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Clinical and Economic Implications of Inconclusive Noninvasive Test Results in Stable Patients With Suspected Coronary Artery Disease: Insights From the PROMISE Trial

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Abstract

Background: Inconclusive noninvasive tests (NITs) complicate the care of patients with suspected coronary artery disease, but their prevalence and impact on management, outcomes, and costs are not well described.

Methods: PROMISE patients were randomized to stress testing (n=4533) or CT angiography (CTA) (n=4677). We assessed relationships between inconclusive results, subsequent testing, a composite outcome (death, myocardial infarction, or hospitalization for unstable angina), and healthcare expenditures.

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Results: Overall, 8.0% of tests were inconclusive (9.7% stress, 6.4% CTA). Compared with negative tests, inconclusive tests were more often referred to a second NIT (stress: 14.6% vs. 8.5%, OR 1.91; CTA: 36.5% vs. 8.4%, OR 5.95, p<0.001) and catheterization (stress: 5.5% vs. 2.4%, OR 2.36; CTA: 23.4% vs. 4.1%, OR 6.49, p<0.001), and composite outcomes were higher for both inconclusive tests (stress: 3.7% vs. 2.0%, HR 1.81, p=0.034; CTA: 5.0% vs. 2.2%, HR 1.85, p=0.044) and positive tests (stress: 8.3% vs. 2.0%, HR 3.50; CTA: 9.2% vs. 2.2%, HR 3.66, p<0.001). 24-month costs were higher for inconclusive tests than negative tests by $2905 (stress) and $4030 (CTA).

Conclusion: Among patients with stable chest pain undergoing an NIT, inconclusive results occurred in 6% of CTA and 10% of stress tests. Compared to those with conclusive negative tests, individuals with inconclusive results more often underwent subsequent testing, had increased medical costs and experienced worse outcomes.

Clinical Summary

Evaluation of suspected coronary artery disease with noninvasive testing can sometimes yield inconclusive results. The current study sought to characterize the frequency of such inconclusive results and their implications on subsequent testing, clinical outcomes, and costs stratified by a randomized assignment to functional (stress) or anatomic (CT angiography) testing strategy. We found that about 1 in 12 noninvasive tests were inconclusive; when compared to negative tests, inconclusive tests led to more secondary noninvasive and invasive testing, with higher 24-month costs regardless of testing strategy. Patients with inconclusive results had worse clinical outcomes (all-cause mortality, myocardial infarction, or hospitalization for unstable angina) when compared to those with negative noninvasive tests even after adjustment for important clinical variables. Although we cannot directly address the reasons for these worse outcomes, only one third of patients went on to receive additional testing. Our findings highlight the possibility that in current real-world practice, patients with an inconclusive noninvasive test are at higher risk than those with a negative test, and may therefore warrant consideration for follow-up testing or further investigation, as clinically appropriate.

Journal Subject Terms

Diagnostic Testing; Exercise Testing; Coronary Artery Disease; Cost-Effectiveness

Keywords

Non-Invasive Testing; CT Angiography; Stress Testing; Inconclusive Results; Cost-Effectiveness

Introduction

Stable chest pain triggering suspicion of obstructive coronary artery disease (CAD) is often managed by noninvasive testing (NITs)[1–3] and is associated with over $500 million in United States annual healthcare expenditures.[4,5] Although data from the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) indicated that the type of NIT chosen (anatomic vs. functional stress testing) did not affect midterm clinical outcomes,[6] different types of tests may vary in their ability to provide conclusive, diagnostic

information among different patient populations. Obtaining conclusive results from NITs is important to guide proper diagnosis, risk stratification and management and enhances patient satisfaction by providing a conclusive “answer” to the cause of their symptoms. Despite this, little has been published on the prevalence and predictors of inconclusive diagnostic testing, and on the impact inconclusive results have on downstream management, clinical outcomes, and healthcare expenditures.

The PROMISE trial randomized patients with stable chest pain undergoing evaluation for suspected CAD to either functional stress testing or anatomic testing with coronary computed tomographic angiography (CTA).[6] The trial followed patients over a median of 25 months, allowing for an in-depth evaluation of the prevalence and impact of NIT results. The purpose of the current study is to 1) assess the prevalence of inconclusive NIT results and patient characteristics associated with inconclusive results; 2) determine the association between inconclusive tests, subsequent patient management, and clinical outcomes across testing modality; and 3) estimate the economic impact of inconclusive results.

Methods

The complete data set for the PROMISE trial has been deposited with the National Institutes of Health and is publicly available (https://biolincc.nhlbi.nih.gov/studies/promise/).

