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Prevalence and predictors of coronary artery disease in patients with a calcium score of zero

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Abstract The absence of coronary calcification is associated with an excellent prognosis. However, a calcium score of zero does not exclude the presence of coronary artery disease (CAD) or the possibility of future cardiovascular events. Our aim was to study the prevalence and predictors of coronary artery disease in patients with a calcium score of zero. Prospective registry consisted of 3,012 consecutive patients that underwent cardiac CT (dual source CT). Stable patients referred for evaluation of possible CAD that had a calcium score of zero (n = 864) were selected for this analysis. The variables that were statistically significant were included in a multivariable logistic regression model. From 864 patients with a calcium score of zero, 107 (12.4 %) had coronary plaques on the contrast CT (10.8 %, n = 93 with nonobstructive CAD and 1.6 %, n = 14 with obstructive CAD). By logistic regression analysis, the independent predictors of CAD in this population were age >55 years [odds ratio (OR) 1.63 (1.05–2.52)], hypertension [OR 1.64 (1.05–2.56)] and dyslipidemia [OR 1.54 (1.00–2.36)]. In the presence of these 3 variables, the probability of having coronary plaques was 21 %. The absence of coronary artery calcification does not exclude the presence of coronary artery disease, but the prevalence of obstructive disease is very low. In this population, the independent predictors of CAD in the setting of a calcium score of zero were hypertension, dyslipidemia, and age above 55 years. In the presence of these 3 predictors, the probability of having CAD was almost 2 times higher than in the general population.

Keywords Zero calcium score · Coronary artery disease · Noncalcified plaque

Introduction

Coronary artery disease (CAD) is a major cause of death in developed countries and it is expected to remain the most important disease in the upcoming years [1].

Quantification of coronary artery calcium [calcium scoring (CaSc)] can provide a measure of the atherosclerotic plaque burden, since coronary arterial calcification occurs almost exclusively in atherosclerotic plaques [2, 3]. Also, it has been demonstrated in many large clinical trials, that CaSc is a strong predictor of cardiovascular events [4–7].

On the other hand, the absence of calcium in the coronary arteries, although it does not rule out atherosclerotic disease, is consistent with an excellent long-term prognosis [8] and has a high sensitivity and negative predictive value for excluding obstructive CAD. This fact prompted some recent guidelines to suggest that a calcium score of zero might exclude the need for coronary angiography in symptomatic patients [9]. Nevertheless, in previous studies, a high variation was reported in the incidence of obstructive CAD in patients with a CaSc of zero, ranging from 2 to 32 % [10–15]. For instance, in the recent CONFIRM registry, it was shown that in patients with a CaSc of zero, obstructive CAD is

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possible and is associated with increased cardiovascular events [16]. The aim of this study was to assess the prevalence and predictors of coronary artery disease in a population of stable patients referred for evaluation of possible CAD who had a calcium score of zero.

Methods

Study design and patient population

Single center prospective registry including 3,012 consecutive patients undergoing dual source coronary CT angiography (CCTA) from February 2007 to March 2012. For this analysis, 864 stable patients (with symptoms and/or positive or inconclusive stress tests) referred for evaluation of possible CAD that had a calcium score of zero were included.

Exclusion criteria included: (1) preoperative CAD assessment prior to noncoronary valvular or aortic surgery (n = 51); (2) evaluation of possible CAD in cardiomyopathies (dilated cardiomyopathy or hypertrophic cardiomyopathy) (n = 162); (3) cardiac CT for atrial fibrillation ablation (n = 330); (4) previous myocardial infarction and/or revascularization procedures (n = 257); (5) suspected ACS (n = 70); (6) other indications (n = 102). Patients with atrial fibrillation or other significant arrhythmias during scan acquisition or artifacts that significantly compromised image quality were also excluded, as every patient with a CaSc >0 (Fig. 1).

The study was approved by the local ethics committee and all patients gave a written informed consent.

A detailed medical history with a questionnaire investigating risk factors was obtained from the patients to assess for the presence of: (1) Diabetes mellitus (defined as a fasting glucose level of ≥ 126 mg/dl or the need for insulin or oral hypoglycemic agents) [17]; (2) Dyslipidemia (defined as a total cholesterol level ≥ 200 mg/dl or treatment with lipid-lowering drugs) [18]; (3) Hypertension (defined as blood pressure $\geq 140/90$ mmHg or the use of antihypertensive medication) [19]; (4) Obesity (body mass index ≥ 30 kg/m^2); (5) positive family history of premature CAD (defined as the presence of CAD in first-degree relatives younger than 55 (male) or 65 (female) years of age) [20]; (6) smoking (defined as previous (less <1 year) or current smoker).

