Coronary calcium score influences referral for invasive coronary angiography after normal myocardial perfusion SPECT

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Background. **In patients with normal SPECT but persistent complaints, invasive angiography may exclude obstructive coronary disease. We assessed whether high coronary artery calcium (CAC) scores are associated with increased referral for invasive angiography following normal SPECT.**

Methods and results. **2286 consecutive patients (mean age 60 ± 12, 39% male) with normal SPECT were assessed. All patients underwent simultaneous CAC scoring. Patients were categorized into four groups based on their CAC score: CAC = 0 (n = 694), CAC 1 to 100 (n = 891), CAC 101 to 400 (n = 368), and CAC >400 (n = 333). The decision to perform angiography was left to the discretion of treating physician. Follow-up angiography was confined to the first 60 days after SPECT. Occurrence of MACE (late revascularization, myocardial infarction or death) was recorded. Overall, 100 patients (4.4%) underwent early angiography with increasing rates in higher CAC score groups (1.0%, 2.6%, 8.4%, and 11.7%), respectively, $P < .001$). A CAC score >400 (OR 3.56, 95% CI 2.19 to 5.77, $P < .001$) was independently associated with referral to angiography. Similarly, CAC score >400 was an independent predictor for MACE (HR 9.26, 95% CI 5.06 to 16.93). Early angiography did not influence prognosis (HR 1.57, 95% CI 0.91 to 2.73).**

Conclusions. **CAC scoring impacts clinical decision-making and increases referral rates for invasive angiography after normal SPECT. (J Nucl Cardiol 2019;26:602–12.)**

Key Words: Single-photon emission computed tomography • myocardial perfusion imaging • stable coronary artery disease • coronary artery calcium scoring • invasive coronary angiography

Abbreviations

CAC	Coronary artery calcium
CAD	Coronary artery disease
CZT	Cadmium zinc telluride
FFR	Fractional flow reserve
HR	Hazard ratio
ICA	Invasive coronary angiography
LVEF	Left ventricular ejection fraction
MPI	Myocardial perfusion imaging
OR	Odds ratio
SPECT	Single-photon emission computed tomography

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INTRODUCTION

Myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) is widely used and has been proven to provide valuable diagnostic and prognostic information.[1,2] However, as in all diagnostic tests, there may be false-negative and false-positive results. Coronary artery calcium (CAC) scoring is a non-invasive technique to estimate the amount of coronary atherosclerosis.[3,4] Simultaneous CAC scoring together with MPI may offer additional diagnostic and prognostic information.[5–8] Although initial studies have assessed the impact of simultaneous CAC scoring on medical treatment,[9,10] the impact on downstream invasive testing in patients with normal MPI results remains unknown. Therefore, we assessed whether higher CAC scores are associated with increased rates of referral for invasive coronary angiography (ICA) following normal SPECT in patients with suspected stable coronary artery disease (CAD).

MATERIALS AND METHODS

Study Population

From January 2009 to December 2011, a total of 3078 consecutive patients with suspected (but unconfirmed) stable CAD, and a low to intermediate pre-test likelihood for CAD according to Diamond and Forrester criteria,[11] underwent clinically indicated SPECT imaging using a stress-first protocol. CAC scoring was performed as a routine component of each study when feasible. Patients with a history of myocardial infarction or coronary revascularization were excluded. From January 2009 until April 2010, patients ($n = 974$) were scanned on a conventional SPECT/CT camera (Ventri-LightSpeed VCT XT, GE Healthcare), and from May 2010 until December 2011, patients ($n = 2104$) were scanned with a CZT-based SPECT/CT camera (Discovery NM/CT 570c, GE Healthcare).

After acquisition and post-processing, data were immediately analyzed by two experienced readers. In case of normal stress perfusion and function, further tests were omitted. However, patients with equivocal or abnormal stress perfusion were referred for rest SPECT imaging. For the current analysis, we retrospectively selected patients with normal stress-only and normal stress-rest SPECT results. All procedures were performed in accordance with the Declaration of Helsinki. The study was approved by the Committee on Research Ethics of our hospital, and written informed consent was obtained from all patients.

Clinical Information

At the time of examination, all patients completed a questionnaire regarding demographic information, prior medical history, cardiac risk factors, and current medication use.

These data were verified and complemented with demographic and clinical information collected from medical records.

