Stable Angina Pectoris: Head-to-Head Comparison of Prognostic Value of Cardiac CT and Exercise Testing[1]

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Purpose: To determine and compare the prognostic value of cardiac computed tomographic (CT) angiography, coronary calcium scoring, and exercise electrocardiography (ECG) in patients with chest pain who are suspected of having coronary artery disease (CAD).

Materials and Methods: This study complied with the Declaration of Helsinki, and the local ethics committee approved the study. Patients (n = 471) without known CAD underwent exercise ECG and dual-source CT at a rapid assessment outpatient chest pain clinic. Coronary calcification and the presence of 50% or greater coronary stenosis (in one or more vessels) were assessed with CT. Exercise ECG results were classified as normal, ischemic, or nondiagnostic. The primary outcome was a major adverse cardiac event (MACE), defined as cardiac death, nonfatal myocardial infarction, or unstable angina requiring hospitalization and revascularization beyond 6 months. Univariable and multivariable Cox regression analysis was used to determine the prognostic values, while clinical impact was assessed with the net reclassification improvement metric.

Results: Follow-up was completed for 424 (90%) patients; the mean duration of follow-up was 2.6 years. A total of 44 MACEs occurred in 30 patients. Four of the MACEs were cardiac deaths and six were nonfatal myocardial infarctions. The presence of coronary calcification (hazard ratio [HR], 8.22 [95% confidence interval {CI}: 1.96, 34.51]), obstructive CAD (HR, 6.22 [95% CI: 2.77, 13.99]), and nondiagnostic stress test results (HR, 3.00 [95% CI: 1.26, 7.14]) were univariable predictors of MACEs. In the multivariable model, CT angiography findings (HR, 5.0 [95% CI: 1.7, 14.5]) and nondiagnostic exercise ECG results (HR, 2.9 [95% CI: 1.2, 7.0]) remained independent predictors of MACEs. CT angiography findings showed incremental value beyond clinical predictors and stress testing (global χ^2, 37.7 vs 13.7; $P < .001$), whereas coronary calcium scores did not have further incremental value (global χ^2, 38.2 vs 37.7; $P = .40$).

Conclusion: CT angiography findings are a strong predictor of future adverse events, showing incremental value over clinical predictors, stress testing, and coronary calcium scores.

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Over the past decade, cardiac computed tomographic (CT) angiography has emerged as a valuable diagnostic tool to evaluate coronary artery disease (CAD) and has found use as an anatomic alternative to functional testing and a noninvasive alternative to conventional (catheter-based) coronary angiography (1,2). Functional assessment of CAD severity with exercise electrocardiography (ECG) is well established, and its prognostic value has been studied extensively (3,4). Although evidence regarding the prognostic value of CT angiography findings is emerging (5–7), the question remains if this angiographic modality holds incremental prognostic value beyond functional evaluation with exercise ECG. In this study, in a prospectively enrolled population, we sought to determine and compare the prognostic value of cardiac CT angiography, coronary calcium scoring (CCS), and exercise ECG in patients with chest pain who were suspected of having CAD.

Materials and Methods

From September 2006 to December 2008, 471 consecutive patients without a history of CAD were evaluated at our rapid assessment outpatient chest pain clinic (mean age, 56 years ± 10 [standard deviation]; age range, 18–84 years; 244 men) (8). They had been referred by their general practitioner because of chronic complaints of chest pain potentially caused by CAD to undergo additional testing with exercise ECG, CT angiography, and CCS. Information on risk factors was prospectively acquired, and clinical risk estimators—that is, the Systematic Coronary Risk Evaluation (SCORE) (9) and Diamond and Forrester metrics (10)—were calculated from these data. According to the SCORE, 291 patients had a 10-year risk of less than 5% of developing fatal cardiovascular disease, 130 patients had a risk of 5%–10%, and 50 patients had a risk of greater than 10%.

The study complied with the Declaration of Helsinki, and the local ethics committee approved the study.

CCS Protocol

Calcium detection was performed with an ECG-triggered step-and-shoot acquisition mode, by using a 120-kV tube voltage, a mean tube current of 78 mAs ± 26, and a section thickness of 3 mm. The coronary calcium score was assessed by using dedicated software (Syngo CaScore; Siemens, Forchheim, Germany) and was quantified with the Agatston method with a standard 130-HU attenuation threshold (11). To account for the skewed distribution, all calcium scores were transformed by taking the natural logarithm of the calcium score +1.