Study Cohort and Design

The PROMISE trial recruited outpatients without known CAD who presented with stable angina between July 2010 and September 2013 across 193 sites in North America.[6,7] In brief, after obtaining informed written consent, the trial randomized 10,003 patients to anatomic evaluation (CTA with ≥64-slice multidetector scanning) versus functional stress testing (with the modality at the sites’ discretion including: exercise electrocardiography [ECG], exercise or pharmacologic stress echocardiography, or exercise or pharmacologic stress nuclear testing). For both arms, the local clinician was responsible for performing the test, its interpretation, and any subsequent clinical decision making. Local or central institutional review board at each center and enrolling site approved the study protocol.

For this per-protocol analysis, we included all patients in the primary PROMISE analysis except those who were not tested as randomized (n=770) or were missing key information regarding conclusiveness (n=23) (see Figure I in the Data Supplement). An intention-to-treat sensitivity analysis was also performed for comparative purposes (see Tables I and II in the Data Supplement) which excluded those who did not have the randomized test or had missing data (n=464). The relationships between test results (positive, negative, and inconclusive), NIT type, subsequent testing, and a composite outcome of all-cause death, myocardial infarction (MI), and unstable angina hospitalization (UAH) were assessed, and conclusive negative results were used as the reference group for comparisons with either inconclusive or positive results. In addition, the economic impact of inconclusive versus conclusive negative testing was evaluated.

Definitions of Conclusive and Inconclusive Testing

All “positive” and “negative” tests were considered to be conclusive (see result classification algorithms for each test type in Supplemental Figures II-VII). In brief, a positive exercise ECG (non-imaging) was defined as ST-segment changes consistent with ischemia during stress or early termination (<3 minutes) due to symptom reproduction, hypotension, and/or arrhythmia. Positive stress nuclear and stress echocardiography testing were defined as inducible ischemia in at least one of either anterior, inferior, or lateral territory corresponding to an expected, left anterior descending, right coronary, or left circumflex artery distribution or if an exercise stress test was terminated early (<3 minutes) due to ST-segment changes consistent with ischemia, symptom reproduction, hypotension, and/or arrhythmia. A positive CTA was defined as ≥70% stenosis in at least one epicardial artery or ≥50% stenosis in the left main artery. A negative test was defined as the absence of the above criteria in an otherwise technically conclusive study; for the purposes of this study, scar alone was insufficient for a positive result as this can arise from etiologies other than CAD.

Inconclusive test results were defined as a non-positive test considered by the site to be non-diagnostic or if maximum achieved heart rate with exercise or dobutamine stress was <85% age-predicted without evidence of ischemia. In addition, exercise ECG testing was considered to be inconclusive if the stress ECG was deemed borderline or indeterminate by the site due to poor technical quality. To maximize generalizability to a real-world clinic setting, all tests were performed and interpreted by each individual site. Reasons for inconclusiveness are heterogeneous (Supplemental Figures II-VII). Positive invasive coronary angiography (ICA) was defined as site interpretation with ≥70% stenosis in at least one epicardial artery or ≥50% stenosis in the left main artery.

Statistical Analyses

All analyses were performed on a per-protocol basis, except for the intention-to-treat sensitivity analyses (Supplemental Tables I and II). Baseline characteristics including demographics, cardiac risk factors, likelihood of CAD, and type of NIT were described using the median (25th, 75th percentile) for continuous variables and percentages for categorical variables. Descriptive statistical testing included the Wilcoxon rank sum test for continuous variables and chi-square testing for categorical variables. An unadjusted logistic regression model was used to assess the association between randomized NIT modality (functional testing vs. CTA), NIT type, and NIT inconclusiveness. Unadjusted logistic regression was also used to assess the association between NIT inconclusiveness and referral to second NIT and ICA. A multivariable logistic regression model assessed these associations after adjusting with prespecified variables including age, sex, race, body mass index, diabetes, smoking status/history, CAD equivalent, site characterization of chest pain (e.g. typical, atypical, or non-cardiac), provider estimation of likelihood of obstructive epicardial disease (high or very high), hypertension, dyslipidemia, family history of premature CAD, participation in physical activity, Framingham Risk Score (2008), and Diamond-Forrester score (2011). The linearity assumption was used for all continuous adjustment variables, and an appropriate nonlinear form was used in cases where the assumption did not hold..

The frequency and raw rate of the primary clinical event (time to all-cause death, MI, or UAH) was tabulated by comparison groups. An unadjusted Cox proportional hazards model was fitted to assess the association between NIT inconclusiveness and clinical outcomes. Proportional hazards assumptions were assessed for NIT inconclusiveness. If a substantial violation was found, measures were taken to identify an appropriate time-dependent representation that was used throughout. A multivariable Cox regression model was fitted to assess this association after adjustment for confounding variables as above. Both logistic regression and Cox regression models used patients with conclusive negative tests as the reference cohort.

