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Value of CACS Compared With ETT and Myocardial Perfusion Imaging for Predicting Long-Term Cardiac Outcome in Asymptomatic and Symptomatic Patients at Low Risk for Coronary Disease

Clinical Implications in a Multimodality Imaging World

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ABSTRACT

OBJECTIVES This prospective, observational study in 988 asymptomatic or symptomatic low-risk patients without prior coronary artery disease was conducted to define the relative value of coronary artery calcium score (CACS), exercise treadmill testing (ETT), and stress myocardial perfusion single-photon emission computed tomography (SPECT) variables in predicting long-term risk stratification.

BACKGROUND CACS, ETT, and stress myocardial perfusion SPECT results predict patients' outcome. There are currently no data comparing their relative value in long-term risk stratification.

METHODS Patients were stratified by Framingham risk score (FRS), with a median follow-up of 6.9 years. *Cardiac events* were defined as a composite of cardiac death, nonfatal myocardial infarction, and the need for coronary revascularization. Most patients (87%) were considered appropriate candidates for functional testing as defined by current appropriate use criteria.

RESULTS The long-term cardiac event rate was 11.2% (1.6% per year). Multivariate risk predictors in all patients and in the appropriate use cohort were abnormal SPECT (hazard ratio [HR]: 1.83 and 1.99), ETT ischemia (HR: 1.70 and 1.76), decreasing exercise capacity (HR: 1.11 and 1.17), decreasing Duke treadmill score (HR: 1.07 for both), and CACS severity (HR: 1.29 for both), respectively. Throughout the 10-year follow-up, CACS improved risk prediction, with event rates ranging from 0.6% per year (CACS ≤10) to 3.7% per year (CACS >400) ($p < 0.0001$). CACS also improved risk prediction in all patients, in the appropriate use cohort and among those with low-risk ETT and SPECT results (all, $p < 0.001$). Area under the receiver-operating characteristic curve was increased when CACS variables (from 0.63 to 0.70; $p = 0.01$) but not ETT variables (from 0.63 to 0.65) were added to FRS. Moreover, net reclassification improvement was significantly increased when CACS was added to FRS + functional variables in all patients and in the appropriate use cohort (both, $p < 0.0001$).

CONCLUSIONS CACS significantly improved long-term risk stratification beyond FRS, ETT, and SPECT results across the spectrum of clinical risk and importantly even among those who are currently considered appropriate candidates for functional testing or have low-risk functional test results. Our findings support CACS as a first-line test over ETT or SPECT for accurately assessing long-term risk in such patients. (J Am Coll Cardiol Img 2015;8:134–44) © 2015 by the American College of Cardiology Foundation.

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The coronary artery calcium score (CACS) severity has been reported to predict patients' cardiac outcomes (1,2), and CACS is considered an appropriate test in asymptomatic patients at intermediate to high clinical risk for coronary artery disease (CAD) (3,4). Likewise, exercise treadmill testing (ETT), performed with or without cardiac imaging, identifies those at high or low risk for mortality on the basis of the presence of stress-induced ischemia (5), peak exercise capacity (in metabolic equivalents of task [METs]) (6,7), and Duke treadmill score (DTS) (7,8). Current guidelines (3,9) and appropriate use criteria (4) support both ETT and stress myocardial perfusion single-photon emission computed tomography (SPECT) for evaluating risk in selected asymptomatic patients with risk factors for CAD. However, there are no studies addressing which of these tests offer the most benefit in CAD detection and long-term risk stratification.

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The purpose of this study was to examine the relative value of CACS, ETT, and SPECT in predicting long-term risk stratification in a large cohort of generally asymptomatic patients who had all tests performed within a close temporal period and who were followed up for up to a decade.

METHODS

STUDY POPULATION. This substudy analyzed data from a previously published prospective, observational follow-up trial in 1,175 predominantly middle-aged (40 to 65 years) men and women who had both CACS and stress SPECT performed for clinically indicated reasons (10). All patients had risk factors for, but no history of, CAD. The substudy included 988 patients (84%) who were stressed with ETT during SPECT (10). CACS was performed as the first-line test in 84% and SPECT in 16% of patients who were either asymptomatic (71% and 13%, respectively) or who had atypical chest pain (13% and 3%, respectively). No one had coronary revascularization performed between tests (median, 47 days), but 10 did so <60 days after testing. The overall results did not differ with the inclusion or exclusion of these 10 patients, and no statistical interaction was observed between SPECT and ETT variables on patients' outcome (all, $p > 0.20$). Testing sequence also had no effect on outcome on univariate ($p = 0.66$) or multivariate ($p = 0.69$) analysis. For these reasons, the data on all 988 patients are presented, of whom 946 (96%) had adequate follow-up.

ELECTRON BEAM COMPUTED TOMOGRAPHY. CACS assessment was performed using electron beam CT (Imatron C-150, Imatron, San Francisco, California). *Coronary artery calcification* was defined as a lesion of >130 Hounsfield units, with an area equal to 3 pixels. CACS was calculated using the standard Agatston criteria, and patients were classified as having normal (≤10), mild (11 to 100), moderate (101 to 400), or severe (>400) calcification (10). None of the patients underwent CT angiography as a part of their CACS procedure.

EXERCISE TREADMILL TESTING. Patients underwent symptom-limited ETT using the standard Bruce protocol. *Ischemia* was defined as ≥1 mm of ST-segment depression occurring >80 ms after the J point. ETT was interpreted by investigators blinded to the CACS and SPECT results. *High* and *low risk* were defined as the presence and absence of ischemia, respectively. DTS was calculated and classified as low (≥5), intermediate (4 to -10), or high (≤-11) risk (8). Risk on the basis of peak exercise capacity was classified as low (>8 METs), intermediate (5 to 8 METs), or high (<5 METs) (6).

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY. SPECT was performed according to standard guidelines (10). Images were visually interpreted in all 3 standard projections, as previously reported, along with gated and raw image data to assess for study normalcy/abnormalcy and perfusion defect reversibility (10).

CLINICAL ASSESSMENT AND PATIENT FOLLOW-UP. Baseline demographic characteristics, symptom status, and medical history were prospectively recorded during interviews with experienced technical staff at the time of CACS testing. Patients were stratified, on the basis of standard FRS criteria, into categories of low (<6%), intermediate (6% to 20%), or high (>20%) 10-year risk for cardiac events (11). Because absolute cholesterol and blood pressure measurements were not available, we calculated the FRS using conservative definitions of *hyperlipidemia* (cholesterol 200 to 239 mg/dl) and *hypertension* (systolic blood pressure 140 to 159 mm Hg) as previously reported (10).