CT Angiographic Parameters

Contrast material–enhanced dual-source multisection CT (Definition; Siemens) was performed by using the following parameters: number of detector rows, 32; section thickness, 0.6 mm; 64-channel acquisition by z-axis focal spot alternation; rotation time, 330 msec; temporal resolution, 83 msec; spiral acquisition mode with prospectively ECG-triggered tube modulation depending on the heart rate regularity; tube voltage, 120 kV; tube current, 380–412 mAs depending on patient size; and variable pitch depending on the heart rate. Iopromide 70–100 mL (Ultravist, 370 milligrams of iodine per milliliter; Schering, Berlin, Germany), followed by a 40-mL saline bolus chaser, was peripherally injected at 5.0–5.5 mL/sec. Patients received sublingual nitroglycerin before the examination but no additional β-blockers. Effective radiation doses for CCS and CT angiography were 0.8 mSv ± 0.2 (range, 0.4–1.6 mSv) and 11.0 mSv ± 3.5 (range, 4.7–17.8 mSv), respectively.

The coronary arteries were evaluated on axial images, multiplanar reconstructions, and maximum intensity projections according to readers' preferences. Readers (including A.M., with 5 years of experience), who were assisted by research fellows with a minimum of 1 year of experience in coronary imaging, were blinded to patients' symptoms and exercise ECG results. Vessels were qualitatively scored as significantly stenosed (≥50% diameter narrowing) or less than significantly stenosed (<50%) or free from plaque. To assess the prognostic value of CT angiography, we constructed a model comparing obstructive plaque to nonobstructive plaque. In a second model, we assessed the prognostic value of obstructive and nonobstructive plaque versus no plaque.

Advances in Knowledge

- Coronary CT angiography has incremental prognostic value over exercise testing.
- Coronary calcium scoring seems to have no additive prognostic value beyond coronary CT angiography.
- Inability to perform a diagnostic exercise test is associated with unfavorable outcome.

Implication for Patient Care

- Coronary CT angiography can be used for risk assessment as well as diagnostic purposes.

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Abbreviations

AUC = area under the receiver operating characteristic curve
CAD = coronary artery disease
CCS = coronary calcium scoring
CI = confidence interval
ECG = electrocardiography
HR = hazard ratio
IQR = interquartile range
MACE = major adverse cardiac event
NRI = net reclassification improvement
SCORE = Systematic Coronary Risk Evaluation

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Potential conflicts of interest are listed at the end of this article.

Exercise ECG

Patients underwent stress testing on a bicycle ergometer by using a standardized protocol. Use of any β-blockers was ceased 72 hours before stress testing, if possible. During continuous ECG registration and 12-lead printing at 1-minute intervals, the workload was increased from 40 W in 20-W increments at 1-minute intervals. Blood pressure was measured every 2 minutes. In cases of established contraindications, patients did not undergo exercise ECG (12). Criteria for myocardial ischemia included horizontal or downsloping ST-segment depression or elevation of 0.1 mV or greater during or after exercise or typical, increasing angina during exercise. A nondiagnostic test was defined as when there was an inability to perform the test or the test was discontinued without evidence of myocardial ischemia before reaching 85% of the predicted maximum heart rate (12). Additionally, for every patient, we approximated the Duke Treadmill Score by using a standardized formula as follows: DE − (5 · STD) − (4 · TAI), where DE is duration of exercise in minutes, STD is maximum net ST-segment deviation during or after exercise in millimeters, and TAI is treadmill angina index (where a score of 0 = no complaints, a score of 1 = nonlimiting angina, and a score of 2 = angina requiring discontinuation) (3).

Follow-up

Follow-up data were obtained by consulting the national death registry for the occurrence of mortality and through standardized telephone interviews, questionnaires, or hospital visits. All events were confirmed with death records, hospital records, or correspondence with treating physicians and hospitals. If patients experienced multiple events during follow-up, only the first event counted. Patients lost to follow-up were censored. All events were reviewed by an independent cardiologist (K.N., with 3 years of postresidency experience as a Cardiology Department staff member) who was blinded to both CT angiography and exercise ECG results.

Outcome Measures

The primary outcome measure was a composite of cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalization, and coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery).

