Prognostic Value of Coronary Artery Calcium Scoring in Addition to Single-Photon Emission Computed Tomographic Myocardial Perfusion Imaging in Symptomatic Patients

Elsemiek M. Engbers, MD; Jorik R. Timmer, MD, PhD; Jan Paul Ottervanger, MD, PhD; Mohamed Mouden, MD, PhD; Siert Knollema, MD, PhD; Pieter L. Jager, MD, PhD

Background—The prognostic value of coronary artery calcium (CAC) scoring on top of myocardial perfusion imaging with single-photon emission computed tomography (SPECT) in patients suspected for coronary artery disease is not well established.

Methods and Results—Four thousand eight hundred ninety-seven symptomatic patients without a history of coronary artery disease referred for SPECT and CAC scoring were included. Major adverse cardiac events (MACEs) were defined as late revascularization (>90 days after scanning), nonfatal myocardial infarction, and all-cause mortality. The frequency of abnormal SPECT increased with higher CAC scores, from 12% in patients with CAC scores of 0 to 19%, 32%, 37%, and 50% among those with CAC scores 1 to 99, 100 to 399, 400 to 999, and ≥1000, respectively (P<0.001). During a median follow-up of 940 days (25th to 75th percentile, 581–1377), a total of 278 MACEs were observed. Overall incidence of MACE was 2.3% per year. A stepwise increase of MACE was present with increasing CAC scores, both in patients with normal SPECT (annual event rate CAC score 0: 0.6%; CAC score ≥1000: 5.5%) and abnormal SPECT (annual event rate CAC score 0: 0.4%; CAC score ≥1000: 7.6%). After multivariate analysis, both SPECT and CAC score were independent predictors of MACE (CAC score ≥1000: hazard ratio, 7.7; P<0.001 and large perfusion defect on SPECT: hazard ratio, 3.7; P<0.001).

Conclusions—CAC score and SPECT are independent predictors of MACE in patients suspected for coronary artery disease. Our findings strongly support performing a CAC score in addition to SPECT in symptomatic patients to better define the risk of events during follow-up. **(*Circ Cardiovasc Imaging*. 2016;9:e003966. DOI: 10.1161/CIRCIMAGING.115.003966.)**

Key Words: coronary artery disease ■ incidence ■ myocardial infarction ■ prognosis ■ tomography, emission-computed, single-photon

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Myocardial perfusion imaging with single-photon emission computed tomography (SPECT) is well established for the prognostic evaluation of patients suspected for coronary artery disease (CAD).[1] However, this functional imaging modality is not able to detect nonflow-limiting CAD. There has been increasing interest to reveal subclinical atherosclerosis by coronary artery calcium (CAC) scoring, which has demonstrated a close correlation with atherosclerotic plaque burden.[2] With the advent of combined SPECT/CT cameras, it is possible to acquire both SPECT and CAC score in a single session.

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In asymptomatic populations, CAC scoring provides incremental prognostic information on top of SPECT myocardial perfusion imaging.[3,4] However, in symptomatic patients, the prognostic value of CAC scoring on top of SPECT imaging is less well established. The aim of the current study was to investigate the prognostic value of CAC score as an adjunct to SPECT in a low- to intermediate-risk population suspected for stable coronary artery disease.

Methods

Study Population

We studied stable patients with suspected CAD prospectively enrolled in a SPECT/CT registry. It was approved by the Isala Medical Ethics committee and included a waiver of consent. Consecutive patients referred for clinically indicated noninvasive CAD detection with SPECT/CT in the Isala Hospital between January 2009 and June 2013 were included. Patients were referred from the cardiology outpatient clinics of our hospital, which is a large cardiovascular center with a local, regional, and supraregional catchment area. Patients with unstable chest pain syndromes, a known history of CAD, and patients in whom no CAC score could be acquired (mainly because of high or irregular heart rate, n=121) were excluded. No other exclusion criteria were applied. Information on

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From the Departments of Cardiology (E.M.E., J.R.T., J.P.O., M.M.) and Nuclear Medicine (E.M.E., M.M., S.K., P.L.J.), Isala Hospital, Zwolle, Netherlands.

Correspondence to Elsemiek M. Engbers, MD, Department of Cardiology, Isala, Dokter van Heesweg 2, 8025, AB Zwolle, Netherlands. E-mail e.engbers@isala.nl

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medication use and the presence of risk factors was prospectively collected by written questionnaires. Height and weight were measured, and body mass index (BMI) was calculated. The pretest likelihood of CAD was assigned according to the criteria of Diamond and Forrester,[5] with a risk threshold of <13.4% for low risk, between 13.4% and 87.2% for intermediate risk, and >87.2% for high risk. All patients underwent initial ^{99m}Tc-tetrofosmin stress-first SPECT combined with CAC scoring. Immediately after acquisition of stress SPECT and CAC scan, a cardiologist and a nuclear physician together assessed the need for additional rest SPECT imaging. In case of an abnormal stress perfusion, additional rest SPECT was performed.

