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First-line evaluation of coronary artery disease with coronary calcium scanning or exercise electrocardiography

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ABSTRACT

Background: Although conventional (CAG) and computed tomography angiography (CTA) are reliable diagnostic modalities for exclusion of obstructive coronary artery disease (CAD), they are costly and with considerable exposure to radiation and contrast media. We compared the accuracy of coronary calcium scanning (CCS) and exercise electrocardiography (X-ECG) as less expensive and non-invasive means to rule out obstructive CAD.
Methods: In a rapid-access chest pain clinic, 791 consecutive patients with stable chest pain were planned to undergo X-ECG and dual-source CTA with CCS. According to the Duke pre-test probability of CAD patients were classified as low (<30%), intermediate (30–70%) or high risk (>70%). Angiographic obstructive CAD (>50% stenosis by CAG or CTA) was found in 210/791 (27%) patients, CAG overruling any CTA results.
Results: Obstructive CAD was found in 12/281 (4%) patients with no coronary calcium and in 73/319 (23%) with a normal X-ECG (p<0.001). No coronary calcium was associated with a substantially lower likelihood ratio compared to X-ECG; 0.11, 0.13 and 0.13 vs. 0.93, 0.55 and 0.46 in the low, intermediate and high risk group. In low risk patients a negative calcium score reduced the likelihood of obstructive CAD to less than 5%, removing the need for further diagnostic work-up. CCS could be performed in 754/756 (100%) patients, while X-ECG was diagnostic in 448/756 (59%) patients (p<0.001).
Conclusions: In real-world patients with stable chest pain CCS is a reliable initial test to rule out obstructive CAD and can be performed in virtually all patients.

1. Introduction

Angina pectoris is a common and disabling condition that affects millions of people worldwide. The diagnostic evaluation and subsequent management of patients suspected of coronary artery disease (CAD) is aimed at reducing complaints and improving prognosis. Although invasive coronary angiography (CAG) remains the gold standard for the diagnosis of obstructive CAD, coronary computed tomography (CTA) has emerged as a reliable non-invasive alternative, with an excellent accuracy for ruling out obstructive CAD [1–4]. However increasing concern about the costs, radiation exposure and contrast agents involved with either angiographic modalities justifies exploration of alternative approaches [5–8].

Exercise electrocardiography (X-ECG) is a widely available, well-established and cost-effective means to assess ischemic heart disease, despite its limited diagnostic accuracy and substantial rate of inconclusive test results [9]. Alternatively, coronary calcium scanning (CCS) is inexpensive, fast, operator-independent, associated with a much lower radiation exposure and without need for contrast media [10,11].

In this study we compared the ability of CCS and X-ECG as an initial test to rule out obstructive CAD in a large group of patients with stable angina from a rapid-access chest pain clinic. According to pre-test probabilities of obstructive CAD patients were assigned to low, intermediate and high risk groups.

2. Methods

2.1. Study population

From September 2006 to April 2010 we evaluated 791 consecutive patients with stable chest complaints and no history of CAD at our rapid-access chest pain clinic. Patients were planned to undergo both dual-source CTA and X-ECG, in addition to a clinical examination and blood analysis. Referral to CAG was clinically driven.

Using the Duke Clinical Score (DCS), based on the type of chest discomfort, age, gender and cardiovascular risk factors, patients were classified as having a low (<30%), intermediate (30–70%) or high (>70%) pre-test probability of obstructive CAD [12].

Chest pain was classified using the three categories by Diamond: typical angina pectoris, atypical angina pectoris and non-anginal chest pain [13].

Angiographic obstructive CAD was found in 210/791 (27%) patients, defined as the presence of >50% stenosis in ≥1 coronary branches by CAG or CTA (CAG overruling any

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CTA result). Obstructive CAD was absent in 546/791 (69%) patients, defined as none or <50% coronary stenosis by CAG (overruling any CTA result) or CTA.

In total 27/791 (3%) patients, without sufficient cause for invasive angiography, did not undergo CTA, because of renal failure, contrast allergy, patient preference, Parkinson disease, patient willingness to cooperate, failed venous access and severe obesity. Because of premature scan initiation or movement during scan 8 (1%) scans were considered non-diagnostic.

The mean age in the study population was 56 ± 10 years, with significantly more elderly patients in higher risk groups. Males were at higher risk for obstructive CAD, although overall the gender was evenly divided (369/756 = 49% female) (Table 1).