Follow-Up

Clinical management. Post-imaging treatment strategy was left to the discretion of the referring physician. Downstream treatment strategy within a 60-day interval after MPI and CAC imaging was assessed, including decision for conservative treatment, ICA, and coronary revascularization procedure. Follow-up regarding subsequent treatment strategy was confined to the first 60 days after imaging as this allows best to assess the treatment strategy decisions, while later interventions may not be directly triggered by the imaging results but rather reflect events of the natural course of the disease process.

Prognostic outcome. Follow-up outcome data were based on clinical visits or standardized telephone interviews.

The time between the stress test and the date of the final examination or consultation was used to determine follow-up length. The endpoint was a composite of the following major adverse cardiac events (MACE): all-cause mortality, non-fatal myocardial infarction, and late coronary revascularization (angioplasty or coronary artery bypass surgery, >60 days after scanning). Early elective revascularizations within 60 days after imaging were excluded from the survival analysis to eliminate events driven by imaging findings. Patients undergoing early revascularization were included for the remaining follow-up to monitor for other end-points. The first event in each patient was used for the survival analysis. Based on the difference in inclusion date, the follow-up time varied among patients with a minimal follow-up duration of 12 months for those without an event.

SPECT MPI Data Acquisition

All patients underwent a 1-day ^{99m}Tc-Tetrofosmin MPI protocol. Patients were instructed to refrain from caffeine-containing beverages for at least 24 hours before the test. Owing to logistic reasons in our high volume center, stress testing was performed with pharmacological stress induced by intravenous administration of adenosine (97% of the patients) (continuous infusion at a rate of 140 μg·kg·min for 6 minutes) or dobutamine in the case of contraindication for adenosine (3%) (starting with 10 μg·kg·min and increased at 3-minute intervals to a maximum of 50 μg·kg·min until 85% of the predicted heart rate had been reached). Whenever possible, patients without left bundle branch block (LBBB) performed additional low-level bicycle exercise to reduce side effects of adenosine. ECG and blood pressure were monitored before, throughout, and following the infusion. A weight-adjusted dose of ^{99m}Tc-Tetrofosmin (standard 370 MBq, 500 MBq for patients >100 kg) was injected after 3 minutes of adenosine infusion. SPECT images were acquired 45 to 60 minutes after tracer injection.

On the conventional dual-detector gamma camera (Ventri, GE Healthcare), images were acquired using a low-energy, high-resolution collimator, a 20% symmetrical window at 140 keV, a 64 × 64 matrix, and an elliptical orbit with stepand-shoot acquisition at 6° intervals over a 180° arc (45° anterior oblique to 45° left posterior oblique) with 15 steps (15 views). All patients were imaged in supine position with arms placed above the head. Acquisition time was 12 minutes for the stress images and 15 minutes for the rest images.[12]

The CZT-based SPECT images were acquired using a multi-pinhole camera (Discovery NM/CT 570c, GE Healthcare) and 19 stationary detectors simultaneously imaging the heart. Each detector contained 32 × 32 pixelated (2.46 × 2.46 mm) CZT elements. A 20% symmetrical energy window at 140.5 keV was used as previously described.[12] All patients were imaged in supine position with arms placed above the head. Acquisition time was 5 minutes for the stress images and 4 minutes for the rest images.[12]

All SPECT studies were followed by an unenhanced low-dose CT scan during a breath-hold to provide the attenuation map for attenuation correction. These scans covered the entire chest with scanning parameters: 5.0 mm slice thickness using a reconstruction algorithm with a 512 × 512 matrix, and 800 ms rotation times at 120 kV and 20 mA. Emission images as well as attenuation map data were entered in a dedicated reconstruction algorithm to provide 3D volume data (available in a Xeleris workstation, GE Healthcare). These were reorientated in the standard way and displayed in the three traditional cardiac axes.

SPECT MPI Analysis

Two experienced nuclear cardiac readers (each with more than 10 years of experience) interpreted the images using MPI polar maps. Segments were scored in consensus by using a 17-segment model for the left ventricle using the following five-point scoring system (0, normal; 1, equivocal; 2, moderate; 3, severe reduction in radiotracer uptake; and 4, absence of detectable tracer in a segment).[13,14]

Perfusion defects were identified on the stress images (a segment with a score ≥2 was considered to have a defect). A stress study was interpreted as normal if perfusion was assessed to be homogeneous throughout the myocardium and summed stress score was ≤3 with normal function.[13,14] Left ventricular ejection fraction (LVEF) <50% was considered as abnormal. Subsequent rest imaging was performed if the stress images did not fulfill these criteria and were therefore deemed to be either abnormal or equivocal.

