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Prognostic Value of Noninvasive Cardiovascular Testing in Patients with Stable Chest Pain: Insights from the PROMISE Trial

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Abstract

Background—Optimal management of patients with stable chest pain relies on the prognostic information provided by noninvasive cardiovascular testing, but there are limited data from randomized trials comparing anatomic with functional testing.

Methods—In the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial, patients with stable chest pain and intermediate pre-test probability for obstructive coronary artery disease (CAD) were randomized to functional testing (exercise electrocardiography, nuclear stress, or stress echocardiography) or coronary computed tomography angiography (CTA). Site-based diagnostic test reports were classified as normal or mildly, moderately, or severely abnormal. The primary endpoint was death, myocardial infarction, or unstable angina hospitalizations over a median follow-up of 26.1 months.

Results—Both prevalence of normal test results and incidence rate of events in these patients were significantly lower among 4500 patients randomized to CTA compared to 4602 patients randomized to functional testing (33.4% vs. 78.0%, and 0.9% vs. 2.1%, respectively; both P<0.001). In CTA, 54.0% of events (n=74/137) occurred in patients with nonobstructive CAD (1-69% stenosis). Prevalence of obstructive CAD and myocardial ischemia was low (11.9% vs. 12.7%, respectively), with both findings having similar prognostic value (hazard ratio [HR], 3.74 [95% CI, 2.60–5.39] and 3.47 [95% CI, 2.42–4.99]. When test findings were stratified as mildly, moderately, or severely abnormal, HRs for events as compared to normal tests increased proportionally for CTA (2.94, 7.67, 10.13; all P<0.001) but not for corresponding functional testing categories (0.94 [P=0.87], 2.65 [P=0.001], 3.88 [P<0.001]). The discriminatory ability of CTA in predicting events was significantly better than functional testing (c-index, 0.72 [95% CI, 0.68–0.76] vs. 0.64 [95% CI, 0.59–0.69]; P=0.04). If 2714 patients with at least intermediate Framingham Risk Score (>10%) who had a normal functional test were reclassified as being mildly abnormal, the discriminatory capacity improved to 0.69 (95% CI, 0.64–0.74).

Conclusions—Coronary CTA, by identifying patients at risk due to nonobstructive CAD, provides better prognostic information than functional testing in contemporary stable chest pain patients with a low burden of obstructive CAD, myocardial ischemia, and events.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01174550

Key Words: coronary artery disease; prognosis; diagnostic testing

Clinical Perspective

What is new?

- This was a large (N >9000) randomized comparison of the prognostic value of anatomic imaging by coronary CTA with functional stress testing in patients with stable chest pain.
- Contemporary chest pain populations referred for testing have a low burden of obstructive CAD and myocardial ischemia, and both findings have similar prognostic value.
- Coronary CTA, by visualizing nonobstructive CAD, identifies additional at-risk patients and imparts better prognostic and discriminatory information than functional testing.
- Consideration of the Framingham Risk Score as an accepted, global risk estimation significantly improves the prognostic value of functional assessment.

What are the clinical implications?

- This study provides generalizable comparative evidence on the relative prognostic value of the diagnostic tests most commonly used to evaluate patients with stable chest pain.
- This may improve the use of this information to guide management of these patients.
- Given the low prevalence of myocardial ischemia and obstructive CAD in contemporary chest pain populations, the detection of nonobstructive CAD identifies additional at-risk patients.
- A normal functional test result, including information on exercise, and symptoms, has moderate prognostic value, and consideration of the Framingham Risk Score improves risk stratification.

Evaluation of chest pain is a fundamental element of cardiology patient care. On a daily basis, many physicians experience the clinical pressures to accurately rule out obstructive coronary artery disease (CAD) or myocardial ischemia as a cause of chest pain, while limiting the performance of unnecessary diagnostic testing. This difficulty is compounded by the fact that presenting symptoms are often unspecific, and traditional risk factors, while associated with CAD and myocardial ischemia, do not alone permit accurate diagnosis in the vast majority of patients. Hence, knowledge about the prognostic implications of imaging-based findings is imperative to properly assess, prognosticate, and treat these patients. In this climate, functional cardiac testing (exercise electrocardiography [ECG], stress nuclear single-photon emission computed tomography, stress echocardiography) has been the traditional way (> 4 million patients each year in the United States) to assess stable outpatients with suspected but not previously diagnosed CAD.[1,2] However, major changes in referral patterns, improvements in lifestyle, and preventive medical therapy over the last 40 years have contributed to decreasing rates of functional tests positive for myocardial ischemia,[3] and lower cardiovascular event rates.[4,5] With fewer patients demonstrating classical findings of myocardial ischemia indicating the need for interventional therapy, the latest American Heart Association/American College of Cardiology guidelines recommend stress ECG or stress imaging for patients with intermediate to high likelihood of CAD and emphasize the importance of prognostic assessment by cardiovascular imaging to predict future cardiovascular events and to guide medical therapy.[6]

Observational studies and registries provide ample evidence that traditional assessment with functional testing, especially the detection of myocardial ischemia using echocardiography and myocardial perfusion imaging, provides excellent prognostic value to predict future cardiovascular events. Historically such findings were associated with a 5-10-fold increase in

risk for cardiovascular events.[5,7-18] Coronary computed tomography angiography (CTA) is a relatively new test that enables direct and noninvasive visualization of the presence and extent of coronary plaque and stenosis. Consistent with previous studies in invasive coronary angiography, a finding of obstructive CAD in coronary CTA is associated with a significant (6-12-fold) increase in risk of future cardiovascular events, independent of traditional cardiovascular risk factors.[19,20] In addition, the absence of CAD carries a nearly perfect negative predictive value (>99%).[21-25] These data suggest that both anatomic (coronary CTA) and functional assessment provide excellent risk prediction for cardiovascular events. However, the number of diagnostic tests that are positive for myocardial ischemia or obstructive CAD is relatively low in contemporary practice (10-15%).[3] Instead, the detection of nonobstructive CAD defined as coronary atherosclerosis causing between 1 and 69% luminal narrowing has emerged as a significant and frequent finding that while often not associated with myocardial ischemia carries a substantial risk for major adverse cardiovascular events (MACE) as compared to patients without any CAD.[19,26]

Moreover, a randomized comparison of the ability of anatomic and functional testing to correctly classify risk in symptomatic patients has not been performed. To accomplish this, we performed a prespecified secondary analysis of the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial, comparing the prognostic value of an anatomic versus a functional testing strategy in stable symptomatic patients with suspected CAD.

Methods

Study Design and Population

PROMISE (ClinicalTrials.gov # NCT01174550) is a pragmatic comparative effectiveness trial

that enrolled 10,003 patients at 193 sites in North America with expertise in the fields of cardiology, primary care, radiology, and anesthesia and representing both community practices and academic medical centers. Details regarding the PROMISE study population, selection criteria, design, and primary results have been described elsewhere.[27,28] Briefly, the study participants were stable symptomatic outpatients without known CAD who were referred to noninvasive cardiovascular testing for further evaluation. Local or central institutional review boards approved the study at the coordinating centers and each of the 193 enrolling sites in North America.

For this analysis we included patients who received the initial diagnostic test as randomized. We excluded subjects who received other tests as their first test, did not undergo any diagnostic test, or received non-contrast CTA only. In addition, we excluded patients whose test results could not be assigned to prespecified test strata due to indeterminate test results, including patients who underwent functional testing with exercise but achieved less than 75% of maximum predicted heart rate. The flow of patients is described in Figure 1.

Study Procedures

After providing written informed consent, participants were randomly assigned to either the CTA group or the functional testing group, with stratification according to study site and according to the choice, as indicated before randomization by the site clinician, of the intended functional test if the patient were to be assigned to that study group.[28] Enrollment began July 27, 2010, and was completed on September 19, 2013. Tests were performed and interpreted by local physicians who made all subsequent clinical decisions. Appropriate medical therapy was encouraged, and guideline-based educational materials were provided to patients and providers. Follow-up visits were performed at 60 days at the study sites and centrally by means of telephone or mail at 6-

month intervals after randomization, for a minimum of 1 year until October 31, 2014. Diagnostic testing was performed in compliance with professional society guidelines. Functional testing included exercise ECG, exercise or pharmacologic nuclear myocardial perfusion imaging, and exercise or pharmacologic stress echocardiography. Coronary CTA was performed with at least 64-slice multidetector computed tomographic technology.