There were fewer smokers, diabetics and patients with dyslipidemia in the low risk group. There were more patients with hypertension and a history of vascular disease in the high risk group.

The study complied with the Declaration of Helsinki and the ethical committee at our institution approved the study. Informed consent was obtained from all patients.

2.2. Non-enhanced coronary calcium scan

The calcium scan was performed using an ECG-triggered sequential scan mode, with 120-kV tube voltage, 78 ± 26-mAs tube current and 3-mm slice thickness. Quantification was performed by the Agatston method with a standard 130-HU attenuation threshold. The absence of detectable calcium was considered as a negative CCS result. Patients with detectable coronary calcium were divided in two groups: moderate (1–400) and severe (>400 Agatston units) [14,15].

2.3. Contrast-enhanced CT angiography

Computed tomography angiography was performed in the absence of the following contraindications: pregnancy, renal dysfunction or known allergy to iodine contrast media.

Image acquisition was conducted using a dual-source CT: Siemens Definition (Forchheim, Germany) from September 2006 to April 2009 and Siemens Flash from April 2009 to April 2010. Technical details regarding image acquisition are summarized in Table 2. Before the scan patients received a sublingual dose of nitro-glycerine but no additional beta-blockers.

Effective radiation doses for CCS and CTA were 0.8 ± 0.2 mSv (range 0.4 to 1.6) and 8.5 ± 3.4 mSv (range 0.5 to 17.8).

Readers were blinded for patients' symptoms or exercise test results. Data was sent to an offline workstation for image analysis. All coronary segments were evaluated on axial images, multiplanar reformations, and maximum intensity projections according to readers' preferences. In a joint session, two readers evaluated the coronary anatomy, and vessels were qualitatively scored as normal, not significantly stenosed (<50% stenosis) or significantly stenosed (>50% stenosis).

2.4. Exercise electrocardiography

Bicycle X-ECG was performed by standardized protocol, with established criteria for performance and exercise discontinuation. Criteria for myocardial ischemia included horizontal or down sloping ST-segment depression or elevation ≥0.1 mV during or after exercise or typical, increasing angina during exercise. In case of established contra-indications patients did not perform an X-ECG [16]. A non-diagnostic result was defined by discontinuation without evidence of myocardial ischemia before reaching 85% of the target heart rate.

Table 2
Scan parameters.

	64-slice DSCT[a]	128-slice DSCT[b]
Patients (n)	527	234
Conventional spiral mode (n)	527	35
Sequential mode (n)	0	169
High pitch spiral mode (n)	0	30
Collimation (mm)[c]	64(32 × 2)	128(64 × 2)
Gantry rotation time (ms)	0.33	0.28
Effective temporal resolution (ms)[d]	83	75
Pitch (conventional spiral mode)	0.2–0.53	0.2–3
Tube voltage (kV)	120	100–120
Tube current (ma)[e]	370–412	320–412

Scan parameters of patients undergone CTA (761/791) using dual source computed tomography (DSCT): Siemens Definition[a] and Flash[b], Forchheim, Germany; [c]by alternating focal spot (Z-sharp®), [d]using a single-segmental reconstruction algorithm, [e]depending on patient size.

2.5. Coronary angiography

Clinically indicated quantitative coronary angiography (QCA) was performed using standard techniques, with assessment of the most severe obstruction from ≥2 orthogonal projections using quantitative software (CAAS, Pie Medical, Maastricht, The Netherlands).

2.6. Statistical analysis

Statistical analyses were performed using SPSS software (version 15.0, SPSS Inc, Chicago, Ill). Categorical variables are presented as proportions. Continuous variables are expressed as mean (± SD) or median (± IQR) as appropriate. All probability values refer to 2-tailed tests of significance; a probability value < 0.05 was considered significant. Differences between groups were compared using 2-sided unpaired *t* test, chi-square test, or analysis of variance, as appropriate. Diagnostic performance parameters in terms of sensitivity and specificity were calculated with 95% confidence intervals. Post-test probabilities were calculated for low, intermediate and high risk patients using likelihood ratios.

Because of the known high number of not performed or inconclusive tests, we also analyzed X-ECG results using an intention-to-diagnose approach, considering inconclusive tests as positive tests.

Additionally, we hypothesized that a calcium threshold slightly above the conventional zero calcium would reduce the false positive results without significant sacrifice on the negative predictive value. A ROC analysis was performed to find calcium scores optimally discriminating angiographic obstructive CAD in our study population.