Follow-up was prospectively performed using questionnaires, telephone interviews, and review of medical records (median follow-up: 6.9 years; 25th to 75th percentile: 4.7 to 8.8 years), with events corroborated as previously reported (10). *Cardiac events* were defined as a composite of cardiac death, nonfatal myocardial infarction (MI), and the need for

ABBREVIATIONS AND ACRONYMS

AER = annualized event rate

AUC = area under the receiver-operating characteristic curve

CACS = coronary artery calcium score

DTS = Duke treadmill score

ETT = exercise treadmill test

FRS = Framingham risk score

IDI = integrated discrimination improvement

METs = metabolic equivalents of task

NRI = net reclassification improvement

SPECT = single-photon emission computed tomography

TABLE 1 Baseline Demographic Characteristics, CACS, and Exercise Test Results in All Patients With Follow-Up and on the Basis of Events

	All Patients With Follow-Up (N = 946)	Subgroups		p Value
		Without Events (n = 840)	With Event (n = 106)	
Age, yrs	57.5 ± 9.3	57.2 ± 9.3	59.6 ± 8.9	0.01
Male	712 (75.3)	623 (74.2)	89 (84.0)	0.03
Cardiac risk factors				
Diabetes	91 (9.6)	75 (8.9)	16 (15.1)	0.05
Hypertension	469 (49.6)	402 (47.9)	67 (63.2)	0.004
Hyperlipidemia	540 (57.1)	470 (56.0)	70 (66.0)	0.06
Smoking	440 (46.5)	386 (46.0)	54 (50.9)	0.35
Family history for CAD	407 (43.0)	369 (43.9)	38 (35.9)	0.12
≥2 cardiac risk factors	645 (68.2)	567 (67.5)	78 (73.6)	0.06
FRS				
Score	11.1 ± 6.5	10.8 ± 6.4	13.3 ± 6.5	0.0002
Risk				0.02
Low (<6%)	160 (16.9)	149 (17.7)	11 (10.4)	
Intermediate (6%–20%)	655 (69.2)	583 (69.4)	72 (67.9)	
High (>20%)	131 (13.9)	108 (12.9)	23 (21.7)	
Atypical chest pain	156 (16.5)	148 (17.6)	8 (7.6)	0.008
SPECT				
Abnormal	103 (10.9)	75 (8.9)	28 (26.4)	<0.0001
Normal	843 (89.1)	765 (91.1)	78 (73.6)	<0.0001
CACS				
Score				
Mean ± SD	314 ± 514	276 ± 462	622 ± 748	<0.0001
Median (IQR)	118 (14–401)	104 (7–325)	412 (118–743)	<0.0001
CACS 0	167 (17.7)	160 (19.1)	7 (6.6)	0.001
Risk				<0.0001
Low (CACS 0–10)	229 (24.2)	219 (26.1)	10 (9.4)	
Intermediate (CACS 11–100)	205 (21.7)	192 (22.9)	13 (12.3)	
Intermediate (CACS 101–400)	274 (29.0)	246 (29.3)	28 (26.4)	
High (CACS >400)	238 (25.2)	183 (21.8)	55 (51.9)	
ETT variables				
Peak heart rate	153 ± 17	154 ± 16	148 ± 18	0.0003
Peak systolic BP	178 ± 26	178 ± 26	182 ± 29	0.09
Peak diastolic BP	82 ± 15	81 ± 15	85 ± 17	0.03
Rate pressure product	27,253 ± 4,911	27,291 ± 4,809	26,948 ± 5,665	0.5
Ischemic exercise ECG	116 (12.3)	92 (11.0)	24 (22.6)	0.001
DTS				
Score	8.4 ± 3.9	8.6 ± 3.8	6.8 ± 4.4	<0.0001
Risk				0.02
Low (≥5)	795 (84.0)	715 (85.1)	80 (75.5)	
Intermediate (4 to −10)	143 (15.1)	119 (14.2)	24 (22.6)	
High (≤−11)	8 (0.9)	6 (0.7)	2 (1.9)	
Peak exercise capacity				
METs	10.4 ± 3.2	10.5 ± 3.2	9.5 ± 2.8	0.005
Risk				0.06
Low (>8 METs)	707 (74.7)	636 (75.7)	71 (67.0)	
Intermediate (5–8 METs)	210 (22.2)	177 (21.1)	33 (31.1)	
High (<5 METs)	29 (3.1)	27 (3.2)	2 (1.9)	

Values are mean ± SD for continuous variables, medians (interquartile ranges) if continuous variables were skewed, and n (%) for categorical variables. p Values on the basis of chi-square or the Fisher exact test for categorical variables and *t*-test or Mann-Whitney *U* test for continuous variables for comparisons between patients with and without follow-up, or between patients with and without events.

BP = blood pressure; CACS = coronary artery calcium score; CAD = coronary artery disease; DTS = Duke treadmill score; ECG = electrocardiographic; ETT = exercise treadmill test; FRS = Framingham risk score; METs = metabolic equivalents of task; SPECT = single-photon emission computed tomography.

coronary revascularization following the development of symptomatic CAD (10).

STATISTICAL ANALYSIS. Baseline characteristics were summarized according to clinical follow-up and cardiac event status. All data are presented as mean ± SD for continuous variables, median and interquartile range for skewed continuous variables, and number and percentage for categorical variables. The chi-square or Fisher exact test (for categorical variables) and the Student *t* test or Mann-Whitney *U* test (for continuous variables) were used to compare data from patients with and without follow-up and those with and without events and to determine associations between CACS severity and FRS categories, ETT, and SPECT variables.

Kaplan-Meier survival curves were calculated in strata defined by CACS risk categories and those of FRS, ETT, and SPECT variables. The date on which CACS was performed defined *time 0*. Two-sided log-rank tests defined significance. To explore risk factors that could be associated with total cardiac events and cardiac death and/or MI, a univariate Cox proportional hazards model was initially applied, using clinical, CACS, ETT, and SPECT variables. CACS was transformed to the natural logarithm to stabilize the variance before the analysis. Multivariate analysis was then performed by entering into the model a set of variables that were considered significant on univariate analysis ($p < 0.10$). There was no significant interaction between sex and other risk factors, or between SPECT and CACS/ETT variables. The proportionality assumption of Cox models was verified by including time-dependent interaction of each covariate with the event time in the model. There was no violation of this assumption with any covariate. A separate analysis was performed on data from 824 patients (87% of the total cohort) currently considered acceptable candidates for functional testing on the basis of recent appropriate use criteria (i.e., intermediate to high FRS risk and/or chest pain symptoms) (4). These patients were defined as the appropriate use cohort.

