Statistical Analysis Plan

Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization (PRECISE)

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Summary of Changes

Date	Description
9/28/2020	• Initial version
7/07/2022	• Revisions for the final analysis o Database sources o Analysis population o Subgroups o Radiation o Outcomes in low and elevated o Sensitivity analysis o Prognostic assessment o Alternative Treatment Assignment Analyses

List of Abbreviations

ABI	Ankle-brachial Index
ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AHA	American Heart Association
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CAC	Coronary Artery Calcium
CAD	Coronary Artery Disease
CEC	Clinical Events Committee
CV	Cardiovascular
CI	Confidence Interval
CK-MB	Creatine Kinase-Myocardial Band
CMS	Centers for Medicare & Medicaid Services
COCATS	Core Cardiology Training Symposium
CPC	Colorado Prevention Center
CRF-NY	Cardiovascular Research Foundation
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
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
ITT	Intention-To-Treat
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
MM	Medical Monitor
MOP	Manual of Procedures
MPI	Myocardial Perfusion Imaging
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
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
SAP	Statistical Analysis Plan
ULN	Upper Limit of Normal

Table of Contents

1. Study Title

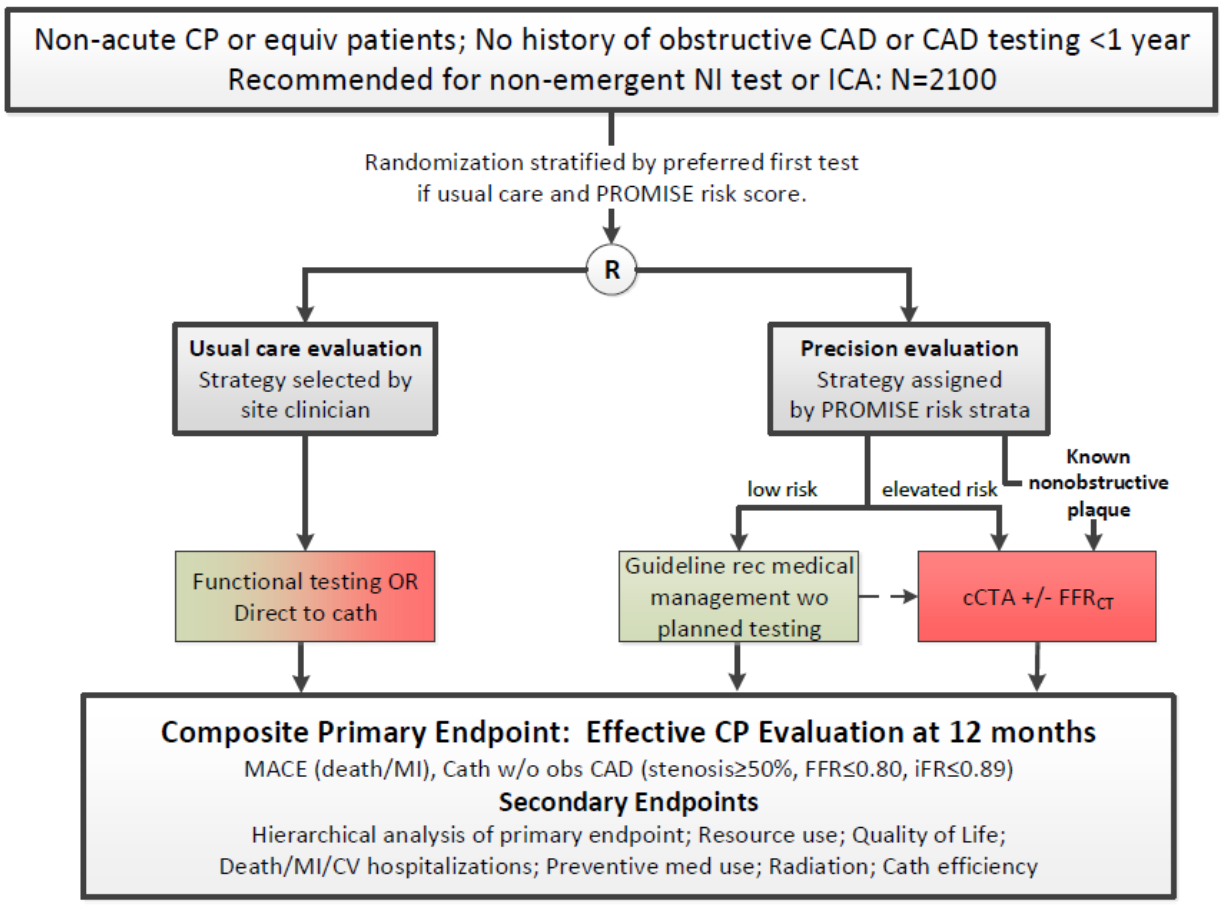
Prospective **R**andomized Trial of the Optimal **E**valuation of **C**ard**i**ac **S**ymptoms and R**e**vascularization (PRECISE).

2. Study Design

The study is a prospective, pragmatic, randomized clinical trial of the comparative effectiveness of diagnostic evaluation strategies for suspected stable CAD, performed in outpatient settings. Qualifying patients are those presenting with new symptoms suspicious for clinically significant CAD (and without known obstructive CAD), who are recommended for diagnostic testing and have not received any testing for cardiovascular ischemia with the past 12 months. Patients meeting these criteria will be randomized to an initial strategy of either precision care or usual care. The Usual Care Arm requires initial testing in all participants using either noninvasive testing (of the site's choice, including stress nuclear, stress echocardiography, stress MRI, or exercise ECG) or invasive testing (invasive coronary angiography) according to the pre-randomization intended testing strata. cCTA and calcium scoring are prohibited as a subsequent test for the first 45 days after randomization. Participants randomized to the Precision Evaluation Arm will be assigned to either no immediately planned testing, if Low Risk (see derivation below), or cCTA with selective FFR_{CT} if Elevated Risk or with known non obstructive atherosclerosis. If Low Risk participants develop a need for testing, such increasing angina, cCTA with selective FFR_{CT} must be used. All subsequent decisions in the usual care arm regarding additional testing, medications, and/or procedures are at the discretion of the responsible clinical care team.

See Figure 1 for a description of the participant flow.

Figure 1. Participant flow in the study.



