Multimodality imaging in coronary artery disease: plaque characterization, computational haemodynamic simulation and risk stratification

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CHAPTER 6

Impact of Clinical Characteristics and Statins on Coronary Plaque Progression by Serial Computed Tomography Angiography

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ABSTRACT

Background: Progression of coronary artery disease (CAD) using serial coronary computed tomography angiography (CTA) is of clinical interest. Our primary aim was to prospectively assess the impact of clinical characteristics and statin use on quantitatively assessed coronary plaque progression in a low-risk study population during long-term follow-up.

Methods: Patients who previously underwent coronary CTA for suspected CAD were prospectively included to undergo follow-up coronary CTA. The primary endpoint was CAD progression, defined as the absolute annual increase in total, calcified and non-calcified plaque volume by quantitative CTA analysis.

Results: In total, 202 patients underwent serial coronary CTA with a mean interscan period of 6.2 ± 1.4 years. On a per-plaque basis, increasing age (β = 0.070; P = 0.058) and hypertension (β = 1.380; P = 0.075) were non-significantly associated with annual total plaque progression. Male gender (β = 1.676; P = 0.009), diabetes (β = 1.725; P = 0.012) and statin use (β = 1.498; P = 0.046) showed an independent association with annual progression of calcified plaque. While hypertension (β = 2.259; P = 0.015) was an independent determinant of non-calcified plaque progression, statin use (β = -2.178; P = 0.050) was borderline significantly associated with a reduced progression of non-calcified plaque.

Conclusions: Statin use was associated with an increased progression of calcified coronary plaque and a reduced progression of non-calcified coronary plaque, potentially reflecting calcification of the non-calcified plaque component. Whereas hypertension was the only modifiable risk factor predictive of non-calcified plaque progression, diabetes mainly led to an increase in calcified plaque. These findings could yield the need for intensified preventive treatment of patients with diabetes and hypertension to slow and stabilize CAD progression and improve clinical outcome.

CLINICAL PERSPECTIVE

Progression of coronary artery disease (CAD) using serial coronary computed tomography angiography (CTA) is of clinical interest. In the present study, we prospectively assessed the impact of clinical characteristics and statin use on quantitatively assessed coronary plaque progression in a low-risk study population during long-term follow-up. For this purpose, patients who previously underwent coronary CTA for suspected CAD were prospectively included to undergo follow-up coronary CTA. We demonstrated that statin use was associated with an increased progression of calcified coronary plaque and a reduced progression of non-calcified coronary plaque. Whereas hypertension was the only modifiable risk factor predictive of non-calcified plaque progression, diabetes mainly led to an increase in calcified plaque. The present findings significantly add to our current knowledge on the long-term effects of clinical characteristics and statin use on coronary plaque progression. It could be hypothesized that the increase in coronary calcification represents a 'healing' mechanism of statins, whereby coronary plaques become increasingly stabilized through calcification of the necrotic core. In addition, our study findings could yield the need for intensified preventive treatment of patients with diabetes and hypertension to slow and stabilize CAD progression and improve clinical outcome.

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of mortality and disability-adjusted life-years lost worldwide.[1] Multiple studies have evaluated the natural history of CAD and its responsiveness to medical therapy using serial invasive coronary angiography or intravascular ultrasound.[2-6] Coronary computed tomography angiography (CTA) has rapidly emerged as a tool to non-invasively evaluate coronary artery plaque with high diagnostic certainty.[7-9] Therefore, it has become of increased interest to study the progression of CAD using serial coronary CTA. Although prior studies have evaluated coronary plaque progression by serial coronary CTA, most studies were limited by a short follow-up duration, retrospective design or qualitative approach.[10-15] Moreover, little is known about the impact of clinical characteristics on coronary plaque progression in relation to statin use. Accordingly, our aim was to prospectively assess the impact of clinical characteristics and statin use on quantitatively assessed coronary plaque progression in a low-risk study population during long-term follow-up.

METHODS

Study design

The Horizon 2020 funded SMARTool (Simulation Modeling of coronary ARTery disease: a tool for clinical decision support) Project is a prospective, multicenter study in patients who underwent serial coronary CTA.[16] Caucasian patients were included by 7 centers from 5 European countries. The study protocol was approved by all local ethical committees, all patients gave their written informed consent to participate in the study and the procedures followed were in accordance with institutional guidelines. The authors declare that all supporting data are available within the article and its online supplementary files.

