



Contents lists available at ScienceDirect

Journal of Cardiovascular Computed Tomography

journal homepage: www.JournalofCardiovascularCT.com

Research paper

Plaque volume, composition, and fraction versus ischemia and outcomes in patients with coronary artery disease

Jurrien H. Kuneman^a, Inge J. van den Hoogen^a, Jussi Schultz^b, Teemu Maaniitty^b, Alexander R. van Rosendaal^a, Vasileios Kamperidis^a, Michiel A. de Graaf^a, Alexander Broersen^c, J. Wouter Jukema^{a,d}, Jeroen J. Bax^{a,e}, Antti Saraste^{b,e}, Juhani Knuuti^{a,b,*}

^a Department of Cardiology, Leiden University Medical Center, the Netherlands^b Turku PET Centre, Turku University Hospital and University of Turku, Turku, Finland^c Department of Radiology, Division of Image Processing, Leiden University Medical Center, the Netherlands^d Netherlands Heart Institute, Utrecht, the Netherlands^e Heart Center, Turku University Hospital and University of Turku, Turku, Finland

ARTICLE INFO

Keywords:

Coronary artery disease
Coronary computed tomography angiography
Positron emission tomography
Plaque volume
Quantitative plaque analysis
Atherosclerosis

ABSTRACT

Background: The various plaque components have been associated with ischemia and outcomes in patients with coronary artery disease (CAD). The main goal of this analysis was to test the hypothesis that, at patient level, the fraction of non-calcified plaque volume (PV) of total PV is associated with ischemia and outcomes in patients with CAD. This ratio could be a simple and clinically useful parameter, if predicting outcomes.

Methods: Consecutive patients with suspected CAD undergoing coronary computed tomography angiography with selective positron emission tomography perfusion imaging were selected. Plaque components were quantitatively analyzed at patient level. The fraction of various plaque components were expressed as percentage of total PV and examined among patients with non-obstructive CAD, suspected stenosis with normal perfusion, and those with reduced myocardial perfusion. Clinical outcomes included all-cause mortality and myocardial infarction.

Results: In total, 494 patients (age 63 ± 9 years, 55% male) were included. Total PV and all plaque components were significantly larger in patients with reduced myocardial perfusion compared to patients with normal perfusion and those with non-obstructive CAD. During follow-up 35 events occurred. Patients with any plaque component \geq median showed worse outcomes (log-rank $p < 0.001$ for all). In addition, low-attenuation plaque \geq median was associated with worse outcomes independent of total PV (adjusted HR: 2.754, 95% CI: 1.022–7.0419, $p = 0.045$). The fractions of the various plaque components were not associated with outcomes.

Conclusion: Larger total PV or any plaque component at patient level are associated with abnormal myocardial perfusion and adverse events. The various plaque components as fraction of total PV lack additional prognostic value.

1. Introduction

Coronary artery disease (CAD) is the most common cause of mortality globally and remains a major threat to public health¹. Coronary atherosclerosis is a chronic condition that causes pathological changes of the vascular wall including the formation of plaque and luminal narrowing, potentially leading to myocardial ischemia and acute coronary syndrome in case of plaque rupture^{2,3}. Coronary computed tomography angiography (CCTA) enables comprehensive, noninvasive evaluation of CAD

including coronary anatomy, luminal narrowing, and quantification of atherosclerosis using advanced plaque analysis^{4,5}.

However, there is an apparent paradox in the behavior of coronary atherosclerosis. The amount of coronary artery calcification is a general marker of coronary atherosclerosis and has been associated with an increased risk of adverse cardiac events^{6,7}. On the other hand, calcification of coronary artery plaques has been considered as a marker of plaque stabilization^{3,8}. Moreover, serial CCTA studies demonstrated that statin therapy promoted the formation of calcified plaque with a

Abbreviations: CAD, Coronary artery disease; CCTA, Coronary computed tomography angiography; HU, Hounsfield unit; IQR, Interquartile range; PET, Positron emission tomography; PET-CT, Positron emission tomography-computed tomography; PV, Plaque volume.

* Corresponding author. Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333ZA Leiden, the Netherlands.

E-mail address: juhani.knuuti@tyks.fi (J. Knuuti).

<https://doi.org/10.1016/j.jcct.2023.02.004>

Received 26 July 2022; Received in revised form 8 February 2023; Accepted 15 February 2023

Available online xxxx

1934-5925/© 2023 The Authors. Published by Elsevier Inc. on behalf of Society of Cardiovascular Computed Tomography. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

subsequent reduction in non-calcified plaque⁹⁻¹¹, besides its beneficial effect on prognosis¹². In contrast, vulnerable atherosclerotic plaques are characterized by large non-calcified, low-attenuation plaque components, as well as spotty calcifications and vascular remodeling¹³⁻¹⁶.

The fraction of the various plaque components of the total plaque volume (PV) may serve as an additional parameter to identify patients with CAD at risk for adverse events. This ratio could be a simple and clinically useful parameter, if predicting outcomes. Our hypothesis was that the fraction of non-calcified PV (of total PV) at patient level may be associated with a higher incidence of ischemia and an increased risk of adverse events. Accordingly, the aim of the study was to evaluate the association of total plaque, the various plaque components, and their fractions at patient level with myocardial ischemia on positron emission tomography (PET) and clinical outcomes in patients with CAD.

2. Methods

2.1. Patients and combined PET-CT strategy

Onsecutive patients with suspected CAD undergoing clinically indicated CCTA with sequential [¹⁵O]H₂O PET myocardial perfusion imaging at the Turku University Hospital, Turku, Finland between 2007 and 2011 were included in this retrospective analysis. The study design has been reported in detail previously¹⁷. In brief, in patients who had a suspected obstructive stenosis on CCTA scan, a subsequent PET myocardial perfusion imaging scan was performed to assess the presence of myocardial ischemia. In the presence of non-obstructive CAD, no further testing occurred. Patients were excluded in this analysis if a) no atherosclerosis was present by visual CCTA assessment, b) insufficient image quality for quantitative analysis or c) no PET perfusion study was performed despite suspected obstructive CAD. This study was performed according to the Declaration of Helsinki. The protocol was approved by the Ethics committee of the Hospital District of South-West Finland and waived the need for written informed consent.