Area under the receiver-operating characteristic curve (AUC) and global chi-square analyses determined the incremental value of CACS over FRS, and functional variables for predicting events. AUCs were calculated from logistic regression models and compared. The increased discriminative value of CACS was examined with absolute integrated discrimination improvement (IDI), relative IDI, and net reclassification improvement (NRI) methods (12). The p value for relative IDI was obtained using a permutation test. The NRI requires that there exist *a priori* meaningful risk categories (we used <6%, 6% to 20%, and >20% for the risk for cardiac events).

All analyses were performed with STATA version 12 (StataCorp LP, College Station, Texas). Statistical significance was defined as 2-tailed $p < 0.05$ for all tests. The NRIs calculated with STATA may have been lower than if they had been calculated using SAS.

RESULTS

BASELINE CHARACTERISTICS. The mean age of the overall study population was 57.5 ± 9.3 years, and the median was 57 years (interquartile range: 51 to 64 years) (Table 1). Most of the patients (75.3%) were male, and 95% had 1 or more risk factors for CAD (68.2% had 2 or more risk factors). Nearly 10% of patients were diabetic, 43.0% had a family history of CAD, and 16.5% had atypical chest pain symptoms. Most patients had an intermediate or high FRS (83.1%).

Most patients had no ETT ischemia (87.7%), achieved >8 METs (74.7%), had a low DTS (84.0%), and had a normal SPECT (89.1%). The concordance between ETT and SPECT was high (82%), with most patients having normal (785/988 [80%]) or abnormal (24/988 [2%]) results on both tests. The median CACS was 118, with approximately one-fourth of patients in each CACS category. A CACS of 0 was present in 167 patients (17.7%). The only significant differences between patients with and without follow-up were mean age (57.5 ± 9.3 years vs. 50.8 ± 10.3 years; $p < 0.0001$) and mean FRS (11.1 ± 6.5 vs. 7.9 ± 4.1; $p = 0.002$), respectively.

LONG-TERM CARDIAC EVENTS. There were 106 patients with at least 1 cardiac event (11.2%), for an annualized event rate (AER) of 1.6% (cardiac death, n = 17; nonfatal MI, n = 16; and need for coronary revascularization, n = 73). The subgroup of patients with at least 1 event had a higher mean FRS and CACS, more frequently had ETT ischemia or an abnormal SPECT, and had a lower mean DTS and exercise capacity (in METs) than did the subgroup without events (Table 1). Most patients with events had a CACS >100 (78.3%) or >400 (51.9%). All 10 patients (9.4%) with an event after a low-risk CACS also had a normal SPECT. Conversely, 22.6% and 26.4% of patients with events had ETT ischemia and/or an abnormal SPECT, respectively, which minimally increased to 29% and 34% in those with a CACS >400.

TABLE 2 Relationship Between CACS Risk Category and Framingham Risk Score, Exercise Treadmill Test, and SPECT Risk Categories and Subsequent Reclassification on the Basis of CACS

	CACS Risk Category				
	Low (0-10)	Intermediate (11-100)	Intermediate (101-400)	High (>400)	Reclassified by CACS
FRS risk					
Low (n = 160)	70 (43.8)	48 (30.0)	26 (16.3)	16 (10.0)	90 (56)
Intermediate (n = 655)	153 (23.4)	139 (21.2)	199 (30.4)	164 (25.0)	317 (48)
High (n = 131)	6 (4.6)	18 (13.7)	49 (37.4)	58 (44.3)	73 (56)
p Value		<0.0001			Total 480/946 (50.7)
ETT					
No Ischemia (n = 830)	202 (24.3)	184 (22.2)	246 (29.6)	198 (23.9)	628 (76)
Ischemia (n = 116)	27 (23.3)	21 (18.1)	28 (24.1)	40 (34.5)	27 (23)
p Value		0.09			Total 655/946 (69.2)
SPECT					
Normal (n = 843)	225 (26.7)	198 (23.5)	243 (28.8)	177 (21.0)	618 (73.3)
Abnormal (n = 103)	4 (3.9)	7 (6.8)	31 (30.1)	61 (59.2)	4 (4)
p Value		<0.0001			Total 622/946 (65.8)
Peak exercise capacity risk					
Low (>8 METs; n = 707)	165 (23.3)	166 (23.5)	204 (28.9)	172 (24.3)	542 (77)
Intermediate (5-8 METs; n = 210)	56 (26.7)	34 (16.2)	60 (28.6)	60 (28.6)	116 (55)
High (<5 METs; n = 29)	8 (27.6)	5 (17.2)	10 (34.5)	6 (20.7)	23 (79)
p Value		0.34			Total 681/946 (72.0)
DTS risk					
Low (n = 795)	190 (23.9)	187 (23.5)	231 (29.1)	187 (23.5)	605 (76)
Intermediate (n = 143)	38 (26.6)	17 (11.9)	43 (30.1)	45 (31.5)	83 (58)
High (n = 8)	1 (12.5)	1 (12.5)	0	6 (75.0)	2 (25)
p Value		0.001			Total 690/946 (72.9)

Values are n (%).
Abbreviations as in Table 1.

TABLE 3 Reclassification of Long-Term Risk in FRS Groups on the Basis of ETT, SPECT, and CACS Results