Myocardial Perfusion Imaging

Stress testing was routinely performed with pharmacological stress using adenosine (140 μg min^{-1} kg^{-1} for 6 minutes) in all patients unless there was a contraindication for pharmacological stress. Because of the logistical reasons, this is common practice in our high-volume center. Patients were instructed to refrain from caffeine-containing beverages for at least 24 hours before the test. In case of a contraindication for adenosine, patients underwent dobutamine (starting dose of 10 μg kg^{-1} min^{-1}, increased at 3-minute intervals to a maximum of 50 μg kg^{-1} min^{-1}), regadenoson (fixed dose of 400 μg, bolus injection for 15 s), or bicycle testing. A weight-adjusted dose of ^{99m}Tc-tetrofosmin (standard, 370 MBq; 500 MBq for patients >100 kg) was administered after 3 minutes (adenosine), after 35 s (regadenoson), or when the target heart rate of >85% of predicted maximal was reached (dobutamine, bicycle test). Patients scheduled for rest imaging received a dose of ^{99m}Tc-tetrofosmin (standard, 740 MBq; but 1000 MBq for patients >100 kg). Both stress and rest SPECT images were acquired 45 to 60 minutes after tracer injection. Time delay between the stress and rest studies was >3 hours.[6]

From January 2009 until April 2010, patients (n=977) were scanned on a conventional dual-detector γ camera (Ventri-LightSpeed VCT XT, GE Healthcare), using a low-energy high-resolution collimator, a 20% symmetrical window at 140 keV, a 64×64 matrix, and an elliptical orbit with step-and-shoot acquisition at 6° intervals for an 180° arc (45° right anterior oblique to 45° left posterior oblique) with 15 steps (15 views). Acquisition time was 12 minutes for the stress images and 15 minutes for the rest images as previously described.[7]

From May 2010 until June 2013, patients (n=4049) were scanned with a cadmium zinc telluride–based SPECT/CT camera (Discovery NM/CT 570c, GE Healthcare) with 19 stationary cadmium zinc telluride detectors simultaneously imaging 19 cardiac views. Each detector comprised 32×32 pixelated (2.46×2.46 mm) cadmium zinc telluride elements. Acquisition time was 5 minutes for the stress images and 4 minutes for the rest images. This was derived from the recommendations of the manufacturer, published experience, and our own qualitative assessment in heart phantom studies and our initial experience in patients.[8] All SPECT studies were followed by an unenhanced low-dose CT scan during a breath-hold at end expiration to provide the attenuation map for attenuation correction as previously described.[9]

Perfusion images were interpreted unblinded and semiquantitative using a 17-segment model.[10] Segments were scored by consensus of 2 experienced nuclear cardiology observers using a 5-point scoring system (0=normal, 1= equivocal, 2=moderate, 3=severe reduction of radioisotope uptake, and 4=absence of detectable tracer uptake).[11] The combination of attenuation corrected and nonattenuation corrected images was reviewed. A stress study was interpreted as normal if the summed stress scores was ≤3.[11] Additional rest SPECT was acquired if the stress images did not fulfill these criteria. An ischemic defect was defined as a summed difference score ≥2.[11] Reversible defects not fulfilling these criteria were assessed as equivocal for ischemia. Perfusion defects that demonstrated no reversibility were defined as fixed defects. Perfusion defects were rated as small, moderate, or large. Small defect represents <10%, moderate 10% to 20%, and large defects represent ≥20% of the left ventricular myocardium. The SPECT was defined as abnormal if the perfusion images demonstrated either reversible (both ischemia and equivocal for ischemia) or fixed defects.

CAC Scoring

All patients with heart rates >70 bpm received oral β-blocker therapy, with 50 or 100 mg of metoprolol tartrate (AstraZeneca, Zoetermeer, the Netherlands) after stress testing to achieve a heart rate <70 bpm for the CAC scan.

A nonenhanced CT scan (LightSpeed VCT XT; GE Healthcare) during breath-hold at end expiration to calculate the total CAC score was acquired with ECG triggering at 75% of the R-R interval and the following scanning parameters: 40 or 48 sections and 2.5-mm section thickness; gantry rotation time, 330 ms; tube voltage, 120 kV; and a tube current of 125 mA. If patients were not able to hold their breath, a free breathing CT was acquired. Postprocessing was conducted at a dedicated workstation using Smartscore software (GE Healthcare). The CAC score was calculated using the standard Agatston criteria.[12]

Follow-Up

Follow-up data were based on clinical visits or standardized telephone interviews. Major adverse cardiac events (MACEs) were defined as late revascularization (angioplasty or coronary artery bypass surgery, >90 days after scanning), nonfatal myocardial infarction, or all-cause mortality. Early elective revascularizations within 90 days after imaging were excluded from the survival analysis to eliminate events driven by imaging findings. Patients undergoing early revascularization were censored. Nonfatal myocardial infarction was defined based on the criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the ECG as defined by Thygesen et al.[13]

