CV Update: Review and documentation of any cardiovascular diagnostic test, cardiovascular procedure, or hospitalizations/clinic visits due to cardiovascular symptoms and complications since last visit
- Review and documentation of concomitant medication changes since enrollment
- Complete the following 2 questionnaires:
    - Seattle Angina Questionnaire
    - EQ-5D-5L Questionnaire

V.E. Cross-over in precision evaluation arm participants

While precision evaluation participants determined to be at very low risk and assigned to the strategy of guideline-recommended medical management with no immediately planned testing are highly unlikely (by definition) to have significant obstructive CAD, their managing clinicians will be encouraged to treat them with guideline recommended preventive care and other medical therapy as deemed appropriate to their clinical circumstances. This is expected to control or eliminate symptoms in most participants. However, additional testing may be warranted for those with intractable or accelerating symptoms despite reasonable medical treatment or other compelling reasons for testing. The reasons for this will be carefully documented in the eCRF. Unless there are urgent or emergent indications to proceed with invasive testing, all such participants who require testing will have a cCTA followed by selective FFR_{CT} rather than either stress testing or elective invasive catheterization.

V.F. Participant Withdrawal

In accordance with the Declaration of Helsinki, each participant is free to withdraw from the study at any time. Investigator(s) also have the right to withdraw participants from the study in the event of illness or other reasons concerning the health or wellbeing of the participant, or in the case of lack of cooperation. Should a participant decide to withdraw or should the investigator(s) decide to withdraw the participant, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. If possible, a complete final evaluation at the time of the participant's withdrawal should be made. The reason for withdrawal must be noted in the eCRFs.

V.G. Schedule of Assessments

	Screening	**Randomization Day 1**	**Day 45 (+/-14 d)**	**6-mo. (+/- 30d)**	**12-mo.** (+/- 30d**)**	**24-mo.** (+/- 30d)
Informed consent	X					
Medical history	X					
Cardiovascular update [1]			X	X	X	X
Concomitant medications	X		X	X	X	X
Cardiovascular Risk factors (including PROMISE risk tool data entry for randomization)	X					
Pregnancy test[2]	X					
Creatinine[3]	X					
Resting 12-lead ECG[4]	X					
QoL evaluation: SAQ, EQ5D-5L	X		X	X	X	
Participant Satisfaction Questionnaire			X			
Randomization		X				
Initial diagnostic invasive or noninvasive test performed (if assigned)		Prior to 45 day visit				
Cardiac imaging/testing clinical report and image collection			X	X	X	
Interval assessment for CV events and testing			X	X	X	X
Endpoint assessments			X	X	X	X

1. During cardiovascular update, if participants have received an additional diagnostic test, a cardiovascular procedure or have been hospitalized since the last visit, additional data will be collected
2. For a female participant of childbearing potential, a pregnancy test must be performed with negative results known within 7 days prior to randomization
3. Creatinine blood draw required only for participants without a recent normal value (within previous 90 days)
4. Resting 12-lead ECG preferred in last 30 days (optional, clinical care only)
5. Use of specific medications such as beta blockers, ACE inhibitors/ARBs, statins, aspirin, and antiplatelet agent

VI.ADDITIONAL ASSESSMENTS AND SUBSTUDIES

VI.A. Quality of Life Assessments

A short battery of instruments will be used to provide a relevant assessment of health-related quality of life that will capture the most likely health benefits to be associated with the precision strategy while not being burdensome to study participants. Quality of life (QoL) assessments will be conducted at baseline, 45 days, 6 months, and 12 months. Chest pain specific QOL will be assessed with the Seattle Angina Questionnaire (SAQ). While the full instrument has 19 items covering 5 dimensions of the impact of chest pain on QoL, we will use the scales for physical limitations, angina frequency, and disease perception/quality of life (14 items total) [1]. These three scales will also allow calculation of the recently described 7-item short SAQ[2]. The SAQ has been used as the primary disease-specific QoL outcome measure in a number of major clinical trials (including COURAGE, PROMISE, and ISCHEMIA) and is useful for this trial because it assesses chest pain and its impact on functioning and well-being regardless of whether the symptoms are due to coronary disease or are non-coronary. Since many participants in this study will be found not to have significant coronary disease and will be provided with that reassuring finding, the SAQ will allow us to assess the extent to which such information is associated with changes in the 3 dimensions noted above.

Overall health status will be assessed briefly using the EQ-5D-5L, a standardized generic measure that can also be used to link specific health states to general population-based utilities[5]. The EQ-5D-5L consists of two parts: (1) a descriptive assessment of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which can take one of five responses corresponding to the level of severity within each dimension, and (2) a self-rating 0-100 "thermometer" of current health-related quality of life.

VI.B. Economic and Resource Utilization Assessments

The primary economic analyses in PRECISE will be performed from the perspective of the US health care system. Detailed information regarding the quantity and cost of health care services received by participants in each treatment group will be collected prospectively as part of the trial. Relevant health care resource consumption during initial testing through 2-year follow-up will be collected on the clinical trial electronic case report form (eCRF). (The cost of acute and non-acute hospital care will be derived from billing data collected from patients enrolled at US sites.) Physician and other outpatient care reported in the eCRF will be valued using secondary sources. Primary resource use and cost comparisons will be based on participants enrolled in the US. Secondary analyses will examine the consistency of treatment related differences in resource use in the US with the sites outside the US.

VI.C. Imaging and other Cardiac Assessments

For all participants in either arm in whom an invasive coronary angiogram is performed within the first 12 months, procedural reports and angiographic images will be uploaded via the electronic data capture (EDC) system to create an angiographic image repository. In addition the report, as well as imaging and / or graphic data from any procedures performed to assess stenosis significance or severity such as, FFR, NHPR, IVUS, OCT should be uploaded. Similarly, for all participants receiving cCTA imaging within the first 12 months, the cCTA images and reports will

be uploaded via the EDC system to create an image repository. A core lab may be added to analyze these images. Data collection for these elements will be coordinated by the DCRI Outcomes Group for North American patients followed by the call center and by site coordinators for all other sites.

VII. ENDPOINT DETERMINATION, SAFETY, AND MONITORING

VII.A. Primary Endpoint Definitions

Major Adverse Cardiovascular Events (all cause death, non-fatal myocardial infarction)

All cause death

All cause death is defined as death resulting from any cause. In addition, the cause of death will be adjudicated, including cardiovascular death defined as death due to myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage, or death due to other cardiovascular causes [51].

Myocardial infarction

Acute myocardial infarction (MI) is defined as having evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia[51]. Specifically, MI is defined as having:

1) Typical rise and/or gradual fall in cardiac biomarker level (cardiac troponin preferred) with values exceeding the 99th percentile of the institutional upper limit of normal (ULN) (generally 2x the ULN)

AND either:

2) Clinical presentation defined as typical cardiac ischemic type pain/discomfort or dyspnea felt to be due to ischemia and consistent with the diagnosis of myocardial ischemia and infarction

Or

3) ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy and left bundle branch block) including evolving ST elevation, ST depression, T-wave changes, new pathological Q-waves (R waves in V1-2) in at least two consecutive leads or new left bundle branch block.

A complete definition of the criteria for MI can be found in the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials[51]. Peri-procedural infarctions are defined as greater than 3x ULN for serum CK-MB for PCI and greater than 5x ULN for CABG.

Cardiac catheterization without obstructive coronary artery disease (diameter stenosis <50%, any FFR >0.80 or NHPR ≥0.90)

Cardiac catheterization without obstructive coronary artery disease will be defined as the absence of any ≥50% stenosis or hemodynamic indication of significance in any major epicardial vessel including side branches ≥2 mm in diameter, as determined by the clinical site interpretation.

VII.B. Secondary Endpoint Definitions

Hierarchical analysis

Finkelstein and Schoenfeld (FS) or Pocock's win ratio analysis of primary endpoint is defined in section VII B Statistical Analysis Plan.

Resource use

Resource use is defined as counts and types of baseline testing, follow up testing, diagnostic and therapeutic procedures, and both inpatient and outpatient care at 12 months. Costs from the US perspective will be estimated.

Quality of Life Metrics

Quality of Life assessments to be completed by the participants are the Seattle Angina Questionnaire and the EQ-5D-5L.

Death

Death will be categorized as all-cause, cardiovascular, non-cardiovascular.

Myocardial infarction

Myocardial infarction will be characterized according to Universal MI definition subtypes as Type 1, 2, 3, 4a, 4b, 4c and 5.

Hospitalizations

All, cardiovascular, non-cardiovascular, and for progressive or unstable angina. Urgent and unscheduled hospitalizations for other cardiovascular causes that do not meet the criteria for the specific events listed above will be classified as hospitalization for other cardiovascular causes (e.g., hospitalization for cardiac chest pain that does not meet the criteria for MI, hospitalization for arrhythmias, hospitalization for pulmonary embolism). Non-cardiovascular hospitalization are defined as any hospitalization whose primary cause is not thought to be CV in nature.

Preventive medication use

Information on preventive medication use will be acquired at study entry and 45 days. Participants with a clear clinical indication for use of ASA/antiplatelet agents and or, statins eg: hyperlipidemia, diabetes, documented CAD, will be characterized according to use/nonuse for each medication class.

DECISION co-primary end point

MACE, defined as all-cause death myocardial infarction, or ischemia-driven revascularization at 24 months as defined by the DECISION trial.

DECISION co-primary end point

All-cause death, MI, all follow-up unplanned revascularization procedures, cardiac catheterizations without actionable findings at 24 months as defined by the DECISION trial.

PRECISE primary endpoint at 24 months

The PRECISE primary endpoint will be determined at 24 months.

Radiation safety endpoint – cumulative dose at 1 year

The cumulative radiation exposure over the 12 months following enrollment will be calculated based on the participant's exposure to radiation for cardiovascular care from one or more of the following modalities. For cCTA, the administered radiation dose (computed tomography dose index volume and dose length product for cCTA) will be recorded by the individual sites. For stress nuclear imaging, the radiotracer dose(s) will be collected and converted to equivalent radiation doses for comparison to cCTA. For ICA, the radiation dose from fluoroscopy administered will be recorded by sites and converted using standardized approaches to allow for comparison to radiation from cCTA. In instances in which the information required to assess actual dose is not available, a standard dose based on accepted average exposures will be imputed for that form of testing. Cumulative radiation exposure from additional cardiac testing and procedures during the entire follow-up period will also be collected.

Catheterization efficiency

The proportion of invasive cardiac catheterization patients who undergo revascularization (PCI or CABG) within 6 months of enrollment will be determined.

VII.C Testing Complications and Reporting

The study intervention is the implementation of a precision evaluation strategy compared to usual care evaluation in non-acute chest pain participants with no history of CAD or recent testing whose clinicians recommend non-emergent non-invasive testing or ICA. Since all trial procedures represent standard of care for the eligible study population, there are no specific safety events associated with investigative procedures in this trial. However, there are known complications from these clinically recommended tests and procedures which are outlined below. These complications will be reported by site personnel.

For Precision Evaluation Strategy

For Guideline-recommended Medical Management

While participants assigned to the guideline-recommended care with no planned testing arm will have exceedingly low risk of events and are predicted to derive minimal or no value from noninvasive testing[33, 34], there is a very small risk of missing left main or 3-vessel disease for which revascularization may be life-prolonging.

For cCTA with selective FFR_{CT}:

Mild contrast reaction such as rash and hives.

1. Severe contrast reactions including anaphylaxis or death occurring within 24 hours of contrast administration.
2. Extravasation of contrast into the surrounding tissue of the extremity where contrast was administered intravenously.
3. Symptomatic bradycardia or hypotension in relation to beta blockade or nitrates administered for cCTA.

4. Acute bronchospasm following beta blockade administered for cCTA.

For Usual Care (noninvasive or invasive testing)

For exercise testing including during stress echo or stress nuclear (including PET)**:**

1. Hypotension defined as systolic BP less than 80 mmHg or fall in systolic BP >20 mmHg
2. Stress-induced symptoms or ECG changes that do not resolve within 20 minutes
3. Rapid atrial fibrillation that does not slow or convert with standard interventions
4. Ventricular tachycardia
5. Hospital admission not otherwise captured by pre-specified study endpoints, due to one of the above

For stress nuclear (including PET)**:**

1. Any adverse reactions potentially related to the use of vasodilators such as adenosine, regadenoson, or dipyridamole

For stress echo:

1. Any stress-induced wall motion abnormality that does not resolve within 20 minutes
2. Any adverse reaction to echo contrast
3. Any adverse reaction to dobutamine, including sustained ventricular tachycardia or other tachyarrhythmias

For stress cardiac MRI:

1. Any adverse reactions potentially related to the use of vasodilators such as adenosine, regadenoson, or dipyridamole
2. Any adverse reaction to MRI contrast agents, including gadolinium-based agents

For cardiac catheterization:

1. Any adverse reactions potentially related to the use of sedatives, local anesthetics, contrast agent or other medication's
2. Any adverse reactions potentially related to arterial puncture and wire/catheter introduction
3. Any adverse reaction to coronary catheterization including dissection, embolization, stroke, malignant arrhythmias and asystole, and death

VII.D. Independent Clinical Event Adjudication Committee

An independent clinical event committee (CEC) will be responsible for the blinded review and adjudication of the primary endpoint. The CEC will settle any disputes with committee review and discussion. Any uncertainty regarding the finding of cardiac catheterization without obstructive disease will prompt review of the original cardiac catheterization images for further independent adjudication. Collection of medical records and other documentation required for CEC reviews will be coordinated by the DCRI call center for North American participants and by site coordinators for participants in all other regions.

VII.E. Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be appointed to monitor participant safety and to review study performance. The DSMB will periodically review the study data and assess participant safety and adherence to the study protocol. The DSMB will define the operating guidelines and processes for study evaluation, interim analyses, event triggers for unscheduled review; these will be agreed upon at the initial meeting of the DSMB. Periodic reports will be prepared by HeartFlow (or its designee) for the DSMB on based on the operational plan outlined by the DSMB charter. The DSMB will make its recommendations to the study Steering Committee and the sponsor following their meeting. Details on statistical stopping rules guidelines will be provided in the DSMB charter.

VIII. Statistical Methods

Separate, complete Statistical Analysis Plan (SAP) documents will be prepared for the clinical outcome analyses and the economics and quality of life (EQOL) outcomes.

VIII.A. Sample Size Determination and Statistical Power

Sample size and power calculations for this study are based on the hypothesis that the precision evaluation arm is superior to the usual care arm on the time-to-first event of the composite MACE endpoint (defined as: all-cause death, non-fatal MI) or invasive cardiac catheterization without obstructive CAD (obstructive CAD defined as diameter -stenosis ≥50%, FFR≤0.80 or NHPR <0.90). Time to event analysis will use the date of the event, including the date of catheterization which is used to determine the absence of obstructive CAD. Assuming 10% of usual care participants will receive angiography as a first test results in an 8% primary endpoint event rate at 1 year in the usual care group and 5% (absolute) event rate in the precision care group (i.e., 37.5% relative effect size) with 30% assigned to guideline-recommended care with symptom management and no planned testing. Assumptions used in the primary endpoint event rate calculations (i.e. 8% vs. 5%) were: an overall 10% will not receive randomized testing and within the precision evaluation arm, 30% of those assigned to guideline-recommended care will cross over to cCTA with selective FFR_{CT}.

Enrolling 1050 patients per group (2100 total participants) would provide at least 90% power to detect a relative risk reduction of 37.5% in the precision evaluation arm. Sample size calculations are based on the log-rank test [52] with 12-month accrual period, a minimum 12-month follow-up (i.e., last participant will be followed for at least 12-months), 10% attrition rate (i.e., lost to follow-up, dropouts) and a two-sided type I error rate of 0.05.

1-yr event rate in precision evaluation arm	Power	Total number of participants needed	Total number of MACE events needed
5% (37.5% effect size)	85%	1792	173
	90%	**2096**	**202**
	95%	2592	250

Table shows total number of participants needed for 85%, 90% and 95% power. Although, this is not an event-driven study, the table below also provides total number of MACE needed.

Power curves (**Figure: Long-Rank for Two Survival Curves**) provide total sample size needed for several relative effect size (i.e., 1-hazard ratio) scenarios.

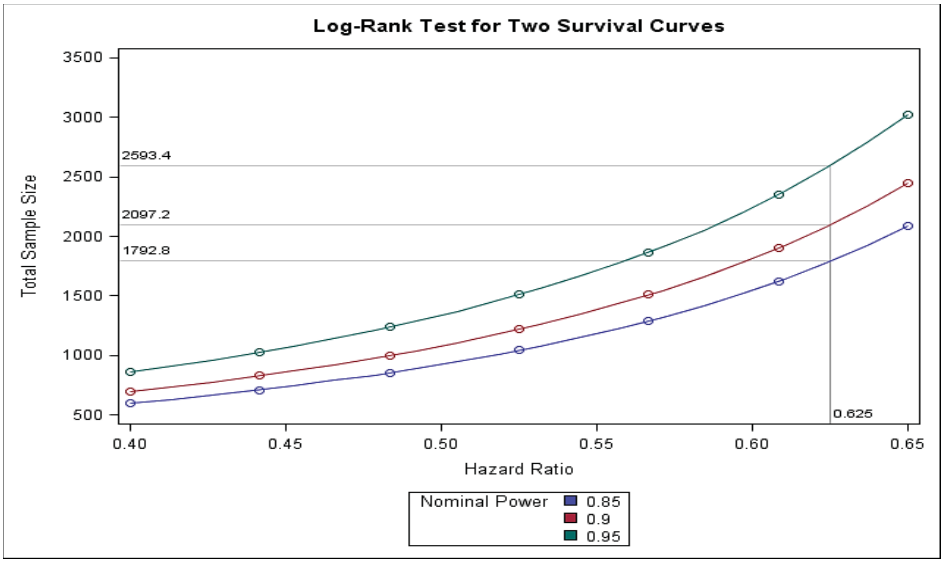


Figure: Long-Rank for Two Survival Curves

VIII.B. Statistical Analysis Plan

Analysis of the Primary Endpoint

The primary endpoint of this study is based on time-to-first occurrence of any of the MACE components, which is defined as a composite of all-cause death, non-fatal MI or invasive cardiac catheterization without obstructive CAD (obstructive CAD defied as diameter stenosis ≥50%, FFR≤0.80, or NHPR<0.90). The time from randomization to the first event among the components of the MACE endpoint will be measured (in days) for those who experienced an event and calculated as the date of the first event minus the date of randomization. For participants who do not experience any of the MACE component events or who withdraw consent or drop out of the study before experiencing an event, time from randomization to the date of last contact will be used in the analysis, and those participants will be considered as censored observations in the time-to-event analysis.

The primary and secondary endpoint comparisons between the randomized groups in this study will be performed according to the principle of "intention-to-treat" (ITT); that is, participants will be analyzed according to the treatment arm to which they were randomized, regardless of subsequent crossover or post-randomization strategy.

The log-rank test[53] will be the primary analytic tool for statistically assessing outcome differences between the two randomized treatment strategies with respect to the primary composite endpoint. Cox proportional hazards model[54] will be used to estimate the hazard ratio (HR) and 95% confidence interval (CI) summarizing the difference in outcome between the two randomized arms, using treatment as the only predictor in the model. Proportionality assumption in the Cox model (i.e., constant hazard over time) will be checked and tested.

Cumulative event rates will be calculated according to the method of Kaplan and Meier[55] for each randomized arm as a function of time from randomization, and the estimated event probabilities

will be displayed graphically. Adjusted HR and its 95% CI will be estimated using Cox proportional hazards model by including pre-specified baseline risk factors as covariates in the model.

A sensitivity analysis for the primary composite MACE endpoint will be conducted using the method of "win-ratio"[56]. The win-ratio method of Pocock et al is an extension of Finkelstein and Schoenfeld rank-test method[57] which order-rank composite endpoints based on their clinical importance. More details on primary, secondary and sensitivity analyses will be provided in the complete Statistical Analysis Plan (SAP).

