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Research article

Coronary plaque volume and predictors for fast plaque progression assessed by serial coronary CT angiography—A single-center observational study

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A B S T R A C T

Purpose: The rationale of this study was to identify patients with fast progression of coronary plaque volume PV and characterize changes in PV and plaque components over time.
Method: Total PV (TPV) was measured in 350 patients undergoing serial coronary computed tomography angiography (median scan interval 3.6 years) using semi-automated software. Plaque morphology was assessed based on attenuation values and stratified into calcified, fibrous, fibrous-fatty and low-attenuation PV for volumetric measurements. Every plaque was additionally classified as either calcified, partially calcified or non-calcified.
Results: In total, 812 and 955 plaques were detected in the first and second scan. Mean TPV increase was 20 % on a per-patient base (51.3 mm^3 [interquartile range (IQR): 14.4, 126.7] vs. 61.6 mm^3 [IQR: 16.7, 170.0]). TPV increase was driven by calcified PV (first scan: 7.6 mm^3 [IQR: 0.2, 33.6] vs. second scan: 16.6 mm^3 [IQR: 1.8, 62.1], $p < 0.01$). Forty-two patients showed fast progression of TPV, defined as > 1.3 mm^3 increase of TPV per month. Male sex (odds ratio 3.1, $p = 0.02$) and typical angina (odds ratio 3.95, $p = 0.03$) were identified as risk factors for fast TPV progression, while high-density lipoprotein cholesterol had a protective effect (odds ratio per 10 mg/dl increase of HDL cholesterol: 0.72, $p < 0.01$). Progression to > 50 % stenosis at follow-up was observed in 34 of 327 (10.4 %) calcified plaques, in 13 of 401 (3.2 %) partially calcified plaques and 2 of 221 (0.9 %) non-calcified plaques ($p < 0.01$).
Conclusion: Fast plaque progression was observed in male patients and patients with typical angina. High HDL cholesterol showed a protective effect.

1. Introduction

Ischemic heart disease still remains the most common cause of death worldwide [1]. This reflects the ongoing need for further research to understand and detect the temporal evolution of coronary atherosclerosis. Besides the established invasive techniques including invasive coronary angiography and intravascular ultrasound (IVUS), coronary computed tomography angiography (CTA) is effective for the quantitative assessment of coronary artery plaque burden [2,3]. Furthermore, coronary artery atherosclerosis burden assessed with coronary CTA has a considerable impact on prognosis [4,5]. Quantified total plaque volume (TPV) and low attenuation plaque volume (LAPV) provide an

additive prognostic value for cardiac events over the present clinical risk, obstructive coronary artery disease (CAD), coronary artery calcium score (CACS) and segment-involvement score [6]. On the other hand, absence of CAD is associated with an excellent outcome [7].

Although there is a substantial need for additional investigation about the progress of CAD, there is still a deficit of longitudinal observations regarding patients with a low or intermediate risk for CAD. Semi-automated plaque analysis software produces exact and reproducible quantitative measurements of coronary plaque volume (PV) with low intra- and inter-observer variability and thus allows for evaluation of changes of plaque burden and plaque composition over time [8]. The aim of this observational single-center study was to examine the change of TPV and its components over time and to identify patient based risk factors for fast progression of TPV.

2. Materials and methods

2.1. Study patients

We retrospectively identified 413 patients undergoing serial coronary CTA between August 2002 and July 2015. Patients were referred by cardiologists because of suspected obstructive CAD based on clinical presentation. All patients gave written consent. Baseline characteristics and patient-related data (such as medication and cardiac risk factors) were collected with interviews and standardized questionnaires. Arterial hypertension was defined as a systolic blood pressure over 140 mmHg or by prescription of antihypertensive medication. Hyperlipoproteinemia was defined as elevated total or low-density lipoprotein (LDL) cholesterol or use of any lipid-lowering medication. Smoking was characterized as active, prior or never smoking. Positive family history was defined as known CAD in first-degree relatives younger than 55 years in male or 65 years in female relatives. Diabetes mellitus was determined as fastening blood glucose levels > 7 mmol/l or prescription of antidiabetic medication divided in insulin or diabetes drug.