Cardiac death was defined as death caused by acute myocardial infarction, ventricular arrhythmia, refractory heart failure, or cardiogenic shock. Nonfatal myocardial infarction was defined as ischemia resulting in abnormal cardiac biomarkers (>99th percentile of the upper limits of normal). Unstable angina was defined as chest pain with altered frequency or character that was suspicious for acute coronary syndrome; a diagnosis of unstable angina also required ischemic ECG changes or significantly obstructive CAD at invasive conventional angiography (13). Coronary revascularizations initiated as a result of the initial diagnostic work-up and performed within 6 months were not considered as an end point.

Statistical Analysis

Statistical analyses were performed by using SPSS (version 15.0; SPSS, Chicago, Ill) and STATA (version 11.1; Stata, College Station, Tex). All probability values refer to two-tailed tests of significance; $P < .05$ was considered to indicate a significant difference. Categoric variables are presented as proportions. Continuous variables are expressed as means ± standard deviations or as medians ± interquartile ranges (IQRs) as appropriate. Clinical patient characteristics are summarized by the SCORE 10-year cardiovascular mortality risk (9).

Univariable Cox regression analyses of each potential clinical predictor, as well as coronary calcification, CT angiography results, and exercise ECG results, were performed to evaluate their effect in predicting major adverse cardiac events (MACEs) during follow-up.

Cumulative event rates as a function over time were estimated according to the Kaplan-Meier method. Unadjusted comparison of survival between groups defined by the two CT angiography results, coronary calcium categories, and exercise ECG results was performed by using the log-rank test. Annual event rates were calculated by dividing the cumulative event rates by the median number of follow-up years.

A multivariable Cox proportional hazards model was used to assess the independent prognostic value of exercise ECG, CT angiography, and CCS. Risk adjustment for clinical characteristics was performed by using patients' SCORE results. To assess the incremental value of exercise ECG, CT angiography, and CCS, the global χ^2 values were compared between models with and those without the addition of each incrementally. Using logistic regression, receiver operating characteristic curves with estimates of the area under the receiver operating characteristic curve (AUC, or the C-statistic) were obtained to compare the discriminative performance of the different models.

To quantify the clinical impact of adding exercise ECG, CT angiography, and CCS to the model predicting MACE, we calculated the net reclassification improvement (NRI), which is a measure of correctly reclassified subjects that is penalized for those incorrectly classified. In this context, clinically relevant cutoff values for the risk of a MACE (ie, the thresholds of risk where reclassification to another category would influence clinical management) are absent. Thus we used an extension of the traditional NRI that was recently introduced by Pencina et al (14). The so-called continuous NRI (or category-free NRI) does not depend on the existence of risk categories and allows NRI estimation in the context of survival data. The continuous NRI is the weighted sum of the observed event rate increase among the individuals for whom the predicted risk goes up and observed event rate decrease among thosefor whom the predicted risk goes down.

Results

Coronary CT could not be performed in 16 (3%) patients because of renal failure ($n = 2$), known allergy to contrast material ($n = 1$), patient preferences

(*n* = 8), Parkinson disease (*n* = 1), patient noncooperation (*n* = 1), lack of venous access (*n* = 1), and severe obesity (*n* = 2). Two examinations (0.4%) failed because of patient movement or premature scanning initiation. Three patients (0.6%) had mild to moderate allergic reactions.

Exercise ECG could not be performed in 48 (10%) patients because of orthopedic restraints (*n* = 13), neurologic restraints (*n* = 8), severe obesity (*n* = 3), abnormalities at resting ECG (*n* = 8), pulmonary disease (*n* = 2), inability to bicycle (*n* = 3), and a combination of these factors or an unspecified factor (*n* = 11). Results were considered inconclusive in 140 (30%) patients, mostly because the target heart rate was not reached. These patients together (*n* = 188) were considered to have had nondiagnostic tests in the survival analysis (Fig 1).

Follow-up

Follow-up data were obtained for 424 (90%) patients. Forty-four adverse cardiac events occurred in 30 patients. These events consisted of four cardiac deaths, six acute myocardial infarctions, 23 coronary revascularizations, and 11 instances of unstable angina pectoris. The occurrence of mortality was obtained for all patients, and, according to the national bureau of statistics, another four patients died of a noncardiac cause—that is, respiratory failure, stroke, or malignancy (*n* = 2). The median follow-up time was 2.6 years (IQR, 2.1–3.2 years). The overall rate of events was 3.2% per year.