Subgroup analyses

If there is an overall difference in MACE outcome between treatment strategies, subgroup analyses will be performed to assess whether the intervention effect is consistent across all participants, or whether it varies according to specific participant characteristics. In particular, these analyses will focus on whether the relative intervention effect compared to usual care differs according to the following baseline variables:

- Low risk vs. elevated risk by PROMISE Risk score
- Intended first test: functional vs. invasive
- Sex (male vs. female)
- Age (<65, 65 to 74, and >75 years)
- History of diabetes
- Presentation: primary symptom (chest pain vs. other), SAQ angina score (daily/weekly angina at baseline versus less frequent)
- Geographic region (US, Canada, Europe, Other Regions)

These analyses will utilize the Cox model and will be accomplished by testing for interactions between the randomized treatment strategy and the specific baseline variables listed above. In addition to the formal assessment of treatment by covariate interactions, the effect of the treatment strategy characterized by a hazard ratio and 95% confidence interval will be calculated and displayed using a forest plot for the subgroups of participants defined by the variables listed above. These descriptive hazard ratios will be carefully interpreted in conjunction with the formal interaction tests.

The effect of the treatment strategy may also be examined in other subgroups of clinical interest in addition to those listed above.

Analysis of the Secondary Endpoints

The secondary endpoints listed in section III.C. Secondary Endpoints that are measured as time-to-event will be analyzed using the same statistical methods used for the primary efficacy endpoint (Section VI.A. Primary Endpoint Definitions). Specifically, the log-rank test will be the primary analytic tool for statistically assessing mortality differences between the two randomized treatment strategies. A hazard ratio and 95% confidence interval summarizing the difference in outcome between the two randomized arms will be computed using the Cox model.

Participant deaths will be classified by the Clinical Events Committee (CEC) as to whether the mode of death was due to a cardiovascular (CV) cause. If insufficient source documents are obtained to allow CEC adjudication of the cause of death, and the CEC classifies the cause of death as "unknown," then the site-reported cause of death (if available) will be used. If neither the site nor the CEC can provide a classification of the cause of death, the death will not be

considered as a cardiovascular death. As supplemental analyses, however, this endpoint will also be examined using (a) only the deaths classified by the CEC as cardiovascular, and (b) using deaths classified by the CEC as cardiovascular, but also including any deaths in the cardiovascular category that are classified as unknown by the CEC.

Competing risks methodology of Fine and Gray[58], where death due to a non-cardiovascular cause is considered as a competing risk. This methodology, rather than treating non-cardiovascular death as a censoring event, makes incidence use of the cumulative function, and is performed within the proportional hazards framework using the marginal failure sub-distribution associated with the event of interest (cardiovascular death). Similar analyses will be conducted for time-to-event endpoints in which death is not part of the endpoint of interest.

Analysis of Resource Use Endpoints

For the Economics outcomes, we will compare resource use at 12 months between treatment arms by intention-to-treat. All-cause hospitalizations, cardiovascular hospitalizations, ER visits not resulting in hospitalization, and major outpatient procedures will be enumerated. In addition, we will examine length of stay by intensity of care, numbers of CTAs, noninvasive stress tests (stress perfusion imaging, stress echocardiography, exercise electrocardiography, stress cardiac magnetic resonance imaging), invasive tests (invasive coronary angiography, invasive fractional flow reserve or equivalent, optical coherence tomography, intravascular ultrasound), coronary revascularization procedures (coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI), number of coronary stents), and cardiac medications (beta blockers, aspirin, statins, antiplatelet medications).

Confidence intervals for differences will be estimated using the bootstrap approach. Differences in resource use will be interpreted in the context of the trial clinical results, looking for both consistency and plausibility. Descriptive comparisons of intensity of care/resource consumption according to clinical variables defining subgroups of interest will be performed. The primary economic analyses will focus on the US enrollment and in secondary analyses, resource use patterns for all patients enrolled in the trial will be compared by intention-to-treat to develop an understanding of the degree to which treatment related differences in the trial are region dependent.

Analyses of Medical Costs (US participants)

To compare medical costs between treatment arms, we must: 1) assign costs to all medical resources consumed during the study period; 2) compute mean costs by treatment group (defined by the principle of intention-to-treat); and 3) calculate the difference in mean costs between treatment arms and generate confidence intervals.

A) Derivation of Cost Estimates.

The cost of US hospital-based care will be estimated by applying hospital-specific, revenue center level cost-to-charge ratios to empirical billing data collected during the study. This approach, which has been used successfully in numerous previous clinical trials including the PROMISE trial takes advantage of the objective, detailed account in hospital bills of services provided to patients, and recalibrates hospital charges to more closely reflect costs. Based on experience in similar studies, we anticipate having complete billing data for 95% of patients treated in hospitals that generate bills. For the small percentage of patients without billing data, we will impute costs using a generalized linear model developed using study data. In this model, the dependent variable will be defined as total cost, and independent variables will include resource use elements available in the case report form, such as number of hospitalized nights

by intensity of care and number of relevant high cost procedures. Coefficients for model parameters will be estimated using study data of patients with complete costs and then used to predict costs for patients without billing information.

The cost of stays at non-acute care facilities will be estimated by multiplying the length of stay by the corresponding per-diem/reimbursement rate.

Costs for physician services will be estimated by mapping major inpatient and outpatient procedures and services recorded on the case report form to appropriate CPT codes in the Medicare Fee Schedule. We will also assign rounding fees for inpatient stays based on type of unit.

Costs for diagnostic testing procedures done in an outpatient or standalone facility will be derived from secondary sources available to the DCRI Outcomes Group at the time of study analysis.

The cost of medications of interest/relevance will be estimated on the basis of medication use recorded in the eCRF and unit costs by medication type and class, based on current estimates of acquisition cost.

B) Cost Comparisons

Primary statistical comparisons of costs between the two treatment groups will be performed using the intention-to-treat principle in the US cohort. A nonparametric partitioned estimator will be used to estimate diagnostic strategy-specific, 2-year medical costs with 8 partitions corresponding to 3-month intervals following randomization. Comparisons between the two testing strategies will be made using a normal approximation with standard errors estimated using the bootstrap approach. Bootstrapping will be performed using 10,000 repetitions, with percentile-based confidence intervals reported. The primary cost comparison will be made for cumulative costs at 12 months. The primary effect size will be the mean cost difference between the two arms with 95% confidence intervals. P values will be calculated for selective comparisons, with a “significant” p value equivalent to a 95% confidence interval that excludes 0. No adjustment in significance levels for multiple comparisons will be used.

Differences in cost will be interpreted in the context of the trial clinical results, looking for both consistency and plausibility. Costs will be presented both overall and by category (e.g., inpatient hospitalization, outpatient procedures, concomitant medications, non-acute institutional care). Hospitalizations will be classified as cardiovascular or non-cardiovascular by the Clinical Events Committee. For illustrative purposes, we will use bootstrap methods to plot the probability of a difference in total costs greater than arbitrary thresholds of interest (such as $500, $750, or $1000).

C) Cost Sensitivity Analyses

In secondary sensitivity analyses, we will apply US unit costs to all resource use of all patients and compare costs between treatment groups across all patients enrolled in the trial. While US unit costs may not reflect the absolute or relative costs of health care services internationally, their application to all patients will permit a weighted aggregation and comparison of resource use in the total trial population. In this manner, the effect of overall patterns of resource use in the US cohort versus ex-US on cost differences by treatment group can be assessed. We will also perform a per protocol analysis of costs.

Analyses of Quality of Life Outcomes

For each of the QOL measures examined in this study, we will provide simple descriptive and

comparative analyses by intention-to-treat. To address the multiple comparisons problem arising from testing each individual scale and time point separately, we propose two complementary approaches. First, we will pre-specify the angina frequency scale from the SAQ as the primary QOL comparison of interest and assign all other comparisons to a secondary (supportive) status. Second, we will use a repeated-measures mixed model with the baseline score as a covariate, Day 45, Month 6, Month 12, Month 18, and Month 24 responses included as outcome variables, and time as a fixed variable. Restricted maximum likelihood estimation will be used to model all available data from each subject without imputing missing values. An unstructured covariance matrix will be used.

Point estimates for each diagnostic strategy arm and strategy arm mean differences (precision strategy – usual care) with 95% confidence intervals (CIs) will be generated for each time point. The primary assessment will be based on the strategy arm difference at Month 12. Additional analyses will examine the intervention effect at the other contact time points. Additionally, the intervention effect will be averaged across all the follow-up time points. The estimated intervention difference and 95% CIs will be obtained using the ESTIMATE Statement in SAS PROC MIXED.

We expect to have analyzable data on ≥95% of survivors at each follow-up interview, and, with 90%+ data collection (945+ patients per treatment group), consistent with our past performance in trials of this size and complexity and using similar methods, even accounting for loss of data due to death or incapacity, we should have 90% or greater statistical power to detect clinically significant differences in our major QOL measures.

Major QOL subgroups to be examined will be those prespecified for the clinical analysis of this trial. In addition, we will use baseline angina frequency from the SAQ to create a subgroup of subjects with daily or weekly chest pain versus those with less frequent symptoms.

IX. ETHICAL CONSIDERATIONS AND RISK ANALYSIS

IX.A. Ethical Considerations

PRECISE will be conducted in accordance with the recommendations for human research from the 18th World Medical Assembly, Helsinki 1964. All potential sites will obtain Institutional Review Board (IRB) or Ethics Committee (EC) approval of the protocol, the associated consent form and any participant facing recruitment tools. Written informed consent will be obtained from each patient before any study procedures are performed. Patients will have the option to consent for the study after receiving a full explanation of the risks, benefits, and available diagnostic options, with the right to refuse participation. Clinicians will have the option to pursue alternative diagnostic pathways if they deem it to be in the best interest of the patient, with the reason for study protocol deviation documented. Participants can withdraw from the study at any time.

IX.B. Study Risks and Benefits

Potential Risks

Participation in PRECISE does not present any extra risks other than the risks associated with the clinically indicated care recommended by the participant's treating physicians to evaluate and treat symptoms suggestive of CAD. As all approaches included in the trial are recognized as standard of care, the risk associated with the trial can be described in detail by the treating physician.

Noninvasive diagnostic imaging is generally considered a safe and effective diagnostic approach. FFR_{CT} does not pose any additional risk to participants beyond the performance of cCTA itself. It does offer the potential benefit to participants of the recognition of hemodynamically significant lesions (FFR $\leq$0.80 or NHPR <0.90) that may not demonstrate anatomic significance (<50% diameter stenosis) and avoidance of unnecessary revascularization of $\geq$50% lesions that are not hemodynamically significant (FFR>0.80).

The risks of guideline-recommended care without planned testing in the lowest risk participants has not been extensively studied prospectively. However, validation of the PROMISE Risk Tool in SCOT-HEART indicate that participants in this risk category have a CV death/MI event rate <1%/year, similar to the event rate observed in an age and sex matched US population. While the risk of guideline-recommended care without planned testing in the precision evaluation arm has not been quantified prospectively it is not expected to differ from the excellent outcomes noted above in such patients who do undergo testing. Further, participants with continued symptoms not controlled by medications will be permitted to cross over to the precision strategy arm and receive, cCTA with selective FFR_{CT}.

Potential Loss of Confidentiality

In any clinical trial, there is a possible risk of loss of confidentiality. To prevent this from occurring, HeartFlow has strict procedures in place to ensure that all study data are confidential and anonymized except as required for centralized follow-up data collection for North America, which will be performed by the DCRI Outcomes Call Center. For all data transferred from enrolling sites or from the Call Center, participants will be identified only by unique patient identifiers. Data transmitted will not contain any protected health information and participants will be identified only by unique patient identifiers. Data transmitted will not contain any protected health information. All applicable study data will be transferred in a secure manner and in accordance with applicable regulations.

Potential Benefits

The PRECISE results should improve the care of future patients recommended for additional evaluation 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 evaluation and management strategies that will be examined in a large real-world experience. All participants may benefit from increased contact with health care providers due to study-required visits.

X. DATA HANDLING AND QUALITY ASSURANCE

X.A. Completing and Signing Case Report Forms

Electronic CRFs will be employed. Trained site personnel or the trained DCRI Outcomes Group will enter data into the eCRFs. Data changes and corrections should be done within the electronic system. The audit trail will record all changes made, the date and time of the

correction, the person making the change and a reason for the change. The appropriate electronic signature will be provided by the investigator as indicated.

X.B. Clinical Data Management

The sponsor or its designees will be responsible for the handling, processing, and quality control of the data in compliance with all applicable regulatory guidelines.

The training of clinical site personnel and the DCRI Outcomes Group on eCRF completion will be the responsibility of the sponsor or its designees. To ensure uniform data collection, a Case Report Form Guide will be created to assist with eCRF completion. All clinical site research coordinators will undergo site initiation training to become thoroughly familiar with the protocol, case report forms, and with methods of data verification.

X.C. Archiving of Data

All study documentation at the investigator site and sponsor site will be archived in accordance with ICH GCP. It is HeartFlow's policy to retain the data collected in this clinical study for a minimum of 5 years after termination of the study. Clinical sites will be asked to retain the data for at least 2 years following completion of the study or longer as required by local laws.

XI. STUDY MONITORING, AUDITING, AND INSPECTING

HeartFlow or its designees will monitor this clinical study to check the adequacy of clinical site staff and facilities, and to ensure adherence to the protocol, study procedures, and applicable regulations. In accordance with ICH E6 GCP guidelines, the clinical site monitor will also assess proper eCRF completion and source document retention. The investigator and clinical site staff are expected to provide adequate space for monitoring visits and to allocate sufficient time to permit adequate review of the study's progress. The investigator will permit study-related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source data/documents and study-related facilities (e.g., pharmacy, diagnostic testing and laboratories).

XI.A. Study Monitoring

Study monitoring will be performed in accordance with ICH E6GCP, this protocol, and applicable local regulations. A Clinical Monitoring Plan will be written at the outset of the study to provide project-specific operational guidelines for the clinical monitoring process and procedures, define responsibilities of the Site Management/Monitoring Team, which will in turn ensure the quality and integrity of data collected.

XI.B. Auditing and Inspecting

HeartFlow quality assurance personnel and/or their designee(s) may conduct audits at the study site(s). Audits may include, but not be limited to: audit trail of data handling and processes, SOPs, presence of required documents, the informed consent process, and comparison of case report forms/database with source documents. The investigator agrees to accommodate and participate in audits conducted at a reasonable time in a reasonable manner, as needed.

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The **PRECISE** Protocol

Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization

Study Objective	The primary objective of the PRECISE trial is to assess clinical outcomes, decision making regarding noninvasive testing and invasive angiography, and costs using a precision evaluation strategy as compared to a usual care strategy in participants with stable symptoms suggestive of significant coronary artery disease. The precision evaluation strategy will be based on a pre-test risk assessment and will incorporate cCTA with selective FFR_{CT} and guideline-recommended care with symptom and risk factor management and no immediately planned testing.
Study Design	The study will be a prospective, pragmatic, randomized clinical trial of the comparative effectiveness of diagnostic evaluation strategies for stable suspected CAD, to be performed in outpatient settings, including primary care and cardiology practices. Qualifying patients presenting with new symptoms suspicious for clinically significant CAD (and without known CAD), who are recommended for diagnostic testing and did not receive any cardiovascular testing within the past 12 months, will be randomized to an initial strategy of either precision care or usual care. All subsequent decisions in the usual care arm regarding additional testing, medications, and/or procedures will be at the discretion of the responsible clinical care team.
Study Principal Investigator	Pamela S. Douglas, MD Duke University Durham, NC 27701 USA
Sponsor	HeartFlow, Inc. 1400 Seaport Blvd., Building B Redwood City, CA 94063 Campbell Rogers, MD Chief Medical Officer

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 assigned physicians, nurses, and other professional personnel who will participate in the study and will be responsible for their compliance and adherence to the study protocol. 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 HeartFlow and may be utilized by HeartFlow 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 HeartFlow monitors and auditors and their designees full access to all medical records at the research facility for participants screened or randomized in the study. I agree to provide all participants with informed consent forms and will ensure adequate informed consent is obtained, as required by government regulations and International Conference on Harmonization guidelines.

Version Date: Oct 15, 2019

Site Name	**Site Number**

Principal Investigator (print name)

Principal Investigator (Signature)	**Date**

DocuSigned by:
Manesh Patel
A34FA8AA40884C4...

Manesh Patel, MD, Trial Co-Principal Investigator	10/15/2019 Date

DocuSigned by:
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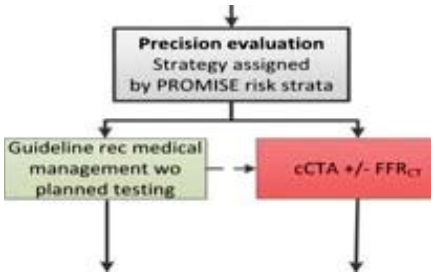
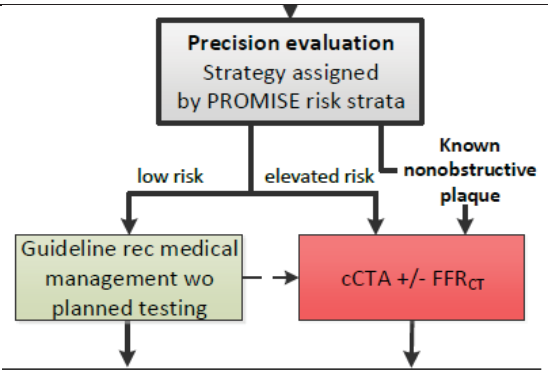
Campbell Rogers, MD, HeartFlow CMO	10/15/2019 Date

Protocol Version and Amendment Tracking

Version Number/Amendment	Approval Date
1.0	Jun 29, 2018
1.1	Jul 31, 2018
1.2	Sept 10, 2018
1.3	Nov 21, 2018
1.4	Feb 1, 2019
1.5	Oct 15, 2019

Amendment from version 1.4 dated February 1, 2019 to version 1.5 dated October 15, 2019

Section	Version 1.4	Version 1.5
Investigator Protocol Signature Page	NA	Included separate line for PI signature
Table of Abbreviations	NA	AG: Agatston units
Table of Abbreviations	DECISION: Decisive Evaluation of Cardiac Ischemia, Symptoms and Revascularization	Removed
Table of Abbreviations	HU: Hounsfield units	Removed
IV. Study Overview and Objectives - Study duration	The anticipated total duration of the PRECISE study will be approximately 48 months for start-up, enrollment, follow up, and close out. Participants will be followed for 24 months after enrollment.	Overall study duration reduced to 36 month and patient follow up to 12 month after enrollment. "The anticipated total duration of the PRECISE study will be approximately 36 months for start-up, enrollment, follow up, and close out. Participants will be followed for 12 months after enrollment."
IV.A. Overview of PRECISE – figure of the trial design		 Figure updated to remove 24 month and co-primary endpoints of DECISION. Arrows leading to GRMT or cCTA annotated "low risk" and "elevated risk" respectively. Patients with known nonobstructive coronary plaque or extensive coronary calcium randomized to the precision arm are mandated to undergo cCTA +/- FFR_{CT}, independent from PROMISE risk score strata.
IV.B. Primary Objective and Endpoints	Per the exclusion criteria, any previous noninvasive or invasive CV diagnostic testing for suspected CAD must have been >1 year prior to enrollment. Patients with known obstructive CAD (prior myocardial infarction, CABG or PCI, any stenosis ≥50%) are ineligible for PRECISE.	Replaced with: "Patients with known nonobstructive coronary plaque or extensive coronary calcium randomized to the precision arm are mandated to undergo cCTA +/- FFR_{CT}, independent from their PROMISE risk score strata."
IV.C. Secondary Endpoints	Endpoints will be assessed at 45 days, 6 months, 1 year and 2 years.	Removed secondary endpoint assessment at 2 years: "Endpoints will be assessed at 45 days, 6 months and 1 year."
IV.C. Secondary Endpoints	9. PRECISE primary endpoint at 24 month	Removed PRECISE primary endpoint at 24 month

Section	Version 1.4	Version 1.5
IV.C. Secondary Endpoints	10. MACE, defined as all-cause death myocardial infarction, or ischemia-driven revascularization at 24 months (DECISION co-primary end point)	Removed DECISION co-primary endpoint
IV.C. Secondary Endpoints	11. All-cause death, MI, all follow-up unplanned revascularization procedures, invasive coronary angiograms without actionable findings at 24 months (DECISION co-primary end point)	Removed DECISION co-primary endpoint
V.A. Patient Screening for Eligibility – Inclusion Criteria	NA	Added inclusion criteria #3 "3. If prior CV testing has occurred, it must have been performed greater than one year prior to randomization, and the following must be met: a) cCTA or invasive coronary angiography (ICA) with stenosis < 50% b) Quantified coronary artery calcium (CAC) < 100 AG
V.A. Patient Screening for Eligibility – Exclusion Criteria	3. Noninvasive or invasive CV testing within 1 year (for suspected CAD). CV testing for CAD refers to any stress tests, ICA, and cCTA (including calcium scoring) only. Resting ECG and resting echocardiogram are not exclusionary.	Including resting CMR (MRI) as not exclusionary: "3. Noninvasive or invasive CV testing for CAD within 1 year. CV testing for CAD refers to any stress tests, invasive coronary angiography (ICA), and cCTA (including calcium scoring) only. a) Resting ECG, resting echocardiogram and resting CMR (MRI) are not exclusionary regardless of when they were performed.