Diagnostic Test Results

Site-reported test results were prospectively classified as normal or mildly, moderately, or severely abnormal. Broadly, for coronary CTA, we defined nonobstructive CAD (stenosis of 1-69% for primary and 1-49% for secondary analysis) as mildly abnormal, single-vessel obstructive CAD as moderately abnormal (stenosis of >70% for primary and >50% for secondary analysis), and multivessel or proximal left anterior descending (>70%), or left main obstructive CAD >50% as severely abnormal. For functional testing, late positive treadmill or abnormal ECG in the absence of reversible ischemia was defined as mildly abnormal, inducible ischemia or mixed defect with perfusion or wall motion in one coronary territory for myocardial perfusion imaging and stress echocardiography, respectively, or early positive treadmill was defined as moderately abnormal, and multivessel, large territory inducible ischemia or mixed defect was defined as severe. A more detailed description of the classification of test results can be found in Table 1.

Cardiovascular Risk Factors

Patient demographics and traditional cardiovascular risk factors were assessed and documented in a standard fashion at the time of enrollment into the PROMISE trial.[27]

Study Endpoints

The primary endpoint was a composite of time to MACE including death from any cause,

myocardial infarction, or hospitalization for unstable angina. The secondary endpoint was defined as a composite of cardiovascular death, myocardial infarction, or hospitalization for unstable angina, and the tertiary endpoint was a composite of cardiovascular death or myocardial infarction. An independent clinical events committee adjudicated all primary and secondary endpoint events in a blinded fashion on the basis of standard, prospectively determined definitions.[27,28]

Statistical Analysis

Descriptive statistics are presented as mean and standard deviation for continuous variables and frequencies and percentages of patients for categorical variables. The Cox proportional hazards regression model was used to assess the relationship of test results to the time to the first clinical event (or censoring) for each composite endpoint.[29] To appropriately account for heterogeneity among the subjects, analyses were adjusted for a prespecified set of baseline covariates, including age, sex, CAD risk equivalent (history of either diabetes, peripheral artery disease, or cerebrovascular disease), and the prespecification of the intended functional test (if randomized to the functional testing arm). For each testing strategy, adjusted hazard ratios (HRs) and 95% confidence intervals were computed using Cox models to characterize the relative risks of patients with normal versus mildly, moderately and severely abnormal test results.[29] For secondary analyses, we reclassified patients with at least intermediate Framingham Risk Score (>10%) who had a normal functional test as mildly abnormal. In addition, we compared the predictive value of the absence (normal and mildly abnormal) and presence (moderately and severely abnormal) of obstructive CAD and myocardial ischemia. Cumulative event rates based on test results were computed for each testing strategy (CTA and functional testing) using the method of Kaplan and Meier.[30] Based on the test results, the ability of each testing strategy to

discriminate between patients who subsequently suffered an event versus those who did not was assessed using the c-statistic.[31] The c-statistic was calculated based on the predicted probability of 26-month risk from the Cox regression model. Data from each testing strategy were analyzed separately using the Cox model. A c-statistic comparison between the 2 testing strategies (anatomic vs. functional) was based on z-statistics. Analyses were performed for the primary endpoint and for the secondary and tertiary endpoints. All p-values are 2-sided, and were considered significant if < 0.05. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary NC).

Results

Study Population

Overall, 91% of all patients enrolled in the PROMISE trial were eligible for this analysis (n=9102/10003). Major reasons for exclusion were receiving no test or a test other than the randomized test (Figure 1). The demographics, cardiovascular risk factors, and cardiovascular event rates were similar between patients included in this analysis and those excluded (Supplemental Table 1). Of the patients included, 4500 were randomized to and received coronary CTA, and 4602 were randomized to functional testing. There were no clinically meaningful differences in baseline patient demographics, cardiovascular risk, medication, or clinical presentation between coronary CTA and functional testing (Table 2). Overall, patients were on average 61 years of age, 53% were women, 78% were white, >90% had an intermediate or high Framingham Risk Score, about half were on at least one preventive medication, and the majority had atypical chest pain at presentation.

Outcomes

During the median follow-up of 26.1 months (interquartile range: 18.0, 34.4), event rates were similar in the anatomic and functional arms: overall, 137 (3.1%) versus 132 (3.0%); death, 62 (1.4%) versus 66 (1.4%); myocardial infarction, 26 (0.6%) versus 31 (0.7%); and unstable angina, 52 (1.2%) versus 41 (0.9%).

Test Results

The distribution of test results was significantly different between coronary CTA and functional testing. There were twice as many patients who had completely normal functional testing as compared to a normal coronary CTA (78.0% vs. 33.4%; P<0.001).

HRs for events increased proportionally for mildly, moderately, and severely abnormal CTA results as compared to normal CTA tests (HRs: 2.94, 7.67, 10.13; all P<0.001) (Table 3). In contrast, the increase in risk for functional testing is only significant in moderately and severely abnormal categories (HRs: 2.65 [P=0.001], 3.88 [P<0.001]), with no difference in risk between normal and mildly abnormal test results (HR, 0.94 [P=0.87]). The discriminatory ability of CTA in predicting events was significantly better than functional testing (c-index, 0.72 [95% CI, 0.68–0.76] vs. 0.64 [95% CI, 0.59–0.69]; P=0.04) (Figure 2). The results were similar for secondary analyses in which nonobstructive CAD was defined as 1-49% (Supplemental Table 2; c-index, 0.73 [95% CI, 0.69–0.78]; P=0.01). The better discrimination of events by coronary CTA was the result of the ability to define a very low risk group using a normal CTA which nearly excluded events (14 out of 137 events; 10.2% of all events), corresponding to an incidence rate of 0.93% over 2 years. In contrast, the majority of events in the functional arm (75 out of 132 events; 56.8% of all events), corresponding to an incidence rate of 2.09%, occurred in those with completely normal functional tests (including no reversible or irreversible ischemia, normal

ECG, normal duration of exercise without symptoms). A second reason was that detection of nonobstructive CAD by coronary CTA identified an at-risk group of patients (62.1% of CTAs; n=2461/3966), in which the majority of events in the CTA arm occurred (54%, n=74/137; 3.0% event rate). If nonobstructive CAD was defined as 1-49% luminal stenosis, a still significant 33.6% of the events (n=46/137) occurred in this group (Supplemental Table 2). In contrast, very few patients had mildly abnormal tests in the functional arm (9.4%, n=432/4602). Similar results were seen for the secondary endpoints of cardiovascular death/myocardial infarction/unstable angina and tertiary end points of cardiovascular death and myocardial infarction (Table 2 and Supplemental Table 2).

Important from a clinical management standpoint, when we compared anatomic versus functional binary test results—absence or presence of ≥50% LM or ≥70% stenosis elsewhere versus presence or absence of reversible myocardial ischemia in any segment—we found that both the prevalence (obstructive CAD: 11.9% [n=534/4500] vs. myocardial ischemia: 12.6% [n=582/4602]; p=0.257) and the event rates (9.2% vs. 8.2%, respectively; p=0.58) were similar. Thus, obstructive CAD and reversible myocardial ischemia were each associated with a similarly significantly increased relative risk for cardiovascular events for the primary endpoint (HR, 3.74 [95% CI, 2.60–5.39] vs. HR, 3.47 [95% CI, 2.42–4.99]; p<0.0001 for both) (Table 4) as well as with a similar discriminatory ability in predicting the primary endpoint (c-index, 0.65 [95% CI, 0.60–0.69] vs. 0.65 [95% CI, 0.60–0.69], respectively; p=0.946; Supplemental Figure 1).