Model	All Patients			Appropriate Use Cohort			Low FRS			Intermediate FRS			High FRS		
	NRI (%)	IDI (%)	rIDI (%)	NRI (%)	IDI (%)	rIDI (%)	NRI (%)	IDI (%)	rIDI (%)	NRI (%)	IDI (%)	rIDI (%)	NRI (%)	IDI (%)	rIDI (%)
FRS + CACS	30.2	3.5	285	28.5	3.7	303	42.6	0.5	303,100	28.6	2.9	162	34.9	3.7	2,190
p Value vs. FRS	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.01	0.02	0.004	<0.0001	<0.0001	<0.0001	0.06	0.03	0.04
FRS + ETT	9.6	1.4	110	11.1	1.6	128	0	0.1	591	18.9	1.7	92	8.1	0.88	522
p Value vs. FRS	0.007	0.006	<0.0001	0.005	0.006	<0.0001	1.0	0.75	0.35	0.01	0.01	0.004	0.38	0.39	0.19
FRS + ETT + CACS	30.6	3.4	130	31.0	3.6	127	42.6	4.9	4,970	16.3	2.8	79	26.2	3.6	339
p Value vs. FRS + ETT	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.01	0.02	<0.0001	0.02	<0.0001	<0.0001	0.09	0.03	<0.0001
FRS + SPECT	14.7	2.4	193	17.3	2.9	233	8.4	0.88	53,420	14.5	3.0	163	11.9	0.86	513
p Value vs. FRS	0.005	0.0008	<0.0001	0.003	0.0006	<0.0001	0.36	0.49	0.12	0.04	0.003	<0.0001	0.33	0.35	0.31
FRS + SPECT + CACS	23.3	2.6	71	22.5	2.7	67	42.6	4.2	474	19.5	2.1	43	24.2	3.1	300
p Value vs. FRS + SPECT	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.01	0.04	<0.0001	0.0009	<0.0001	<0.0001	0.10	0.04	<0.0001
FRS + METS	7.8	0.57	46	8.5	0.71	57	0	0.002	145	1.9	0.13	7	28.1	4.9	2,940
p Value vs. FRS	0.005	0.007	0.03	0.004	0.006	0.03	1.0	0.94	0.95	0.77	0.39	0.44	0.09	0.01	0.008
FRS + METS + CACS	29.8	3.8	208	33.2	4.0	208	42.3	5.1	125,700	28.4	3.2	161	35.0	5.3	103
p Value vs. FRS + METS	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.01	0.02	<0.0001	<0.0001	<0.0001	<0.0001	0.003	0.04	<0.0001
FRS + DTS	15.7	1.8	149	16.1	2.1	172	4.1	0.04	2,690	12.4	1.4	76	27.5	4.6	2,710
p Value vs. FRS	0.0002	0.001	<0.0001	0.0002	0.002	<0.0001	0.01	0.81	0.81	0.05	0.05	0.002	0.07	0.01	0.04
FRS + DTS + CACS	22.7	3.6	116	26.5	3.8	115	38.2	5.1	11,080	20.8	3.1	96	13.6	4.6	98
p Value vs. FRS + DTS	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.02	0.02	<0.0001	0.002	<0.0001	<0.0001	0.28	0.02	<0.0001

Risk categories on the basis of 6% and 20% at a median follow-up of 6.9 years.
IDI = integrated discrimination improvement; NRI = net reclassification improvement; rIDI = relative IDI; other abbreviations as in Table 1.

A high risk on DTS or poor exercise capacity was observed in 1.9% of patients with events.

RISK RECLASSIFICATION WITH CACS: FRS, ETT, AND SPECT VARIABLES. Mean CACS was significantly increased within increasing FRS risk categories (low: 109 ± 192 [median: 21]; intermediate: 318 ± 523 [median: 122]; and high: 553 ± 621 [median: 336]; $p < 0.0001$). The addition of CACS to FRS reclassified 50.7% of patients with similar results when CACS was added to any of the functional ETT or SPECT variables (Table 2). CACS significantly increased overall NRI (30.2%), IDI (3.5%), and relative IDI (285%) when added to the FRS (all, $p < 0.0001$), and this was observed across all FRS categories as well as in the appropriate use cohort (Table 3). Similarly, NRI, IDI, and relative IDI were significantly increased in all patients when CACS was added to models containing FRS and any SPECT or ETT variable (all, $p < 0.0001$). Importantly, this finding occurred within each FRS category in addition to the appropriate use cohort (Table 3). Whereas no functional variables reclassified risk in the low-risk FRS group, CACS reclassified risk in this group beyond the FRS and in all models containing FRS and any of the functional variables.

UNIVARIATE AND MULTIVARIATE PREDICTORS OF LONG-TERM EVENTS. Univariate risk predictors of all events included FRS, an abnormal SPECT and ETT ischemia, increasing CACS, and decreasing METs and DTS. On multivariate analysis, all significant findings were retained, except for the FRS (Table 4). Similar findings were observed in the appropriate use cohort (Table 4). When the models estimated cardiac death and/or MI, only decreasing DTS and increasing CACS severity added to the multivariate model (Table 5). In the appropriate use cohort, decreasing METs, decreasing DTS, and increasing CACS severity were the only multivariate predictors of the risk for cardiac death and/or MI (Table 5).

LONG-TERM CARDIAC EVENTS ON THE BASIS OF FRS, CACS, AND ETT RESULTS. Cardiac event rates were significantly increased with increasing FRS category (Figure 1A), presence of ETT ischemia (Figure 1B), increasing CACS severity (Figure 1C), and decreasing DTS. AERs were significantly increased with increasing categories of risk on FRS (low: 0.97% [95% CI: 0.54% to 1.75%]; high: 2.60% [95% CI: 1.73% to 3.92%]; $p = 0.02$) (Figure 1A) and DTS (low: 1.49% [95% CI: 1.2% to 1.86%]; intermediate: 2.7% [95% CI: 1.81% to 4.02%]; and high: 4.21% [95% CI: 1.05% to 16.85%]; $p = 0.008$) and between the subgroup without versus that with ETT ischemia (without: 1.48% [95% CI: 1.19% to 1.84%] vs. with: 3.11% [95% CI: 2.08% to 4.64%]; $p = 0.001$) (Figure 1B). CACS best

defined risk, with a very low AER of 0.62% in patients with a CACS ≤10 (0.59% if CACS = 0), which was increased to 3.73% in those with a CACS >400 (Figure 1C).

LONG-TERM CARDIAC EVENTS IN LOW ETT/ SPECT RISK GROUPS ON THE BASIS OF CACS SEVERITY. Event rates were compared across CACS severities within low-risk ETT and SPECT subgroups (Table 6, Figure 2). A CACS ≤10 defined a hazard ratio (HR) of 1. In patients without ETT ischemia, AER was increased from 0.56% with CACS ≤10 to 3.15% with CACS >400 ($p < 0.0001$) (Figure 2A), with an HR of 5.25 with CACS >400 (Table 6). Time point analysis showed separation of event curves at year 4 after initial testing. The AER in the subgroup with a low-risk DTS was increased from 0.58% with CACS ≤10 to 3.00% with CACS >400 ($p < 0.0001$), with separation of event curves at year 5 (Figure 2B) and an HR of 5.13 with CACS >400 (Table 6). The AER (95% CI) in the subgroup achieving >8 METs was increased from 0.52% (0.23% to 1.16%) with CACS ≤10, to 1.06% (0.60% to 1.86%) with CACS 11 to 100, to 1.15% (0.70% to 1.87%) with CACS 101 to 400, to 3.41% (2.47% to 4.70%) with CACS >400 ($p < 0.0001$), with separation of event curves at year 3 ($p = 0.005$) and an HR of 6.51 with CACS >400 (Table 6). In patients with a normal SPECT, HR was increased to 4.92 with CACS >400 ($p < 0.0001$) (Table 6). The HR for any event also increased in the appropriate use cohort in the subgroup that had a CACS >400 (normal ETT: 5.17; low-risk DTS: 4.85; >8 METs: 6.51; and normal SPECT: 4.12) (Table 6).