Section	Version 1.4	Version 1.5
V.D. Participant Follow-Up	24 months (+/-30 days) follow-up contact At the 24-month follow-up visit, participants will be asked to report the following: • Assessment if any MACE has occurred since the last visit/phone call • CV Update: Review and documentation of any cardiovascular diagnostic test, cardiovascular procedure, or hospitalizations/clinic visits due to cardiovascularsymptoms and complications since last visit • Review and documentation of concomitant cardiovascular medication changes since enrollment • Complete the following 2 questionnaires: ○ Seattle Angina Questionnaire ○ EQ-5D-5L Questionnaire • Collection of the following: ○ Any cardiovascular test – both written report and test output ○ Any cardiovascular imaging – both written report and image file	Removed participant follow-up requirement at 24 month
VII.A. Primary Endpoint Definitions – Myocardial infarction	The exception will be for peri procedural myocardial infarctions, which are defined as biomarker elevation ≥10 times the upper reference limit (URL) for creatine kinase MB (CKMB) and/or ≥70 URL for troponin as outlined in the most recent SCAI definition[60].	Reference 60 (Moussa ID, Klein LW, et al) removed and updated with reference 51 (Thygesen K, Alpert JS, et al) “This definition will be followed for spontaneous as well as periprocedural MIs, for which the elevation in cTn must be at least cTn values >5 times the 99th percentile URL for PCI and >10 times for CABG related infarctions[51]”
VIII.B. Statistical Analysis Plan – Analysis of the Primary Endpoint	A sensitivity analysis for the primary composite MACE endpoint will be conducted using the method of “win-ratio”[56]. The win-ratio method of Pocock et al is an extension of Finkelstein and Schoenfeld rank-test method[57] which order-rank composite endpoints based on their clinical importance.	A sensitivity analysis for the primary composite MACE (all cause death and non-fatal MI) or invasive cardiac catheterization without CAD (no coronary stenosis ≥50% according to QCA by core-lab adjudication or site interpretation if QCA is not available, or with FFR≤0.80, or instantaneous wave free ratio (iFR) ≤0.89) endpoint will be conducted using the method of “win-ratio”[56] and Finkelstein and Schoenfeld rank-test method[57].

TABLE OF CONTENTS

TABLE OF ABBREVIATIONS

ACC	American College of Cardiology
ACS	acute coronary syndrome
AHA	American Heart Association
AG	Agatston units
BMI	body mass index
BP	blood pressure
CAC	Coronary Artery Calcium
CAD	coronary artery disease
CV	Cardiovascular
CI	confidence interval
CK-MB	creatine kinase-myocardial band
CMS	Centers for Medicare & Medicaid Services
COCATS	Core Cardiology Training Symposium
cCTA	coronary computed tomographic angiography
CP	chest pain
cTn	cardiac troponin
DCRI	Duke Clinical Research Institute
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
Echo	Echocardiogram
EDC	electronic data capture
EQ-5D-5L	a standardized instrument developed by the *EuroQol* Group as a measure of health-related quality of life.
eCRF	electronic case report form
FFR	fractional flow reserve
FS	Finkelstein and Schoenfeld statistical method
FFR_{CT}	non-invasive technique using cCTA to determine FFR

g/L	grams per liter

HDL	high-density lipoprotein
ICA	invasive coronary angiography
iFR	instantaneous wave free ratio
IRB	institutional review board
IVUS	intravascular ultrasound
IXRS	interactive voice/web response system
LDL	low-density lipoprotein
LV	left ventricular
MACE	major adverse cardiovascular event
MAR	missing at random
MDCT	multidetector computed tomography
MI	myocardial infarction
MOP	manual of procedures
MPI	myocardial perfusion imaging
mSv	milliSievert
NI	non-invasive
NICE	National Institute for Health and Care Excellence (In the United Kingdom's National Health Service)
NHPR	non-hyperemic pressure ratio
OCT	optical coherence tomography
PAD	peripheral arterial disease
PCI	percutaneous coronary intervention
PI	principal investigator
PLATFORM	Prospective LongitudinAl Trial of FFR_{CT}: Outcome and Resource Impacts study
PRECISE	Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization
PROMISE	PROspective Multicenter Imaging Study for Evaluation of Chest Pain randomized clinical trial

QCA	quantitative coronary angiography
QoL	quality of life
ROC	receiver operating characteristic
SAQ	Seattle Angina Questionnaire
SCAI	Society for Cardiovascular Angiography and Interventions
SCOT-HEART	Scottish Computed Tomography of the HEART randomized clinical trial
ULN	upper limit of normal
URL	upper reference limit

I.STUDY SYNOPSIS

Protocol Title	**PRECISE:** Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization
Investigational Strategy	Precision diagnostic evaluation as the initial strategy for suspected significant CAD in patients with stable symptoms
Study Principal Investigator	Pamela S Douglas, MD Duke Clinical Research Institute, Duke University, Durham NC
Academic Research Organizations	Duke Clinical Research Institute (DCRI), Durham, NC, USA Cardiovascular Research Foundation (CRF), New York, NY, USA
Clinical Research Organization	Medpace Research, Inc.
Sponsor	HeartFlow, Inc. 1400 Seaport Blvd Redwood City, CA 94063
Participants and Study Centers	Approximately 2100 participants randomized at approximately 100 sites in the US and outside of the US
Planned Study Duration	Approximately 36 months
Primary Study Objective	To assess clinical outcomes, decision making regarding noninvasive testing and invasive angiography, and costs using a precision evaluation strategy as compared to a usual care strategy in participants with stable symptoms suggestive of significant coronary artery disease. The precision evaluation strategy will be based on a pre-test risk assessment and will incorporate cCTA with selective FFR_{CT} and guideline-recommended care with symptom and risk factor management and no additional immediately planned testing.
Primary Hypotheses	In stable participants with a clinical recommendation for testing to evaluate suspected significant CAD a precision evaluation strategy, incorporating a risk-based assignment to guideline recommended medical management without planned testing for selected low risk participants or cCTA with selective FFR_{CT} in elevated risk participants, will result in improved clinical outcomes of death/MI and a lower rate of catheterization without obstructive CAD as compared to usual care strategy.
Population	Stable patients who have a clinical recommendation for testing (noninvasive or invasive) for suspected significant CAD
Study Design and Methods	Prospective, pragmatic, randomized clinical trial of diagnostic evaluation strategies for stable suspected significant CAD, to be performed in outpatient settings, including primary care and cardiology practices. Qualifying patients presenting with new symptoms suspicious for clinically significant CAD (and without known obstructive CAD), who are recommended for diagnostic testing and did not receive any cardiovascular testing within the past 12 months, will be randomized to an initial strategy of either precision care or usual care of the site's choosing. All subsequent decisions in the usual care arm regarding additional testing, medications, and/or procedures will be at the discretion of the responsible clinical care team; the use of cCTA as the

	initial diagnostic strategy is not allowed in the usual care arm and is prohibited as a subsequent test for the first 45 days after randomization. **Precision evaluation:** Participants randomized to a precision strategy will then be assigned to either guideline-recommended care without immediately planned testing (low risk) or cCTA with selective FFR_{CT} (for those with elevated risk or known non-obstructive atherosclerosis) using a risk tool based on pre-test clinical characteristics derived from the PROMISE trial and validated in SCOT-HEART trial. As is recommended for all participants, those assigned to guideline-recommended care without planned testing will be treated with preventive and antianginal medical treatment per guideline recommendations and clinical judgment and followed without testing. Participants and their providers will be provided informational resources explaining the safety and rationale of this strategy based on pre-test probabilities and the PROMISE Minimal Risk Score. Participants with documented intractable symptoms despite maximal medical management may undergo cCTA with selective FFR_{CT} at the participant's or site clinician's discretion. **Usual Care:** For participants randomized to usual care, the participant's care team will select the specific noninvasive stress test (exercise electrocardiogram, stress nuclear imaging [including PET], stress MR, or stress echocardiogram); OR invasive test: (direct to diagnostic catheterization). The use of cCTA as the initial diagnostic strategy is explicitly excluded in this arm and prohibited as a subsequent test for the first 45 days after randomization. In both arms, the participant's care team will be provided with physician and patient informational resources summarizing current recommendations for test interpretation and preventive care. Optimal medical management will be recommended but not mandated in either arm.
Randomization and Stratification	Participants will be randomized using a 1:1 randomization scheme via an interactive web or voice-based system (IXRS). Randomization will be stratified by intended first test if randomized to usual care, low vs. elevated pre-test risk, and site. Enrollment in the strata of intended noninvasive test first (vs. intended invasive angiography first) will be capped at 90%.
Primary Endpoint	Time to a composite of: MACE (all cause death, non-fatal MI) or invasive cardiac catheterization without obstructive CAD (obstructive CAD defined as diameter stenosis ≥50% according to core-lab adjudicated quantitative coronary angiography (QCA), FFR≤0.80, or iFR≤0.89) at one year (intention to treat)
Secondary Effectiveness Endpoints	Endpoints will be assessed at 45 days, 6 months, and 1 year. 1. Hierarchical analysis (Finkelstein and Schoenfeld (FS) and Pocock's win ratio) of primary endpoint 2. Resource use patterns and medical costs 3. QoL: measured by the Seattle Angina Questionnaire (SAQ) to assess angina-specific Quality of Life and the EuroQoL 5D (EQ-5D-5L) survey to assess overall (generic) health status

	4. Death: All-cause, cardiovascular, non-cardiovascular 5. Myocardial infarction: All, procedural, spontaneous MI 6. Hospitalizations: All, cardiovascular, non-cardiovascular, and for progressive or unstable angina 7. Preventive medication use (ASA, statins) in participants with clinical indication for use: e.g.: hyperlipidemia, diabetes, documented CAD 8. Cumulative radiation exposure at 1 year 9. Proportion of invasive coronary angiogram patients who undergo revascularization (PCI or CABG) within 6 months of enrollment
Pre-specified subgroup analyses	1. Low risk vs. elevated risk by PROMISE score or pre-existing non-obstructive CAD 2. Intended initial test: functional stress test vs. invasive (direct to cath) 3. Clinical factors: sex, age, diabetes 4. Presentation: primary symptom (chest pain vs. other), SAQ angina frequency score
Inclusion Criteria	Inclusion criteria (all must be present): 1. Age ≥18 years 2. Stable typical or atypical symptoms suggesting possible significant coronary artery disease (CAD) with further non-emergent testing or elective catheterization recommended to evaluate the presence of suspected significant CAD. Stable chest pain (or equivalent) includes those who have fully been ruled out for Acute Coronary Syndrome (ACS) and for whom elective testing is recommended, regardless of the venue in which they are seen. 3. If prior CV testing has occurred, it must have been performed greater than one year prior to randomization, and the following must be met: a. cCTA or invasive coronary angiography (ICA) with stenosis < 50% b. Quantified coronary artery calcium (CAC) < 100 AG 4. Safe performance of cCTA: a. Creatinine clearance ≥45 ml/min per most recent measurement within 90 days b. For a female participant of childbearing potential (those who have not been surgically sterilized or are not postmenopausal), a pregnancy test must be performed with negative results known within 7 days prior to randomization 5. Willingness to comply with all aspects of the protocol, including adherence to the assigned strategy and follow-up visits 6. Ability to provide written informed consent
Exclusion criteria	Exclusion criteria (all must be absent): 1. Acute chest pain (in patients who have not been ruled out for ACS) 2. Unstable clinical status

	3. Noninvasive or invasive CV testing for CAD within 1 year. CV testing for CAD refers to any stress tests, invasive coronary angiography (ICA) and cCTA (including calcium scoring) only. a. Resting ECG, resting echocardiogram and resting CMR (MRI) are not exclusionary regardless of when were performed 4. Lifetime history of known obstructive CAD (prior myocardial infarction, CABG or PCI, stenosis ≥50%), known EF ≤40% or other moderate to severe valvular or congenital cardiac disease 5. Contraindications to cCTA including but not limited to creatinine clearance (GFR) <45 ml/min as per most recent measurement taken within 90 days 6. Exceeds the site's weight or size limit for cCTA or cardiac catheterization 7. Any condition leading to possible inability to comply with the protocol procedures or follow-up 8. Any condition that might interfere with the study procedures or follow-up 9. Enrolled in an investigational trial that involves a non-approved cardiac drug or device which has not reached its primary endpoint 10. Life expectancy less than 2 years due to non-cardiovascular comorbidities
Study Follow-up	Participant follow-up will be done at 45 days, 6 months, and 1 year.
Sample Size Considerations	Primary superiority testing hypothesis of all cause death/MI or invasive cardiac catheterization without obstructive CAD (diameter stenosis ≥50% or FFR≤0.80/ or iFR≤0.89) at one year (intention to treat, time to first event analysis): Assuming an 8% event rate at 1 year in the usual care group and 5% in the precision care group (3% absolute [37.5% relative] effect magnitude). Assumed rates are based on estimated ~20% assigned to guideline- recommended care with symptom management and no planned testing (within which 30% will cross over to cCTA with selective FFR_{CT}); and overall 10% will not receive assigned testing; enrolling 1050 participants per group (2100 total participants) would provide at least 90% power to demonstrate superiority accounting for 10% attrition rate.

II. INTRODUCTION

II.A. Primary Hypotheses

The primary goal of the Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization (PRECISE) research program is to assess clinical outcomes, decision making regarding noninvasive testing and invasive angiography, and costs using a precision evaluation strategy as compared to a usual care strategy in participants with stable symptoms suggestive of significant coronary artery disease. The precision evaluation strategy will be based on a pre-test risk assessment and the presence or absence of known non-obstructive atherosclerosis; participants in this arm will undergo either cCTA with selective FFR_{CT} or no immediately planned testing. All participants are encouraged to have guideline- recommended care with symptom management.

The primary hypothesis of PRECISE is: in stable participants with a clinical recommendation for testing to evaluate suspected significant coronary artery disease (CAD), a precision evaluation strategy will result in improved clinical outcomes of death/MI and a lower rate of catheterization without obstructive CAD as compared to a usual care strategy.

An important secondary hypothesis is that the precision evaluation strategy will result in improved patient-reported outcomes, reflected in the SAQ angina frequency and quality of life scores. We also expect the precision strategy to result in reduced resource utilization and net cost savings compared to usual care evaluation.

The usual care arm participants will undergo either noninvasive stress testing, with the specific modality at the discretion of the participant's clinician, or invasive coronary angiography (ICA) as the initial test.

The precision evaluation arm starts with the use of the PROMISE Risk Tool to categorize patient risk for CAD and events. The PROMISE Risk Tool is a validated risk model that has been shown to accurately identify chest pain patients who are unlikely to benefit from non-invasive testing (i.e. have minimal or no atherosclerosis and likely to have no events within two years). The lowest risk group in the precision arm identified using this model will be assigned to guideline-recommended care focused on symptom and risk factor management without planned cardiac diagnostic testing. Those participants who are identified to be of elevated risk or those with known non-obstructive coronary atherosclerosis (regardless of risk score results) will be initially evaluated with cCTA with selective FFR_{CT}.

I.B. Significance of the Study

The goal of PRECISE is to define the optimal evaluation and management strategy of stable, symptomatic participants with suspected significant CAD. If the hypotheses of PRECISE are supported by the results of the trial, PRECISE will form the core of a compelling body of evidence supporting important changes in clinical practice guidelines and clinical care that will both improve outcomes for patients and reduce the use of unnecessary (low yield) testing and associated medical costs. Chest pain is one of the most common symptoms that bring patients into the health care system and one of the most difficult for providers to address confidently. The variability of current practice and the frequent overuse of testing derive from the lack of consensus among experts and among guidelines about how best to achieve a secure diagnosis and appropriate management plan. The results of PRECISE will have major implications for all health systems where stable chest pain is a common reason for participants to seek care.

III. BACKGROUND AND STUDY RATIONALE

III.A. Prior Literature and Studies

Unmet need to develop novel approaches for the diagnostic evaluation in stable chest pain patients

CAD is an extremely common diagnosis worldwide and results in significant morbidity and mortality[1, 2]. Among the common presentations, stable symptoms of chest pain or exertional dyspnea can be diagnostically puzzling and often require diagnostic testing or angiography to be certain of the diagnosis and treatment. Current US, EU and UK guidelines recommend risk stratification using presentation characteristics and risk factors to determine which patients require noninvasive testing or should be referred directly to invasive catheterization[3]. However, in the current era, the results of using these recommended strategies are unsatisfactory. The population undergoing noninvasive testing has a low rate of obstructive CAD (10-20%) and very low annual event rates (~1-2%/year) [4, 5, 59], while patients undergoing invasive angiography frequently don't have actionable CAD[6]. These patterns of care have resulted in high costs without accompanying clinical benefit[7]. A new approach to the risk stratification and subsequent diagnostic evaluation and management of patients with stable symptoms suggestive of CAD is urgently needed.

Uncertainty Regarding the Optimal First Test for Detection and Exclusion of Coronary Artery Disease: Evidence For cCTA

While a number of functional and anatomic non-invasive tests are available for the evaluation of stable chest pain patients, the optimal evaluation strategy for patients with stable chest pain is uncertain, and recommendations in current guidelines differ markedly. In a recent attempt to address these issues systematically, two large, multicenter, open-label, randomized controlled trials explored the diagnostic evaluation of patients with symptoms that may represent coronary artery disease. The SCOT-HEART (Scottish Computed Tomography of the HEART)[4, 59] and PROMISE (PROspective Multicenter Imaging Study for Evaluation of chest pain)[5] trials sought to address evidence gaps in noninvasive testing in stable chest pain, an area in which few randomized trials had previously been conducted.

Key findings from SCOT-HEART and PROMISE: The overall results and important similarities and differences between the two trials have been recently described[8]. The SCOT-HEART study enrolled 4,146 patients with stable chest pain to cCTA in addition to usual care (which generally included electrocardiogram [ECG] stress testing) or to usual care alone. The trial used an upstream primary endpoint related to diagnostic thinking: managing clinician certainty of the diagnosis of angina secondary to CAD, which showed an increase in the cCTA group (RR: 1.79; 95% confidence interval [CI]: 1.62 to 1.96), as did the secondary endpoint of certainty of diagnosis of CAD (RR: 2.56; 95% CI: 2.33 to 2.79). The clinical outcomes-related secondary endpoint of the rate of cardiovascular death or nonfatal myocardial infarction (MI) appeared to be reduced in the cCTA group at 20 months (RR: 0.62, 95% CI: 0.38 to 1.01; p=0.0527), although the overall event rates were low in both arms, reflecting the inclusion of a large number of patients without

CAD. Of note, a landmark analysis excluding the 7 week delay to receiving a cCTA yielded a hazard ratio of 0.50 for CV death and MI[9].