Patients without follow-up were younger ($P < .001$) and more often smokers ($P = .02$). Lower coronary calcium scores and fewer abnormal CT angiography and exercise ECG results were observed for patients without follow-up, although this did not reach statistically significance (Table E1 [online]). There was no significant difference in Duke Treadmill Score between the patients with and those without follow-up (median score, 5 [IQR, 1–7] vs 5 [IQR, 0.5–7]). Only six patients were classified as having high risk, and they all completed follow-up.

Descriptive Analysis

Coronary calcium score.—Patients with no coronary calcium had excellent prognoses. No cardiac deaths and no nonfatal myocardial infarctions were observed (Table 1). However, three hospitalizations for unstable angina occurred, and one late revascularization was performed.

Coronary CT.—In the group of patients with obstructive CAD, 22 (17%) events occurred, consisting of three cardiac deaths (2%) and four myocardial infarctions (3%). Patients without obstructive CAD experienced significantly fewer total events (eight patients [3%]; $P < .001$), one cardiac death (0.4%), and two (0.7%) myocardial infarctions (Table 1). Patients who did not undergo CT angiography or in whom the study was nondiagnostic did not experience a MACE.

Exercise ECG.—Patients with a normal exercise ECG result experienced seven (4%) events during follow-up, of which one (0.6%) was a myocardial infarction. An abnormal exercise ECG result was associated with the occurrence of four (5%) events, of which one (1%) was a myocardial infarction. We observed 19 (11%) events in the group of patients who were unable to perform the test or who had an inconclusive test; of these events, four (2%) were cardiac deaths and four (2%) were myocardial infarctions (Table 1).

Univariable Analysis

The clinical risk estimators SCORE and Diamond and Forrester score were both significant predictors of MACEs (Table 2). Of the traditional risk factors, only sex was a statistically significant predictor. A typical angina presentation was associated with an HR of 3.86 (95% CI: 0.88, 16.87) compared with nonanginal complaints, while atypical presentation was associated with an HR of 1.91 (95% CI: 0.43, 8.47).

Detectable coronary calcium was a significant predictor of MACE (HR, 8.22 [95% CI: 1.96, 34.51]; $P = .004$), along with nondiagnostic exercise ECG results (HR, 3.00 [95% CI: 1.26, 7.14]; $P = .01$). Regarding CT angiography results, in the first model, obstructive CAD was associated with a significantly higher hazard (HR, 6.22 [95% CI: 2.77, 13.99]; $P < .001$). In the second model, the presence of nonobstructive plaque was also associated with a higher hazard (HR, 5.03 [95% CI: 0.62, 40.85]), although this did not reach statistical significance ($P = .13$), while obstructive CAD remained a significant predictor (HR, 20.80 [95% CI: 2.80, 154.33]; $P = .003$).

Figure 1

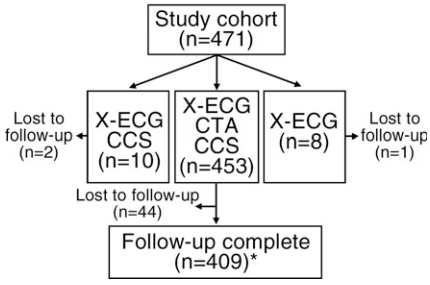

Figure 1: Flowchart of patients included in the survival analysis. *Included in multivariable analysis. *CTA* = CT angiography, *X-ECG* = exercise ECG.

Survival Analysis

Unadjusted comparison between patients with and those without coronary calcium showed significantly higher event-free survival in the group with no calcium (Fig 2a) ($P = .001$). The annual event rate in patients without calcium was 0.5%.

Absence of obstructive CAD at CT angiography was associated with a significantly lower event rate than the presence of obstructive CAD at CT angiography (Fig 2b) ($P < .001$). The annual event rates were 6.8% versus 1.2% for obstructive versus nonobstructive CAD (Table 1).

Nondiagnostic exercise ECG results were associated with significantly higher event rates than normal or ischemic exercise ECG results (Fig 2c) ($P = .016$). The observed annual event rate for patients with nondiagnostic results compared with that for patients with normal or ischemic results was substantially higher (4.6% vs 1.6% and 1.9%, respectively).

