Comparison of an Initial Risk-Based Testing Strategy vs Usual Testing in Stable Symptomatic Patients With Suspected Coronary Artery Disease
The PRECISE Randomized Clinical Trial

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IMPORTANCE Trials showing equivalent or better outcomes with initial evaluation using coronary computed tomography angiography (cCTA) compared with stress testing in patients with stable chest pain have informed guidelines but raise questions about overtesting and excess catheterization.

OBJECTIVE To test a modified initial cCTA strategy designed to improve clinical efficiency vs usual testing (UT).

DESIGN, SETTING, AND PARTICIPANTS This was a pragmatic randomized clinical trial enrolling participants from December 3, 2018, to May 18, 2021, with a median of 11.8 months of follow-up. Patients from 65 North American and European sites with stable symptoms of suspected coronary artery disease (CAD) and no prior testing were randomly assigned 1:1 to precision strategy (PS) or UT.

INTERVENTIONS PS incorporated the Prospective Multicenter Imaging Study for the Evaluation of Chest Pain (PROMISE) minimal risk score to quantitatively select minimal-risk participants for deferred testing, assigning all others to cCTA with selective CT-derived fractional flow reserve (FFR-CT). UT included site-selected stress testing or catheterization. Site clinicians determined subsequent care.

MAIN OUTCOMES AND MEASURES Outcomes were clinical efficiency (invasive catheterization without obstructive CAD) and safety (death or nonfatal myocardial infarction [MI]) combined into a composite primary end point. Secondary end points included safety components of the primary outcome and medication use.

RESULTS A total of 2103 participants (mean [SD] age, 58.4 [11.5] years; 1056 male [50.2%]) were included in the study, and 422 [20.1%] were classified as minimal risk. The primary end point occurred in 44 of 1057 participants (4.2%) in the PS group and in 118 of 1046 participants (11.3%) in the UT group (hazard ratio [HR], 0.35; 95% CI, 0.25-0.50). Clinical efficiency was higher with PS, with lower rates of catheterization without obstructive disease (27 [2.6%]) vs UT participants (107 [10.2%]; HR, 0.24; 95% CI, 0.16-0.36). The safety composite of death/MI was similar (HR, 1.52; 95% CI, 0.73-3.15). Death occurred in 5 individuals (0.5%) in the PS group vs 7 (0.7%) in the UT group (HR, 0.71; 95% CI, 0.23-2.23), and nonfatal MI occurred in 13 individuals (1.2%) in the PS group vs 5 (0.5%) in the UT group (HR, 2.65; 95% CI, 0.96-7.36). Use of lipid-lowering (450 of 900 [50.0%] vs 365 of 873 [41.8%]) and antiplatelet (321 of 900 [35.7%] vs 237 of 873 [27.1%]) medications at 1 year was higher in the PS group compared with the UT group (both *P* < .001).

CONCLUSIONS AND RELEVANCE An initial diagnostic approach to stable chest pain starting with quantitative risk stratification and deferred testing for minimal-risk patients and cCTA with selective FFR-CT in all others increased clinical efficiency relative to UT at 1 year. Additional randomized clinical trials are needed to verify these findings, including safety.

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+ **Visual Abstract**

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+ **Supplemental content**

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Coronary artery disease (CAD) commonly presents with stable symptoms, often requiring multiple diagnostic tests.[1] Previous randomized clinical trials including the Scottish Computed Tomography of the Heart (SCOT-HEART) and Prospective Multicenter Imaging Study for the Evaluation of Chest Pain (PROMISE) have shown similar or better clinical outcomes using coronary computed tomographic angiography (cCTA) as the initial or subsequent evaluation.[2,3] Significant questions remain regarding unneeded testing in low-risk patients and excess referral to invasive catheterization using cCTA.

The American Heart Association(AHA)/American College of Cardiology (ACC) guidelines are agnostic regarding testing modalities, rating both cCTA and stress imaging as class 1 based on randomized clinical trials showing an excellent prognosis with both.[2-4] Further, the evaluation of lesion-specific ischemia in intermediate (40%-90%) stenoses using noninvasive cCTA-derived fractional flow reserve (FFR-CT) is recommended as class 2a and may simplify the clinical care pathway.[5,6] Current data suggest that the use of FFR-CT may improve catheterization yield in initial testing[7-9] and compared with use of functional stress testing (predominantly stress electrocardiogram) as a second test in patients with intermediate lesions on cCTA.[10]

Risk-based determination of the need for testing in low-risk patients is accepted in the AHA/ACC,[11] European Society of Cardiology,[12] and National Institute for Health and Care Excellence[5] guidelines, but implementation into routine practice remains limited.[5,11-15] Risk algorithms to assess pretest likelihood of disease have been derived from multiple cohorts,[13-15] but none have been prospectively validated for the purpose of selecting patients for deferred testing in a randomized clinical trial.

The Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization (PRECISE) study was designed to address unresolved concerns raised by the SCOT-HEART and PROMISE trials regarding the effects of a cCTA-based initial strategy on low-benefit referrals to invasive catheterization and to assess the opportunity to avoid all testing in select low-risk patients.

Methods

Study Design

PRECISE was a pragmatic randomized clinical trial enrolling from December 3, 2018, to May 18, 2021, of patients without known CAD or prior testing, who had stable symptoms of suspected CAD recommended for nonemergent testing.[16] The study population was typical for a European/North American patient cohort with the majority self-identifying with non-Hispanic White race and ethnicity. Privacy rules precluded assessing more detail about non-White race and ethnicity. Patients with unstable symptoms, previous CAD testing with the past year, or cCTA contraindications were excluded, and study conduct followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines (Supplement 1, Supplement 2, Supplement 3, and the

Key Points

Question What is the optimal initial evaluation pathway to reduce unnecessary testing and catheterization referral for stable, symptomatic patients with suspected coronary artery disease (CAD)?

Findings In this randomized clinical trial including 2103 participants, prior to any testing, a precision strategy using the validated Prospective Multicenter Imaging Study for the Evaluation of Chest Pain (PROMISE) minimal risk score to guide deferred testing for minimal-risk patients and coronary computed tomographic angiography with selective fractional flow reserve for all others improved clinical efficiency (catheterization without obstructive CAD) with no statistically significant impact on safety (death, nonfatal myocardial infarction) at 1 year.

Meaning The precision strategy is a clinically efficient and potentially safe initial approach for evaluating patients with new-onset stable symptoms and suspected CAD.

eAppendix and eMethods in Supplement 4). The protocol was approved by the appropriate regulatory bodies for the coordinating center, sites, and core laboratories. All participants provided written informed consent.