The larger PROMISE trial randomly assigned 10,003 symptomatic, stable outpatients requiring evaluation for suspected CAD to either initial cCTA or functional stress testing (exercise treadmill testing [ETT], nuclear stress testing, or stress echocardiography), with a median follow-up of 25 months. The event related composite primary endpoint (death, MI, hospitalization for unstable angina, or major cardiovascular procedural complication) occurred at similar rates in the cCTA and functional testing groups (3.3% and 3.0%), which was lower than previously established historical rates. More patients in the cCTA group underwent cardiac catheterization within 90 days after randomization (12.2% vs. 8.1%), but the secondary endpoint of the frequency of catheterization showing no obstructive CAD was significantly lower in the cCTA group (3.4% vs. 4.3%, p=0.02) as was the rate of death and MI at 12 months (HR 0.66; p=0.049). Furthermore, among patients randomized to an intended nuclear testing strategy, the mean cumulative radiation exposure was lower in the cCTA group compared with the functional testing group (12.0
- 8.4 mSv vs. 14.1 - 7.6 mSv). This encompassed all downstream radiation within 90 days, including that associated with cardiac catheterization, and is particularly intriguing because more cCTA patients received cardiac catheterization.

In addition to improving triage to the cardiac catheterization lab and potentially reducing radiation exposure, mounting evidence has demonstrated that use of cCTA, compared to functional testing, yields improved preventive medical treatment and better prognostic information[4, 5, 10]. Patients in the PROMISE trial who underwent cCTA experienced greater uses of indicated cardio-protective medications such as aspirin and statins[10]. This increase is prognostically important, as data from the CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes International Multicenter) demonstrated that baseline statin therapy among patients with non-obstructive CAD[11] identified on cCTA was associated with a reduction in mortality compared to non-use[12], while statin therapy among patients with obstructive CAD identified on cCTA was associated with a reduction in MACE[13].

The identification of non-obstructive CAD with high risk plaque characteristics can only be accomplished non-invasively by cCTA and is an important prognostic indicator, with even mild abnormalities conferring nearly three times the risk of death, MI and unstable angina compared to patients with a normal study[14, 15]. Furthermore, cCTA leads to higher yield of positive results with actionable or obstructive CAD, among patients undergoing cardiac catheterization[5]. This is in line with data from the CONFIRM registry, where investigators demonstrated that cCTA could be used as an effective gatekeeper prior to invasive coronary angiography[16].

Most importantly, a recent meta-analysis largely based on PROMISE and SCOT-HEART data showed a clear benefit in ‘hard’ cardiovascular outcomes to a cCTA first strategy, with a 29% reduction in MI[17]. This was potentially driven by the increase in medication utilization in the cCTA arm of the study as well as more catheterization and revascularization[17].

To summarize, there are several practical and clinical implications of SCOT-HEART and PROMISE which inform the proposed design of PRECISE:

- Contemporary patients with stable chest pain are at low risk of clinical events. Therefore, a strategy to test only those with an elevated likelihood of having obstructive CAD or risk for events, while instituting optimal medical care including deferring testing in those unlikely to benefit (i.e. using the PROMISE Risk Score), may be feasible, clinical important and efficient.

- cCTA is a reasonable first test for routine assessment of patients with stable chest pain, and when compared to functional testing, is associated with an increase in preventive medication use and a reduction in myocardial infarction.
- Future trials investigating the optimal evaluation of patients with stable chest pain should include the evaluation of clinical outcomes and other measures of testing efficiency (i.e., cardiac catheterization without obstructive CAD).

The Case for the Use of cCTA with selective FFR_{CT} as the Optimal First Test

The current noninvasive diagnostic testing strategies using functional testing have relatively poor accuracy given the low disease prevalence in this population, leading to high rates of false- positive results[18]. Specifically, current diagnostic strategies lead to high rates (~50%) of cardiac catheterization without significant obstructive disease or need for revascularization[5,7]. As described above, incorporating cCTA into testing strategies can reduce the frequency of cardiac catheterization without obstructive disease but tends to increase rates of invasive angiography [4, 5].

Non-invasive computationally-derived FFR_{CT} has been developed using resting coronary CT images without the administration of adenosine or change in underlying cCTA protocols[18-21]. The methodology has been previously described elsewhere.[22] In short, FFR_{CT} uses the accurate anatomical model of the coronary arteries and myocardium obtained with conventional cCTA and applies the physical laws that govern flow, microcirculatory resistance, coronary branching, and simulated hyperemia. The Navier-Stokes equations that solve for velocity, resistance and pressure for all Newtonian fluids are applied to provide a 3-dimensional pressure map across the coronary tree. This use of computational fluid dynamics generates FFR values from 0 to 1, with $\leq$0.80 considered hemodynamically significant. The values are congruent with invasive FFR, as shown in several prospective validation studies[18-20]. Finally, the anatomical modeling has been improved by the use of advanced deep and machine learning techniques applied to the large data sets acquired via central analysis.

The addition of FFR_{CT} may reduce a potential limitation of a cCTA-first approach, excess invasive angiography, by providing both functional and anatomic data. Specifically, FFR_{CT} markedly reduces the false positive rate of cCTA alone vs. invasive FFR adjudicated ischemia with 68% of false positive CT interpretations in the NXT Trial reclassified as true negative. A retrospective analysis from the PROMISE trial in 181 patients with cCTA, cardiac catheterization and FFR_{CT} revealed that FFR_{CT} was a better predictor of revascularization and events than cCTA alone. Modelling of the incorporation of FFR_{CT} into catheterization decision making suggested a reduction in catheterization rate with cCTA from 12.2% to 7.8% while reducing the rate of catheterization without obstructive CAD from 27% to 15% and increasing the yield of catheterization leading to revascularization from 49% to 61%[23]. Given that PCI of lesions with negative FFR is associated with worse outcomes[24, 25], while treatment of FFR positive lesions with PCI vs. optimal medical therapy results in improved clinical outcomes, the potential clinical value of adding FFR_{CT} to a cCTA based diagnostic strategy is evident.

The safety and utility of a CT/ FFR_{CT} strategy were further tested in the PLATFORM Study (Prospective LongitudinAl Trial of FFR_{CT}: Outcome and Resource Impacts) which evaluated rates of invasive catheterization without obstructive CAD in patients undergoing invasive evaluation. Patients in 2 sequential non-overlapping cohorts of patients referred for ICA were assigned to either undergo ICA or cCTA/ FFR_{CT} with ICA use based on the results of the cCTA and FFR_{CT}. The cCTA/FFR_{CT} strategy resulted in a significant reduction in the rate of cath lab finding of no obstructive disease, from 73 to 12%[7]. Furthermore, ICA was deferred in 61% of cCTA/FFR_{CT} strategy patients. A follow-up at one year demonstrated that cCTA with selective FFR_{CT} strategy yielded similar clinical outcomes and quality of life, at a substantially reduced cost.

While much of the early focus has been on a reduction in referral for ICA in the absence of actionable CAD, more recently there has been growing interest in using FFR_{CT} to enhance catheterization lab efficiency by increasing the proportion of catheterizations that include revascularization (PCI or CABG / ICA ratio) and providing guidance regarding revascularization strategies before the invasive angiogram. Importantly, in this case FFR_{CT} is not being used only in a binary fashion but rather to provide a richer understanding of the pattern and degree of pressure loss across the epicardial coronary system and its connection to the extent of ischemia present.
The value of cCTA and FFR_{CT} has been recognized by The National Institute for Health and Care Excellence (NICE) in their advisory for stable chest pain (Clinical Guidance 95) and technical evaluation of FFR_{CT}, as well as by establishment of reimbursement standards by the Centers for Medicare and Medicaid Services (CMS) [26, 27]. The 2016 NICE guidance recognized the difficulties with risk stratification in an era of reduced obstructive CAD prevalence in the population undergoing evaluation and the importance of anatomical assessment of CAD[26, 27]. In response, it recommends coronary cCTA as the first-line investigation for patients presenting with new-onset chest pain felt to be due to CAD based on its superior clinical diagnostic utility and cost- effectiveness[26, 27]. Further, based on the results of the PLATFORM trial, the NHS recommends addition of FFR_{CT} to cCTA as a cost savings measure[26]. In the United States, CMS approved a New Technology Ambulatory Payment Classification (APC) for HeartFlow FFR_{CT} analysis on January 1, 2018[28]. The acknowledgement of FFR_{CT} by CMS is a critical step toward increasing the availability of the technology to patients who may benefit. However, other organizations' standards documents have not yet been revised to incorporate the emerging evidence base supporting CCTA and FFR_{CT}, indicating that there is still a need for additional evidence to support the routine use of FFR_{CT} in clinical practice.

<u>Rationale and Evidence for Incorporation of a Strategy of Guideline-recommended Care without Planned Testing in Low Risk patients</u>

Given the low prevalence of obstructive CAD (10-20%) and very low annual event rates (~1-2%/year) among stable chest pain patients undergoing non-invasive testing, combined with the high cost of testing[4, 5], prospective evaluation of the safety and efficacy of an approach of guideline-recommended care without planned testing has become a necessity. Although there are no data regarding outcomes and costs of a guideline-recommended care without planned testing in symptomatic patients, it is possible to define in principle a cohort in whom deferred testing might be the optimal strategy. The argument for testing this is further strengthened by the equivalence of medical and invasive strategies in preventing cardiovascular events in stable CAD, as several trials have shown no benefit of revascularization over optimal medical treatment [29, 30]. It is reasonable to hypothesize that this may be especially true for those at lowest risk, in whom noninvasive testing is even less likely to lead to outcomes-improving revascularization, thereby removing the need for testing as a gateway to the catheterization laboratory.

The COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) demonstrated no significant difference in a composite of death, myocardial infarction, and stroke between patients with objective evidence of myocardial ischemia and significant CAD on medical therapy vs. those undergoing PCI (19.5% vs. 20.0%, p=0.62)[29]. The more recent ORBITA trial (Percutaneous coronary intervention instable angina) randomized 200 patients with stable angina and a single-vessel stenosis to optimal medical therapy + PCI vs. optimal medical therapy plus a sham procedure, with a primary endpoint of difference in exercise time during a 6-week follow-up period[30]. The authors found no significant difference in improvement in exercise time (+28.4 seconds in PCI group vs. +11.8 seconds in sham group, p=0.2), nor any significant change in the secondary outcome of Seattle Angina Questionnaire (SAQ)-angina frequency from baseline (14.0 in PCI group vs. 9.6 in sham group, p=0.26)[30]. The ongoing improvements in medical management of CAD risk, angina and established coronary artery disease further emphasize the need for diagnostic strategies that minimize unnecessary invasive angiography and revascularization by emphasizing guideline-recommended care in patients at very low risk for obstructive disease.

These studies support the development of a patient-centric strategy to identify those who may derive minimal benefit from testing, a strategy which carries several desirable implications for patients, clinicians, and clinical practice in general. For patients, this process can mean a reduction in use of testing from which they would not benefit, thereby saving time, anxiety, and cost, as well as potential reductions in radiation exposure and false-positive test results that could lead to more invasive, unnecessary procedures. For clinicians, a tool identifying the lowest risk patients has the potential to help optimize office-based decision making. From a practice and societal perspective, in an era in which practitioners are increasingly held accountable for costs and quality, the ability to confidently identify patients highly unlikely to benefit from potentially expensive testing and who may therefore be managed conservatively has many potential economic and process-of-care advantages.

The PROMISE Risk Tool was expressly developed to identify low-risk patients with stable chest pain who are unlikely to benefit from non-invasive testing, and for whom guideline-recommended medical management alone may be safe. Current guidelines recommend using a version of the Diamond and Forrester risk score for pretest likelihood of obstructive CAD, but multiple investigators have found that this tool grossly over estimates actual presence of disease[5, 31, 32]. The consequence is an imprecise evaluation strategy for millions of patients, resulting in unhelpful testing of lower risk individuals. For a significant portion of these, a false positive functional testing leads them to have invasive cardiac catheterizations to rule out the disease they do not have. The Risk Tool developed using the PROMISE cohort employs 10 readily available clinical variables (such as tobacco usage, ethnicity/race, and age) and has been validated in the SCOT-HEART population[33, 34]. This risk tool identifies patients with stable chest pain who have no coronary plaque or calcification by cCTA and no cardiac events over 2 years, and who therefore would be predicted to derive minimal or no value from noninvasive testing[33, 34]. Testing whether this risk tool can be employed prospectively to safely and effectively risk stratify low risk patients into a strategy of guideline-recommended care with symptom and risk factor management and without diagnostic testing is one of the core secondary objectives of the PRECISE research program.

III.B. Rationale for the Current Study: A Precision Approach to Chest Pain Evaluation

Despite the high-burden of stable chest pain in the U.S., and the enormous research literature reporting on the comparative effectiveness of different options, no single diagnostic strategy has emerged with a broad consensus of support. Each testing community continues to favor its own technology and the clinicians who must select the testing approach to use for their patients are caught in the middle, unable to resolve the controversies that have characterized this area of cardiovascular medicine for decades. The situation is complicated by the heterogeneity of the current population's burden of disease. More than a quarter (27%) of the PROMISE cohort had no coronary plaque whatsoever, while high-risk CAD, defined as left main stenosis (≥50% stenosis) or either (a) ≥50% stenosis '[50]' or (b) ≥70% stenosis '[70]' of 3 vessels or 2-vessel CAD involving the proximal left anterior descending artery was identified in 6.6% [50] and 2.4%
[70] of patients. Thus, the first goal of any optimal management strategy for stable symptoms in patients with suspected CAD is determination of an individual patient's risk. Using the PROMISE Risk Tool to accurately assess patient risk[33, 34], we will prospectively test the hypothesis that low risk patients can be correctly identified with only baseline clinical data and that emphasizing guideline-recommended care while deferring testing in these patients improves chest pain decision making by reducing unnecessary invasive angiography without leading to an increase in MACE, and by reducing cost.

Among patients in whom contemporary risk evaluation suggests an elevated risk for obstructive CAD, the observational data suggest that cCTA with selective FFR_{CT} may improve appropriate triage to invasive angiography[5, 23], while reducing cost[9].

Thus, the case for an adequately powered randomized clinical trial with a pragmatic design, comparing clinical outcomes following testing strategies regularly used in current clinical practice to a precision evaluation strategy is compelling. PRECISE is designed to be that trial.

If the findings of PRECISE are positive as hypothesized, it is expected that the trial will lead to updates in appropriate use criteria, clinical practice guidelines, and payer policies such that cCTA with selective FFR_{CT} receives a class IA recommendation for stable chest pain patients to improve outcomes and reduce costs. PRECISE will identify those chest pain patients for whom non- invasive testing may be safely deferred and simultaneously improve the efficiency of testing for elevated risk patients. The results of this study will shift the paradigm of clinical thinking in this area from the current approach of identifying a single best test for all, to incorporating a patient- centric risk-based evaluation and management strategy for stable chest pain patients.

IV. STUDY OVERVIEW AND OBJECTIVES

IV.A. Overview of PRECISE

PRECISE is a multicenter, randomized, trial that will enroll approximately 2100 participants in a comparison of a risk-based precision evaluation strategy of guideline-recommended medical management without planned testing (in minimal risk participants) and cCTA with selective FFR_{CT} (in elevated risk participants) with usual care in stable symptomatic patients with suspected significant CAD.

<u>Location</u>

Participants will be enrolled at approximately 100 sites in the US and outside of the US. No center may enroll more than 315 (15%) participants in the trial.

Participant Population and Selection

Participants will be symptomatic patients with suspected significant CAD and a stable clinical course who are recommended by their managing clinician to have a non-invasive diagnostic test or ICA. Patients will be excluded if they have any history of documented CAD (including revascularization, myocardial infarction or any degree of CAD proven by imaging) or have had diagnostic cardiovascular testing for suspected CAD within the last year. Patients will also be excluded if their symptoms are not clearly stable or if their managing clinician feels testing is needed on an urgent or emergent basis.

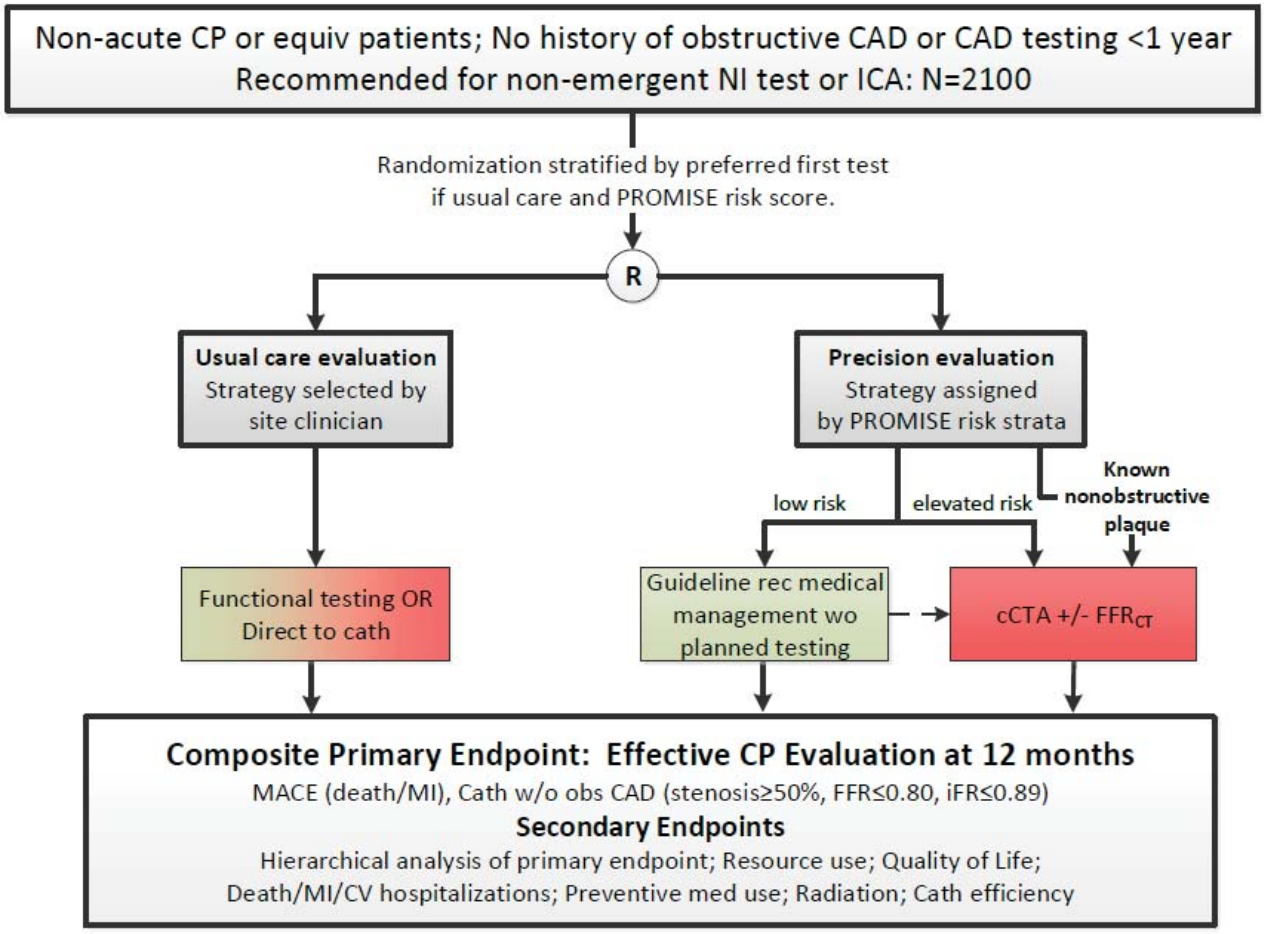
Diagnostic testing for the assessment of CAD symptoms is ordered by physicians and other clinicians from many specialties and is performed in multiple settings, including physician offices, hospital outpatient departments, and diagnostic testing facilities. A trial, such as PRECISE, that seeks to improve the management of non-ACS chest pain must incorporate this diversity in order to be broadly relevant to the target population under study. PRECISE site selection will seek to encompass this diversity.

Study duration

The anticipated total duration of the PRECISE study will be approximately 36 months for start-up, enrollment, follow up, and close out. Participants will be followed for 12 months after enrollment.

Study design

The figure below represents a diagrammatic representation of the trial design.