2.2. Image acquisition and analysis

All patients were scanned with commercially available CT systems with at least 16 slices (all Siemens Healthcare, Erlangen, Germany). The detailed scan protocols have been described previously in more detail [4]. In brief, contrast-enhanced scans were performed with $80 - 150$ ml contrast agent (Iomeprol, Imeron 350, Bracco Altana Pharma GmbH, Konstanz, Germany) injected at a rate of $4-6$ ml/s and followed by a 50 ml saline chaser. To achieve a good image quality oral nitroglycerin was administered for coronary vasodilatation when systolic blood pressure was over 100 mmHg and intravenous metoprolol was applied to reach a heart rate below 60 beats per minute. Whenever possible, dose saving strategies were applied [9–12]. Images were obtained in diastolic heart phase.

The plaque volume quantifications were performed on a personal computer equipped with dedicated software (QAngio CT Research Edition V2.1.16.1, Medis medical image systems bv, Leiden, The Netherlands). All datasets were analyzed by two experienced readers in consensus. In case of discrepancies a third reader with over 9 years' experience in coronary CTA analysis was consulted. After the extraction of the coronary tree from the raw data, the software performed an automated detection of the inner vessel lumen and the outer vessel wall from the ostium to a fixed distal end of each artery (entire left main, proximal 6 cm of left circumflex coronary artery, proximal 8 cm of left anterior descending and right coronary artery). If necessary, manual corrections to the contours of the coronary lumen or vessel wall were applied, but limited to an unavoidable minimum. Coronary plaques were defined as any discernible structure in the coronary artery wall and were identically marked with the help of landmarks (for example coronary branches) in the first and second CT-scans. Coronary plaques

were subdivided in non-calcified (fibrous, fibrous-fatty, low-attenuation) and calcified PV using an adaptive algorithm, which incorporates for different enhancement patterns and uses adaptive attenuation thresholds for differentiation [13]. The vessel´s media volume was removed automatically using a dedicated algorithm.

Finally, marked plaques were summed up for every patient to obtain total plaque volume per patient. Progression and regression of overall TPV were defined as any increase or decrease of TPV between the two scans on a per-patient base. The utilized software is described in more detail elsewhere [13,14].

In addition, every plaque was classified as either calcified, partially calcified or non-calcified for plaque based analysis.

2.3. Statistical analysis

Statistical analysis was performed with SPSS 24.0 software (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, U.S.A.) and R version 3.5.1. Continuous variables are presented as means with standard deviations or median with interquartile ranges. Categorical variables are presented as absolute counts and percentages. To compare groups we used Fisher's exact test, chi-square test, Wilcoxon Mann–Whiney U test or student's t-test as appropriate. Changes in PV were calculated as the difference of volumes between follow-up and baseline CT examinations. Correlation between baseline PV and progression of PV was tested with Spearman´s rho. Univariate and multivariate binomial logistic regression analysis was performed to identify predictors for fast TPV progression over time. Variables showing significant association ($p < 0.05$) in univariate binomial logistic regression analysis were included in the multivariate analysis. A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1. Patients

We retrospectively identified 413 patients with serial CT scans, of whom 63 had to be excluded because of prior coronary stent placement or coronary artery bypass surgery (n = 21), incomplete data (n = 29), an aortic dissection (n = 1) or insufficient image quality (n = 12). Accordingly, the analysis is based upon 350 patients. At the time of the first scan, mean patient age was 60.7 $\pm$ 9.6 years, the mean body mass index (BMI) was 26.6 $\pm$ 3.7 kg/m² and 255 (73 %) patients were male. The detailed patient baseline characteristics including leading indications for 1st and 2nd CT scan are provided in Table 1. After the first scan, acetylsalicylic acid (ASA) therapy and statin therapy was initiated in 70 and 71 patients, respectively. A 16 slice CT scanner was used in 47 patients (13.4 %) at baseline scan and 3 patients at follow-up scan (0.9 %), 64 slice CT scanners were used in 118 (33.7 %) patients at baseline scan and 36 (10.3 %) at follow-up scan. All others examinations were performed with 64 or 128 slice dual-source CT scanners.

3.2. Plaque volume quantification results

Median time interval between the two scans was 42 [IQR 23–69] months. The mean number of coronary plaques per patient was 2.3 $\pm$ 2.2 in scan 1 and 2.7 $\pm$ 2.2 in scan 2 (p < 0.01). Out of the 955 coronary plaques, 391 were located in the left anterior descending artery (LAD), 275 in the right coronary artery (RCA), 189 in the left circumflex artery (LCX) and 100 in the left main artery (LM). Overall, 223 patients showed a progression of TPV, of whom 29 showed completely new plaque formations. Seventy-four patients showed a regression of TPV and 53 patients had no CAD in both scans. Fig. 1 illustrates the changes of TPV among the study cohort. A representative example for plaque progression can be seen in Fig. 2. When patients with overall progression of TPV were compared to patients with overall

Table 1

Patient characteristics.

