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## **Imaging of coronary atherosclerosis and vulnerable plaque**

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# CHAPTER 13

Comparison of the Relation  
between the Calcium Score and  
Plaque Characteristics in Patients  
with Acute Coronary Syndrome  
versus Patients with Stable  
Coronary Artery Disease, assessed  
by CTA and VH IVUS

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## ABSTRACT

**Background:** A considerable number of patients with an acute coronary syndrome (ACS) who present with a zero or low calcium score (CS) still demonstrate coronary artery disease (CAD) and significant stenosis. The aim of the present study was to evaluate the relationship between the CS and the degree and character of atherosclerosis in patients suspected of ACS versus patients with stable CAD, obtained by computed tomography angiography (CTA) and virtual histology intravascular ultrasound (VH IVUS).

**Methods:** Overall, 112 patients were studied; 53 with ACS and 59 with stable CAD. CS and CTA was performed and followed by VH IVUS. On CTA, each segment was evaluated for plaque and classified as non-calcified, mixed or calcified. Vulnerable plaque characteristics on VH IVUS were defined by % necrotic core and presence of thin cap fibroatheroma (TCFA).

**Results:** If CS was zero, patients with ACS had a higher mean number of plaques ( $5.0 \pm 2.0$  vs  $2.0 \pm 1.9$ ,  $p < 0.05$ ) and non-calcified plaques ( $4.6 \pm 3.5$  vs  $1.3 \pm 1.9$ ,  $p < 0.05$ ) on CTA than stable CAD. In zero CS, VH IVUS demonstrated that patients with ACS had a larger amount of necrotic core area ( $0.58 \pm 0.73$  vs  $0.22 \pm 0.43$  mm<sup>2</sup>,  $p < 0.05$ ) and higher mean number of TCFA ( $0.6 \pm 0.7$  vs  $0.1 \pm 0.3$ ,  $p < 0.05$ ) than stable CAD.

**Conclusion:** Even in the presence of a zero CS, patients with ACS have increased plaque burden as well as increased vulnerability as compared to stable CAD. Accordingly, absence of coronary calcification does not exclude the presence of clinically relevant and potentially vulnerable atherosclerotic plaque burden in patients with ACS.

## INTRODUCTION

The prognostic value of the coronary calcium score (CS) has been extensively investigated, and very low rates of cardiac events have been demonstrated in individuals with a zero CS.<sup>1-4</sup> However, preliminary data in patients presenting with acute coronary syndrome (ACS) suggest a larger contribution of non-calcified plaque to the overall plaque burden as compared with patients with stable coronary artery disease (CAD).<sup>5,6</sup> As a consequence, a zero or low CS may significantly underestimate the overall plaque burden in the setting of ACS.<sup>7</sup> However, at present, data on how clinical presentation impacts the relation between CS and coronary plaque characteristics are still scarce. An important advantage of computed tomography angiography (CTA) over the CS is that additional information on stenosis severity and plaque composition can be obtained.<sup>8,9</sup> Invasively, virtual histology intravascular ultrasound (VH IVUS) offers detailed information on coronary plaque characteristics.<sup>10-12</sup> The aim of the present study was to compare the relationship between the CS and plaque characteristics in patients with ACS versus patients with stable CAD, assessed non-invasively by CTA and invasively by VH IVUS.

## METHODS

### Patients and Study Protocol

The study population consisted of 112 patients without known CAD (defined as previous myocardial infarction, coronary arterial bypass grafting and percutaneous coronary intervention) who were referred for CTA imaging for non-invasive evaluation of chest pain. Subsequently, patients were referred for invasive coronary angiography (ICA) in combination with VH IVUS based on patient's clinical presentation and/or imaging results. Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analyzed. Patients with diagnostic CTA image quality were selected from an ongoing registry addressing the relative merits of CTA in relation to other imaging modalities. A total of 53 patients were included with suspected ACS, which was defined according to the guidelines of the European Society of Cardiology and the American College of Cardiology/American Heart Association.<sup>13,14</sup> The remaining 59 patients presented to the outpatient clinic with stable chest pain complaints.<sup>15</sup> Contra-indications for CTA were 1) (supra) ventricular arrhythmias, 2) renal insufficiency (glomerular filtration rate <30 ml/min), 3) known allergy to iodine contrast material, 4) severe claustrophobia, 5) pregnancy.

