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Research paper

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

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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 ≥ median showed worse outcomes (log-rank $p < 0.001$ for all). In addition, low-attenuation plaque ≥ 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 health[1]. 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.

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subsequent reduction in non-calcified plaque[9-11], besides its beneficial effect on prognosis[12]. In contrast, vulnerable atherosclerotic plaques are characterized by large non-calcified, low-attenuation plaque components, as well as spotty calcifications and vascular remodeling[13-16].

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

Consecutive patients with suspected CAD undergoing clinically indicated CCTA with sequential [^{15}O]H_2O 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 previously[17]. 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 previously[17-19]. 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. [^{15}O]H_2O (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 guidelines[20]. 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 previously[19]. 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 guidelines[20]. Multiplanar 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 algorithm[19]. 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 guidelines[22]. 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 infraction and the log-rank test was used to compare patients with the various plaque components ≥ 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 ± 9	63 ± 9	64 ± 8	63 ± 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 ± 14	83 ± 15	83 ± 13	83 ± 15	0.79
Atrial fibrillation, n (%)	55 (11)	26 (13)	14 (10)	15 (10)	0.53
Lipid profile					
Total cholesterol, mmol/l	4.90 ± 1.07	4.95 ± 1.06	4.85 ± 0.97	4.88 ± 1.18	0.78
HDL-c, mmol/l	1.53 ± 0.46	1.55 ± 0.47	1.63 ± 0.49	1.41 ± 0.40[a b]	0.002
LDL-c, mmol/l	2.69 ± 0.94	2.73 ± 0.94	2.60 ± 0.84	2.73 ± 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 ± 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.

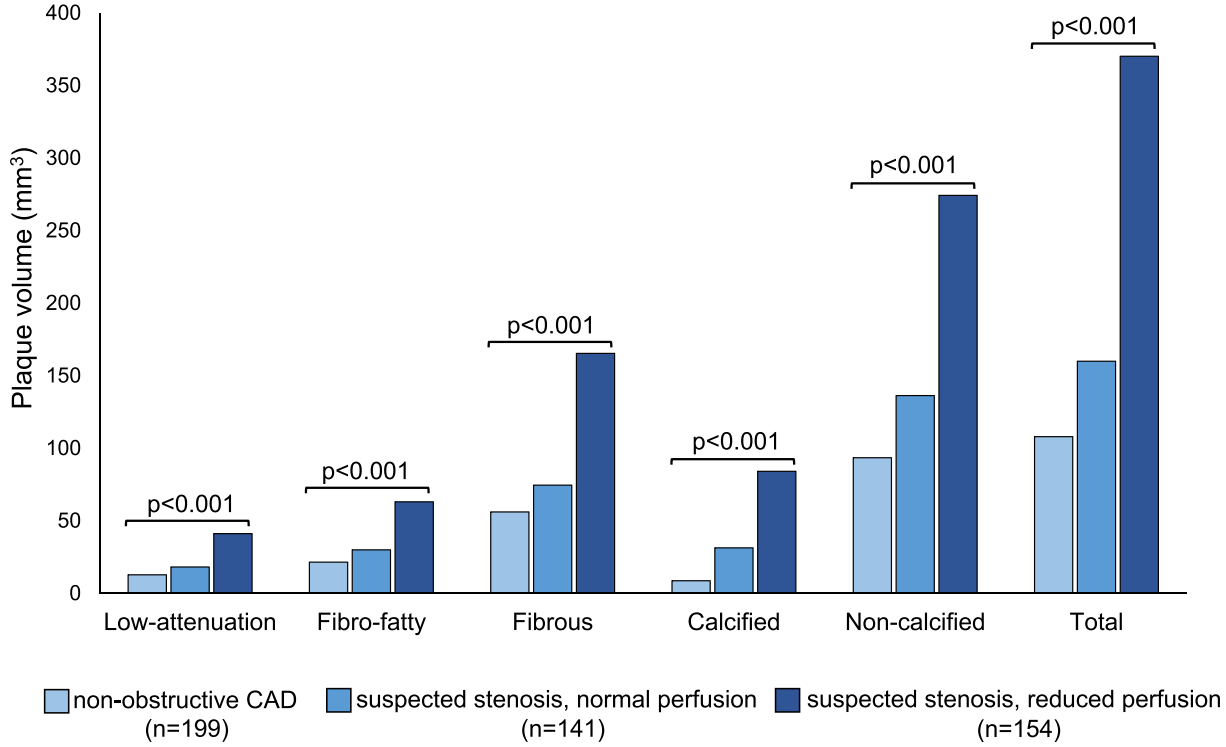

Fig. 1. Bar chart showing the plaque volumes of the various plaque components. The median plaque volumes of the various plaque components for patients with non-obstructive CAD (light blue), patients with suspected obstructive CAD and normal myocardial perfusion (blue), and patients with suspected obstructive 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

