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Measurement of coronary calcium scores by electron beam computed tomography or exercise testing as initial diagnostic tool in low-risk patients with suspected coronary artery disease

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Abstract We determined the efficiency of a screening protocol based on coronary calcium scores (CCS) compared with exercise testing in patients with suspected coronary artery disease (CAD), a normal ECG and troponin levels. Three-hundred-and-four patients were enrolled in a screening protocol including CCS by electron beam computed tomography (Agatston score), and exercise testing. Decision-making was based on CCS. When CCS≥400, coronary angiography (CAG) was recommended. When CCS<10, patients were discharged. Exercise tests were graded as positive, negative or nondiagnostic. The combined endpoint was defined as coronary event or obstructive CAD at CAG. During 12±4 months, CCS≥400, 10–399 and <10 were found in 42, 103 and 159 patients and the combined endpoint occurred in 24 (57%), 14 (14%) and 0 patients (0%), respectively. In 22 patients (7%), myocardial perfusion scintigraphy was performed instead of exercise testing due to the inability to perform an exercise test. A positive, non-diagnostic and negative exercise test result was found in 37, 76 and 191 patients, and the combined endpoint occurred in 11 (30%), 15 (20%) and 12 patients (6%), respectively. Receiver-operator characteristics analysis showed that the area under the curve of 0.89 (95% CI: 0.85–0.93) for CCS was superior to 0.69 (95% CI: 0.61–0.78) for exercise testing ($P<0.0001$). In conclusion, measurement of CCS is an appropriate initial screening test in a well-defined low-risk population with suspected CAD.

Keywords Coronary calcium · Exercise test · MDCT · EBCT · Coronary artery disease

Introduction

The management of patients presenting with chest pain remains a major challenge. Although the majority is at low risk of acute coronary syndrome (ACS), obstructive coronary artery disease (CAD) is present in 20% of patients [1]. Furthermore, at least 2% of patients with ACS are mistakenly discharged, resulting in increased mortality [2].

Clinical assessment, an electrocardiogram (ECG), and cardiac markers, such as troponin, allow initial discrimination between a high- and low-risk of ACS [3]. However, risk stratification often requires additional diagnostic testing. Exercise testing and measurement of CCS are frequently used for coronary risk stratification [4–9]. However, exercise testing has a sensitivity and specificity for obstructive CAD of 68% and 77%, respectively, while sensitivity for left main/three-vessel CAD is 86% [10]. Therefore, exercise testing does not detect all patients with (severe) obstructive CAD and the finding of a negative test does not rule out the presence of CAD [1]. Measurement of coronary calcium scores (CCS) may provide more effective triage. The finding of any coronary calcium has a 93–99% sensitivity and 23–75% specificity for obstructive CAD, while the negative predictive value ranges from 95 to 100% [7, 8, 11–16]. A few studies have studied the value of CCS

at the emergency department and have shown promising results [6–8]. However, studies comparing CCS and exercise tests have included only patients selected by abnormal exercise tests [17] or the need of coronary angiography [18, 19]. We therefore evaluated a screening protocol based on CCS in low-risk patients suspected of CAD and compared these findings with exercise test results.

Materials and methods

Patients

Consecutive low-risk patients with chest pain or other symptoms of CAD were included. Low-risk was defined as a normal 12-lead ECG, normal troponin, no hemodynamic instability and no abnormalities on physical examination or chest roentgenogram. Coronary risk factors were assessed by history and review of the medical record. Typical angina was defined as the presence of retrosternal pain, increasing with effort and responding to rest or nitroglycerin. If less than three of these characteristics were fulfilled, or a patient suffered from dyspnea, these patients were regarded as having atypical complaints. Other symptoms suggestive of CAD were arrhythmia, history of collaps or referral for screening. Patients with previously documented CAD were excluded. The pretest probability of significant CAD was assessed according to the method by Pryor et al. [20]. A high, and low test probability was defined as a probability of equal to or higher than, and below 44%, respectively [20].