### CTA acquisition

The CS and CTA scans were performed using either a 64-row or a 320-row scanner (Aquilion 64 or Aquilion ONE, Toshiba Medical Systems, Otawara, Japan). Beta-blocking medication (metoprolol 50 or 100 mg) was administered if the patient's heart rate was  $\geq 65$  beats/minute and no contra-indications existed. A non-contrast enhanced low dose

scan (tube voltage of 120 kV and tube current of 200 mA) was performed to assess the total CS.<sup>16</sup> A total CS of 0 was defined as no calcium, a CS of 1-399 was defined as mild calcium and a CS of  $\geq 400$  was defined as severe calcium. A standard scanning protocol was followed for the 64-row as well as for the 320-row contrast enhanced CTA scan, as previously described.<sup>17,18</sup>

### **CTA analysis**

CTA datasets were evaluated using dedicated software (Vitrea 2.0 or Vitrea FX 1.1 Vital images, Minnetonka, MN, USA) by two experienced readers, blinded to baseline patient characteristics, CS and VH IVUS results. The coronary arteries were divided into 17 segments according to a modified American Heart Association classification.<sup>19</sup> Per segment one coronary plaque (if present) was selected at the site of the most severe luminal narrowing. To describe plaque composition, plaques were further classified as: 1) non-calcified plaque (plaques with lower density compared to contrast-enhanced lumen without any calcification), 2) mixed plaque (non-calcified and calcified elements in single plaque) 3) calcified plaque (plaques with high density compared to contrast-enhanced lumen).

### **VH IVUS acquisition**

The VH IVUS examinations were performed during ICA according to standard protocols. A dedicated IVUS-console (Volcano Corporation, Rancho Cordova, CA, USA) was used for the examination. VH IVUS was performed with a 20 MHz, 2.9 F phased-array IVUS catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, CA, USA). Subsequently, with a speed of 0.5 mm/s, motorized automated IVUS pullback was performed until the IVUS catheter reached the guiding catheter. Images were stored for off-line analysis.

### **VH IVUS analysis**

VH IVUS analysis was performed by two experienced observers blinded to baseline patient characteristics, CS and CTA results. Offline analysis of the VH IVUS images was performed using dedicated software (pcVH 2.1 and VIAS 3.0, Volcano Corporation, Rancho Cordova, CA, USA). The lumen and the media-adventitia interface were defined by automatic contour detection and on all individual frames manual editing was performed. Analysis was performed on a per plaque basis. Plaque area ( $\text{mm}^2$ ) was defined as plaque area plus media area and was calculated as vessel area minus lumen area. Four plaque components were differentiated into different color-codes (fibrotic tissue displayed in dark green, fibro-fatty in light green, necrotic core in red and dense calcium in white), as validated previously.<sup>20</sup> Vulnerable plaque characteristics on VH IVUS were defined by % of necrotic core and presence of thin cap fibroatheroma (TCFA). A TCFA was defined as a lesion with a plaque burden  $\geq 40\%$ , the presence of confluent necrotic core of  $> 10\%$ , and no evidence of an overlying fibrous cap.<sup>21,22</sup>

## Statistical analysis

Statistical analysis was performed using SPSS 16.0 (SPSS, Inc., Chicago, Illinois). The impact on clinical presentation (ACS versus stable CAD) of coronary plaque characteristics (plaque burden and composition) on CTA was explored in all patients and related to the CS score (no, mild or severe). Finally, the impact of clinical presentation on coronary plaque characteristics in relation to the CS score was also evaluated using VH IVUS. Continuous values are expressed as means ( $\pm$ SD). Continuous values were assessed with the Student's t test if normally distributed or with the Mann-Whitney test if not normally distributed. Categorical values are expressed as number (%) and compared between groups with the 2-tailed Chi-square test. A p-value of  $<0.05$  was considered statistically significant.