Table 1
Baseline characteristics.

	Overall (n = 756)	Low[a] (n = 284)	Intermediate[a] (n = 270)	High[a] (n = 202)	P value[b]
Age (years)	56 ± 10	52 ± 9	56 ± 9	62 ± 9	<0.001
Women	369 (49%)	220 (78%)	122 (45%)	27 (13%)	<0.001
Nicotine abuse	198 (26%)	49 (17%)	91 (34%)	58 (29%)	<0.001
Hypertension	404 (53%)	141 (50%)	139 (52%)	124 (61%)	0.04
Diabetes mellitus	129 (17%)	27 (10%)	49 (18%)	53 (26%)	<0.001
Dyslipidemia	451 (60%)	125 (44%)	187 (69%)	139 (69%)	<0.001
Family history of cardiovascular disease	357 (47%)	146 (51%)	138 (51%)	73 (36%)	0.001
History of vascular disease	83 (11%)	22 (8%)	27 (10%)	34 (17%)	0.04
Body-mass index	28 ± 5	28 ± 5	27 ± 5	28 ± 5	0.63
CCS performed	754 (100%)	284 (100%)	268 (99%)	202 (100%)	0.25
CTA performed	753 (100%)	284 (100%)	268 (99%)	201 (100%)	0.39
X-ECG performed	675 (89%)	259 (91%)	241 (89%)	175 (87%)	0.22
Inconclusive X-ECG	227 (30%)	72 (25%)	90 (33%)	65 (32%)	0.06
Catheter angiography	180 (24%)	24 (9%)	69 (26%)	87 (43%)	<0.001
Revascularisation	112 (15%)	11 (4%)	32 (12%)	69 (34%)	<0.001
PCI	87 (12%)	10 (4%)	26 (10%)	51 (25%)	<0.001
CABG	25 (3%)	1 (<1%)	6 (2%)	18 (9%)	<0.001

CCS = coronary calcium scanning, CTA = computed tomography angiography, X-ECG = exercise electrocardiography, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft surgery.

[a] Duke clinical score: pre-test probability of significant CAD. Low: ≤30%; intermediate: 30–70%; high: >70%.

[b] ANOVA or nonparametric test.

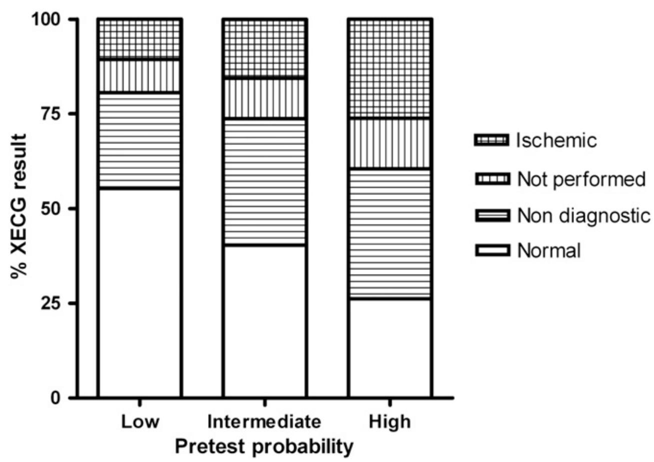

Fig. 1. Distribution of groups with no detectable calcium, intermediate calcium scores and high calcium scores considering pre-test probability of CAD.

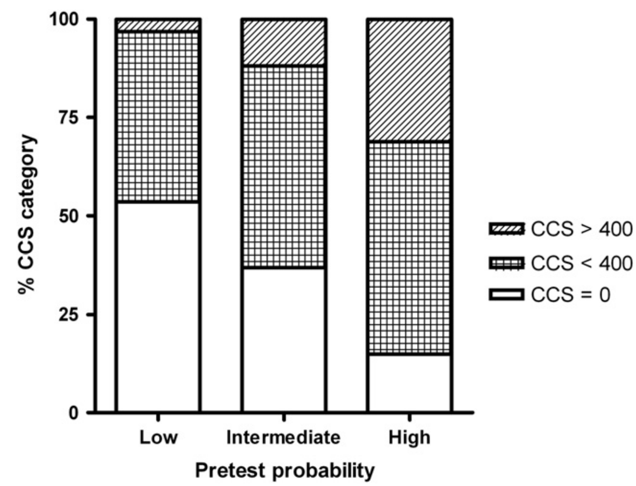

Fig. 3. Distribution of exercise electrocardiography results considering pre-test probability of CAD.