CAC Score Acquisition and Analysis

A non-enhanced CT study was performed for the CAC scoring by using the 64-section CT scanner of the integrated SPECT/CT scanner (LightSpeed VCT XT; GE Healthcare). All patients with heart rates greater than 70 beats per minute received oral beta-blocker therapy, with 50 or 100 mg of metoprolol tartrate (AstraZeneca, Zoetermeer, the Netherlands) after the pharmacologic stress test and radiotracer injection. Images were obtained with electrocardiographic gating at 75% of the R-R interval and with the following scanning parameters: 40 or 48 sections and 2.5 mm section thickness; gantry rotation time, 330 msec; tube voltage, 120 kV; and a tube current ranging from 125 to 250 mA, depending on patient size. Post-processing was conducted at a dedicated workstation using Smartscore software (GE Healthcare). The total calcium burden in the coronary arteries was manually depicted and allocated to the corresponding coronary artery by an experienced reader using the Agatston method for quantification of the CAC.[15] Absolute CAC score values and percentile scores were reported without providing any information regarding the interpretation of the CAC scores. Hence, further interpretation of these CAC score values was left to the discretion of the referring physician.

All CAC scans were read by two additional readers, (all with more than 5 years of experience in CAC scoring) at the time of SPECT interpretation. Patients were categorized into four groups based on their CAC score; CAC = 0, CAC 1 to 100, CAC 101 to 400, and CAC >400. Additionally, CAC percentile scores were assigned based on age and sex.

Invasive Coronary Angiography

Invasive coronary angiography was performed according to clinical standards by experienced interventional cardiologists with the Judkins or radial approach. Coronary stenoses of 70% or greater were considered to be severe for the left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA) coronary territories. Severe left main (LM) disease was defined as >50% diameter stenosis.[16] When fractional flow reserve (FFR) measurements were performed, visual grading was overruled by FFR, where a value of ≤0.80 was considered significant.

Statistical Analysis

Statistical analysis was performed with a commercially available software package (SPSS, version 20.0 for Windows; SPSS Inc., Chicago, Illinois, USA). Quantitative variables are expressed as mean ± SD and categorical variables as frequencies, or percentages. Quantitative data were compared using an unpaired two-tailed Student's *t* test or the Mann–Whitney *U* test where appropriate. Categorical data were compared using *Chi*-square test or Fisher's exact test as appropriate.

To determine independent predictors for downstream referral to ICA within 60 days after simultaneous SPECT and CAC imaging, a multivariate logistic regression was performed. A *P* value of less than 0.05 in univariate analysis was required for entry into the multivariate analysis. Absolute CAC scores were entered in the models as a dichotomous variable (CAC score ≤400 vs CAC score >400) and as a categorical variable. An additional analyses was performed for the different CAC score percentiles as a categorical variable. Continuous predictors with a linear relationship were included in the model as a continuous variable. Significant variables analyzed are reported with their respective odds ratio (OR) and 95% confidence intervals (CIs). Two-sided *P* values of less than 0.05 were considered statistically significant in all tests.

Differences in event-free survival over time were analyzed by the Kaplan–Meier method. The log-rank test was used to compare the survival curves. Univariate and multivariate

Cox's proportional regression analyses was used to identify independent predictors for events. Covariables were included in the models according to univariate significance. For each variable, a hazard ratio (HR) with a corresponding 95% CI was calculated. Two-sided P values of less than 0.05 were considered to indicate a significant difference.

RESULTS

Patient Characteristics

Between January 2009 and December 2011, a total of 3078 consecutive patients underwent stress-first SPECT imaging. After exclusion of all patients with abnormal SPECT results ($n = 735$) and those in whom CAC scoring was omitted due to fast heart rates ($n = 57$), 2286 patients were included for current analysis. Stress-only imaging was performed in 1620 (71%) of these patients, while 666 patients (29%) with normal SPECT findings underwent additional rest imaging. Mean age of the patients was 60 ± 12 years, 39% were male, and the mean body mass index (BMI) was 27 ± 4 kg/m^2. In 2229 patients (98%), pharmacological stress was induced with adenosine and in 57 patients (2%) with dobutamine. A total of 1643 (72%) patients were scanned with the CZT camera and 643 patients (28%) with a conventional gamma camera. The mean radiation doses for stress MPI, rest MPI, the unenhanced CAC scan, and the attenuation correction CT were 2.7, 5.4, 0.50, and 0.29 mSv, respectively.