IV.B. Primary Objective and Endpoints

The primary objective of the PRECISE study is to assess clinical outcomes, patient-reported outcomes, decision making regarding noninvasive testing and invasive angiography, and costs using a precision evaluation strategy as compared to a usual care strategy in participants with stable symptoms suggestive of significant coronary artery disease. The precision evaluation strategy will be based on a pre-test risk assessment which will be used to assign participants to either cCTA with selective FFR_{CT} or guideline-recommended care with symptom and risk factor management and no immediately planned testing. In addition, patients with known mild coronary plaque without obstructive stenosis or extensive coronary calcium randomized to the precision evaluation arm are mandated to undergo cCTA +/- FFR_{CT}, independent of their PROMISE risk score strata. We hypothesize that in stable patients with a clinical recommendation for testing to evaluate suspected significant CAD, the proposed precision evaluation strategy will improve outcomes and reduce costs compared to usual care evaluation.

The primary endpoint is a composite of: MACE (all cause death and non-fatal MI) or invasive cardiac catheterization without CAD (no coronary stenosis ≥50% according to QCA by core-lab adjudication or site interpretation if QCA is not available, or with FFR≤0.80, instantaneous wave free ratio (iFR) ≤0.89) or other validated NHPR. The primary study hypothesis will be tested at one

year using an intention to treat analysis.

IV.C. Secondary Endpoints

Endpoints will be assessed at 45 days, 6 months, and 1 year. Secondary endpoints include:

1. Hierarchical analysis (Finkelstein and Schoenfeld (FS) and Pocock's win ratio) of primary endpoint (gives priority to clinical importance of the components of the composite outcome rather than time to event)
2. Resource use patterns (all participants) and medical costs (US participants): resources to be assessed include index testing, follow up testing, diagnostic and other cardiac procedures and hospitalizations. Primary comparisons will be made at 12 months.
3. QoL: the Seattle Angina Questionnaire (SAQ) will be used to assess angina-specific Quality of Life; the EuroQoL 5D (EQ-5D-5L) survey will be used for a brief assessment of overall (generic) health status; patient satisfaction with diagnostic process will be assessed once at 45 days using a 4-item instrument created for this trial.
4. Death: All-cause, cardiovascular, non-cardiovascular
5. Myocardial infarction: All, procedural, spontaneous MI
6. Hospitalizations: All, cardiovascular, non-cardiovascular, and for progressive or unstable angina
7. Rates of preventive medication use (ASA, statins) in participants with clinical indication for use: hyperlipidemia, diabetes, documented CAD
8. Cumulative radiation exposure at 1 year
9. Proportion of invasive coronary angiogram patients who undergo revascularization (PCI or CABG) within 6 months of enrollment (catheterization efficiency)

IV.D. Rationale for the Selection of Outcome Measures

Rationale for Clinical Assessments

Major adverse cardiovascular events (MACE) are a primary concern for clinicians and patients presenting with stable chest pain. The primary composite endpoint of MACE at 12 months (all cause death, non-fatal MI), invasive cardiac catheterization without obstructive CAD (diameter stenosis ≥50% by QCA, FFR≤0.80 or iFR≤0.89) is clinically relevant and, the components taken together, represent a sound measure of an effective diagnostic chest pain evaluation[4, 5, 35, 36]. The selection of 12 months is based on the rationale that the longer the duration between the evaluation strategy and an eventual outcome, the less likely it is that the evaluation strategy is directly related to the outcome of interest. In PROMISE, there was a significant reduction in death and MI in the cCTA arm compared to the usual care arm at 12 months, which was no longer significant after a median 25 months of follow-up[5]. The use of this composite clinical endpoint will be critical to assessing the PRECISE hypothesis that a precision evaluation strategy with cCTA and selective FFR_{CT} and guideline-recommended medical management without planned testing will yield superior outcomes at lower cost compared with a usual care testing strategy.

Rationale for Economic and Quality of Life (QoL) Assessments in PRECISE

Non-invasive diagnostic testing for the evaluation of stable chest pain represents a significant cost

to the U.S. and other healthcare systems. In the past when payers in the US have attempted to control costs by reducing the reimbursements provided for diagnostic testing, clinicians responded by increasing the number of tests obtained. An emphasis on generating evidence for cost-savings via a safer and more efficient approach is critical in enhancing value while reducing the financial burden on patients, providers, and the system alike. In addition, this precision-based approach to diagnostic evaluations in CAD participants may result in improvements in the quality of care of our participants. Further, since there has been no prospective trial of guideline- recommended care without planned testing, the ability of such an approach to provide equivalent symptom relief compared with usual care is of great importance and critical to the evaluation of this approach. For these reasons, the potential impact of a precision-based approach on resource use and QoL must be evaluated in PRECISE.

IV.E. Rationale for Selection of Testing in Each Arm

Usual Care Arm

Functional stress testing with stress nuclear, stress echocardiography, and exercise ECG for the diagnosis of CAD is well-established in clinical practice (ACC/AHA 2012 Stable Ischemic Heart Disease guidelines, class I, Level of Evidence (LOE) B[37]. While stress CMR is less commonly used, it also receives a class IIa, LOE B recommendation in patients who are unable to exercise[37] and is used in some centers. In contrast, it is common for patients to be referred direct to diagnostic angiography without undergoing a functional test. This group represents up to 50% of elective catheterization populations and is thus an important usual care approach to suspected CAD[35, 38, 39]. In order to accurately capture the wide variety of testing strategies available to and used by community clinicians and real-world practice patterns, a usual care strategy arm with site clinician decision-making should include all of the above options. This will improve the generalizability of the trial while accurately capturing the potential impact of the implementation of a precision approach. Participants with history of known obstructive CAD (prior myocardial infarction, CABG or PCI, stenosis ≥50%) are excluded from enrollment into the trial. In all participants in the usual care arm, cCTA is prohibited as a subsequent test for the first 45 days after randomization.

Precision Evaluation Arm

PRECISE will evaluate whether a precision evaluation strategy that combines contemporary risk stratification using the PROMISE Risk Tool with functional and anatomic non-invasive evaluation with cCTA with selective FFR_{CT} can improve outcomes over usual care in stable chest pain patients while safely deferring further testing in low-risk patients and reducing cost overall. While current guidelines recommend the non-invasive and invasive initial testing approaches for patients with stable chest pain[37], current practice is known to lead to high rates of ICA without obstructive CAD[6, 40]. Further, although guidelines also recommend no testing in the lowest risk groups (pre-test probability of obstructive CAD <10 or 15%), currently available risk tools result in many clinicians appearing to ignore this recommendation: current patterns of care using available risk stratification tools results in testing populations with a prevalence of obstructive CAD of only 10-20%, and a prevalence of no coronary plaque of >25%[4, 5]. The intervention in PRECISE will triage patients into two risk groups who will be assigned to receive either guideline-recommended medical management without planned testing or cCTA with selective FFR_{CT}. The PROMISE Risk Tool can identify low-risk patients with stable chest pain that would be expected to derive minimal value from noninvasive testing and is superior to either Framingham Risk Score or Diamond and Forrester assessments[33,

[34]. cCTA with selective FFR_{CT} represents a combined functional and anatomic testing modality that can lower the frequency of finding no obstructive CAD at catheterization and thus reduce costs[7, 41].

IV.F. Randomization Method

Participants who meet all inclusion criteria and none of the exclusion criteria will be randomized in a ratio of 1:1 within a clinical center to either a precision evaluation strategy or usual care using an interactive web or voice-based system (IXRS). Randomization will be stratified by intended first test (if randomized to usual care) and by classification as low vs. elevated risk by the minimal risk model. Participants with known non-obstructive plaque will be included in the elevated risk strata regardless of risk score. The randomization scheme within a clinical center will be carried out by the method of random permuted block design with variable block size.

Enrollment in the randomization strata of intended first test being noninvasive (vs. direct to catheterization) will be capped at 90% of the sample size.

Risk will be classified by a risk tool using pre-test clinical characteristics (including tobacco usage, ethnicity, and age) derived in the PROMISE trial and validated in SCOT-HEART or by the presence of non-obstructive plaque/CAC < 100 AU. Participants randomized to follow a precision strategy group will be assigned to either guideline-recommended care with symptom and risk factor management and no immediately planned testing (low risk group) or cCTA with selective FFR_{CT} (elevated risk of obstructive coronary disease and/or events). Participants randomized to precision evaluation and risk stratified into the low risk group and their providers will be provided informational materials explaining the rationale for this decision and the safety of this strategy based on outcomes of similar participants in the PROMISE trial.

Participants randomized to usual care will undergo either noninvasive stress testing or invasive testing (direct to diagnostic catheterization), as recommended by their managing clinician and agreed to by the participant. Acceptable noninvasive testing options will include exercise electrocardiogram, stress nuclear imaging (including PET), stress MR or stress echocardiogram. The use of cCTA is explicitly excluded as the initial diagnostic strategy in this arm and prohibited as a subsequent test for the first 45 days after randomization.

In both arms, all subsequent decisions regarding additional testing, medications, and/or procedures will be at the discretion of the responsible clinical care team. Each care team will be provided with informational materials summarizing current standards for test interpretation and preventive care. However, specific medical treatment will not be mandated by the study.

IV.G. Diagnostic Evaluations and Subsequent Care

Description of Evaluations to be performed

Participants will be assessed per the individual clinicians' routine approach to patients presenting with stable chest pain. Initial evaluation will include an appropriate medical history, physical examination, resting 12-lead ECG, and other routine blood work. A pregnancy test will be required for female participants of childbearing potential (those who have not been surgically sterilized or are not postmenopausal), and a creatinine blood test will be required for participants without a

recent normal value (most recent measurement taken within previous 90 days). At the time of randomization, the site clinician will specify the preferred first diagnostic strategy (noninvasive stress test vs. direct to catheterization) if randomized to the usual care arm and this choice will be used to stratify randomization. Also part of the randomization process, every participant will undergo risk stratification with the PROMISE risk calculator although sites will be blinded to results. Participants randomized to the precision evaluation arm will be assigned to either no planned testing vs cCTA/FFR_{CT} based on risk score results and the presence of known non-obstructive coronary atherosclerosis.

Sites will be provided with informational materials outlining standards of care for all noninvasive test interpretation. Guideline recommendations for care and informational materials on symptom and risk factor management will also be provided. These are intended to be followed for all participants. Participant-friendly versions of these materials will be provided to sites and may be used as handouts.

Symptoms and Quality of Life (QoL) will be assessed by the EuroQoL 5D (EQ-5D-5L) survey to assess overall (generic) health status and the Seattle Angina Questionnaire (SAQ) to assess angina-specific Quality of Life.

Equipment, Protocols & Interpretation

All participating sites will use standard equipment and procedures for usual care testing, including diagnostic angiography, stress echocardiography, stress nuclear perfusion imaging, stress CMR, and exercise ECG as defined by current practice guidelines[42-49]. Sites must also use at least 64-slice multi-detector computed tomography (MDCT) for coronary cCTA[49, 50]. All testing protocols will be in accordance with current best-practice standards[42-48, 50].

Interpretation

The interpretation of all diagnostic tests will be performed in a timely fashion and will capture the presence and extent of findings including diagnosing or excluding CAD (diagnostic angiography), fixed or inducible LV perfusion and wall motion abnormalities (stress echo, cMR and stress nuclear), and functional capacity (in the case of exercise ECG, exercise echo and exercise nuclear). The site interpretation and clinical report of all diagnostic tests, including noninvasive stress testing, cCTA and invasive angiography, will be uploaded through the EDC.

cCTA study interpretation will be carried out by site physicians with at least ACC COCATS (Core Cardiology Training Symposium) level 2 training, Society of Cardiovascular Computed Tomography level 2, recognized by the Certification Board of Computed Cardiovascular Tomography, or equivalent[50]. Certification by the Certification Board of Nuclear Cardiology or Board Certification in nuclear medicine or radiology will be considered satisfactory for interpretation of stress nuclear imaging studies. Stress echo and cMR readers also be at least COCATS level 2 trained or equivalent. Prior to being opened to participant enrollment, sites will be certified to ensure that quality cCTA images can be obtained.

Referral of precision evaluation cCTA participants for FFR_{CT} determinations

Participants randomized to the precision evaluation arm who are either 1) determined to be at elevated risk or 2) have known non-obstructive coronary atherosclerosis will undergo cCTA as the initial diagnostic strategy according to current best practice standards. Image sets showing at least

one 30-90% stenosis in epicardial vessels of 2mm diameter or greater should be promptly sent to HeartFlow for analysis of FFR_{CT}. Results will be returned to sites in < 24 hours to enable rapid incorporation into clinical decision making.

Subsequent Care

Subsequent care will be provided by the individual site clinicians at their own discretion, with encouragement to follow guideline-based approaches. Information will be provided to the individual sites on diagnostic test interpretation and subsequent management approaches for the various imaging modalities, including relevant guideline recommendations for primary and secondary prevention.

For patients in the Precision Evaluation Arm, ICA should not be performed unless at least one of the following criteria are met:

- Any stenosis ≥90% identified by cCTA
- Left Main stenosis ≥30% identified by cCTA
- Plaque rupture identified by cCTA
- Lesion-specific FFR_{CT} ≤0.85 in vessels with reference vessel diameter of 2.0mm or greater

Need for testing in low risk participants randomized to the precision care arm

Participants randomized to the precision evaluation arm and determined to be at low risk will be treated for symptoms and risk factor management according to current guideline recommendations. While it is expected that this will resolve symptoms in nearly all cases it is recognized that chest pain will persist in some despite medical treatment. In some cases, additional non-cardiac diagnostic testing may be pursued. In other cases, the site clinician may decide that further cardiac testing is warranted, in which case a cCTA followed by selective FFR_{CT} should be performed. Details regarding such decision making will be captured in the case report form.

V.STUDY PROCEDURES

V.A. Patient Screening for Eligibility

Patients will be screened by site personnel for eligibility and provided information about the study. Patients' not meeting inclusion and or having exclusion criteria will be documented as being excluded. Patients meeting inclusion and not meeting any exclusion criteria will be provided an informed consent form to review and sign prior to being randomized into the study.

Inclusion Criteria

1. Age ≥18 years
2. Stable typical or atypical symptoms suggesting possible significant coronary artery disease (CAD) with further non-emergent testing or elective catheterization recommended to evaluate the presence of suspected significant CAD. Stable chest pain (or equivalent) includes those who have fully been ruled out for Acute Coronary Syndrome (ACS) and for whom elective testing is recommended, regardless of the venue in which they are seen.
3. If prior CV testing has occurred, it must have been performed greater than one year prior to randomization, and the following must be met:
    a) cCTA or invasive coronary angiography (ICA) with stenosis < 50%
    b) Quantified coronary artery calcium (CAC) < 100 AG
4. Safe performance of cCTA:
    a) Creatinine clearance ≥45 ml/min per most recent measurement within 90 days
    b) For a female participant of childbearing potential (those who have not been surgically sterilized or are not postmenopausal), a pregnancy test must be performed with negative results known within 7 days prior to randomization
5. Willingness to comply with all aspects of the protocol, including adherence to the assigned strategy and follow-up visits regardless of actual testing performed
6. Ability to provide written informed consent

Exclusion Criteria

1. Acute chest pain (in patients who have not been ruled out for ACS)
2. Unstable clinical status
3. Noninvasive or invasive CV testing for CAD within 1 year. CV testing for CAD refers to any stress tests, invasive coronary angiography (ICA), and cCTA (including calcium scoring) only.
    a) *Resting ECG, resting echocardiogram and resting CMR (MRI) are not exclusionary regardless of when they were performed.*
4. Lifetime history of known obstructive CAD (prior myocardial infarction, CABG or PCI, stenosis ≥50%), known EF≤40% or other moderate to severe valvular or congenital cardiac disease
5. Contraindications to cCTA including but not limited to creatinine clearance (GFR) <45 ml/min as per most recent measurement taken within 90 days
6. Exceeds the site's weight or size limit for cCTA or cardiac catheterization
7. Any condition leading to possible inability to comply with the protocol procedures and follow-up
8. Any condition that might interfere with the study procedures or follow-up
9. Enrolled in an investigational trial that involves a non-approved cardiac drug or device which has not reached its primary endpoint
10. Life expectancy less than 2 years due to non-cardiovascular comorbidities

Screening visit (in-person)

Participant will be randomized to either the usual care arm or the precision evaluation arm within 14 days of screening.

At the screening visit, patients will undergo the following:

- Review consent form and have all questions appropriately answered.
- Provide consent by signing the Informed Consent Form
- Review of medical history
- Review of concomitant medications
- Pregnancy test (for females of child-bearing potential – those who have not been surgically sterilized or are not postmenopausal)
- Creatinine test (if not done in last 90 days)

Resting 12-lead ECG (optional, clinical care only) Assessment of CAD risk will be performed during screening to ensure eligibility. It will include:

- General medical history
- Cardiovascular risk factors and comorbidities as well as prior testing or events
- Physical exam
- Laboratory testing

The following major cardiac risk factors will be assessed:

- Age
- Sex
- BP/hypertension
- Diabetes
- Cholesterol (including low-density lipoprotein [LDL], high-density lipoprotein [HDL]), if available
- Smoking status
- Family history
- Sedentary life style
- Obesity (BMI, waist hip ratio)
- Cerebrovascular and peripheral arterial disease (PAD)
- Ankle brachial index (ABI)

V.B. Randomization and Enrollment

Once a participant has consented to participate in the trial, participant information will be entered into the database. If a patient is a screen failure, the data that has been collected up until this point for the patient for screening purposes will be entered into the case report forms (CRF) in the electronic data capture (EDC) system. No additional information will be collected after this point for such a patient.

For eligible participants, medical history data will be captured in the EDC. In addition, sites will need to specify the intended first test which would be performed if the participant is randomized to the usual care arm. The participant will then be randomized to either the usual care arm or the precision evaluation arm. Once randomization occurs, the participant is considered enrolled in the study. If randomized to the precision evaluation arm, participants will be further assigned to guideline-

recommended without planned testing or cCTA with selective FFR_{CT}.

V.C. Participant Cohort Assignment

Participant will be randomized to either the usual care arm or the precision evaluation arm within 14 days of screening.

Usual Care Arm
Participants randomized to the usual care arm will undergo either noninvasive stress testing (exercise electrocardiogram, stress nuclear imaging including PET, stress MR, or stress echocardiogram), with the specific modality at the discretion of the participant's clinician, or invasive catheterization. In all participants in the usual care arm, cCTA is prohibited as a subsequent test for the first 45 days after randomization.

Precision Evaluation Arm
Participants randomized to the precision evaluation arm will be assigned a management approach based on their PROMISE Risk Score, a risk model based on pre-test clinical characteristics derived from the PROMISE trial and validated in SCOT-HEART[34] or the presence of known non- obstructive atherosclerosis. Participants will be assigned to either 1) guideline-recommended medical management without planned testing (low risk) or 2) cCTA with selective FFR_{CT} (elevated risk or those with known plaque. independent of the PROMISE Risk Tool assessment). Participants assigned to the strategy of guideline-recommended medical management without planned testing will be treated with risk-appropriate preventive care and symptom control (including therapeutic trials of anti-anginal medications). Participants and their providers will be provided informational materials demonstrating the safety of this strategy based on pre-test probabilities and the PROMISE Risk Score. Participants with intractable symptoms despite maximal medical management whose clinicians opt for further testing (crossovers) will undergo cCTA with selective $FFR_{CT.}$

Participants undergoing cCTA as the initial test (both assigned or crossover) should have FFR_{CT} analysis ordered if cCTA shows at least one 30-90% stenosis in epicardial vessels of 2mm diameter or greater. Image sets will be sent promptly to HeartFlow for analysis and results will be returned to sites in < 24 hours to enable rapid incorporation into clinical decision making.

V.D. Participant Follow-Up

Participants will be followed up at 45 (+/-14) days and at 6 and 12 months (+/- 30 days) after enrollment. For US participants, follow-up at 45 days and at 6 and 12 months will be done by phone interviews conducted by the DCRI Outcomes Call Center, unless not allowed by their enrolling site. For participants outside of the US, follow-up will be conducted by the site coordinators.

Activities to be conducted at each follow up contact are described below and in the Schedule of Events.