Number of patients	350
Age (years)	60.7 ± 9.6
BMI (kg/m^2)	26.6 ± 3.7
Male Sex	255 (73)
Arterial hypertension	79 (23)
Hyperlipoproteinemia	197 (56)
Total cholesterol (mg/dl)	205.6 ± 45.9
LDL-cholesterol (mg/dl)	120.9 ± 37.1
HDL-cholesterol (mg/dl)	57.1 ± 17.8
Diabetes	30 (9)
Insulin	2 (1)
Oral medication	12 (3)
Smoking	106 (30)
Current smoking	35 (10)
Positive family history	119 (34)
Creatinine (mg/dl)	1.0 ± 1.2
Statin therapy	134 (38)
ASA therapy	75 (21)
Leading indication for 1st CT	
Typical angina	12 (3)
Atypical angina	120 (34)
Non-anginal chest pain or dyspnea at exertion	218 (62)
Leading indication for 2nd CT	
Typical angina	4 (1)
Atypical angina	126 (36)
Non-anginal chest pain or dyspnea at exertion	220 (63)

Data is presented as mean with standard deviation or numbers (%). ASA denotes acetylsalicylic acid. Medication refers to treatment at Scan 1.

regression of TPV there were no statistically significant differences regarding their baseline characteristics (see Supplemental Table 1). However, a trend was observed for a higher BMI in patients with TPV progression (26.9 ± 3.9 vs. 25.8 ± 3.2, p = 0.08).

Over time, there was a significant increase of TPV (51.3 mm^3 [interquartile ranges 14.4 and 126.7] vs. 61.6 mm^3 [interquartile ranges 16.7 and 170.0], p < 0.01, see also Table 2). This resembles an average progress of 20 %. Progress of TPV in relation to baseline TPV is shown in Fig. 3. There was a weak but statistically significant correlation between baseline TPV and TPV progression (spearman's rho = 0.33, p < 0.01).

Progress in TPV was driven by a significant progress of calcified PV (7.6 mm^3 [interquartile ranges 0.2 and 33.6] vs. 16.6 mm^3 [interquartile ranges 1.8 and 62.1], p < 0.01). There were no significant changes in total non-calcified PV or its components (low-attenuation, fibrous and fibrous-fatty PV). Fig. 4 illustrates TPV composition at baseline and follow-up scan.

3.3. Progression to obstructive coronary artery disease

Obstructive CAD, defined as any stenosis > 50 %, was found in 13 (3.7 %) patients at baseline and 35 (10 %) patients at follow-up CT scans. Patients with obstructive CAD at follow-up had significantly higher TPV on a per-patient base at baseline (384.9 mm^3 [interquartile ranges 182.8 and 538.1] vs. 45.1 mm^3 [interquartile ranges 10.3 and 102.9], p < 0.01) and significantly higher calcified, fibrous, fibrous-fatty and low-attenuation PV (measurements provided in Supplemental Table 2). Patients with typical angina at baseline were 4.9fold more likely to develop obstructive CAD (p = 0.02).

On a plaque basis, 16 plaques at baseline and 49 plaques at follow-up showed > 50 % luminal narrowing. Plaques with > 50 % stenosis at follow-up showed significantly higher TPV (128.6 mm^3 [interquartile ranges 51.6 and 313.0] vs. 17.6 mm^3 [interquartile ranges 9.0 and 41.8] and higher degree of stenosis (38.2 % [interquartile ranges 27.1 and 48.0] vs. 11.4 % [interquartile ranges 5.6 and 19.8] at baseline. Progression to > 50 % stenosis at follow-up was observed in 34 327 (10.4 %) of calcified plaques, in 13 of 401 (3.2 %) partially calcified plaques and 2 of 221 (0.9 %) non-calcified plaques (p < 0.01). Univariate binomial regression analysis confirmed a gradually increasing likelihood of progression to > 50 % stenosis for increasing percentages of calcified plaque volume (odds ratio 1.55 (95 % CI 1.37–1.77) per 10 % increase).