Precision Strategy Intervention

Participants were randomly assigned 1:1 to precision strategy (PS) or usual testing (UT), stratified by site, intended first test if randomly assigned to UT, and minimal vs moderate-high risk using the validated PROMISE minimal risk score (PMRS).[14,17-19] Participants in the PS group with a PMRS threshold value of greater than 0.46 were assigned to deferred testing. This cut point defined the lowest risk decile among PROMISE participants.[3] All other participants in the PS group (ie, those with a PMRS <0.46), or those with known atherosclerosis such as vascular calcification on chest CT, received cCTA with selective FFR-CT for site-read 30% to 90% stenoses.

Among participants in the UT group, site clinicians chose the initial testing modality, including exercise electrocardiogram, stress echocardiogram, stress nuclear myocardial perfusion imaging (single-photon emission CT or positron emission tomography), stress cardiovascular magnetic resonance imaging, or catheterization.

All PS and UT testing was performed according to local protocols, and all subsequent testing and care decisions were made locally. Guideline-directed medical management was recommended for participants in both arms, and relevant resources were provided.

Outcomes and Follow-Up

The centrally adjudicated primary end point was a composite of clinical efficiency as a gatekeeper to invasive testing (catheterization without obstructive CAD) and safety (death, nonfatal myocardial infarction [MI]) at 1 year. Catheterization without obstructive disease has been used as a primary,[7,10] secondary, or component end point[3] in other studies. Obstructive CAD was defined as any angiographic stenosis with invasive FFR of 0.80 or less or instantaneous wave-free ratio of 0.89

Figure 1. The Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization (PRECISE) Trial Profile
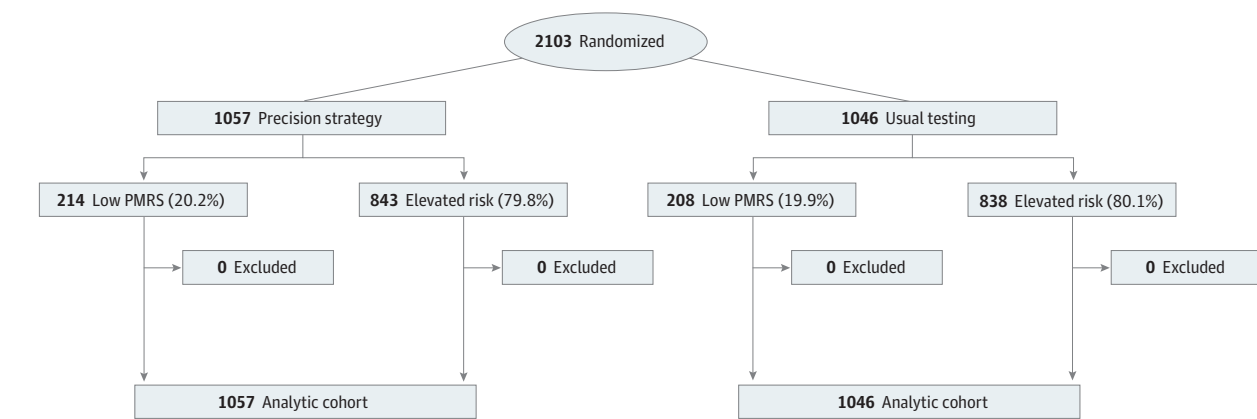
This diagram describes each phase of the PRECISE trial, including enrollment and intervention, allocation, follow-up, and data analysis. Data on all 2103 participants were included in this intention-to-treat analysis. PMRS indicates Prospective Multicenter Imaging Study for the Evaluation of Chest Pain (PROMISE) minimal risk score.

or less, or, if not performed, any stenosis of 50% or greater on quantitative coronary angiography, in a vessel 2 mm or larger in diameter (eMethods in Supplement 4). Prespecified secondary safety end points included a win-ratio analysis of the primary end point (hierarchy: 1 = death, 2 = MI, and 3 = catheterization without obstructive CAD),[20] individual safety components of the primary end point (death, MI), unplanned cardiovascular hospitalizations, and unstable angina. Prespecified secondary efficiency end points were catheterization without obstructive disease and revascularization after catheterization. Other end points included anginal symptoms using the Seattle Angina Questionnaire,[21] medication use, and radiation exposure obtained at 45 days, 6 months, and 12 months. One nonfatal MI was determined by the Clinical Events Committee to have preceded randomization and was excluded. One fatal MI was included as a death, as per the protocol (eMethods in Supplement 4) and the statistical analysis plan (Supplement 2 and Supplement 3). Testing was confirmed by medical records; events, unplanned cardiovascular hospitalizations, and ischemia-driven revascularizations were independently adjudicated.

Statistical Analysis

Assuming an 8.0% 1-year event rate with UT, we estimated that a 90% or greater power to detect a 37.5% reduction in the primary end point, with a 2-sided α of .05, would require 2096 participants. This estimate included a 10% attrition rate, 10% crossovers, 10% in whom site clinicians planned initial catheterization, and assignment of 20% of PS to deferred testing with subsequent testing in 30% (eMethods in Supplement 4).

Baseline characteristics were reported as mean (SD) or median (IQR) for continuous variables and as count (percentage) for categorical variables. Comparisons were conducted using the Wilcoxon rank sum test and Pearson χ^2 test.

Primary treatment comparisons were performed as intention to treat with a time-to-first-event analysis using the log-rank test. Kaplan-Meier event rates were estimated from the

time of randomization. Relative treatment effect size was quantified using hazard ratios (HRs), with 95% CIs estimated using Cox proportional hazards models. Proportional hazards assumptions were checked by examining treatment by log (time) interaction terms and by Schoenfeld residuals (eMethods in Supplement 4). A significance threshold of 0.049 was adjusted for 2 interim analyses (eMethods in Supplement 4).

Adjusted HRs and 95% CIs were estimated using Cox proportional hazards models including age, sex, CAD equivalent (diabetes, peripheral artery disease, or cerebrovascular disease), and intended first test stratum if randomized to UT. Treatment effect sizes were estimated for the primary end point in prespecified subgroups.

To further investigate the impact of PS vs UT, we conducted 2 sensitivity analyses: 1 prespecified per-protocol and 1 post hoc using the Society of Cardiac Angiography and Interventions (SCAI) definition[22] instead of the Fourth Universal Definition of MI[23] for periprocedural MI. All analyses used SAS software, version 9.4 (SAS Institute Inc).