45 (+/-14) day follow-up visit (in-person, portions may be done by phone) At the 45-day follow-up visit, participants will be asked the following:

- Assessment if any MACE has occurred since enrollment

- CV Update: Review and documentation of any cardiovascular diagnostic test, cardiovascular procedure, or hospitalizations/clinic visits due to cardiovascular symptoms and complications since enrollment
- Review and documentation of concomitant cardiovascular medication changes since enrollment
- Complete the following 3 questionnaires:
    - Seattle Angina Questionnaire
    - EQ-5D-5L Questionnaire
    - Participant Satisfaction Questionnaire
- Collection of the following:
    - Any cardiovascular test – both written report and test output
    - Any cardiovascular imaging – both written report and image file

6 months (+/-30 days) follow-up contact

At the 6-month follow-up contact, participants will be asked the following:

- Assessment if any MACE has occurred since the 45-day visit
- CV Update: Review and documentation of any cardiovascular diagnostic test, cardiovascular procedure, or hospitalizations/clinic visits due to cardiovascular symptoms and complications since last visit
- Review and documentation of concomitant cardiovascular medication changes since enrollment
- Complete the following 2 questionnaires:
    - Seattle Angina Questionnaire
    - EQ-5D-5L Questionnaire
- Collection of the following:
    - Any cardiovascular test – both written report and test output
    - Any cardiovascular imaging – both written report and image file

12 months (+/-30 days) follow-up contact

At the 12-month follow-up visit, participants will be asked the following:

- Assessment if any MACE has occurred since the 6-month visit/phone call
- CV Update: Review and documentation of any cardiovascular diagnostic test, cardiovascular procedure, or hospitalizations/clinic visits due to cardiovascular symptoms and complications since last visit
- Review and documentation of concomitant cardiovascular medication changes since enrollment
- Complete the following 2 questionnaires:
    - Seattle Angina Questionnaire
    - EQ-5D-5L Questionnaire
- Collection of the following:
    - Any cardiovascular test – both written report and test output
    - Any cardiovascular imaging – both written report and image file

V.E. Testing in precision evaluation arm for participants assigned to no immediate testing

Precision evaluation participants determined to be at very low risk and assigned to the strategy of guideline-recommended medical management with no immediately planned testing are highly

unlikely (by definition) to have significant obstructive CAD. The managing clinician is encouraged to treat them with guideline-recommended preventive care, anti-anginal medications and other medical therapy as deemed appropriate to their clinical circumstances. This is expected to control or eliminate symptoms in most participants. In the unlikely event that symptoms are intractable or accelerating, despite reasonable medical treatment or if other compelling reasons for additional evaluation are present, testing may be warranted.

Unless there are urgent or emergent indications to proceed with invasive testing, all such participants requiring testing should have a cCTA followed by selective FFR_{CT} rather than stress testing or elective invasive catheterization. cCTA with selective FFR_{CT} should only be pursued if the participant is having:

1. Unstable/accelerating symptoms (i.e. no longer falls into stable angina cohort)
2. Continued stable symptoms despite risk factor modification including:
    a) Optimized blood pressure control with goal <130/80 mmHg
    b) Optimized lipid management with high-intensity statin in appropriate patients
    c) Optimized diabetes management with blood glucose control in appropriate patients
    d) Antiplatelet therapy in appropriate patients
    e) Tobacco cessation in patients who smoke
    f) Lifestyle counseling regarding diet exercise and stress reduction
    g) Anti-anginal therapy including utilization of beta-blockers, calcium channel blockers, short and long-acting nitrates, and/or ranolazine

The assignment to no immediate testing is not time limited and is valid for the duration of the participant's enrollment in the trial. Testing in such participants should be infrequent and the reasons for this will be carefully documented and monitored.

V.F. Participant Withdrawal

In accordance with the Declaration of Helsinki, each participant is free to withdraw from the study at any time. Investigator(s) also have the right to withdraw participants from the study in the event of illness or other reasons concerning the health or wellbeing of the participant, or in the case of lack of cooperation. Should a participant decide to withdraw or should the investigator(s) decide to withdraw the participant, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. If possible, a complete final evaluation at the time of the participant's withdrawal should be made. The reason for withdrawal must be noted in the eCRFs.

V.G. Schedule of Assessments

	Screening	**Randomization Day 1**	**Day 45** (+/-14 d)	**6-mo.** (+/- 30d)	**12-mo.** (+/- 30d)
Informed consent	X				
Medical history	X				
Cardiovascular update [1]			X	X	X
Concomitant cardiovascular medications	X		X	X	X
Cardiovascular risk factors (including PROMISE minimal risk score data entry for randomization)	X				
Pregnancy test [2]	X				
Creatinine [3]	X				
Resting 12-lead ECG [4]	X				
QoL evaluation: SAQ, EQ5D-5L	X		X	X	X
Participant Satisfaction Questionnaire			X		
Randomization		X			
Initial diagnostic invasive or noninvasive test performed (if assigned)		Prior to 45 day visit			
Cardiac imaging/testing clinical report and image collection			X	X	X
Interval assessment for CV events and testing			X	X	X
Endpoint assessments			X	X	X

1. During cardiovascular update, if participants have received an additional diagnostic test, a cardiovascular procedure or have been hospitalized since the last visit, additional data will be collected
2. For a female participant of childbearing potential, a pregnancy test must be performed with negative results known within 7 days prior to randomization
3. Creatinine blood draw required only for participants without a recent normal value (most recent within previous 90 days)
4. Resting 12-lead ECG preferred in last 30 days (optional, clinical care only)

VI. ADDITIONAL ASSESSMENTS AND SUBSTUDIES

VI.A. Quality of Life Assessments

A short battery of instruments will be used to provide a relevant assessment of health-related quality of life that will capture the most likely health benefits to be associated with the precision strategy while not being burdensome to study participants. Quality of life (QoL) assessments will be conducted at baseline, 45 days, 6 months, and 12 months. Chest pain specific QOL will be assessed with the Seattle Angina Questionnaire (SAQ). While the full instrument has 19 items covering 5 dimensions of the impact of chest pain on QoL, we will use the scales for physical limitations, angina frequency, and disease perception/quality of life (14 items total)[1]. These three scales will also allow calculation of the recently described 7-item short SAQ[2]. The SAQ has been used as the primary disease-specific QoL outcome measure in a number of major clinical trials (including COURAGE, PROMISE, and ISCHEMIA) and is useful for this trial because it assesses chest pain and its impact on functioning and well-being regardless of whether the symptoms are due to coronary disease or are non-coronary. Since many participants in this study will be found not to have significant coronary disease and will be provided with that reassuring finding, the SAQ will allow us to assess the extent to which such information is associated with changes in the 3 dimensions noted above.

Overall health status will be assessed briefly using the EQ-5D-5L, a standardized generic measure that can also be used to link specific health states to general population-based utilities[5]. The EQ-5D-5L consists of two parts: (1) a descriptive assessment of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which can take one of five responses corresponding to the level of severity within each dimension, and (2) a self-rating 0- 100 "thermometer" of current health-related quality of life.

VI.B. Economic and Resource Utilization Assessments

The primary economic analyses in PRECISE will be performed from the perspective of the US health care system. Detailed information regarding the quantity and cost of health care services received by participants in each treatment group will be collected prospectively as part of the trial. Relevant health care resource consumption during initial testing through 1-year follow-up will be collected on the clinical trial electronic case report form (eCRF). (The cost of acute and non-acute hospital care will be derived from billing data collected from patients enrolled at US sites.) Physician and other outpatient care reported in the eCRF will be valued using secondary sources. Primary resource use and cost comparisons will be based on participants enrolled in the US. Secondary analyses will examine the consistency of treatment related differences in resource use in the US with the sites outside the US.

VI.C. Imaging and other Cardiac Assessments

For all participants in either arm in whom an invasive coronary angiogram is performed, procedural reports and angiographic images will be uploaded via the electronic data capture (EDC) system to create an angiographic image repository. In addition, the report, as well as imaging and / or graphic data from any procedures performed to assess stenosis significance or severity such as, FFR, iFR, IVUS, OCT should be uploaded. Similarly, for all participants receiving cCTA imaging, the cCTA images and reports will be uploaded via the EDC system to create an image repository. Invasive angiography will be evaluated by a core lab for QCA; other core lab(s) may be added to analyze

additional images.

VII. ENDPOINT DETERMINATION, SAFETY, AND MONITORING

VII.A. Primary Endpoint Definitions

Major Adverse Cardiovascular Events (all cause death, non-fatal myocardial infarction) All cause death

All cause death is defined as death resulting from any cause. In addition, the cause of death will be adjudicated, including cardiovascular death defined as death due to myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage, or death due to other cardiovascular causes[51].

Myocardial infarction

Acute myocardial infarction (MI) is defined as having evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Specifically, the Fourth Universal Definition[51] of type I MI is defined as:

Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and with at least 1 of the following:

- Symptoms of acute myocardial ischemia;
- New ischemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.*

cTn indicates cardiac troponin; ECG, electrocardiogram; URL, upper reference limit.

*Postmortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial hemorrhage, meets the type 1 MI criteria regardless of cTn values.

A complete definition of the criteria for MI can be found in the Fourth Universal Definition of Myocardial Infarction (2018). This definition will be followed for spontaneous as well as periprocedural MIs, for which the elevation in cTn must be at least cTn values >5 times the 99th percentile URL for PCI and >10 times for CABG related infarctions[51].

Cardiac catheterization without obstructive coronary artery disease (diameter stenosis <50%, any FFR >0.80 or iFR >0.89)

Cardiac catheterization without obstructive coronary artery disease will be defined as the absence of any ≥50% stenosis or hemodynamic indication of significance in any major epicardial vessel including side branches ≥2 mm in diameter, as determined by core-lab adjudicated QCA. The Steering Committee may consider the use of other validated NHPRS as they become clinically available. Equivalent cut points for each approved test will be determined

at that time.

VII.B. Secondary Endpoint Definitions

Hierarchical analysis

Finkelstein and Schoenfeld (FS) and Pocock's win ratio analysis of primary endpoint is defined in section VII B Statistical Analysis Plan.

Resource use

Resource use is defined as counts and types of baseline testing, follow up testing, diagnostic and therapeutic procedures, and both inpatient and outpatient care. Costs from the US perspective will be estimated.

Quality of Life Metrics

Quality of Life assessments to be completed by the participants are the Seattle Angina Questionnaire and the EQ-5D-5L.

Death

Death will be categorized as all-cause, cardiovascular, non-cardiovascular.

Myocardial infarction

Myocardial infarction will be characterized according to the 4th Universal MI definition for both spontaneous and for periprocedural MI[51] MIs.

Hospitalizations

All, cardiovascular, non-cardiovascular, and for progressive or unstable angina. Urgent and unscheduled hospitalizations for other cardiovascular causes that do not meet the criteria for the specific events listed above will be classified as hospitalization for other cardiovascular causes (e.g., hospitalization for cardiac chest pain that does not meet the criteria for MI, hospitalization for arrhythmias, hospitalization for pulmonary embolism). Non-cardiovascular hospitalization are defined as any hospitalization whose primary cause is not thought to be CV in nature.

Preventive medication use

Information on preventive medication use will be acquired at study entry and 45 days. Participants with a clear clinical indication for use of ASA/antiplatelet agents and or, statins eg: hyperlipidemia, diabetes, documented CAD, will be characterized according to use/nonuse for each medication class.

Radiation safety endpoint – cumulative dose at 1 year

The cumulative radiation exposure over the 12 months following enrollment will be calculated based on the participant's exposure to radiation for cardiovascular care from one or more of the following modalities. For cCTA, the administered radiation dose (computed tomography dose index volume and dose length product for cCTA) will be recorded by the individual sites. For stress nuclear imaging, the radiotracer dose(s) will be collected and converted to equivalent radiation doses for comparison to cCTA. For ICA, the radiation dose from fluoroscopy administered will be recorded by sites and converted using standardized approaches to allow for comparison to radiation from cCTA. In instances in which the information required to assess actual dose is not available, a standard

dose based on accepted average exposures will be imputed for that form of testing. Cumulative radiation exposure from additional cardiac testing and procedures during the entire follow-up period will also be collected.

Catheterization efficiency

The proportion of invasive cardiac catheterization patients who undergo revascularization (PCI or CABG) within 6 months of enrollment will be determined.

VII.C Testing Complications and Reporting

The study intervention is the implementation of a precision evaluation strategy compared to usual care evaluation in non-acute chest pain participants with no history of CAD or recent testing whose clinicians recommend non-emergent non-invasive testing or ICA. Since all trial procedures represent standard of care for the eligible study population, there are no specific safety events associated with investigative procedures in this trial. However, there are known complications from these clinically recommended tests and procedures which are outlined below. These complications will be reported by site personnel.

For Precision Evaluation Strategy

For Guideline-recommended Medical Management

While participants assigned to the guideline-recommended care with no planned testing arm will have exceedingly low risk of events and are predicted to derive minimal or no value from noninvasive testing[33, 34], there is a very small risk of missing left main or 3-vessel disease for which revascularization may be life-prolonging.

For cCTA with selective FFR_{CT}:

Mild contrast reaction such as rash and hives.

1. Severe contrast reactions including anaphylaxis or death occurring within 24 hours of contrast administration.
2. Extravasation of contrast into the surrounding tissue of the extremity where contrast was administered intravenously.
3. Symptomatic bradycardia or hypotension in relation to beta blockade or nitrates administered for cCTA.
4. Acute bronchospasm following beta blockade administered for cCTA.

For Usual Care (noninvasive or invasive testing)

For exercise testing including during stress echo or stress nuclear (including PET)**:**

1. Hypotension defined as systolic BP less than 80 mmHg or fall in systolic BP >20 mmHg
2. Stress-induced symptoms or ECG changes that do not resolve within 20 minutes
3. Rapid atrial fibrillation that does not slow or convert with standard interventions
4. Ventricular tachycardia
5. Hospital admission not otherwise captured by pre-specified study endpoints, due to one of the above

For stress nuclear (including PET)**:**

1. Any adverse reactions potentially related to the use of vasodilators such as adenosine, regadenoson, or dipyridamole

For stress echo:

1. Any stress-induced wall motion abnormality that does not resolve within 20 minutes
2. Any adverse reaction to echo contrast
3. Any adverse reaction to dobutamine, including sustained ventricular tachycardia or other tachyarrhythmias

For stress cardiac MRI:

1. Any adverse reactions potentially related to the use of vasodilators such as adenosine, regadenoson, or dipyridamole
2. Any adverse reaction to MRI contrast agents, including gadolinium-based agents

For cardiac catheterization:

1. Any adverse reactions potentially related to the use of sedatives, local anesthetics, contrast agent or other medication's
2. Any adverse reactions potentially related to arterial puncture and wire/catheter introduction
3. Any adverse reaction to coronary catheterization including dissection, embolization, stroke, malignant arrhythmias and asystole, and death

VII.D. Independent Clinical Event Adjudication Committee

An independent clinical event committee (CEC) will be responsible for the blinded review and adjudication of the primary endpoint. The CEC will settle any disputes with committee review and discussion. Any uncertainty regarding the finding of cardiac catheterization without obstructive disease will prompt review of the original cardiac catheterization images for further independent adjudication. Collection of medical records and other documentation required for CEC reviews will be coordinated by the DCRI call center for US participants and by site coordinators for participants in all other regions.

VII.E. Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be appointed to monitor participant safety and to review study performance. The DSMB will periodically review the study data and assess participant safety and adherence to the study protocol. The DSMB will define the operating guidelines and processes for study evaluation, interim analyses, event triggers for unscheduled review; these will be agreed upon at the initial meeting of the DSMB. Periodic reports will be prepared by HeartFlow (or its designee) for the DSMB on based on the operational plan outlined by the DSMB charter. The DSMB will make its recommendations to the study Steering Committee and the sponsor following their meeting.

VIII. Statistical Methods

Separate, complete Statistical Analysis Plan (SAP) documents will be prepared for the clinical outcome analyses and the economics and quality of life (EQOL) outcomes.

VIII.A. Sample Size Determination and Statistical Power

Sample size and power calculations for this study are based on the hypothesis that the precision evaluation arm is superior to the usual care arm on the time-to-first event of the composite MACE endpoint (defined as: all-cause death, non-fatal MI) or invasive cardiac catheterization without obstructive CAD (obstructive CAD defined as diameter -stenosis ≥50%, FFR≤0.80 or iFR ≤0.89). Time to event analysis will use the date of the event, including the date of catheterization which is used to determine the absence of obstructive CAD. Assuming 10% of usual care participants will receive angiography as a first test results in an 8% primary endpoint event rate at 1 year in the usual care group and 5% (absolute) event rate in the precision care group (i.e., 37.5% relative effect size) with an estimated ~20% assigned to guideline-recommended care with symptom management and no planned testing. Assumptions used in the primary endpoint event rate calculations (i.e. 8% vs. 5%) were: an overall ~10% will not receive randomized testing and within the precision evaluation arm, 30% of those assigned to guideline-recommended care will cross over to cCTA with selective FFR_{CT}.

Enrolling 1050 patients per group (2100 total participants) would provide at least 90% power to detect a relative risk reduction of 37.5% in the precision evaluation arm. Sample size calculations are based on the log-rank test[52] with 12-month accrual period, a 12-month follow-up in all participants , 10% attrition rate (i.e., lost to follow- up, dropouts) and a two-sided type I error rate of 0.05.

1-yr event rate in precision evaluation arm	Power	Total number of participants needed	Total number of cath and MACE needed
5% (37.5% effect size)	85%	1792	173
	90%	**2096**	**202**
	95%	2592	250

Table shows total number of participants needed for 85%, 90% and 95% power. Although, this is not an event-driven study, the table also provides total number of cath and MACE needed.

Power curves (**Figure: Long-Rank for Two Survival Curves**) provide total sample size needed for several relative effect size (i.e., 1-hazard ratio) scenarios.

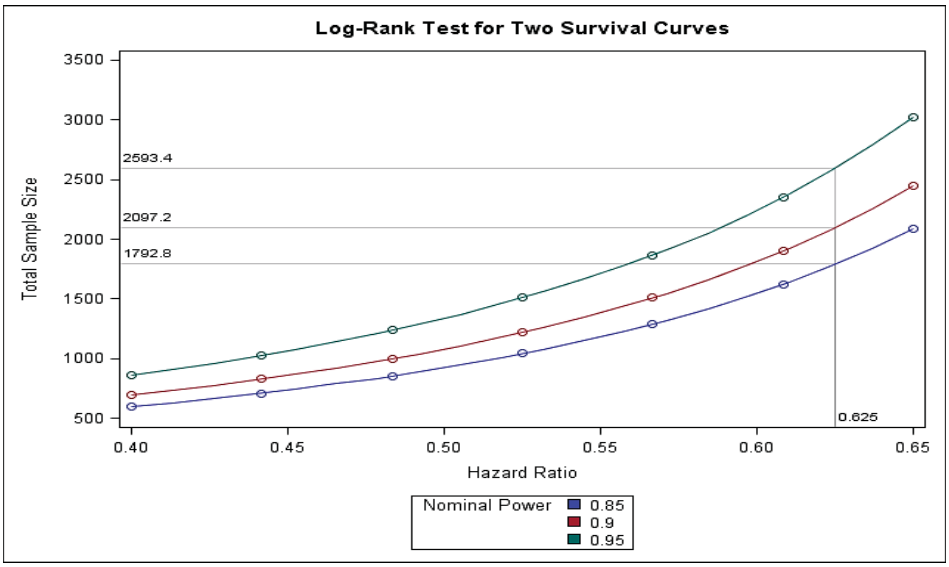


Figure: Long-Rank for Two Survival Curves

VIII.B. Statistical Analysis Plan

Analysis of the Primary Endpoint

The primary endpoint of this study is based on time-to-first occurrence of any of the components, which is defined as a composite of MACE (all-cause death, non-fatal MI) or invasive cardiac catheterization without obstructive CAD (obstructive CAD defied as diameter stenosis ≥50%, FFR≤0.80, or iFR≤0.89) over 12-month follow-up. The time from randomization to the first event among the components of the primary endpoint will be measured (in days) for those who experienced an event and calculated as the date of the first event minus the date of randomization. For participants who do not experience any of the primary endpoint component events or who withdraw consent or drop out of the study before experiencing an event, time from randomization to the date of last contact will be used in the analysis, and those participants will be considered as censored observations in the time-to-event analysis.