3.4. Identification of patients with fast plaque volume progression

To identify patients who might be at higher risk for considerable progression of CAD, we compared patients with fast progression of TPV to the remaining patients. Therefore, an explorative cut-off value was defined based upon the distribution of monthly change in TPV. The cut-off was set to the point where the graph rose steeply and corresponded to an increase of TPV of 1.31 mm^3 per month (see Fig. 5). Application of this cut-off classified 12 % of patients as patients with fast plaque progression. Those patients were significantly more likely to be men, had lower high-density lipoprotein (HDL) cholesterol and more often typical angina (Table 3). There was no significant difference regarding the initiation of statin or ASA therapy between both scans.

Univariate binomial regression analysis revealed that male patients were 3.1fold (95 % CI 1.45–7.49, p = 0.02) more likely to have fast TPV progression and patients with typical angina were 3.95fold (95 % CI 1.29–10.88, p = 0.03) more likely to have fast TPV progression.
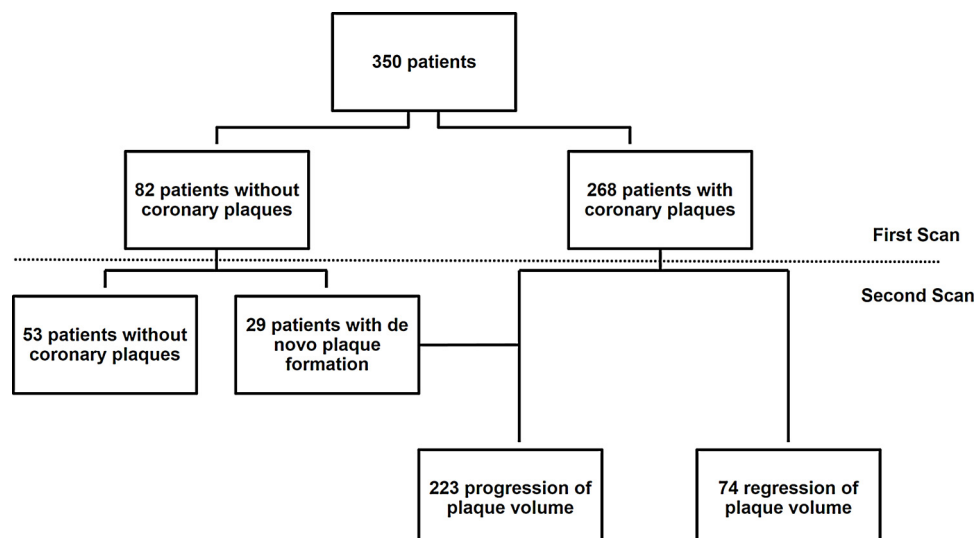