Measurement of coronary calcium scores

Coronary calcium was measured using electron beam computed tomography (EBCT) (e-Speed, GE Medical Systems, South San Francisco, USA). According to patients' weight and size the beam speed was set to 50 ms (for small or slender patients) or 100 ms (for larger patients). Prospective electrocardiographic triggering was used and set at 42% of the R-R interval. Scans were made without the use of a contrast agent with 130 kV and 895 mAs. A single collimation of 3.0 mm and an increment of 3.0 mm was applied. Radiation exposures were 0.3 mSv and 0.6 mSv for the 50 ms and 100 ms protocols, respectively. Individual exposures were not measured. Assessment of all CCS was performed by one reviewer blinded to the clinical data and the exercise test results. The CCS was obtained by multiplying each area of interest with a factor indicating peak density within the individual area, as was proposed by Agatston et al. [21].

Exercise testing

Bicycle exercise tests were performed in accordance with the guidelines [22, 23]. All tests were independently reviewed by a cardiologist (R.T.) and a research physician (C.G.), who reached a consensus in case of discriminative results. Exercise test end points were defined as follows: positive, in case of ECG evidence of myocardial ischemia (0.1 mV horizontal shift of the ST segment at 80 ms after the J point); intermediate, in case of 30 mmHg decrease in systolic blood pressure and/or ventricular arrhythmia and/ or <0.1 mV ST depression and/or anginal complaints in the absence of ECG evidence of ischemia; negative, in the absence of any of the above mentioned criteria; and noninterpretable, if <85% of the predicted heart rate or a rate pressure product <18,000 was achieved. The predicted heart rate was corrected for length, age and sex, making use of a standardized table [24]. Intermediate and noninterpretable results are considered as "nondiagnostic results". In case exercise testing was not possible, myocardial perfusion imaging was performed.

Myocardial perfusion scintigraphy

Six-hundred MBq of ^{99} ^{m}Tc-tetrofosmin was injected at rest and the next day after adenosine or bicycle stress. SPECT images were acquired 1 h after tracer administration using a double-headed gamma-camera (Siemens E.Cam) equipped with low-energy high-resolution collimators. The camera heads were in perpendicular position. Other acquisition parameters were: 32 steps rotation, 20 s per step, 128×128 matrix size, rotation from the 45° right anterior oblique to the 135° left posterior oblique position with the patient laying supine. The scans were reconstructed after filtered-back-projection using a Butterworth 0.30/6 filter. All data were reorientated in order to produce short-axis (SA), horizontal long-axis (HLA) and vertical long-axis (VLA) sections. The perfusion images were scored on CAD by using a 17-segment polar map.

Screening protocol

The former screening protocol for low-risk patients with chest pain included exercise testing. In the current study, measurement of CCS was added. Exercise testing and measurement of CCS were performed in random order. Decision making was based on CCS (Fig. 1). In case of a low CCS, defined as CCS<10, patients were discharged and followed for the occurrence of cardiac events. In case of a high CCS, defined as CCS≥400, coronary angiography (CAG) was recommended to evaluate the presence of obstructive CAD. In case of an intermediate CCS, defined as CCS 10–399, primary prevention measures were recommended, and the decision to perform additional testing was
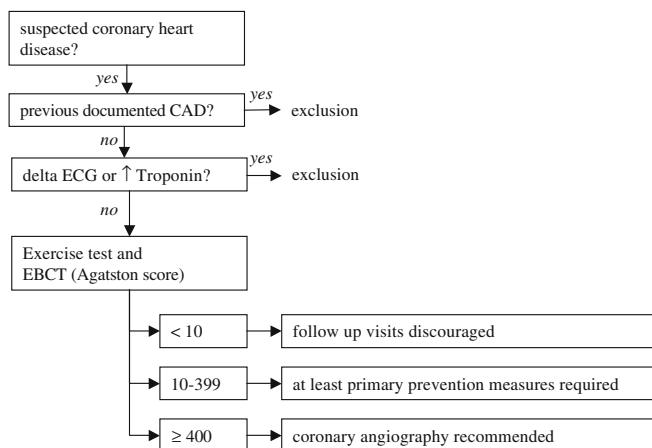
Fig. 1 Flow chart