## RESULTS

### Patients

Overall, 112 patients were studied of which 53 patients presented with ACS and 59 presented with stable CAD. No differences were observed in the prevalence of risk factors for CAD between the 2 groups (Table 1). In patients with ACS, cardiac troponin levels were

**Table 1.** Patient characteristics

Patient characteristics of the study population compared between patients with suspected acute coronary syndrome (ACS) and stable coronary artery disease (CAD). Only the calcium score was significantly higher in patients presenting with stable CAD as compared to patients with suspected ACS.

Patient characteristics	Suspected ACS (n=53)	Stable CAD (n=59)	p-value
Age (years)	57 $\pm$ 11	58 $\pm$ 11	0.69
Male	37 (70%)	35 (59%)	0.25
Obesity (body mass index $\geq$ 30 kg/m <sup>2</sup> )	12 (23%)	8 (14%)	0.24
Hypertension <sup>†</sup>	28 (53%)	36 (61%)	0.38
Hypercholesterolemia <sup>‡</sup>	32 (60%)	29 (49%)	0.23
Positive family history	25 (47%)	29 (49%)	0.83
Smoker	25 (47%)	22 (37%)	0.29
Type 2 diabetes mellitus	9 (17%)	17 (29%)	0.14
Mean calcium score	149 $\pm$ 141	530 $\pm$ 1258	$<0.001$
Presence of significant stenosis <sup>§</sup> ( $\geq$ 50% luminal narrowing)	31 (58%)	35 (59%)	0.93

Data are absolute values, percentages or means  $\pm$  standard deviation.

<sup>†</sup>Defined as systolic blood pressure  $\geq$ 140 mm Hg or diastolic blood pressure  $\geq$ 90 mm Hg or the use of antihypertensive medication.

<sup>‡</sup>Serum total cholesterol  $\geq$ 230 mg/dL or serum triglycerides  $\geq$ 200 mg/dL or treatment with lipid lowering drugs.

<sup>§</sup>Visually assessed on invasive coronary angiography

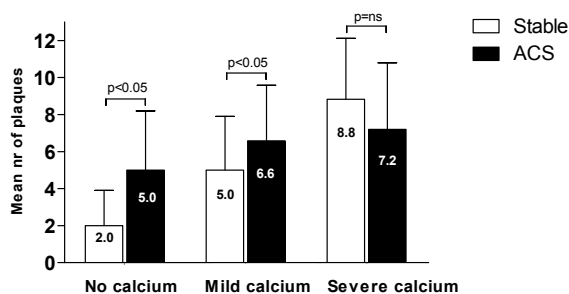
Abbreviations: CAD, coronary artery disease; ACS, acute coronary syndrome.

elevated in 11 patients (21%) and in 31 patients (58%) significant CAD was demonstrated on ICA. VH IVUS could be performed in all patients and was obtained in 241 vessels (124 vessels (51%) in ACS and 117 vessels (48%) in stable CAD). Regarding the CS, calcium was absent (CS of 0) in 11 patients (21%) with ACS and 10 patients (17%) with stable CAD. Moreover, mild calcium (CS of 1-399) was observed in 37 patients (70%) with ACS and in 32 patients (54%) with stable CAD. Severe calcium (CS of  $\geq 400$ ) was demonstrated in 5 patients (9%) with ACS and 17 patients (29%) with stable CAD ( $p=0.04$ ).

### CTA findings

In total, 662 coronary plaques were identified on CTA. Overall, 327 coronary plaques (49% of the total amount of plaques) were observed in patients with ACS whereas 335 coronary plaques (51% of the total amount of plaques) were observed in patients with stable CAD ( $p=0.14$ ). No difference in total plaque burden on CTA, reflected by the mean number of total plaques per patient, was observed between patients with ACS ( $6.3\pm 3.1$ ) and stable CAD ( $5.7\pm 3.7$ ,  $p=0.30$ ). Subsequently, the mean number of plaques per patient was compared between patients with ACS and stable CAD within the various CS categories (Figure 1). If coronary calcium was absent, significantly more plaques were present in patients with ACS ( $5.0\pm 3.2$ ) than patients with stable CAD ( $2.0\pm 1.9$ ,  $p=0.04$ ). Similarly, if coronary calcium was mild, significantly more plaques were still detected in patients with ACS ( $6.6\pm 3.0$ ) than patients with stable CAD ( $5.0\pm 2.9$ ,  $p=0.02$ ). However, if coronary calcium was severe, no differences were observed.