3. Objectives

The primary objective of the PRECISE trial is to compare the clinical outcomes, downstream decision making regarding noninvasive testing and invasive angiography, and costs of using a precision care with a usual care strategy in participants with stable symptoms suggestive of coronary artery disease. The precision care will start with a pre-test risk assessment. Participants at low risk will be managed initially without cardiac diagnostic testing. Participants not at low risk and those with known atherosclerosis will undergo cCTA with selective FFR_{CT} as the initial evaluation. These results will inform the decision to use invasive coronary angiography. All participants in the trial will also receive guideline-recommended care with symptom and risk factor management.

This SAP contains definitions of analysis populations, derived variables, and details on the statistical methods for the analyses and summaries of study data for the PRECISE trial. This SAP will supersede the protocol in defining the trial endpoints and analysis plans. Mock ups of tables, figures, and data listings are contained in a separate document. A draft list of planned tables and

figures to be created from the final trial data sets can be found in section 10 of this document. Some of these tables and figures will be created as part of the Clinical Study Report and will not be duplicated in the Statistical Report. Details of the economic endpoints analyses are presented in a separate PRECISE Economics and QoL SAP.

4. Analysis Endpoints

4.1 Primary Endpoint

The PRECISE primary endpoint will be a composite of three participant outcomes and will be measured (in days) as the time to first occurrence during a 12 month (365 days ± 30 days) trial follow-up of: 1) all-cause death, 2) non-fatal myocardial infarction, (MI) or 3) invasive cardiac catheterization without obstructive CAD (obstructive CAD defined as diameter stenosis ≥50% according to core-lab adjudicated quantitative coronary angiography or site read in an epicardial vessel >2 mm, or FFR≤0.80 or iFR≤0.89). (See section 9.2 for more detail along with figure describing derivation of the cath catheterization component of the primary endpoint).

4.1.1 Secondary Endpoints

The following secondary endpoints will be assessed using Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995).

1. Hierarchical analysis of the primary endpoint using the unmatched win ratio method
2. Resource use patterns and medical costs (See PRECISE Economics and QoL SAPs)
3. QoL measured by the Seattle Angina Questionnaire (SAQ) summary score to assess angina-specific QoL, and the EuroQoL 5D (EQ-5D-5L) survey to assess overall (generic) health status (See PRECISE Economics and QoL SAPs)

4.1.2 Additional Protocol Specified Endpoints

Additional protocol-defined endpoints include:

1. Death, including separate analyses for all-cause and cardiovascular
2. Nonfatal MI, including separate analyses for all, procedural, and spontaneous
3. Hospitalizations, including separate analyses for all-cause, cardiovascular and for progressive or unstable angina.
4. Preventive medication use, defined as use of aspirin/anti-platelet drugs and/or statins, in participants with clinical indication for use
5. Cumulative trial strategy-related radiation exposure
6. Proportion of participants who undergo revascularization (PCI or CABG) within 6 months of diagnostic catheterization, overall, and controlling for rates of diagnostic catheterization.

4.2 Pre-specified Subgroup Analyses

4.2.1 Primary endpoint subgroup analyses

The following subgroup treatment/strategy comparisons will be conducted for the primary endpoint at 12 months as a forest plot with an interaction p-value.

1. Demographic and clinical subgroups

- Sex: Male/Female
- Age: <65, 65 to 74, ≥75 years
- Race/ethnicity:
    - White/non-Hispanic vs. other
- Risk score:
    - Low vs. elevated (All Participants);
    - Low vs. elevated (excluding known obstructive atherosclerosis);
    - Above and below PRECISE median score
      Risk score cut point based on the top 10% of low risk of the PROMISE Risk Score in the PROMISE cohort. Low Risk is defined as an absolute score >0.46 (see derivation in section 6.1 below).
- History of diabetes: Yes/No
- History of CAD/PAD/abnormal ABI: Yes/No
- Obesity: (BMI< 25, 25-30, >30)
- Geographic region: United States vs. Outside the United States

2. Intended first test is noninvasive vs. invasive
3. Symptoms and risk subgroups at presentation/randomization
    - Primary symptom presentation: 1) Typical Angina, 2) Atypical Pain, 3) Dyspnea, and 4) Non-Cardiac Pain/other
    - ESC modified Diamond-Forrester Pre Test Probability score (2019) with the population divided as <5% pretest probability, 5-15%, and >15%.
    - Tertiles of ASCVD risk score
        - SAQ angina score at presentation: More frequent angina (</= 80) vs. Rare/absent angina (>80)

5. Population Treatment Assignment for Analysis

5.1 Intention-To-Treat

All randomized participants will be evaluated according to the randomized group and assigned evaluation within that group (if any), regardless of testing or treatment received. Unless otherwise indicated, all primary summaries and analyses will be performed using this definition of treatment.

5.2 Per-Protocol

Clinicians have the option to pursue alternative diagnostic pathways if they deem it to be in the best interest of the participant, with the reason for study protocol deviation documented. The per-protocol treatment assignment is met when randomized participants received their initial evaluation as randomized. Trial participants who crossed over to the other randomized arm and those who were assigned to testing in either arm and who received no testing are excluded from analysis using this definition of treatment assignment. In addition, participants in whom all inclusion criteria were not present or in whom one or more exclusion criterion were present will be excluded from the per protocol population.

Per Protocol Definition

- Meets all inclusion/exclusion criteria
- Precision Care Participants
    - Low Risk
        - No testing OR
        - First test is a CTA
    - Elevated Risk
        - First test is a CTA
- Usual Care
    - No CTA performed < 45 days post randomization
    - Low Risk
        - First test is a Usual Care Test
            - Coronary angiography without noninvasive testing
            - Stress cardiac MRI
            - Stress echocardiography (exercise or pharmacologic stress)
            - Stress nuclear perfusion (MPI or PET; exercise or pharmacologic stress)
            - Treadmill ECG without imaging
    - Elevated Risk
        - First test is a Usual Care Test
            - Coronary angiography without noninvasive testing
            - Stress cardiac MRI
            - Stress echocardiography (exercise or pharmacologic stress)
            - Stress nuclear perfusion (MPI or PET; exercise or pharmacologic stress)
            - Treadmill ECG without imaging

5.3 Subgroups of Intention-To-Treat and Per-Protocol

Four treatment comparisons will be made.

- Including only Intention-To-Treat participants from the low risk strata
- Including only Intention-To-Treat participants from the elevated risk or known atherosclerosis strata
- Including only Per-Protocol participants from the low risk strata
- Including only Per-Protocol participants from the elevated risk or known atherosclerosis strata

6. Participant Randomization and Enrollment

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

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 of the following 2 groups using an IXRS.