left to the judgment of the treating cardiologist. Both EBCT and exercise testing were performed during office hours. Therefore, in some patients the tests were performed directly after presentation, while others were discharged first and underwent the tests within 3 weeks at the outpatient clinic. Follow-up was obtained in all patients to determine the clinical status at least 4 months after the measurement of CCS by review of the patient's medical record, telephone interviews of patients or general practitioners. The project is part of a continuous quality-improvement program of the Thoraxcenter, initiated by the board of directors of the University Medical Center Groningen. The protocol was approved by the Institutional Review Board. Informed consent was given by all patients.

Angiographic analysis

All CAGs were analyzed by a senior cardiologist (F.Z.), blinded to the clinical data. By qualitative analysis the coronary arteries were graded as follows: normal coronary arteries, defined as the absence of any coronary lesion; non-obstructive CAD, if maximal luminal obstructions were <50%; and obstructive CAD, if lesions obstructed the lumen ≥50%.

Endpoints

The combined endpoint was defined as a combination of the angiographic endpoint and a cardiac event. The angiographic endpoint was defined as obstructive CAD at CAG (≥50% luminal obstruction). Cardiac events were defined as a revascularization procedure, myocardial infarction or coronary death. Myocardial infarction was defined as ST-elevation myocardial infarction (chest pain and ST-elevation over 1 mm in at least two contiguous leads) or non-ST-elevation acute coronary syndrome

[defined as chest pain with positive cardiac markers (troponin or creatinin kinase) and/or dynamic ST-segment changes] [25, 26]. Revascularization procedures included percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG). Decisions to perform a revascularization procedure were taken by the Thoraxcenter multidisciplinary heart team, which has extensive experience with the RAND-UCLA criteria and takes decisions in accordance with the ESC and ACC/AHA guidelines for PCI and CABG [27–31].

Statistical analysis

Continuous data are expressed as mean ± standard deviation. Significance was reached when $P<0.05$. To compare the diagnostic yield of CCS with exercise test results, receiver operating characteristic (ROC) curve analysis was performed, and positive and negative predictive values were measured. We compared the area under the curves (AUCs) of both tests for the combined endpoint in all patients and after exclusion of subjects with typical angina. Additional analysis on clinical outcome was performed in those patients in whom exercise testing was not possible and myocardial perfusion scintigraphy was performed, and in those with CCS≥400 in whom the cardiologist decided not to perform CAG. Calculations were performed using the statistical package SPSS version 12.0 (SPSS, Chicago, USA) and STATA 9.0 (College Station, Tex., USA).

Results

Baseline characteristics

From May 2004 till September 2005, 304 patients were consecutively enrolled. Of all exercise tests performed during this period in patients without previous CAD, 90% were included in the study. Clinical characteristics are shown in Table 1. Most patients (*n*=225) underwent diagnostic testing for atypical complaints. Typical anginal complaints were present in 59 patients, while in 20 patients diagnostic testing was performed for routine screening (*n*=10), collapse (*n*=3) or arrhythmia (*n*=7). The large majority (84%) had a low pretest probability of significant CAD. In 22 patients (7%) myocardial perfusion scintigraphy was performed instead of exercise testing due to the inability to perform an exercise test. The study population represented 90% of the exercise tests performed in new patients.