Pre-test probability of CAD was determined using both the modified Diamond and Forrester [21] and the Morise score [22]. The cardiovascular risk was assessed with the Heart Score [23]. In the modified Diamond–Forrester, patients were classified into very low (<5 %), low (<10 %), intermediate (10–90 %) and high probability (>90 %). For the Morise score, patients were classified into low (scores 0–8), intermediate (scores 9–15) and high probability (scores ≥ 16). For the Heart Score, the cut-off of ≥ 5 % (high-risk) was used.

Fig. 1 Patient selection and study design
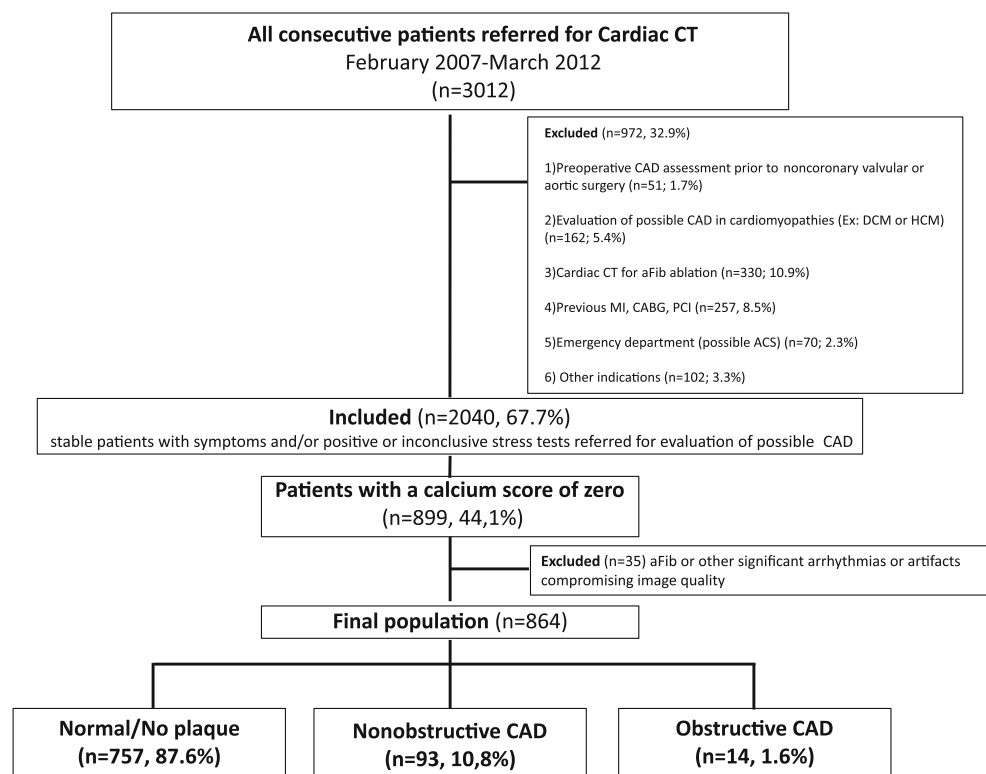
Scan protocol and image reconstruction

All scans were performed with the first generation of dual-source scanner (Somatom Definition, Siemens Medical, Germany), with the patient in dorsal decubitus and in deep inspiration breath-hold.

The calcium score acquisition consisted of step and shoot—prospective ECG triggering at 70 % of the R–R interval if the heart rate was below 80 beats per min (bpm) or at 40 % of the R–R interval if the heart rate was higher. From the topogram, a cranio-caudal scan was obtained from the carina to the plane just below the heart *silhouette*, with 120 kV and 128 mAs/rot tube current, with CARE-Dose 4D mAs modulation. The value of the calcium score was obtained with the analysis of consecutive non-contrast 3 mm slices, with a reconstruction b35f Kernel and a small (cardiac) FOV, with a dedicated software (CaSc–Siemens), where every area at least with 3 mm^2 within a coronary vessel with a density above 130 HU (Hounsfield Units) was selected.

For CCTA, sublingual nitroglycerin was administered to all patients, except when contraindicated, and intravenous metoprolol (5 mg, with a titration dose up to 20 mg) was administered in patients with heart rate >70 bpm.