Cost Analyses

Cost estimates were derived from 1) Premier Research Database for diagnostic testing, 2) hospital billing data, and 3) 2014 Medicare reimbursement schedule for physician costs. An adjusted repeated measures, mixed model was used to assess the association between inconclusive test results and costs over the first 24 months as previously described (see also the Data Supplement).[8]

Results

Baseline Characteristics

Among the 9210 patients in the PROMISE trial receiving testing, 737 (8.0%) had an inconclusive result (6.4% CTA, 9.7% stress). By stress modality, inconclusive frequency was 23.7% for exercise ECG, 11.9% for stress echocardiography, and 6.9% for stress nuclear. Among stress echocardiography and nuclear testing, the frequency of inconclusive results by stressor was 3.3% for pharmacologic stress and 10.5% for exercise stress ($p<0.001$). The CTA test result groups varied significantly with respect to age, race, sex, body mass index, smoking status, CAD risk equivalent, site characterization of chest pain, provider assessment of obstructive epicardial disease, ASCVD risk, Framingham risk score, Diamond-Forrester score, and prevalence of diabetes, hypertension, and dyslipidemia ($p<0.01$) (Table 1). Median coronary artery calcium (CAC) score was 402 (31, 1109) in inconclusive CTA results compared to 387 (131, 771) and 9 (0, 95) in conclusive positive and negative CTA results, respectively ($p<0.001$). The stress test result groups also varied significantly with respect to age, sex, smoking status, CAD risk equivalent, site characterization of chest pain, provider assessment of obstructive epicardial disease, ASCVD risk, Framingham risk score, Diamond-Forrester score, and prevalence of hypertension and diabetes ($p<0.05$) (Table 1). Notably, inconclusiveness was most often attributed to submaximal heart rate for stress tests, and calcifications and motion artifact for CTA (Table 2).

Association by NIT Type and Inconclusive Results

Stress testing overall was more likely to produce inconclusive results compared with CTA (adjusted OR 1.56, 95% CI 1.33–1.82, $p<0.001$) (Table 3). Specifically, exercise ECG (adjusted OR 4.78, 95% CI 3.69–6.20, $p<0.001$) and stress echocardiography (adjusted OR 2.11, 95% CI 1.68–2.66, $p<0.001$) more frequently had inconclusive results compared with CTA, but not nuclear testing (adjusted OR 1.06, 95% CI 0.88–1.27, $p=0.564$) (Supplemental Figure VIII). Both stress nuclear (adjusted OR 0.23, 95% CI 0.17–0.30, $p<0.001$) and stress

echocardiography (adjusted OR 0.44, 95% CI 0.32–0.59, p<0.001) were less likely than exercise ECG to have inconclusive results (Supplemental Table III and Figure IX). A sensitivity analysis was performed using an intention-to-treat definition of treatment group, which showed similar results (Supplemental Data, Tables I and II).

Subsequent Processes of Care and Clinical Outcomes

Inconclusive NIT results were more often followed with a second NIT compared with conclusive negative results for both stress and CTA (14.6% vs. 8.5%, adjusted OR 1.91, 95% CI 1.42–2.56, p<0.001; 36.5% vs. 8.4%, adjusted OR 5.95, 95% CI 4.52–7.85, p<0.001, respectively) (Table 4). Referral to ICA within 90 days was also more frequent with inconclusive versus conclusive negative stress and CTA testing (5.5% vs. 2.4%, adjusted OR 2.36, 95% CI 1.47–3.78, p<0.001; 23.4% vs. 4.1%, adjusted OR 6.49, 95% CI 4.67–9.02, p<0.001, respectively). For the composite outcome, inconclusive results had higher rates of all-cause death, MI, or UAH compared to conclusive negative results for both stress and CTA (3.7% vs. 2.0%, adjusted HR 1.81, 95% CI 1.05–3.13, p=0.034; 5.0% vs. 2.2%, adjusted HR 1.85, 95% CI 1.02–3.36, p=0.044, respectively) (Table 4). See Supplemental Tables IV and V for data on individual stress testing modalities.

Compared to conclusive negative stress and CTA tests, conclusive positive tests had higher referral to second NIT (25.7% vs. 8.5%, adjusted OR 3.59, 95% CI 2.85–4.53, p<0.001; 23.2% vs. 8.4%, adjusted OR 2.97, 95% CI 2.32–3.78, p<0.001, respectively) and ICA within 90 days (46.6% vs. 2.4%, adjusted OR 34.62, 95% CI 26.08–45.98, p<0.001; 66.3% vs. 4.1%, adjusted OR 42.81, 95% CI 33.18–55.24, p<0.001, respectively) (Table 4). Compared to conclusive negative stress and CTA tests, conclusive positive tests had higher composite outcomes of death, MI, or UAH (8.3% vs. 2.0%, adjusted HR 3.50, 95% CI 2.38–5.15, p<0.001; 9.2% vs. 2.2%, adjusted HR 3.66, 95% CI 2.51–5.35, p<0.001, respectively) (Table 4).