Functional Testing Stratified by Modality

Supplemental Table 3 lists the distribution of test results and events among the 4602 patients randomized in the functional arm by modality. The data demonstrate that only 10.1% of patients underwent exercise treadmill testing while the vast majority (67.8%) underwent nuclear

perfusion stress testing. The observed event rate was much lower in the patients undergoing ETT (n=6/467; 1.3%) as compared to those undergoing either stress echo (n=20/1019; 2%) or stress nuclear (n=106/3116; 3.4%), most likely reflecting the fact that physicians very appropriately referred patients at lowest risk to ETT and those at highest to stress nuclear testing. Lastly, only a minority of events occurred in those with normal or mildly abnormal ETT (n=4, 3, and 2 for the primary, secondary, and tertiary endpoints, respectively).

Stress Nuclear Perfusion Testing vs. Coronary CTA

Although we used an aggregate of the functional tests as the primary approach to compare the prognostic value of an anatomical vs. a functional strategy, Supplemental Table 4 provides a comparison of nuclear stress testing with coronary CTA based on the pre-randomization intended functional test. In that analysis, only patients whose pre-randomization intended functional test was nuclear were included in the analysis in both arms. Briefly, the data demonstrate that the HRs for coronary CTA are higher than for functional testing across test result categories and endpoints with differences being higher as compared to the overall cohort.

Functional Testing plus Risk Factors

Given the large number of normal functional tests and the importance of pre-test probability in interpreting test results, we performed a secondary analysis in which we reclassified patients with at least intermediate Framingham Risk Score (>10%) who had a normal functional test as being mildly abnormal. As a result, 2714 patients were reclassified from normal to a mildly abnormal functional test, while only 874 patients remained in the normal category. This reclassification resulted in stronger association of functional test strata with clinical outcomes as compared to test results only, although there was still no significant difference in event rates between normal and mildly abnormal test results with the new classification for functional

imaging (HR, 1.61 [95% CI, 0.75–3.45]; p=0.22) (Supplemental Table 5 and Table 5). The discriminatory value of functional testing strata improved from a c-index of 0.64 (95% CI, 0.59–0.69) using test data only to a c-index of 0.69 (95% CI, 0.64–0.74) using the Framingham Risk Score for reclassification. The inclusion of Framingham Risk Score to stratify functional testing results rendered no significant difference in discriminatory capacity between anatomic and functional testing (c-index for CTA, 0.72 [95% CI, 0.68–0.76]; vs. c-index for functional testing including the Framingham Risk Score, 0.69 [95% CI, 0.64–0.74]; P=0.29) (Figure 2C).

Discussion

Overall, our study provides comparative evidence on the prognostic value of findings of the most commonly performed diagnostic tests, including presence and extent of myocardial ischemia and CAD and the associated absolute and relative risks for future cardiovascular events in a contemporary patient stable chest pain population at intermediate risk for CAD using the PROMISE randomized trial data from 193 North American sites. Our results may contribute to a better understanding of how to use information from these tests to guide management of this large group of patients. We found that anatomic assessment with coronary CTA provided significantly better prognostic information compared to functional testing (c-index: 0.72 vs. 0.64; P=0.04), which was a result of the detection of an at-risk group of patients with nonobstructive CAD by coronary CTA and the indiscriminatory nature of a normal functional test. Adding the Framingham Risk Score to functional test results significantly improved the prognostic value of functional testing.

The strengths of this study include 1) this is the first large (N > 9000) prospective randomized comparison of the prognostic value of anatomic imaging by coronary CTA with

functional exercise- or stress-based testing results in patients with stable chest pain, 2) this uniquely allows for a direct comparison of test findings of anatomic and functional testing, and the understanding of which particular diagnostic findings are differential between the strategies in their ability to identify patients at risk for MACE, and 3) the multicenter nature of this study recruiting patients at 193 North American sites, which provides generalizable data from a contemporary stable chest pain population. One of the insights from the data is the low prevalence of obstructive CAD (11.9%) and myocardial ischemia (12.6%), which only 2 decades ago was between 30% and 40% in patients undergoing nuclear stress perfusion imaging.[3] A related important observation is that the majority of clinical events over a 2-year follow-up occurred in patients without obstructive CAD or myocardial ischemia, indicating a significant risk burden undetected by conventional measures of test positivity. For coronary CTA, our data demonstrate that a finding of nonobstructive CAD identifies a large additional group of "at-risk" patients, in which the majority of events occurred (n=74/137, 54.0%) with similar observations made in smaller studies from Japan.[16,19,32-35] In contrast, parameters from the exercise portion of functional tests (symptoms and duration of exercise as well as ECG changes) and imaging findings, such as fixed defects without ischemia, did not identify patients at risk for events. Mechanistically, these data corroborate many years of research in interventional cardiology, suggesting that at least one-third, in the context of aggressive medical therapy, or up to two-thirds of future cardiovascular events occur at locations in the coronary artery tree where previously no obstructive CAD was present.[34-36] Thus, in an era of imaging patients with a relatively low burden of demonstrable myocardial ischemia or obstructive CAD, the relative importance of detecting subclinical atherosclerotic disease becomes substantially greater and is an important consideration for test choice.[37]

Our results further emphasize the importance of cardiovascular risk profile in contemporary populations with stable chest pain, especially in those patients with completely normal functional testing. We demonstrate that addition of the Framingham Risk Score, as an accepted global risk estimation tool, improved the discriminatory capacity of functional assessment (c-index, 0.64–0.69), which rendered the comparison to anatomic testing nonsignificant (p=0.29).

Another important implication of our study is that a normal CTA, in contrast to a completely normal functional test, is highly unlikely to be associated with MACE for at least 2 years. As similar findings have been reported in the acute chest pain setting,[38] this determination of a "warranty period" is an important additional benefit of coronary CTA for patients and providers.

Our results confirm evidence from observational studies that both findings of obstructive CAD and reversible myocardial ischemia are associated with significantly increased relative risk for future MACE,[14,16-18,32,33] but we extend these studies by demonstrating that the prognostic power of both findings is essentially equivalent in identifying patients with a substrate that can explain symptoms (HR, 3.74 [95% CI, 2.60–5.39] vs. HR, 3.47 [95% CI, 2.42–4.99]). The primary results of the PROMISE trial demonstrated that the aggregate of actions taken by physicians and patients based on a strategy of either initial anatomic or functional testing did not yield a difference in clinical outcomes.[28] In contrast, this prespecified secondary analysis is the first to report on the ability of diagnostic test results to accurately distinguish patients who subsequently experience a clinical event from patients who do not. Although this is presumably related to events, it represents a different, relevant clinical question.

Our study has limitations. While the PROMISE trial was designed to compare two fundamentally different approaches to management of stable chest pain patients—anatomic versus functional testing—we acknowledge that the sensitivities, specificities, predictive values, and prognostic values can vary between different functional testing modalities and by age, sex, and other patient characteristics (e.g., BMI). We further acknowledge that the choice of functional test was dictated by physician preferences and patient presentation, and thus will vary by individual clinician choices. However, because physicians in the PROMISE trial had to prespecify before randomization their preference for which functional test the patient should undergo if he or she were randomized to the functional arm, we were able to perform a matched comparison of CTA with nuclear testing, which demonstrated similar results as seen for the entire population. Unfortunately, the much smaller numbers of patients receiving treadmill exercise or stress echo precluded a valid subanalysis for these two modalities.

It is further important to note that treatments based on imaging results were not accounted for in our analysis but may have affected the CV outcomes assessed. However, one could argue that based on the intention of the trial as a strategy comparison, it may be desirable to include the effects of medical treatments or interventions and their effect on prognosis as a result of the study. Indeed, in keeping with the results of this analysis, it has been shown that the prognostic importance of coronary anatomic information is maintained and that of functional testing is lost or markedly attenuated when aggressive medical therapy and either elective or as-needed revascularization is pursued.[39]

Our study had a relatively small number of events and a short median follow-up of 26 months. In addition, we stratified test results for functional testing and coronary CTA based on site reads collected on case report forms to identify abnormal and normal tests. Further, the study

excluded patients with abnormal left ventricular function or a history of myocardial infarction, and hence the prognostic value of diagnostic hallmarks of functional testing such as left ventricular function or fixed perfusion defects could not be assessed.