Statistical Analysis

Continuous variables are expressed as mean±SD or median (25th to 75th percentile), and categorical variables are expressed as frequency (percentage). Differences between groups were assessed by unpaired Student *t* test, Mann–Whitney *U* test, and by χ^2 test, where appropriate. The patient's pretest likelihood for CAD was determined with the standard Diamond criteria with the assumption that chest pain was atypical.[5] SPECT findings and patient clinical characteristics were compared across different CAC score categories using the χ^2 test for trend. We calculated annualized event rates on the basis of events per patient per year and compared differences in annualized events between patients with normal and abnormal SPECT in the different CAC score categories by Poisson regression for rate data. Multivariate logistic regression was performed to investigate whether CAC score was an independent predictor for an abnormal SPECT result after adjusting for the effects of age, sex, BMI, and traditional risk factors, which were significant variables in univariate analysis (diabetes mellitus and hypertension). The CAC score was entered in the model as a categorical variable. Continuous predictors with a linear relationship were included in the model as a continuous variable. We used Cox proportional hazard regression to analyze the association between imaging results, patient characteristics, and clinical outcomes. The Cox model was adjusted for age, sex, and all traditional risk factors. We evaluated interaction terms for CAC score, SPECT findings, and MACE outcome. Effect modification by sex, BMI, age, and traditional risk factors was evaluated. Cox survival curves were constructed with separate lines for the different CAC score categories and were adjusted for age, sex, and traditional risk factors. We examined the discriminatory power for both the logistic regression and the Cox regression model by means of the *C*-index. *C*-indexes for the models with and without including the CAC score as a predictive variable were reported. Two-sided *P* values of <0.05 were considered statistically significant in all tests. Statistical analysis was performed with a commercially available software package (SPSS, version 20.0 for Windows); the Poisson regression for rate data was performed with Medcalc (version 16.2 for Windows).

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Results

Study Population

During a period of 4.5 years, a total of 4905 patients were included. Follow-up information was not available for 8 (0.2%) of the patients. The remaining 4897 patients are the subject of this report. Relevant general characteristics of the study population are demonstrated in Table 1. Pretest likelihood was considered to be low in 9% of the patients and intermediate in 91% of the patients. The mean age was 61±11 years, 43% of the patients were men, and 13% were diabetic. Stress testing was performed with adenosine in 4746 (96.9%), with dobutamine in 97 (2.0%), with regadenoson in 14 (0.3%), and with exercise testing in 40 (0.8%) of the patients.

CAC Score and SPECT Findings

The median CAC score was 39 (25th to 75th percentile, 0–282) with a range from 0 to 18 041. The distribution of CAC score and patient characteristics in the different CAC score categories are demonstrated in Table 2. Patients with a higher CAC score were more frequently men and older and demonstrated more cardiac risk factors. SPECT was normal in 3702 patients (76%); the remaining 1195 patients (24%) showed abnormal SPECT. Increasing CAC scores were significantly associated with a higher frequency of abnormal SPECT (Figure 1) and a higher frequency of large perfusion defects (Table 2). Of the 3702 patients with normal SPECT, 2546 (69%) had a CAC score >0, with a CAC score ≥400 in 569 (15%) and a CAC score ≥1000 in 231 (6%).

Predictors of Abnormal SPECT

General characteristics of patients with normal and abnormal SPECT were significantly different (Table 1). Patients with abnormal SPECT were more likely to be older, men, diabetic, hypertensive, and had higher BMI and CAC scores. After adjustment for differences in patient characteristics, a higher CAC score was still associated with risk of abnormal SPECT (P=0.001; Table 3). The odds ratio for an abnormal SPECT was 5.24 (95% confidence interval [CI], 3.95–6.96; P<0.001) for patients with a CAC score of ≥1000 compared with patients with a CAC score of 0. Other significant independent predictors for abnormal SPECT were male sex (odds ratio, 1.61; 95% CI, 1.40–1.86; P<0.001) and higher BMI (odds ratio, 1.07 per 1 kg/m^2; 95% CI, 1.05–1.09; P<0.001). Other risk factors such as age, diabetes mellitus, and hypertension were not associated with abnormal SPECT in multivariate analysis. The C-index increased from 0.66 to 0.71 when the CAC score was included in the model on top of clinical characteristics.