Of the 737 patients with inconclusive results, 67.7% did not receive any additional testing (46.5% CTA; 82.2% stress). These patients had lower average ASCVD and Framingham risk scores and lower pretest probability for CAD (p<0.001) when compared to those who did receive additional testing (Supplemental Table VI).

Economic Impact of Inconclusive Results

Cumulative medical costs at 24 months of follow up for patients with an inconclusive versus conclusive negative stress test were 38% higher (mean cost difference $2905, 95% CI $1197-$4614, p<0.001; Figure 1 and Supplemental Table VII). Patients with an inconclusive CTA had 140% higher mean cumulative medical costs than those with a conclusive negative result (mean cost difference $4030, 95% CI $1656-$6404, p<0.001), with a significant difference first seen at the 3-month time point, after which costs continued to diverge (Figure 1).

Discussion

In this large, multicenter study of symptomatic outpatients without prior history of CAD undergoing noninvasive evaluation, we found that approximately one in 12 patients had an

inconclusive result and only one third of these had subsequent testing. Compared to conclusive negative results, inconclusive stress and CTA results more often led to second NIT and ICA referral and were associated with worse clinical outcomes and up to 140% higher 24-month healthcare expenditures.

Inconclusive results were less often seen with CTA than stress testing overall, although nuclear stress and CTA had similar inconclusive rates. Evaluating individual modalities, we found that exercise ECG was most likely to yield an inconclusive result occurring in 24% of studies, 33% of which were due to submaximal heart rate. These rates are consistent with previous literature showing that 17–29% of exercise ECGs are inconclusive, with up to 57% due to submaximal heart rate.[9–11] In stress echocardiography, we found an inconclusive rate of 12%, with 67% due to submaximal heart rate. Others have reported similar inconclusive rates of 15–29%, with 80–100% due to submaximal heart rate.[9,12] Stress nuclear testing had a 7% inconclusive rate comparable to the rate found in previous studies.[9,13–15] With regard to CTA testing, our observed inconclusive rate was 6%, similar to the 5% inconclusive rate found in the Scottish Computed Tomography of the Heart (SCOT-HEART) trial,[10] but lower than the 11–13% rates found in smaller, older cohorts.[16,17] The most commonly cited reasons for inconclusive CTA results are motion artifact and calcifications, which we observed in our study as well. As shown in Table 1, compared to conclusive negative results, the median CAC score for inconclusive CTAs was over forty times higher suggesting a possible anatomic rationale for the difficulty with interpretation.

Previous research on the implications of inconclusive NIT results is scant. One study by Christman et al. found that 21.6% patients with inconclusive exercise ECGs received an additional NIT. Patients with inconclusive results had adverse 3-year outcomes compared to those with negative results, but they did not evaluate other modalities.[9] To our knowledge, the present study is the first to comprehensively evaluate subsequent processes of care, outcomes, and resource utilization across several NIT modalities, including CTA, and in a single cohort with uniform data collection methods. For both stress and CTA tests, patients with inconclusive results were more likely to receive a second NIT than those with a conclusive negative test. Still, approximately 80% of patients with an inconclusive stress test and 50% of patients with an inconclusive CTA did not receive additional testing (Supplemental Table VIII), even though an inconclusive result should neither increase nor decrease the pretest probability for CAD. Those with inconclusive results who did not have additional testing had slightly lower overall pretest probability of significant CAD (Supplemental Table VI) compared to those who did receive additional testing, suggesting that perhaps providers had enough clinical data to forego additional testing despite an inconclusive result. In particular, we were not able to capture the impact of “hidden” but significant information that even inconclusive results may provide (e.g., a finding of extensive or zero calcification, or excellent exercise tolerance) in spite of an overall inconclusive result, which may have an impact on additional testing decisions.

When compared to those with conclusive negative tests, individuals with inconclusive stress and CTA tests had a higher composite outcome of death, MI, or hospitalization for unstable angina. This is unlikely to be due to the higher burden of diabetes, hypertension, and dyslipidemia in the inconclusive group, since findings persisted after adjusting for these and

other variables, suggesting that those with inconclusive results may be a high-risk population that warrants further clinical and research investigation.

Despite the relative frequency of inconclusive NITs, the optimal diagnostic strategy following an inconclusive result remains unclear. The most recent 2012 American College of Cardiology/American Heart Association guideline on stable ischemic heart disease gives a Class IIa recommendation for obtaining a CTA following an inconclusive functional NIT in patients with intermediate CAD pretest probability.[18] This recommendation stems from an observational cohort study of 529 patients by de Azevedo et al. suggesting that an inconclusive NIT followed by CTA predicted adverse events based on stenosis severity.[19] There is no stated recommendation on the optimal next test following an indeterminate CTA, but our data suggests that additional investigation is warranted in addition to risk-factor (e.g. hypertension, obesity, dyslipidemia, diabetes) optimization. Future studies should prospectively test various diagnostic algorithms following an inconclusive NIT to delineate preferred testing strategies.