2.2. CCTA and PET acquisition

Patients underwent both non-contrast computed tomography for calcium scoring and contrast-enhanced CCTA. CCTA image acquisition has been described previously¹⁷⁻¹⁹. In short, CCTA was performed using a 64-row hybrid PET-CT scanner (GE Discovery VCT or GE D690, General Electric Medical Systems, Waukesha, Wisconsin, USA). Intravenous metoprolol 0–30 mg was administered before the scan to achieve a heart rate <60 bpm. Sublingual nitroglycerine (800 µg) or isosorbide dinitrate (1.25 mg) were also administered. Iodinated contrast infusion (60–80 mL of 400 mg iodine/mL iomeprol at 4–4.5 mL/s) was followed by a saline flush. The collimation was 64 × 0.625 mm, gantry rotation time was 350 msec, tube current 600–750 mA, and tube voltage 100–120 kV depending on patient size. Whenever feasible, prospectively triggered acquisition was applied to reduce radiation dose. If obstructive CAD was suspected after the initial evaluation of the CCTA scan, a dynamic quantitative PET perfusion scan during adenosine stress was performed using a hybrid PET-CT device in the same session. [¹⁵O]H₂O (900–1100 MBq) was intravenously injected as a radiotracer (Radiowater Generator, Hidex Oy, Finland) and hereafter an adenosine-stress scan was performed. Adenosine was infused 2 min before the start of the scan and was infused at 140 µg/kg/min^{17,18}. Patients were instructed to avoid intake of caffeine for 24 h before the PET study.

2.3. Imaging analysis

CCTA data were visually analyzed according to current guidelines²⁰. Coronary artery stenosis was defined as any atherosclerotic plaque ≥30% luminal diameter stenosis and graded as non-obstructive (<50% diameter stenosis) or as obstructive lesions (≥50% diameter stenosis). PET perfusion data were quantitatively analyzed using Carimas software

(version 1.1.0, Turku PET Center, Turku, Finland) by experienced readers blinded to CCTA and clinical data. An absolute regional myocardial stress perfusion <2.4 mL/g/min was considered abnormal^{17,18}.

Quantitative computed tomography angiography image analysis was performed using dedicated software (QAngio CT Research Edition, version 1.3.6, Medis Medical Imaging, Leiden, The Netherlands) by an experienced reader (V.K.) blinded to PET perfusion data, and has been described in detail previously¹⁹. In brief, a 3-dimensional coronary tree and its side branches were extracted from the CCTA data set. All coronary vessels >1.5 mm diameter were evaluated and each vessel and segment were automatically labeled according to current guidelines²⁰. Multi-planar reconstructions were created for each coronary artery. Subsequently, the lumen and vessel wall were automatically detected. All atherosclerotic lesions were automatically detected and quantitatively analyzed. The reader confirmed the detected lesions and manually adjusted the presence and location of a lesion, if needed. For each lesion, the software provided quantitative data for stenosis location, stenosis severity and plaque composition. In addition, plaque volume according to plaque composition were determined using pre-defined intensity thresholds in Hounsfield units (HU): low-attenuation plaque –30 to 75 HU, fibro-fatty plaque 76 to 130 HU, fibrous plaque 131 to 350 HU and calcified plaque >350 HU^{5,21}. Chronic total occlusions were visually identified and automatically quantified using a dedicated algorithm¹⁹. The PV of the different plaque components were calculated on a per-patient level. Non-calcified PV was defined as plaque composition ≤350HU (i.e. including fibrous plaque, fibro-fatty plaque, and low-attenuation plaque). The fractions of the various plaque components (calcified PV fraction, non-calcified PV fraction, and low-attenuation PV fraction) were calculated by dividing the respective plaque components by the total PV and expressed as a percentage.

2.4. Clinical outcomes and follow-up

Baseline patient characteristics including cardiac risk factors, symptoms (chest pain and dyspnea on exertion), medication use, exercise electrocardiography and laboratory tests were retrospectively collected from the hospital clinical database. CCTA and PET imaging data were obtained from an imaging database and electronic medical records. Patients were divided into three groups according to CCTA and PET perfusion findings: 1) patients with non-obstructive CAD evaluated by CCTA; 2) suspected obstructive CAD and normal myocardial perfusion by PET imaging; or 3) suspected obstructive CAD and reduced myocardial perfusion by PET imaging. Obstructive CAD was defined as any coronary lesion ≥50% diameter stenosis. The cut-off values to dichotomize the PV of the various plaque components and its fractions were defined by the median value of the overall population of the respective plaque components. Data on all-cause mortality, myocardial infarction and revascularization were obtained using registries of the Finnish National Institute for Health and Welfare and Center for Clinical Informatics of the Turku University Hospital. Myocardial infarction was defined according to the criteria of the European Society of Cardiology guidelines²². Follow-up time was recorded from initial CCTA until the end of 2016.

2.5. Statistical analysis

Continuous variables following a normal distribution are presented as mean ± standard deviation and were compared using the One-way analysis of variance test. Non-normally distributed continuous variables are presented as median with interquartile range (IQR) and were compared using the Mann-Whitney *U* test or Kruskal-Wallis test. Post hoc analysis was performed with the Bonferroni's test if there was a significant difference in the 3-group comparison. The distribution of continuous variables was evaluated using histograms and Q-Q plots. Categorical variables are presented as numbers and percentages and were compared using the χ^2 test or Fisher's exact test. Kaplan-Meier curves were generated to estimate the cumulative survival rates of all-cause mortality or

myocardial infarction and the log-rank test was used to compare patients with the various plaque components \geq median vs. $<$ median. Multivariable Cox proportional hazards regression analysis was used to adjust for age, statin use, and total PV. A two-sided p-value <0.05 was considered significant. Data analysis was performed with SPSS version 25.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York, USA).

3. Results

3.1. Patients

In total, 922 consecutive patients with suspected CAD had undergone a clinically indicated CCTA scan between 2007 and 2011. Patients without atherosclerosis ($n = 261$), insufficient image quality for quantitative plaque analysis ($n = 153$), or who failed to adhere to the sequential PET-CT protocol ($n = 14$) were excluded. Subsequently, 494 patients (age 63 ± 9 years, 55% male) were included in the analysis (Supplemental Fig. 1). Baseline patient demographic and clinical characteristics are summarized in Table 1.

