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The Prevalence and Extent of Coronary Atherosclerosis among Patients with a Zero Calcium Score and the Influence of Patient Characteristics

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ABSTRACT

Purpose: Coronary artery calcium (CAC) is a specific indicator of and an independent risk factor for atherosclerosis; however, calcium scoring may miss noncalcified plaques, which may have clinical importance. The aim of this study was both to identify the presence and extent of coronary plaques during computed tomography coronary angiography (CTCA) in patients with a zero CAC score and to evaluate the effect of risk factors and symptom status on the presence of noncalcified plaques.

Materials and Methods: In this retrospective study, we analyzed the cases of 842 consecutive patients between October 2006 and November 2011. Of these patients, we included 357 with a zero calcium score in the study. Information regarding patient age, sex, coronary risk factors, and symptom status were recorded. Coronary calcium-scoring scans were followed by CTCA. The calcium scores were calculated, and the presence of noncalcified plaques and significant stenoses (>50% of vessel diameter) was evaluated.

Results: Of the 357 patients with a zero calcium score, 37 (10.36%) had atherosclerotic plaques; 9 patients (2.52%) had significant coronary stenosis. Among coronary risk factors, only diabetes mellitus was significantly correlated with any risk factors (presence of atherosclerosis and obstructive coronary artery disease; P = .030 and .013, respectively).

Conclusion: Although CAC scoring is a safe and a reliable test to exclude obstructive coronary artery disease, the absence of CAC does not definitively exclude the presence of atherosclerosis. CTCA is a more appropriate method for determining the atheroma burden.

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INTRODUCTION

Coronary artery disease (CAD) due to atherosclerosis is the leading cause of mortality and morbidity in adults worldwide [Budoff 2008, 2009; Oudkerk 2008; Taylor 2010]. Coronary artery calcium (CAC) is a specific indicator of and an independent risk factor for atherosclerosis. Many large clinical trials have shown CAC to be of strong prognostic value in predicting future cardiovascular events [Budoff 2008, 2009; Oudkerk 2008]. The frequency of adverse events is low among patients with a zero CAC score, and the absence of CAC has often been assumed to represent the absence of any underlying atherosclerosis [Budoff 2008, 2009; Oudkerk 2008; Taylor 2010]. Coronary artery calcification represents only one of the components of atherosclerotic plaques, however, and it develops late in the atherosclerotic process [Budoff 2008; Gottlieb 2010]. Additionally, most of the vulnerable coronary plaques that lead to acute cardiac events are not calcified, and such plaques correspond to an earlier phase of atherosclerosis [Gottlieb 2010]. Therefore, calcium scoring may miss noncalcified plaques that could have clinical importance. Consequently, several recent studies have compared the findings of calcium scoring scanning and contrast-enhanced computed tomography coronary angiography (CTCA) and have found varying degrees of coronary plaques among patients with a zero CAC score [Nikolaou 2003; Budoff 2008; Choi 2008; Kelly 2008; Akram 2009; Sarwar 2009; Cademartiri 2010; Drosch 2010; Gottlieb 2010; Ergün 2011; Uretsky 2011].

Given these observations, the aim of our study was to identify the presence and extent of coronary plaques during CTCA in patients with a zero CAC score and to evaluate the effect of risk factors and symptom status on the presence of noncalcified plaques.

MATERIALS AND METHODS

Patient Enrollment

This study was a single-center retrospective investigation of consecutive patients who underwent same-day CAC scoring and contrast-enhanced CTCA examination between October 2006 and November 2011.

A total of 1132 patients were examined. These patients were referred because of chest pain and/or risk factors in order to rule out or detect CAD. Exclusion criteria included a history of a known CAD, such as previous myocardial infarction, percutaneous coronary intervention, or coronary bypass surgery. We excluded 226 patients with a history of previous coronary artery stenting or bypass surgery. We also excluded 74 studies because of the inadequate quality of the calcium scan and/or CTCA images. Of the remaining 842 patients who met the criteria, 357 cases with a zero calcium score were selected for inclusion in the study. We included all of the patients who met the inclusion criteria without determining the pretest probability. All patients gave informed consent to be examined, and the institutional review board approved the study.