Multivariable Risk-adjusted Analysis

In the multivariable Cox regression analysis, after adjusting for SCORE, the presence of obstructive CAD (HR,

Table 1

Events Sorted according to Test

Test and Result	Total No. of Patients	No. of Patients with MACE	No. of Patients with CD	No. of Patients with AMI	No. of Patients with LR	No. of Patients with UAP	Annual Event Rate (%)
Coronary calcium score = 0	151	2 (1)	0	0	1 (0.7)	3 (2)	0.5
Coronary calcium score > 0	266	28 (11)	4 (2)	6 (2)	22 (8)	8 (3)	4.2
CT angiography stenosis < 50%	277	8 (3)	1 (0.4)	2 (0.7)	3 (1)	3 (1)	1.2
CT angiography stenosis > 50%	132	22 (17)	3 (2)	4 (3)	20 (15)	8 (6)	6.8
Normal exercise ECG result	172	7 (4)	0	1 (0.6)	6 (4)	3 (2)	1.6
Ischemic exercise ECG result	85	4 (5)	0	1 (1)	5 (6)	1 (1)	1.9
Nondiagnostic exercise ECG result	167	19 (11)	4 (2)	4 (2)	12 (7)	7 (4)	4.6

Note.—Numbers in parentheses are percentages. AMI = acute myocardial infarction, CD = cardiac death, LR = late revascularization, UAP = unstable angina pectoris requiring hospitalization.

6.61 [95% CI: 2.83, 15.43]) and nondiagnostic exercise ECG result (HR, 2.93 [95% CI: 1.23, 6.99]) remained independent predictors of MACE (Table 3). The addition of CCS led to a slight decrease in the HRs of CT angiography (HR, 5.00 [95% CI: 1.72, 14.52]) and exercise ECG (HR, 2.80 [95% CI: 1.17, 6.73]), whereas CCS itself was not an independent predictor (HR, 1.09 [95% CI; 0.89, 1.33]).

A statistically significant increase in the global χ^2 value was seen after adding CT angiography results to a risk-adjusted model with exercise ECG (global χ^2 value, 37.7 vs 13.7; $P < .001$) but not with the subsequent addition of CCS (global χ^2 value, 38.2 vs 37.7; $P = .40$).

Detectable calcium was an independent predictor in a risk-adjusted model with exercise ECG alone (HR, 1.33 [95% CI: 1.13, 1.56]). Subsequent addition of CT angiography improved model performance significantly (global χ^2 value, 38.2 vs 26.3; $P = .002$) (Table E2 [online]).

Receiver Operating Characteristics

The obtained curves and their AUC estimates demonstrated that the combination of clinical characteristics and exercise ECG findings resulted in an AUC of 0.71 (95% CI: 0.63, 0.79) (Fig 3). A risk-adjusted model with CT angiography resulted in an AUC of 0.75 (95% CI: 0.67, 0.83), while clinical characteristics and CCS produced an AUC of 0.73 (95% CI: 0.65, 0.81).

When clinical characteristics, exercise ECG findings, and CT angiography findings were combined in a model, we found an AUC of 0.80 (95% CI: 0.72, 0.88). Insertion of CCS into this model did not improve its predictive value considerably (AUC, 0.81 [95% CI: 0.73, 0.88]).

NRI Results

The NRI was 54% (number of patients classified upward: 160; downward: 249) when exercise ECG was added to the clinical Cox proportional hazards model using only the SCORE. The addition of CT angiography to the model with both SCORE and exercise ECG resulted in a NRI of 80% (number of patients classified upward: 132; downward: 277). Finally, the full model that included CCS resulted in an NRI of 47% (number of patients classified upward: 182; downward: 227) (Table 3).

Discussion

Our results show that the presence of obstructive CAD at CT angiography, the degree of exercise tolerance, and the extent of coronary calcification predict future adverse events in patients with stable symptoms of chest pain. After adjustment for clinical characteristics, CT angiography showed incremental value beyond exercise testing, whereas the additive prognostic value of CCS was limited compared with CT angiography.

For the past decades, exercise testing has been the diagnostic cornerstone for the evaluation of ischemic heart disease and can help identify patients at increased risk for adverse events (3,4). Exercise tolerance is a powerful predictor of prognosis (15,16), which is confirmed in our study by the fact that inability to perform and complete exercise ECG predicted unfavorable outcome. Exercise capacity is an important predictor of adverse outcome, representing contractile left ventricular function as well as overall physical health. Most nondiagnostic exercise tests were the result of a low exercise capacity and consequent inability to reach the target heart rate.