INCREMENTAL PROGNOSTIC VALUE OF CACS OVER FRS AND ETT VARIABLES. Global chi-square increased significantly versus the FRS alone with the addition of METs (14.68) and ETT ischemia (16.16) information (Figure 3A). The addition of CACS to the clinical model increased the global chi-square from 11.72 to 45.33 ($p < 0.0001$). When CACS was added to the FRS and any ETT variable, global chi-square was markedly increased, whereas minor, albeit significant, increases were observed when METs and ETT ischemia information was added to the FRS + CACS model.

AUC demonstrated the largest improvement when CACS was added to the FRS variable (from 0.63 to 0.70; $p = 0.01$) versus the ETT variable (from 0.63 to 0.65; $p = 0.3$) (Figure 3B) or SPECT (from 0.63 to 0.67; $p = 0.02$) (Figure 3C). AUC was increased with the addition of CACS to the FRS + ETT variables (from 0.65 to 0.71; $p = 0.01$), with a numerical but statistically nonsignificant improvement with the addition of CACS to FRS + SPECT (from 0.67 to 0.71; $p = 0.08$). The addition of ETT or SPECT did not improve the model of CACS + FRS (both, from 0.70 to 0.71; $p = 0.15$).

TABLE 4 Univariate and Multivariate Predictors of All Cardiac Events

	Univariate			Multivariate*		
	HR	95% CI	p Value	HR	95% CI	p Value
All patients (n = 946)						
Increasing FRS	1.04	1.02–1.07	<0.0001	1.01	0.98–1.04	0.66
Atypical chest pain	0.45	0.22–0.93	0.03	0.60	0.29–1.25	0.17
Abnormal SPECT	3.25	2.11–5.01	<0.0001	1.83	1.15–2.90	0.01
ETT ischemia	2.06	1.31–3.25	0.002	1.70	1.07–2.70	0.02
Decreasing METs	1.10	1.04–1.17	0.002	1.11	1.04–1.18	0.002
Decreasing DTS	1.10	1.06–1.14	<0.0001	1.07	1.03–1.11	<0.0001
Log(CACS + 1)	1.39	1.25–1.56	<0.0001	1.29	1.15–1.49	<0.0001
Appropriate use cohort (n = 824)						
Increasing FRS	1.04	1.02–1.07	0.001	1.01	0.98–1.04	0.56
Atypical chest pain	0.42	0.20–0.86	0.02	0.62	0.30–1.30	0.21
Abnormal SPECT	3.32	2.14–5.16	<0.0001	1.99	1.25–3.19	0.004
ETT ischemia	2.08	1.30–3.32	0.002	1.76	1.09–2.83	0.02
Decreasing METs	1.10	1.03–1.18	0.004	1.17	1.04–1.20	0.002
Decreasing DTS	1.10	1.05–1.14	<0.0001	1.07	1.03–1.11	<0.0001
Log(CACS + 1)	1.40	1.24–1.58	<0.0001	1.29	1.13–1.46	<0.0001

*Multivariate model included FRS, atypical chest pain, abnormal SPECT, log(CACS + 1), and DTS or ETT Ischemia and METs.

HR = hazard ratio; other abbreviations as in Table 1.

DISCUSSION

We followed up a large-scale, generally asymptomatic cohort of men and women for up to a decade in order to assess the utility of CACS findings in

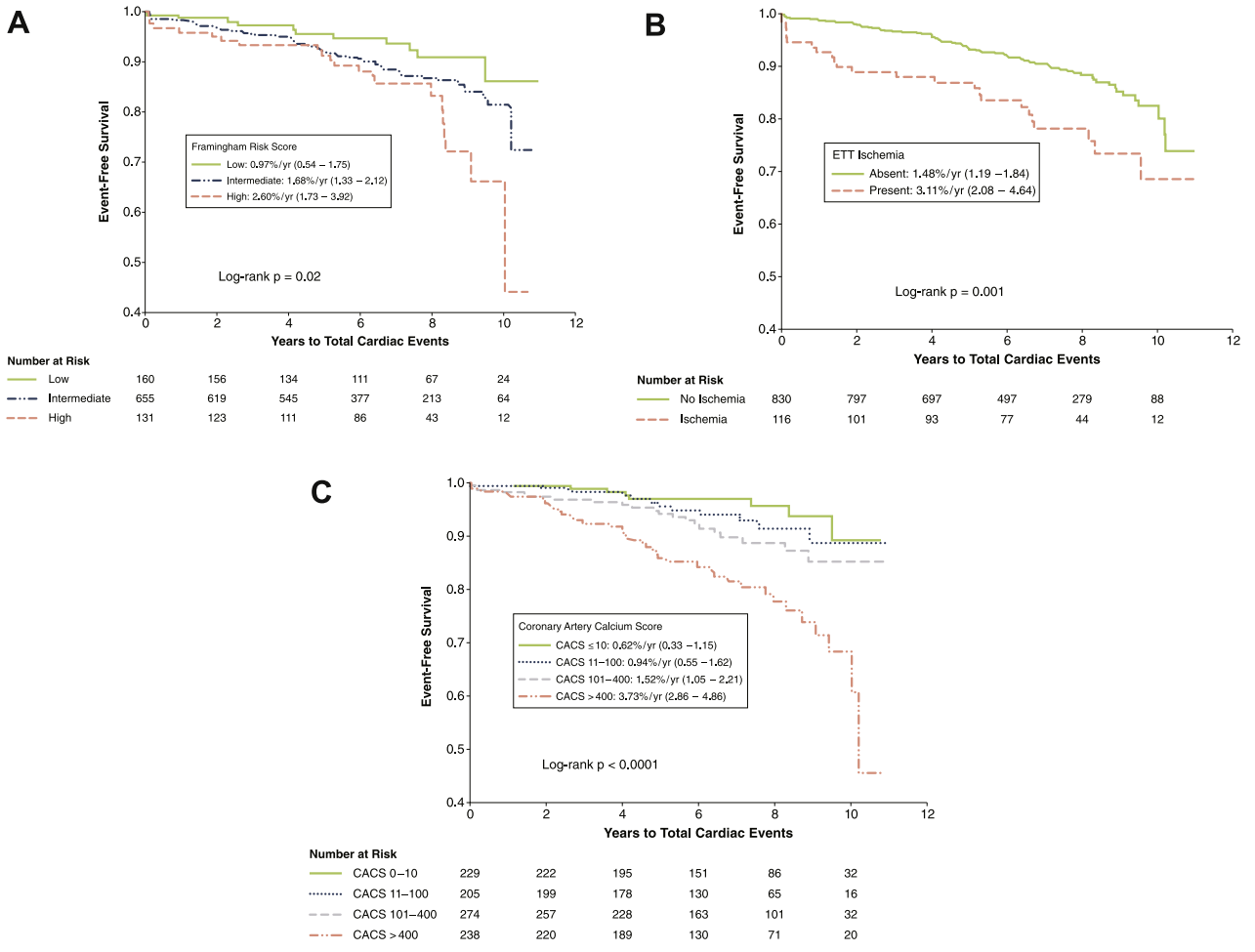
TABLE 5 Univariate and Multivariate Predictors of Cardiac Death and MI