Follow-up

Follow-up was obtained in all 304 patients (100%). During 12±4 months, 83 CAGs were performed. In 38 patients

Table 1 Baseline characteristics (*LDL* low-density lipoprotein, *HDL* high-density lipoprotein)

Characteristics	n=304	
Age, mean (range), years	55	(26–85)
Male gender, n (%)	169	(56)
Current Smoking, n (%)	109	(38)
Diabetes, n (%)	37	(13)
Blood pressure, mean (SD), mm Hg		
Systolic	141	(81)
Diastolic	81	(12)
Cholesterol, mean (SD), mg/dl		
Total	208	(46)
LDL	124	(39)
HDL	54	(14)
Glucose, mean (SD), mmol/l	5.8	(1.9)
Hypertension, n (%)	113	(38)
Hypercholesterolemia, n (%)	128	(44)
Positive family history, n (%)	157	(54)
Medication, n (%)		
ASA	59	(19)
Betablocker	75	(25)
Statin	75	(25)
Anginal complaints, n (%)		
Typical angina	59	(19)
Atypical complaints	225	(74)
Other[a]	20	(7)
Pretest probability of obstructive CAD[b] (%)	15	(0–36)
Pretest probability of obstructive CAD, n (%)		
High (≥44%)	49	(16)
Low (<44%)	255	(84)

[a]See text for explanation
[b]Median (p25-p75)

obstructive CAD was found, followed by a revascularization procedure in 28 patients (21 PCIs and 11 CABGs) (Tables 2, 3). No myocardial infarctions or deaths occurred.

Coronary calcium scores by computed tomography

Low, intermediate and high CCS were detected by EBCT in 159 (52%), 103 (34%) and 42 (14%) patients, respectively. In one patient (0.3%) the CCS quantification failed due to respiration artifacts. In this patient calcium was visible in all coronary arteries and was graded to be of intermediate amount.

Calcium score ≥400

In 42 patients with a high CCS, positive, negative and nondiagnostic exercise test results were present in 13, 15 and 14 patients, respectively. These results are presented in Table 2. In 37 patients a CAG was performed, showing one- or two-vessel disease in 15 (40%) and three-vessel or left main disease in nine (24%) patients (Table 3). In five patients CAG was not performed because symptoms disappeared with anti-ischemic medication. All patients with CAD received pharmacologic therapy, a revascularization procedure was performed in 17 patients. No myocardial infarctions or deaths occurred. The combined endpoint was observed in 24 of 42 (57%) patients.

Calcium score 10–399

In 103 patients with an intermediate CCS, most patients had negative (n=63) or nondiagnostic (n=31) exercise test results, while the remainder (n=9) had positive exercise test results (Table 2). In 33 patients a CAG was performed,

Table 2 Numbers of angiographic endpoints and cardiac events during follow-up (within 12±4 months)

Calcium score		Result of exercise test	n (%)		No. of angiographic endpoints[a]	No. of cardiac events[a]
≥400	(n=42)	Positive	13/42	(31%)	7	7 (revascularization)
		Negative	15/42	(36%)	8	5 (revascularization)
		Nondiagnostic	14/42	(33%)	9	5 (revascularization)
10–399	(n=103)	Positive	9/103	(9%)	4	4 (revascularization)
		Negative	63/103	(61%)	4	3 (revascularization)
		Nondiagnostic	31/103	(30%)	6	4 (revascularization)
<10	(n=159)	Positive	15/159	(9%)	0	0
		Negative	113/159	(71%)	0	0
		Nondiagnostic	31/159	(20%)	0	0

[a]Definitions of endpoints: *angiographic endpoint* ≥50% luminal obstruction at coronary angiography; *cardiac event* coronary death, myocardial infarction or revascularization procedure

Table 3 Coronary angiographic findings

Calcium score	CAG, n	Normal coronary arteries, n (%)	Nonobstructive CAD, n (%)	One-vessel disease, n (%)	Two-vessel disease, n (%)	Three-vessel or left main disease, n (%)
≥400 (n=42)	37	1 (3)	12 (33)	9 (24)	6 (16)	9 (24)
10–399 (n=103)	33	5 (15)	14 (43)	10 (30)	2 (6)	2 (6)
<10 (n=159)	13	11 (85)	2 (15)	0	0	0

showing obstructive CAD in 14 patients (Tables 2, 3). In these 14 patients the CCS ranged from 23 to 379. All patients with CAD received pharmacologic treatment, a revascularization procedure was performed in nine patients. One patient presented with unstable angina 4 months after PCI due to in-stent-restenosis and underwent repeat PCI. One patient underwent re-PCI for stable angina. No myocardial infarctions or deaths occurred. The combined endpoint occurred in 14 of 103 (14%) patients.