Fig. 1. Illustrates the changes on coronary atherosclerosis among the study population.
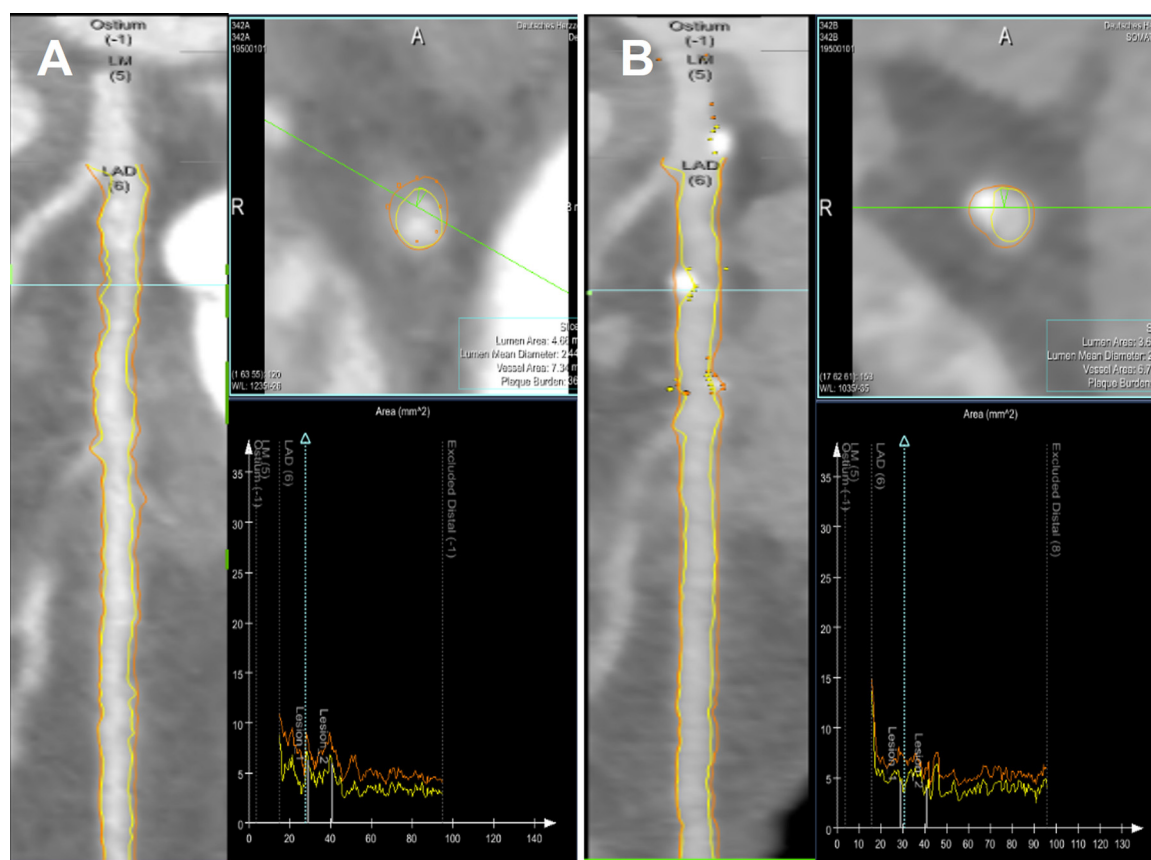
Fig. 2. Example of 58 year old male patient with 6 years between the first (shown on the left side, panel A) and second scan (shown on the rights side, panel B). The investigated vessel is the left anterior descending artery. The orange line marks the outer vessel wall and the yellow line the lumen of the coronary artery.

Table 2
Plaque Volume Measurements on a per-patient base.

	Scan 1	Scan 2	p-value
Number of plaques	2.3 ± 2.2	2.7 ± 2.2	< 0.01
Total plaque volume (mm³)	51.3 [14.4–126.7]	61.6 [16.7–170.0]	< 0.01
Calcified plaque volume (mm³)	7.6 [0.2–33.6]	16.6 [1.8–62.1]	< 0.01
Fibrous plaque volume (mm³)	33.8 [8.5–77.3]	30.0 [8.5–75.9]	0.67
Fibrous-fatty plaque volume (mm³)	6.4 [1.2–17.3]	5.7 [1.3–15.5]	0.26
Low-attenuation plaque volume (mm³)	2.0 [0.1–6.9]	1.9 [0.2–6.5]	0.35
Maximal stenosis, %	18.3 [7.1–29.7]	19.9 [7.8–31.2]	0.3
Patients with any stenosis > 50 %	13 (3.7 %)	35 (10 %)	< 0.01

Data is presented as median with interquartile ranges unless otherwise stated.

Higher HDL cholesterol was associated with significantly lower odds to develop fast plaque progression (odds ratio per 10 mg/dl increase of HDL cholesterol: 0.72 with 95 % CI 0.58–0.87, p < 0.01). Typical angina (odds ratio: 4.88 with 95 % CI 1.49–14.88, p = 0.02) and HDL cholesterol (odds ratio per 10 mg/dl increase of HDL cholesterol: 0.77 with 95 % CI 0.62–0.94, p = 0.04) were confirmed as independent predictors for fast TPV progression by multivariate analysis, while male sex lost statistical significance (odds ratio: 2.37 with 95 % CI 0.99–6.77, p = 0.13). The entire analysis is shown in Table 4.

4. Discussion

In this study on patients with intermediate risk for CAD undergoing clinically indicated serial coronary CTA, we found that CAD is a dynamic disease with an increase of TPV in the majority of the investigated patients. However, there was a large variance of TPV progression among the investigated patients, reflected by the fact that the majority of patients demonstrated with slow TPV progression, while some patients had de-novo plaque formations, a few had fast progression of TPV and some showed regression of TPV.