3.2. Imaging findings

In 494 patients, 1872 coronary lesions were detected. The presence of obstructive CAD was ruled out by CCTA in 199 patients (40%). In the remaining 295 patients, obstructive CAD was suspected after the initial CCTA evaluation and subsequent PET perfusion imaging was conducted. In PET perfusion study, reduced myocardial perfusion was detected in 154 patients (31% of the overall population) and a normal PET perfusion study in 141 patients (29%). Anatomical CCTA evaluation demonstrated a higher number of atherosclerotic lesions and more severe stenosis as

well as more calcified plaques and a higher CAC score in the group of patients with suspected obstructive CAD and reduced myocardial perfusion ($p < 0.001$ for all, Table 2).

3.3. Calcified and non-calcified plaque volumes

The median total PV of the overall population was 169 [IQR 80–350] mm^3 , the calcified PV 28 [IQR 93–39] mm^3 , the non-calcified PV 136 [IQR 71–256] mm^3 , and low-attenuation PV 20 [IQR 9–39] mm^3 . The PV of the different plaque components according to stenosis severity and PET perfusion findings are displayed in Fig. 1. All plaque components were significantly larger in patients with abnormal myocardial perfusion compared to patients with suspected stenosis and normal perfusion and those with non-obstructive CAD (total PV: 370 [IQR 197–739] mm^3 vs. 160 [IQR 78–312] mm^3 and vs. 108 [IQR 59–177] mm^3 ; calcified PV: 84 [IQR 23–220] mm^3 vs. 31 [IQR 6–83] mm^3 and vs. 9 [IQR 1–34] mm^3 ; non-calcified PV: 274 [IQR 157–500] mm^3 vs. 136 [IQR 70–214] mm^3 and vs. 94 [IQR 53–140] mm^3 ; and low-attenuation PV: 41 [IQR 22–67] mm^3 vs. 18 [IQR 8–32] mm^3 and vs. 13 [IQR 6–23] mm^3 , respectively, $p < 0.001$ for all). All plaque components were significantly different between groups on post hoc analysis.

3.4. Plaque volume fraction

The median calcified PV fraction of the overall population was 17 [IQR 5–30] %, the median non-calcified PV fraction 83 [IQR 70–94] %, and the median low-attenuation PV fraction 10 [IQR 7–15] %. The calcified PV fraction was significantly larger in patients with reduced myocardial perfusion by PET imaging as compared to patients with suspected obstructive CAD and normal perfusion, and those with non-

Table 1

Baseline patient demographic and clinical characteristics of the overall population and according to stenosis severity and PET perfusion findings.

Variable	Overall population n = 494	Non-obstructive CCTA n = 199	Suspected stenosis, normal perfusion n = 141	Suspected stenosis, reduced perfusion n = 154	p-value
Age, y	63 \pm 9	63 \pm 9	64 \pm 8	63 \pm 9	0.197
Male, n (%)	269 (55)	98 (49)	58 (41)	113 (71)	<0.001
Body Mass Index, kg/m ²	27 [25–31]	30 [26–35]	27 [25–29] ^a	28 [25–31]	0.001
Hypertension, n (%)	386 (78)	140 (70)	115 (82)	131 (85)	0.002
Dyslipidemia, n (%)	358 (73)	137 (69)	99 (70)	122 (79)	0.075
Diabetes mellitus, n (%)	84 (17)	29 (15)	19 (14)	36 (23)	0.039
Family history of CAD, n (%)	219 (44)	86 (43)	61 (43)	72 (47)	0.77
Current smoking, n (%)	67 (14)	32 (16)	15 (11)	20 (13)	0.34
Previous smoking, n (%)	111 (23)	40 (20)	29 (21)	42 (27)	0.23
eGFR (CKD-EPI), ml/min	83 \pm 14	83 \pm 15	83 \pm 13	83 \pm 15	0.79
Atrial fibrillation, n (%)	55 (11)	26 (13)	14 (10)	15 (10)	0.53
Lipid profile					
Total cholesterol, mmol/l	4.90 \pm 1.07	4.95 \pm 1.06	4.85 \pm 0.97	4.88 \pm 1.18	0.78
HDL-c, mmol/l	1.53 \pm 0.46	1.55 \pm 0.47	1.63 \pm 0.49	1.41 \pm 0.40 ^{a, b}	0.002
LDL-c, mmol/l	2.69 \pm 0.94	2.73 \pm 0.94	2.60 \pm 0.84	2.73 \pm 1.04	0.55
Triglycerides, mmol/l	1.30 [0.90–1.80]	1.30 [1.0–1.7]	1.10 [0.90–1.60]	1.50 [0.95–2.00]	0.090
Chest pain, n (%)					
Typical AP	128 (28)	41 (22)	35 (27)	52 (35)	0.04
Atypical AP	246 (53)	100 (54)	70 (53)	76 (51)	0.80
Exercise ECG changes (>1 mm ST segment depression)	208 (61)	57 (48)	71 (68)	80 (68)	0.002
Medication, n (%)					
Beta-blocker	252 (58)	80 (48)	75 (60)	97 (70)	<0.001
Statin	249 (58)	86 (51)	68 (55)	95 (69)	0.004
Antiplatelet	297 (69)	104 (62)	82 (65)	111 (82)	<0.001
Anticoagulant	28 (7)	13 (8)	6 (5)	9 (7)	0.63
Long-acting nitrate	60 (15)	19 (12)	18 (15)	23 (17)	0.41
Diuretic	103 (25)	44 (27)	29 (24)	30 (22)	0.64
ACE-I or ARB	189 (44)	77 (47)	47 (38)	65 (46)	0.27
Calcium-channel blocker	81 (19)	31 (19)	24 (20)	26 (19)	0.97
Antiarrhythmic	4 (1)	2 (1)	1 (1)	1 (1)	0.91

Values are presented as mean \pm standard deviation, median [interquartile range], or n (%). ACE = angiotensin converting enzyme inhibitor; AP = angina pectoris; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; ECG = electrocardiography, eGFR (CKD-EPI) = estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration); PET = positron emission tomography.

^a $p < 0.05$ vs. group 'Non-obstructive CCTA' with Bonferroni's post hoc analysis.