Table 1. General Patient Characteristics and Comparison of Patients With Normal and Abnormal SPECT Perfusion

	Overall (n=4897)	Normal SPECT (n=3702)	Abnormal SPECT (n=1195)	*P* Value
Age	61±11	60±12	63±11	<0.001
Male sex	2098 (43)	1438 (39)	660 (55)	<0.001
Risk factors				
Diabetes mellitus	649 (13)	427 (12)	222 (19)	<0.001
Current smoking	775 (16)	567 (15)	208 (18)	0.08
Hypertension	2991 (61)	2231 (60)	760 (64)	0.047
Hypercholesterolemia	2108 (43)	1577 (43)	531 (44)	0.28
Family history of CAD	2665 (55)	2027 (55)	638 (53)	0.40
BMI	27.6±4.8	27.2±4.5	28.7±5.3	<0.001
CAC score	39 (0–282)	21 (0–184)	183 (16–730)	<0.001
CAC score >0	3582 (73)	2546 (69)	1036 (87)	<0.001
Medication use				
Aspirin	1948 (40)	1385 (37)	563 (47)	<0.001
β-blocker	2579 (53)	1906 (52)	673 (56)	0.004
Statin	3106 (63)	1286 (35)	505 (42)	<0.001
ACE inhibitor	3202 (65)	1209 (33)	486 (41)	<0.001
Abnormal SPECT findings				
Small perfusion defect			691 (58)	
Moderate perfusion defect			359 (30)	
Large perfusion defect			145 (12)	

Values are shown as n (%), mean±SD, and median (25th to 75th percentile). ACE indicates angiotensin-converting enzyme; BMI, body mass index; CAC, coronary artery calcium; CAD, coronary artery disease; and SPECT, single-photon emission computed tomography.

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Table 2. General Patient Characteristics According to CAC Score

	CAC Score 0 (n=1315)	CAC Score 1–99 (n=1668)	CAC Score 100–399 (n=918)	CAC 400–999 (n=539)	CAC ≥1000 (n=457)	*P* Value
Age, y	54±11	60±11	65±9	68±9	70±9	<0.001
Male sex	386 (29)	668 (40)	453 (49)	290 (54)	301 (66)	<0.001
Cardiac risk factors, amount	1.6±1.1	1.9±1.1	2.0±1.1	2.0±1.1	2.2±1.1	<0.001
Diabetes mellitus	85 (7)	192 (12)	130 (14)	111(21)	131 (29)	<0.001
Hypertension	646 (50)	1012 (61)	636 (69)	377 (70)	320 (70)	<0.001
Current smoking	230 (18)	236 (14)	139 (15)	98 (18)	72 (16)	0.91
Hyperlipidemia	434 (33)	718 (43)	455 (50)	251 (47)	250 (55)	<0.001
Family history of CAD	758 (58)	928 (56)	494 (54)	253 (47)	232 (51)	<0.001
Abnormal SPECT	159 (12)	320 (19)	289 (32)	201 (37)	226 (50)	<0.001
Small perfusion defect	107 (67)	212 (66)	165 (57)	107 (53)	100 (44)	<0.001
Moderate perfusion defect	46 (29)	93 (29)	96 (33)	55 (27)	69 (31)	0.67
Large perfusion defect	6 (4)	15 (5)	28 (10)	39 (19)	57 (25)	<0.001
Reversible defect	93 (7)	191 (11)	202 (22)	131 (24)	182 (40)	<0.001
Small reversible defect	64 (69)	134 (70)	125 (62)	62 (47)	101 (56)	<0.001
Moderate reversible defect	29 (31)	54 (28)	70 (35)	55 (42)	62 (34)	0.14
Large reversible defect	0 (0)	3 (2)	7 (4)	14 (11)	19 (10)	<0.001

Values are shown as n (%) and mean±SD. CAC indicates coronary artery calcium; CAD, coronary artery disease; and SPECT, single-photon emission computed tomography.

Follow-Up

During a median follow-up of 940 days (25th to 75th percentile, 581–1377), a total of 278 MACEs were observed (140 deaths, 31 nonfatal myocardial infarctions, and 107 late revascularizations). A total of 315 patients underwent early revascularization. Table 4 demonstrates an overview of the incidence of MACEs stratified by SPECT and CAC score. Overall incidence of MACE was 2.3% per year. Unadjusted annualized event rates for patients stratified by SPECT and CAC score are shown in Figure 2. A stepwise increase of MACE was present with increasing CAC scores, both in patients with normal SPECT and abnormal SPECT. After multivariate analysis, patients with a CAC score of 1 to 99 did not demonstrate a statistically significant greater risk of events during follow-up compared with patients with a CAC score of 0 (hazard ratio [HR], 1.35; 95% CI, 0.80–2.28;