3. Results

3.1. Coronary calcium scanning

In two patients CCS was not performed because of patient preference or severe obesity. There was no detectable coronary calcium in 281/756 (37%) patients, 152 (54%) in the low, 99 (37%) in the intermediate and 30 (15%) in the high risk group (Fig. 1). Angiographic obstructive CAD was found in 10/281 (4%) patients with no calcium, 2/152 (1%) with low risk, 4/99 (4%) with intermediate risk and 4/30 (13%) with high risk. In comparison, these patients did not differ in age (55 vs. 56 years, $p = 0.67$), gender (30 vs. 49%, $p = 0.21$), smoking (30 vs. 26% $p = 0.75$), hypertension (50 vs. 54% $p = 0.82$), dyslipidemia (60 vs. 59% $p = 0.94$), family history (60 vs. 47% $p = 0.41$) or BMI (27 vs. 28 $p = 0.66$). However, none had a prior history of vascular disease or diabetes mellitus.

A ROC analysis with consideration for pre-test probability of CAD revealed calcium thresholds of 2, 2.5 and 15 Agatston units in low, intermediate and high risk group, respectively, to optimally differentiate patients with or without obstructive CAD (Fig. 2).

3.2. Exercise electrocardiography

In 81 (11%) patients X-ECG could not be performed because of inability to cycle, resting ECG abnormalities, pulmonary disease and combined or unspecified reasons. In 227 (30%) patients X-ECG did not yield a diagnostic result, mostly because the target heart rate was not reached. A normal X-ECG was found in 319/756 (42%) patients, 157 (49%) in the low, 109 (34%) in the intermediate and 53 (17%) in the high risk group (Fig. 3). A normal X-ECG was found in 55/319 (17%) patients with angiographic obstructive CAD, 15/157 (10%) with low risk, 17/109 (16%) with intermediate risk and 23/53 (43%) with high risk.

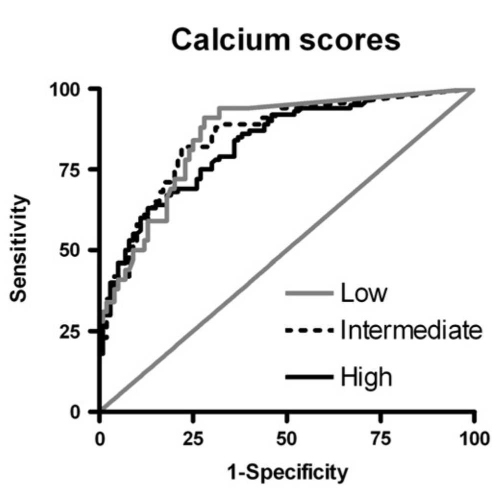

Fig. 2. ROC-curve of coronary calcium scores predicting obstructive coronary disease considering pre-test probabilities.

3.3. Coronary angiography

Invasive coronary angiography was performed in 180 patients (24%), with subsequent need for coronary revascularisation in 112 (15%) patients: 87 (12%) percutaneous coronary intervention, 25 (3%) coronary bypass surgery.

Table 3
Operating characteristics.

	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR− (95% CI)
Overall				
CCS (>0)	95 (91–98)	50 (45–54)	1.9 (1.7–2.1)	0.1 (0.05–0.2)
Optimal CCS	94 (89–96)	58 (54–63)	2.3 (2.0–2.5)	0.1 (0.06–0.2)
X-ECG	56 (47–65)	82 (77–86)	3.1 (2.4–4.1)	0.5 (0.4–0.7)
X-ECG-itd	70 (63–76)	54 (49–58)	1.5 (1.3–1.7)	0.6 (0.5–0.7)
Low				
CCS (>0)	94 (78–99)	60 (53–66)	2.3 (1.9–2.8)	0.1 (0.03–0.4)
Optimal CCS	94 (78–99)	68 (62–74)	2.9 (2.4–3.6)	0.1 (0.02–0.3)
X-ECG	21 (7–46)	85 (78–89)	1.4 (0.5–3.5)	0.9 (0.7–1.2)
X-ECG-itd	44 (26–64)	61 (55–67)	1.1 (0.7–1.8)	0.9 (0.6–1.3)
Intermediate				
CCS (>0)	94 (84–98)	47 (40–54)	1.8 (1.5–2.0)	0.1 (0.05–0.3)
Optimal CCS	94 (84–98)	52 (45–59)	2.0 (1.7–2.3)	0.1 (0.02–0.3)
X-ECG	55 (38–71)	81 (73–88)	3.0 (1.8–4.8)	0.5 (0.4–0.8)
X-ECG-itd	73 (60–83)	51 (44–59)	1.5 (1.2–1.9)	0.5 (0.4–0.8)
High				
CCS (>0)	96 (90–99)	29 (20–39)	1.3 (1.2–1.5)	0.1 (0.05–0.3)
Optimal CCS	94 (87–97)	46 (36–57)	1.7 (1.4–2.1)	0.1 (0.06–0.3)
X-ECG	67 (54–77)	73 (57–85)	2.5 (1.5–4.2)	0.5 (0.3–0.6)
X-ECG-itd	76 (65–84)	37 (27–49)	1.2 (1.0–1.5)	0.7 (0.4–1.0)