^b $p < 0.05$ vs. group 'Suspected stenosis, normal perfusion' with Bonferroni's post hoc analysis.

Table 2
CCTA results.

	Overall population n = 494	Non-obstructive CCTA n = 199	Suspected stenosis, normal perfusion n = 141	Suspected stenosis, reduced perfusion n = 154	p-value
CAC score (Agatston)	113 [16–404]	38 [5–145]	152 [31–322] ^a	422 [108–998] ^{a b}	<0.001
Coronary artery dominance					
Right, n (%)	449 (91)	180 (91)	127 (90)	142 (92)	0.79
Left, n (%)	40 (8)	17 (9)	13 (9)	10 (7)	0.66
Co-dominance, n (%)	5 (1)	2 (1)	1 (1)	2 (1)	0.88
Stenosis severity					
No. of plaques ≥30%	3.1 ± 2.2	2.1 ± 1.7	2.8 ± 1.8 ^a	4.6 ± 2.3 ^{a b}	<0.001
No. of plaques 30–50%	1.4 ± 1.2	1.3 ± 1.1	1.3 ± 1.1	1.7 ± 1.3 ^{a b}	0.010
No. of plaques ≥50%	1.6 ± 1.8	0.7 ± 1.2	1.5 ± 1.4 ^a	2.9 ± 2.1 ^{a b}	<0.001
No. of severe stenosis >70%	0.6 ± 1.1	0.2 ± 0.6	0.4 ± 0.7 ^a	1.3 ± 1.4 ^{a b}	<0.001
No. of proximal stenosis ≥50%	0.9 ± 1.1	0.4 ± 0.7	0.9 ± 1.0 ^a	1.4 ± 1.2 ^{a b}	<0.001
Plaque composition					
No. of calcified plaques (≥30%)	1.8 ± 2.0	1.0 ± 1.3	1.6 ± 1.8	2.9 ± 2.3 ^{a b}	<0.001
No. of non-calcified plaques (≥30%)	0.5 ± 0.7	0.6 ± 0.7	0.4 ± 0.6 ^a	0.5 ± 0.7	0.029
No. of mixed plaques (≥30%)	0.6 ± 0.9	0.3 ± 0.6	0.6 ± 0.8 ^a	0.9 ± 1.1 ^{a b}	<0.001

Values are presented as mean ± standard deviation, median [interquartile range], or n (%). CAC = coronary artery calcification, CCTA = coronary computed tomography angiography.

^a p < 0.05 vs. group 'Non-obstructive CCTA' with Bonferroni's post hoc analysis.

^b p < 0.05 vs. group 'Suspected stenosis, normal perfusion' with Bonferroni's post hoc analysis.

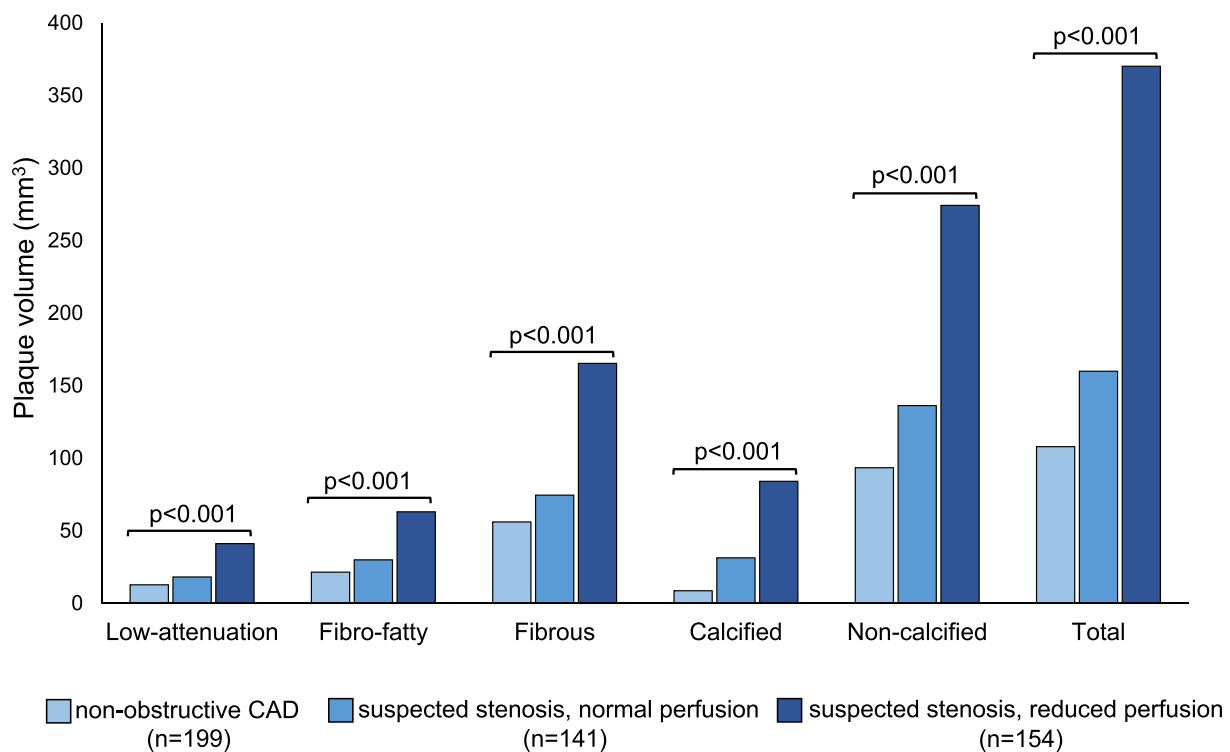


Fig. 1. Bar chart showing the plaque volumes of the various plaque components. The median plaque volumes of the various plaque components for patients with non-obstructive CAD (light blue), patients with suspected obstructive CAD and normal myocardial perfusion (blue), and patients with suspected obstructive CAD and reduced myocardial perfusion (navy blue). P-value is for three group comparison with the Kruskal-Wallis test. All plaque components were significantly different between groups on Bonferroni's post hoc analysis. CAD = coronary artery disease.

obstructive CAD (24 [12–36] % vs. 19 [7–32] % and vs. 9 [1–23] %, respectively, p < 0.001). In contrast, the non-calcified PV fraction was significantly smaller in patients with reduced myocardial perfusion compared to those with normal perfusion and non-obstructive CAD (75 [IQR 63–86] % vs. 81 [IQR 68–93] % and vs. 89 [IQR 76–98] %, respectively, p < 0.001), whereas the low-attenuation PV fraction was comparable between the groups (11 [7–15] % vs. 10 [7–14] % and vs. 11 [7–16] %, respectively, p = 0.32, Fig. 2). The distribution of the calcified, non-calcified, and low-attenuation PV fractions according to total PV are presented in Supplemental Fig. 2.