Although we and other groups have evaluated comparative cost-effectiveness between imaging modalities,[8,16,20–22] our study extends this discussion to consider the adverse financial implications of inconclusive results. We found higher costs in inconclusive versus conclusive negative stress and CTA results, possibly due to increased second NIT and ICA referral. For CTA tests, this cost difference started at 3 months following randomization and continued to diverge throughout the 24-month follow-up period.

Study Limitations

The trial design of PROMISE excluded patients whom clinicians opted for either conservative management or proceeded directly to ICA. Thus, the current study only addresses inconclusive results in patients between the two extremes of pretest probability for CAD. Further, the primary endpoint 2-year event rate was low at 3.0% indicating that this group was overall low risk. Given this low event rate, we were unable to make comparative statements between stress testing modalities with regard to outcomes and costs. Further, although all imaging readers were at least Level 2 trained in their respective modality, there may have been significant variability in how individual readers reported a test as conclusive. Finally, the current study does not evaluate the decision-making processes of clinicians regarding the subsequent care plan after receiving an inconclusive result

Conclusion

Inconclusive noninvasive testing is a relatively common occurrence seen in 8% of noninvasive diagnostic studies, and is less common in anatomic versus functional stress testing. Inconclusive stress and CTA test results are associated with higher cumulative healthcare expenditures, possibly driven by increased referral to additional noninvasive testing and catheterization. Patients with inconclusive results had worse clinical outcomes when compared to conclusive negative results regardless of testing modality, and may represent an under-investigated or higher-risk population or both.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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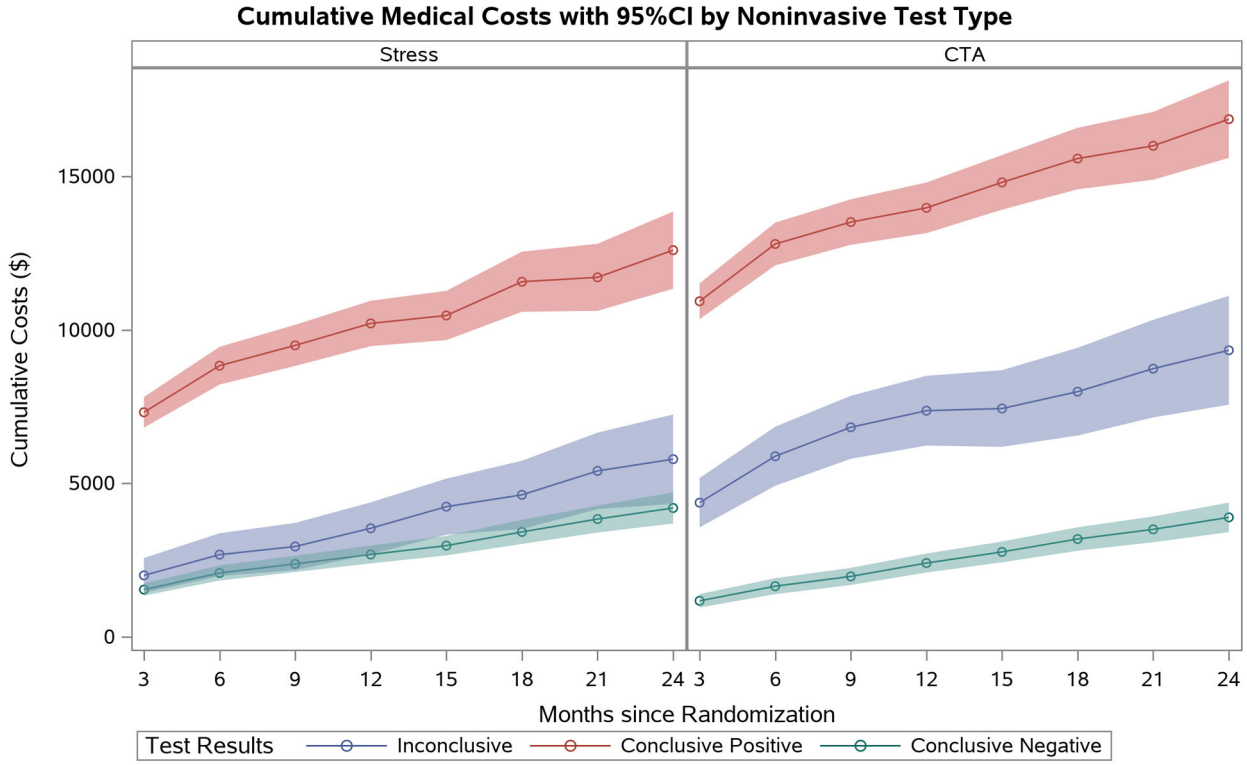

Figure 1 –.