Conclusions

Contemporary stable chest pain populations present with a low prevalence of myocardial ischemia and obstructive CAD. In this population, the detection of nonobstructive CAD identifies additional at-risk patients while consideration of the Framingham Risk Score is important for proper risk stratification of patients with normal stress testing. These results may contribute to a better understanding of how to use this information to guide management of these patients.

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Table 1. Prospective Risk Stratification of Noninvasive Imaging Test Results in the Anatomic (Coronary Computed Tomographic Angiography [CTA]) and Functional (Exercise Treadmill Test, Stress Myocardial Perfusion Imaging [MPI], and Stress Echocardiography) Testing Arms of the Study.

	Anatomic	**Functional**		
Test Strata	**Coronary CTA**	**Exercise Treadmill Test**	**Stress MPI**	**Stress Echo**
Severely abnormal	**High Risk CAD** 2 or more vessel disease (≥70%) or ≥50% left main stenosis or ≥70% proximal LAD stenosis	**Ischemic ECG** ST changes consistent with ischemia during stress + either severe ventricular arrhythmia OR Hypotension	**Large territory inducible Ischemia or mixed defect** Septal/anterior/apical territory or other single territory with transient ischemic dilatation or 2 or more coronary territories with ischemia	**Large territory inducible Ischemia or mixed defect** Wall motion abnormality or mixed abnormality (infarct and ischemia) Isolated Septal/anterior/apical or other single territory +↓EF <35 % during stress or 2 or more coronary territories
Moderately abnormal	**Obstructive CAD** ≥70% stenosis in one major vessels/branch	**Early positive TM** Failure to reach stage 2 (<3:00 min) with ST changes OR symptoms reproduced OR any arrhythmia or hypotension	Inducible Ischemia or mixed defect Perfusion abnormality in one coronary territory (Lateral or Inferior/posterior) OR Normal imaging but Early positive TM Failure to reach stage 2 (<3:00 min) with ST changes OR symptoms reproduced OR any arrhythmia or hypotension	Inducible Ischemia or mixed defect Wall motion abnormality or mixed abnormality (infarct and ischemia) in one coronary territory (Lateral or Inferior/posterior) OR Normal imaging but Early positive TM Failure to reach stage 2 (<3:00 min) with ST changes OR symptoms reproduced OR any arrhythmia or hypotension
Mildly abnormal	**Non-obstructive CAD*** 1-69% stenosis in any major vessels/branch OR <50% left main stenosis	**Late positive TM** More than stage 2 (>3:00 min) but failure to finish protocol or target heart rate achieved due to ST changes OR symptoms reproduced OR any arrhythmia or hypotension	**Positive ECG** **Normal perfusion or fixed perfusion defect (Scar)** **OR** **Normal imaging but Late positive TM** More than stage 2 (>3:00 min) but failure to finish protocol or target heart rate achieved due to	Positive ECG but normal wall motion or resting wall motion abnormality without inducible ischemia OR Normal imaging but Late positive TM More than stage 2 (>3:00 min) but failure to finish protocol or target heart rate achieved due to ST

			ST changes OR symptoms reproduced OR any arrhythmia or hypotension	changes OR symptoms reproduced OR any arrhythmia or hypotension
Normal	Absence of coronary atherosclerosis	Normal ECG, absence of symptoms during exercise, and normal exercise duration†	Normal ECG, absence of symptoms during exercise, normal exercise duration, and normal imaging (absence of any findings suggesting myocardial abnormalities including fixed perfusion defects)†	Normal ECG, absence of symptoms during exercise, normal exercise duration, and normal imaging (absence of any findings suggesting myocardial abnormalities including fixed wall motion abnormalities)†

To standardize test reporting, site-reported test results were abstracted by a cardiology faculty or senior fellow physician using a prospectively designed protocol to deal with ambiguous test results, thereby standardizing interpretation of ambiguous test reports and harmonizing data across imaging modalities. CAD indicates coronary artery disease; ECG, electrocardiography; LAD, left anterior descending; and TM, treadmill test.
*For secondary risk stratification, nonobstructive CAD was defined as 1-49% luminal narrowing. †For secondary risk stratification, normal functional testing was defined as normal imaging PLUS a Framingham Risk Score >10%

Table 2. Characteristics of the Trial Participants at Baseline, According to Study Group*

Variable	Anatomic Testing (N=4500)	Functional Testing (N=4602)
Demographics		
Age (yrs)	60.4 ± 8.2	61.0 ± 8.3
Female sex	2332 (51.8%)	2458 (53.4%)
Racial or ethnic minority†	1018 (22.8%)	983 (21.5%)
Cardiac risk factors		
BMI (kg/m^2)‡	30.4 ± 5.9	30.5 ± 6.1
Hypertension	2893 (64.3%)	2999 (65.2%)
Diabetes	936 (20.8%)	999 (21.7%)
Dyslipidemia	3029 (67.3%)	3127 (67.9%)
Family history of premature CAD§	1460 (32.6%)	1426 (31.1%)
Peripheral or cerebrovascular disease	228 (5.1%)	264 (5.7%)
CAD equivalent‖	1097 (24.4%)	1189 (25.8%)
History of heart failure	163 (3.6%)	176 (3.8%)
Metabolic syndrome#	1673 (37.2%)	1763 (38.3%)
Current or past tobacco use	2292 (50.9%)	2367 (51.4%)
Sedentary lifestyle**	2179 (48.5%)	2229 (48.5%)
History of depression	885 (19.7%)	992 (21.6%)
Risk factor burden and risk score††		
No risk factors	116 (2.6%)	130 (2.8%)
Risk factor burden	2.4 ± 1.1	2.4 + 1.1
Combined Diamond-Forrester and Coronary Artery Surgery risk score‡‡	53.2 ± 21.3	53.3 ± 21.2
Framingham risk score		
Low risk (<10%)	1028 (22.9%)	1036 (22.5%)
Intermediate risk (10-20%)	1632 (36.3%)	1591 (34.6%)
High risk (>20%)	1832 (40.8%)	1971 (42.9%)
ASCVD pooled cohort risk prediction (2013)		
Low risk (<7.5%)	1471 (33.0%)	1444 (31.7%)
Elevated risk (>=7.5%)	2980 (67.0%)	3118 (68.3%)
Relevant medications		
Beta blocker	1065 (24.8%)	1095 (24.9%)
ACE or ARB	1860 (43.2%)	1952 (44.3%)
Statin	1973 (45.9%)	2008 (45.6%)
Aspirin	1945 (45.2%)	1941 (44.1%)
Clopidogrel	56 (1.3%)	69 (1.6%)
Prasugrel	1 (<0.1%)	1 (<0.1%)
Warfarin	68 (1.6%)	82 (1.9%)
Primary presenting symptom and anginal type		
Chest pain	3322 (73.9%)	3299 (71.7%)
Dyspnea on exertion	633 (14.1%)	734 (16.0%)

Anginal type - site-reported		
Typical	521 (11.6%)	521 (11.3%)
Atypical	3501 (77.8%)	3595 (78.1%)
Non-anginal	478 (10.6%)	486 (10.6%)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAD, coronary artery disease; and CTA, computed tomographic angiography.

* Plus–minus values are means ± standard deviation. There were no significant between-group differences at baseline, except with respect to racial or ethnic minority group and history of depression.

† Racial or ethnic minority group was self-reported, with the status of “minority” being defined by the patient.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

§ A family history of premature CAD was defined as diagnosis of the disease in a male first-degree relative before 55 years of age or in a female first-degree relative before 65 years of age.

‖ CAD risk equivalent was defined as diabetes, peripheral vascular disease, or cerebrovascular disease.

The metabolic syndrome was defined according to consensus criteria of the American Heart Association and the National Heart, Lung, and Blood Institute.

** Sedentary lifestyle was defined by the patient as not participating in regular physical activities at least one time per week over the previous month.

†† Risk factors included hypertension, diabetes, dyslipidemia, family history of premature CAD, and tobacco use.

‡‡ Combined Diamond and Forrester and Coronary Artery Surgery Study risk scores range from 0 to 100, with higher scores indicating a greater likelihood of obstructive CAD.