Results

Participants and Characteristics

The PRECISE trial enrolled 2103 participants at 65 North American (1125 [53.5%]) and European sites from December 3, 2018, to May 18, 2021. Median (IQR) follow-up was 11.8 (11.3-12.3) months; 12-month data were obtained for 2027 participants (96.3%) (Figure 1). Mean (SD) age was 58.4 (11.5) years, 1056 were male (50.2%), and 1047 were female (49.8%). A total of 1767 participants self-identified as non-Hispanic White (84%) race and ethnicity (Table 1; eTable 1 in Supplement 4). Chest pain was the most common primary symptom (PS group, 870 [82.3%]; UT group, 876 [83.7%]), with pretest probability of obstructive CAD of 16.0% (IQR, 10.0%-26.0%).[13] Cardiac risk factors included dyslipidemia (PS group, 668 [63.2%]; UT group, 681 [65.1%]), hypertension (PS group, 642 [60.7%]; UT group,

Table 1. Characteristics of Trial Participants at Baseline, According to Study Group

Characteristic	No. (%)	
	Precision strategy (n = 1057)	Usual testing (n = 1046)
Age, mean (SD), y	58.0 (11.5)	58.9 (11.6)
Sex		
Women	508 (48.1)	539 (51.5)
Men	549 (51.9)	507 (48.5)
Racial or ethnic minority group[a]	165 (15.6)	171 (16.3)
Cardiac risk factors		
Body mass index, mean (SD)[b]	30.2 (6.6)	29.9 (6.2)
Hypertension	642 (60.7)	606 (57.9)
Diabetes	176 (16.7)	197 (18.8)
Dyslipidemia	668 (63.2)	681 (65.1)
Family history of premature CAD	404 (38.2)	395 (37.8)
Peripheral arterial or cerebrovascular disease	65 (6.1)	56 (5.4)
Current or past tobacco use	544 (51.5)	554 (53.0)
Sedentary lifestyle, No./total No. (%)	388/1056 (36.7)	379/1046 (36.2)
Risk burden[c]		
Absence of any CV risk factors	67 (6.3)	61 (5.8)
No. of risk factors per patient, mean (SD)	2.3 (1.2)	2.3 (1.2)
PROMISE minimal risk score, median (IQR)	0.24 (0.12-0.41)	0.23 (0.11-0.41)
PROMISE minimal risk score >0.46 (minimal risk)	214 (20.2)	219 (20.9)
Pretest probability, median (IQR)	16.0 (10.0-26.0)	16.0 (10.0-26.0)
ASCVD 10-y risk, mean (SD), %	11.32 (10.77)	12.28 (12.0)
ASCVD 10-y risk, median (IQR), %	7.92 (3.41-15.71)	8.22 (3.29-17.25)
Use of relevant cardiovascular medications		
β-Blocker	253 (23.9)	240 (22.9)
ACE inhibitor, ARB, or ARNI	377 (35.7)	359 (34.3)
Lipid-lowering medication	437 (41.3)	430 (41.1)
Antiplatelet medication	314 (29.7)	312 (29.8)
Antianginal medication	109 (10.3)	118 (11.3)
Anticoagulant medication	30 (2.8)	30 (2.9)

(continued)

Table 1. Characteristics of Trial Participants at Baseline, According to Study Group (continued)

Characteristic	No. (%)	
	Precision strategy (n = 1057)	Usual testing (n = 1046)
Primary presenting symptom[d]		
Chest pain	870 (82.3)	876 (83.7)
Dyspnea on exertion	107 (10.1)	105 (10.0)
Other	80 (7.6)	65 (6.2)
Type of angina		
Typical (cardiac)	249 (23.6)	257 (24.6)
Atypical (possible cardiac)	600 (56.8)	597 (57.1)
Nonanginal (noncardiac)	14 (1.3)	7 (0.7)
Dyspnea	86 (8.1)	77 (7.4)
Unable to characterize	108 (10.2)	108 (10.3)
Diagnostic test performed[e]	883 (83.5)	978 (93.5)
Results of first test after randomization		
Positive for obstructive CAD or ischemia, No./total No. (%)[f]	162/883 (18.3)	130/978 (13.3)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CV, cardiovascular; PROMISE; Prospective Multicenter Imaging Study for the Evaluation of Chest Pain.

[a] Racial or ethnic minority group was self-reported by the participant. Privacy rules only permitted collection of White/non-White and Hispanic/non-Hispanic race and ethnicity information from participants. We have summarized these data as White/non-Hispanic vs other (ie, either non-White or Hispanic).

[b] Body mass index is the weight in kilograms divided by the square of the height in meters.

[c] Risk factors included hypertension, diabetes, dyslipidemia, family history of CAD, and tobacco use.

[d] Other primary symptoms were (in descending order of frequency for overall group): palpitations, arm or shoulder pain, fatigue/weakness, epigastric/abdominal pain, neck or jaw pain, dizziness/lightheadedness, back pain, syncope, and diaphoresis.

[e] The P value for the comparison between precision strategy and usual testing is P < .001.

[f] Positive diagnostic test results include inducible ischemia or obstructive CAD on functional or anatomic testing, as defined in the eMethods in Supplement 3, and excludes uninterpretable tests. The P value for the comparison between precision strategy and usual testing is P = .003.

606 [57.9%]), any tobacco use (PS group, 544 [51.5%]; UT group, 554 [53.0%]), and diabetes (PS group, 176 [16.7%]; UT group, 197 [18.8%]), with median (IQR) 10-year atherosclerotic cardiovascular disease (ASCVD) risk (based on asymptomatic individuals) of 8.0% (3.4%-16.5%) (Table 1).[15]

Trial Intervention: Initial Testing

Overall, 1937 participants (92.2%) were tested (or deferred) as randomized. Compared with the UT group, in the PS group, testing was less frequent (883 [83.5%] vs 978 [93.5%]; P < .001), and a positive test was more likely (162 of 883 [18.3%] vs 130 of 978 [13.3%]; P = .003) (eTable 2 in Supplement 4). Among the 1057 randomly assigned to the PS group, 422 (20.1%) were classified as minimal risk and assigned to deferred testing (Table 1 and Figure 1). Most participants classified as minimal risk (138

[64.4%]) did not undergo testing during follow-up (Figure 1). Among all PS participants, 835 (78.9%) underwent cCTA (including 323 of 337 [95.8%] successful FFR-CT) at a median (IQR) of 15 (7-29) days. Among 1046 participants in the UT group, initial testing included 333 stress nuclear (31.8%), 313 stress echocardiography (29.9%), 116 exercise electrocardiogram (11.1%), 101 stress cardiac magnetic resonance imaging (9.7%), and 101 catheterization (9.7%) (eTable 3 and eFigure 1 in Supplement 4). Median (IQR) time to first test was 15 (6-33) days. Testing complications were rare (eTable 4 in Supplement 4).