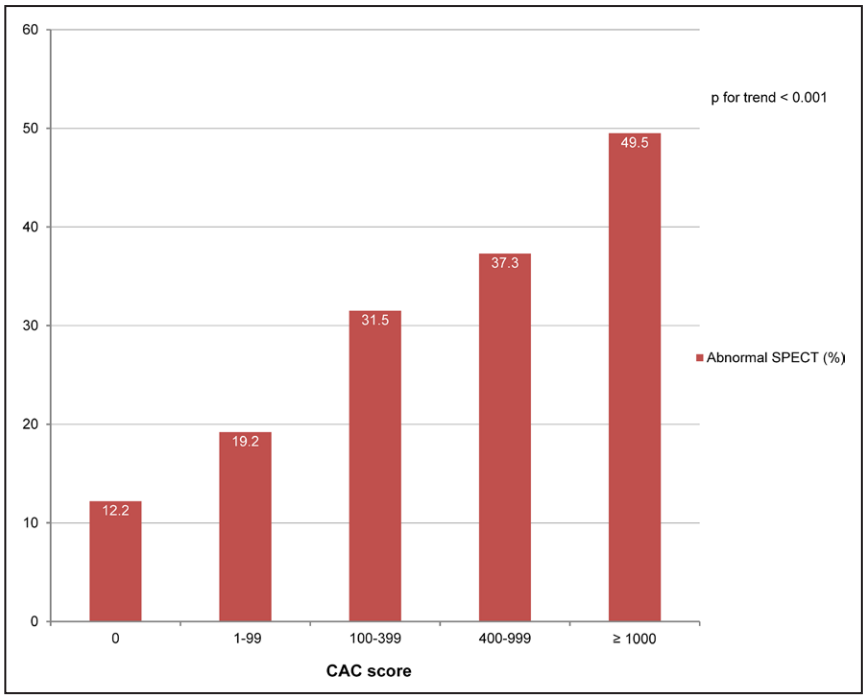

Figure 1. Prevalence of abnormal single-photon emission computed tomography (SPECT) according to coronary artery calcium (CAC) score.

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Table 3. Independent Predictors of Abnormal Single-Photon Emission Computed Tomography

	OR	95% CI	*P* Value
Age, +10 y	1.06	0.99–1.13	0.12
Male sex	1.61	1.39–1.87	<0.001
Diabetes mellitus	1.10	0.91–1.34	0.34
Hypertension	0.87	0.75–1.01	0.07
BMI, +1 kg/m^2	1.07	1.05–1.09	<0.001
CAC score			
1–99	1.44	1.17–1.79	0.001
100–399	2.78	2.20–3.51	<0.001
400–999	3.44	2.63–4.49	<0.001
≥1000	5.24	3.95–6.96	<0.001

Adjusted for the effects of age, sex, body mass index, and traditional risk factors, which were significant in univariate analysis (diabetes mellitus and hypertension). CAC indicates coronary artery calcium (reference, CAC 0); CI, confidence interval; and OR, odds ratio.

P=0.27). In patients with a CAC score of 100 or higher, a significant stepwise increase of risk for events with higher CAC score was demonstrated independent of SPECT (Table 5). Older age was also a significant independent predictor of events (+10 years: HR, 1.40; 95% CI, 1.22–1.60; *P*<0.001). The *C*-index of the model increased from 0.73 to 0.77 when the CAC score was included on top of clinical characteristics and SPECT findings. Adjusted survival curves based on CAC score severity in patients with both normal and abnormal SPECT are demonstrated in Figure 3. Interaction terms for CAC score, SPECT findings, and MACE outcome were not significant. No significant effect modification by sex, BMI, age, and traditional risk factors was demonstrated.

Discussion

Our study shows that in symptomatic patients, CAC score is a strong independent predictor of events irrespective of SPECT results. Combining functional imaging with SPECT and anatomic imaging with CAC scoring provides incremental information with regard to the degree of CAD. We suggest routinely performing CAC scoring in adjunct to SPECT in patients suspected for CAD to better define the risk of events during follow-up.

In this large cohort of patients, the frequency of an abnormal SPECT was significantly higher in patients with higher CAC scores. This finding seems logical as CAC is a direct marker of the extent of coronary sclerosis, which translates into the subsequent risk of significant stenosis. The association between CAC and SPECT results proved to be independent even after adjustment for the higher risk baseline characteristics in patients with higher CAC score. Patients with a CAC score ≥1000 were roughly 5× more likely to have abnormal SPECT compared with patients without CAC. Other significant predictors for abnormal SPECT were male sex and higher BMI. Current results are in concordance with previous findings.[4,14,15] Interestingly, after adjustment for CAC score, other known risk factors for CAD, such as age, diabetes mellitus, and hypertension, were no longer associated with abnormal SPECT. This indicates that CAC score is a stronger predictor for abnormal SPECT than more traditional risk factors for CAD.

Although the association between increasing CAC and abnormal SPECT score was evident, they represent different conditions (coronary sclerosis versus myocardial perfusion). About half of the patients with extensive CAC demonstrated no SPECT abnormalities. This finding has been demonstrated before in asymptomatic patients, although the reported frequencies of normal SPECT vary considerably.[3,4,16] On the other end of the spectrum, 12% of patients with CAC score 0 showed abnormal perfusion. This incomplete agreement between CAC and SPECT could be explained by different mechanisms. First, extensive CAC can be present without hemodynamically relevant stenosis and therefore normal SPECT.[17] Second, normal SPECT can occur in the presence of balanced ischemia because of significant stenoses in multiple coronary regions.[18,19] Third, SPECT abnormalities caused by attenuation artifacts (caused by fat or breast tissue) could be present in the absence of CAD. Finally, although rare, significant coronary stenosis may be caused by noncalcified plaque in patients with CAC scores of 0.[20] As the correlation between CAC score and