Coronary Artery Calcium Scores

The median CAC score was 18 (25th to 75th percentile, 0 to 167), with a range from 0 to 4914. CAC scores of 0, 1 to 100, 101 to 400, and >400 were demonstrated in 694 (30%), 891 (39%), 368 (16%), and 333 (15%) of the patients, respectively. A total of 666 patients (29%) had a CAC score ≤25th percentile, while a CAC score between 26th and 50th percentiles, between 51st and 75th percentiles, and >75th percentile was demonstrated in 554 (24%), 477 (21%), and 589 (26%) of the patients, respectively.

Invasive Coronary Angiography

Follow-up information regarding referral for early ICA was available for all 2286 (100%) patients. A total of 100 patients (4.4%) underwent ICA within 60 days after SPECT/CT imaging, with increasing rates in higher CAC score groups (1.0%, 2.6%, 8.4% and 11.7%, respectively, $P < .001$), Figure 1. Patients who underwent early ICA after imaging were older, had more often diabetes, hypertension and hypercholesterolemia, and had higher CAC scores. The baseline characteristics of the two groups are summarized in Table 1. FFR was performed in only 13 patients. Among the patients referred for early ICA, 32 patients had obstructive CAD on ICA, including 5 patients with abnormal FFR values. Among the patients referred for ICA, obstructive CAD increased with higher CAC score groups; 0%, (0 out of 7 patients), 22% (5 out of 23 patients), 26% (8 out of 31 patients), and 49% (19 out of 39 patients), respectively, $P = .019$ (Table 2). Seventeen patients had single-vessel disease, 7 patients had 2-vessel disease, and 6 patients had 3-vessel disease without left main involvement. Only 1 patient had isolated left main disease, while 1 patient had 2-vessel disease with concomitant left main involvement. High-risk CAD (defined as 3-vessel disease [$n = 6$], LM stenosis [$n = 2$], and/or proximal LAD stenosis [$n = 5$]) was found in 13 patients. Overall, early coronary revascularization was performed in 25 out of all 2286 studied patients with normal SPECT (1.1%).

Predictors of Subsequent Invasive Coronary Angiography <60 Days

All variables that were associated with early referral for ICA are summarized in Tables 3, 4, and 5. Univariate analysis showed that age (OR 1.03, 95% CI 1.01 to 1.04, $P = .01$), diabetes mellitus (OR 1.94, 95% CI 1.17 to 3.22, $P = .01$), hypertension (OR 1.87, 95% CI 1.19 to 2.95, $P = .01$), hypercholesterolemia (OR 1.83, 95% CI 1.22 to 2.75, $P = .01$), a CAC score >400 (OR 4.11, 95% CI 2.70 to 6.26, $P < .001$), use of aspirin (OR 2.00, 95% CI 1.33 to 2.99, $P = .001$), use of beta-blockers (OR 1.68, 95% 1.11 to 2.54, $P = .014$), and use of statin (OR 1.99, 95% CI 1.33 to 2.98, $P = .001$) were predictive for referral to ICA.

Depending on the multivariate regression model used, only elevated CAC score categories and age were independently associated with referral to ICA (Tables 3, 4, 5).

Clinical Follow-Up

Follow-up was obtained for 2276 (99.6%) patients, while ten patients were lost to follow-up.

For the entire cohort, 136 MACE occurred including 78 all-cause deaths (6 cardiac deaths), 14 non-fatal myocardial infarctions, and 44 late coronary revascularizations during a mean follow-up time of 40 ± 14 months (median follow-up time 40 months, interquartile range 29 to 50 months). Overall incidence of MACE was 1.9% per year.

The Kaplan-Meier survival curves in Figure 2 illustrate the cumulative incidence of MACE. A stepwise increase of MACE was present with increasing