Table 3. Frequency of Test Findings and Association with Clinical Events for Anatomic and Functional Testing.*

	Anatomic Testing (N=4500)				Functional Testing (N=4602)			
Initial Test Results	**Frequency n/N(%)**	**Event Rate n/N(%)**	**HR (95% CI)**	**P-value**	**Frequency n/N(%)**	**Event Rate n/N(%)**	**HR (95% CI)**	**P-value**
All cause death/MI/UA								
Severely Abnormal	266/4500 (5.91)	28/266 (10.53)	10.13 (5.15–19.92)	<.0001	365/4602 (7.93)	35/365 (9.59)	3.88 (2.58–5.85)	<.0001
Moderately Abnormal	268/4500 (5.96)	21/268 (7.84)	7.67 (3.83–15.37)	<.0001	217/4602 (4.72)	13/217 (5.99)	2.65 (1.46–4.83)	0.0014
Mildly Abnormal	2461/4500 (54.69)	74/2461 (3.01)	2.94 (1.64–5.26)	0.0003	432/4602 (9.39)	9/432 (2.08)	0.94 (0.47–1.89)	0.8666
Normal	1505/4500 (33.44)	14/1505 (0.93)			3588/4602 (77.97)	75/3588 (2.09)		
CV death/MI/UA								
Severely Abnormal	266/4500 (5.91)	26/266 (9.77)	17.26 (7.55–39.46)	<.0001	365/4602 (7.93)	31/365 (8.49)	4.59 (2.93–7.19)	<.0001
Moderately Abnormal	268/4500 (5.96)	18/268 (6.72)	12.03 (5.14–28.19)	<.0001	217/4602 (4.72)	13/217 (5.99)	3.50 (1.89–6.48)	<.0001
Mildly Abnormal	2461/4500 (54.69)	57/2461 (2.32)	4.08 (1.93–8.66)	0.0002	432/4602 (9.39)	8/432 (1.85)	1.11 (0.53–2.34)	0.7834
Normal	1505/4500 (33.44)	8/1505 (0.53)			3588/4602 (77.97)	56/3588 (1.56)		
CV death/MI								
Severely Abnormal	266/4500 (5.91)	9/266 (3.38)	4.87 (1.72–13.75)	0.0028	365/4602 (7.93)	14/365 (3.84)	2.13 (1.16–3.91)	0.0141
Moderately Abnormal	268/4500 (5.96)	5/268 (1.87)	3.09 (0.96–9.97)	0.0594	217/4602 (4.72)	5/217 (2.30)	1.53 (0.60–3.90)	0.3681
Mildly Abnormal	2461/4500 (54.69)	39/2461 (1.58)	2.73 (1.20–6.25)	0.0170	432/4602 (9.39)	5/432 (1.16)	0.81 (0.32–2.04)	0.6542
Normal	1505/4500 (33.44)	7/1505 (0.47)			3588/4602 (77.97)	48/3588 (1.34)		

*****Secondary test result stratification sets CTA threshold for moderate abnormality to 70%.

CV indicates cardiovascular; MI, myocardial infarction; and UA, unstable angina. Nonobstructive CAD is defined as 1-69% of stenosis.

Table 4. Frequency of Obstructive Coronary Artery Disease and Myocardial Ischemia and Association With Clinical Events.

	Anatomic Testing (N=4500)				Functional Testing (N=4602)			
Initial Test Results	**Frequency n/N (%)**	**Event Rate n/N (%)**	**HR (95% CI)**	**P-value**	**Frequency n/N (%)**	**Event Rate n/N (%)**	**HR (95% CI)**	**P-value**
All-cause death/MI/UA								
Abnormal	534/4500 (11.87)	49/534 (9.18)	3.74 (2.60–5.39)	<0.0001	582/4602 (12.65)	48/582 (8.25)	3.47 (2.42–4.99)	<0.0001
Normal	3966/4500 (88.13)	88/3966 (2.22)			4020/4602 (87.35)	84/4020 (2.09)		
Cardiovascular death/MI/UA								
Abnormal	534/4500 (11.87)	44/534 (8.24)	4.63 (3.10–6.92)	<0.0001	582/4602 (12.65)	44/582 (7.56)	4.15 (2.80–6.14)	<0.0001
Normal	3966/4500 (88.13)	65/3966 (1.64)			4020/4602 (87.35)	64/4020 (1.59)		
Cardiovascular death/MI								
Abnormal	534/4500 (11.87)	14/534 (2.62)	1.76 (0.95–3.25)	0.0730	582/4602 (12.65)	19/582 (3.26)	1.98 (1.16–3.37)	0.0120
Normal	3966/4500 (88.13)	46/3966 (1.16)			4020/4602 (87.35)	53/4020 (1.32)		

MI indicates myocardial infarction; UA, unstable angina. Obstructive CAD is defined as >50% stenosis in the left main coronary artery and >70% stenosis elsewhere.

Table 5. Frequency of Test Findings and Association with Clinical Events for Anatomic Test Strata and for Functional Test Strata including the Framingham Risk Score.