During the scan acquisition, a bolus of iodinated contrast was injected at a 6 ml/s infusion rate, followed by a 50-ml saline flush. The dose of contrast was calculated according to the following formula: (acquisition time + 6 s delay) × flow (6 ml/s). A ROI was defined in the ascending aorta for the bolus trigger technique, set at 120 HU.

Dose reduction strategies—including electrocardiogram-gated tube current modulation, reduced tube voltage, and prospective axial triggering—were used whenever feasible.

Mean estimated radiation dose was 0.8 ± 0.5 mSv for CaSc and 4.6 ± 3.8 mSv for CT scan. Mean contrast dose was 96.2 ± 13.6 ml and heart rate was 67.8 ± 12.9 bpm.

Transaxial images were reconstructed with a temporal resolution of 83 ms and slice thickness of 0.75 mm with 0.4 mm increments. Post-processing was carried out using Circulation® software, with multiplanar reconstructions, maximum intensity projection and volume rendering technique. All scans were analysed independently in the same session by both a cardiologist and a radiologist with level III equivalent experience by the Society of Cardiovascular Computed Tomography. In case of disagreement, a joint reading was performed and a consensus decision was reached.

In each coronary artery segment, coronary atherosclerosis was defined as tissue structures >1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself [24]. Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. Percent obstruction of coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque. Obstructive CAD was defined by presence of at least one plaque with ≥50 % stenosis.

Statistical analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation. Categorical variables were expressed as percentages and their frequencies were compared with the Chi square test.

Binary logistic regression models were built to elucidate independent predictors of CAD without coronary calcification.

The objective of this model was the assessment of clinical variables that aid to predict the presence of CAD in patients with a calcium score of zero. All the demographic, risk factors and clinical variables present in Table 2 that had a p <0.1 in univariate analysis were included in a multivariate logistic regression model (Enter method).

Statistical analysis was performed with SPSS 17.0 software for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline and procedural characteristics

In the final study population of 864 patients, most of the patients were female (55 %) and mean age was 53.8 ± 11.0 years. The prevalence of traditional risk factors was low, with only 9.0 % of patients with diabetes. This was predominantly a low risk population with few high risk patients (only 9.0 % with the Morise score and 3.1 % with the modified Diamond–Forrester had a high CAD probability). Likewise, most of the patients were not considered as high cardiovascular risk, as assessed by the Heart Score (only 11.9 % had a Heart Score ≥5 %)—Table 1.

Coronary plaques were detected on CCTA in 107 patients (12.4 %): 10.8 % (n = 93) with nonobstructive CAD and 1.6 % (n = 14) with obstructive CAD—Fig. 2. Considering the degree of stenosis of the obstructive CAD group, 64 % (n = 9) had a 50–70 % stenosis and 36 % (n = 5) a >70 % stenosis. Considering the extent of disease, all these patients had obstructive CAD in only 1 vessel and 93 % had a single lesion. Regarding the distribution, most of the obstructive CAD lesions were found in proximal or mid segment locations (87 %), and the most affected artery was the right coronary artery 50 % (n = 7).

**Table 1** Demographic, clinical and CCTA characteristics of the study population

	All patients (n = 864)
Demographic	
Age	53.8 ± 11.0
Male sex	389 (45.0)
Risk factors	
Obesity (BMI ≥ 30)	160 (18.5)
Diabetes	78 (9.0)
Hypertension	459 (53.1)
Dyslipidemia	454 (52.5)
Smoking	206 (23.8)
Family history of premature CAD	284 (32.9)
Chest pain	
Asymptomatic	441 (51.0)
Noncardiac	194 (22.5)
Atypical	182 (21.1)
Typical	47 (5.4)
CAD probability—Morise	
Score ≥16	78 (9.0)
Score 9–15	446 (51.6)
Score 0–8	340 (39.4)
CAD probability—modified Diamond Forrester	
Very low	188 (21.8)
Low	391 (45.3)
Intermediate	257 (29.7)
High	27 (3.1)
CV risk	
Heart Score ≥5 %	103 (11.9)
CCTA	
Normal/no plaque	757 (87.6)
Non obstructive CAD	93 (10.8)
Obstructive CAD	14 (1.6)
Technical data	
Heart rate (bpm)	67.8 ± 12.9
Contrast dose (ml)	96.2 ± 13.6
Radiation dose—CTA (mSv)	4.6 ± 3.8
Radiation dose—CaSc (mSv)	0.8 ± 0.5

Values are mean ± SD or n (%)

BMI body mass index, *CAD* coronary artery disease, *CV* cardiovascular, *CCTA* coronary computed tomography angiography, *bpm* beats per minute, *mSv* milisievert

Left anterior descendent was affected in 5 patients, while left main was affected in one patient and the circumflex artery in other patient.