Patients

Patients who previously underwent coronary CTA for suspected CAD, as part of the EVINCI (FP7-222915) (n = 152) or ARTreat (FP7-224297) (n = 18) clinical studies, were prospectively included to undergo follow-up coronary CTA. Additionally, patients who underwent coronary CTA in the period 2009-2012 for clinical indications (n = 32) and were not originally included in the EVINCI and ARTreat studies, were also prospectively included. A full list of inclusion and exclusion criteria is provided in the Supplemental Materials. The baseline characteristics of excluded patients without (visually assessed) atherosclerosis development at follow-up are shown in Supplemental Table 1. In total, 275 patients were enrolled in the SMARTool Project, 263 patients underwent follow-up coronary CTA and 202

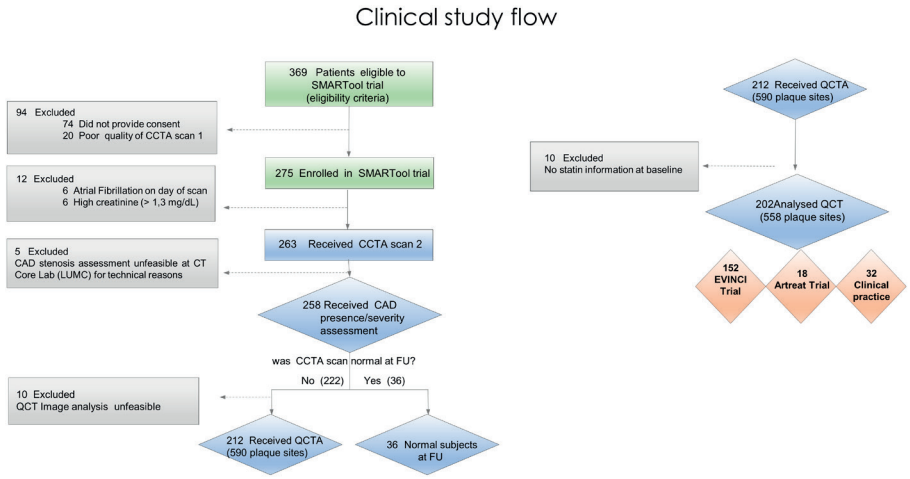

Figure 1: Flow diagram of patients included in SMARTool. In total, 275 patients were enrolled in the SMARTool Project and 263 patients underwent follow-up coronary CTA. Finally, 202 patients were included in the current analysis. CAD = coronary artery disease; CCTA = coronary computed tomography angiography; QCT = quantitative CTA analysis.

patients were included in the current study (Figure 1). For all patients, clinical and blood data were collected prior to the baseline and follow-up coronary CTA.

Coronary CTA analysis

Coronary CTA was performed according to a predefined standard operating procedure to ensure optimal image quality (see Supplemental Materials). All baseline and follow-up coronary CTA images were analysed blinded to clinical data by a separate core laboratory (Leiden University Medical Center). Coronary arteries were assessed according to the modified 17-segment American Heart Association classification.[17] First, a visual, side-by-side analysis of the baseline and follow-up coronary CTAs was performed to assess the presence, location, severity and composition of coronary plaques. Subsequently, quantitative CTA analysis was performed for all visually determined plaques, using a dedicated software package (QAngio CT Research Edition version 3.1.2.0). Baseline and follow-up coronary lesions were matched using fiduciary landmarks (e.g. side branches, distance from the ostium) and analysed side-by-side. The complete workflow of quantitative CTA analysis has been described in detail previously (see Supplemental Materials for a detailed description of the quantitative CTA analysis).[18]

Clinical characteristics and study endpoints

Cardiovascular risk factors, including age, gender, family history of CAD, smoking status, diabetes, dyslipidemia, hypertension, obesity, medication use and lipid profiles were prospectively collected prior to the baseline and follow-up coronary CTA (see Supplemental Materials for the definitions of the clinical variables). Statin use was evaluated at baseline and follow-up visits and patients were divided into 2 groups:

1. Statin users: if statins were used at baseline and/or follow-up (i.e. at baseline and follow-up, only at baseline, only at follow-up).
2. Non-statin users: if statins were not used at baseline nor at follow-up.