The differences in plaque composition were evaluated within the various CS categories between patients with ACS and stable CAD. Regarding non-calcified plaques, if coronary calcium was absent, significantly more non-calcified plaques were observed in patients



**Figure 1.** Relation between CS and plaque burden on CTA

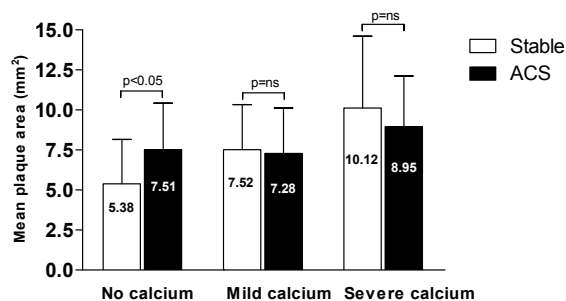
Bar graph demonstrating the difference in the mean number of plaques per patient on CTA within different calcium score categories (no, mild and severe calcium) between patients presenting with ACS and stable CAD. As demonstrated, if coronary calcium was absent or mild on CTA, patients with ACS had a significantly higher mean number of plaques than patients with stable CAD. However, in severe calcium, the mean number of plaques on CTA was not different between patients with ACS and stable CAD. ACS, acute coronary syndrome; CAD, coronary artery disease; CTA, computed tomography angiography.

with ACS ( $4.6\pm 3.5$ ) than patients with stable CAD ( $1.3\pm 1.9$ ,  $p=0.03$ ). Similarly, if coronary calcium was mild, significantly more non-calcified plaques were observed in patients with ACS ( $2.9\pm 2.5$ ) than patients with stable CAD ( $1.9\pm 2.4$ ,  $p=0.03$ ). However, with regard to severe coronary calcium, no significant differences were identified in the mean number of non-calcified plaques between patients with ACS ( $0.8\pm 1.1$ ) and stable CAD ( $1.5\pm 1.5$ ,  $p=0.36$ ). Regarding mixed plaques, if coronary calcium was mild, more mixed plaques were observed in patients with ACS than patients with stable CAD ( $3.0\pm 2.1$  vs  $1.6\pm 1.9$ ,  $p=0.002$ ). In contrast, regarding calcified plaques, in patients with mild or severe calcium, calcified lesions were more prominent in patients with stable CAD as compared to patients with ACS for each CS category.

### VH IVUS findings

VH IVUS was available in 429 coronary plaques of which 219 plaques were present in patients with ACS (49% of total amount of plaques) and 210 plaques were present in patients with stable CAD (51% of total amount of plaques). No difference in total plaque burden on VH IVUS, reflected by the mean plaque area per patient, was observed between patients with ACS ( $7.55\pm 3.09$  mm<sup>2</sup>) and stable CAD ( $7.68\pm 3.14$  mm<sup>2</sup>,  $p=0.66$ ). In addition, the difference in plaque area between patients with ACS and stable CAD within the various CS categories was assessed as presented in Figure 2. Accordingly, if coronary calcium was absent, plaque area (mm<sup>2</sup>) was significantly higher in coronary plaques of patients with ACS as compared to patients with stable CAD. However, in case of mild or severe coronary calcium, plaque area (mm<sup>2</sup>) was not significantly different between patients with ACS and stable CAD.