There were no significant differences in the prevalence of CAD in patients referred for CCTA because of positive/inconclusive stress tests (93/722 = 12.9 %) versus patients referred without previous stress tests (14/142 = 9.9 %), p = 0.403.

Prevalence of CAD

87,6%
12,4%
10,8%
1,6%

■ No CAD
■ Non Obstructive CAD
■ Obstructive CAD
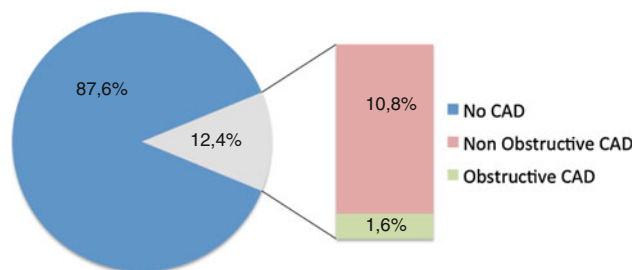
Fig. 2 Distribution of CT angiographic findings

Table 2 Prevalence of CAD according to the pretest probability (Morise)

Pretest probability	Nonobstructive CAD	Obstructive CAD
Low (n = 340)	27 (7.9 %)	6 (1.8 %)
Intermediate (n = 446)	64 (14.3 %)	6 (1.3 %)
High (n = 78)	16 (20.5 %)	2 (2.6 %)
p	0.002	0.708

We further analyzed the distribution of CAD in the different pretest probability subgroups. Using those defined by Morise, the prevalence of CAD (any plaque) was 7.9, 14.3 and 20.5 % in low, intermediate and high pretest probability patients, respectively. Regarding obstructive CAD, a higher prevalence was also found in patients with high pretest probability, but this increase was not statistically significant (Table 2).

Univariate analysis

Patients with CAD were older (prevalence of age ≥55 years 64 vs. 47 %, p = 0.001) than patients without CAD and had a higher prevalence of dyslipidemia (65 vs. 51 %, p = 0.010) and hypertension (67 vs. 51 %, p = 0.002).

The pre-test CAD probability assessed both by the Morise score and the modified Diamond–Forrester was higher in the CAD group and these patients had a 2–4 times higher probability of being of a high CAD probability group. Cardiovascular risk, estimated by the Heart Score, was also significantly higher in patients with CAD. Although there was a trend in this group towards a higher prevalence of diabetes and male gender, these differences were not statistically significant—Table 3.

Multivariate analysis

By multivariate analysis, the independent predictors of CAD in patients with a calcium score of zero were age ≥55 (OR 1.631, 95 % CI 1.054–2.524, p = 0.028), hypertension (OR

Table 3 Univariate analysis

	No CAD (n = 757)	CAD (n = 107)	p
Demographic			
Age ≥55 years	355 (47.0)	68 (63.6)	**0.001**
Male gender	335 (44.3)	54 (50.5)	0.254
Risk factors			
Diabetes	64 (8.5)	14 (13.1)	0.147
Obesity (BMI ≥ 30)	139 (18.4)	21 (19.6)	0.790
Hypertension	387 (51.1)	72 (67.3)	**0.002**
Dyslipidemia	385 (50.9)	69 (64.5)	**0.010**
Smoking	184 (24.3)	22 (20.6)	0.467
Family history of premature CAD	248 (32.8)	36 (33.6)	0.913
Symptoms			
Chest pain	371 (49.0)	52 (48.6)	1.000
CAD probability—Morise			
Score ≥16	62 (8.2)	16 (15.0)	**0.002**
Score 9–15	382 (50.5)	64 (59.8)	
Score 0–8	313 (41.3)	27 (25.2)	
CAD probability—modified Diamond Forrester			
Very low	171 (22.6 %)	17 (15.9)	**0.005**
Low	342 (45.2)	49 (45.8)	
Intermediate	225 (29.8)	32 (29.9)	
High	18 (2.4)	9 (8.4)	
CV risk			
Heart Score ≥5	79 (10.4)	24 (22.4)	**0.001**