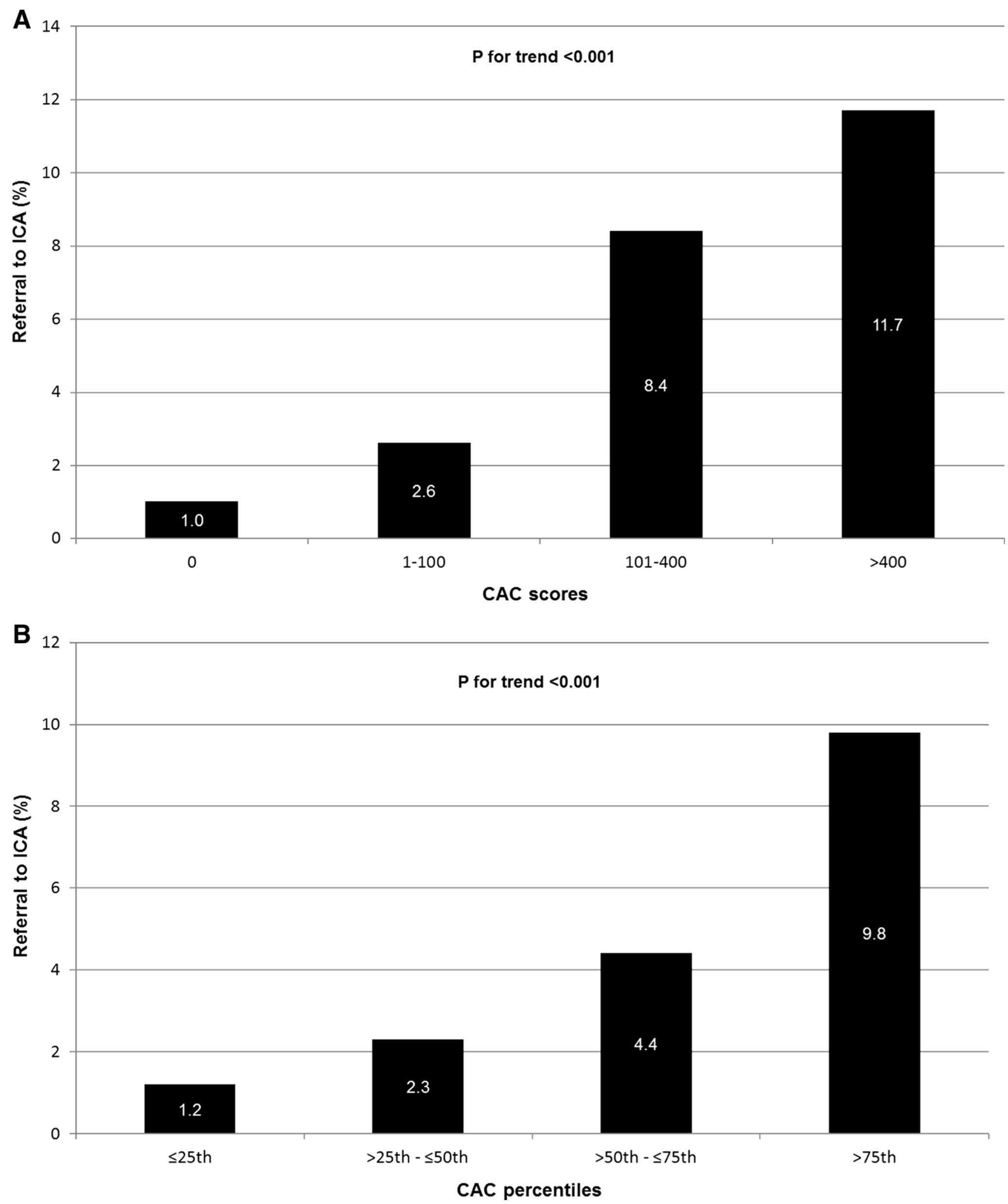

Figure 1. Frequency of referral for invasive coronary angiography in 2286 patients with normal SPECT MPI according to different CAC score categories (**A**) and CAC percentile categories (**B**). *CAC*, coronary artery calcium; *ICA*, invasive coronary angiography.

CAC scores with an incidence of 0.6% per year for patients with a CAC score of 0, 1.1% per year for patients with a CAC score 1 to 100, 2.9% per year for patients with a CAC score 101 to 400, and 5.3% per year for patients with a CAC score >400 (log rank $P < .001$).

In univariate analysis diabetes, male gender, a higher age, early ICA, a CAC score >0, and use of aspirin were significantly associated with an increased risk of MACE (Table 6). Multivariate Cox regression analysis showed that age, male gender, and a CAC score >100 were independently associated with the occurrence of MACE during follow-up.