Information regarding patient age, sex, and coronary risk factors, such as hypertension (systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or blood pressure–lowering therapy), diabetes (fasting glucose level >120 mg/dL or medication for glycemic control), smoking (current and former), hyperlipidemia (total cholesterol >200 mg/dL or lipid-lowering medication), and a family history of CAD, were obtained from the patients before the CT study. In addition, the patients were questioned about the presence of symptoms. Chest pain was evaluated with the Diamond-Forrester classification [Diamond 1979]. Accordingly, the patients were questioned regarding substernal chest pain of typical quality, exacerbation upon physical or emotional stress, and relief by nitrates and/or rest for <10 minutes. The presence of 3, 2, or 1 of these features was regarded as typical angina, atypical angina, and noncardiac chest pain, respectively.

Acquisition of Multidetector CT Scan

All CT examinations were performed on a 32 × 2 multidetector CT scanner (Somatom Sensation 64; Siemens, Erlangen, Germany)

Acquisition of CAC Scan

CAC scoring was obtained without contrast media before CTCA. Values for the acquisition parameters were as follows: gantry rotation, 330 milliseconds; pitch, 0.2; tube voltage, 120 kV; tube current, 250 mA. The prospective electrocardiography triggering was done at 60% to 70% of the cardiac cycle. The effective slice thickness was 3 mm. The scanning time was approximately 6 to 7 seconds in a single breath hold, and the scan direction was craniocaudal. For reconstruction, we used a medium-sharp non–edge-enhancing convolution kernel (B35).

Evaluation of CAC Scans

The calcium score of each coronary artery and the total CAC score were calculated on another workstation (Siemens Wizard). A radiologist with a cardiac CT experience of 9 years (G.O.) identified coronary calcifications and scored them with the aid of semiautomated software. Calcium scores were calculated according to the Agatston method. A coronary calcification was identified as a lesion of at least 3 contiguous pixels (voxel size, 1.03 mm3) and a peak density of >130 Hounsfield units (HU).

Acquisition of CTCA Data

For CTCA examinations, we used an individual detector collimation of 0.6 mm, a rotation time of 330 milliseconds (effective temporal resolution, 165 milliseconds), a tube voltage of 120 kV, an effective tube current of 900 mA, a table feed per tube rotation of 3.84 mm (pitch, 0.2), and a craniocaudal scan direction. The scanning time was approximately 10 seconds (depending on the field of view) in a single breath hold.

To achieve better image quality, we aimed to scan patients with a heart rate of <70 beats/minute (bpm). Therefore, patients with higher heart rates were administered 5 to 15 mg metoprolol (Beloc; AstraZeneca, Istanbul, Turkey) intravenously. Before the β-blocker was administered, we looked for any contraindication. The use of the β-blocker helped ensure better patient compliance, fewer cardiac-motion artifacts, and a higher vascular enhancement. We also administered 5 mg nitroglycerin (Isordil; Fako, Istanbul, Turkey) sublingually for coronary dilatation.

We injected 80 to 90 mL of nonionic contrast medium (iomeprol [Iomeron 400]; Bracco, Milan, Italy) into the antecubital vein at a flow rate of 5.5 mL/second. This infusion was followed by a chaser bolus of 40 mL saline at a flow rate of 4 mL/second. This chaser bolus was used to wash out contrast material from the right ventricle to eliminate high-density artifacts over the right coronary artery.

To optimize the timing of the start of data acquisition, we used automatic bolus tracking. A prescan was performed at the level of the aortic root, and a region of interest was identified in the ascending aorta. The threshold value was set to 150 HU. The scan started when the signal density in the ascending aorta reached the predefined level.