Mean cumulative medical costs with 95% CI (shaded area) by noninvasive test type. Tests are separated by conclusive positive (red line), inconclusive (blue line), or conclusive negative (green line) results.

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Table 1:

Patient Characteristics at Baseline by Inconclusiveness and Test Modality

	CTA (N=4677)				Stress Test (N=4533)			
Characteristic	**Inconclusive (N=299)**	**Conclusive Positive (N=534)**	**Conclusive Negative (N=3844)**	**P-value**	**Inconclusive (N=438)**	**Conclusive Positive (N=564)**	**Conclusive Negative (N=3531)**	**P-value**
Demographics								
Age (Years)	62.9 (57.0, 68.7)	62.5 (56.5, 68.6)	59.1 (53.9, 65.3)	<0.001	59.6 (54.6, 65.4)	62.6 (56.9, 68.1)	60.1 (54.6, 66.0)	<0.001
Female sex	140 (46.8%)	184 (34.5%)	2078 (54.1%)	<0.001	215 (49.1%)	274 (48.6%)	1932 (54.7%)	0.004
Race				0.004				0.389
Multi-Racial	7 (2.4%)	2 (0.4%)	50 (1.3%)		5 (1.2%)	4 (0.7%)	22 (0.6%)	
White	236 (79.5%)	471 (89.5%)	3187 (83.6%)		355 (82.0%)	479 (84.9%)	3009 (86.0%)	
Black	42 (14.1%)	31 (5.9%)	426 (11.2%)		59 (13.6%)	61 (10.8%)	360 (10.3%)	
Asian	10 (3.4%)	17 (3.2%)	109 (2.9%)		8 (1.8%)	13 (2.3%)	74 (2.1%)	
Indian	2 (0.7%)	3 (0.6%)	31 (0.8%)		2 (0.5%)	5 (0.9%)	22 (0.6%)	
Hawaiian	0 (0.0%)	2 (0.4%)	9 (0.2%)		4 (0.9%)	2 (0.4%)	12 (0.3%)	
BMI (kg/m^2)	30.1 (27.1, 35.9)	30.0 (26.7, 33.9)	29.4 (26.3, 33.8)	0.010	29.8 (25.9, 33.9)	30.0 (26.5, 35.1)	29.8 (26.4, 33.7)	0.186
Cardiac Risk Factors								
Diabetes	83 (27.8%)	139 (26.0%)	764 (19.9%)	<0.001	90 (20.5%)	150 (26.6%)	746 (21.1%)	0.011
Smoking (ever)	130 (43.5%)	217 (40.6%)	1936 (50.4%)	<0.001	179 (40.9%)	261 (46.3%)	1764 (50.0%)	<0.001
CAD risk equivalent	96 (32.1%)	160 (30.0%)	900 (23.4%)	<0.001	113 (25.8%)	178 (31.6%)	883 (25.0%)	0.004
Site characterization of chest pain				<0.001				0.031
Typical	42 (14.0%)	88 (16.5%)	419 (10.9%)		51 (11.6%)	83 (14.7%)	379 (10.7%)	
Atypical	227 (75.9%)	404 (75.7%)	3003 (78.1%)		330 (75.3%)	424 (75.2%)	2782 (78.8%)	
Non-cardiac	30 (10.0%)	42 (7.9%)	422 (11.0%)		57 (13.0%)	57 (10.1%)	370 (10.5%)	
Provider estimation of likelihood of obstructive epicardial disease (High or Very High)	24 (8.0%)	57 (10.7%)	138 (3.6%)	<0.001	29 (6.6%)	64 (11.4%)	127 (3.6%)	<0.001
Hypertension	218 (72.9%)	362 (67.8%)	2448 (63.7%)	0.002	304 (69.4%)	404 (71.6%)	2255 (63.9%)	<0.001
Dyslipidemia	217 (72.6%)	384 (71.9%)	2561 (66.6%)	0.008	306 (69.9%)	383 (67.9%)	2398 (67.9%)	0.707