The observation that CAD burden increases with time in most patients is in line with other published results investigating serial CACS measurements and more recently with a study investigating TPV progression in a large registry [8,15,16]. The amount of coronary atherosclerosis as well as the progression of CACS or TPV are strong predictors of adverse cardiovascular outcome [15,17–19]. Interestingly, the overall increase of TPV among the investigated population in our study was mainly driven by an increase in calcified PV. A possible explanation for this finding may be that calcified plaques resemble more stable disease stages [20]. It has been demonstrated that patients presenting with ACS show significantly less large calcifications compared to patients with stable CAD [21]. In a meta-analysis investigating intensive statin therapy, Andelius et al. report a significant reduction of TPV and non-calcified plaque volume but an increase of calcified plaque volume under statin therapy [22]. The progress in calcification on a patient base could thus be an expression of stabilization of coronary atherosclerosis [20]. However, although severely calcified plaques are not considered at high risk for rupture and causing ACS, our analysis revealed that they are more likely to progress to > 50 % stenosis over time than other plaque types.

In this analysis, 12 % of patients showed fast TPV progression. Univariate binomial regression analysis performed in the study cohort revealed a significant positive effect between male sex and typical angina for fast TPV progression and a protective effect of higher HDL cholesterol levels for fast TPV progression. In the multivariate analysis, only HDL-cholesterol and typical angina remained significant.
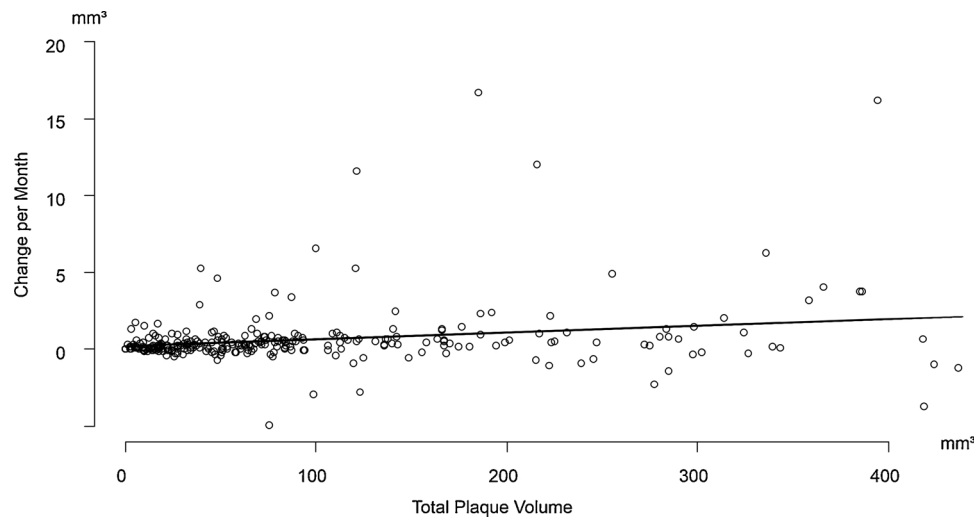
Fig. 3. Illustrates the change of total plaque volume per month in relation to total plaque volume at baseline (scan 1).

Interestingly, the presence of established cardiovascular risk factors including diabetes, arterial hypertension, LDL cholesterol, smoking and a positive family history was not higher among patients with fast TPV progression. However, we have to acknowledge that only very few patients in our cohort had diabetes and even fewer patients were on insulin therapy. Thus, the explanatory power regarding the impact of diabetes on CAD progression of our results is limited. Indeed, studies conducted by Nakanishi et al. and Kim et al. report a significantly higher progression of TPV in diabetic patients compared to propensity-matched non-diabetic patients [16,23].

In another analysis by Lee et al. 1345 patients with serial coronary CTA examinations were divided into two groups using the median of TPV progression [15]. In their analysis, all cardiovascular risk factors including diabetes were observed more frequently in patients with higher TPV progression. However, no multivariate analysis was performed in their analysis.

The finding that patients with fast progression of TPV had lower HDL-cholesterol is in line with results that HDL-cholesterol levels are negatively associated with CAD burden and progression when assessed with IVUS [24,25]. In addition, our data shows that patients with fast progression of TPV were more often male and had significantly more typical angina. There are consistent observations that the incidence of CAD in women is lower than in men, their symptoms are more likely to be considered atypical and CAD appears 10 years later [26,27].