Table 4. Incidence of Major Adverse Cardiac Event Stratified by SPECT and CAC Score

	CAC Score Category	Late Revascularization	MI	Death
Normal SPECT (n=3702)	0 (n=1156)	1 (0.1)	4 (0.3)	14 (1.2)
	1–99 (n=1348)	3 (0.2)	6 (0.4)	22 (1.6)
	100–399 (n=629)	13 (2.1)	2 (0.3)	27 (4.3)
	400–1000 (n=338)	11 (3.3)	5 (1.5)	19 (5.9)
	≥1000 (n=231)	17 (7.4)	2 (0.9)	15 (6.5)
Abnormal SPECT (n=1195)	0 (n=159)	1 (0.6)	0 (0)	1 (0.6)
	1–99 (n=320)	4 (1.3)	2 (0.6)	7 (2.2)
	100–399 (n=289)	11 (3.8)	2 (0.7)	14 (4.8)
	400–1000 (n=201)	15 (6.5)	2 (1.0)	13 (6.5)
	≥1000 (n=226)	31 (13.7)	6 (2.7)	8 (3.5)

Values are shown as number (percentage); CAC, coronary artery calcium; MI, myocardial infarction; SPECT, single-photon emission computed tomography

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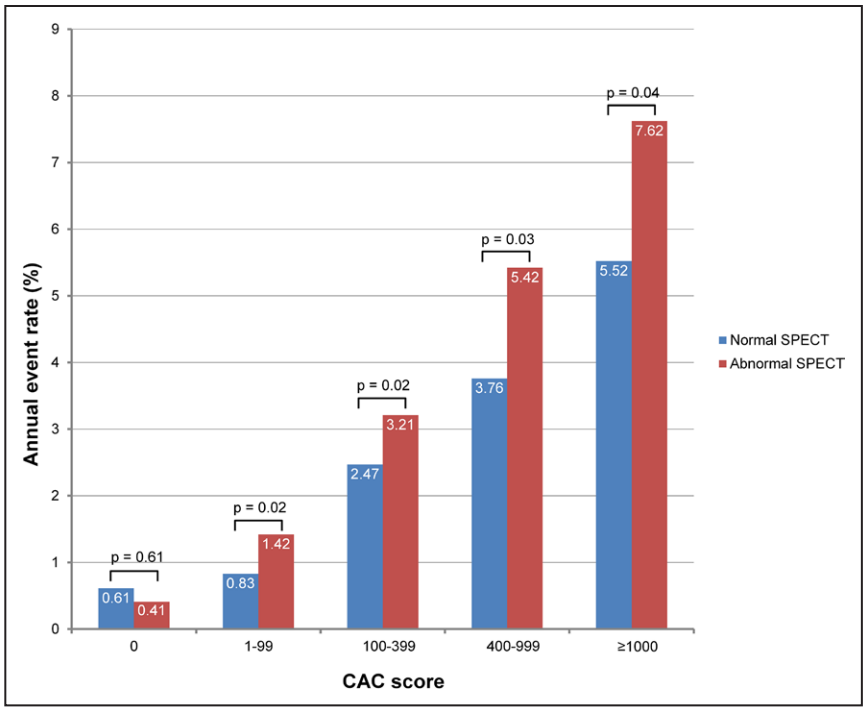

Figure 2. Incidence of major adverse cardiac events (MACEs) stratified by coronary artery calcium (CAC) score and single-photon emission computed tomography (SPECT).

luminal narrowing is poor, CAC scoring is not recommended to identify patients with significant CAD.[21] However, the current data clearly show that concomitant CAC scoring provides additional information on CAD not obtained by SPECT alone.

A significant increase of MACE was demonstrated in patients with higher CAC scores. This increase in MACE was evident in patients with both abnormal and normal SPECT, although event rates were significantly lower in the latter

Table 5. Cox Survival Analysis for Major Adverse Cardiac Event During Follow-Up

	Univariate			Multivariate		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age, +10 y	1.84	1.65–2.06	<0.001	1.40	1.22–1.60	<0.001
Male gender	1.64	1.29–2.07	<0.001	1.32	1.02–1.70	0.04
Risk factors						
Hypercholesterolemia	1.12	0.89–1.42	0.34	0.91	0.71–1.16	0.43
Current smoking	1.14	0.84–1.55	0.41	1.24	0.90–1.71	0.19
Diabetes mellitus	2.09	1.58–2.76	<0.001	1.31	0.98–1.75	0.07
Hypertension	1.29	1.01–1.66	0.04	1.01	0.78–1.32	0.94
Family history of CAD	0.89	0.70–1.13	0.34	1.20	0.94–1.53	0.14
CAC score						
1–99	1.69	1.00–2.84	0.048	1.35	0.80–2.28	0.27
100–399	5.54	3.40–9.02	<0.001	3.31	1.97–5.55	<0.001
400–999	9.70	5.93–15.86	<0.001	4.87	2.83–8.36	<0.001
≥1000	17.42	10.76–28.20	<0.001	7.57	4.38–13.07	<0.001
BMI (more than upper quartile)	1.10	0.83–1.42	0.52	…	…	…
SPECT findings						
Small perfusion defect	2.27	1.69–3.03	<0.001	1.64	1.22–2.21	0.001
Moderate perfusion defect	3.11	2.14–4.52	<0.001	2.21	1.51–3.23	<0.001
Large perfusion defect	9.04	5.73–14.26	<0.001	3.74	2.33–5.99	<0.001