Primary Net Effectiveness End Point

The primary end point event occurred in 44 participants (4.2%) in the PS group and 118 participants (11.3%) in the UT group (unadjusted HR, 0.35; 95% CI, 0.25-0.50; adjusted HR, 0.29; 95% CI, 0.20-0.41; P < .001) (Table 2, Figure 2A),[24] due to a

Table 2. Primary End Point and Additional Clinical Events According to Study Group

End point or clinical event	No. (%) Precision strategy (n = 1057)	No. (%) Usual testing (n = 1046)	Hazard ratio (95% CI) Unadjusted	Hazard ratio (95% CI) Adjusted[a]	P value
Primary composite end point	44 (4.2)	118 (11.3)	0.35 (0.25-0.50)	0.29 (0.20-0.41)	
Death or nonfatal myocardial infarction (first event only)	18 (1.7)	12 (1.1)	1.52 (0.73-3.15)	1.57 (0.76-3.27)	
Death from any cause	5 (0.5)	7 (0.7)	0.71 (0.23-2.23)	0.74 (0.24-2.35)	<.001
Nonfatal myocardial infarction	13 (1.2)	5 (0.5)	2.65 (0.96-7.36)	2.67 (0.94-7.52)	
Invasive cardiac catheterization without obstructive coronary disease	27 (2.6)	107 (10.2)	0.24 (0.16-0.36)	0.19 (0.12-0.30)	
Unplanned hospitalizations, including admissions with death or MI, No. (%)					
CV	31 (2.9)	21 (2.0)			.17
For unstable angina	9 (29.0)	5 (23.8)			.30
Catheterization and revascularization procedures					
Invasive catheterization, No. (%)	135 (12.8)	177 (16.9)			.007
Rate of finding obstructive CAD on catheterization, No./total No. (%)	108/135 (80.0)	70/177 (39.5)			<.001
Participants in trial without obstructive CAD (QCA), No. (%)	27 (2.6)	107 (10.2)			<.001
Catheterizations with subsequent revascularization, No./total No. (%)	97/135 (71.9)	54/177 (30.5)			<.001
Total revascularizations, No. (%)	97 (9.2)	54 (5.2)			
PCI, No. (%)	77 (79.4)	37 (68.5)			<.001
CABG, No. (%)	21 (21.6)	18 (33.3)			
Revascularizations performed for high-risk anatomy, No. (%)[b]	49 (50.5)	26 (48.2)			NS
Revascularizations during unplanned hospitalizations, No. (%)	15 (1.4)	8 (0.8)	NA	NA	NS
Ischemia-driven revascularizations, No. (%)	96 (99.0)	54 (100)			NS
Lesion-specific FFR-CT, No. (%) (FFR-CT data available for 76/97 participants with revascularizations)					
>0.80	2 (2.6)	NA			NA
≤0.80	74 (97.4)	NA			NA
0.76-0.80	12 (15.8)	NA			NA
≤0.75	62 (81.6)	NA			NA
Total clinical events, including first and recurrent nonfatal MI and death, (No.[%])[c]	41 (40 [3.8] participants)	30 (30 [2.9] participants)			
All death or nonfatal MI	18 (1.7)	12 (1.1)			
All death	5 (0.5)	7 (0.7)			.20
All nonfatal MI	13 (1.2)	5 (0.5)			
Unplanned CV hospitalization excluding admissions with MI or death	23 (22 [2.1] participants)	18 (18 [1.7] participants)			

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; CV, cardiovascular; FFR-CT, noninvasive coronary computed tomographic angiography-derived fractional flow reserve; MI, myocardial infarction; NA, not applicable; NS, not significant; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography.

[a] Hazard ratio was adjusted for age, sex, and coronary artery disease equivalent (diabetes, history of peripheral artery disease or cerebrovascular disease), and intended first test strata (invasive or noninvasive).

[b] High-risk anatomy was defined using QCA data as 2- or 3-vessel disease, left anterior descending artery with 70% or more stenosis or left main artery with 50% or more stenosis.

[c] Statistical testing for recurrent events was performed using the negative binomial methods for recurrent events.[24]

lower rate of catheterization without obstructive CAD in PS (PS group, 27 [2.6%]; UT group, 107 [10.2%]; HR, 0.24; 95% CI, 0.16-0.36), with no statistically significant difference in the safety components of death (PS group, 5 [0.5%]; UT group, 7 [0.7%]; HR, 0.71; 95% CI, 0.23-2.23), death or nonfatal MI (PS group, 18 [1.7%]; UT group, 12 [1.1%]), and nonfatal MI (PS group, 13 [1.2%]; UT group, 5 [0.5%]; HR, 2.65; 95% CI, 0.96-

7.36) (Figure 2B). The nonsignificant difference of 6 more events in the PS group (0.3% of trial cohort) was largely attributable to differences in type 2 MIs (5 vs 2) and periprocedural MIs (4 vs 1) (eTable 5A-B in Supplement 4). One-third of MIs occurred before testing (PS group, 3 of 13 [23%]; UT group, 2 of 5 [40%]). No PS participant assigned to deferred testing died or had an MI.

Figure 2. Composite Primary End Point and Components as a Function of Time After Randomization
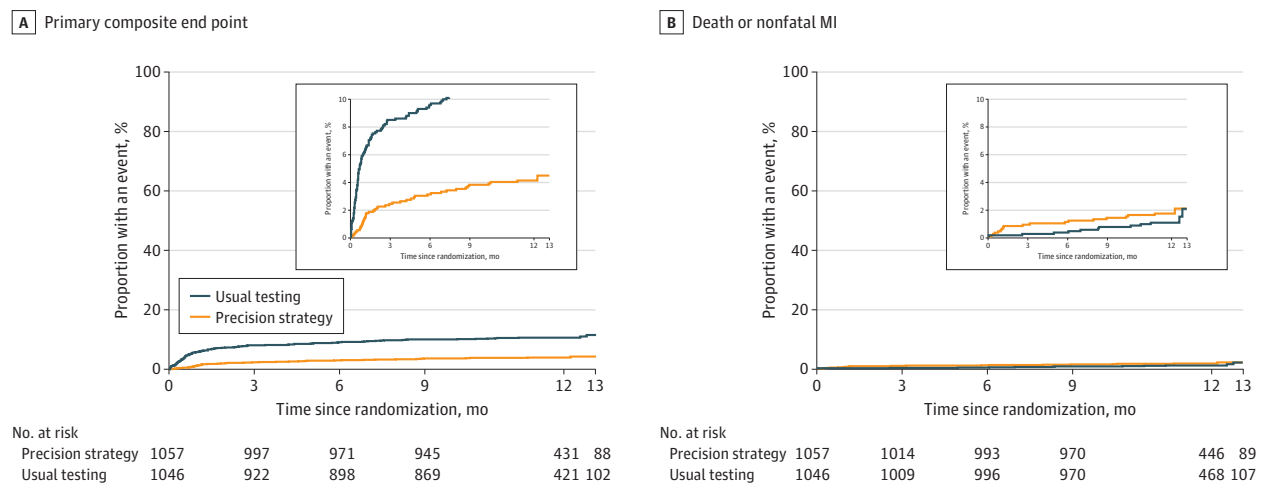
Shown are unadjusted Kaplan-Meier estimates of the primary composite end point (death from any cause, nonfatal myocardial infarction [MI], invasive catheterization without obstructive coronary artery disease [CAD]) (A) and the components death or nonfatal MI (B). In both panels, the inset shows the same data on an enlarged y-axis. The hazard ratios were adjusted for age, sex, risk equivalent of CAD (history of diabetes, peripheral arterial disease, or cerebrovascular disease), and the prespecified intended functional test if the patient were to be randomly assigned to the usual testing (UT) group. A, The adjusted hazard ratio for the primary end point for the precision strategy (PS), as compared with UT, was 0.29 (95% CI, 0.20-0.41). B, The adjusted hazard ratio for death or nonfatal MI for the PS, as compared with UT, was 1.57 (95% CI, 0.76-3.27).