Calcium score <10

In 159 patients with a low CCS, the majority had a negative exercise test result (n=113), but positive and nondiagnostic tests were present in, respectively, 15 and 31 patients. In 13 patients CAG was performed for the following reasons: abnormal exercise test or myocardial perfusion scintigraphy (n=7); typical angina (n=2) and miscellaneous reasons (n=4). In none of these patients obstructive CAD was found (Tables 2, 3). The combined endpoint therefore occurred in 0 (0%) patients.

Comparison with exercise testing

A positive, nondiagnostic and negative exercise test was present in 37 (12%), 76 (25%) and 191 patients (73%), respectively. The rates of high, intermediate and low CCS in these groups were, respectively, 35%, 24% and 41% (positive exercise test); 18%, 41% and 41% (nondiagnostic exercise test); and 8%, 33% and 59% (negative exercise test). The rates of the combined endpoint in the groups with positive and negative exercise test results were, respectively, 30% (11/37) and 6% (12/191). A combined endpoint occurred in 15 (20%) of the 76 subjects with an intermediate exercise test result, namely in nine of 39 subjects with a nondiagnostic test results and in six of 37 subjects with a noninterpretable exercise test result. The rates of the combined endpoint according to CCS and exercise test results are shown in Fig. 2. ROC statistics show an AUC of 0.89 (0.85–0.93) for CCS and 0.69 (0.61–0.78) for exercise testing (P<0.0001; Fig. 3). A CCS>400 yielded a positive

predictive value of 57% (41–72%), while the negative predictive value of a CCS<10 was 100% (98–100%). The positive predictive vale of a positive exercise test was 30% (16–47%; P>0.05 compared with CCS>400). The negative predictive value of a negative exercise test result was 94% (89–97%; P<0.05 compared with CCS<10). The AUC for CCS and exercise testing were 0.90 (0.86–0.95) and 0.67 (0.57–0.77) for subjects with a low pretest probability of CAD , and 0.81 (0.68–0.94) and 0.88 (0.76–0.99) for subjects with a high pretest probability of CAD, respectively.

After exclusion of 59 patients with typical angina, ROC analysis showed an AUC of 0.93 (0.88–0.97) for CCS and 0.64 (0.51–0.78) for exercise testing (P<0.001). Additional analysis was performed in 277 patients, after exclusion of five patients with CCS ≥400 without CAG and 22 patients with myocardial perfusion imaging instead of exercise testing. The combined endpoint occurred in 21 (64%) of 33 patients with CCS≥400; in 11 (12%) of 93 patients with CCS 10–400, and in 0 (0%) of 151 patients with CCS<10. The combined endpoint occurred in eight (32%) of 25 patients with positive exercise test results, in 15 (20%) of 74 patients with nondiagnostic exercise test results, and in nine (5%) of 178 patients with negative exercise test results. ROC statistics show an AUC of 0.91 (0.86–0.95) for CCS and 0.72 (0.62–0.82) for exercise testing (P<0.001).
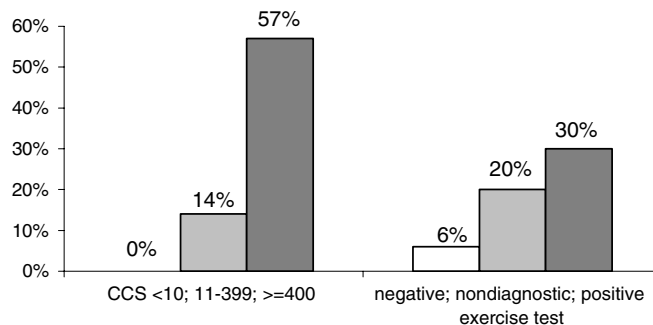