BMI indicates body mass index (upper quartile, 30); CAC, coronary artery calcium (reference, CAC 0); CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; and SPECT, single-photon emission computed tomography (reference, normal SPECT).

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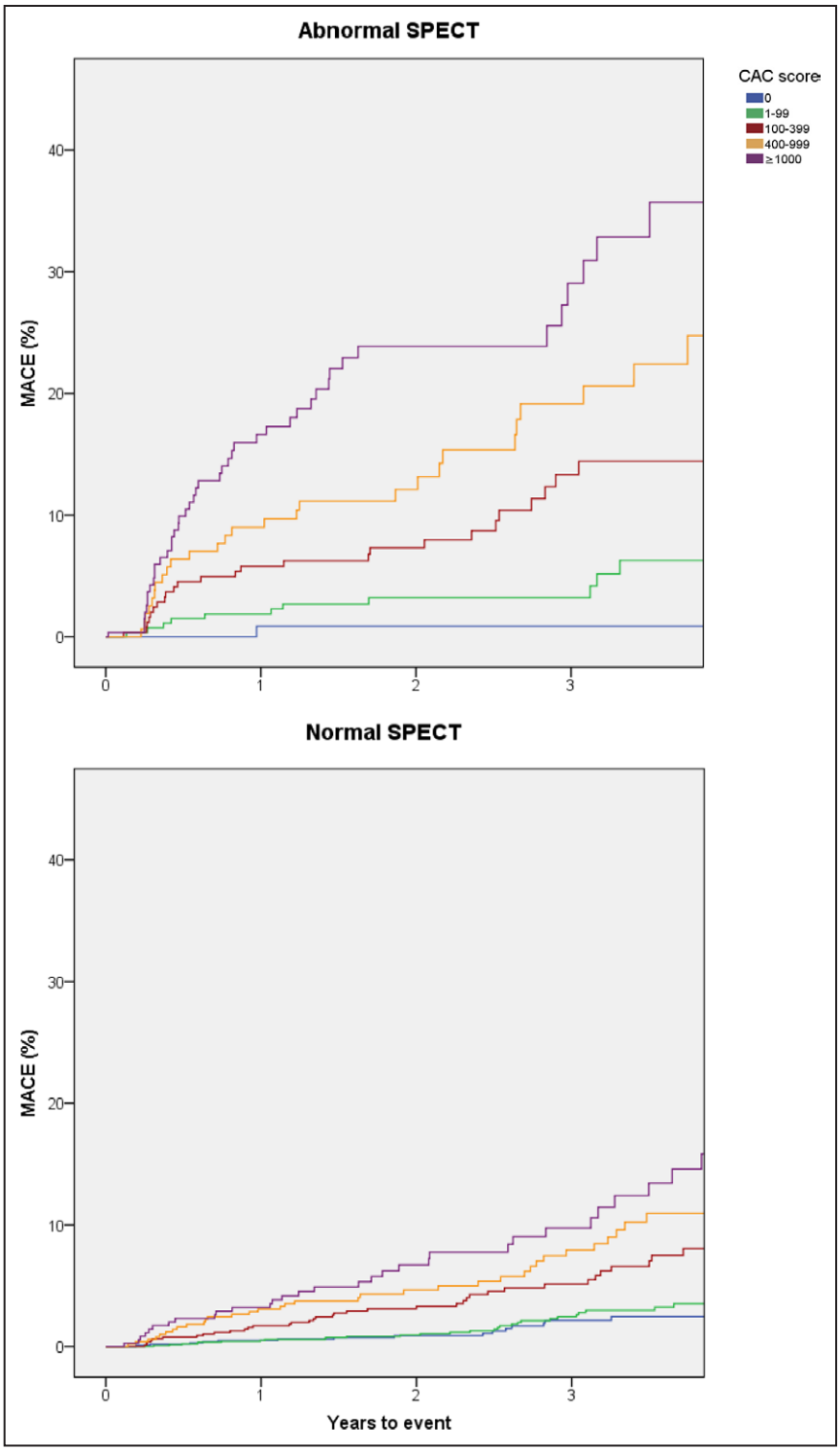

Figure 3. Adjusted event rates based on coronary artery calcium (CAC) score in patients with abnormal and normal single-photon emission computed tomography (SPECT); adjusted for age, sex, and traditional risk factors. MACE indicates major adverse cardiac event.