Primary results were consistent in prespecified subgroups including age, sex, race, geographic region, CAD equivalent, pretest probability, 10-year ASCVD risk, and PMRS risk strata (**Figure 3**). A significant interaction term by intended first test stratum suggests a greater effect in the planned invasive arm. There were 3 SARS-CoV-2–related deaths (1 PS, 2 UT); excluding these events did not change the primary end point.

Secondary Efficiency End Points

Among those receiving an initial noninvasive test, participants in the PS group received fewer second tests (30 of 879 [3.4%] vs 87 of 877 [9.9%] in the UT group). Among PS, 135 (12.8%) underwent catheterization, of which 108 (80.0%) showed obstructive CAD (Table 2; eFigure 2 in Supplement 4).[24] More participants in the UT group underwent catheterization (177 [16.9%] vs 135 [12.8%]; *P* = .007), but fewer showed obstructive CAD (70 [39.5%] vs 108 [80.0%]; *P* < .001). Revascularization was performed more commonly in the PS group than in the UT group (97 [9.2%] vs 54 [5.2%]; *P* < .001), due to more percutaneous coronary interventions with PS (77 [79.4%] vs 37 [68.5%]) with similar number of coronary artery bypass graftings (21 [21.6%] vs 18 [33.3%]) (Table 2).[24] All but 1 revascularization was adjudicated to be ischemia driven (PS group), 15 were unplanned in the PS group vs 8 in the UT group (Table 2),[24] and 49 revascularization procedures (50.5%) were high risk in the PS group vs 26 (48.2%) in the UT group (2- or 3-vessel disease, left anterior descending artery ≥70%, or left main stenosis).

Secondary Safety End Points

The safety composite of death/MI was similar (HR, 1.52; 95% CI, 0.73-3.15). Win-ratio analysis prioritizing the safety components of death and nonfatal MI over catheterization without obstructive disease favored PS (2.81; 95% CI, 1.26-6.41; *P* < .001) (eTable 6 in Supplement 4). In a prespecified per-protocol analysis, the difference in nonfatal MIs in PS (10 [1.4%] vs 4 [0.8%]) was smaller than in the intention-to-treat analysis and remained nonsignificant (eTable 7A in Supplement 4). In a post hoc analysis of the intention-to-treat population using the SCAI definition of periprocedural MI, the difference was also smaller (10 [1.2%] vs 5 [1.3%]) (eTable 7B in Supplement 4). Considering only nonperiprocedural MIs, the difference is further narrowed (8 [0.8%] vs 5 [0.5%]) as is the difference in the composite death/nonfatal MI safety end point, to 3 events.

Unplanned cardiovascular hospitalizations including admissions with death or MI (PS group, 31 of 1057 [2.9%] vs UT group, 21 of 1046 [2.0%]; *P* = .17) and unstable angina (PS group, 9 of 1057 [29%] vs UT group, 5 of 1046 [23.8%]) were uncommon and similar between groups (Table 2).[24] In post hoc analyses, adding unplanned cardiovascular hospitalization to the primary end point did not change results (adjusted HR, 0.39; 95% CI, 0.29-0.53), nor did including unplanned revascularizations (adjusted HR, 0.40; 95% CI, 0.29-0.54) (eTable 7D in Supplement 4). Total clinical events including recurrent death or MI events and unplanned cardiovascular admissions without MI or death during the same episode of care, and excluding catheterization without obstructive disease, did not differ between arms (Table 2).[24] Mean (SD) estimated radiation exposure in PS was 5.2 (5.4) mSv vs 4.7 (6.0) mSv in the UT group (eTable 8 in Supplement 4).

Figure 3. Effects of Precision Strategy on the Primary End Point, According to Baseline Characteristics

Characteristic	Precision strategy No./total No. (%)	Usual testing No./total No. (%)	Hazard ratio (95% CI)		Interaction P value
Sex					.42
Male	27/549 (5.6)	60/507 (12.7)	0.40 (0.253-0.627)		
Female	17/508 (3.4)	58/539 (11.8)	0.30 (0.173-0.511)		
Age, y					.32
<65	20/737 (2.8)	60/693 (9.4)	0.30 (0.183-0.502)		
≥65	24/320 (8.8)	58/353 (18.0)	0.43 (0.267-0.692)		
Race and ethnicity					.96
White/non-Hispanic	39/892 (4.8)	103/875 (12.6)	0.35 (0.244-0.511)		
Other[a]	5/165 (3.2)	15/171 (10.3)	0.34 (0.125-0.943)		
Geographic region					.14
North America	19/609 (3.8)	38/596 (7.7)	0.49 (0.280-0.843)		
Europe	25/448 (5.6)	80/450 (18.0)	0.29 (0.182-0.448)		
CAD equivalent (diabetes or peripheral arterial or cerebrovascular disease)					.68
Yes	12/226 (5.5)	37/237 (15.8)	0.32 (0.165-0.607)		
No	32/831 (4.3)	81/809 (11.2)	0.37 (0.247-0.559)		
Primary symptom presentation					.45
Typical angina (cardiac)	17/249 (7.0)	41/257 (16.3)	0.41 (0.230-0.714)		
Atypical pain (possible cardiac)	16/600 (3.2)	66/597 (11.8)	0.23 (0.132-0.395)		
Dyspnea	4/86 (4.8)	7/77 (15.5)	0.50 (0.145-1.696)		
Nonanginal (noncardiac)/other	0/14 (0.0)	0/7 (0.0)	NA		
Intended first test is					<.001
Invasive	8/105 (7.7)	68/105 (66.1)	0.06 (0.030-0.131)		
Noninvasive	36/952 (4.2)	50/941 (6.3)	0.71 (0.465-1.095)		
PROMISE minimal risk score					.23
Minimal	2/214 (0.9)	13/208 (8.0)	0.15 (0.033-0.653)		
Elevated + atherosclerosis	42/843 (5.4)	105/838 (13.2)	0.38 (0.264-0.541)		
Diamond and Forrester pretest probability, %					.88
<5	0/63 (0.0)	1/44 (2.3)	NA		
5-15	11/411 (2.8)	39/411 (10.5)	0.27 (0.139-0.532)		
>15	26/475 (6.1)	74/483 (16.4)	0.33 (0.214-0.522)		
ASCVD 10 y event risk score, %					.11
<7.5	3/356 (0.9)	25/345 (8.4)	0.11 (0.034-0.374)		
7.5-15	17/374 (4.6)	32/327 (9.9)	0.45 (0.248-0.804)		
>15	24/327 (8.5)	61/374 (17.7)	0.42 (0.265-0.681)		