Precision care - precision care strategy

Usual care- usual care strategy

Randomization will be stratified by intended first test assuming usual care (invasive vs. noninvasive) and by classification as low vs. elevated risk by the PROMISE risk model (see derivation below in Section 6.1). For testing purposes, participants with known non-obstructive coronary atherosclerosis or plaque will be assigned to 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. Participants will be randomized to either the usual care arm or the precision evaluation arm within 14 days of screening. The following tables summarizes the strata:

Summary of Strata

Strata	First Test	Risk
1	Non-Invasive	Low Risk
2	Non-Invasive	Elevated Risk or Known Atherosclerosis
3	Invasive	Low Risk
4	Invasive	Elevated Risk or Known Atherosclerosis

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

For eligible participants, medical history data will be captured in the EDC. In addition, sites will need to specify the intended first test that 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 care without immediately planned testing or cCTA with selective FFR_{CT}.

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), or invasive catheterization as the first evaluation, with the specific modality chosen at the discretion of the participant's clinician. 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.

Participants randomized to the precision evaluation arm will be assigned an initial evaluation and 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, and presence of known mild atherosclerosis. Participants will be assigned to either guideline-recommended medical management without planned testing (low risk) or cCTA with selective FFR_{CT} (elevated risk or known including atherosclerosis; known mild atherosclerosis is defined as any of the following: non-obstructive CAD, CAC 0-99 HU, or unquantified coronary calcium seen on chest CT). Participants assigned to the strategy of no immediately planned testing and their providers will be given 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 (escalation of care) will undergo cCTA with selective FFR_{CT}.

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

Regardless of randomization or evaluation assignment, all participants will be treated with risk-appropriate preventive care and symptom control (including therapeutic trials of anti-anginal medications) as indicated.

6.1 Risk Groups based on PROMISE Risk Score

To calculate the PROMISE risk score use the following table estimates based on the risk score paper (Fordyce, JAMA Cardiology 2017). The Promise Score is equal to 1/(1+exp(logit)).

Logit Equation= γ_1+ γ_2*Age (Years)+ γ_3*Sex(female=1)+ γ_4*Caucasian/Non-Hispanic (no=1)+ γ_5*Tobacco(current or former=1)+ γ_6*Diabetes(yes=1) + γ_7*Dyslipidemia(yes=1)+ γ_8*Family history of premature (<55 years)Coronary artery disease(yes=1) + γ_9*hypertension(yes=1)+ Symptoms unrelated to physical or mental stress (not related=1)+ γ_{11}* Symptoms unrelated to physical or mental stress(unknown=1)+ γ_{12}*HDL (mg/dL)

Logit Equation coefficients

		HDL is available	HDL is not available	
			Female	Male
Intercept	γ_1	-3.7524	-3.7524	-3.7524
Age (Years)	γ_2	0.0842	0.0842	0.0842
Sex (female=1)	γ_3	-1.0264	-1.0264	-1.0264
Caucasian/Non-Hispanic (no=1)	γ_4	-0.1422	-0.1422	-0.1422
Tobacco (current or former=1)	γ_5	0.5264	0.5264	0.5264
Diabetes (yes=1)	γ_6	0.3141	0.3141	0.3141
Dyslipidemia (yes=1)	γ_7	0.4122	0.4122	0.4122
Family history of premature (<55 years) Coronary artery disease (yes=1)	γ_8	0.3086	0.3086	0.3086
Hypertension (yes=1)	γ_9	0.4078	0.4078	0.4078

Symptoms unrelated to physical or mental stress (not related=1)	γ_{10}	0.3086	-0.3086	-0.3086
Symptoms unrelated to physical or mental stress (unknown=1)	γ_{11}	-0.195	-0.195	-0.195
HDL (mg/dL)	γ_{12}	-0.00559	-0.318682 HDL constant	-0.252855 HDL constant

Risk groups will be defined as the following:

- Low Risk: Promise Score>0.46
- Elevated Risk: Promise Score≤0.46

Low Risk and Elevated Risk groups are defined using a cut point based on the top 10% of low risk of the PROMISE Risk Score in the PROMISE cohort. Thus, in PRECISE, Low Risk is defined as an absolute score >0.46.

7. Sample Size and Power Calculations

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 3-component endpoint: 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) over a 12-month of follow-up. Time to event analysis will use the date of the event, including the date of catheterization at which the absence of obstructive CAD is demonstrated. Assuming 10% of usual care participants will receive angiography as a first test results in and an 8% primary endpoint event rate at 1 year in the usual care group and 5% event rate in the precision care group (i.e., 3% absolute [37.5% relative] effect size). Assumptions used in the primary endpoint event rate calculations (i.e., 8% vs. 5%) were: overall 10% will not receive randomized evaluation, and within the precision evaluation arm, approximately 20% will be assigned to guideline-recommended care with symptom management and no planned testing, of whom about 30% will have escalation of care to cCTA with selective FFR_{CT}.

Randomizing 1050 participants per group (2100 total participants) is estimated to provide at least 90% power to detect a relative risk reduction of 37.5% in the precision evaluation arm (see Table 1 below, or refer to the power curves in the protocol). Sample size/power calculations are based on the log-rank test 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.

The DSMB will review interim analysis data for efficacy as well as possible sample size re-estimation. At any interim analyses, the O'Brien-Fleming boundary generated by Lan-DeMets alpha-spending function will be utilized as a statistical stopping rule (See DSMB charter for more details).

Table 1. The 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.

1-year event rate in precision evalulation arm	Power	Total number of Primary Events needed	Total number of participants needed
5% (37.5% effect size)	85%	173	1792
	90%	202	2096
	95%	250	2592

8. Database Sources

There are several data sources and responsibility parties in PRECISE, as follows:

- All clinical data and angiographic core lab QCA results will be collected via EDC. Collection and data quality will be managed by Medpace and overseen by HeartFlow.
- The determination of the catherization component of the primary endpoint is complex (see below section 9.2 for details). Briefly, clinical data present in the EDC will be extracted and processed through a HeartFlow Cath Algorithm to be classified as Obstructive CAD, No Obstructive CAD, Indeterminate (Require Medical Montior Review), CEC Adjudication Required, or Incomplete data. Each ICA classified as either Obstructive CAD, No Obstructive CAD, Indeterminate, or CEC Adjudication Required will undergo individual Medical Monitor review. For ICAs receiving a final classification as confirmed Obstructive CAD, No Obstructive CAD, or CEC Adjudication Required a signed Excel spread sheet will be transferred to CRF-NY and the data uploaded into a SAS data set for later transfer to DCRI. CEC Adjudication Required or Ambiguous ICAs will be adjudicated by the independent CEC. Data on Incomplete Caths will be queried and when complete, returned to the Cath Algorithm for repeat analysis.
- Results of CEC adjudicated clinical events and adjudicated ICAs receiving a final classification as confirmed Obstructive CAD or No Obstructive CAD will be entered into a separate EDC by CPC.