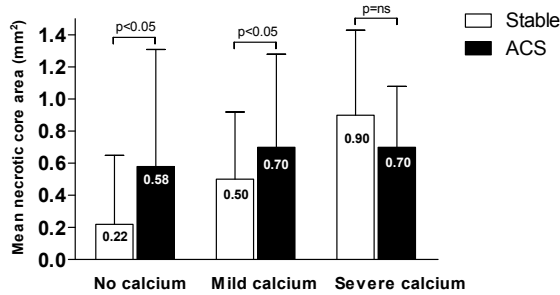
Plaque composition on VH IVUS was compared between patients with ACS and stable CAD within the different CS categories as illustrated in Figure 3. Interestingly, if coronary



**Figure 2.** Relation between CS and plaque burden on VH IVUS

Bar graph demonstrating the difference in mean plaque area (mm<sup>2</sup>) on VH IVUS within different calcium score categories (no, mild and severe calcium) between patients with ACS and stable CAD. As demonstrated, if coronary calcium was absent, patients with ACS had significantly larger mean plaque area on VH IVUS than patients with stable CAD. However, in mild or severe calcium, plaque area was not different between patients with ACS and stable CAD. ACS, acute coronary syndrome; CAD, coronary artery disease; VH IVUS, virtual histology intravascular ultrasound.

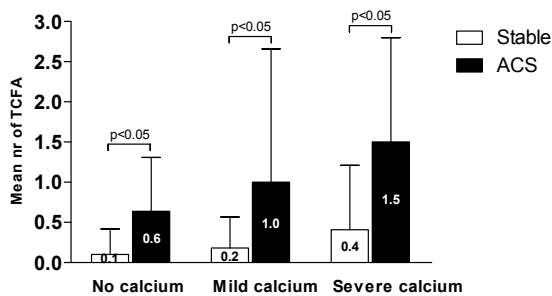




**Figure 3.** Relation between CS and plaque composition on VH IVUS

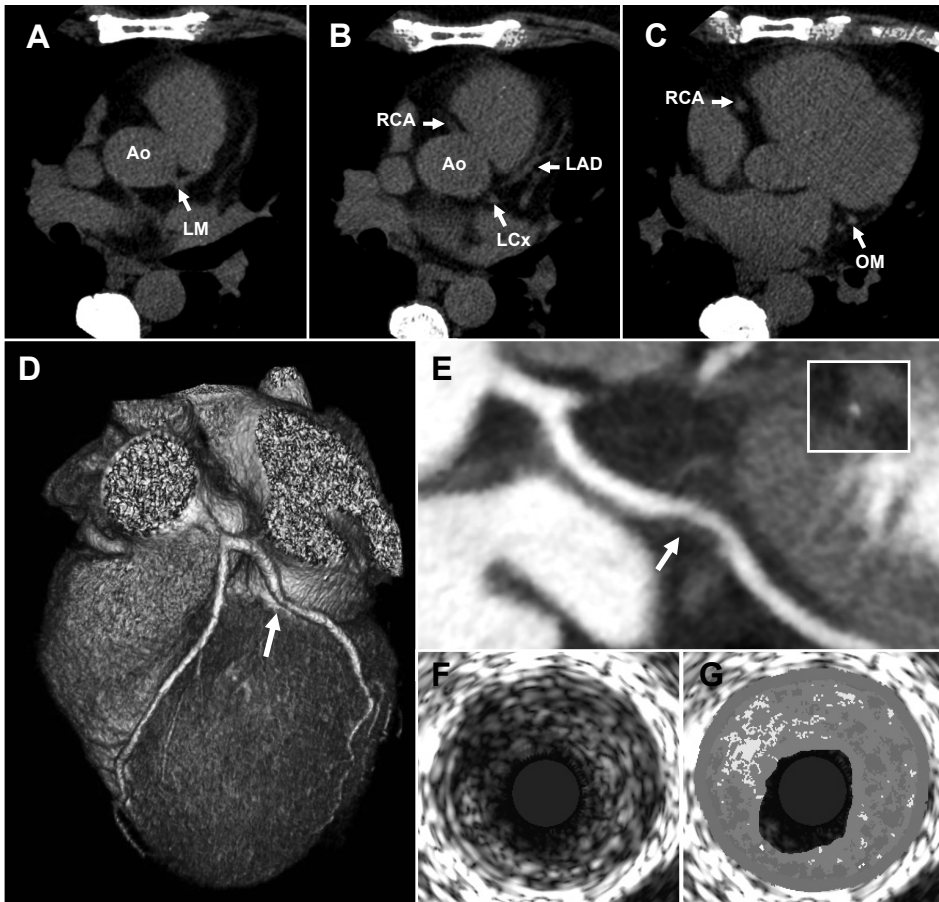
Bar graph demonstrating the difference in mean necrotic core area (mm<sup>2</sup>) on VH IVUS within different calcium score categories (no, mild and severe calcium) between patients with ACS and stable CAD. As demonstrated, if coronary calcium was absent or mild, patients with ACS had significantly larger mean necrotic core area on VH IVUS than patients with stable CAD. However, in the presence of severe calcium, mean necrotic core area was not different between patients with ACS and stable CAD. ACS, acute coronary syndrome; CAD, coronary artery disease; VH IVUS, virtual histology intravascular ultrasound.