DISCUSSION

Our observational study suggests that CAC scores influence clinical decision-making and increases early referral for ICA in stable low-intermediate risk patients

Table 1. Baseline characteristics of 2286 stable patients with normal SPECT findings with and without subsequent invasive coronary angiography within 60 days after SPECT

	Overall *N* = 2286	No angiography *N* = 2186	Angiography *N* = 100	*P* value
Age (years)	60.1 ± 12	59.9 ± 12	63.3 ± 11	.005
Male gender	39	39	44	.27
Current smoker	23	23	16	.06
Diabetes	12	11	20	.009
Hypercholesterolemia	43	42	57	.003
Hypertension	61	60	74	.006
Family history	53	53	55	.70
BMI (kg/m^2)	27 ± 4	27 ± 5	27 ± 4	.95
LBBB	2	2	2	.894
CAC score (median)	18 (0.01-167)	14 (0.01-145.25)	249 (72.5-755)	<.001
PTP (%)	36 ± 16	36 ± 16	41 ± 16	.86
Aspirin	39	38	55	<.001
Beta-blocker	51	50	63	.013
Statin	32	32	48	<.001
LVEF (%)	62 ± 8	62 ± 8	62 ± 11	.80
Reason for referral				.31
Chest pain (%)	83	86	84	
Dyspnea (%)	6	6	9	
Other (%)	10	11	7	

Data are percentages or mean ± standard deviation unless otherwise denoted
BMI, body mass index; *LBBB*, left bundle branch block; *CAC*, coronary artery calcium; *PTP*, pre-test probability; *LVEF*, left ventricular ejection fraction

Table 2. Frequency of early ICA, obstructive coronary disease, and early revascularization according to CAC scores

	CAC score 0 (*n* = 694)	CAC score 1-100 (*n* = 891)	CAC score 101-400 (*n* = 368)	CAC score >400 (*n* = 333)
Early ICA	7 (1)	23 (2.6)	31 (8.4)	39 (11.7)
Obstructive CAD	0 (0)	5 (0.6)	8 (2.2)	19 (5.7)
1 VD	0	2	4	11
2 VD	0	3*	2	3
3 VD	0	0	1	5
LM involvement	0	1*	0	0
Isolated LM stenosis	0	0	1	0
Early revascularization	0 (0)	4 (0.4)	8 (2.2)	13 (3.9)

Data are presented as numbers. Data in parentheses are percentages
CAC, coronary artery calcium; *ICA*, invasive coronary angiography; *CAD*, coronary artery disease
*1 patient had 2 VD and left main involvement

with normal MPI. Particularly, patients with a high CAC score (>400) or a high percentile score (>75th) had a strong and independent risk of referral for ICA.

SPECT MPI is well validated for the diagnostic and prognostic evaluation of patients with suspected CAD.[1,2] Stress SPECT can serve as a gatekeeper, accurately

Table 3. Uni- and multivariate predictors of referral for ICA

	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Diabetes	1.94 (1.17-3.22)	.01	1.20 (0.70-2.06	.50
Hypertension	1.87 (1.19-2.95)	.01	1.46 (0.91-2.36)	.12
Hypercholesterolemia	1.83 (1.22-2.75)	.01	1.40 (0.87-2.26)	.17
Male gender	1.25 (0.84-1.88)	.27	-	-
Age (per year)	1.03 (1.01-1.04)	.01	1.00 (0.98-1.02)	.84
CAC score >400	4.11 (2.70-6.26)	<.001	3.56 (2.21-5.74)	<.001
LVEF <50%	1.93 (0.87-4.30)	.11	-	-
Symptoms				
Chest pain	1.05 (0.61-1.82)	.86	-	-
Dyspnea	1.50 (0.74-3.05)	.26	-	-
Medication use				
Aspirin	2.00 (1.33-2.99)	.001	1.51 (0.97-2.34)	.07
Beta-blocker	1.68 (1.11-2.54)	.014	1.26 (0.81-1.96)	.30
Statin	1.99 (1.33-2.98)	.001	1.10 (0.67-1.81)	.72

Multivariate analysis using CAC score as a dichotomous variable in the model (CAC score ≤400 vs CAC score >400)
CAC, coronary artery calcium; *ICA*, invasive coronary angiography; *LVEF*, left ventricular ejection fraction

identifying low-risk patients and appropriately directing the use of invasive procedures.[17] However, there has always been concern that MPI can miss high-risk CAD,[18,19] while this group is particularly prone to adverse cardiac events and may have benefit of revascularization.[19,20] This may be explained by underlying CAD, in case of balanced ischemia due to flow-limiting three-vessel CAD or left main stenosis which may remain undetected with a merely functional imaging technique such as SPECT.