Since overall progression of TPV in this study of patients with intermediate cardiovascular risk was rather low, two major questions for clinical management of patients worth discussing arise. First, in whom is a second coronary CTA scan useful to reassess the risk of coronary events? And second, what is the optimal time interval between those two scans? There is evidence that patients with no or very little evidence of CAD have a very favorable prognosis with warranty periods of up to 15 years [4,28,29]. Patients with high evidence of CAD are likely to receive maximal medical treatment anyway and the consequence of quantifying CAD burden again is doubtful from a clinical perspective. Yet, in patients with intermediate CAD burden, a second coronary CTA scan might be useful to discover whether patients have fast progression of TPV. An analysis by Lehmann et al. investigating serial CACS measurements in 3281 patients with a mean scan interval of 5.1 years revealed best prognosis in patients with CACS = 0 in both scans and significantly higher adverse event rate in patients moving from CACS category 1-399 to CACS category > 400. Those patients had twofold higher incidences of cardiovascular events than patients who remained in CACS category 1-399 [19]. However, the ideal time interval between two scans remains unanswered and warrants further investigation.

A limiting circumstance of the study is that it was conducted in a retrospective fashion and no follow-up information regarding clinical events was available. Owing to the retrospective study conduct, the investigated sample size and the lack of multiple testing, our results should be considered hypothesis generating and need further validation. Due to the long interval between scans, newer CT scanners were used for the second scan in most patients. Furthermore, there might have been a relevant selection bias, since the second coronary CTA scan
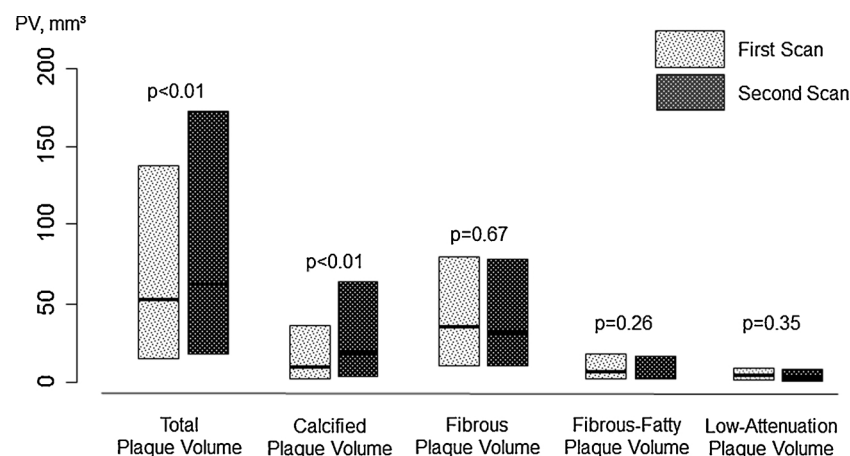

Fig. 4. Illustrates the difference in total plaque volume and its four components between Scan 1 and Scan 2.
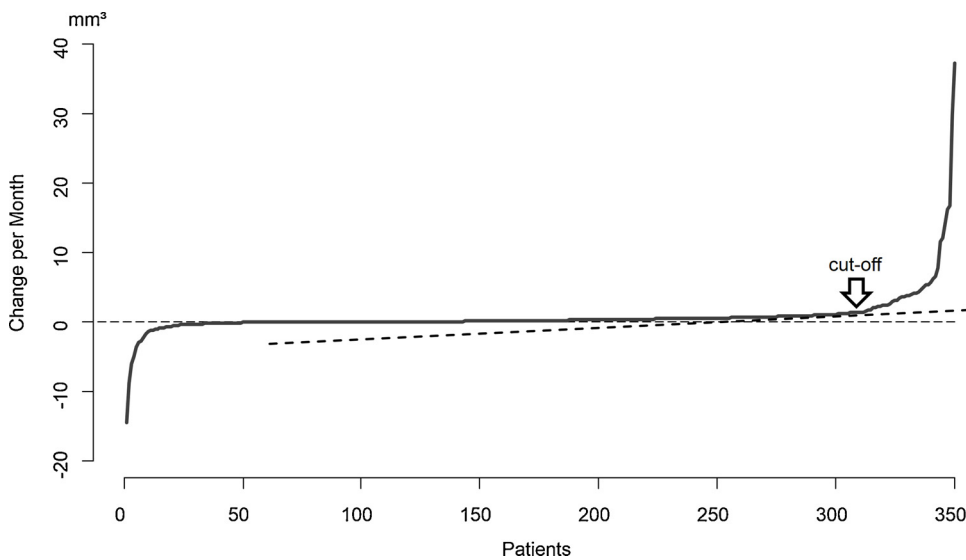
mm³

Fig. 5. Shows changes of total plaque volume for every patient. To define patients with fast total plaque volume progression, we used an explorative cut-off value based upon the distribution of monthly change in total plaque volume. The cut-off is set to the point where the graph begins to rise steeply and corresponds to a monthly increase of 1.31 mm³. The application of this cut-off classifies 12 % of patients as patients with fast plaque progression.