calcium was absent, necrotic core area (mm<sup>2</sup>) was significantly higher in coronary plaques of patients with ACS than stable CAD. This difference was still preserved when coronary calcium was mild. However, regarding severe coronary calcium, no differences in necrotic core area between coronary plaques of patients with ACS and patients with stable CAD were identified. Regarding the mean number of TCFA within different CS categories, the number of TCFA was significantly higher in patients with ACS in all CS categories as compared to stable CAD, which is demonstrated in Figure 4. An example of a patient with ACS without coronary calcium but with considerable atherosclerosis is provided in Figure 5.



**Figure 4.** Relation between CS and TCFA on VH IVUS

Bar graph demonstrating the difference in mean number of TCFA on VH IVUS within different calcium score categories (no, mild and severe calcium) between patients with ACS and stable CAD. As demonstrated, patients with ACS had significantly larger number of TCFA on VH IVUS than patients with stable CAD in all calcium score categories. ACS, acute coronary syndrome; CAD, coronary artery disease; TCFA, thin cap fibroatheroma; VH IVUS, virtual histology intravascular ultrasound.



**Figure 5.** Example of patient with zero CS and extensive atherosclerosis

Example of a patient suspected of an acute coronary syndrome without coronary calcification but with relevant coronary atherosclerosis. The coronary calcium score showed no presence of coronary calcium in the entire coronary artery tree (Panel A, B, C). Additionally, 320-row CTA was performed. The 3D volume reconstruction showed signs of luminal narrowing in the LCx (Panel D, white arrow). On the multiplanar reconstruction of the LCx a substantial non-calcified plaque (white arrow) was demonstrated suggestive of significant luminal narrowing on cross-sectional view (enlargement) (Panel E). Grayscale IVUS confirmed substantial non-calcified plaque burden with significant luminal narrowing and signs of thrombus (Panel F). Virtual histology IVUS showed a large plaque without calcifications and large necrotic core area (red). Ao, aorta; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LM, left main; OM, obtuse marginal; RCA, right coronary artery.

## DISCUSSION

The main finding of the present study was that clinical presentation (ACS versus stable CAD) has a strong impact on the relation between the CS and coronary plaque characteristics. Although the mean number of plaques was similar between patients with ACS and stable CAD, when coronary calcium was absent the plaque burden on CTA was significantly larger in patients with ACS than in patients with stable CAD. Invasive VH IVUS findings paralleled non-invasive CTA findings. When coronary calcium was absent, a significantly larger plaque area ( $\text{mm}^2$ ) was observed in patients with ACS as compared to patients with stable CAD. Regarding plaque composition, when coronary calcium was absent or mild, a significantly higher number of both non-calcified and mixed plaques on CTA was observed in patients with ACS as compared to patients with stable CAD. Importantly, as demonstrated invasively with VH IVUS, when coronary calcium was absent, a higher degree of high-risk plaque features (more TCFA and necrotic core) was noted in ACS. Consequently, the present findings indicate that if the CS is zero in patients with ACS, the presence of substantial atherosclerotic plaque burden cannot be reliably excluded, as demonstrated both non-invasively by CTA and invasively by VH IVUS.