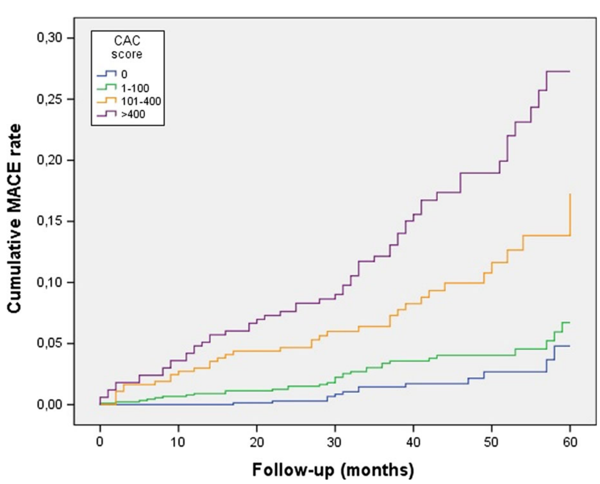

Figure 2. Kaplan-Meier curves of cumulative MACE rates according to CAC score group (log rank $P < .001$).

The recent advent of hybrid SPECT/CT and positron emission tomography/CT scanners have increased the interest in understanding the direct impact of simultaneous CAC scoring in patients referred for MPI. Underlying (subclinical) atherosclerosis can now be easily detected with simultaneous low-dose CAC scoring. In our population with normal SPECT findings, the majority of patients (70%) had subclinical CAD, which was severe (CAC score >400) in 15%. Higher CAC scores are associated with an increased risk for false-negative SPECT findings and cardiovascular events, even in the setting of normal SPECT MPI.[5,7,8]

Combining SPECT MPI with CAC scoring results in improved diagnostic confidence [21] and patient risk assessment,[5] and the presence of a high CAC score could potentially influence post-imaging clinical management and patient behavior.[22–25] We tried to extend the potential role of simultaneous CAC scoring by assessing the direct impact of CAC score knowledge on downstream ICA. Clinicians may reclassify patients into higher risk categories than expected based on SPECT findings alone.[5,8,22] Indeed, in our study, a stepwise increase of referral for ICA was present with increasing CAC scores. However, whether the aggressive management of risk factors and an early invasive strategy induced by CAC scoring knowledge averts future adverse cardiovascular events, especially in patients

Table 4. Multivariate predictors of referral for ICA using a model with CAC score categories

	Multivariate analysis	
	OR (95% CI)	***P* value**
Diabetes	1.17 (0.68-2.01)	.58
Hypertension	1.32 (0.81-2.14)	.27
Hypercholesterolemia	1.35 (0.84-2.17)	.22
Age (per year)	0.98 (0.96-1.00)	.06
Medication use		
Aspirin	1.42 (0.91-2.20)	.12
Beta-blocker	1.32 (0.85-2.07)	.22
Statin	1.00 (0.61-1.66)	.99
CAC score categories		
CAC score 0	Reference	-
CAC score 1-100	2.57 (1.08-6.10)	.03
CAC score 101-400	9.24 (3.59-22.12)	<.001
CAC score >400	14.23 (5.78-35.03)	<.001

CAC, coronary artery calcium; *ICA*, invasive coronary angiography

Table 5. Multivariate predictors of referral for ICA using a model with CAC percentiles

	Multivariate analysis	
	OR (95% CI)	***P* value**
Diabetes	1.24 (0.72-2.12)	.43
Hypertension	1.30 (0.80-2.11)	.28
Hypercholesterolemia	1.27 (0.78-2.04)	.34
Age (per year)	1.02 (1.00-1.04)	.03
Medication use		
Aspirin	1.47 (0.95-2.27)	.09
Beta-blocker	1.26 (0.81-1.96)	.31
Statin	1.11 (0.68-1.82)	.69
CAC score percentile		
<25th percentile	Reference	-
25th-50th percentile	1.48 (0.54-4.03)	.45
50th-75th percentile	2.50 (1.11-5.602)	.03
>75th percentile	7.27 (3.40-15.51	<.001

CAC, coronary artery calcium; *ICA*, invasive coronary angiography; *OR*, odds ratio; *CI*, confidence interval

with extensive CAC, remains unclear. Although early referral to ICA was a univariate predictor for MACE in our study (mainly driven by coronary revascularizations following early ICA), multivariate analysis showed no significant value in predicting outcome. More future prospective studies are warranted.