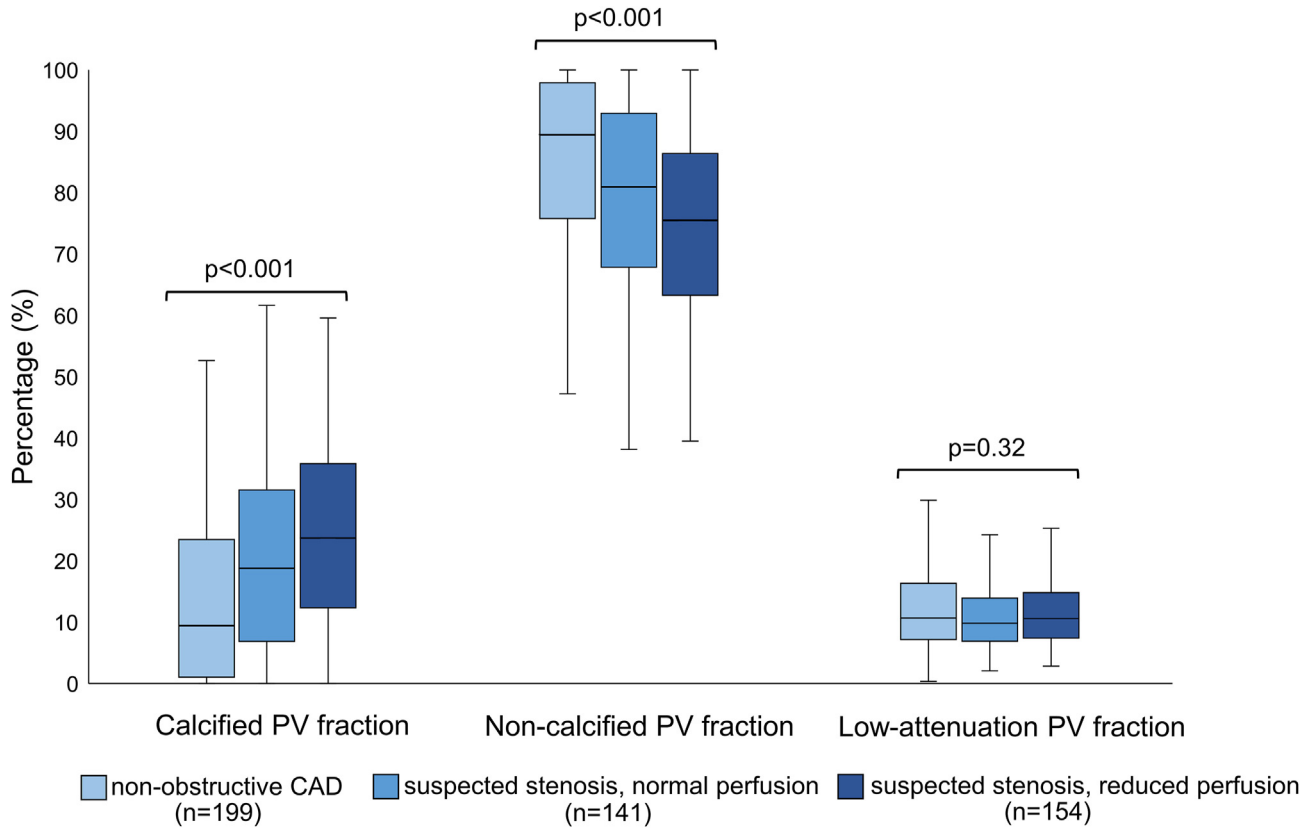

Fig. 2. Boxplot of the various plaque components as fraction of total PV. The median calcified PV fraction, non-calcified PV fraction, and low-attenuation PV fraction according to stenosis severity and positron emission tomography perfusion findings. *P*-value is for three group comparison with the Kruskal-Wallis 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 ≥ 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 ≥ 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 ≥ 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 previously[17].