The primary and secondary endpoint comparisons between the randomized groups in this study will be performed according to the principle of "intention-to-treat" (ITT); that is, participants will be analyzed according to the treatment arm to which they were randomized, regardless of subsequent crossover or post-randomization strategy.

The log-rank test[53] will be the primary analytic tool for statistically assessing outcome differences between the two randomized treatment strategies with respect to the primary composite endpoint. Cox proportional hazards model[54] will be used to estimate the hazard ratio (HR) and 95% confidence interval (CI) summarizing the difference in outcome between the two randomized arms, using treatment as the only predictor in the model. Proportionality assumption in the Cox model (i.e., constant hazard over time) will be checked and tested.

Cumulative event rates will be calculated according to the method of Kaplan and Meier[55] for each randomized arm as a function of time from randomization, and the estimated event probabilities

will be displayed graphically. Adjusted HR and its 95% CI will be estimated using Cox proportional hazards model by including pre-specified baseline risk factors as covariates in the model.

A sensitivity analysis for the primary composite MACE (all cause death and non-fatal MI) or invasive cardiac catheterization without CAD (no coronary stenosis ≥50% according to QCA by core-lab adjudication or site interpretation if QCA is not available, or with FFR≤0.80, or instantaneous wave free ratio (iFR) ≤0.89) endpoint will be conducted using the method of "win-ratio"[56] and Finkelstein and Schoenfeld rank-test method[57]. More details on primary, secondary and sensitivity analyses will be provided in the complete Statistical Analysis Plan (SAP).

Subgroup analyses

Subgroup analyses will be performed to assess whether the intervention effect is consistent across all participants, or whether it varies according to specific participant characteristics. In particular, these analyses will focus on whether the relative intervention effect compared to usual care differs according to the following baseline variables:

- Low risk vs. elevated risk by PROMISE Risk score or presence of known non-obstructive atherosclerosis
- Intended first test: functional vs. invasive
- Sex (male vs. female)
- Age (<65, 65 to 74, and >75 years)
- History of diabetes
- Presentation: primary symptom (chest pain vs. other), SAQ angina score (daily/weekly angina at baseline versus less frequent)
- Geographic region (US, Canada, Europe, Other Regions)

These analyses will utilize the Cox model and will be accomplished by testing for interactions between the randomized treatment strategy and the specific baseline variables listed above. In addition to the formal assessment of treatment by covariate interactions, the effect of the treatment strategy characterized by a hazard ratio and 95% confidence interval will be calculated and displayed using a forest plot for the subgroups of participants defined by the variables listed above. These descriptive hazard ratios will be carefully interpreted in conjunction with the formal interaction tests.

The effect of the treatment strategy may also be examined in other subgroups of clinical interest in addition to those listed above.

Analysis of the Secondary Endpoints

The secondary endpoints listed in section III.C. Secondary Endpoints that are measured as time-to-event will be analyzed using the same statistical methods used for the primary efficacy endpoint (Section VI.A. Primary Endpoint Definitions). Specifically, the log-rank test will be the primary analytic tool for statistically assessing mortality differences between the two randomized treatment strategies. A hazard ratio and 95% confidence interval summarizing the difference in outcome between the two randomized arms will be computed using the Cox model.

Participant deaths will be classified by the Clinical Events Committee (CEC) as to whether the mode of death was due to a cardiovascular (CV) cause. If insufficient source documents are obtained to allow CEC adjudication of the cause of death, and the CEC classifies the cause of

death as “unknown,” then the site-reported cause of death (if available) will be used. If neither the site nor the CEC can provide a classification of the cause of death, the death will not be considered as a cardiovascular death. As supplemental analyses, however, this endpoint will also be examined using (a) only the deaths classified by the CEC as cardiovascular, and (b) using deaths classified by the CEC as cardiovascular, but also including any deaths in the cardiovascular category that are classified as unknown by the CEC.

Competing risks methodology of Fine and Gray[58], where death due to a non-cardiovascular cause is considered as a competing risk. This methodology, rather than treating non-cardiovascular death as a censoring event, makes incidence use of the cumulative function, and is performed within the proportional hazards framework using the marginal failure sub-distribution associated with the event of interest (cardiovascular death). Similar analyses will be conducted for time-to- event endpoints in which death is not part of the endpoint of interest.

Analysis of Resource Use Endpoints

For the Economics outcomes, primary comparison will be at 12 months between treatment arms by intention-to-treat. All-cause hospitalizations, cardiovascular hospitalizations, ER visits not resulting in hospitalization, and major outpatient procedures will be enumerated. In addition, we will examine length of stay by intensity of care, numbers of CTAs, noninvasive stress tests (stress perfusion imaging, stress echocardiography, exercise electrocardiography, stress cardiac magnetic resonance imaging), invasive tests (invasive coronary angiography, invasive fractional flow reserve or equivalent, optical coherence tomography, intravascular ultrasound), coronary revascularization procedures (coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI), number of coronary stents), and cardiac medications (beta blockers, aspirin, statins, antiplatelet medications).

Confidence intervals for differences will be estimated using the bootstrap approach. Differences in resource use will be interpreted in the context of the trial clinical results, looking for both consistency and plausibility. Descriptive comparisons of intensity of care/resource consumption according to clinical variables defining subgroups of interest will be performed. The primary economic analyses will focus on the US enrollment and in secondary analyses, resource use patterns for all patients enrolled in the trial will be compared by intention-to-treat to develop an understanding of the degree to which treatment related differences in the trial are region dependent.

Analyses of Medical Costs

To compare medical costs between treatment arms, we must: 1) assign costs to all medical resources consumed during the study period; 2) compute mean costs by treatment group (defined by the principle of intention-to-treat); and 3) calculate the difference in mean costs between treatment arms and generate confidence intervals.

A) Derivation of Cost Estimates

The cost of US hospital-based care will be estimated by applying hospital-specific, revenue center level cost-to-charge ratios to empirical billing data collected during the study. This approach, which has been used successfully in numerous previous clinical trials including the PROMISE trial takes advantage of the objective, detailed account in hospital bills of services provided to patients and recalibrates hospital charges to more closely reflect costs. Based on experience in similar studies, we anticipate having complete billing data for 95% of patients treated in hospitals that generate bills. For patients without billing data (including patients outside US), we will impute costs using a generalized linear model developed using study data. In this model, the dependent variable will be

defined as total cost, and independent variables will include resource use elements available in the case report form, such as:

Number of hospitalized nights by intensity of care and number of relevant high cost procedures. Coefficients for model parameters will be estimated using study data of patients with complete costs and then used to predict costs for patients without billing information.

The cost of stays at non-acute care facilities will be estimated by multiplying the length of stay by the corresponding per-diem/reimbursement rate.

Costs for physician services will be estimated by mapping major inpatient and outpatient procedures and services recorded on the case report form to appropriate CPT codes in the Medicare Fee Schedule. We will also assign rounding fees for inpatient stays based on type of unit.

Costs for diagnostic testing procedures done in an outpatient or standalone facility will be derived from secondary sources available to the DCRI Outcomes Group at the time of study analysis.

The cost of medications of interest/relevance will be estimated on the basis of medication use recorded in the eCRF and unit costs by medication type and class, based on current estimates of acquisition cost.

B) Cost Comparisons

Primary statistical comparisons of costs between the two treatment groups will be performed using the intention-to-treat principle. A nonparametric partitioned estimator will be used to estimate diagnostic strategy-specific, 1-year medical costs with 4 partitions corresponding to follow-up intervals following randomization. Comparisons between the two testing strategies will be made using a normal approximation with standard errors estimated using the bootstrap approach. Bootstrapping will be performed using 10,000 repetitions, with percentile-based confidence intervals reported. The primary cost comparison will be made for cumulative costs at 12 months. The primary effect size will be the mean cost difference between the two arms with 95% confidence intervals. P values will be calculated for selective comparisons, with a “significant” p value equivalent to a 95% confidence interval that excludes 0. No adjustment in significance levels for multiple comparisons will be used.

Differences in cost will be interpreted in the context of the trial clinical results, looking for both consistency and plausibility. Costs will be presented both overall and by category (e.g., inpatient hospitalization, outpatient procedures, concomitant medications, non-acute institutional care). Hospitalizations will be classified as cardiovascular or non-cardiovascular by the Clinical Events Committee. For illustrative purposes, we will use bootstrap methods to plot the probability of a difference in total costs greater than arbitrary thresholds of interest (such as $500, $750, or $1000).

C) Cost Sensitivity Analyses

In secondary sensitivity analyses, we will compare resource use and costs between treatment groups in the US. In this manner, the effect of overall patterns of resource use in the US cohort versus ex-US on cost differences by treatment group can be assessed. We will also perform a per protocol analysis of costs.

Analyses of Quality of Life Outcomes

For each of the QOL measures examined in this study, we will provide simple descriptive and comparative analyses by intention-to-treat. To address the multiple comparisons problem arising from testing each individual scale and time point separately, we propose two complementary approaches. First, we will pre-specify the angina frequency scale from the SAQ as the primary QOL comparison of interest and assign all other comparisons to a secondary (supportive) status.

Second, we will use a repeated-measures mixed model with the baseline score as a covariate, Day 45, Month 6, and Month 12 responses included as outcome variables, and time as a fixed variable. Restricted maximum likelihood estimation will be used to model all available data from each participant without imputing missing values. An unstructured covariance matrix will be used.

Point estimates for each diagnostic strategy arm and strategy arm mean differences (precision strategy – usual care) with 95% confidence intervals (CIs) will be generated for each time point. The primary assessment will be based on the strategy arm difference at Month 12.
Additional analyses will examine the intervention effect at the other contact time points. Additionally, the intervention effect will be averaged across all the follow-up time points. The estimated intervention difference and 95% CIs will be obtained using the ESTIMATE Statement in SAS PROC MIXED.

We expect to have analyzable data on ≥95% of survivors at each follow-up interview, and, with 90%+ data collection (945+ patients per treatment group), consistent with our past performance in trials of this size and complexity and using similar methods, even accounting for loss of data due to death or incapacity, we should have 90% or greater statistical power to detect clinically significant differences in our major QOL measures.

Major QOL subgroups to be examined will be those prespecified for the clinical analysis of this trial. In addition, we will use baseline angina frequency from the SAQ to create a subgroup of participants with daily or weekly chest pain versus those with less frequent symptoms.

IX. ETHICAL CONSIDERATIONS AND RISK ANALYSIS

IX.A. Ethical Considerations

PRECISE will be conducted in accordance with the recommendations for human research from the 18th World Medical Assembly, Helsinki 1964. All potential sites will obtain Institutional Review Board (IRB) or Ethics Committee (EC) approval of the protocol, the associated consent form and any participant facing recruitment tools. Written informed consent will be obtained from each patient before any study procedures are performed. Patients will have the option to consent for the study after receiving a full explanation of the risks, benefits, and available diagnostic options, with the right to refuse participation. Clinicians will have the option to pursue alternative diagnostic pathways if they deem it to be in the best interest of the patient, with the reason for study protocol deviation documented. Participants can withdraw from the study at any time.

IX.B. Study Risks and Benefits

Potential Risks

Participation in PRECISE does not present any extra risks other than the risks associated with the clinically indicated care recommended by the participant's treating physicians to evaluate and treat symptoms suggestive of CAD. As all approaches included in the trial are recognized as standard of care, the risk associated with the trial can be described in detail by the treating physician.

Noninvasive diagnostic imaging is generally considered a safe and effective diagnostic approach. FFR_{CT} does not pose any additional risk to participants beyond the performance of cCTA itself. It

does offer the potential benefit to participants of the recognition of hemodynamically significant lesions (FFR ≤0.80 or iFR ≤0.89) that may not demonstrate anatomic significance (<50% diameter stenosis) and avoidance of unnecessary revascularization of ≥50% lesions that are not hemodynamically significant (FFR>0.80 or iFR >0.89).

The risks of guideline-recommended care without planned testing in the lowest risk participants has not been extensively studied prospectively. However, validation of the PROMISE Risk Tool in SCOT-HEART indicate that participants in this risk category have a CV death/MI event rate <1%/year, similar to the event rate observed in an age and sex matched US population. While the risk of guideline-recommended care without planned testing in the precision evaluation arm has not been quantified prospectively it is not expected to differ from the excellent outcomes noted above in such patients who do undergo testing. Further, participants with continued symptoms not controlled by medications will be permitted to cross over to the precision strategy arm and receive, cCTA with selective FFR_{CT}.

Potential Loss of Confidentiality

In any clinical trial, there is a possible risk of loss of confidentiality. To prevent this from occurring, HeartFlow has strict procedures in place to ensure that all study data are confidential and anonymized except as required for centralized follow-up data collection for the US, which will be performed by the DCRI Outcomes Call Center. For all data transferred from enrolling sites or from the Call Center, participants will be identified only by unique patient identifiers. Data transmitted will not contain any protected health information and participants will be identified only by unique patient identifiers. Data transmitted will not contain any protected health information. All applicable study data will be transferred in a secure manner and in accordance with applicable regulations.

Potential Benefits

The PRECISE results should improve the care of future patients recommended for additional evaluation for suspected significant CAD. In addition, the trial will deliver high-quality data on radiation exposure, incidental findings, and other clinically important “side effects” of the evaluation and management strategies that will be examined in a large real-world experience. All participants may benefit from increased contact with health care providers due to study-required visits.

X. DATA HANDLING AND QUALITY ASSURANCE

X.A. Completing and Signing Case Report Forms

Electronic CRFs will be employed. Trained site personnel or the trained DCRI Outcomes Group will enter data into the eCRFs. Data changes and corrections should be done within the electronic system. The audit trail will record all changes made, the date and time of the correction, the person making the change and a reason for the change. The appropriate electronic signature will be provided by the investigator as indicated.

X.B. Clinical Data Management

The sponsor or its designees will be responsible for the handling, processing, and quality control of the data in compliance with all applicable regulatory guidelines.

The training of clinical site personnel and the DCRI Outcomes Group on eCRF completion will be the responsibility of the sponsor or its designees. To ensure uniform data collection, a Case Report Form Guide will be created to assist with eCRF completion. All clinical site research coordinators will undergo site initiation training to become thoroughly familiar with the protocol, case report forms, and with methods of data verification.

X.C. Archiving of Data

All study documentation at the investigator site and sponsor site will be archived in accordance with ICH GCP. It is HeartFlow's policy to retain the data collected in this clinical study for a minimum of 5 years after termination of the study. Clinical sites will be asked to retain the data for at least 2 years following completion of the study or longer as required by local laws.

XI. STUDY MONITORING, AUDITING, AND INSPECTING

HeartFlow or its designees will monitor this clinical study to check the adequacy of clinical site staff and facilities, and to ensure adherence to the protocol, study procedures, and applicable regulations. In accordance with ICH E6 GCP guidelines, the clinical site monitor will also assess proper eCRF completion and source document retention. The investigator and clinical site staff are expected to provide adequate space for monitoring visits and to allocate sufficient time to permit adequate review of the study's progress. The investigator will permit study-related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source data/documents and study-related facilities (e.g., pharmacy, diagnostic testing and laboratories).

XI.A. Study Monitoring

Study monitoring will be performed in accordance with ICH E6GCP, this protocol, and applicable local regulations. A Clinical Monitoring Plan will be written at the outset of the study to provide project-specific operational guidelines for the clinical monitoring process and procedures, define responsibilities of the Site Management/Monitoring Team, which will in turn ensure the quality and integrity of data collected.

XI.B. Auditing and Inspecting

HeartFlow quality assurance personnel and/or their designee(s) may conduct audits at the study site(s). Audits may include, but not be limited to: audit trail of data handling and processes, SOPs, presence of required documents, the informed consent process, and comparison of case report forms/database with source documents. The investigator agrees to accommodate and participate in audits conducted at a reasonable time in a reasonable manner, as needed.

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Summary of Protocol Amendments

Amendment from version 1.0 dated June 29, 2018 to version 1.1 dated July 31, 2018

Section	Version 1.0	Version 1.1
Table of Contents	Sections listed	Sections listing updated based on the changes
I. Study Synopsis Secondary Effectiveness Endpoints	#2. Resource use patterns (all patients) and medical costs (US patients) to 12 months	#2. Resource use patterns and medical costs
V. STUDY PROCEDURES V.A. Patient Screening for Eligibility (Exclusion Criteria)	#3. Noninvasive CV testing within 1 year (for suspected CAD)	#3. Noninvasive CV testing within 1 year (for suspected CAD), including coronary artery calcium score
V. STUDY PROCEDURES V.D. Participant Follow-Up (D45)	45 (+/-14) day follow-up visit (in-person)	45 (+/-14) day follow-up visit (in-person, portions may be done by phone)
V. STUDY PROCEDURES V.D. Participant Follow-Up (D45, 6M and 12M)	Review and documentation of concomitant medication changes since enrollment	Review and documentation of concomitant cardiovascular medication changes since enrollment
V. STUDY PROCEDURES V.D. Participant Follow-Up (24M)	NA	Collection of the following: • Any cardiovascular test – both written report and test output • Any cardiovascular imaging – both written report and image file
V.I. ADDITIONAL ASSESSMENTS AND SUBSTUDIES V.I.A. Quality of Life Assessments	Quality of life (QoL) assessments will be conducted at baseline, 45 days, 6 months and 12 months.	Quality of life (QoL) assessments will be conducted at baseline, 45 days, 6 months, 12 months, and 24 months.
VIII.B. Statistical Analysis Plan C) Cost Sensitivity Analyses	In secondary sensitivity analyses, we will apply US unit costs to all resource use of all patients and compare costs between treatment groups across all patients enrolled in the trial.	In secondary sensitivity analyses, we will compare resource use and costs between treatment groups in the US.
XII. REFERENCES	References listed	References updated via EndNote

Amendment from version 1.1 dated July 31, 2018 to version 1.2 dated September 10, 2018

Section	Version 1.1	Version 1.2
Table of Contents	V.E. Cross Over Participants	V.E. Testing in precision evaluation arm for participants assigned to no immediate testing
I. Study Synopsis – Study Design and Methods	All subsequent decisions in the usual care arm regarding additional testing, medications, and/or procedures will be at the discretion of the responsible clinical care team; the use of cCTA as the initial diagnostic strategy is not allowed in the usual care arm. **Usual Care:** For participants randomized to usual care, the participant's care team will select the specific noninvasive stress test (exercise electrocardiogram, stress nuclear imaging [including PET], stress MR, or stress echocardiogram); OR invasive test: (direct to diagnostic catheterization). The use of cCTA as the initial diagnostic strategy is explicitly excluded in this arm.	All subsequent decisions in the usual care arm regarding additional testing, medications, and/or procedures will be at the discretion of the responsible clinical care team; the use of cCTA as the initial diagnostic strategy is not allowed in the usual care arm and prohibited as a subsequent test for the first 45 days after randomization. **Usual Care:** For participants randomized to usual care, the participant's care team will select the specific noninvasive stress test (exercise electrocardiogram, stress nuclear imaging [including PET], stress MR, or stress echocardiogram); OR invasive test: (direct to diagnostic catheterization). The use of cCTA as the initial diagnostic strategy is explicitly excluded in this arm and prohibited as a subsequent test for the first 45 days after randomization.
I. Study Synopsis - Sample Size Considerations	Assumed rates are based on 30% assigned to guideline- recommended care with symptom management and no planned testing (within which 30% will cross over to cCTA with selective FFR_{CT}); and overall 10% will not receive assigned testing; enrolling 1050 participants per group (2100 total participants) would provide at least 90% power to demonstrate superiority accounting for 10% attrition rate.	Assumed rates are based on 20% assigned to guideline-recommended care with symptom management and no planned testing (within which 30% will cross over to cCTA with selective FFR_{CT}); and overall 10% will not receive assigned testing; enrolling 1050 participants per group (2100 total participants) would provide at least 90% power to demonstrate superiority accounting for 10% attrition rate.