In patients with normal non-invasive functional test results, other causes for their complaints should be considered. However, when symptoms do not improve despite a trial of optimal medical treatment, further intensification of medical treatment is recommended. In case of persistent complaints despite optimal medical treatment, ICA with FFR measurement should be considered.[26] Only a small number of studies have examined referral to ICA in patients with normal stress SPECT MPI. The referral rates reported by four nuclear cardiology laboratories, examining patients with normal SPECT results numbering between approximately 300 and 7500 patients, have been low, between 1% and 6%.[27–35] In addition, early revascularization was

Table 6. Cox survival analysis for major adverse cardiac events during follow-up

	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Diabetes	2.27 (1.53-3.37)	<.001	1.48 (0.99-2.32	.06
Hypertension	1.48 (1.02-2.14)	.04	1.12 (0.77-1.64)	.56
Hypercholesterolemia	1.22 (0.87-1.71)	.25	-	-
Family history of CAD	1.01 (0.72-1.41)	.98	-	-
Male gender	1.49 (1.07-2.09)	.02	1.51 (1.06-2.14)	.02
Age (per year)	1.06 (1.04-1.08)	<.001	1.04 (1.02-1.06)	<.001
BMI (>upper quartile)	1.05 (0.72-1.53)	.82	-	-
Angiography <60 days	2.98 (1.64-4.78)	<.001	1.57 (0.91-2.73)	.11
Absolute CAC score				
0	Reference	-	Reference	-
1-100	1.92 (1.01-3.65)	.048	1.41 (0.73-2.73)	.30
101-400	5.17 (2.74-9.77)	<.001	2.88 (1.46-5.71)	.002
>400	9.26 (5.06-16.93)	<.001	4.16 (2.10-8.24)	<.001
LVEF <50%	1.72 (0.87-3.38)	.15	-	-
Symptoms				
Chest pain	0.86 (0.56-1.32)	.49	-	-
Dyspnea	1.70 (0.96-3.02)	.07	-	-
Medication use				
Aspirin	1.58 (1.13-2.21)	.008	1.17 (0.83-1.64)	.38
Beta-blocker	1.38 (0.98-1.94)	.07	-	-
Statin	1.35 (0.96-1.91)	.09	-	-

CAD, coronary artery disease; *BMI*, body mass index; *HR*, hazard ratio; *CI*, confidence interval; *LVEF*, left ventricular ejection fraction

performed in only 0.1% to 1.5% of patients, again confirming the safety of SPECT imaging as a gatekeeper for ICA. *Miller et al* demonstrated that patients with normal SPECT results referred for early angiography, are a highly selected group, with evidence of high-risk non-perfusion markers such as exercise-induced hypotension or ventricular arrhythmia.[35] In addition, current guidelines recommended ICA in patients with heart failure who suffer from angina pectoris recalcitrant to medical therapy.[36] The findings in our study demonstrate the impact of CAC score knowledge on downstream invasive testing in patients without perfusion abnormalities or high-risk non-perfusion markers. Our current findings are in line with previous reports from our center, with high rates of ICA in patients with extensive coronary atherosclerosis when compared to a similar population with lower CAC scores.[10,22]

Although our study included consecutive patients with normal SPECT MPI who underwent simultaneous CAC scoring, we have to acknowledge several limitations. This is a single-center registry in patients with suspected CAD and a low to intermediate pre-test likelihood undergoing predominantly pharmacological stress. Extrapolation of the current results is difficult for patients who underwent physical exercise and to patients with different pre-test likelihood or different patient characteristics. Our study design was observational and as a result the prognostic impact of an early invasive strategy remains to be studied. However, early revascularization was performed in only 1.1% of all patients, hence, the potential impact on prognosis was expected to be low. Furthermore, FFR measurements were performed in only a minority of the patients referred for ICA with subsequent revascularization. Finally, it cannot completely be excluded that other factors than CAC scoring may have influenced the choice for ICA. Future studies are warranted to assess whether the increased downstream referral for ICA is justified, ideally with additional FFR verification and longer term prognostic outcome data.

CONCLUSION

Coronary artery calcium scores impact clinical decision-making with regard to referral for invasive angiography in stable low-intermediate risk patients with normal MPI.

NEW KNOWLEDGE GAINED

Knowledge of higher CAC scores influences treating physicians in their post-imaging clinical decision-making regarding downstream invasive angiography in patients with normal MPI.

Disclosures

None.

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