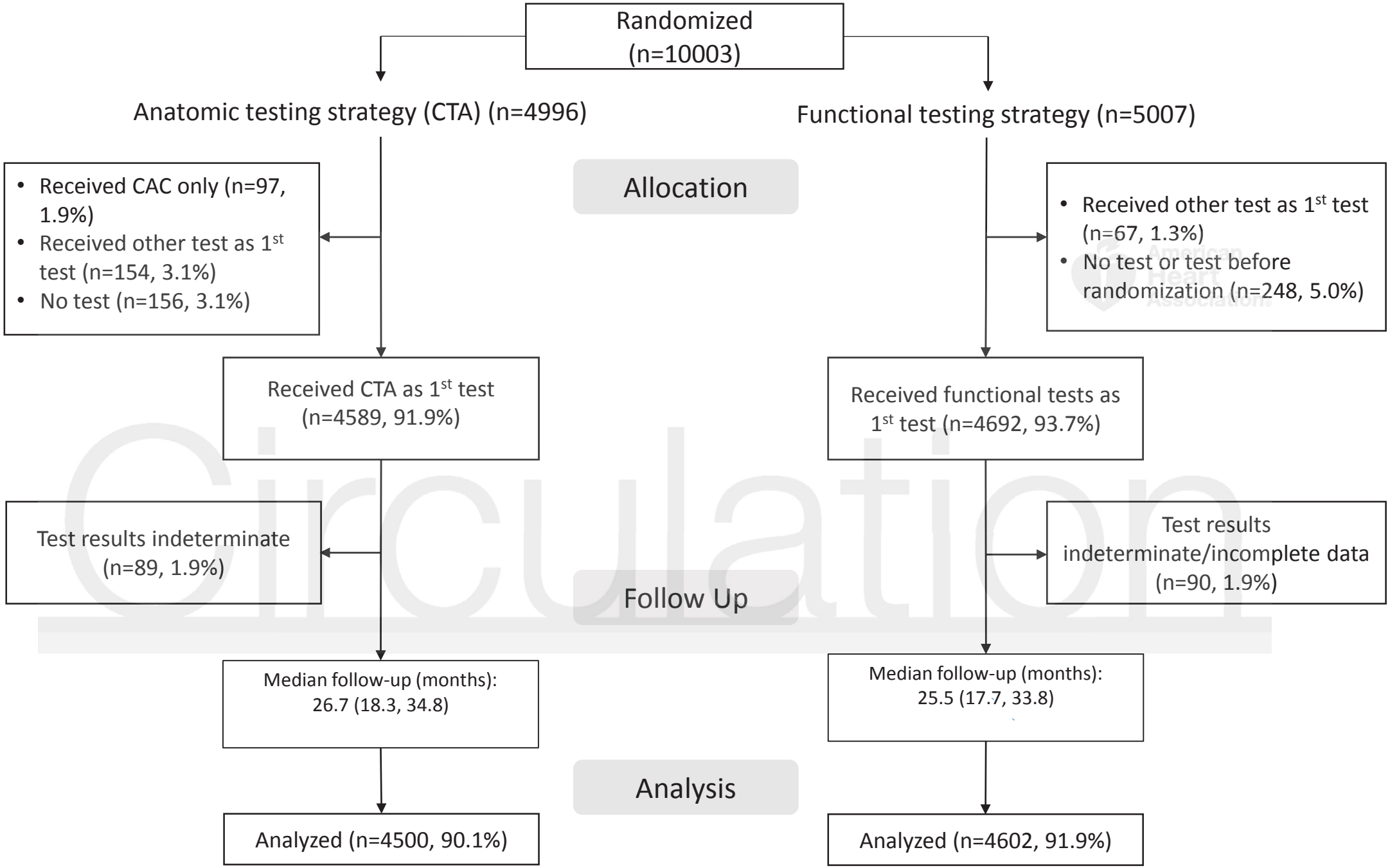
	Anatomic Testing (N=4500)				Functional Testing* (N=4602)			
Initial Test Results	**Frequency n/N(%)**	**Event Rate n/N(%)**	**HR (95% CI)**	**P-value**	**Frequency n/N(%)**	**Event Rate n/N(%)**	**HR (95% CI)**	**P-value**
All cause death/MI/UA								
Severely Abnormal	266/4500 (5.91)	28/266 (10.53)	10.13 (5.15–19.92)	<.0001	365/4602 (7.93)	35/365 (9.59)	6.01 (2.68–13.51)	<.0001
Moderately Abnormal	268/4500 (5.96)	21/268 (7.84)	7.67 (3.83–15.37)	<.0001	217/4602 (4.72)	13/217 (5.99)	4.14 (1.64–10.45)	0.0026
Mildly Abnormal	2461/4500 (54.69)	74/2461 (3.01)	2.94 (1.64–5.26)	0.0003	3146/4602 (68.36)	76/3146 (2.42)	1.61 (0.75–3.45)	0.2219
Normal	1505/4500 (33.44)	14/1505 (0.93)			874/4602 (18.99)	8/874 (0.92)		
CV death/MI/UA								
Severely Abnormal	266/4500 (5.91)	26/266 (9.77)	17.26 (7.55–39.46)	<.0001	365/4602 (7.93)	31/365 (8.49)	6.05 (2.54–14.41)	<.0001
Moderately Abnormal	268/4500 (5.96)	18/268 (6.72)	12.03 (5.14–28.19)	<.0001	217/4602 (4.72)	13/217 (5.99)	4.63 (1.76–12.24)	0.0020
Mildly Abnormal	2461/4500 (54.69)	57/2461 (2.32)	4.08 (1.93–8.66)	0.0002	3146/4602 (68.36)	57/3146 (1.81)	1.38 (0.61–3.15)	0.4433
Normal	1505/4500 (33.44)	8/1505 (0.53)			874/4602 (18.99)	7/874 (0.80)		
CV death/MI								
Severely Abnormal	266/4500 (5.91)	9/266 (3.38)	4.87 (1.72–13.75)	0.0028	365/4602 (7.93)	14/365 (3.84)	2.22 (0.83–5.88)	0.1103
Moderately Abnormal	268/4500 (5.96)	5/268 (1.87)	3.09 (0.96–9.97)	0.0594	217/4602 (4.72)	5/217 (2.30)	1.60 (0.47–5.38)	0.4490
Mildly Abnormal	2461/4500 (54.69)	39/2461 (1.58)	2.73 (1.20–6.25)	0.0170	3146/4602 (68.36)	46/3146 (1.46)	1.02 (0.43–2.39)	0.9678
Normal	1505/4500 (33.44)	7/1505 (0.47)			874/4602 (18.99)	7/874 (0.80)		

CV indicates cardiovascular; MI, myocardial infarction; and UA, unstable angina. Nonobstructive CAD is defined as 1-69% of stenosis. * Normal Functional Testing is defined as completely normal functional testing and a Framingham Risk Score of <10%

Figure Legends

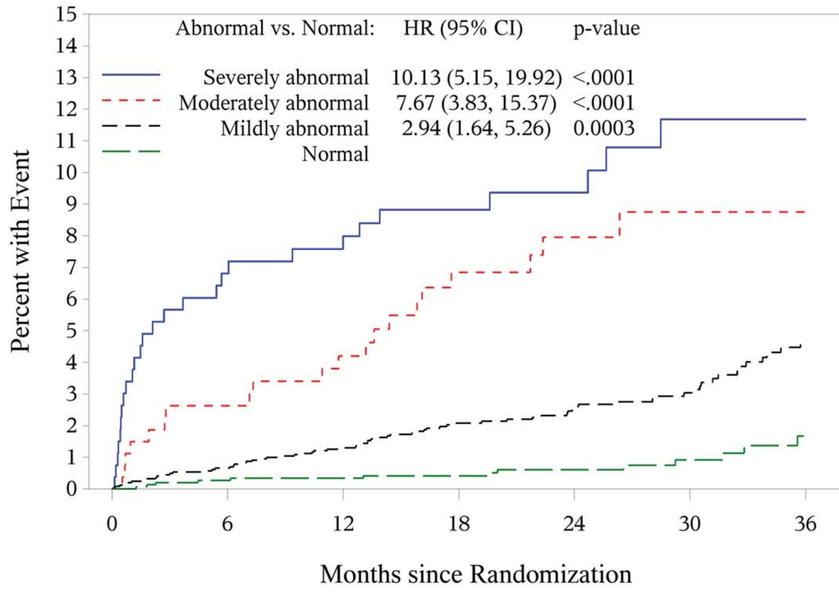
Figure 1. Patient flow and analytical population.

Figure 2. Kaplan-Meier curves demonstrating cumulative event rates for the primary endpoint based on test results (normal or mildly, moderately, or severely abnormal) for anatomic testing (using 1-69% criterion for nonobstructive CAD on CTA) (A), functional testing (B), and functional testing including the Framingham Risk Score (C).



A

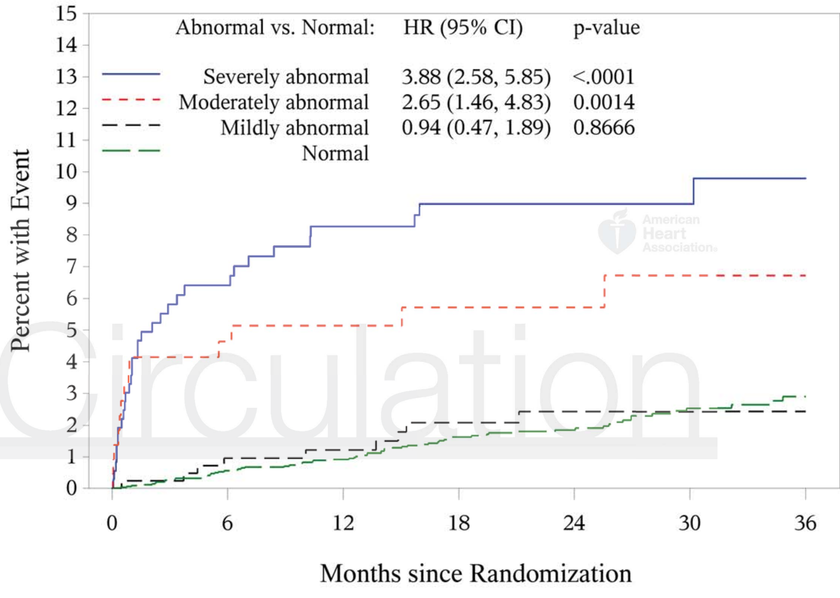
Anatomic Testing



# at Risk	Baseline (0)	6 Mo.	12 Mo.	18 Mo.	24 Mo.	30 Mo.	36 Mo.
Severe	266	242	229	188	138	87	43
Moderate	268	254	237	190	141	82	38
Mild	2461	2359	2199	1781	1362	898	459
Normal	1505	1452	1357	1127	828	532	296