Favors precision strategy — Favors usual testing

0.05   0.25   0.5   1   2   3
Hazard ratio (95% CI)

The primary end point was the combination of all-cause death, nonfatal myocardial infarction, or invasive catheterization without obstructive coronary artery disease (CAD). Unadjusted hazard ratios for the precision strategy as compared with usual testing are shown; the horizontal lines indicate 95% CIs. ASCVD indicates atherosclerotic cardiovascular disease; PROMISE, Prospective Multicenter Imaging Study for the Evaluation of Chest Pain.

[a] Other indicates non-White or Hispanic race and ethnicity. Privacy rules only permitted collection of White/non-White and Hispanic/non-Hispanic race and ethnicity information from participants. We have summarized these data as White/non-Hispanic vs other (ie, either non-White or Hispanic).

Medication Use and Quality of Life

Use of antiplatelet and lipid-lowering medications increased among PS (*P* = .004 and *P* < .001 for Cochrane-Armitage time trends, respectively) but not UT (*P* = .15 and *P* = .79, respectively), resulting in higher use among PS at 1 year: antiplatelet agents, (321 of 900 [35.7%] vs 237 of 873 [27.1%]; *P* < .001) and lipid-lowering medications (450 of 900 [50.0%] vs 365 of 873 [41.8%]; *P* < .001) without a significant difference in antihypertensives (eTable 8 in Supplement 4). The proportion of participants with frequent angina (Seattle Angina Questionnaire angina frequency score <80) declined from baseline in both groups and was similar at 12 months (141 of 894 [15.8%] for PS vs 140 of 868 [16.1%] for UT; *P* = .84); results were similar in typical angina (eTable 9 and 10 in Supplement 4).

Discussion

For the first time, to our knowledge, the PRECISE study demonstrates in a large randomized clinical trial that a novel initial care pathway of risk-guided patient-specific testing deferral for minimal-risk patients combined with cCTA with selective FFR-CT for the remaining patients improves clinical efficiency (catheterization without obstructive CAD) with no statistically significant adverse effect on safety (death or MI) at 1 year.

The PRECISE trial was designed to test patient selection and refinements of cCTA-based evaluation strategies in patients with stable chest pain who were previously tested in 2

large randomized clinical trials.[2,3] Those trials clearly demonstrated equivalent or better outcomes for cCTA compared with usual stress testing but a propensity for initial cCTA testing to lead to over testing and unnecessary catheterization referral. The PRECISE PS was designed to improve these 2 weak points: (1) to reduce excess testing in the lowest-risk patients where diagnostic yield is extremely low and (2) to reduce excess referral to catheterization. The use of a validated risk score in the PS addressed the former problem, whereas the selective use of FFR-CT addressed the latter. Of note, the PRECISE trial cannot address alternative approaches not tested in the trial. The PS tested in this trial is concordant with current AHA/ACC Chest Pain guideline recommendations[11] and extends the evidence base supporting them for management of stable chest pain.

Both the PROMISE and SCOT-HEART trials confirmed excellent prognosis in the population of patients with stable chest pain while also highlighting unresolved inefficiencies in noninvasive and invasive testing. The PROMISE trial showed a low rate of the composite end point of death, nonfatal MI, unstable angina hospitalization, and major procedural complications of 1.5% per year, with no difference between arms.[3] However, the trial has been criticized for testing very low-risk patients and a 50% higher rate of catheterization in the cCTA arm.[3] The initial report of the SCOT-HEART trial also showed a low rate of cardiovascular death or MI (2% per year) and a borderline difference which became significant by 5 years.[2] The SCOT-HEART trial also noted higher initial new referrals to catheterization in the cCTA arm (94 vs 8) with higher late referrals with standard care.[2] The PRECISE trial provides a pragmatic pathway addressing both concerns, providing randomized evidence in support of a quantitative algorithm for deferred testing and for the use of cCTA with selective FFR-CT as the initial test. Our findings provide practical data addressing the recognized need to improve the evaluation of patients with chest pain.[11,12]

Catheterization without obstructive disease was selected as the clinical efficiency measure reflecting the role of noninvasive testing as a gatekeeper and its association with an excess risk of major procedural complications,[4] lower health-related quality of life, and increased costs.[25] Additionally, invasive procedures may lead to unnecessary revascularization of borderline lesions in the absence of ischemia.[26] Further, catheterization without obstructive disease has been used as a primary or secondary end point or component in previous trials[3,4,7,10] and adopted as a quality metric within the US (National Cardiovascular Data Registry CathPCI).[27] It is inefficient in clinical practice and represents a failure of the goals of chest pain guidelines,[5,11,12] which seek to limit unnecessary testing and maximize diagnostic yield. In the PRECISE trial, PS efficiency is supported by reduced diagnostic testing overall, reduced layered testing, and a higher likelihood of an abnormal test result (test yield).

The use of selective FFR-CT to provide hemodynamic information in the PRECISE trial likely avoided pitfalls of previous studies. Unlike trials of cCTA alone, the PS in the PRECISE trial reduced diagnostic catheterizations, did not change the frequency of unplanned cardiovascular hospitalizations (including those for unstable angina[3]), and matched the reduction of symptom burden achieved by UT. These results are consistent with previously reported trials of CTA with selective FFR-CT in patients with stable chest pain. The Fractional Flow Reserve-Derived from Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain (FORECAST) trial was a smaller trial with an economic primary end point[8] and only considered safety and effectiveness as secondary outcomes. The Effect of On-Site CT-Derived Fractional Flow Reserve on the Management of Decision-Making for Patients With Stable Chest Pain (TARGET) trial compared locally determined FFR-CT vs standard care (87.5% exercise electrocardiogram) as a second test in participants with known CAD.[10] The addition of FFR-CT reduced unnecessary catheterizations while increasing catheterization yield for revascularization, with no impact on adverse events or angina reduction. Although these results are similar, the PRECISE trial addresses the substantially larger population of patients without any previous testing and therefore without known CAD, and selectively applies cCTA with or without FFR-CT only in patients with a predefined threshold of pretest risk.