Values are mean ± SD or n (%)

*CAD* coronary artery disease, *BMI* body mass index, *CV* cardiovascular

Bold indicates *p* value with statistical significance

Fig. 3 Independent predictors of CAD in patients with a CaSc of zero

1.641, 95 % CI 1.051–2.560, *p* = 0.029) and dyslipidemia (OR 1.538, 95 % CI 1.002–2.361, *p* = 0.049) (Fig. 3). In the presence of these 3 variables (n = 176 patients, 20.4 % of the population), the probability of having coronary plaques was 21 % (vs. 12.4 % in the total studied population). We also analyzed the prevalence of CAD according to the presence of none, one, two or three of these risk factors. The results are shown in Table 4.

Discussion

In this single center cohort of stable patients without known CAD, referred for cardiac CT angiography, we found a very low prevalence of obstructive CAD (1.6 %) in the subset with a CaSc of zero. When considering the degree of stenosis, only 0.6 % had a stenosis >70 %.

The prevalence and clinical significance of obstructive CAD on coronary CT angiography among patients with a
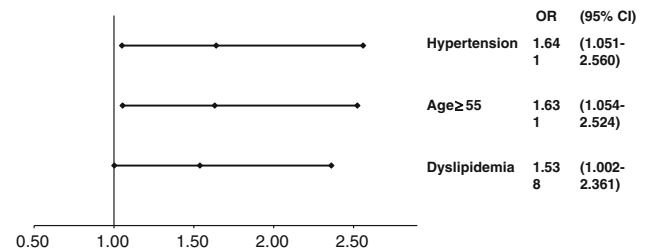
calcium score of zero has been evaluated in several cohorts, but with conflicting results, depending on the population included. Data from Nieman et al. [14], the CONFIRM registry [16], Rubinshtein et al. [13] and Akram et al. [11], are in line with our results, with a low prevalence of obstructive CAD (2, 3.5, 7.2 and 8.2 %, respectively). Our prevalence was even lower, and this might be explained by a high prevalence of patients with a low pretest probability of CAD.

In contrast, in the work of Harberl et al. [10] and Gottlieb et al. [12], there was a high prevalence of CAD (32 and 19.4 %, respectively), which can be related to the fact that these studies included patients referred for conventional angiography, including patients with possible acute coronary syndromes.

In our population, the prevalence of CAD in patients with positive/inconclusive stress tests (exercise electrocardiography in most cases) was not significantly different from that of patients referred to CCTA without previous tests, as in the study from Nieman et al. [14].

Calcium scoring enables a noninvasive quantification of the total coronary atherosclerotic burden, although it underestimates the burden of disease, by not measuring noncalcified plaques [25]. Nevertheless, it has been shown to outperform traditional risk stratification tools, such as clinical risk factor assessment, ankle-brachial index, carotid intima-media thickness and high-sensitivity C-reactive protein, as a predictor of cardiovascular events [4, 5].

Our data suggests that, although the absence of calcium does not exclude the presence of CAD, it was associated with a very low probability of obstructive lesions. This was especially true in cases of low and intermediate pretest CAD probability, as in the study from Werkhoven et al. [15] in which the prevalence of obstructive CAD, in the absence of calcium, was only 3.4 and 3.8 % in patients with low and intermediate pretest CAD probability, respectively. This is in line with the excellent prognosis that has been demonstrated for patients with a calcium score of zero [8].

In our population, older age (≥55 years), hypertension and dyslipidemia were independent predictors of CAD in

Table 4 Prevalence of CAD according to the presence of risk factors found to be independent predictors

Independent preditors	No CAD	Nonobstructive CAD	Obstructive CAD	Total	p
0	158 (96.9 %)	5 (3.1 %)	0 (0 %)	163	<0.001
1	210 (86.8 %)	25 (10.3 %)	7 (2.9 %)	242	
2	250 (88.3 %)	28 (9.9 %)	5 (1.8 %)	283	
3	139 (79.0 %)	35 (19.9 %)	2 (1.1 %)	176	
	757	93	14	864	