During scanning, electrocardiographic data were recorded simultaneously. The transverse images were reconstructed retrospectively at different phases of the R-R interval. When necessary, R-wave indicators were manually repositioned by one radiologist (G.O.) to improve the quality of synchronization. Images were reconstructed at 10% intervals of the cardiac cycle to enable assessment of coronary arteries in the cardiac phase with minimal vessel motion, and the phases with the fewest artifacts (for left and right coronary arteries separately, if necessary) were used for further analysis.

Transverse images were reconstructed with a section thickness of 0.75 mm and a section width of 0.5 mm. For reconstruction, we used a medium-soft tissue kernel (B30f).

CTCA Evaluation

CT images were evaluated in a remote workstation (Siemens Leonardo) by 2 radiologists (D.O. and G.O., each with 9 years of experience in cardiac CT analysis) who reviewed the images jointly. In cases of disagreement, a final decision was reached by consensus.

The coronary arteries were evaluated for the presence of noncalcified plaques and significant stenoses. A significant stenosis was defined as a narrowing of the coronary artery lumen by >50% of the diameter. Each vessel was analyzed on at least 2 planes, 1 parallel and 1 perpendicular to the course of the vessel. The degree of coronary artery stenosis was measured with electronic calipers at the level of the greatest stenosis, and the measurement was compared with measurements of normal coronary segments just proximal and distal to the lesion.

All atherosclerotic plaques were evaluated and noted, regardless of whether they caused significant stenosis or not. If no atherosclerotic plaque was detected, the study was considered as normal. Studies with atherosclerotic plaques were further classified as significant stenosis or nonsignificant.

We also evaluated the radiation doses for the CAC and CTCA scans. The dose-length product was displayed by the CT system and then converted into effective-dose values by means of a conversion factor (0.017 mSv/mGy per cm, in accordance with the Commission of the European Communities guidelines on quality criteria [CEC 2000].

Statistical Analysis

Continuous variables are expressed as the mean SD. Categorical data are presented as an absolute number and a percentage. The Fisher exact test was used to evaluate the correlation of coronary risk factors with the presence of CAD. This analysis was done both for patients with atherosclerotic plaques not leading to significant stenosis and for those with plaques leading to obstructive CAD. In addition to the univariate analysis, a logistic regression model was used to assess multivariate predictors of coronary plaque detected by CTCA. A P value <.05 was considered statistically significant. Data were analyzed with SPSS software (version 15.0; IBM/SPSS, Chicago, IL, USA).

RESULTS

The study group consisted of 357 patients. We administered a β-blocker intravenously to the 287 patients who had a heart rate >70 bpm and succeeded in lowering the heart rate to <70 bpm in 223 of these patients. The remaining 64 patients with higher heart rates (mean, 78.3 bpm; range, 73-84 bpm) were evaluated. The higher heart rates did not produce any imaging artifacts that would lead any patient to be excluded from the study population. The mean heart rate of the patients with lower heart rates was 67.6 bpm (range, 56-70 bpm).

The mean patient radiation dose was 1.1 mSv (range, 0.8-1.3 mSv) for calcium scoring and 10.8 mSv (range, 9.5-12.6 mSv) for CTCA scanning.

Of the 357 patients, 272 (76.2%) were male. The mean (SD) age was 51.27 ± 5.397 years (range, 39-67 years). The primary risk factors were hyperlipidemia (301 patients, 84.3%) and hypertension (239 patients, 66.9%). The characteristics of the patients are summarized in Table 1. Of the 357 patients with a zero calcium value, 37 (10.36%) had atherosclerotic plaques that were detected during contrast-enhanced CTCA examinations, and 9 (2.52%) of these patients had a clinically significant coronary artery stenosis (>50%; Figure 1).

Of the patients with atherosclerotic plaques, 32 were male. The mean age of these patients was 52.13 ± 4.824 years (range, 43-66 years). We detected 48 plaques in these 37 patients, 26 patients with only 1 atherosclerotic plaque and 11 patients with 2 plaques each. No more than 2 plaques per patient were detected. All of the patients had multiple risk factors (mean, 3.54 1.02; range, 2-5), and 19 of the patients were symptomatic (Figure 2). Two of the symptomatic patients described typical angina symptoms, and 5 patients had atypical angina. The symptoms of the remaining 12 patients had noncardiac chest pain according to the Diamond-Forrester classification [Diamond 1979].