III.A. Prior Literature and Studies – Rationale and Evidence for Incorporation of a Strategy of Guideline-Recommended Care without Planned Testing in Low Risk patients	The Risk Tool developed using the PROMISE cohort employs 10 readily available clinical variables and has been validated in the SCOT-HEART population[33, 34]	The Risk Tool developed using the PROMISE cohort employs 10 readily available clinical variables (such as tobacco usage, ethnicity/race, and age) and has been validated in the SCOT-HEART population[33, 34]
IV.E. Rationale for Selection of Testing in Each Arm – Usual Care Arm	The use of cCTA is explicitly excluded as the initial diagnostic strategy in this arm.	The use of cCTA is explicitly excluded as the initial diagnostic strategy in this arm and prohibited as a subsequent test for the first 45 days after randomization.
IV.F. Randomization Method	Risk will be classified by a risk tool using pre-test clinical characteristics derived in the PROMISE trial and validated in SCOT-HEART.	Risk will be classified by a risk tool using pre-test clinical characteristics (including tobacco usage, ethnicity/race, and age) derived in the PROMISE trial and validated in SCOT-HEART.
IV.F. Randomization Method	The use of cCTA is explicitly excluded as the initial diagnostic strategy in this arm.	The use of cCTA is explicitly excluded as the initial diagnostic strategy in this arm and prohibited as a subsequent test for the first 45 days after randomization.
V.C. Participant Cohort Assignment – Usual Care Arm	Performance of cCTA as the initial test is excluded in this arm.	Performance of cCTA as the initial test is excluded in this arm and prohibited as a subsequent test for the first 45 days after randomization.
V.E Cross over in precision evaluation arm participants	Section title: Cross over in precision evaluation arm participants Previous text deleted and replaced	Section title: Testing in precision evaluation arm for participants assigned to no immediate testing New text

VIII.A. Sample Size Determination and Statistical Power	Assuming 10% of usual care participants will receive angiography as a first test results in an 8% primary endpoint event rate at 1 year in the usual care group and 5% (absolute) event rate in the precision care group (i.e., 37.5% relative effect size) with 30% assigned to guideline-recommended care with symptom management and no planned testing.	Assuming 10% of usual care participants will receive angiography as a first test results in an 8% primary endpoint event rate at 1 year in the usual care group and 5% (absolute) event rate in the precision care group (i.e., 37.5% relative effect size) with 20% assigned to guideline-recommended care with symptom management and no planned testing.

Amendment from version 1.2 dated September 10, 2018 to version 1.3 dated November 21, 2018

Section	**Version 1.2**	**Version 1.3**
Throughout protocol	Non hyperemic pressure ratio (NHPR) … NHPR… NHPR <0.90	Instantaneous wave free ratio (iFR) … iFR… iFR ≤0.89
I. Study Synopsis – Primary Endpoint	Time to a composite of: MACE (all cause death, non-fatal MI) or invasive cardiac catheterization without obstructive CAD (obstructive CAD defined as diameter stenosis ≥50% according to clinical site interpretation, FFR≤0.80, or NHPR<0.90) at one year (intention to treat)	Time to a composite of: MACE (all cause death, non-fatal MI) or invasive cardiac catheterization without obstructive CAD (obstructive CAD defined as diameter stenosis ≥50% according to core-lab adjudicated quantitative coronary analysis (QCA), FFR≤0.80, or iFR≤0.89) at one year (intention to treat)
I. Study Synopsis – Inclusion Criteria	Stable typical or atypical symptoms suspicious for coronary artery disease with further non-emergent testing or elective catheterization recommended to evaluate the presence of suspected coronary artery disease Safe performance of cCTA: Creatinine clearance ≥45 ml/min For a female participant of childbearing potential, a pregnancy test must be performed with negative results known within 7 days prior to randomization	Stable typical or atypical symptoms suggesting possible coronary artery disease (CAD) with further non-emergent testing or elective catheterization recommended to evaluate the presence of suspected CAD. Stable chest pain includes those who have fully been ruled out for Acute Coronary Syndrome (ACS) and for whom elective testing is recommended, regardless of the venue in which they are seen. Safe performance of cCTA: Creatinine clearance ≥45 ml/min per most recent measurement within 90 days For a female participant of childbearing potential (those who have not been surgically sterilized or are not postmenopausal), a pregnancy test

		must be performed with negative results known within 7 days prior to randomization
I. Study Synopsis – Exclusion Criteria	3. Noninvasive or invasive CV testing for CAD within 1 year 4. Lifetime history of any obstructive CAD (no prior CABG or PCI, stenosis ≥505) or known EF ≤40% or moderate to severe valvular or congenital cardiac 5. Contraindications to cCTA including but not limited to estimated creatinine clearance (GFR) <45 m/min measured within 90 days. 6. Exceeds local weight or size limit for cCTA or cardiac catheterization	3. Noninvasive or invasive CV testing within 1 year (for suspected CAD). CV testing for CAD refers to any stress tests, ICA and cCTA (including calcium scoring) only. Resting ECG and resting echocardiogram are not exclusionary. 4. Lifetime history of known obstructive CAD (prior myocardial infarction, CABG or PCI, stenosis ≥50%), known EF ≤40% or other moderate to severe valvular or congenital cardiac disease. 5. Contraindications to cCTA including but not limited to creatinine clearance (GFR) <45 ml/min as per most recent measurement taken within 90 days. 6. Exceeds the site's weight or size limit for cCTA or cardiac catheterization
IV.B. Primary Objective and Endpoints	The primary endpoint is a composite of: MACE (all cause death and non-fatal MI) or invasive cardiac catheterization without CAD (no coronary stenosis ≥50%, or with FFR≤0.80, or non-hyperemic pressure ratio (NHPR) <0.90). The primary study hypothesis will be tested at one year using an intention to treat analysis	The primary endpoint is a composite of: MACE (all cause death and non-fatal MI) or invasive cardiac catheterization without CAD (no coronary stenosis ≥50% according to QCA by core-lab adjudication, or with FFR≤0.80, or instantaneous wave free ratio (iFR) ≤0.89). The primary study hypothesis will be tested at one year using an intention to treat analysis
IV.G. Diagnostic Evaluations and Subsequent Care – Description of Evaluations to be performed	A pregnancy test will be required for female participants of childbearing potential, and a creatinine blood test will be required for participants without a recent normal value (within previous 90 days).	A pregnancy test will be required for female participants of childbearing potential (those who have not been surgically sterilized or are not postmenopausal), and a creatinine blood test will be required for participants without a recent normal value (most recent measurement taken within previous 90 days).

IV.G. Diagnostic Evaluations and Subsequent Care – Subsequent Care		Added text: For patients in the Precision Evaluation Arm, ICA cannot be performed unless one of the following criteria are met: • Any stenosis ≥90% identified by cCTA • Left Main stenosis ≥30% identified by cCTA • Plaque rupture identified by cCTA • Lesion-specific FFR_{CT} ≤0.85 in vessels with reference vessel size 2.0mm or greater in diameter
V.A. Patient Screening for Eligibility – Screening visit (in-person)	At the screening visit, patients will undergo the following: ... Pregnancy test (for females of child-bearing potential) …	At the screening visit, patients will undergo the following: … Pregnancy test (for females of child-bearing potential – those who have not been surgically sterilized or are not postmenopausal) …
V.A. Patient Screening for Eligibility – Inclusion Criteria	2. Stable typical or atypical symptoms suggesting possible coronary artery disease (CAD) with further non-emergent testing or elective catheterization recommended to evaluate the presence of suspected CAD. 3. Safe performance of cCTA: a. Creatinine clearance ≥45 ml/min b. For a female participant of childbearing potential, a pregnancy test must be performed with negative results known within 7 days prior to randomization	2. Stable typical or atypical symptoms suggesting possible coronary artery disease (CAD) with further non-emergent testing or elective catheterization recommended to evaluate the presence of suspected CAD. Stable chest pain includes those who have fully been ruled out for Acute Coronary Syndrome (ACS) and for whom elective testing is recommended, regardless of the venue in which they are seen. 3. Safe performance of cCTA: a. Creatinine clearance ≥45 ml/min per most recent measurement within 90 days

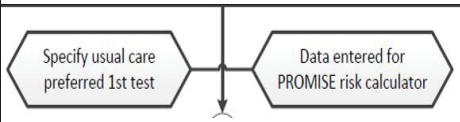
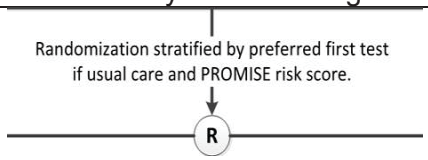
		b. For a female participant of childbearing potential (those who have not been surgically sterilized or are not postmenopausal), a pregnancy test must be performed with negative results known within 7 days prior to randomization
V.A. Patient Screening for Eligibility – Exclusion Criteria	1. Acute chest pain 2. Unstable clinical status 3. Noninvasive CV testing within 1 year (for suspected CAD), including coronary artery calcium score 4. History of known obstructive CAD (prior myocardial infarction, CABG or PCI, stenosis ≥50%), known EF≤40% or other moderate to severe valvular or congenital disease 5. Contraindications to cCTA including but not limited to estimated creatinine clearance (GFR) <45 ml/min 6. Any condition leading to possible inability to comply with the protocol 7. Exceeds the weight or size limit for cCTA or cardiac catheterization at the site 8. Life expectancy less than 2 years due to non-cardiovascular comorbidities 9. Enrolled in an investigational trial that involves a non-approved cardiac drug or device which has not reached its primary endpoint 10. Any condition that might interfere with the study procedures or follow-up	1. Acute chest pain 2. Unstable clinical status 3. Noninvasive or invasive CV testing within 1 year for suspected CAD, CV testing refers to stress tests, ICA, and cCTA (including coronary artery calcium score) only. Resting ECG and resting echocardiogram are not exclusionary. 4. Lifetime history of known obstructive CAD (prior myocardial infarction, CABG or PCI, coronary artery stenosis ≥50%), known EF≤40% or other moderate to severe valvular or congenital cardiac disease 5. Contraindications to cCTA including but not limited to creatinine clearance (GFR) <45 ml/min as per most recent measurement taken within 90 days 6. Exceeds the site's weight or size limit for cCTA or cardiac catheterization 7. Any condition leading to possible inability to comply with the protocol procedures and follow-up 8. Any condition that might interfere with the study procedures or follow-up 9. Enrolled in an investigational trial that involves a non-approved cardiac drug or device which has not reached its primary endpoint 10. Life expectancy less than 2 years due to non-cardiovascular

		comorbidities
VII.A. Primary Endpoint Definitions – Cardiac catheterization without obstructive coronary artery disease (diameter stenosis <50%, any FFR >0.80 or NHPR ≥0.90)	Cardiac catheterization without obstructive coronary artery disease will be defined as the absence of any ≥50% stenosis or hemodynamic indication of significance in any major epicardial vessel including side branches ≥2 mm in diameter, as determined by the clinical site interpretation.	Cardiac catheterization without obstructive coronary artery disease will be defined as the absence of any ≥50% stenosis or hemodynamic indication of significance in any major epicardial vessel, including side branches, ≥2 mm in diameter, as determined by core-lab adjudicated QCA or invasive FFR or iFR.
II.B. Secondary Endpoint Definitions	Myocardial infarction Myocardial infarction will be characterized according to Universal MI definition subtypes as Type 1, 2, 3, 4a, 4b, 4c, and 5.	Myocardial infarction Myocardial infarction will be characterized according to the 4th Universal MI definition for Spontaneous MI and the SCAI definition for periprocedural MIs.

Amendment from version 1.3 dated November 21, 2018 to version 1.4 dated February 1, 2019

Section	Version 1.3	Version 1.4
VII.A. Primary Endpoint Definitions – Myocardial infarction	Acute myocardial infarction (MI) is defined as having evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia[51]. Specifically, MI is defined as having: 1) Typical rise and/or gradual fall in cardiac biomarker level (cardiac troponin preferred) with values exceeding the 99th percentile of the institutional upper limit of normal (ULN) (generally 2x the ULN) AND either: 2) Clinical presentation defined as typical cardiac ischemic type pain/discomfort or dyspnea felt to be due to ischemia and consistent with the diagnosis of myocardial ischemia and infarction	Acute myocardial infarction (MI) is defined as having evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Specifically, the Fourth Universal Definition[51] of type I MI is defined as: Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and with at least 1 of the following: • Symptoms of acute myocardial ischemia; • New ischemic ECG changes; • Development of pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; • Identification of a coronary thrombus by angiography

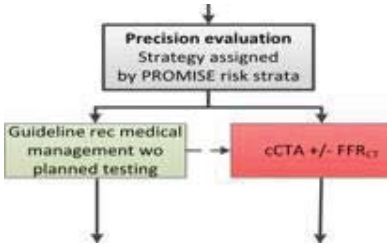
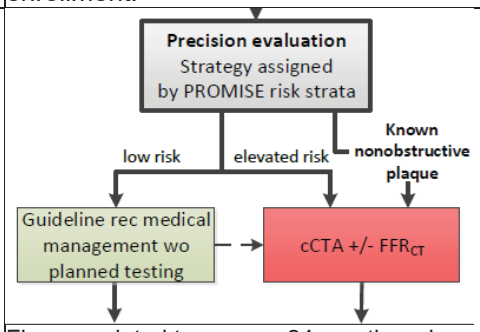
	Or 3) ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy and left bundle branch block) including evolving ST elevation, ST depression, T-wave changes, new pathological Q-waves (R waves in V1-2) in at least two consecutive leads or new left bundle branch block. A complete definition of the criteria for MI can be found in the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials[51]. Peri-procedural infarctions are defined as greater than 3x ULN for serum CK-MB for PCI and greater than 5x ULN for CABG.	including intracoronary imaging or by autopsy* cTn indicates cardiac troponin; ECG, electrocardiogram; URL, upper reference limit. *Postmortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial hemorrhage, meets the type 1 MI criteria regardless of cTn values. A complete definition of the criteria for MI can be found in the Fourth Universal Definition[51] of Myocardial Infarction (2018). The exception will be for peri-procedural myocardial infarctions, which are defined as biomarker elevation ≥10 times the upper reference limit (URL) for creatine kinase MB (CKMB) and/or ≥70 URL for troponin as outlined in the most recent SCAI (Society for Cardiovascular Angiography and Interventions) definition[60].
Table of Abbreviations	Not applicable	CAC: Coronary Artery Calcium added
Table of Abbreviations	Not applicable	SCAI: Society for Cardiovascular Angiography and Interventions
Exclusion criteria	Not applicable	New exclusion criteria #11 added: 11. Known CAD by coronary calcium presence, either by prior CAC scoring or definite coronary calcium reported on a non-cardiac chest CT scan.
Secondary Effectiveness Endpoints	Proportion of invasive cardiac catheterization patients who undergo revascularization (PCI or CABG) within 6 months of enrollment	“Invasive cardiac catheterization” has been updated to invasive coronary angiogram. Proportion of invasive coronary angiogram patients who undergo revascularization (PCI or CABG) within 6 months of enrollment

V.D. Participant Follow-Up	For North American participants, follow-up after 45 days will be done by phone interviews conducted by the DCRI Outcomes Call Center.	Visit 45 day has been added along with further clarification on site participation: For North American participants, follow-up at 45 days and at 6, 12, and 24 months visits will be done by phone interviews conducted by the DCRI Outcomes Call Center, unless not allowed by their enrolling site.
IV.A Overview of PRECISE-Diagram	 Diagram from version 1.3.	 Diagram updated to provide clarification on the pre-randomization step.
Referral of precision evaluation on cCTA participants for FFR_{CT} determinations	Image sets showing at least one 30-90% stenosis in epicardial vessels of 2mm diameter or greater will be….	Language updated to “should” from “will”: Image sets showing at least one 30-90% stenosis in epicardial vessels of 2mm diameter or greater should be …….
IV.G. Diagnostic Evaluations and Subsequent Care	For patients in the Precision Evaluation Arm, ICA cannot be performed unless at least one of the following criteria are met:	With this amendment, the language has been softened from “cannot” to “should not”: For patients in the Precision Evaluation Arm, ICA should not be performed unless at least one of the following criteria are met:
IV.E. Rationale for Selection of Testing in Each Arm	Use of cCTA as the initial diagnostic strategy is specifically excluded in the usual care strategy arm and prohibited as a subsequent test for the first 45 days after randomization	With this amendment, “or a calcium score” has been added to the protocol. Use of cCTA or a calcium score as the initial diagnostic strategy is specifically excluded in the usual care strategy arm and prohibited as a subsequent test for the first 45 days after randomization

IV.E. Rationale for Selection of Testing in Each Arm	The intervention in PRECISE will triage patients into two risk groups who will be assigned to receive either guideline-recommended medical management without planned testing or cCTA with selective FFR_{CT}	"Including no CAC" language has been added with this amendment: The intervention in PRECISE will triage patients into two risk groups who will be assigned to receive either guideline- recommended medical management without planned testing (including no CAC) or cCTA with selective FFR_{CT}
V.C Participant Cohort Assignment	Performance of cCTA as the initial test is excluded in this arm and prohibited as a subsequent test for the first 45 days after randomization.	With this amendment, "or a calcium score" has been added to the protocol. Performance of cCTA or a calcium score as the initial test is excluded in this arm and prohibited as a subsequent test for the first 45 days after randomization.
V.C Participant Cohort Assignment	Participants will be assigned to either guideline-recommended medical management without planned testing (low risk) or cCTA with selective FFR_{CT} (elevated risk).	"Including no CAC score" has been added: Participants will be assigned to either guideline-recommended medical management without planned testing (low risk) including no CAC score or cCTA with selective FFR_{CT} (elevated risk).
References- 51 and 60	Reference 51 51. Hicks KA, Mahaffey KW, et al.	Reference 51 is updated and reference 60 is added with the new amendment v1.4: 51.Thygesen K, Alpert JS, et al 60. Moussa ID, Klein LW, et al

Amendment from version 1.4 dated February 1, 2019 to version 1.5 dated October 15, 2019

Section	**Version 1.4**	**Version 1.5**
Investigator Protocol Signature Page	NA	Included separate line for PI signature
Table of Abbreviations	NA	AG: Agatston units
Table of Abbreviations	DECISION: Decisive Evaluation of Cardiac Ischemia, Symptoms and Revascularization	Removed
Table of Abbreviations	HU: Hounsfield units	Removed

IV. Study Overview and Objectives - Study duration	The anticipated total duration of the PRECISE study will be approximately 48 months for start-up, enrollment, follow up, and close out. Participants will be followed for 24 months after enrollment.	Overall study duration reduced to 36 month and patient follow up to 12 month after enrollment. "The anticipated total duration of the PRECISE study will be approximately 36 months for start-up, enrollment, follow up, and close out. Participants will be followed for 12 months after enrollment."
IV.A. Overview of PRECISE – figure of the trial design		 Figure updated to remove 24 month and co-primary endpoints of DECISION. Arrows leading to GRMT or cCTA annotated "low risk" and "elevated risk" respectively. Patients with known nonobstructive coronary plaque or extensive coronary calcium randomized to the precision arm are mandated to undergo cCTA +/- FFR_{CT}, independent from PROMISE risk score strata.
IV.B. Primary Objective and Endpoints	Per the exclusion criteria, any previous noninvasive or invasive CV diagnostic testing for suspected CAD must have been >1 year prior to enrollment. Patients with known obstructive CAD (prior myocardial infarction, CABG or PCI, any stenosis ≥50%) are ineligible for PRECISE.	Replaced with: "Patients with known nonobstructive coronary plaque or extensive coronary calcium randomized to the precision arm are mandated to undergo cCTA +/- FFR_{CT}, independent from their PROMISE risk score strata."
IV.C. Secondary Endpoints	Endpoints will be assessed at 45 days, 6 months, 1 year and 2 years.	Removed secondary endpoint assessment at 2 years: "Endpoints will be assessed at 45 days, 6 months and 1 year."
IV.C. Secondary Endpoints	9. PRECISE primary endpoint at 24 month	Removed PRECISE primary endpoint at 24 month