Fig. 4 Non-calcified plaque on cardiac CT (on the *right*) in a patient with a CaSc of zero; the angiography (on the *left*) confirmed the presence of a 50–70 % stenosis in the mid-RCA; intravascular ultrasound with virtual histology (in the *middle*) suggests the presence of microcalcifications
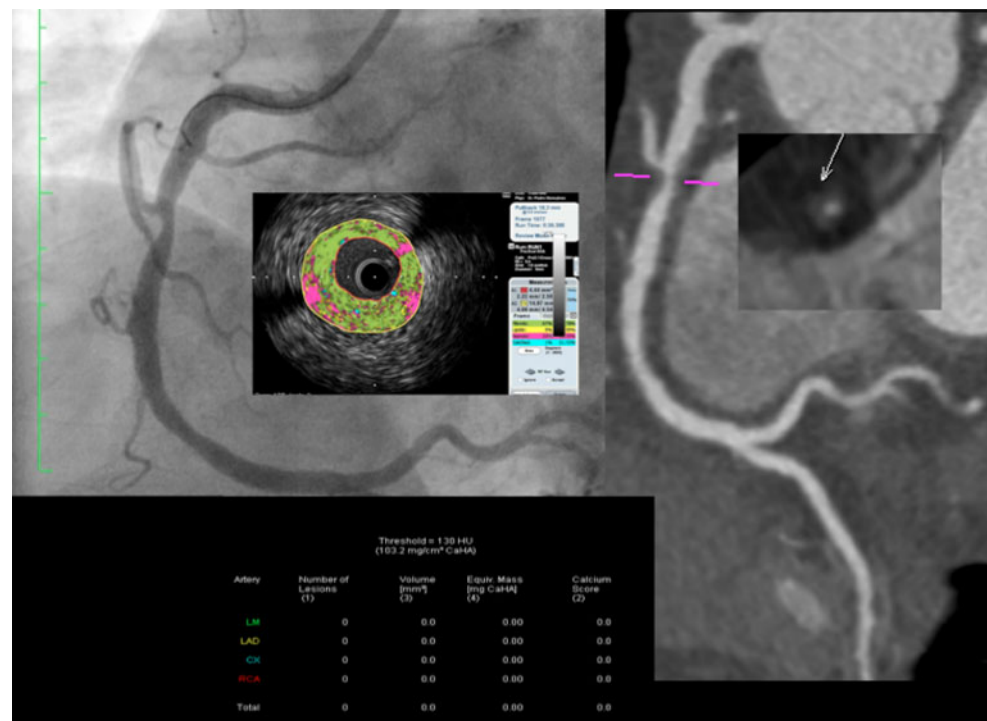
this subset of patients without calcium, and in the presence of these 3 predictors, the probability of having CAD was almost 2 times higher than in the general population. Nevertheless, the odds ratios for the independent predictors were rather modest and other traditional CAD risk factors were not found to be independent predictors. This way, we could hypothesize that coronary plaques without calcium could be a different phenotypical subset of CAD. Another possibility could be that these patients with coronary plaques in the absence of calcium represent CAD at earlier stages, since calcium is considered to be associated with more advanced forms of atherosclerotic lesions [2]. In fact, in our population, all the patients with obstructive CAD had only 1 vessel disease, most (93 %) with a single lesion, and only a minority (36 %) had >70 % stenosis.

One last hypothesis could be that these plaques can have microcalcifications below the threshold of cardiac CT spacial resolution, as in the case example (Fig. 4), in which small spots of calcium were only detected by intravascular ultrasound (IVUS) virtual histology.

Limitations

There are a number of limitations related to this report: (1) this is a single center retrospective study with medium size cohort; (2) our population in mainly of low CAD probability and CV risk; the very low percentage of obstructive CAD found can not be extrapolated to cohorts with more patients with higher CAD probability and CV risk (3) the definition of CAD was made using CCTA and not invasive angiography, which may lead to false-positive findings, although this is unlikely in the absence of calcium; (4) lack of prognostic information, since we did not evaluate the prognostic importance of obstructive CAD in patients with a CaSc of zero.

Conclusions

In this population of stable patients referred for evaluation of possible CAD that had a calcium score of zero, 12.4 % had coronary plaques and 1.6 % had obstructive (≥50 %) CAD.

Therefore, and despite the known high negative predictive value of CaSc for coronary events, the absence of coronary artery calcification does not exclude the presence of coronary artery disease, but the prevalence of obstructive disease is very low.

In this population, we found that age ≥55, hypertension, dyslipidemia were independent predictors of CAD in the setting of a calcium score of zero. In the presence of these 3 predictors, the probability of having CAD was almost 2 times higher than in the total studied population.

Conflict of interest All the authors declare that they have no conflict of interest.

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