Remarkably, ischemic ECG changes were not associated with increased event rates. Presumably, patients with these changes were treated more aggressively, explaining their better event-free survival. Second, patients developing ischemic ECG changes during exercise, but straining themselves outstandingly, apparently tolerate ischemia well and may be in good general shape. The fact that only a minority of the study population was categorized as having high-risk disease according to the Duke Treadmill Score supports this hypothesis.

Nonenhanced CT imaging can be used to help detect and quantify calcified CAD, and its findings have independent prognostic value in both symptomatic and asymptomatic individuals (17–21). Also in our study, the presence of coronary calcium was associated with an adverse outcome. In particular, our results confirm the idea that patients with no detectable calcium have an excellent outcome (annual event rate, 0.5%).

More recently, CT coronary angiography has emerged as a noninvasive

Table 2

Results of Cox Univariable Analysis

Variable	MACE ($n = 30$)	No MACE ($n = 392$)	HR*	*P* Value
Age (y)†	58 ± 8	56 ± 10	1.02 (0.99, 1.06)	.21
Male sex	22 (73)	195 (50)	2.68 (1.19, 6.02)	.02
Smoking	9 (30)	107 (27)	1.15 (0.53, 2.52)	.72
Hypertension	20 (67)	193 (49)	1.99 (0.93, 4.25)	.08
Diabetes	7 (23)	51 (13)	1.92 (0.82, 4.47)	.13
Dyslipidemia	20 (67)	229 (58)	1.29 (0.60, 2.76)	.52
Family history of CAD	16 (53)	173 (44)	1.39 (0.68, 2.85)	.37
History of vascular disease	2 (7)	28 (7)	0.94 (0.22, 3.94)	.93
Body mass index (kg/m^2)‡	26.9	26.8	1.01 (0.94, 1.08)	.86
Chest pain				
Nonanginal	2 (7)	64 (16)	1	
Atypical	13 (43)	207 (53)	1.91 (0.43, 8.47)	.39
Typical	15 (50)	121 (31)	3.86 (0.88, 16.87)	.07
SCORE‡	6 (2.75–8.25)	3 (1–6)	1.06 (1.01, 1.12)	.03
Diamond and Forrester score‡	67 (53–92)	54 (28–79)	1.02 (1.01, 1.04)	.003
Low (<22)			1	
Intermediate (22–78)			2.83 (0.64, 12.47)	.17
High (>78)			5.16 (1.17, 22.70)	.03
Calcium score				
0	2 (7)	149 (39)	1	
0–10	2 (7)	43 (11)	3.19 (0.45, 22.65)	.25
10–100	10 (33)	82 (21)	8.45 (1.85, 38.58)	.006
100–400	7 (23)	59 (15)	8.50 (1.77, 40.793)	.008
>400	9 (30)	54 (14)	11.66 (2.52, 54.01)	.002
>0	28 (93)	238 (62)	8.22 (1.96, 34.51)	.004
CT angiography model 1			6.22 (2.77, 13.99)	<.001
Nonobstructive CAD	8 (27)	269 (71)		
Obstructive CAD	22 (73)	108 (29)		
CT angiography model 2				
No plaque	1 (3)	114 (30)	1	
Nonobstructive plaque	7 (23)	155 (41)	5.03 (0.62, 40.85)	.13
Obstructive plaque	22 (73)	110 (29)	20.80 (2.80, 154.33)	.003
Exercise ECG result				
Normal	7 (23)	164 (42)	1	
Ischemic	4 (13)	80 (20)	1.19 (0.35, 4.08)	.78
Nondiagnostic	19 (63)	148 (38)	3.00 (1.26, 7.14)	.01

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses.

* HR = hazard ratio. Numbers in parentheses are 95% confidence intervals (CIs).

† Data are means ± standard deviations.

‡ Data are medians, with IQRs in parentheses.

alternative for direct assessment of CAD. Evidence of its prognostic value is emerging (5–7), although results from some studies were affected by work-up bias, selected populations, and short follow-up periods (22–24). In our consecutive population we can confirm the good predictive value of CT angiography for future adverse events.

Because of the nature of our diagnostic work-up, we could directly compare the prognostic value of the different diagnostic modalities in patients with stable chest pain and a low-to-intermediate probability of CAD. To the best of our knowledge, ours is the first study to evaluate the incremental predictive value of CT angiography over exercise ECG in a consecutive patient population.