Table 2. Data sources and locations

Data Source	Data Location
All clinical data	Main Trial EDC managed by MedPace
CEC results	Database managed by CPC
Angio core lab	Main Trial EDC managed by MedPace
Cath Algorithm	Medical Monitor spreadsheet transferred into database managed by CRF-NY

Compilation of the trial's master analytic data set will require transfers of the databases from MedPace, CRF-NY, and CPC to the responsible party. All data from all sources will be combined into one analyzable master trial data set using SAS, which will in turn be shared with those responsible for trial analyses.

9. Statistical Analyses

9.1 General Approach

Continuous variables will be summarized as means (standard deviations), medians (25^{th} and 75^{th} percentiles), minimum and maximum. Number (percentage) of participants in each category will be presented for categorical variables. Comparisons of categorical variables between the two randomized arms or between pre-specified subgroups will be performed using Pearson's chi-square test or Fisher's exact test depending on expected cell sizes; comparisons of continuous variables will be performed using the Wilcoxon rank-sum test.

Unless otherwise stated, all hypothesis tests will be performed using two-sided tests. No adjustment for multiplicity is planned.

All primary statistical analyses will be conducted using the intention-to-treat principle to define treatment assignment, except as indicated.

In addition to the pre-specified subgroup analyses (see Section 9.4), response magnitude analyses may be considered, in which participants are evaluated based on a binary variable indicating improvement or no improvement with respect to a given assessment.

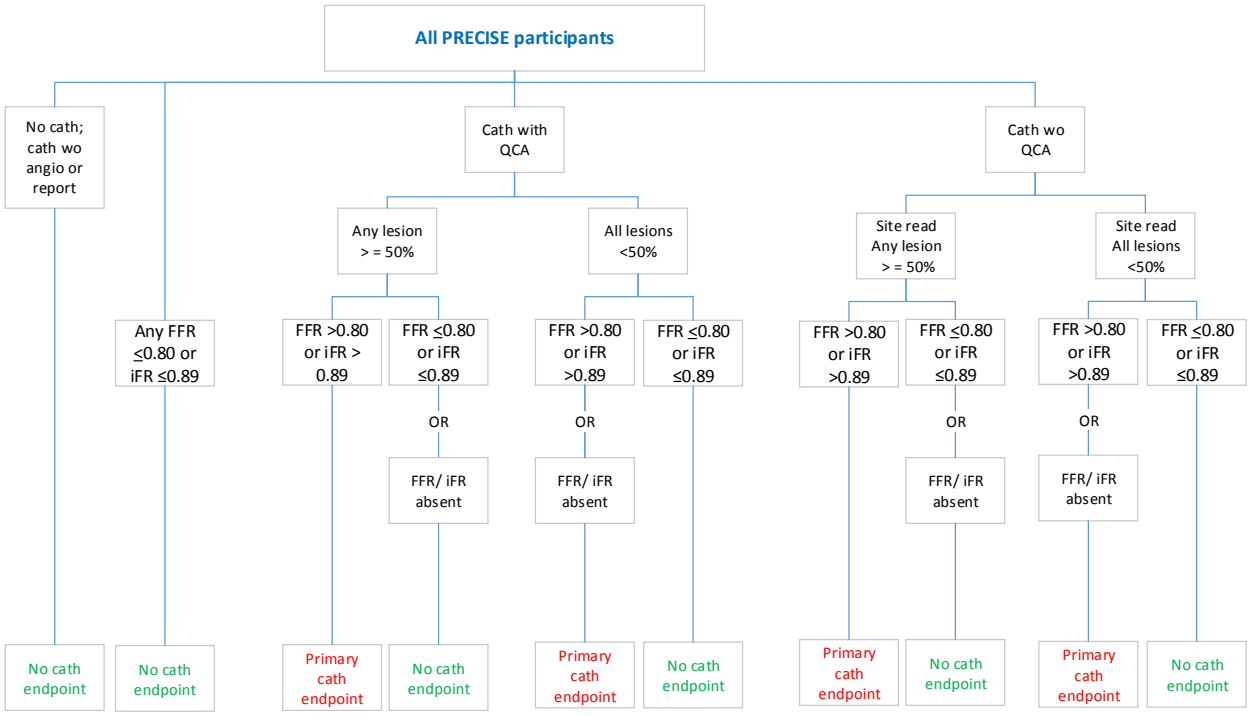
Analyses will be performed using SAS software version 9.4 or higher (SAS Institute, Inc., Cary, NC).

9.2 Primary Efficacy Analysis

The primary endpoint of this study is estimated as time to first occurrence of any of its three following components:

- All-cause death
- Non-fatal MI
- Invasive cardiac catheterization without obstructive CAD

Each death will be adjudicated for cause and date by the CEC. Potential MI cases will be adjudicated for MI yes/no, fatal/non-fatal, MI type, and date of MI by the CEC. Cath without obstructive CAD is the absence of obstructive CAD, defined as diameter stenosis ≥50% in a vessel ≥2 mm both assessed by QCA (or site read if QCA is not available), FFR≤0.80, or iFR≤0.89. The catheterization component of the primary endpoint will be determined according to the algorithm diagrammed below:



To derive the catherization component of the primary endpoint, site, core lab and DCRI entered clinical data present in the clinical EDC will be extracted and processed through a HeartFlow Cath Algorithm to be classified as Obstructive CAD, No Obstructive CAD, Indeterminate, or Incomplete data. Each ICA classified as either Obstructive CAD, No Obstructive CAD, or Indeterminate will undergo individual Medical Monitor review. For ICAs receiving a final classification as confirmed Obstructive CAD or No Obstructive CAD, the results are considered final. For ICAs confirmed by the Medical Monitor as Indeterminate or ambiguous, CEC adjudication will make the final determination. Incomplete ICAs will be reprocessed through the Cath Algorithm once data are complete and query free.