Fig. 2 Outcome according to CCS and exercise testing. The percentage of patients with the combined endpoint are shown per group
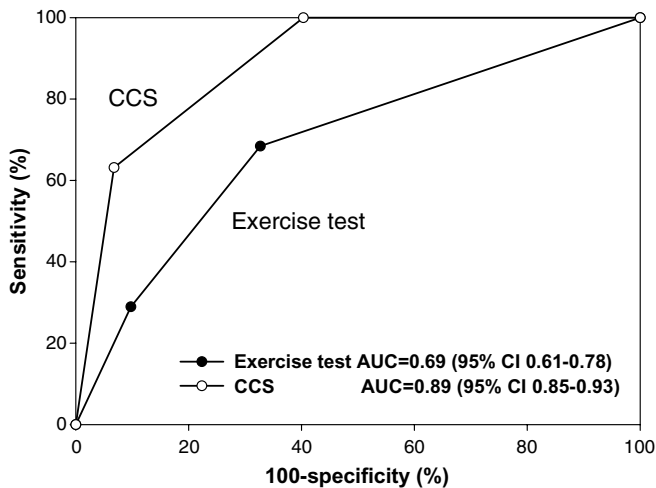
Fig. 3 ROC curves of CCS (<10, 10–399 and ≥400) and exercise testing (negative, nondiagnostic, positive) for the combined endpoint. The difference in AUCs of both tests show the incremental diagnostic yield of measurement of CCS when compared with exercise testing (*P*<0.0001)

Discussion

The results of this study confirm that measurement of CCS provides effective triage in a well-defined patient group with suspected but low risk of coronary artery disease. In addition, our results indicate that the diagnostic yield of CCS is superior to exercise testing. We included only low-risk patients, which was defined as the absence of prior evidence of CAD, an abnormal 12-lead ECG or elevated serum cardiac markers. The major clinical advantage of our strategy has been facilitation of safe discharge from the hospital in a majority (52%) of these patients, as defined by a low CCS derived from CT. The diagnostic efficacy of our strategy is further demonstrated by high rates of obstructive CAD (especially three-vessel and left main disease) and revascularization procedures in patients with a high CCS.

Measurement of CCS and exercise testing provide fundamentally different diagnostic information. The first test provides information on the amount of calcium in the coronary arteries, while the second test's purpose is to detect myocardial ischemia. Both an "anatomical" and "functional" approach as initial diagnostic tests in patients with suspected CAD may lead to effective risk stratification [1, 4]. The few studies on risk stratification based on CCS in low-risk patients with chest pain have shown promising results [6–8]. However, studies comparing CCS with exercise testing have not yet been performed in low-risk populations [18, 19]. The former approach at our institution was exercise testing. This was replaced by a protocol in which all patients underwent both exercise testing and CT, and decision making was based on CCS. The efficiency of the current protocol was confirmed by the following observations. First, during a mean follow-up of 12±4 months, no single hard event (myocardial infarction

or death) occurred. Second, a large majority (57%) of patients with CCS≥400 had obstructive CAD, and 21% had three-vessel or left main disease. In a majority of these patients a revascularization procedure was necessary according to the ESC and ACC/AHA guidelines for PCI and CABG [27–31]. In subjects with a CCS<10, no coronary events occurred during follow-up. This contrasts with the exercise test results, with 6% of patients with negative exercise test results having obstructive CAD. The high negative predictive value of a low CCS is in concert with many earlier studies [8, 11, 14].