In the risk-adjusted multivariable analysis, obstructive atherosclerosis at CT angiography and nondiagnostic exercise ECG results remained independent predictors of late cardiac adverse events, whereas coronary calcium did not remain a significant predictor. This finding is confirmed by a recent study (25) that reported no additive prognostic value of CCS next to CT angiography. It appears that the information obtained with calcium scanning largely overlaps with the information obtained with CT angiography, while the latter

Figure 2

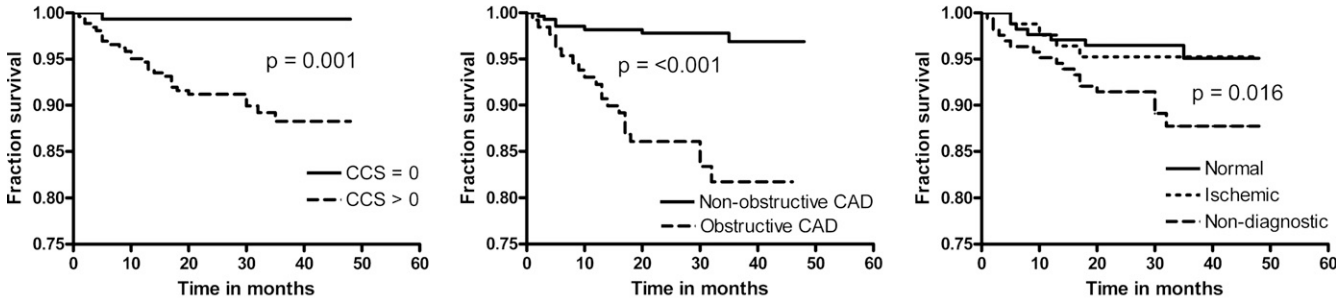

Figure 2: Graphs show Kaplan-Meier estimates of survival as compared between **(a)** patients with and those without visible coronary calcium *(CCS)*, **(b)** patients with and those without obstructive CAD at CT angiography, and **(c)** patients with normal, those with ischemic, and those with nondiagnostic exercise ECG results.

Table 3

Results of Cox Multivariable Analysis

Model	HR	*P* Value	Global χ^2	Model Comparison *P* Value	AUC	Continuous NRI (%)
SCORE	1.06 (1.01, 1.12)	.03	5.1		0.66 (0.57, 0.75)	Reference
SCORE	1.07 (1.01, 1.12)	.02	13.7	.01	0.71 (0.63, 0.79)	54
Normal ECG result	1	.98				
Ischemic ECG result	1.02 (0.29, 3.52)	.01				
Nondiagnostic ECG result	2.96 (1.24, 7.04)					
SCORE	1.02 (0.96, 1.09)	.54	37.7	<.001	0.80 (0.72, 0.88)	80
Normal ECG result	1	.57				
Ischemic ECG result	0.69 (0.20, 2.41)	.02				
Nondiagnostic ECG result	2.93 (1.23, 6.99)	<.001				
CT angiography	6.61 (2.83, 15.43)					
SCORE	1.02 (0.95, 1.08)	.67	38.2	.40	0.81 (0.73, 0.88)	47
Normal ECG result	1	.56				
Ischemic ECG result	0.69 (0.20, 2.39)	.02				
Nondiagnostic ECG result	2.80 (1.17, 6.73)	.003				
CT angiography	5.00 (1.72, 14.52)	.41				
CCS	1.09 (0.89, 1.33)					

Note.—Numbers in parentheses are 95% CIs. Here, CCS = natural logarithm of the calcium score +1, ECG = exercise ECG.

also provides such additional characteristics as total plaque burden and luminal obstruction.

The performance of the final model with clinical predictors, exercise ECG, and CCS improved significantly after the addition of CT angiography results.

In addition, we assessed the potential clinical value of the considered predictors by calculating the continuous NRI, an extension of the traditional NRI that is independent of risk categories. Our results suggest that CT angiography is most effective in improving risk prediction, since the NRI was substantial. For CCS, the NRI was 47%, although the addition of CCS did not improve model performance in terms of the χ^2 value or AUC. This finding is explained by the fact that the continuous NRI does not take into account the magnitude of the increase (or decrease) in predicted risk. In other words, the predictions were not substantially influenced when CCS was added, but among patients with a higher predicted risk, the observed event rate increased compared with the overall mean. Similarly, for patients with a lower predicted risk, the observed event rate decreased compared with the overall mean. Finally, it should be noted that the continuous NRIs reported in the current study cannot be compared directly with the traditional NRIs that have been reported in other studies because of the differences in definition and calculation described earlier.