Current guidelines for initial evaluations recognize the problem of overtesting and suggest deferring testing using either clinical gestalt or pretest probability models, none of which have been prospectively tested.[13,14] Our stratified randomization of low-risk participants allows direct comparison of PS and UT and provides much-needed prospective, pragmatic, randomized evidence supporting the PMRS as an effective and safe pretest probability algorithm for selecting patients suitable for deferred testing.

The PRECISE trial recognized the importance of safety by including this in the primary end point. The small nonsignificant difference in death and an opposite nonsignificant difference in nonfatal MIs are of uncertain clinical import. Because CIs were very wide, these comparisons are inconclusive, and type II error cannot be excluded. However, numerous factors weigh against causality. Most important among these is the prespecified per-protocol analysis, excluding participants who did not receive their assigned evaluation strategy, which showed a smaller difference in nonfatal MI, as did a post hoc analysis using the alternative SCAI definition for periprocedural MIs (eTable 7B in Supplement 4),[22] indicating that the magnitude of the nonsignificant difference in nonfatal MI is sensitive to definition. Further, the prognostic significance of periprocedural MI remains unclear. Finally, post hoc analyses enlarging the primary end point to include unplanned cardiovascular hospitalizations and unplanned revascularizations remained strongly in favor of the safety and efficacy of PS.

A noteworthy advantage of PS is higher use of lipid-lowering (50.0% vs 41.8%) and antiplatelet (35.7% vs 27.1%) medications at 1 year compared with UT, despite less frequent use of catheterization (135 vs 177). These findings closely replicate previous trials[2,3] and show that the detailed anatomic and physiological data provided by cCTA with or without FFR-CT enhance the use of prognostically beneficial preventive medical therapies.[28,29] Importantly, in the

SCOT-HEART trial, the 40% reduction in MIs in the CTA arm was fully attributable to higher preventive medication use.

Crucially, the PRECISE cohort was similar in risk burden and symptoms to other large trials of initial testing in stable symptoms and suspected CAD.[2,3,16] Given the PRECISE trial's pragmatic design, management including medical therapy and decisions regarding revascularization in both arms was site directed, thereby improving the generalizability of results. Site decisions resulted in total catheterizations being less frequent in PS and revascularization more frequent, reflecting real-world practice where revascularization is commonly used for hemodynamically significant obstructive disease. This finding is similar to that of the TARGET trial[10] (although invasive catheterization was performed per protocol for any positive FFR-CT or functional test) and complementary to, not in conflict with, the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial.[30,31] Indeed, the physiologic discipline that FFR-CT imposes on cCTA anatomic results, by downgrading anatomically significant stenoses and identifying hemodynamic significance in more modest lesions,[31] appears to have protected PRECISE participants from excess cardiac catheterization seen in earlier cCTA-only trials.[3] Importantly, the nearly 2-fold greater number of participants with high-risk anatomy who underwent revascularization in the precision arm suggests that, given our randomized cohort, there may have been underdetection of this group with usual testing. However, the greater rates of revascularization in the precision arm do not translate into fewer MIs and cardiovascular hospitalizations, which were numerically higher in the precision arm.

Limitations

Several limitations of the trial should be considered. The PS addresses choices often considered simultaneously in real-world decision-making, as they are in the PRECISE trial: risk stratification, deferred testing, and use of cCTA with selective FFR-CT as the initial test. The separate effects of each choice cannot be determined. The pragmatic trial design precludes evaluation of different UT choices or close monitoring of trial recommendations to use optimal medical treatment in all participants. Interaction testing indicated a point estimate of 0.71 for the primary end point in the noninvasive arm, but the CI upper bound is 1.09, indicating that this potentially favorable subgroup estimate lacks sufficient precision to exclude the null effect. Uncertainty remains regarding the prognostic effects of the PS beyond 1-year follow-up of the PRECISE trial, particularly regarding the revascularization rates and beneficial effects of greater preventive medication use, which are likely underestimated at 1 year.[2] Similarly, nonfatal periprocedural and type 2 MIs account for much of the difference between arms and may have variable prognostic importance.[23,32-34] Costs/resource use will be reported separately.

Conclusions

In this pragmatic randomized clinical trial, we sought to address remaining critical questions in the initial evaluation of participants with stable symptoms and suspected CAD but without known coronary disease. A strategy using deferred testing for minimal risk and cCTA with or without FFR-CT for others increased clinical efficiency as assessed by catheterization without obstructive disease at 1 year. Death or MI events were infrequent and not statistically different in the 2 arms, although MI events were numerically higher in PS. These results were obtained while reducing testing use, increasing diagnostic yield, and increasing preventive medical therapy use. Additional randomized clinical trials are needed to verify these findings, including safety, and to fully evaluate current guideline recommendations for initial testing in these patients.

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REFERENCES

1. Hoorweg BB, Willemsen RT, Cleef LE, et al.
Frequency of chest pain in primary care, diagnostic
tests performed and final diagnoses. *Heart*. 2017;
103(21):1727-1732. doi:10.1136/heartjnl-2016-310905

2. Newby DE, Adamson PD, Berry C, et al;
SCOT-HEART Investigators. Coronary CT
angiography and 5-year risk of myocardial
infarction. *N Engl J Med*. 2018;379(10):924-933.
doi:10.1056/NEJMoa1805971

3. Douglas PS, Hoffmann U, Patel MR, et al;
PROMISE Investigators. Outcomes of anatomical vs
functional testing for coronary artery disease.
N Engl J Med. 2015;372(14):1291-1300. doi:10.1056/
NEJMoa1415516

4. Maurovich-Horvat P, Bosserdt M, Kofoed KF,
et al; DISCHARGE Trial Group. CT or invasive
coronary angiography in stable chest pain. *N Engl J
Med*. 2022;386(17):1591-1602. doi:10.1056/
NEJMoa2200963

5. National Institute for Health and Care
Excellence. Recent-onset chest pain of suspected
cardiac origin: assessment and diagnosis. Accessed
July 19, 2023. https://www.nice.org.uk/Guidance/
cg95

6. National Institute for Health and Care
Excellence. HeartFlow FFRCT for estimating
fractional flow reserve from coronary CT
angiography. Accessed July 19, 2023. https://www.
nice.org.uk/guidance/mtg32