3.5. Follow-up

During a median follow-up time of 6.1 [IQR 5.3–7.5] years, 22 patients died. Non-fatal myocardial infarction was detected in 14 patients. Early revascularization (within 6 months after the CCTA scan) was performed in 78 patients. In total, 35 major events occurred (all-cause mortality or myocardial infarction). One patient who had an earlier non-fatal event died later. The absolute plaque volumes and plaque volume fractions of patients who had an event during follow-up vs. those without are displayed in Supplemental Figs. 3 and 4, respectively. Kaplan-Meier

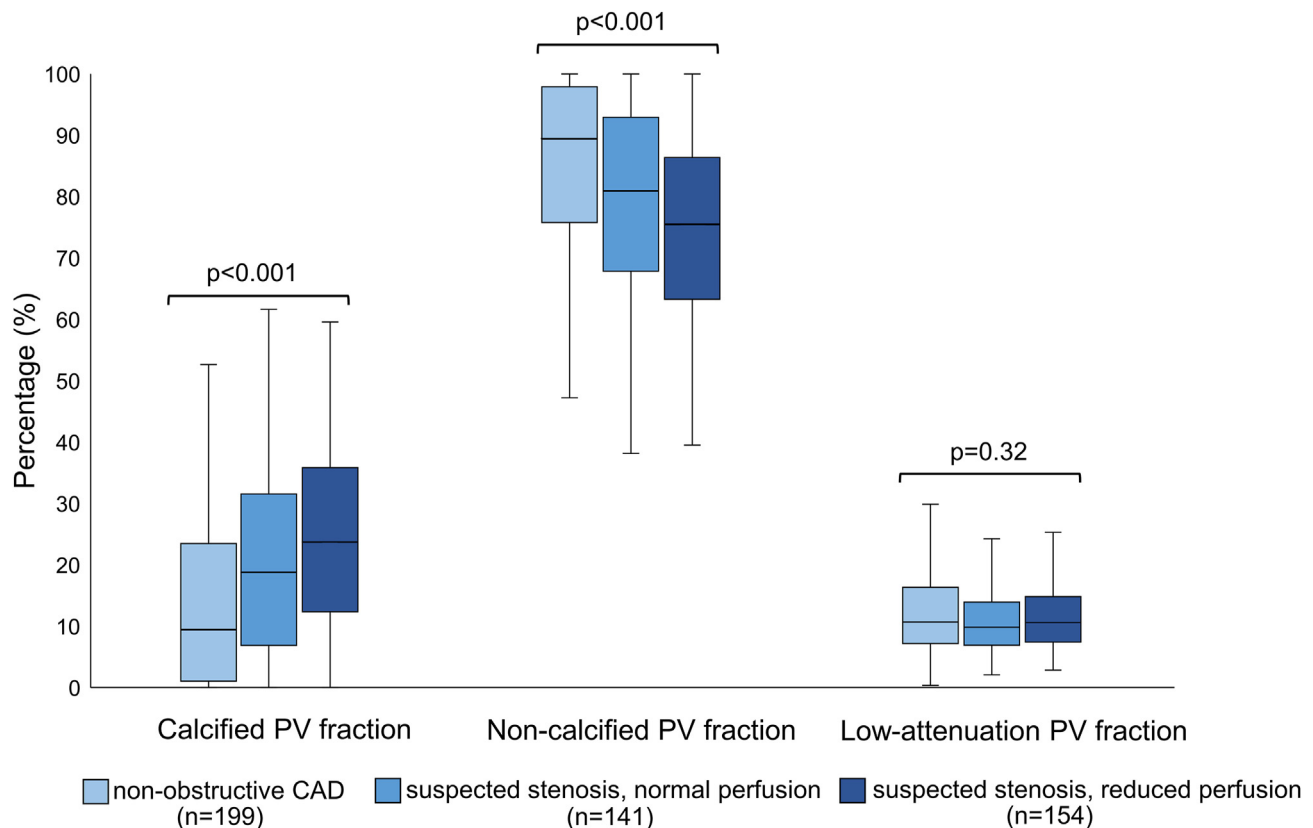


Fig. 2. Boxplot of the various plaque components as fraction of total PV. The median calcified PV fraction, non-calcified PV fraction, and low-attenuation PV fraction according to stenosis severity and positron emission tomography perfusion findings. *P*-value is for three group comparison with the Kruskal-Wallis test. Error bars represent 95% confidence intervals. CAD = coronary artery disease, PV = plaque volume.

survival analysis showed worse outcomes in patients with total PV or PV of any plaque component \geq median vs. those with PV $<$ median (total PV: log-rank $\chi^2 = 15.73$, $p < 0.001$; calcified PV: log-rank $\chi^2 = 11.12$, $p = 0.001$; non-calcified PV: log-rank $\chi^2 = 15.99$, $p < 0.001$; and low-attenuation PV: log-rank $\chi^2 = 16.11$, $p < 0.001$, Fig. 3). Of the different plaque components, only low-attenuation PV \geq median was associated with worse outcomes independent of total PV (adjusted HR: 2.754, 95% CI: 1.022–7.419, $p = 0.045$), whereas the calcified PV and non-calcified PV \geq median vs. $<$ median were not associated with outcomes if adjusted for total PV (adjusted HR: 1.688, 95% CI: 0.664–4.294, $p = 0.27$; and adjusted HR: 2.647, 95% CI: 0.970–7.225, $p = 0.057$, respectively).

The fractions of the different plaque components were not associated with the composite endpoint of all-cause mortality or myocardial infarction in multivariable analysis (Table 3), nor when patients who underwent early revascularization (within 6 months after CCTA) were excluded (calcified PV fraction: adjusted HR: 0.958, 95% CI: 0.363–2.528, $p = 0.93$; non-calcified PV fraction: adjusted HR: 1.124, 95% CI 0.418–3.020, $p = 0.82$; low-attenuation PV fraction, adjusted HR: 1.301, 95% CI 0.560–3.020, $p = 0.54$). Survival analysis according to CCTA and PET perfusion imaging findings has been published previously¹⁷.