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 + 1. For participants who do not experience any of the primary 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 + 1 will be used in the analysis, and those participants will be considered as censored observations in the time-to-event analysis. The 12-month analysis will be censored at 395 days (365 days + 30 day visit window) such that only events on or before this time will be counted in the analysis and event free participants with follow-up greater than 395 will be set to 395.

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

The log-rank a non-parametric test will be the primary statistical methodology to test for outcome differences between precision care arm and usual care arm with respect to the primary composite endpoint. The Cox proportional hazards model will be used to estimate the average treatment effect size using the hazard ratio (HR) and 95% confidence interval (CI) with treatment assignment as the only covariate in the model. The proportionality assumption (constant hazard over time) in the Cox model will be assessed using the cumulative sums of martingale residuals and the Kolmogorov-type Supremum test. Although log-rank statistic (primary method) is robust under non-proportional hazards it's not optimal due to loss of some statistical power. Thus, if the proportional hazards assumption is violated a two-stage procedure will be implemented (Qiu and Sheng 2008). Due to interim analysis conducted by the DSMB, the final analysis type I error rate (α) will be adjusted as $0.05 - \alpha$ spent at any interim analyses. Cumulative event rates will be calculated according to the method of Kaplan-Meier for each randomized arm as a function of time (in days) from randomization to the time of event or censoring + 1, and the estimated event probabilities will be displayed graphically.

As a supportive analysis, adjusted HRs and 95% CIs will be estimated using the Cox proportional hazards model by including pre-specified baseline risk factors as covariates in the model. These covariates will include: age, sex, CAD equivalent (diabetes, history of peripheral artery disease, or cerebrovascular), and intended first test strata: invasive/non-invasive.

9.3 Secondary Endpoint Analyses

9.3.1 Finkelstein-Schoenfeld/Win Ratio Test

The key secondary analysis of PRECISE will use the Finkelstein-Schoenfeld method (Finkelstein and Schoenfeld 1999) as modified by Pocock ("win ratio", calculated without matching). The main objective of the FS/win ratio test is to calculate the treatment comparison test statistic based on relative clinical importance of the components in the primary composite endpoint rather than relying on the time-to-first occurrence approach. For this analysis the win-ratio (95% CI) will be estimated using the three components of the primary endpoint as tie breakers: 1) all-cause death, 2) non-fatal MI, and 3) invasive cardiac catheterization without obstructive CAD. In general terms, each pair of participants assigned to either precision care or usual care arm will be placed into one of the hierarchical groups as follows (with comparison through the shortest follow-up achieved for each member of the pair):

1. Shortest time to occurrence of death; if neither died or there is a tie then move to #2
2. Shortest time to occurrence of first non-fatal MI; if neither had non-fatal MI or there is a tie then move to #3
3. Shortest time to occurrence of first invasive cardiac catheterization without obstructive CAD; if neither had invasive cardiac catheterization without obstructive CAD or there is a tie then move to #4
4. None of the above (a tie is declared)

Handling of Dropouts and Missing Data: All participants with follow-up are expected to have some data to address this endpoint. The win-ratio (WR) approach of (Pocock et al., 2012) will be used to evaluate each composite endpoint as well as the calculations of the WR test statistic p-values. In the unmatched WR approach, all possible pairing between participants in the

precision arm and participants in the usual care arm will be considered. Then, each pair will be classified into one of the categories (1-4) listed above. The 95% CI for the estimated WR will be calculated using a bootstrap approach (Davison and Hinkley, 1997) and the method described in Luo et al., 2015. Multiple imputation method will be used to account for missing follow-up data (Little RJ et al., 2012). Similarly, multiple imputation method will be used to impute missing baseline values.

9.3.1 Analysis of Economic Endpoints

Economic analyses are intended as descriptive analyses with estimates of treatment differences and precision of those estimates as the principal results of analysis. Statistical tests, when performed, will serve a subsidiary role in assisting interpretation. No adjustment for multiplicity is planned. For the economic outcomes, the primary comparisons will be at 6 months between treatment arms by intention-to-treat. Additional comparisons will examine 45-day and 12-month outcomes. Details of these analyses are contained in a separate PRECISE Economics and QoL SAP.

9.3.2 Quality of Life Assessments

For each of the QoL measures examined in this study, we will provide simple descriptive and comparative analyses by ITT. To address the potential for multiple comparisons problems arising from testing each individual scale and time point separately, we propose two complementary approaches. First, we will pre-specify the SAQ summary score as the primary QoL comparison of interest and assign all other comparisons to a secondary (supportive) status. Second, we will use a mixed model repeated measures 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. Change in QoL from baseline to follow-up will be assessed by the mixed models method using an intention to treat approach. Further details of these analyses are contained in a separate PRECISE Economics and QoL SAP.

9.3.3 Additional Analyses

9.3.3.1 Time to Death

Deaths will be classified by the CEC as to whether the mode of death was due to a cardiovascular (CV) or non-cardiovascular (non-CV) cause. If insufficient source document is 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 will be used if available. 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.

The following death endpoints will be analyzed:

- All-cause death
- CV death (including sudden death)
- Non-CV death

For all-cause death endpoint the log-rank test will be the primary statistical methodology to test for outcome differences between precision care arm and usual care arm. The Cox proportional hazards model will be used to estimate the average treatment effect size using the hazard ratio

(HR) and 95% confidence interval (CI) with treatment assignment as the only covariate in the model. Cumulative event rates will be calculated according to the method of Kaplan-Meier for each randomized arm as a function of time from randomization to the time of event or censoring + 1, and the estimated event probabilities will be displayed graphically. For CV death endpoint the competing risks methodology of Fine-Gray (Fine and Gray 1999) will be utilized, where death due to a non-CV cause is considered as a competing risk in analyzing endpoints with CV death as a component. This methodology, rather than treating non-CV death as a censoring event, estimates the cumulative cause-specific function, and is performed within the proportional hazards framework using the marginal failure sub-distribution associated with the event of interest (CV death). Cumulative incidence rates, sub-distribution hazard ratios with 95% CIs, and Wald p-values will be calculated with the Fine-Gray framework. As supplemental analyses, however, this endpoint will also be examined using (a) only the deaths classified by the CEC as CV; and, (b) deaths classified by the CEC as CV, but also including any deaths in the CV category that are classified as unknown by the CEC. Similar analyses will be conducted for non-CV death endpoint in which death is not a part of the endpoint of interest within the Fine-Gray competing risks framework.