Another major advantage of measurement of CCS may become the detection of minor degrees of CAD. In 34% and 25%, respectively, of our study population, an intermediate amount of coronary calcium and a nondiagnostic exercise test result was present. In patients with CCS 10–399, the presence of CAD has been confirmed and therefore the initiation of primary prevention measures such as life style modification, aspirin and/or statin treatment can be initiated. In contrast to intermediate CCS findings, when exercise testing provides nondiagnostic results, uncertainty with regard to the presence of CAD remains.

Some issues remain to be answered. Due to recent technical improvements CCS can now also be measured by multidetector computed tomography (MDCT) [32–40]. Differences between CCS measurements on EBCT and MDCT have been shown to be similar to the reported individual EBCT and MDCT interscan variabilities of around 20% [32, 35]. Exclusion of coronary calcium by MDCT is as feasible as by EBCT [41, 42]. Comparative studies in low-risk patients with suspected CAD at our department, and in large populations of asymptomatic subjects [32], are currently underway.

We propose to use measurement of CCS as gatekeeper for additional invasive and noninvasive testing [43]. Our protocol enabled us to differentiate between high (CCS>400) and low risk (<100) subjects. However, one-third of our study population had an intermediate CCS (10–399) and obstructive CAD was found in 14% of these subjects. Ideally, in this patient category, a test with high sensitivity for myocardial ischemia should guide the decision to perform CAG, in addition to pharmacologic treatment, as stated above. However, so far, the evidence for use of a clinical protocol in such patients is lacking. Exercise testing can not fulfill this task. Stress echocardiography, myocardial perfusion scintigraphy or stress cardiac magnetic resonance imaging may be better options [44]. Another option is MDCT coronary angiography, which may be clinically useful an may may obviate the need of CAG when luminal stenoses are ruled out [45]. The need for optimization of the current protocol was highlighted by the observation that of the 83 CAGs performed obstructive CAD was found in 38 (46%).

Finally, is CCS more accurate than MDCT coronary angiography? So far, the role of MDCT coronary angiog-

raphy in the evaluation of patients with suspected CAD has not become established. Compared with measurement of CCS, the advantage of MDCT coronary angiography lies in its information on luminal stenosis [45, 46]. This probably led to a higher number of patients that could be discharged in the evaluation of chest pain in case of negative results (68% with minimal or no stenoses [47] versus 52% with CCS<10 in the current study).

However, since very low CCS are associated with a high negative predictive value, performance of MDCT coronary angiography in such patients cannot be justified. We believe that CT coronary angiography may play a role in subjects with CCS>10. A recent study showed that, in a population scheduled for CAG, the diagnostic yield of MDCT coronary angiography was superior to exercise testing [48]. Further studies are needed to establish the role of MDCT coronary angiography in low risk subjects. In addition, cost-effectiveness should be taken in mind, since in patients with a high probability of CAD, direct CAG may be more cost-effective than a strategy with MDCT coronary angiography [49].

Remarks and limitations

We have chosen a follow-up study design. Our design was limited by the absence of a "gold standard" in every patient, since the procedure to determine the endpoints was influenced by the test results. The absolute numbers of obstructive CAD or clinical events according to exercise test results may therefore have been somewhat biased, since the screening protocol was based on CCS. Furthermore, in patients with low CCS CAG was not performed, thereby decreasing the likelihood of detecting CAD. Our follow-up design restricted the evaluation of cost-effectiveness, which is a limitation, since it was shown that CCS measurement may not be cost-effective [49]. Further studies should be performed to evaluate this issue. Obstructive CAD was measured by qualitative coronary analysis, which is less accurate when compared to quantitative coronary analysis. For this low risk population without previous CAD, symptoms by itself during exercise testing cannot be classified as a positive exercise test. Therefore, symptoms without ECG changes were classified as an intermediate test result. We did not report the intermediate and noninterpretable exercise test results separately, but presented these as one ("nondiagnostic") group, since both test outcomes do not provide diagnostic certainty and clinical outcome was similar.

Conclusion

In patients with suspected CAD, with a normal ECG and normal cardiac markers, a screening protocol based on coronary calcium scores provides effective triage.

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