4. Discussion

The main findings of the study could be summarized as follows: Larger total PV or any plaque component at patient level in general are associated with abnormal perfusion and increased risk of adverse events. The various plaque components as a fraction of total PV are not independently associated with outcomes.

4.1. Atherosclerotic plaque

Atherosclerosis is a chronic inflammatory process, which enables the development of atherosclerotic plaques via an array of complex cellular mechanisms^{23,24}. Atherosclerotic plaques are composed of various components including a lipid-rich necrotic core, fibrous tissue, and calcifications². Large amount of evidence highlighted the relation between coronary artery calcium, as a general marker of coronary atherosclerosis, and prognosis^{6,7}. Moreover, a study including 23,759 patients from the Western Denmark Heart Registry reported that total coronary atherosclerotic plaque burden was the main predictor of adverse events and emphasized the importance of total plaque burden over stenosis severity²⁵. The present study, which also included PET perfusion showed that increased total PV was associated with myocardial ischemia and worse outcomes.

In addition, the various plaque components, particularly non-calcified plaque, have also been linked with adverse cardiac events when analyzed at lesion level²⁶. Histopathological studies reported that vulnerable plaques with risk of rupture were more likely to have a large necrotic core (detected on CCTA as low-attenuation plaque), thin-cap fibroatheroma, positive remodeling, and spotty calcifications^{13,27}. Correspondingly, data from a sub-analysis of the Scottish Computed Tomography of the HEART trial including 1769 patients with stable chest pain showed that low-attenuation plaque burden was the strongest predictor of myocardial infarction compared to cardiovascular risk scores, coronary artery calcium scoring, and stenosis severity²⁸. In the present study, patients with increased low-attenuation plaque had worse outcomes even if adjusted for total PV. These results emphasize the total burden of atherosclerosis and low-attenuation plaque as a risk for myocardial ischemia and adverse cardiac events.

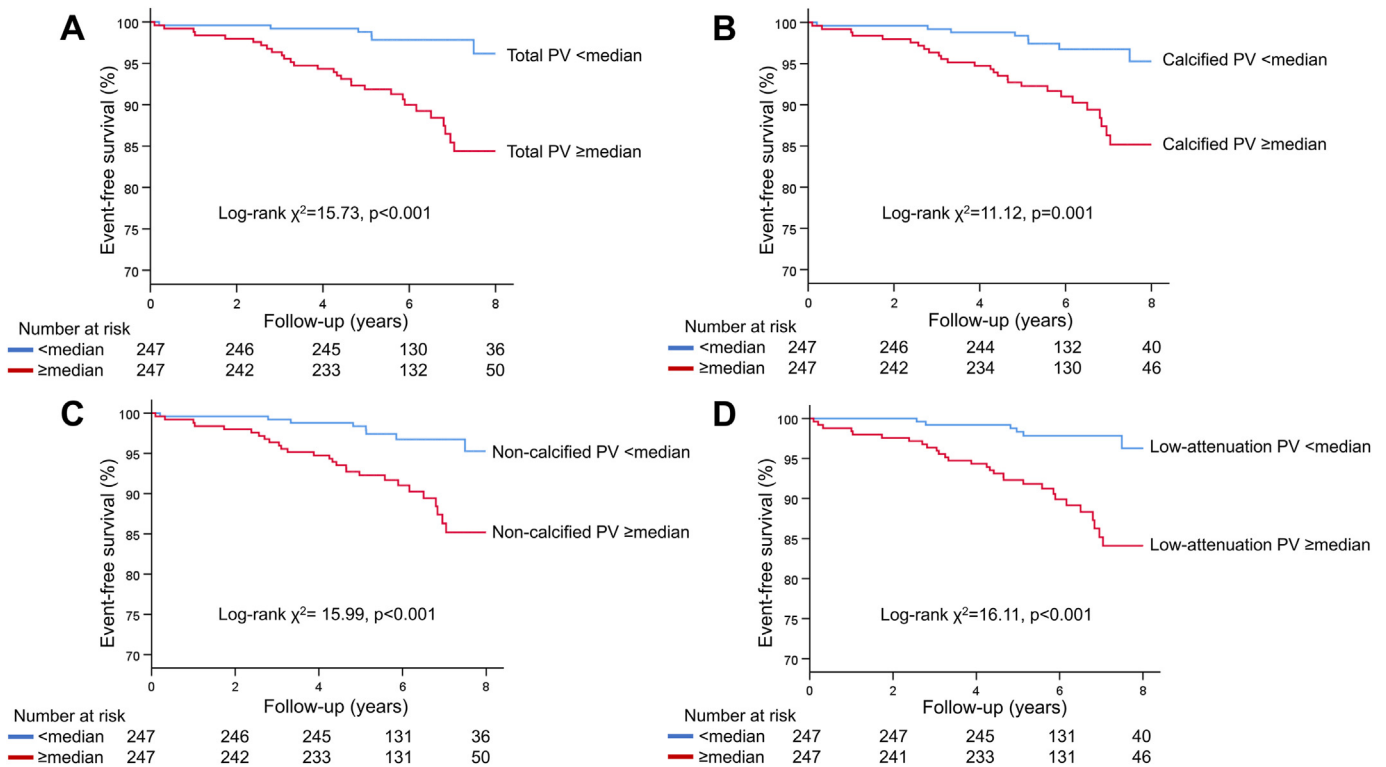


Fig. 3. PV of the various plaque components and risk of future adverse events. Kaplan-Meier curves demonstrating the event-free survival according to PV \geq median (red curves) vs. $<$ median (blue curves) for total PV (Panel A), calcified PV (Panel B), non-calcified PV (Panel C), and low-attenuation PV (Panel D). Clinical events included myocardial infarction or all-cause mortality. PV = plaque volume.

Table 3

Uni- and multivariable analysis of the various PV fractions for the composite endpoint of all-cause mortality and myocardial infarction.