7. Douglas PS, De Bruyne B, Pontone G, et al;
PLATFORM Investigators. 1-Year outcomes of
FFRCT-guided care in patients with suspected
coronary disease: the PLATFORM study. *J Am Coll
Cardiol*. 2016;68(5):435-445. doi:10.1016/j.jacc.2016.
05.057

8. Curzen N, Nicholas Z, Stuart B, et al. Fractional
flow reserve derived from computed tomography
coronary angiography in the assessment and
management of stable chest pain: the FORECAST
randomized trial. *Eur Heart J*. 2021;42(37):3844-
3852. doi:10.1093/eurheartj/ehab444

9. Patel MR, Nørgaard BL, Fairbairn TA, et al. 1-y Impact on medical practice and clinical outcomes of FFRCT: the ADVANCE Registry. *JACC Cardiovasc Imaging*. 2020;13(1 Pt 1):97-105. doi:10.1016/j.jcmg.2019.03.003

10. Yang J, Shan D, Wang X, et al. On-site computed tomography–derived fractional flow reserve to guide the management of patients with stable coronary artery disease: the TARGET randomized trial. *Circulation*. 2023;147(18):1369-1381. doi:10.1161/CIRCULATIONAHA.123.063996

11. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2021;144(22):e368-e454. doi:10.1161/CIR.0000000000001029

12. Knuuti J, Wijns W, Saraste A, et al; ESC Scientific Document Group. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407-477. doi:10.1093/eurheartj/ehz425

13. Juarez-Orozco LE, Saraste A, Capodanno D, et al. Impact of a decreasing pretest probability on the performance of diagnostic tests for coronary artery disease. *Eur Heart J Cardiovasc Imaging*. 2019;20(11):1198-1207. doi:10.1093/ehjci/jez054

14. Fordyce CB, Douglas PS, Roberts RS, et al; Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) Investigators. Identification of patients with stable chest pain deriving minimal value from noninvasive testing: the PROMISE minimal-risk tool, a secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2017;2(4):400-408. doi:10.1001/jamacardio.2016.5501

15. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation*. 2014; 129(25)(suppl 2):S49-S73. doi:10.1161/01.cir.0000437741.48606.98

16. Nanna MG, Vemulapalli S, Fordyce CB, et al. The prospective randomized trial of the optimal evaluation of cardiac symptoms and revascularization: Rationale and design of the PRECISE trial. *Am Heart J*. 2022;245:136-148. doi:10.1016/j.ahj.2021.12.004

17. Adamson PD, Fordyce CB, McAllister DA, Udelson JE, Douglas PS, Newby DE. Identification of patients with stable chest pain deriving minimal value from coronary computed tomography angiography: an external validation of the PROMISE minimal-risk tool. *Int J Cardiol*. 2018;252:31-34. doi:10.1016/j.ijcard.2017.09.033

18. Rasmussen LD, Fordyce CB, Nissen L, et al. The PROMISE minimal risk score improves risk classification of symptomatic patients with suspected CAD. *JACC Cardiovasc Imaging*. 2022;15 (8):1442-1454. doi:10.1016/j.jcmg.2022.03.009

19. Nanna MG, Wang TY, Chiswell K, et al. Estimating the real-world performance of the PROMISE minimal-risk tool. *Am Heart J*. 2021;239: 100-109. doi:10.1016/j.ahj.2021.05.016

20. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite end points in clinical trials based on clinical priorities. *Eur Heart J*. 2012;33(2):176-182. doi:10.1093/eurheartj/ehr352

21. Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol*. 1995;25 (2):333-341. doi:10.1016/0735-1097(94)00397-9

22. Moussa ID, Klein LW, Shah B, et al; Society for Cardiovascular Angiography and Interventions. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *Catheter Cardiovasc Interv*. 2014;83(1):27-36. doi:10.1002/ccd.25135

23. Thygesen K, Alpert JS, Jaffe AS, et al; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *Circulation*. 2018;138(20):e618-e651. doi:10.1161/CIR.0000000000000617

24. Lawless JF. Negative binomial and mixed Poisson regression. *Can J Stat*. 1987;15(3):209-225. doi:10.2307/3314912

25. Eastwood JA, Doering LV, Dracup K, Evangelista L, Hays RD. Health-related quality of life: the impact of diagnostic angiography. *Heart Lung*. 2011;40(2):147-155. doi:10.1016/j.hrtlng.2010.05.056

26. Piccolo R, Giustino G, Mehran R, Windecker S. Stable coronary artery disease: revascularisation and invasive strategies. *Lancet*. 2015;386(9994): 702-713. doi:10.1016/S0140-6736(15)61220-X

27. Dehmer GJ, Weaver D, Roe MT, et al. A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the US: a report from the CathPCI Registry of the National Cardiovascular Data Registry, 2010 through June 2011. *J Am Coll Cardiol*. 2012;60(20):2017-2031. doi:10.1016/j.jacc.2012.08.966

28. Ladapo JA, Hoffmann U, Lee KL, et al. Changes in medical therapy and lifestyle after anatomical or functional testing for coronary artery disease. *J Am Heart Assoc*. 2016;5(10):e003807. doi:10.1161/JAHA.116.003807

29. Hoffmann U, Ferencik M, Udelson JE, et al; PROMISE Investigators. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation*. 2017;135(24): 2320-2332. doi:10.1161/CIRCULATIONAHA.116.024360

30. Hochman JS, Anthopolos R, Reynolds HR, et al; ISCHEMIA-EXTEND Research Group. Survival after invasive or conservative management of stable coronary disease. *Circulation*. 2023;147(1):8-19. doi:10.1161/CIRCULATIONAHA.122.062714

31. Fairbairn TA, Nieman K, Akasaka T, et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE Registry. *Eur Heart J*. 2018;39(41):3701-3711. doi:10.1093/eurheartj/ehy530

32. Chapman AR, Shah ASV, Lee KK, et al. Long-term outcomes in patients with type 2 myocardial infarction and myocardial injury. *Circulation*. 2018;137(12):1236-1245. doi:10.1161/CIRCULATIONAHA.117.031806

33. Gregson J, Stone GW, Ben-Yehuda O, et al. Implications of alternative definitions of periprocedural myocardial infarction after coronary revascularization. *J Am Coll Cardiol*. 2020;76(14): 1609-1621. doi:10.1016/j.jacc.2020.08.016

34. Hara H, Serruys PW, Takahashi K, et al; SYNTAX Extended Survival Investigators. Impact of periprocedural myocardial infarction on outcomes after revascularization. *J Am Coll Cardiol*. 2020;76 (14):1622-1639. doi:10.1016/j.jacc.2020.08.009