9.3.3.2 Other Time to Event Endpoints

Suspected cases of MIs will be triggered from participant interviews and medical record reviews and classified by the CEC as to whether an event has happened (Yes/No) and if the event was either procedural or non-procedural. Coronary revascularization procedures (CABG surgery and PCI) performed will be collected during the follow-up. The hospitalizations recorded on the eCRF will be classified by sites as CV or non-CV. This site classification (CV hospitalization lasting <24h and non-CV hospitalization) will be reviewed by the Medical Monitor (MM) who will determine a final classification as requiring CEC adjudication or not requiring CEC adjudication. Ambiguous hospitalizations will be referred to CEC for adjudication. All site designated or MM designated CV hospitalizations will be reviewed by CEC for confirmation as Yes/No and whether unstable angina was the cause of the hospitalization Yes/No.

The following endpoints will be analyzed:

- MI
- Revascularizations
- All Cause Hospitalization (Unscheduled)
- CV Hospitalizations including unstable angina hospitalizations (Urgent/unscheduled)
- Unstable angina hospitalization (Urgent/unscheduled)
- Non-CV Hospitalizations (Unscheduled)

For All Cause Hospitalization only a descriptive summary will be presented. For the other endpoints similar analyses will be conducted for time-to-event endpoints in which death is not a part of the endpoint of interest within the Fine-Gray competing risks framework.

Additionally catheterization efficiency or cath yield is defined as the proportion of participants with an invasive coronary angiogram who underwent revascularization within 6 months of catheterization. Rates will be summarized by 2 groups and compared using Pearson's chi-square test.

9.3.3.3 Preventive Medication Use

New and total use of preventative medication will be collected during baseline and the participant follow-up at 45 days, 6 months and 12 months, the medication classes of interest will be defined as the following:

- Antiplatelet usage is defined as the usage of any of the following medications: ASA, Clopidogrel, Ticagrelor, or Prasugrel
- Lipid Lowering Medication usage is defined as the usage of any of the following medications: Statins or Other Lipid Lowering Agents
- Anti-Hypertensive Medication usage is defined as the usage of any of the following medications: Calcium Channel Blockers, Beta-Blockers, ACE-Inhibitor/ARB/ARNI, or Diuretic

The number (%) will be summarized between the precision care arm and usual care arm and compared using Pearson's chi-square test for the following combinations: 1) usage at baseline and 45 days, 2) usage at baseline and 6 months, and 3) usage at baseline and 12 months.

9.3.3.4 Cumulative Trial Strategy Related Radiation Exposure

Radiation exposure for diagnostic and procedural testing will be collected for each participant and the average accumulated radiation dose for 1 year, in millisievert (mSV) units, will be calculated. This calculation will be known as the cumulative radiation exposure. For cath, PCI, CTA, and stress nuclear, the missing values will be imputed based on the distribution of data from trial participants with complete radiation information. If data are missing in > 80% or more of the diagnostic and procedural testing, a single fixed estimate of radiation based on the literature will be used to impute.

Table 3. Radiation Estimates for Imputation

Procedure	Imputation Result
CTA (Stocker 2018)	5.1 mSv*
Stress Nuclear Imaging (Mieres 2014)	11mSv Rest or Reinjection Sestamibi (Cardiolite)
	3mSv Stress Sestamibi (Cardiolite)
	11mSv Rest or Reinjection Tetrofosmin (Myoview)
	3mSv Stress Tetrofosmin (Myoview)
	22mSv Thallium
	3mSv Rubidium
	2.0mSv 13N-ammonia
Cardiac Catheterization (Lu 2017)	7 (mSv)
Cardiac Catheterization with PCI (Lu 2017)	15 (mSv)

* 195 mGy/cm, calculated with conversion factor 0.026 mSv/mGy*cm (Stocker 2018), (Trattner 2018), and (Carpeggiani 2017)]

Conversion factor from MBq to mSv (*ICRP 2007*)

- Rest Tc sestamibi 9.0 x 10^{-3} mSv/MBq
- Stress Tc sestamibi 7.9 x 10^{-3} mSv/MBq
- Rest Tc tetrofosmin 6.9 x 10^{-3} mSv/MBq
- Stress Tc tetrofosmin 6.9 x 10^{-3} mSv/MBq
- Rb 3.4 x 10^{-3} mSv/MBq

- N ammonia 2.0 x 10^{-3} mSv/MBq

For exposure observed in this study, data will be summarized using descriptive statistics (mean [SD], median [25^{th}, 75^{th} percentiles], min and max). To compare the radiation exposure distributions between the precision care arm and the usual care arm, a waterfall plot of cumulative radiation exposure will be constructed. Comparison between 2 groups will be conducted using a non-parametric approach such as Wilcoxon rank-sum test. The analysis will be repeated for 2 populations: 1) low risk participants only and 2) elevated risk or known atherosclerosis participants only. The radiation exposure for diagnostic test sources will be summarized descriptively.

9.3.3.5 Revascularization

Coronary revascularization procedures (CABG surgery and PCI) performed will be collected during the follow-up. The number (%) and proportion of catheterizations leading to revascularization will be summarized and compared between the precision care arm and usual care arm. Coronary revascularization procedures determined to be ischemia driven will be summarized descriptively. Similarly, for the invasive coronary angiogram participants the number (%) of revascularizations performed in the first 6 months post catheterization will be summarized in each arm.

9.3.3.6 Prevention Motivation

Prevention motivation information will be assessed at study entry and during the participant follow-up at 45 days, 6 months and 12 months. Specifically, this includes an assessment of the importance of cardiac risk prevention to the participant's future health (5 point Likert scale from not important>>>very important) at baseline, 45 days and 12 months, as well as an assessment of whether the PRECISE evaluation changed the participant's motivation to modify cardiac risk factors and improve heart health, and an inquiry regarding how their testing results were communicated by their healthcare provider (asked at 45 days and 12 months). The number (%) will be summarized between the precision care arm and usual care arm and compared using Pearson's chi-square test at entry, 45 days and 12 months.