	Univariate			Multivariate*		
	HR	95% CI	p Value	HR	95% CI	p Value
All patients (n = 946)						
Increasing FRS	1.07	1.03–1.11	0.001	1.03	0.99–1.08	0.17
Atypical chest pain	0.36	0.09–1.51	0.16	–	–	–
Abnormal SPECT	2.00	0.83–4.86	0.12	–	–	–
ETT ischemia	1.55	0.64–3.75	0.33	–	–	–
Decreasing METs	1.13	1.01–1.26	0.04	1.11	0.98–1.25	0.10
Decreasing DTS	1.10	1.03–1.18	0.005	1.08	1.01–1.15	0.03
Log(CACS + 1)	1.51	1.22–1.88	<0.0001	1.41	1.13–1.76	0.002
Appropriate use cohort (n = 824)						
Increasing FRS	1.06	1.02–1.11	0.005	1.03	0.98–1.08	0.19
Atypical chest pain	0.31	0.07–1.31	0.11	–	–	–
Abnormal SPECT	1.90	0.78–4.65	0.16	–	–	–
ETT ischemia	1.60	0.65–3.91	0.31	–	–	–
Decreasing METs	1.14	1.00–1.28	0.04	1.15	1.01–1.30	0.04
Decreasing DTS	1.10	1.03–1.18	0.006	1.09	1.01–1.16	0.02
Log(CACS + 1)	1.50	1.19–1.90	0.001	1.41	1.12–1.79	0.004

*Multivariate model included FRS, log(CACS + 1), DTS, and METs.

MI = myocardial infarction; other abbreviations as in Table 1.

FIGURE 1 Long-Term Event Rates



Event rates on the basis of Framingham risk score **(A)**, exercise treadmill test (ETT) ischemia **(B)**, and coronary artery calcium score (CACS) **(C)**. Events were cardiac death, nonfatal myocardial infarction, and the need for coronary revascularization.

relation to clinical, ETT, and SPECT results for predicting long-term outcome. Other studies have compared the prognostic values of either ETT (5-8), CACS (1,2,10,11), or SPECT (10,13) alone or in relation to FRS. However, our study is the first to uniquely examine the interrelationship of multiple testing modalities in predicting long-term outcome (mean follow-up: 6.9 years) in patients for whom current appropriate use criteria generally support functional testing—and also in low-risk, asymptomatic patients in whom functional testing is not recommended (4). This finding was achieved through a rigorous statistical analysis using NRI, IDI, relative IDI, global chi-square, and AUC methods. Although the overall event rate in the study cohort was relatively low (1.6% per year), as might be expected in generally asymptomatic patients, the population was heterogeneous as to their risk, which afforded identifying significant differences in risk prediction among testing strategies. Importantly, the AERs observed in our population closely tracked the expected event rates on the basis of a conventional FRS model of low (0.97%), intermediate (1.68%), and high (2.60%) risk.

Our results demonstrate that CACS has incremental long-term prognostic value over and above the FRS and across all FRS categories. This finding was also observed in patients at low clinical risk who are currently not considered appropriate candidates for CACS testing. We also report relative superiority of CACS over all ETT and SPECT variables for identifying high- and low-risk subgroups and even among

TABLE 6 Relative Long-Term Risk of Total Cardiac Events on the Basis of CACS Severity

	Normal Stress ECG (n = 830)			Low-Risk DTS (n = 795)			METs >8 (n = 707)			Normal SPECT (n = 843)		
Cohort/CACS Severity	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
All patients												
Low (CACS 0–10) (ref)	1.00			1.00			1.00			1.00		
Intermediate (CACS 11–100)	1.90	0.77–4.69	0.16	1.75	0.71–4.31	0.22	2.06	0.77–5.49	0.15	1.63	0.71–3.76	0.25
Intermediate (CACS 101–400)	2.44	1.07–5.56	0.03	2.70	1.20–6.09	0.02	2.23	0.86–5.77	0.10	1.71	0.78–3.74	0.18
High (CACS >400)	5.25	2.38–11.55	<0.0001	5.13	2.31–11.41	<0.001	6.51	2.66–15.94	<0.0001	4.92	2.35–10.31	<0.0001
Appropriate use cohort												
Low (CACS 0–10) (ref)	1.00			1.00			1.00			1.00		
Intermediate (CACS 11–100)	1.60	0.55–4.65	0.38	1.46	0.50–4.22	0.49	1.93	0.58–6.42	0.28	1.32	0.51–3.44	0.57
Intermediate (CACS 101–400)	2.67	1.07–6.64	0.04	2.92	1.18–7.20	0.02	2.67	0.88–8.07	0.08	1.71	0.74–3.96	0.21
High (CACS >400)	5.17	2.13–12.55	<0.0001	4.85	1.98–11.85	0.001	6.51	2.25–18.83	0.001	4.12	1.84–9.20	0.001