group, except for patients with a CAC score of 0. As patients with a CAC score of 0 demonstrated excellent prognosis independent of SPECT findings, the additional CAC score is likely to reduce the use of downstream invasive testing in this subset of patients.[22] After multivariate analysis, both CAC score and SPECT were independently associated with MACE. For patients with a CAC score ≥100, a stepwise increase of risk for events was present with higher CAC scores. CAC score ≥1000 seemed to be an even greater predictor for future events than a large perfusion defect (HR, 4.87 for CAC score 400–1000; HR, 7.57 for CAC score ≥1000 and HR, 3.74 for large perfusion defect, respectively). Conflicting results about the additive prognostic value of CAC score in addition to SPECT have been published. In a study by Ramakrishna et al,[4] it was first demonstrated that CAC score and SPECT provided complementary prognostic information. This was confirmed in a study by Chang et al,[3] which demonstrated that asymptomatic patients with CAC score >400 had a 3.55-fold higher risk of events (revascularization, myocardial infarction, or death) compared with patients with CAC score <10, irrespective of

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SPECT. Schenker et al[23] also demonstrated a stepwise increase in the risk of events with increasing CAC scores irrespective of positron emission tomography myocardial perfusion imaging. Other research did not show an increase of events with elevated CAC scores in patients with normal myocardial perfusion imaging.[16] This discrepancy is probably caused by the lower risk profile and relatively shorter follow-up period in the latter study. In a study by Naya et al,[24] it was demonstrated that coronary flow reserve acquired with positron emission tomography provided significant incremental risk stratification rather than the CAC score. Up to now, no reliable assessment of quantitative perfusion can be performed with SPECT.

With our current results, we demonstrate that additional prognostic information is obtained by CAC scoring as an adjunct to SPECT in symptomatic patients. The CAC score is easily acquired on a noncontrast enhanced CT scan and is associated with a modest additional radiation exposure of 1 mSv, whereas it enables clinicians to identify patients in higher risk categories than is expected with SPECT findings alone. The presence of a high CAC score could influence therapy decisions. On the basis of our findings that CAC score is an independent predictor of MACE irrespective of the extent of SPECT abnormality, an earlier invasive strategy could be considered in patients with equivocal or small perfusion defects but extensive CAC. This is strengthened by previous findings in patients with normal SPECT in which the CAC score was able to unmask CAD.[9,18] In patients with extensive CAD, lifestyle advice and medication could be initiated or intensified. It could be considered to treat patients with high CAC score with statins irrespective of SPECT results given the mechanism of action of statins and their effectiveness as shown in prevention trials.[25,26] However, data about the favorable effect of statin treatment in patients with high CAC scores are limited. In 2 observational studies, it was demonstrated that patients with CAD on coronary computed tomographic angiography who were on statin therapy demonstrated better prognosis than patients who were not on statin therapy.[27,28] In a randomized controlled trial, a trend toward reduction of cardiovascular events was observed in patients with CAC scores >400 who were treated with statins in combination with antioxidant vitamins.[29]

Although our study reflects true daily practice and included consecutive patients, we have to acknowledge several limitations. The observational design remains a major limitation of the current study as end points were not prespecified. Also, this is a single-center study in patients with suspected CAD and a low to intermediate pretest likelihood undergoing predominantly pharmacological stress. Therefore, extrapolation of the present results to populations with different pretest likelihood or to patients undergoing traditional exercise testing is difficult. In addition, SPECT observers were not blinded for the CAC score; therefore, it is possible that the SPECT results were biased by CAC score. Moreover, all imaging results were available to referring physicians, and medical management and downstream utilization of invasive testing were left to the discretion of the referring physician. We did not investigate the effect of CAC scoring on downstream intensification of medication and thereby were not able to investigate the possible favorable influence of the knowledge of the CAC score on patient outcome. Finally, we evaluated the additional predictive value of the CAC score on the prediction model with an established measure for prediction increment (*C*-index) and did not use more recently developed statistics (eg, net reclassification index).

Conclusions

CAC score and SPECT findings are independent predictors of events in symptomatic patients. Our findings strongly support performing a CAC score in addition to SPECT in symptomatic patients to better define the risk of events during follow-up.

Disclosures

None.

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CLINICAL PERSPECTIVE

In a large low-to-intermediate-risk population suspected for coronary artery disease, coronary artery calcium score is a strong independent predictor of events irrespective of single-photon emission computed tomographic results. An enhanced patient risk stratification can be obtained by combining functional imaging with single-photon emission computed tomographic and anatomic imaging with coronary artery calcium scoring in symptomatic patients. It is not yet clear which effect the additional prognostic information obtained by coronary artery calcium scoring should have on patient management. Further research should give insight into the effect of statin therapy on survival in patients suspected for coronary artery disease who are identified as high risk with coronary artery calcium scoring.