Parameter	Univariable			Multivariable ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Calcified PV fraction \geq median vs. $<$ median	2.308	1.130–4.712	0.022	1.003	0.399–2.524	0.99
Non-calcified PV fraction \geq median vs. $<$ median	0.435	0.213–0.888	0.022	1.013	0.403–2.548	0.98
Low-attenuation PV fraction \geq median vs. $<$ median	0.811	0.417–1.578	0.54	1.675	0.741–3.787	0.22

CI = confidence interval, HR = hazard ratio, PV = plaque volume.

^a Adjusted for the following: age, statin therapy, total plaque volume.

4.2. Plaque volume fraction

The relation between coronary artery calcification and risk of adverse events is ambiguous. On one hand the amount of coronary artery calcification is an established marker for future adverse events, whereas calcification of coronary artery plaques has also been considered as a marker of plaque stabilization. Hence, the main goal of this analysis was to test the hypothesis that, at patient level, a large non-calcified PV fraction as related to the calcified PV fraction is associated with ischemia and outcomes in patients with CAD. If the hypothesis is proven true, this ratio could serve as a simple and clinically useful parameter for outcomes. In the present study, a larger calcified PV fraction was noted in patients with suspected obstructive stenosis and reduced PET perfusion, whereas the non-calcified PV fraction was smaller. However, the fraction of the different plaque components did not provide additional prognostic information if adjusted for total PV. These results do not support the previous suggestions and our original hypothesis. A potential explanation may be the association between the calcified- and non-calcified PV fractions with overall plaque burden. Patients with a large non-calcified PV fraction had low overall atherosclerotic plaque burden, which may represent an early stage of atherosclerotic disease, characterized by low overall plaque burden and low number of events. In contrast, patients

with a larger calcified PV fraction had more frequently high overall plaque burden, which may be considered as a more advanced stage of atherosclerotic disease and worse outcomes³.

Analyses from the Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging registry showed that a high percent calcified PV (of total PV) was associated with a lower risk of major adverse cardiac events, in contrast to the present study²⁹. However, clinical endpoints also included coronary revascularizations, which were accountable for the majority of events. In addition, the study population had less advanced CAD compared to the present study: patients with chronic total occlusions and who had undergone revascularization between the serial CCTA scans were excluded, therefore potentially excluding the most severe and vulnerable lesions.

4.3. Limitations

Several limitations should be acknowledged. First, the quantitative plaque analyses were performed on a per-patient level. Therefore, it includes the plaque components of all lesions instead of a single culprit lesion. However, coronary artery plaques appear to be dynamic and vulnerable plaques may develop later or at a different location in the coronary vasculature, therefore making it impossible to know which

lesion is causing the event. Second, the clinical endpoint included all-cause mortality although cardiovascular mortality could be theoretically a more specific endpoint in patients with CAD. However, in real life cardiovascular mortality is not a reliable indicator as it is often based on assumptions. Third, the number of events in this study population is limited. Fourth, the limited spatial resolution of CCTA for plaque components, and particularly the use of earlier 64-slice computed tomography scanners, should be taken into consideration as a source of variability. However, the CCTA scans were performed in accordance with current guidelines for best CCTA acquisition. Last, PET perfusion data of patients with non-obstructive CAD is lacking as well as resting PET perfusion data. This did not allow for perfusion reserve analysis. However, not having resting perfusion data cannot be considered as a major limitation for the study. First, our group and others have shown previously that the diagnostic accuracy of stress only PET perfusion imaging with absolute quantitation is as good as stress-rest imaging in a similar population³⁰⁻³². The only limitation of not having resting PET perfusion imaging is that microvascular disease cannot be accurately separated from balanced three vessel CAD, but that was not the focus of the present study.

5. Conclusion

Larger total PV or volume of any plaque component at patient level in general are associated with abnormal myocardial perfusion and are an important prognostic marker of adverse events. However, the various plaque components as a fraction of total PV are not independently associated with outcomes. The results emphasize the total burden of atherosclerosis as a risk for myocardial ischemia or clinical events.

Funding

J. Schulz has received a personal research grant from the Finnish Foundation for Cardiovascular Research. T. Maaniitty was supported by a research grant from the Finnish State Research Funding.

Declaration of competing interest

The department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands has received unrestricted research grants from Bayer, Abbott Vascular, Medtronic, Biotronik, Boston Scientific, GE Healthcare and Edwards Lifesciences. Dr. Knuuti received consultancy fees from GE Healthcare and AstraZeneca and speaker fees from GE Healthcare, Bayer, Lundbeck, Boehringer-Ingelheim, Pfizer and Merck, outside of the submitted work. Dr. Saraste received consultancy fees from Amgen, Astra Zeneca, Boehringer Ingelheim, and Pfizer, and speaker fees from Abbott, Astra Zeneca, and Bayer. Dr. Jukema received research grants from the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands, and the European Commission Seventh Framework Programme, and research support from Amgen, Astellas, AstraZeneca, Daiichi-Sankyo, Lilly, Merck-Schering-Plough, Pfizer, Roche, and Sanofi. Dr. Bax received speaker fees from Abbott Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcct.2023.02.004>.

References

- Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76:2982-3021. <https://doi.org/10.1016/j.jacc.2020.11.010>.
- Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352:1685-1695. <https://doi.org/10.1056/NEJMra043430>.