All of the patients with obstructive CAD were male and symptomatic. The symptoms were considered typical angina in 4 patients, atypical angina in 3 patients, and noncardiac chest pain in 2 patients. The nature of the symptoms was not statistically significant. The most frequent risk factors were smoking, diabetes mellitus, and hyperlipidemia, which were found in 8 patients. All of the patients had multiple risk factors (mean, 3.55 0.94; range, 2-5). Six of the stenoses were detected in left anterior descending coronary artery,

Table 1. Characteristics of the Study Group*

Patient Characteristic	Value
Age, y	51.27 ± 5.397
Male/female sex, n	272/85 (76.2%/23.8%)
Hypertension, n	239 (66.9%)
Diabetes mellitus, n	161 (45.1%)
Smoking, n	235 (65.8%)
Family history of CAD, n	233 (65.3%)
Hyperlipidemia, n	301 (84.3%)
Symptoms, n	99 (27.7%)

*Age data are expressed as the mean ± SD. CAD indicates coronary artery disease.

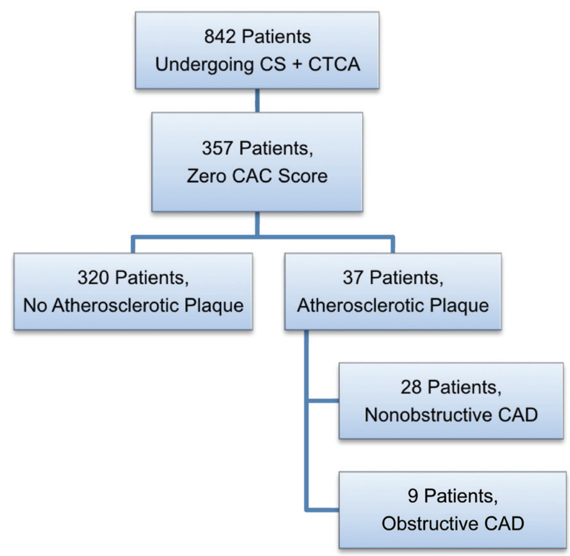

Figure 1. The distribution of the patients on the basis of coronary artery calcium (CAC) scanning (CS) score, the presence of atherosclerotic plaques, and the presence of obstructive coronary artery disease (CAD). CTCA indicates computed tomography coronary angiography.

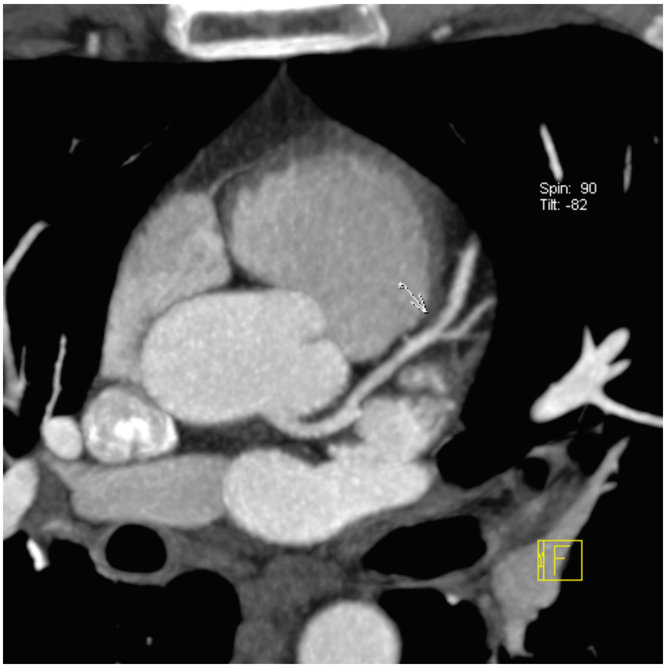

Figure 2. A 56-year-old male patient with multiple risk factors (hypertension, smoking, family history of coronary artery disease, and hyperlipidemia) and atypical angina. A noncalcified atherosclerotic plaque is present in the proximal segment of left anterior descending artery. It does not lead to significant stenosis. In the curved multiplanar reformatted image, the eccentrically located nonobstructive atherosclerotic plaque is indicated (arrow).