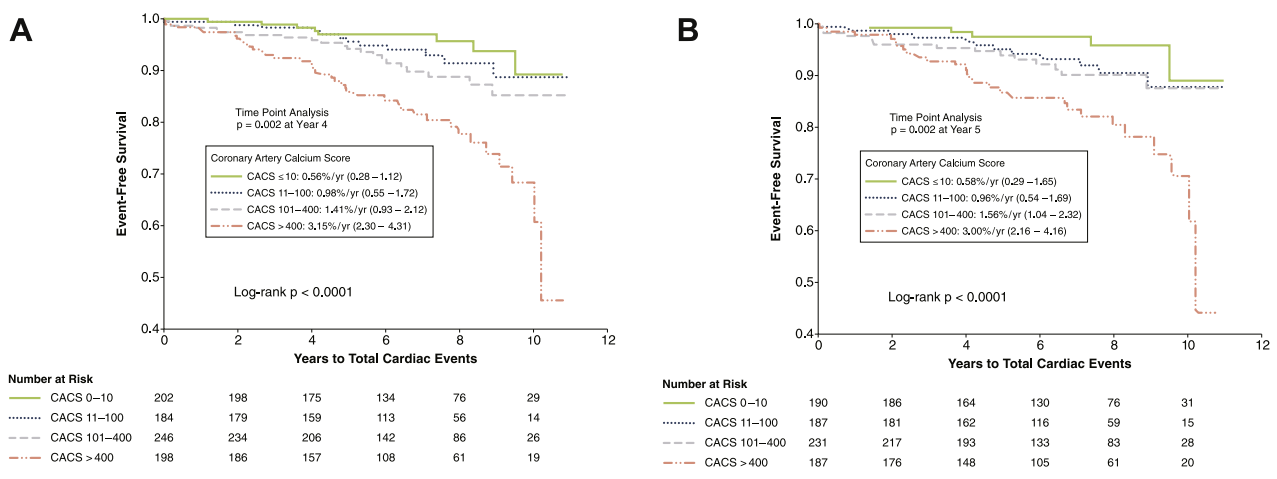
Adjusted for FRS and METs in normal stress ECG model. Adjusted for FRS in low-risk DTS model. Adjusted for FRS and ETT ischemia in METs >8 model.
Abbreviations as in Tables 1 and 4.

patients in whom functional testing is currently considered appropriate. This finding was also true for the >80% of total patients who had low-risk ETT and SPECT findings. Our results reaffirm that functional testing is inappropriate in clinically low-risk patients but also demonstrate that CACS enhances risk prediction in those in whom functional testing is currently considered an appropriate initial strategy (3,4,9). The added value of CACS beyond clinical, ETT, and SPECT information was consistent across 5 different statistical methods.

In a multimodality world where there are many options for evaluating asymptomatic patients at risk for CAD, our results support the selection of CACS, over ETT and SPECT, as the practical initial test for accurately predicting long-term cardiovascular risk in both men and women when used in conjunction with a standard clinical assessment. The cost effectiveness of this approach warrants future study.

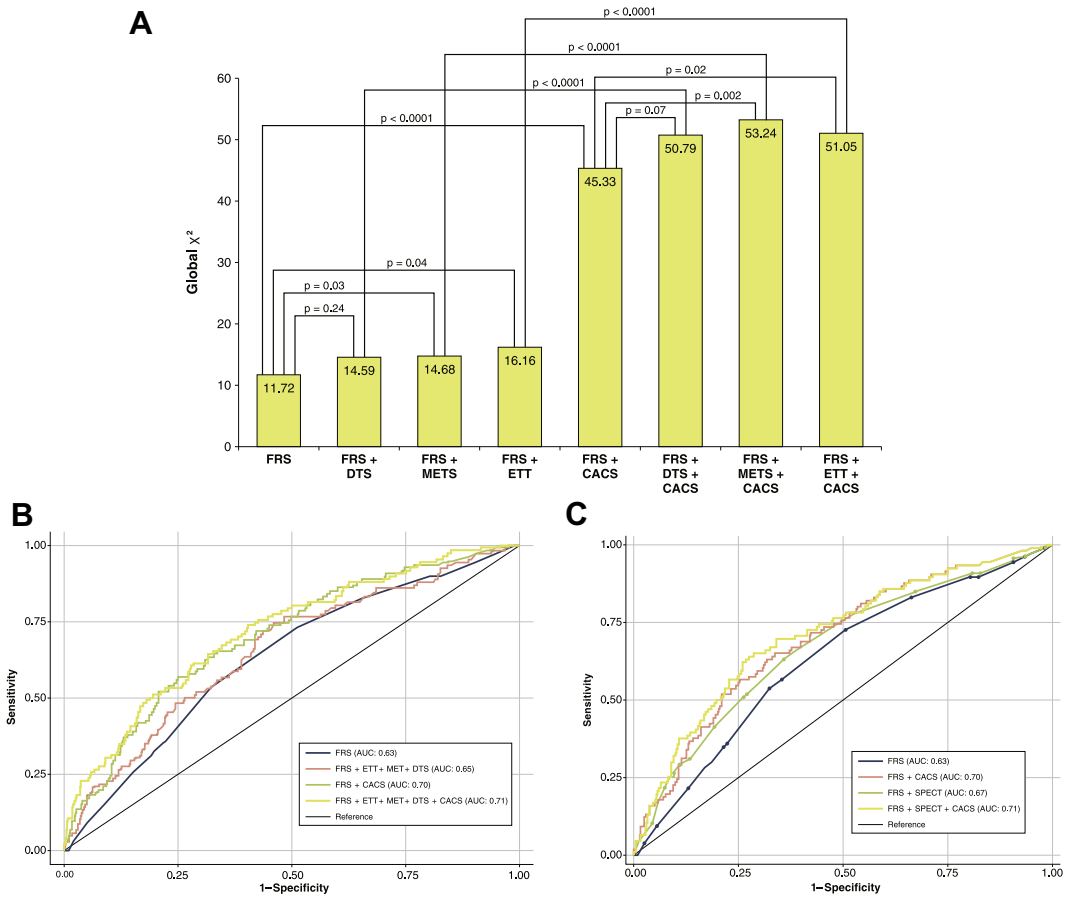
CACS FOR PREDICTING RISK. Many studies have demonstrated the value of CACS in predicting outcome (1,2). Recent evidence suggests that the addition of CACS to clinical information refines risk stratification in a substantial percentage of patients (11,14). We observed a significant increase in both global chi-square (from 11.7 to 45.3) and in AUC (from 0.63 to 0.70) when CACS was added to the FRS.

FIGURE 2 Long-Term Event Rates on the Basis of CACS Results in Low-Risk ETT Groups



Event rates on the basis of CACS results in patients without ETT ischemia **(A)** and low (≥5) Duke treadmill score (DTS) **(B)**. Events as in Figure 1. Abbreviations as in Figure 1.