1. Participants will be characterized by reported cardiac risk prevention importance at baseline and post evaluation at 45 days and 12 months by randomized arm, testing received, and testing results
2. Among participants receiving testing by 45 days, will be characterized by response at 45 days by randomized arm, testing received, and testing results as having:
    1. Increased my motivation
    2. Did not change my motivation
    3. Decreased my motivation
    4. I don't know the results of my evaluation
3. Among those tested by 45 days and who received test results, method of communication of testing results will be characterized by response at 45 days by randomized arm, testing received, and testing results
4. Among those who received test results, association of the method of communication (method of sharing test results) reported at 45 days and reported change in motivation overall and by test results

5. The association of medication use (antiplatelet usage, lipid lowering medication usage, and anti-hypertensive medication usage) and change in modivation responses (increase, decrease no change, did not receive) and rates of medication use (aspirin/anti-platelet agents and statins) at 45 days and 12 months

9.3.4 Sensitivity Analyses

9.3.4.1 Validation of the Cut Point for PROMISE Risk Score

The prognostic cut point used for the PROMISE risk score will be validated in light of the results of PRECISE. The calibration and discrimination of PROMISE cut points in the PRECISE participant population will be evaluated. Logistic regression model will be used estimate the area under the curve quantified by calculating c-index statistic and mean observed and predicted mean plot. The following lists the outcomes and populations to be evaluated:

- Scenario 1: PRECISE primary endpoint all three components for All Randomized Participants
- Scenario 2: PRECISE primary endpoint two components: Death/MI only for All Randomized Participants
- Scenario 3: Prognostic Value of Risk Score for No CAD + No Event for All Randomized Participants, Only Precision Care Arm Receiving CTA
- Scenario 4: Prognostic Value of Risk Score for Significant or Severe CAD for All Randomized Participants, Only Precision Care Arm Receiving CTA

9.3.4.2 Outcomes in Low and Elevated Risk groups

The following subgroup treatment/strategy comparisons will be conducted for the primary endpoint at 12 months as a forest plot with an interaction p-value. The primary endpoint along with the components analyses will be run for the the following populations:

- Including only Intention-To-Treat participants from the low risk strata
- Including only Intention-To-Treat participants from the elevated risk or known atherosclerosis strata

9.3.4.3 COVID-19 Sensitivity Analysis

A sensitivity analysis will be undertaken performing the primary endpoint analysis in all participants, but excluding events deemed to be COVID-19 related by the CEC. This analysis will use the same time from randomization +1 in the primary analysis.

9.4 Subgroup Analyses

Subgroup analyses will be performed on the primary endpoint 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 baseline variables listed in the section 4.2.1.

The effect of the treatment strategy may also be examined in other (post hoc) subgroups of clinical interest based on initial analyses. These subgroups will be described in the CSR.

9.5 Alternative Treatment Assignment Analyses

Five additional analysis will be performed on the primary endpoint to assess whether the intervention effect size estimates vary to a clinically relevant extent according to adherence to the protocol and/or management actually received. The five are as follows:

- Including only Intention-To-Treat participants from the low risk strata
- Including only Intention-To-Treat participants from the elevated risk or known atherosclerosis strata
- Including only Per-Protocol participants
- Including only Per-Protocol participants from the low risk strata
- Including only Per-Protocol participants from the elevated risk or known atherosclerosis strata

10. Planned Table of Contents for Analysis Tables and Figures

The following tables and graphs are required for the Clinical Study Report and trial outcomes analyses. All tables are listed here for completeness.

Standard conventions will be used in table display such that the following data columns will be included: “All Usual Care” including total and additional columns of usual care split into “Low Risk” and “Elevated Risk”; ”All precision care” columns will include total and additional as assigned columns indicated as “No Testing” and “CTA.”

Table/Graph Number	Table/Graph Title
Table 1.1	Participant Disposition All Randomized Participants
Table 2.1	Participant Demographics All Randomized Participants
Table 2.2	Cardiovascular Disease History; atherosclerosis history and Cardiovascular Risk Factors and risk scores All Randomized Participants
Table 2.3	Presenting Symptoms All Randomized Participants
Table 2.4	Medical History/Past Surgeries/ All Randomized Participants
Table 2.5	Physical Examination at Baseline All Randomized Participants
Table 2.6	Rest ECG Findings at Baseline All Randomized Participants
Table 2.7	Laboratory Testing at Baseline All Randomized Participants
Table 2.8	Concomitant Cardiovascular Medications at Baseline All Randomized Participants
Table 2.9	Quality Of Life at Baseline All Randomized Participants
Table 2.10	Prevention Motivation at Baseline All Randomized Participants
Table 3.1	Summary of Follow-up Visits All Randomized Participants

Table/Graph Number	Table/Graph Title
Table 3.4	Flow Chart Diagnostic Testing, Escalation (precision arm only) All Randomized Participants
Table 3.4.1	Flow Chart 1st Diagnostic Testing Randomized Tests All Randomized Participants
Table 3.5.1	1st Diagnostic Test Findings overall and by test type Site interpretation Positive/Negative Results All Randomized Participants
Table 3.5.3	2nd Diagnostic Test Findings by test type Site interpretation Positive/Negative Results All Randomized Participants
Table 3.5.4	Diagnostic Test Findings - Site interpretation Four Tier Results All Randomized Participants
Table 4.1	Primary Efficacy Analysis Endpoint Collection and Summary All Randomized Participants
Figure 4.1.1	Primary Efficacy Analysis Kaplan-Meier Plot of Primary Endpoint All Randomized Participants
Figure 4.1.2	Primary Efficacy Analysis Kaplan-Meier Plot of Primary Endpoint Component All Cause Death All Randomized Participants
Figure 4.1.3	Primary Efficacy Analysis Cumulative Incidence Plot of Primary Endpoint Component 1st Non-fatal MI All Randomized Participants
Figure 4.1.4	Primary Efficacy Analysis Cumulative Incidence Plot of Primary Endpoint Component 1st Invasive cardiac catheterization without obstructive CAD All Randomized Participants
Table 4.2	Primary Endpoint Adjusted Cox Model All Randomized Participants
Table 4.2.1	Sub-group Analyses Primary Endpoint All Randomized Participants
Figure 4.2.1.1	Sub-group Forrest Plot Primary Endpoint All Randomized Participants
Figure 4.2.2.1	Sub-group Forrest Plot Primary Endpoint All Randomized Low Risk Participants
Figure 4.2.2.2	Sub-group Forrest Plot Primary Endpoint All Randomized Elevated Risk + Athero Participants
Figure 4.2.2.3	Sub-group Forrest Plot Primary Endpoint Per Protocol Participants
Figure 4.2.2.4	Sub-group Forrest Plot Primary Endpoint Per Protocol Low Risk Participants
Figure 4.2.2.5	Sub-group Forrest Plot Primary Endpoint Per Protocol Elevated Risk + Athero Participants
Table 4.2.4.1	Primary Endpoint Cox Model Results All Randomized Low Risk Participants
Table 4.2.4.2	Primary Endpoint Cox Model Results All Randomized Elevated Risk + Athero Participants