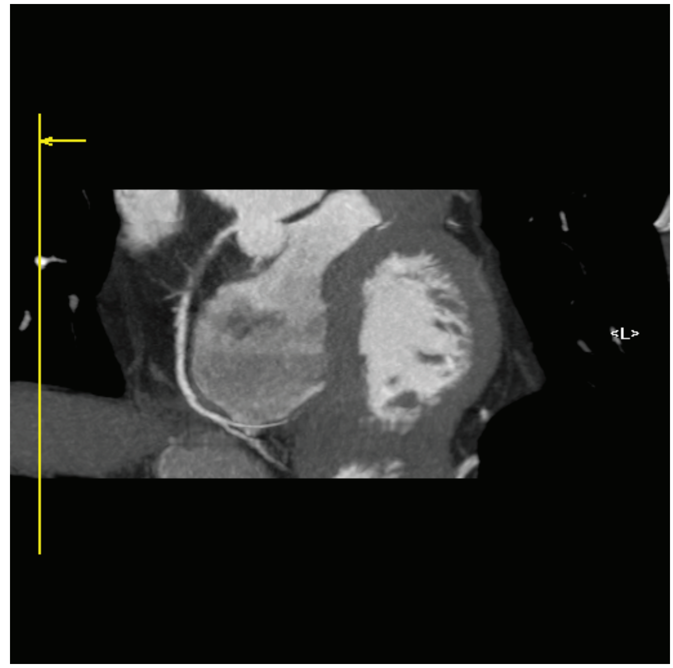

Figure 3. A 47-year-old male patient with multiple risk factors (diabetes mellitus, smoking, and hyperlipidemia) and typical angina. A noncalcified atherosclerotic plaque producing significant stenosis is present in the proximal segment of right coronary artery. Curved multiplanar reformatted image.

2 stenoses occurred in the right coronary artery (Figure 3), and one was in the left circumflex artery (Figure 4). A single obstructive lesion was detected in all patients, and 5 patients had an additional, nonobstructive plaque.

Of the CAD risk factors, only diabetes mellitus showed any significant correlations (with the presence of atherosclerosis and with obstructive CAD; *P* = .030 and .013, respectively; corresponding odds ratios, 2.167 and 10.196). No other clinical variable showed any statistically significant correlation in patients with a zero calcium score, either with the presence of atherosclerosis or with obstructive CAD. Although the incidence of atherosclerosis was observed to increase with increasing age, no statistically significant correlation was found (*P* = .212). Similarly, the symptom status of the patient showed no statistically significant correlation (*P* = .561). Table 2 summarizes the data for age, sex, and CAD risk factors for patients without evidence of coronary atherosclerosis, patients with atherosclerotic plaques, and patients with obstructive CAD, along with the corresponding *P* values for the statistical analyses.

Table 2. Prevalence of Age, Sex, and Coronary Risk Factors among Patients without Evidence of Coronary Atherosclerosis, Patients with Atherosclerotic Plaques, and Patients with Obstructive Coronary Artery Disease (CAD)*

	No Plaque (n = 320)	Atherosclerotic Plaque (n = 37)	*P*	Obstructive CAD (n = 9)	*P*
Age, y	51.29 ± 5.368	51.11 ± 5.719	.846	49 ± 4.435	.212
Male sex, n	240 (75%)	32 (86.4%)	.307	9 (100%)	.146
Female sex, n	80 (25%)	5 (13.51%)	.225	0 (0%)	.232
Hypertension, n	214 (66.87%)	25 (67.56%)	.546	3 (33.33%)	.361
Diabetes mellitus, n	138 (43.12%)	23 (62.16%)	.030	8 (88.88%)	.013
Smoking, n	208 (65%)	27 (72.97%)	.366	8 (88.88%)	.393
Family history of CAD, n	211 (65.93%)	22 (59.45%)	.468	5 (55.55%)	.541
Hyperlipidemia, n	269 (84.06%)	32 (86.48%)	.815	8 (88.88%)	.648
Symptoms, n	87 (27.18%)	12 (32.43%)	.561	9 (100%)	.139

*P values <.05 are statistically significant.