B

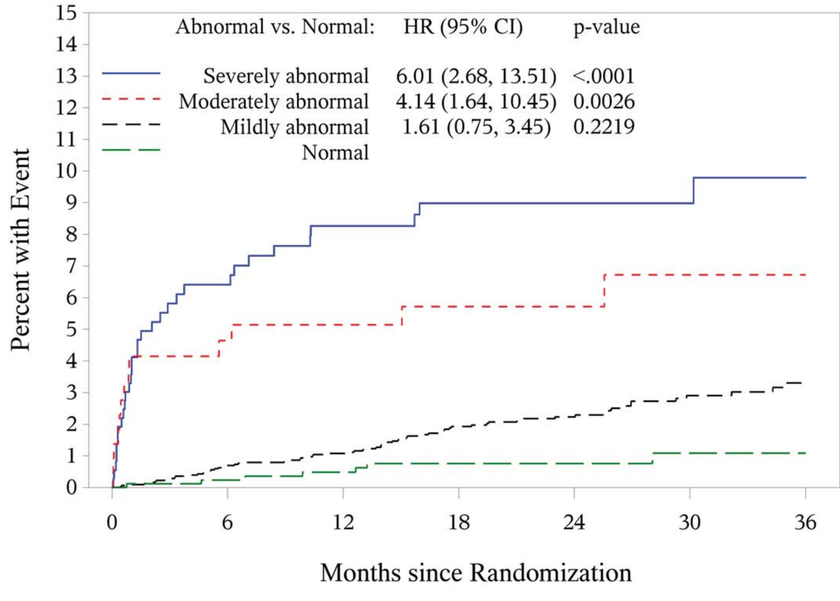
Functional Testing



# at Risk	Baseline (0)	6 Mo.	12 Mo.	18 Mo.	24 Mo.	30 Mo.	36 Mo.
Severe	365	311	277	235	177	114	66
Moderate	217	192	178	151	103	72	36
Mild	432	400	367	314	228	143	75
Normal	3588	3351	3061	2459	1764	1118	615

C

Functional Testing



# at Risk	Baseline (0)	6 Mo.	12 Mo.	18 Mo.	24 Mo.	30 Mo.	36 Mo.
Severe	365	311	277	235	177	114	66
Moderate	217	192	178	151	103	72	36
Mild	3146	2927	2680	2180	1578	1013	552
Normal	874	824	748	593	414	248	138

Prognostic Value of Noninvasive Cardiovascular Testing in Patients with Stable Chest Pain: Insights from the PROMISE Trial

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on behalf of the PROMISE Investigators

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Supplemental Material

Supplement to Hoffmann U, Ferencik M, Udelson JE, et al. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial.

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Supplemental Table 1. Baseline characteristics of the population for prognostic analysis vs. the patients enrolled but not included.*

Variable	Patients included in the Prognostic Analysis (N=9118)	Excluded Patients (N=885)	P Value
Demographics			
Mean age — yr	60.7 ± 8.2	61.1 ± 8.9	0.742
Female sex — no. (%)	4796 (52.6%)	474 (53.6%)	0.585
Racial or ethnic minority — no. (%)	2006 (22.1%)	242 (27.5%)	<0.001
Cardiac risk factors			
Mean body mass index (kg/m^2)	30.4 ± 6.0	31.1 ± 7.1	0.214
Hypertension — no. (%)	5904 (64.8%)	597 (67.5%)	0.098
Diabetes — no. (%)	1940 (21.3%)	204 (23.1%)	0.213
Dyslipidemia — no. (%)	6169 (67.7%)	598 (67.6%)	0.995
Family history of premature CAD — no. (%)	2891 (31.8%)	311 (35.3%)	0.034
Peripheral or cerebrovascular disease — no. (%)	495 (5.4%)	57 (6.4%)	0.205
CAD equivalent — no. (%)	2293 (25.1%)	238 (26.9%)	0.254
History of heart failure — no. (%)	339 (3.7%)	26 (2.9%)	0.239
Metabolic syndrome — no. (%)	3441 (37.7%)	331 (37.4%)	0.843
Current or past tobacco use — no. (%)	4672 (51.3%)	432 (48.9%)	0.176
Sedentary lifestyle — no. (%)	4419 (48.6%)	447 (50.7%)	0.216
History of depression — no. (%)	1878 (20.6%)	180 (20.4%)	0.881
Risk factor burden			
No major risk factors — no. (%)	246 (2.7%)	17 (1.9%)	0.168
Mean number of risk factors per patient	2.4 ± 1.1	2.4 ± 1.0	0.149
Mean combined Diamond and Forrester and Coronary Artery Surgery Study risk score	53.2 ± 21.3	53.6 ± 22.5	0.378
Framingham risk score — no. (%)			
Low risk (<6%)	620 (6.8%)	66 (7.5%)	0.668
Intermediate risk (6-20%)	4672 (51.3%)	442 (50.1%)	
High risk (>20%)	3814 (41.9%)	374 (42.4%)	
ASCVD pooled cohort risk prediction (2013) — no. (%)			
Low risk (<7.5%)	2919 (32.3%)	285 (32.7%)	0.831
Elevated risk (≥7.5%)	6110 (67.7%)	587 (67.3%)	
Relevant medications — no. (%)			
Beta-blocker	2166 (24.8%)	233 (27.6%)	0.079
ACE inhibitor or ARB	3823 (43.8%)	371 (43.9%)	0.963
Statin	3994 (45.8%)	395 (46.7%)	0.591
Aspirin	3896 (44.7%)	384 (45.4%)	0.661
Primary presenting symptom and anginal type — no. (%)			
Chest pain	6630 (72.8%)	642 (72.6%)	0.931
Dyspnea on exertion	1369 (15.0%)	121 (13.7%)	0.287
Anginal type — site-reported			
Typical	1044 (11.4%)	122 (13.8%)	0.099
Atypical	7107 (77.9%)	666 (75.3%)	
Non-anginal	967 (10.6%)	97 (11.0%)	

* Plus-minus values are means ±SD. ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; and CAD, coronary artery disease.

Supplemental Table 2. Frequency of test findings and association with clinical events for anatomic and functional testing for a definition of nonobstructive coronary artery disease from 1-49%.

	Anatomic Testing (N=4516)				Functional Testing (N=4602)			
Test Results	**Results Frequency— no./N (%)**	**Event Rate— no./N (%)**	**Hazard Ratio (95% CI)**	**P Value**	**Results Frequency— no./N (%)**	**Event Rate— no./N (%)**	**Hazard Ratio (95% CI)**	**P Value**
All-cause death/MI/UA								
Severely Abnormal	632/4516 (14.0)	56/632 (8.9)	8.55 (4.62–15.83)	<0.0001	365/4602 (7.9)	35/365 (9.6)	3.88 (2.58–5.85)	<0.0001
Moderately Abnormal	449/4516 (9.9)	21/449 (4.7)	4.82 (2.42–9.63)	<0.0001	217/4602 (4.7)	13/217 (6.0)	2.65 (1.46–4.83)	0.0014
Mildly Abnormal	1930/4516 (42.7)	46/1930 (2.4)	2.38 (1.30–4.38)	0.0051	432/4602 (9.4)	9/432 (2.1)	0.94 (0.47–1.89)	0.8666
Normal	1505/4516 (33.3)	14/1505 (0.9)	REF		3588/4602 (78.0)	75/3588 (2.1)	REF	
CV death/MI/UA								
Severely Abnormal	632/4516 (14.0)	50/632 (7.9)	14.11 (6.50–30.65)	<0.0001	365/4602 (7.9)	31/365 (8.5)	4.59 (2.93–7.19)	<0.0001
Moderately Abnormal	449/4516 (9.9)	19/449 (4.2)	7.97 (3.44–18.47)	<0.0001	217/4602 (4.7)	13/217 (6.0)	3.50 (1.89–6.48)	<0.0001
Mildly Abnormal	1930/4516 (42.7)	32/1930 (1.7)	2.99 (1.37–6.56)	0.0061	432/4602 (9.4)	8/432 (1.9)	1.11 (0.53–2.34)	0.7834
Normal	1505/4516 (33.3)	8/1505 (0.5)	REF		3588/4602 (78.0)	56/3588 (1.6)	REF	
CV death/MI								
Severely Abnormal	632/4516 (14.0)	20/632 (3.2)	4.85 (1.96–12.04)	0.0007	365/4602 (7.9)	14/365 (3.9)	2.13 (1.16–3.91)	0.0141
Moderately Abnormal	449/4516 (9.9)	9/449 (2.0)	3.65 (1.33–10.04)	0.0122	217/4602 (4.7)	5/217 (2.3)	1.53 (0.60–3.90)	0.3681
Mildly Abnormal	1930/4516 (42.7)	24/1930 (1.2)	2.23 (0.94–5.27)	0.0671	432/4602 (9.4)	5/432 (1.2)	0.81 (0.32–2.04)	0.6542
Normal	1505/4516 (33.3)	7/1505 (0.5)	REF		3588/4602 (78.0)	48/3588 (1.3)	REF	

CV indicates cardiovascular; MI, myocardial infarction; and UA, unstable angina.