- Mori H, Torii S, Kutyna M, Sakamoto A, Finn AV, Virmani R. Coronary artery calcification and its progression: what does it really mean? *J Am Coll Cardiol Img*. 2018;11:127-142. <https://doi.org/10.1016/j.jcimg.2017.10.012>.
- The SCOT-HEART Investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet*. 2015;385:2383-2391. [https://doi.org/10.1016/S0140-6736\(15\)60291-4](https://doi.org/10.1016/S0140-6736(15)60291-4).
- de Graaf MA, Broersen A, Kitslaar PH, et al. Automatic quantification and characterization of coronary atherosclerosis with computed tomography coronary angiography: cross-correlation with intravascular ultrasound virtual histology. *Int J Cardiovasc Imag*. 2013;29:1177-1190. <https://doi.org/10.1007/s10554-013-0194-x>.
- Budoff MJ, Young R, Burke G, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). *Eur Heart J*. 2018;39:2401-2408. <https://doi.org/10.1093/eurheartj/ehy217>.
- Grandhi GR, Mirbolouk M, Dardari ZA, et al. Interplay of coronary artery calcium and risk factors for predicting CVD/CHD mortality: the CAC consortium. *J Am Coll Cardiol Img*. 2020;13:1175-1186. <https://doi.org/10.1016/j.jcimg.2019.08.024>.
- Huang H, Virmani R, Younis H, Burke AP, Kamm RD, Lee RT. The impact of calcification on the biomechanical stability of atherosclerotic plaques. *Circulation*. 2001;103:1051-1056. <https://doi.org/10.1161/01.cir.103.8.1051>.
- van Rosendaal AR, van den Hoogen IJ, Gianni U, et al. Association of statin treatment with progression of coronary atherosclerotic plaque composition. *JAMA Cardiol*. 2021;6:1257-1266. <https://doi.org/10.1001/jamacardio.2021.3055>.
- Smit JM, van Rosendaal AR, El Mahdoui M, et al. Impact of clinical characteristics and statins on coronary plaque progression by serial computed tomography angiography. *Circ Cardiovasc Imaging*. 2020;13, e009750. <https://doi.org/10.1161/CIRCIMAGING.119.009750>.
- Lee SE, Chang HJ, Sung JM, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. *J Am Coll Cardiol Img*. 2018;11:1475-1484. <https://doi.org/10.1016/j.jcimg.2018.04.015>.
- Cholesterol Treatment Trialists C, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670-1681. [https://doi.org/10.1016/S0140-6736\(10\)61350-5](https://doi.org/10.1016/S0140-6736(10)61350-5).
- Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol*. 2006;47:C13-C18. <https://doi.org/10.1016/j.jacc.2005.10.065>.
- Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol*. 2009;54:49-57. <https://doi.org/10.1016/j.jacc.2009.02.068>.
- Chang HJ, Lin FY, Lee SE, et al. Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol*. 2018;71:2511-2522. <https://doi.org/10.1016/j.jacc.2018.02.079>.
- Thomsen C, Abdulla J. Characteristics of high-risk coronary plaques identified by computed tomographic angiography and associated prognosis: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging*. 2016;17:120-129. <https://doi.org/10.1093/ehjci/jev325>.
- Maaniitty T, Stenstrom I, Bax JJ, et al. Prognostic value of coronary CT angiography with selective PET perfusion imaging in coronary artery disease. *J Am Coll Cardiol Img*. 2017;10:1361-1370. <https://doi.org/10.1016/j.jcimg.2016.10.025>.
- Kajander S, Joutsiniemi E, Saraste M, et al. Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease. *Circulation*. 2010;122:603-613. <https://doi.org/10.1161/CIRCULATIONAHA.109.915009>.
- Uusitalo V, Kamperidis V, de Graaf MA, et al. Coronary computed tomography angiography derived risk score in predicting cardiac events. *J Cardiovasc Comput Tomogr*. 2017;11:274-280. <https://doi.org/10.1016/j.jcct.2017.04.010>.
- Leipsic J, Abbara S, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr*. 2014;8:342-358. <https://doi.org/10.1016/j.jcct.2014.07.003>.
- Boogers MJ, Broersen A, van Velzen JE, et al. Automated quantification of coronary plaque with computed tomography: comparison with intravascular ultrasound using a dedicated registration algorithm for fusion-based quantification. *Eur Heart J*. 2012;33:1007-1016. <https://doi.org/10.1093/eurheartj/ehr465>.
- Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:2999-3054. <https://doi.org/10.1093/eurheartj/ehr236>.
- Hutchison JD, Goettsch C, Bertazzo S, et al. Genesis and growth of extracellular-vesicle-derived microcalcification in atherosclerotic plaques. *Nat Mater*. 2016;15:335-343. <https://doi.org/10.1038/nmat4519>.
- Raggi P, Genest J, Giles JT, et al. Role of inflammation in the pathogenesis of atherosclerosis and therapeutic interventions. *Atherosclerosis*. 2018;276:98-108. <https://doi.org/10.1016/j.atherosclerosis.2018.07.014>.
- Mortensen MB, Dzaye O, Steffensen FH, et al. Impact of plaque burden versus stenosis on ischemic events in patients with coronary atherosclerosis. *J Am Coll Cardiol*. 2020;76:2803-2813. <https://doi.org/10.1016/j.jacc.2020.10.021>.
- Andreini D, Magnoni M, Conte E, et al. Coronary plaque features on CTA can identify patients at increased risk of cardiovascular events. *J Am Coll Cardiol Img*. 2020;13:1704-1717. <https://doi.org/10.1016/j.jcimg.2019.06.019>.
- Otsuka F, Sakakura K, Yahagi K, Joner M, Virmani R. Has our understanding of calcification in human coronary atherosclerosis progressed? *Arterioscler Thromb Vasc Biol*. 2014;34:724-736. <https://doi.org/10.1161/ATVBAHA.113.302642>.

28. Williams MC, Kwiecinski J, Doris M, et al. Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction: results from the multicenter SCOT-heart trial (scottish computed tomography of the HEART). *Circulation*. 2020;141:1452–1462. <https://doi:10.1161/CIRCULATIONAHA.119.044720>.
29. Jin HY, Weir-McCall JR, Leipsic JA, et al. The relationship between coronary calcification and the natural history of coronary artery disease. *J Am Coll Cardiol Img*. 2021;14:233–242. <https://doi:10.1016/j.jcmg.2020.08.036>.
30. Stuijzand WJ, Uusitalo V, Kero T, et al. Relative flow reserve derived from quantitative perfusion imaging may not outperform stress myocardial blood flow for identification of hemodynamically significant coronary artery disease. *Circ Cardiovasc Imaging*. 2015;8. <https://doi:10.1161/CIRCIMAGING.114.002400>.
31. Danad I, Uusitalo V, Kero T, et al. Quantitative assessment of myocardial perfusion in the detection of significant coronary artery disease: cutoff values and diagnostic accuracy of quantitative [(15)O]H2O PET imaging. *J Am Coll Cardiol*. 2014;64:1464–1475. <https://doi:10.1016/j.jacc.2014.05.069>.
32. Driessen RS, Danad I, Stuijzand WJ, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. *J Am Coll Cardiol*. 2019;73:161–173. <https://doi:10.1016/j.jacc.2018.10.056>.