Table/Graph Number	Table/Graph Title
Table 4.2.4.3	Primary Endpoint Cox Model Results Per Protocol Participants
Table 4.2.4.4	Primary Endpoint Cox Model Results Per Protocol Low Risk Participants
Table 4.2.4.5	Primary Endpoint Cox Model Results Per Protocol Elevated Risk + Athero Participants
Table 4.3	Primary Endpoint using unmatched Win-Ratio All Randomized Participants
Table 4.5	Cardiovascular Death Summary
Figure 4.5.1	Cumulative Incidence Plot of Cardiovascular Death All Randomized Participants
Figure 4.5.2	Cumulative Incidence Plot of Non-Cardiovascular Death All Randomized Participants
Table 4.7	Hospitalization Summary
Figure 4.7.1	Cumulative Incidence Plot of Time to 1st CV Hospitalization (CEC) All Randomized Participants
Figure 4.7.2	Cumulative Incidence Plot of Time to 1st Unstable Angina Hospitalization All Randomized Participants
Figure 4.7.3	Cumulative Incidence Plot of Time to 1st Non-CV Hospitalization All Randomized Participants
Table 4.8	Preventive Medication Summary
Table 4.9	Cumulative Radiation Exposure Summary
Figure 4.9.1	Waterfall plot of Cumulate Radiation Exposure
Figure 4.9.2	Waterfall plot of Cumulate Radiation Exposure All Randomized Participants, Excluding Low Risk Participant
Table 4.10	Revascularization Summary
Figure 4.10.1	Cumulative Incidence Plot of 1st Revascularization All Randomized Participants
Table 4.11.1.1	Prevention Motivation Descriptive Summary Day 45 Descriptive Summary
Table 4.11.1.2	Prevention Motivation Descriptive Summary 12 Month Descriptive Summary
Table 4.11.2	Prevention Motivation Testing Results Response at 45 Days All Randomized, As Tested Participants
Table 4.11.4	Prevention Motivation Method of Communication at 45 Days All Randomized, As Tested Participants
Table 4.11.5	Prevention Motivation Association of Method of Communication and Change in Motivation at 45 Days All Randomized Participants, Received Test Results
Table 4.11.6.1	Prevention Motivation Association of Medication Use and Change in Motivation at 45 Days All Randomized Participants
Table 4.11.6.2	Prevention Motivation Association of Medication Use and Change in Motivation at 12 Months All Randomized Participants
Figure 4.12.1.1	Mean observed and predicted mean Prognostic Value of Risk Score PRECISE primary endpoint all three components All Randomized Participants
Table 4.12.1.2	Mean observed and predicted mean Prognostic Value of Risk Score for PRECISE primary endpoint all three components All Randomized Participants
Figure 4.12.2.1	Mean observed and predicted mean

Table/Graph Number	Table/Graph Title
	Prognostic Value of Risk Score PRECISE primary endpoint two components: Death/MI only All Randomized Participants
Table 4.12.2.2	Mean observed and predicted mean Prognostic Value of Risk Score for PRECISE primary endpoint two components: Death/MI only All Randomized Participants
Figure 4.12.3.1	Mean observed and predicted mean Prognostic Value of Risk Score for Lowest risk: No CAD + No Event All Randomized Participants, Only Precision Care Arm Receiving CTA
Table 4.12.3.2	Mean observed and predicted mean Prognostic Value of Risk Score for Lowest risk: No CAD + No Event All Randomized Participants, Only Precision Care Arm Receiving CTA
Figure 4.12.4.1	Mean observed and predicted mean Prognostic Value of Risk Score for Significant or Severe CAD All Randomized Participants, Only Precision Care Arm Receiving CTA
Table 4.12.4.2	Mean observed and predicted mean Prognostic Value of Risk Score for Significant or Severe CAD All Randomized Participants, Only Precision Care Arm Receiving CTA
Table 4.13.1	Comparisons of outcomes in low PMRS and elevated risk Adjucated Endpoint Collection and Summary All Randomized Participants, Low PRMS Only
Figure 4.13.1.1	Kaplan-Meier Plot of Primary Endpoint All Randomized Participants, Low PRMS Only
Figure 4. 13.1.2	Kaplan-Meier Plot of Primary Endpoint Component All Cause Death All Randomized Participants, Low PRMS Only
Figure 4. 13.1.3	Cumulative incidence Plot of Primary Endpoint Component 1st Non-fatal MI All Randomized Participants, Low PRMS Only
Figure 4. 13.1.4	Cumulative incidence Plot of Primary Endpoint Component 1st Invasive cardiac catheterization without obstructive CAD All Randomized Participants, Low PRMS Only
Table 4.13.2	Comparisons of outcomes in low PMRS and elevated risk Adjucated Endpoint Collection and Summary All Randomized Participants, Elevated PRMS+athero Only
Figure 4.13.2.1	Kaplan-Meier Plot of Primary Endpoint All Randomized Participants, Elevated PRMS+athero Only
Figure 4. 13.2.2	Kaplan-Meier Plot of Primary Endpoint Component All Cause Death All Randomized Participants, Elevated PRMS+athero Only
Figure 4. 13.2.3	Kaplan-Meier Plot of Primary Endpoint Component 1st Non-fatal MI All Randomized Participants, Elevated PRMS+athero Only
Figure 4. 13.2.4	Kaplan-Meier Plot of Primary Endpoint Component 1st Invasive cardiac catheterization without obstructive CAD All Randomized Participants, Elevated PRMS+athero Only
Table 4.15.1	COVID-19 Sensitivity Analysis of Primary Endpoint Endpoint Collection and Summary All Randomized Participants

11. Changes from the Protocol

The current version of the protocol is v1.5, dated 15- OCT-2019. Under section VIII.B., the time to event is defined as the date of the first event minus the date of randomization, and we are adding 1 to this value.

12. References

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Appendix I. Schedule of Activities

	Screening	Randomization Day 1	Day 45 (±14 d)	6-mo. (±30 d)	12-mo. (±30 d)
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 require 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)

PRECISE SAP Version 2 07JUL2022

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