	CTA (N=4677)				Stress Test (N=4533)			
Characteristic	**Inconclusive (N=299)**	**Conclusive Positive (N=534)**	**Conclusive Negative (N=3844)**	**P-value**	**Inconclusive (N=438)**	**Conclusive Positive (N=564)**	**Conclusive Negative (N=3531)**	**P-value**
Family history of premature CAD	100 (33.7%)	185 (34.8%)	1239 (32.3%)	0.493	130 (29.7%)	160 (28.4%)	1112 (31.6%)	0.257
Participate in physical activity	165 (55.2%)	263 (49.3%)	1992 (51.9%)	0.262	220 (50.3%)	273 (48.4%)	1840 (52.2%)	0.211
10-Year CVD Risk								
Framingham Risk Score (2008)	23.3 (13.3, 40.3)	24.8 (15.7, 39.3)	16.0 (10.0, 26.1)	<0.001	18.9 (11.4, 32.7)	20.8 (12.9, 36.4)	16.6 (10.3, 27.6)	<0.001
ASCVD (2013)	16.3 (8.6, 27.6)	16.5 (9.2, 26.9)	10.3 (5.8, 17.8)	<0.001	11.9 (6.6, 21.5)	14.7 (8.6, 24.0)	11.2 (6.0, 19.3)	<0.001
Likelihood of CAD								
Diamond-Forrester (2011)	47.4 (27.7, 59.4)	48.9 (33.6, 59.4)	37.0 (23.8, 48.9)	<0.001	38.4 (24.8, 57.7)	47.1 (27.7, 59.4)	37.0 (24.8, 48.9)	<0.001
Calcium Scores (CTA Only)								
Calcium Score	402.0 (31.0, 1108.5)	386.5 (130.8, 771.0)	8.5 (0.0, 94.5)	<0.001				
Calcium ≥400	136 (50.0%)	237 (48.8%)	265 (7.7%)	<0.001				

Continuous variables are described using median (25^{th}, 75^{th} percentile). Categorical variables are described using frequency (%). Wilcoxon rank sum tests are used for continuous variables, and chi-square tests are used for categorical variables. BMI = body mass index, CTA = computed tomographic angiogram, CAD = coronary artery disease, CVD = cardiovascular disease, ASCVD = atherosclerotic cardiovascular disease.

Table 2:

Frequency of Conclusive/Inconclusive Results by Test Type

Reason	Frequency
Overall Stress	
Conclusive Positive	564 (12.4%)
Conclusive Negative	3531 (77.9%)
Inconclusive	438 (9.7%)
Exercise ECG	
Conclusive Positive	54 (12.3%)
Conclusive Negative	280 (63.9%)
Inconclusive	104 (23.7%)
Target heart rate not attained	34 (32.7%)
Borderline or indeterminate ECG Result	70 (67.3%)
Stress Echo	
Conclusive Positive	75 (7.5%)
Conclusive Negative	805 (80.6%)
Inconclusive	119 (11.9%)
Target heart rate not attained	80 (67.2%)
Respiratory artifact	1 (0.8%)
Poor sound transmission	8 (6.7%)
Other	30 (25.2%)
Stress Nuclear	
Conclusive Positive	435 (14.1%)
Conclusive Negative	2446 (79.0%)
Inconclusive	215 (6.9%)
Target heart rate not attained	152 (70.7%)
Motion artifact	6 (2.8%)
Attenuation	45 (20.9%)
GI uptake	5 (2.3%)
Missing	7 (3.3%)
CTA	
Conclusive Positive	534 (11.4%)
Conclusive Negative	3844 (82.2%)
Inconclusive	299 (6.4%)
Motion artifact	100 (33.4%)
Calcification	131 (43.8%)
Image Noise	18 (6.0%)
Other	32 (10.7%)
Missing	18 (6.0%)
Total	

Reason	Frequency
Conclusive Positive	1098 (11.9%)
Conclusive Negative	7375 (80.1%)
Inconclusive	737 (8.0%)

ECG = electrocardiogram.

Table 3:

Associations between NIT Type, Modality, and Inconclusiveness

	Frequency of Inconclusiveness (# Events/Sample Size)		Unadjusted*		Adjusted†	
Comparison of NIT Modality	**Stress Test**	**CTA**	**Odds Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Stress vs. CTA	438/4533 (9.66%)	299/4677 (6.39%)	1.57 (1.34–1.83)	<0.001	1.56 (1.33–1.82)	<0.001
Comparison of NIT Type						
Stress Nuclear vs. CTA	215/3096 (6.94%)	299/4677 (6.39%)	1.09 (0.91–1.31)	0.338	1.06 (0.88–1.27)	0.564
Stress Echo vs. CTA	119/999 (11.91%)	299/4677 (6.39%)	1.98 (1.58–2.48)	<0.001	2.11 (1.68–2.66)	<0.001
Exercise ECG vs. CTA	104/438 (23.74%)	299/4677 (6.39%)	4.56 (3.55–5.85)	<0.001	4.78 (3.69–6.20)	<0.001

NIT = noninvasive test.

*Unadjusted model contains NIT modality or test type (stress nuclear, stress echo, exercise ECG vs. CTA).