CCS = coronary calcium scanning, Optimal CCS = ROC-based calcium thresholds, X-ECG = exercise electrocardiography, X-ECG-itd = exercise electrocardiography with an intention-to-diagnose approach, LR+ = positive likelihood ratio, LR− = negative likelihood ratio.

3.4. Comparison of diagnostic performance

Overall CCS showed significantly higher negative predictive value compared to X-ECG, 96% (95% CI 93–98) vs. 83% (95% CI 78–87), regardless of pre-test probability of disease. In patients with low and intermediate risk we found excellent negative predictive values of 99% (95–100) and 96% (89–99), respectively (Table 3). No detectable calcium was associated with a likelihood ratio of 0.11 (0.03–0.4), 0.13 (0.05–0.3) and 0.13 (0.05–0.3) in the low, intermediate and high risk group. A normal XECG was associated with a likelihood ratio of 0.93 (0.7–1.2), 0.55 (0.4–0.8) and 0.46 (0.3–0.6) in the low, intermediate and high risk group, respectively.

By increasing the calcium threshold to 2, 2.5 and 15 Agatston units, respectively, based on the previous ROC analysis, the specificity of CCS increased from 60% (53–66), 47% (40–54) and 29% (20–39) to 68% (62–74), 52% (45–59) and 46% (36–57) in the low, intermediate and high risk group, respectively (Table 3). Excluding non-diagnostic results, X-ECG was significantly more specific: overall 82% (77–86) vs.