FIGURE 3 Incremental Prognostic Value of CACS, ETT, and SPECT Variables



Incremental prognostic value of CACS and ETT variables in relation to Framingham risk score (FRS) by global chi-square **(A)**, and area under the receiver-operating characteristic curve (AUC) when incorporating FRS and CACS with either ETT variables **(B)** or stress myocardial perfusion single-photon emission computed tomography (SPECT) **(C)**. Events as in Figure 1. Abbreviations as in Figures 1 and 2.

A comparable increase in AUC of 0.07 (from 0.68 [FRS] to 0.75 [FRS + CACS]) was also observed in the trial by the Heinz Nixdorf Recall Study Investigative Group (11). In our study, CACS reclassified risk even among those considered at low annual risk despite a small sample size of 160 patients. The AER in the low FRS group was 0.97%. However, by adding CACS, the NRI in this group was more than 40%, with a 15-fold difference in event rates (0.37% with CACS ≤10 vs. 5.63% with CACS >400). A low FRS was seen in 17% of our patients—consistent with the 22% prevalence in the Heinz Nixdorf trial (11). In a recent study of 44,000 asymptomatic patients followed up for 5 years, CACS predicted all-cause mortality even among those with no significant CAD risk factors (15). Consistent with others, we also demonstrate the value of CACS in reclassifying risk in intermediate (NRI: 29%) and high (NRI: 35%) FRS groups (11,14).

ETT FOR PREDICTING RISK. Current guidelines and appropriate use criteria generally support performing ETT in intermediate- and high-risk asymptomatic patients and in those with symptoms suggestive of CAD (3,4,9). Most of our patients (87%) would have been considered appropriate candidates for functional testing on the basis of the current guidelines. Studies have demonstrated exercise capacity as a strong predictor of survival in asymptomatic men and women (6,7) and DTS in primarily symptomatic patients with known CAD (8). A recent study in 5,638 asymptomatic women demonstrated a significant reduction in total and cardiac mortality using the DTS, but exercise capacity primarily defined risk rather than symptoms or severity of ETT ischemia (7). This finding may not be surprising because women have a wide variety of cardiac symptoms and frequent false-positive ETTs (9).

We compared CACS to conventional ETT variables of ischemia, DTS, and peak METs. The AER on the basis of CACS alone varied 6-fold, from a low of 0.62% (CACS ≤10) to a high of 3.73% (CACS >400) ($p < 0.0001$). Conversely, the AERs within the low-risk DTS (1.49%), METs (1.50%), and ETT ischemia (1.48%) subgroups were similar to that of the entire population (1.62%), indicating little benefit of a low-risk ETT result. HRs were increased by approximately 5-fold when these low-risk patients were further stratified by CACS. This finding was also true in the appropriate use cohort subgroup with low-risk ETT findings, thereby bringing into question the utility of current appropriate use guidelines that support ETT testing in such patients (**Table 6**). ETT variables also added little incremental prognostic information to FRS on the basis of global chi-square or AUC analysis. Our results differ from those from a recent study in 710 men with CACS >100, in which patients who achieved >10 METs had a similar low event rate irrespective of CACS—but with only a 3.5-year follow-up (16). In our study, the incremental benefit of CACS over ETT occurred only at 4 or more years after initial testing, emphasizing the importance of long-term follow-up. Thus, the "warranty period" of a low-risk ETT is relatively short, especially when viewed from the anticipated 25-year additional life expectancy of the typical middle-aged, asymptomatic patient.

SPECT FOR PREDICTING RISK. Stress SPECT identifies low- and high-risk asymptomatic patients, but an abnormal result is observed in a small minority of patients (17,18). We previously published that a normal SPECT has a short "warranty period" and limited long-term prognostic value compared with CACS (10). In the present study, SPECT was a predictor of total cardiac events (**Table 4**) but did not predict cardiac death and/or MI in all patients or specifically in the appropriate use cohort (**Table 5**). This finding is best illustrated in the ~90% of patients who had a normal SPECT, in whom event rates increased by approximately 4- to 5-fold as CACS increased from low to high risk (**Table 6**). This finding was true in all patients as well as in the appropriate use cohort, in whom SPECT is currently recommended (4). Ultimately, 74% of patients with events had normal SPECT results and would not have warranted further testing under the current guidelines. SPECT imaging appears to be the most appropriate study in the small minority of patients with severe CACS, who are most likely to have stress-induced ischemia (3,4,10,13).

CLINICAL IMPLICATIONS. Noncontrast CT is a rapid, simple test for calculating CACS; has no contraindications; requires no patient preparation; is performed on conventional CT systems; incurs little radiation exposure; is relatively inexpensive compared with ETT; and is applicable to the population of patients currently referred for ETT testing who are generally healthier and are more likely to have atypical symptoms versus those undergoing pharmacological stress testing. CACS severity is directly related to the extent of coronary atherosclerosis, whereas ETT and SPECT can assess only advanced atherosclerotic plaque resulting in flow-limiting coronary stenosis. The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) investigators (19) recently reported a 63% risk reduction with intensive treatment of hyperlipidemia in asymptomatic patients with high C-reactive protein levels. The MESA (Multi-Ethnic Study of Atherosclerosis) investigators matched their patients to those in JUPITER and demonstrated similar results using CACS (20). The findings from these studies and 1 other (21) reinforce the potential therapeutic benefit of identifying early atherosclerotic disease using CACS. On the basis of our data, there appears to be a 3- to 4-year window of opportunity to treat patients aggressively before a significant increase in the risk for cardiac events.

STUDY LIMITATIONS. First, this was not an epidemiological study, so it comes with unavoidable selection bias. After an abnormal CACS, ETT SPECT was recommended, which probably explains why a large proportion of our cohort had a CACS >100. However, many of our patients with a CACS ≤10 also had SPECT because at the time of this study it was not known what CACS cutoff would result in an abnormal SPECT. This registry was conducted before guidelines limiting functional testing to patients with CACS >400, allowing us to study those with broad CACS values, including 17% with a CACS of 0. Second, CACS results were available to patients and referring physicians, who could have initiated life-style changes and/or pharmacological interventions that might have reduced the prevalence of cardiac events. However, this potential occurrence would be expected to have biased our study against observing a relationship between CACS and events. Third, although this was a single-center study, our cohort was similar to those of multicenter trials (1,2,11,14), and our follow-up time was considerably longer.

CONCLUSIONS

CACS significantly improved long-term risk stratification beyond FRS, ETT, and SPECT results across the entire spectrum of clinical risk and, importantly, even

among patients who are currently considered appropriate candidates for functional testing or who have low-risk functional test results. CACS should be selected as the initial test for assessing cardiac risk in middle-aged men and women irrespective of their clinical risk profile.

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