†Adjusted model contains NIT modality or test type (stress nuclear, stress echo, exercise ECG vs. CTA), age, sex, BMI, diabetes, smoker (ever/never), CAD equivalent, site characterization of chest pain, provider estimation of likelihood of obstructive epicardial disease (high or very high), hypertension, dyslipidemia, family history of premature CAD, participate in physical activity, Framingham Risk Score (2008), Diamond-Forrester (2011).

Table 4:

Associations between Inconclusive Test Results and Process of Care and Outcomes by Test Type

	Frequency of Event (# Events/Sample Size)		Unadjusted		Adjusted*	
Process of Care	**Conclusive Positive or Inconclusive**	**Conclusive Negative**	**Odds Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Overall Stress						
Referral to second NIT within 90 days of first NIT						
Conclusive Positive vs. Conclusive Negative	145/564 (25.71%)	299/3531 (8.47%)	3.74 (2.99–4.68)	<0.001	3.59 (2.85–4.53)	<0.001
Inconclusive vs. Conclusive Negative	64/438 (14.61%)	299/3531 (8.47%)	1.85 (1.38–2.47)	<0.001	1.91 (1.42–2.56)	<0.001
Referral to ICA within 90 days of Randomization						
Conclusive Positive vs. Conclusive Negative	263/564 (46.63%)	85/3531 (2.41%)	35.43 (27.00–46.47)	<0.001	34.62 (26.08–45.98)	<0.001
Inconclusive vs. Conclusive Negative	24/438 (5.48%)	85/3531 (2.41%)	2.35 (1.48–3.74)	<0.001	2.36 (1.47–3.78)	<0.001
CTA						
Referral to second NIT within 90 days of first NIT						
Conclusive Positive vs. Conclusive Negative	124/534 (23.22%)	324/3844 (8.43%)	3.29 (2.61–4.14)	<0.001	2.97 (2.32–3.78)	<0.001
Inconclusive vs. Conclusive Negative	109/299 (36.45%)	324/3844 (8.43%)	6.23 (4.80–8.10)	<0.001	5.95 (4.52–7.85)	<0.001
Referral to ICA within 90 days of Randomization						
Conclusive Positive vs. Conclusive Negative	354/534 (66.29%)	159/3844 (4.14%)	45.57 (35.87–57.91)	<0.001	42.81 (33.18–55.24)	<0.001
Inconclusive vs. Conclusive Negative	70/299 (23.41%)	159/3844 (4.14%)	7.08 (5.19–9.67)	<0.001	6.49 (4.67–9.02)	<0.001
Outcome			**Hazard Ratio (95% CI)**	**P-value**	**Hazard Ratio (95% CI)**	**P-value**
Overall Stress						
All-cause death/MI/UAH						
Conclusive Positive vs. Conclusive Negative	47/564 (8.33%)	69/3531 (1.95%)	4.45 (3.07–6.45)	<0.001	3.50 (2.38–5.15)	<0.001
Inconclusive vs. Conclusive Negative	16/438 (3.65%)	69/3531 (1.95%)	1.90 (1.10–3.28)	0.021	1.81 (1.05–3.13)	0.034
CV Death/MI						
Conclusive Positive vs. Conclusive Negative	19/564 (3.37%)	43/3531 (1.22%)	2.74 (1.60–4.71)	<0.001	1.96 (1.11–3.46)	0.019
Inconclusive vs. Conclusive Negative	11/438 (2.51%)	43/3531 (1.22%)	2.09 (1.08–4.06)	0.029	2.04 (1.05–3.97)	0.037
CTA						
All-cause death/MI/UAH						
Conclusive Positive vs. Conclusive Negative	49/534 (9.18%)	83/3844 (2.16%)	4.48 (3.15–6.38)	<0.001	3.66 (2.51–5.35)	<0.001

Inconclusive vs. Conclusive Negative	15/299 (5.02%)	83/3844 (2.16%)	2.43 (1.40–4.20)	0.002	1.85 (1.02–3.36)	0.044
CV Death/MI						
Conclusive Positive vs. Conclusive Negative	14/534 (2.62%)	45/3844 (1.17%)	2.26 (1.24–4.12)	0.008	1.66 (0.88–3.15)	0.120
Inconclusive vs. Conclusive Negative	4/299 (1.34%)	45/3844 (1.17%)	1.18 (0.43–3.29)	0.746	0.74 (0.23–2.43)	0.623

ICA = invasive coronary angiography, MI = myocardial infarction, UAH = unstable angina hospitalization.

*Adjusted model controls for NIT modality (stress test vs. CTA), age, sex, BMI, diabetes, smoker (ever), CAD equivalent, site characterization of chest pain, provider estimation of likelihood of obstructive epicardial disease (high or very high), hypertension, dyslipidemia, family history of premature CAD, participate in physical activity, Framingham Risk Score (2008), and Diamond-Forrester (2011).