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 calcifications[2]. 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 severity[25]. 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 level[26]. 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 severity[28]. 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.

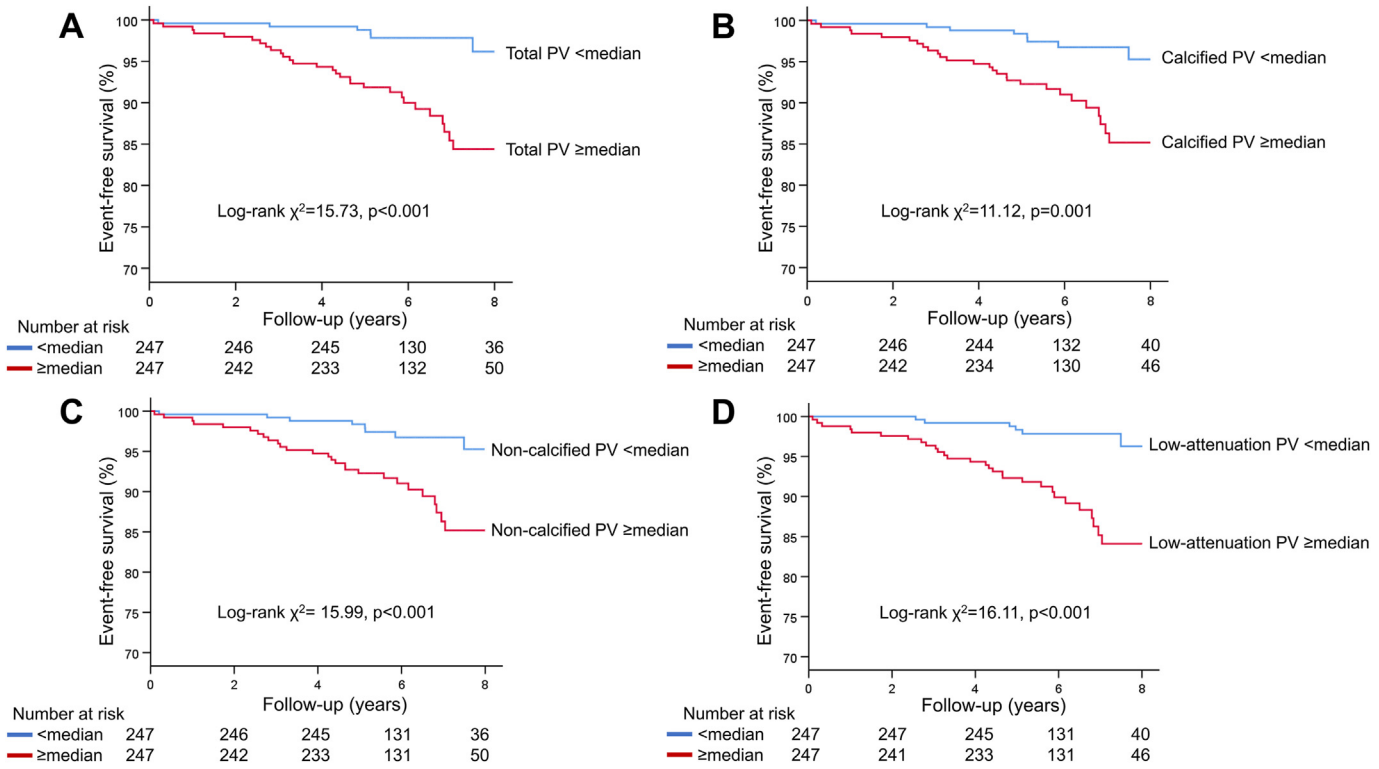

Fig. 3. PV of the various plaque components and risk of future adverse events. Kaplan-Meier curves demonstrating the event-free survival according to PV ≥ median (red curves) vs. <median (blue curves) for total PV (Panel A), calcified PV (Panel B), non-calcified PV (Panel C), and low-attenuation PV (Panel 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.

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

CI = confidence interva l, 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 outcomes[3].

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 study[29]. 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 population[30-32]. 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.

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Declaration of competing interest

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Appendix A. Supplementary data

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

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