Supplemental Table 3. Test findings and clinical events in 4602 patients randomized to the functional arm of PROMISE according to the functional test performed.

	Exercise Treadmill N=467 (10.1%)		**Stress Echocardiography N=1019 (22.1%)**		**Stress Nuclear Perfusion N=3116 (67.8%)**	
	No. of Patients	**No. of Events**	**No. of Patients**	**No. of Events**	**No. of patients**	**No. of Events**
All cause death/MI/UA						
Severely Abnormal	0	0	66	4	299	31
Moderately Abnormal	59	2	16	0	142	11
Mildly Abnormal	316	3	696	14	2134	59
Normal	92	1	241	2	541	5
CV death/MI/UA						
Severely Abnormal	0	0	66	4	299	27
Moderately Abnormal	59	2	16	0	142	11
Mildly Abnormal	316	2	696	8	2134	47
Normal	92	1	241	1	541	5
CV death/MI						
Severely Abnormal	0	0	66	2	299	12
Moderately Abnormal	59	0	16	0	142	5
Mildly Abnormal	316	1	696	5	2134	40
Normal	92	1	241	1	541	5

CV indicates cardiovascular; MI, myocardial infarction; and UA, unstable angina.

Supplemental Table 4. Frequency of test findings and association with clinical events for anatomic and functional testing in patients prespecified to receive stress nuclear perfusion imaging.

	Anatomical Testing (N=3050)				Functional Testing (N=3136)			
Initial Test Results	**Frequency n/N (%)**	**Event Rate n/N (%)**	**Hazard Ratio (95% CI)**	**P-value**	**Frequency n/N (%)**	**Event Rate n/N (%)**	**Hazard Ratio (95% CI)**	**P-value**
All cause death/MI/UA								
Severely Abnormal	199/3050 (6.52)	21/199 (10.55)	14.49 (5.67, 37.04)	<.0001	299/3136 (9.53)	31/299 (10.37)	8.26 (3.09, 22.08)	<.0001
Moderately Abnormal	191/3050 (6.26)	16/191 (8.38)	12.07 (4.63, 31.48)	<.0001	146/3136 (4.66)	12/146 (8.22)	6.04 (2.03, 17.96)	0.0012
Mildly Abnormal	1699/3050 (55.70)	52/1699 (3.06)	4.33 (1.84, 10.21)	0.0008	2145/3136 (68.40)	56/2145 (2.61)	1.98 (0.77, 5.12)	0.1571
Normal	961/3050 (31.51)	6/961 (0.62)	REF		546/3136 (17.41)	5/546 (0.92)	REF	
CV death/MI/UA								
Severely Abnormal	199/3050 (6.52)	19/199 (9.55)	19.59 (6.45, 59.50)	<.0001	299/3136 (9.53)	27/299 (9.03)	7.59 (2.80, 20.57)	<.0001
Moderately Abnormal	191/3050 (6.26)	13/191 (6.81)	14.81 (4.73, 46.39)	<.0001	146/3136 (4.66)	12/146 (8.22)	6.44 (2.15, 19.25)	0.0009
Mildly Abnormal	1699/3050 (55.70)	40/1699 (2.35)	5.03 (1.78, 14.22)	0.0023	2145/3136 (68.40)	45/2145 (2.10)	1.68 (0.64, 4.38)	0.2933
Normal	961/3050 (31.51)	4/961 (0.42)	REF		546/3136 (17.41)	5/546 (0.92)	REF	
CV death/MI								
Severely Abnormal	199/3050 (6.52)	8/199 (4.02)	6.90 (1.74, 27.34)	0.0060	299/3136 (9.53)	12/299 (4.01)	2.76 (0.91, 8.36)	0.0730
Moderately Abnormal	191/3050 (6.26)	4/191 (2.09)	4.36 (0.95, 20.11)	0.0588	146/3136 (4.66)	5/146 (3.42)	2.33 (0.63, 8.62)	0.2061
Mildly Abnormal	1699/3050 (55.70)	27/1699 (1.59)	3.51 (1.04, 11.83)	0.0429	2145/3136 (68.40)	38/2145 (1.77)	1.28 (0.47, 3.43)	0.6306
Normal	961/3050 (31.51)	3/961 (0.31)	REF		546/3136 (17.41)	5/546 (0.92)	REF	

CV indicates cardiovascular; MI, myocardial infarction; and UA, unstable angina.

Supplemental Table 5. Sensitivity analysis of the association of the definition of normal functional testing with and without consideration of the cardiovascular risk factors (Framingham Risk Score).

	Functional Testing – original definition (N=4602)				**Functional Testing – New mildly abnormal definition (N=4602)**			
Initial Test Results	**Frequency n/N (%)**	**Event Rate n/N (%)**	**Hazard Ratio (95% CI)**	**P-value**	**Frequency n/N (%)**	**Event Rate n/N (%)**	**Hazard Ratio (95% CI)**	**P-value**
All cause death/MI/UA								
Severely Abnormal	365/4602 (7.93)	35/365 (9.59)	3.88 (2.58, 5.85)	<.0001	365/4602 (7.93)	35/365 (9.59)	6.01 (2.68, 13.51)	<.0001
Moderately Abnormal	217/4602 (4.72)	13/217 (5.99)	2.65 (1.46, 4.83)	0.0014	217/4602 (4.72)	13/217 (5.99)	4.14 (1.64, 10.45)	0.0026
Mildly Abnormal	432/4602 (9.39)	9/432 (2.08)	0.94 (0.47, 1.89)	0.8666	3146/4602 (68.36)	76/3146 (2.42)	1.61 (0.75, 3.45)	0.2219
Normal	3588/4602 (77.97)	75/3588 (2.09)	REF		874/4602 (18.99)	8/874 (0.92)	REF	
CV death/MI/UA								
Severely Abnormal	365/4602 (7.93)	31/365 (8.49)	4.59 (2.93, 7.19)	<.0001	365/4602 (7.93)	31/365 (8.49)	6.05 (2.54, 14.41)	<.0001
Moderately Abnormal	217/4602 (4.72)	13/217 (5.99)	3.50 (1.89, 6.48)	<.0001	217/4602 (4.72)	13/217 (5.99)	4.63 (1.76, 12.24)	0.0020
Mildly Abnormal	432/4602 (9.39)	8/432 (1.85)	1.11 (0.53, 2.34)	0.7834	3146/4602 (68.36)	57/3146 (1.81)	1.38 (0.61, 3.15)	0.4433
Normal	3588/4602 (77.97)	56/3588 (1.56)	REF		874/4602 (18.99)	7/874 (0.80)	REF	
CV death/MI								
Severely Abnormal	365/4602 (7.93)	14/365 (3.84)	2.13 (1.16, 3.91)	0.0141	365/4602 (7.93)	14/365 (3.84)	2.22 (0.83, 5.88)	0.1103
Moderately Abnormal	217/4602 (4.72)	5/217 (2.30)	1.53 (0.60, 3.90)	0.3681	217/4602 (4.72)	5/217 (2.30)	1.60 (0.47, 5.38)	0.4490
Mildly Abnormal	432/4602 (9.39)	5/432 (1.16)	0.81 (0.32, 2.04)	0.6542	3146/4602 (68.36)	46/3146 (1.46)	1.02 (0.43, 2.39)	0.9678
Normal	3588/4602 (77.97)	48/3588 (1.34)	REF		874/4602 (18.99)	7/874 (0.80)	REF	

CV indicates cardiovascular; MI, myocardial infarction; and UA, unstable angina.

Supplemental Figure 1. Kaplan-Meier curves demonstrating cumulative event rates based on the presence of myocardial ischemia and obstructive CAD for anatomic testing (A) and functional testing (B).