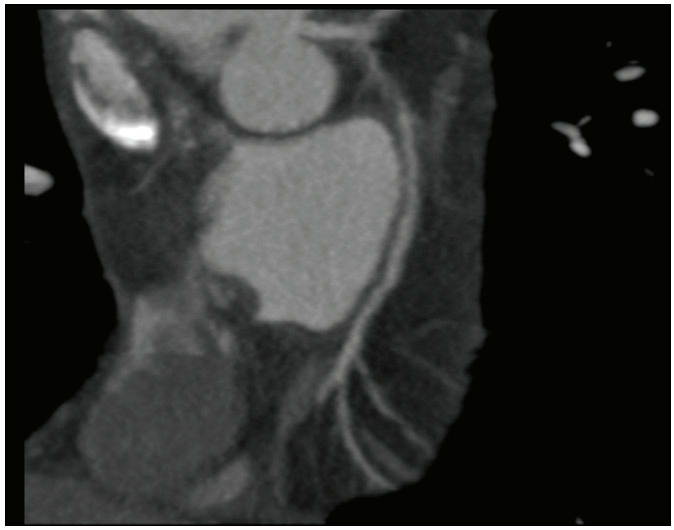

Figure 4. A 54-year-old male patient with multiple risk factors (diabetes mellitus, smoking, family history of coronary artery disease, and hyperlipidemia) and atypical angina. A noncalcified atherosclerotic plaque producing significant stenosis is present in the proximal segment of left circumflex artery. Curved multiplanar reformatted image.

DISCUSSION

The main finding of our study is that only 9 patients (2.52% of the patient population) in a cohort of 357 patients with a zero calcium score had a detectable, significant coronary artery stenosis. Our population consisted of patients referred for CTCA for the purpose of ruling out CAD, however. The patients thus were mainly low- or intermediate-risk patients, because high-risk patients are more likely to be referred for conventional angiography, except for some specific reasons. On the other hand, a small but nonnegligible number of patients (28, 7.84%) had atherosclerotic plaques but no significant stenosis.

All patients with stenosis were symptomatic. This is a remarkable finding. From another point of view, 9 (9.19%) of 99 symptomatic patients had significant stenosis. In this regard, given that all of the patients with obstructive lesions were symptomatic, the main question is whether cardiac catheterization should be chosen as the first diagnostic procedure for symptomatic patients. The answer is not a simple yes or no. First, not all symptomatic patients had obstructive lesions; therefore, calcium scoring in combination with coronary CTCA still could serve as a filter for choosing patients to send to the cardiac catheterization laboratory. This consideration is important, because cardiac catheterization is an invasive procedure that can lead to severe although rare complications. On the other hand, cardiac catheterization may be preferred for first-line treatment if the patient has typical angina along with other risk factors (ie, if there is a high pretest probability of the existence of an obstructive lesion), because in addition to the diagnosis of obstructive lesions, therapeutic intervention procedures can be performed at the same time. Between October 2006 and November 2011, we retrospectively analyzed consecutive patients who underwent same-day CAC scoring and contrast-enhanced CTCA examination to evaluate the presence and extent of coronary plaques in patients with a zero CAC score. We included all patients who met the inclusion criteria without determining the pretest probability or the presence of symptoms; however, a study of a prospective nature would certainly consider these variables.

Diabetes mellitus was the only risk factor to show a statistically significant correlation with risk factors (ie, the presence of coronary atherosclerotic plaques and significant stenosis).