Although our study population consisted of prospectively enrolled "all-comers" with stable angina complaints, the limitations associated with an observational single-center study were still present. Therefore our results may not necessarily reflect populations or

Figure 3

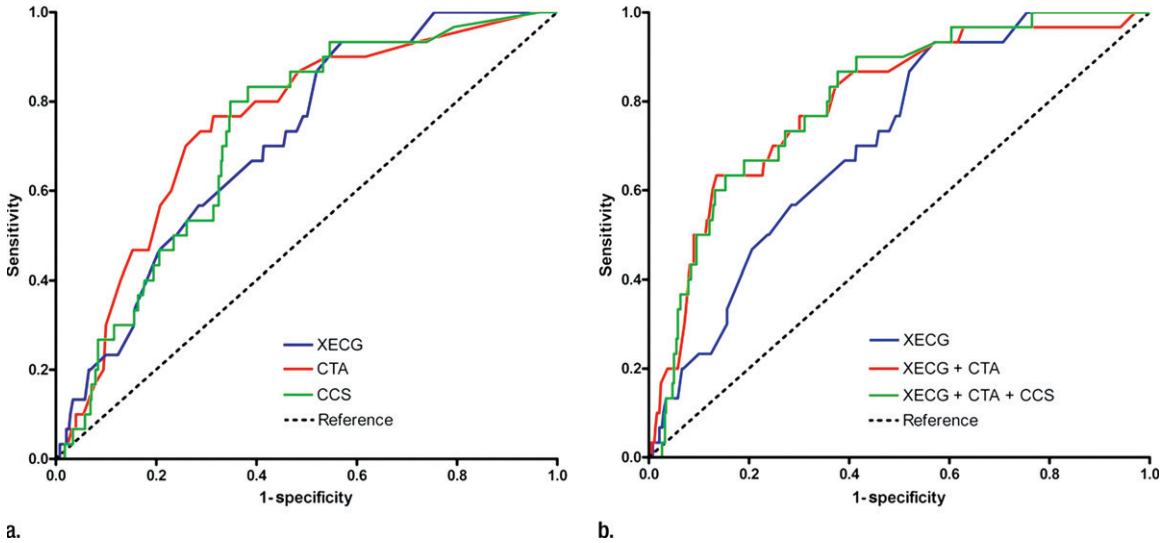

Figure 3: Graphs show receiver operating characteristics curves of multivariable models of **(a)** exercise ECG *(XECG)*, CCS, and CT angiography *(CTA)* and **(b)** incremental value of CT angiography and CCS beyond exercise ECG. The models are risk adjusted with the SCORE 10-year cardiovascular disease mortality risk metric (9).

practices elsewhere. Because of the limited number of hard events, we used a composite end point of cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalization, and coronary revascularization. The use of coronary revascularization as an end point could lead to overestimation of the prognostic value as a result of a potential work-up bias. Revascularizations performed within 6 months from the initial work-up were excluded to minimize this effect. Even though an experienced cardiologist, blinded to the initial test reports, evaluated all events, unstable angina requiring hospitalization can be a subjective end point.

Given the limited number of events, our analysis could be subject to overfitting. Current guidelines stating a minimum of 10 outcome events per predictor variable have been questioned (26). In this view, our findings regarding the additive value of coronary calcium should be considered explanatory, and conclusions should be made with caution. To limit the number of variables in the multivariable analysis, we dichotomized CT angiography results.

Incomplete follow-up may result in underreporting of adverse events. However, the follow-up rate was substantial (90%), and no deaths occurred in the group without follow-up, as confirmed by the national death registry. Patients lost to follow-up appear to have been at lower risk, with fewer abnormal test results (Table E1 [online]). Larger multicenter studies with longer follow-up, or meta-analyses of existing studies, are needed to fully comprehend the prognostic value of these modalities.

In conclusion, both functional and anatomic assessment of CAD has prognostic value. Coronary CT angiography findings are strong predictors of future adverse events, with incremental value over clinical predictors, stress testing, and coronary calcification.

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