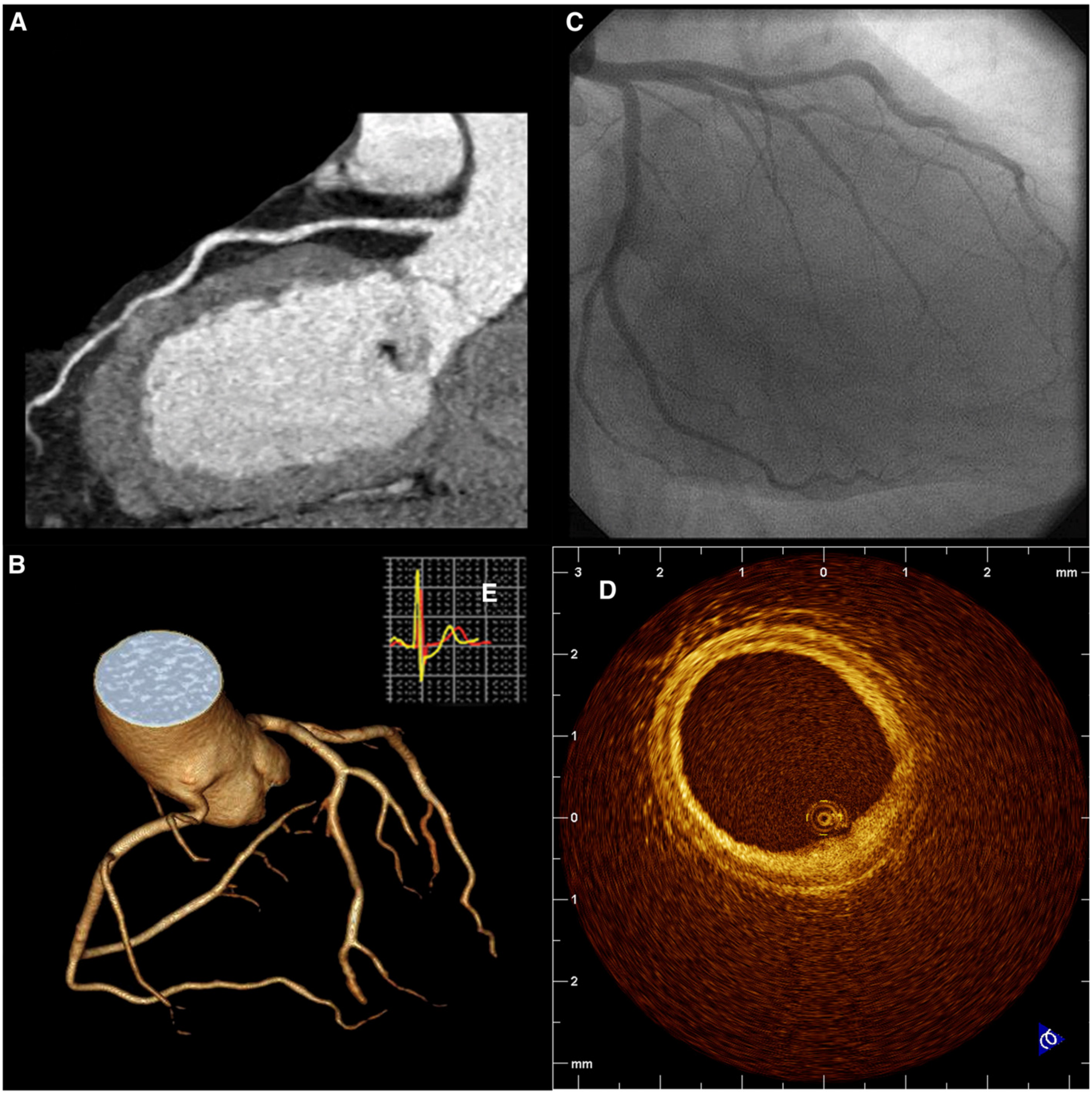

Fig. 4. 52 year old female with typical angina pectoris, positive family history and recent cessation of smoking. A, B: There was no detectable calcium on the non-enhanced CT-scan. CTA curved MPR and volume rendering show a non-obstructive, non calcified plaque in the mid left anterior descending (LAD) coronary artery. C: CAG revealed no significant obstructions. D: Optical Coherence Tomography (OCT) (Lightlab Imagewire®, Lightlab Imaging, Westford, MA, USA) confirmed the presence of a non-obstructive, non calcified plaque in the LAD. The eccentric intimal thickening is visible from 12–6 o'clock. The 3-layered appearance of the vessel is well visible: the inner endoluminal yellow, bright layer corresponds with the intima, the dark middle layer corresponds with the media and the outer, bright layer corresponds with the adventitia. E: X-ECG was borderline positive with slight ST-deviation of ± 1 mm in V4-V6.

50% (45–54), regardless of pre-test probabilities. However, using an intention-to diagnose approach, assuming non-diagnostic tests to be positive, the specificity decreased to a value comparable to CCS.

4. Discussion

From our results we concluded that the absence of calcium rules out angiographic obstructive CAD reliably in real-world patients, particularly in those with low to intermediate risk of CAD, outperforming X-ECG in this setting. No calcium was found in 281/756 (37%) patients and 319/756 (42%) patients had a normal X-ECG result. Patients without detectable calcium were substantially less likely to have obstructive CAD (Fig. 4) in comparison to a normal X-ECG result: 10 (4%) vs. 55 (17%) ($p<0.001$).

5. Clinical implications

Recently a large US registry reported on the low yield of obstructive coronary artery disease by invasive coronary angiography, recommending a more effective non-invasive diagnostic workup [17]. While CCS has been used for exclusion of CAD in asymptomatic and symptomatic individuals for the past decade [15,18], its capacity to rule out obstructive CAD was recently questioned in a paper assessing patients referred for invasive catheterisation [19]. According to the Bayes' theorem test performance is influenced by the pre-test probability of the population. Patients selectively referred for catheterization generally have a higher likelihood of obstructive CAD compared to our outpatient cohort presenting with stable chest pain. Our results demonstrate that the negative predictive value of the calcium scan is excellent in subgroups with low disease prevalence. In line with the observations by Gottlieb et al., the rate of patients with obstructive CAD and no detectable calcium gradually increases concomitantly with their pre-test probability.