Akram et al [2009] explored the impacts of symptoms in patients with a zero calcium value and found that 8.2% of symptomatic patients with a zero CAC score had an obstructive coronary artery stenosis; they detected no obstructive coronary lesions in asymptomatic patients. These findings are in accord with our own. A study by Choi et al [2008] evaluated a large asymptomatic population of patients with a zero CAC score. Four per cent of the patients had noncalcified plaques, and 1.8% had significant stenosis. They concluded that the potential for the presence of occult CAD is not negligible in asymptomatic patients. These results are also consistent with our findings. On the other hand, Cademartiri et al [2010] reported on 279 patients with a zero calcium value, of whom 208 were symptomatic and 71 were asymptomatic. The prevalence of disease in the symptomatic and asymptomatic patients was 19.2% and 1.4%, respectively. The investigators also concluded that the prevalence of significant disease is not negligible in asymptomatic patients [Cademartiri 2010]. Their reported prevalence of obstructive CAD among symptomatic patients is higher than in our study, owing mostly to differences in the characteristics of their patient population.

Recent American Collage of Cardiology/American Heart Association guidelines consider that the lack of a measurable coronary calcium concentration in the symptomatic patient may be an effective filter before a patient undergoes an invasive diagnostic procedure or before hospital admission [Taylor 2010]. Although the absence of CAC is associated with a very low likelihood of significant CAD, approximately 2% of symptomatic individuals with significant CAD do not have evidence of measurable CAC. These individuals tend to be younger than 50 years of age. Therefore, patients with a zero calcium value should be evaluated with caution.

Akram et al [2009] stated that a zero calcium score might reliably rule out obstructive CAD in older patients, whereas caution would be required for young patients [Akram 2009]. Other studies have reported a higher prevalence of CAD in patients with a zero CAC value and who are younger than 45 to 50 years [Sarwar 2009; Ergün 2011; Uretsky 2011]. Nevertheless, the exact age threshold above which a zero CAC score reliably rules out CAD has not yet been determined. In our study population, we found no correlation of age with the presence of CAD.

A study by Ergün et al [2011] found diabetes mellitus and age to be significant risk factors for CAD, both for male patients and for female patients. Nikolaou et al [2003] observed that atherosclerosis was associated with smoking, hypertension, and diabetes in patients with a zero calcium value, whereas Kelly et al [2008] found that male sex was a significant risk factor. In our study, only diabetes mellitus was significantly correlated with the presence of atherosclerosis and significant stenosis in patients with a zero calcium value. Of the risk factors, only diabetes mellitus was significantly correlated with CAD.

The results of our study and an examination of the published literature indicate that the prevalence of obstructive CAD in patients with a zero calcium value is not negligible and that the prevalence of CAD is affected by the characteristics of the patient population and the clinical presentation.

The most important question to be answered is whether we should continue to use CTCA in patients with a zero calcium score. The answer is controversial because of concerns about radiation doses. The mean radiation dose is 12 mSv (8-18 mSv) [Hausleiter 2009]; therefore, the application of CTCA in patients with a zero CAC score is very questionable. Recent improvements in the technology, however, make it possible to decrease the radiation dose to 1 to 5 mSv. Efforts that decrease the radiation dose further will probably expand the indications for CTCA [Park 2011; Srichai 2012].

The main limitations of our study are its retrospective nature and the lack of follow-up for the patients with cardiovascular events. Another important drawback is we did not explore the correlation of CTCA findings with results obtained by conventional angiography. Our aim was not to test the accuracy of CTCA, however. Numerous studies have revealed a significant correlation between CTCA and conventional angiography results, with very high negative predictive values [Sarwar 2009; Taylor 2010].

CONCLUSION

Although CAC scoring is a safe and a reliable test for excluding the presence of obstructive CAD, the absence of a CAC score does not definitively exclude the presence of atherosclerosis. Our study results indicate that calcium scores should be interpreted with caution, especially in symptomatic patients and patients with diabetes. CTCA is more appropriate for determining the atheroma burden.

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