Table 3
Patients Characteristics Stratified for Plaque Progression.

	Fast progression	No Fast progression	p-value
Number of patients	42	308	
Age (years)	62.2 ± 9.4	60.5 ± 9.6	0.31
BMI (kg/m²)	27.2 ± 4.8	26.5 ± 3.6	0.88
Male sex	37 (88)	218 (71)	0.02
Arterial hypertension	7 (17)	72 (23)	0.33
Hyperlipoproteinemia	26 (62)	171 (56)	0.43
Total cholesterol (mg/dl)	198.3 ± 51.1	206.3 ± 45.4	0.3
LDL-cholesterol (mg/dl)	119.9 ± 44.6	121.0 ± 36.1	0.78
HDL-cholesterol (mg/dl)	49.9 ± 12.2	58.0 ± 18.2	< 0.01
Diabetes	5 (12)	25 (8)	0.41
Smoking	9 (21)	97 (31)	0.18
Positive family history	16 (38)	103 (33)	0.55
Typical angina	4 (10)	8 (3)	0.02
Initiation of statin therapy after 1st scan	9 (21)	62 (20)	0.84
Initiation of ASA therapy after 1st scan	7 (17)	63 (20)	0.68

Data is presented as mean with standard deviation or numbers (%). Fast Progression of Total Plaque Volume was defined as an increase of > 1.31 mm³/month. ASA denotes acetylsalicylic acid.

was performed based upon clinical judgement and upon the results of the first scan. It is unlikely that patients suffering from an ischemic coronary event after the first scan will receive a second coronary CTA, which ultimately results in including rather healthy patients. Other limitations are that differences in plaque quantifications might be attributed to measuring inaccuracy to some extent or calcium blooming artefacts. However, a similar study showed a good inter- and intraobserver agreement, reproducibility and very low error of measurement with the used semi-automated plaque quantification software [8].

In conclusion, our study demonstrates that CAD is a dynamic disease with an increase in TPV in most patients, driven by an increase in calcified PV to a major extent in the investigated population. Patients with typical angina, patients with lower HDL cholesterol levels and – to a lesser extent – male patients are at greater risk for fast progression of CAD.

Declaration of Competing Interest

Pieter Kitslaar is employed by Medis medical imaging systems bv, the company that develops the software used for plaque measurements. He was not involved in measuring of plaques, interpreting of data or writing the manuscript. The remaining authors have no conflict of interest.

Table 4
Likelihood of Fast Plaque Progression according to Patients Characteristics.

	Univariate Odds Ratio (with 95 % CI)	p-value	Multivariate Odds Ratio (with 95 % CI)	p-value
Age, per 10 years	1.22 (0.91–1.67)	0.28		
BMI, per 5 kg/m² increase	1.28 (0.87-1-84)	0.28		
Male sex	3.1 (1.45–7.49)	0.02	2.37 (0.99–6.77)	0.13
Arterial hypertension	0.78 (0.37–1.49)	0.55		
Hyperlipoproteinemia	1.67 (0.94–3.11)	0.16		
Total cholesterol, per 10 mg/dl increase	0.95(0.89–1.02)	0.24		
LDL-cholesterol, per 10 mg/dl increase	0.99 (0.92–1.07)	0.88		
HDL-cholesterol, per 10 mg/dl increase	0.72 (0.58-0.87)	< 0.01	0.77 (0.62-0.94)	0.04
Diabetes	1.51 (0.59–3.36)	0.43		
Smoking	0.67 (0.35–1.23)	0.30		
Positive family history	1.29 (0.73–2.24)	0.46		
Typical angina	3.95 (1.29–10.88)	0.03	4.88 (1.49–14.88)	0.02
Initiation of statin therapy after 1st scan	1.06 (0.65–1.66)	0.84		
Initiation of ASA therapy after 1st scan	0.84 (0.48–1.35)	0.57		

Fast Progression of Total Plaque Volume was defined as an increase of > 1.31 mm³/month. Variables showing statistical significance univariate binomial regression analysis were entered in the multivariate model. ASA denotes acetylsalicylic acid.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejrad.2019.108805.

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