In low risk patients (0–30%) a negative calcium score reduced the likelihood of obstructive CAD <5% (Fig. 5), removing the need for further diagnostic work-up in a substantial proportion of patients (19%). For intermediate risk patients (30–70%) the likelihood decreased to 5–25%, reducing the need for further testing, particularly in those with a post-test probability of <10%. In high risk patients (>70%) neither CCS nor X-ECG excluded angiographic obstructive CAD, although a negative X-ECG may be more helpful to exclude hemodynamically relevant lesions and guide patient management.

Furthermore, we found that a cut-off value above the conventional zero calcium score reduced false positive results without sacrifice on the high negative predictive value in patients with a low to intermediate probability.

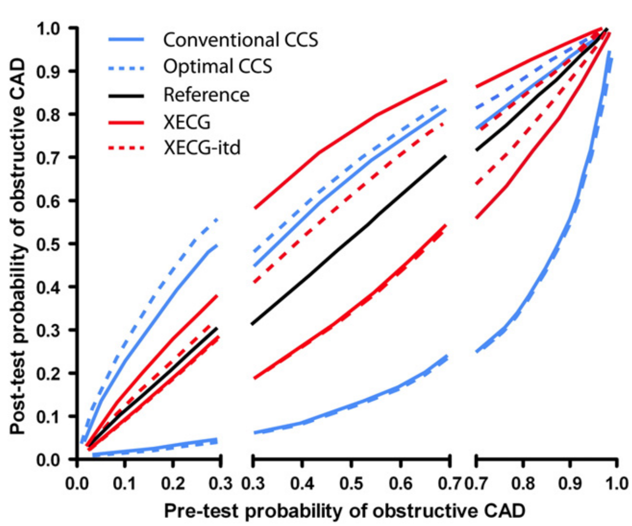

Fig. 5. Post test probability of obstructive coronary artery disease (CAD) considering pre-test probability. Conventional CCS = coronary calcium scanning regarding zero calcium as negative result, exercise electrocardiography, optimal CCS = coronary calcium scanning with ROC analysis based thresholds, XECG = exercise electrocardiography, XECG-itd = exercise electrocardiography with an intention-to-diagnose approach.

6. Limitations

Because not all patients had a clinical indication for invasive angiography, a composite diagnostic endpoint including CT angiography was used. Given the well established diagnostic accuracy of CTA, especially its negative predictive value, performing invasive CAG in every patients would be unethical [20]. However, limiting the study to patients with QCA would have resulted in loss of the real-world character of this study. In this study we focused on reliability of CCS or X-ECG to rule out CAD. We believe that using a composite endpoint of CTA next to invasive angiography does not jeopardize our conclusions. Nevertheless to anticipate overestimation of CTA we performed a sensitivity analysis using a composite diagnostic endpoint of >50% coronary stenosis by CAG (overruling any CTA result) and >50% left main or three-vessel disease or >70% one or two-vessel stenosis by CTA. By excluding patients with intermediate coronary stenosis on one or two vessels, we obtained no significantly different diagnostic performances of CCS and X-ECG.

There was no comparison of CCS to more advanced functional imaging tests, nor was the hemodynamic significance of the coronary lesions routinely determined. Assessment of myocardial ischemia has prognostic consequences and is important for clinical decision making. The incremental value of stress testing applies mostly to those with angiographic coronary disease, and less to patients in whom CAD has been excluded (by CTA or QCA), which involves the majority of patients presenting in a chest pain clinic. Recent work from Esteves et al. demonstrated that the absence of coronary calcium also excludes ischemia on functional testing [21]. In addition, patients with no detectable calcium show slow progression of CAD over time [22].

Nevertheless, clinical outcome studies are needed to evaluate the value of CCS as a tool for exclusion of obstructive CAD, in comparison to functional tests.

7. Conclusions

Coronary calcium scanning is a reliable initial test in real-world patients with stable chest pain to rule out obstructive CAD and it can be performed in virtually all patients. In low risk patients without detectable coronary calcium further diagnostic work-up seems redundant as the post-test probability of obstructive CAD is less than 5% for these patients. In the group of patient with intermediate risk of obstructive CAD the likelihood decreased to 5–25% after a negative CCS, reducing the need for further testing, particularly in those with a post-test probability of <10%. High risk patients do not seem to benefit from neither CCS nor X-ECG to exclude angiographic obstructive CAD, although a normal X-ECG may be more helpful to exclude hemodynamically relevant lesions and guide management.

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