Initially, the observation that a zero CS does not exclude substantial plaque burden appears to be in conflict with data from the general population. Indeed, an extensive body of previous published reports exists supporting the value of CS as a marker of plaque burden, and thus indirectly of prognosis.<sup>1-4 23</sup> Large, multicenter trials have shown that absence of calcium is consistently associated with a low risk of either obstructive stenosis or cardiovascular events. Nonetheless, it should be noted that these data have been based predominantly on asymptomatic, low-risk populations and may not be fully representative of symptomatic patients at higher risk. Several studies have investigated the presence of atherosclerosis or significant stenosis in patients without detectable calcium.<sup>24</sup> <sup>25</sup> Akram et al reported in asymptomatic patients without calcium that the prevalence of significant stenosis was zero.<sup>24</sup> In symptomatic patients, however, the prevalence of significant stenosis increased to 8%. Moreover, these observations may be more pronounced in patients presenting with unstable symptoms, as suggested by Henneman et al.<sup>7</sup> In patients with ACS, the authors showed that significant luminal narrowing was present in 39% of patients with a zero CS.

It is conceivable that underlying differences in plaque composition in relation to clinical presentation may influence the reliability of CS as a marker of plaque burden. Indeed, previous histopathological data have demonstrated that lesions associated with ACS are not often heavily calcified.<sup>26-28</sup> Moreover, several post-mortem series have reported that calcifications develop relatively late in the process of atherosclerosis.<sup>22 29</sup> In fact, intimal thickening with lipid accumulation is typically the first stage of atherosclerosis. This process is followed by the growth of the lipid core, fibrous cap formation and possibly deposition of small calcifications in the plaque.<sup>22</sup> Interestingly, Burke et al demonstrated in a series of sudden cardiac death patients that plaque ruptures show relatively little calcification; the majority of acute plaque ruptures resulting in sudden death occurred in

areas of only mild calcification.<sup>29</sup> Indeed, calcium is not often demonstrated in the culprit lesions of ruptured plaques but is more often related to stable CAD. It seems that, in contrast to the destabilizing effects of the lipid core, calcium is a more stabilizing force.<sup>30</sup> Similarly, previous studies comparing plaque composition between patients presenting with ACS and stable CAD have also revealed a relatively lower proportion of extensive calcifications. Notably this observation has been reported using both non-invasive and invasive imaging modalities.<sup>26 31-34</sup> Also, in the present study relative plaque composition on CTA was significantly different in patients with ACS than in patients with stable CAD. More non-calcified and mixed lesions were observed in patients with ACS, whereas patients with stable CAD showed more calcified plaques. The observed difference in plaque composition was shown to strongly influence the relationship between CS and plaque burden and composition. Importantly, as demonstrated invasively for the first time, absence of calcium in patients presenting with ACS does not exclude the potential presence of vulnerable atherosclerotic plaque. Accordingly, the current study provides a valuable link between previous studies in patients with ACS, reporting a lower extent of calcium on the one hand and an increased rate of obstructive CAD in the absence of calcium on the other hand. Moreover, our observations may also indicate that as compared to stable or asymptomatic patients, the negative predictive value of absent or low CS for cardiovascular events may be reduced in patients at higher risk, such as patients with ACS. In this population, more detailed imaging tools may be preferred to establish or exclude the presence of substantial and potentially vulnerable plaque burden.

The following limitations of the present study should be considered. First, the present study only evaluated 112 patients in a single center. Ideally, a larger patient population should be studied, preferably in a multicenter setting. Second, based on the current small size of the study population it was not possible to draw any firm conclusions if smaller subgroups of the CS were used. Future studies with larger cohorts are necessary to perform analysis with smaller subgroups of the CS. Third, one of the general disadvantages of CTA is the use of ionizing radiation and contrast. Therefore, careful patient selection regarding age, renal function and body mass index are of fundamental importance to optimize use of CTA. Furthermore, image protocols should be carefully selected to prevent unnecessary exposure to radiation. In addition, a referral bias could be present, as in a limited number of cases patients were referred for invasive imaging on the basis of CTA findings. Lastly, correlation with events would be of interest. However, due to the relative novelty of the technology, longer follow-up data have yet to become available.

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