The primary endpoint of this study was CAD progression, defined as the absolute increase in plaque volume by quantitative CTA analysis on a per-plaque as well as on a per-patient basis. Per-patient plaque volume was calculated by summation of the plaques volumes of individual coronary plaques. Total, calcified and non-calcified plaque volume progression were assessed on a per-plaque and per-patient basis and were adjusted for the time interval between the baseline and follow-up coronary CTA (i.e. the interscan period). Accordingly, the annual plaque volume difference was calculated as follows: (plaque volume at follow-up – plaque volume at baseline) / (interscan period). For the per-plaque analysis, coronary arteries with a stent or bypass graft were automatically excluded pairwise to obtain a similar number of evaluated coronary arteries at baseline and follow-up. For the per-patient analysis, the influence of missing segments (due to interscan stenting, coronary bypass

surgery or failure in image reconstruction) on the plaque progression rate was evaluated and ruled out. This was performed by comparing the median annual plaque progression rate between patients with and without all coronary vessels analysed. The annual plaque progression rate was calculated as follows: (annual plaque volume difference / plaque volume at baseline) * 100%.

Statistical analysis

Distribution of continuous variables was determined using histograms and Q-Q plots. For normal distributions, continuous variables are presented as mean ± standard deviation and for non-normally distributed variables as median and 25% to 75% interquartile range (IQR), and depending on the distributions they were compared with the independent Student's t-test and Mann-Whitney U test, respectively. Categorical variables are presented as number and percentages, and were compared with the chi-square test, or Fisher's exact test if 5 or less observations were included in a subclass. Plaque characteristics were compared at baseline and follow-up using the Wilcoxon signed rank test. A univariable linear regression analysis was performed to determine the association between clinical variables, statin use and annual increase in plaque volume (total, calcified and non-calcified). Multivariable analysis was performed to adjust for clinical variables, baseline plaque volume and low-density lipoprotein (LDL) cholesterol response to statin therapy. For the per-plaque analysis, a linear mixed model was used to account for potential intra-patient correlation of coronary plaques. All statistical analyses were performed with the SPSS software package (IBM Corp Released 2017; IBM SPSS Statistics for Windows, Version 25.0; Armonk, New York: IBM Corp). Statistical tests were considered significant if the two-sided P-value was <0.05.

RESULTS

Patients

In total, 202 Caucasian patients (80% statin users) who underwent serial coronary CTA were included in the study with a mean interscan period of 6.2 ± 1.4 years. The patient characteristics are displayed in Table 1. In addition, the change in lipid profile between baseline and follow-up coronary CTA according to statin use is shown in Table 2. In total, 40 (20%) patients at baseline and 63 (31%) patients at follow-up were at therapeutic goals (i.e. had LDL cholesterol levels <70 mg/dl).

Table 1: Patient characteristics.

		Statin use		P-value
	Total (n = 202)	**Yes (n = 161)**	**No (n = 41)**	
Age (years)	61 ± 9	61 ± 9	62 ± 8	0.80
Male	140 (69%)	114 (71%)	26 (63%)	0.36
Family history of CAD	94 (49%)	77 (50%)	17 (45%)	0.56
Current smoker	33 (17%)	29 (19%)	4 (11%)	0.34
Diabetes	41 (21%)	36 (23%)	5 (13%)	0.19
Dyslipidemia	134 (70%)	119 (77%)	15 (40%)	<0.001
Hypertension	131 (68%)	106 (69%)	25 (66%)	0.72
Obesity	38 (20%)	32 (21%)	6 (16%)	0.49
Symptoms				
Typical	47 (26%)	37 (26%)	10 (26%)	0.92
Atypical	95 (52%)	76 (52%)	19 (50%)	0.79
Non-anginal	1 (1%)	1 (1%)	0 (0%)	1.00
Other	23 (13%)	18 (12%)	5 (13%)	1.00
No symptoms	17 (9%)	13 (9%)	4 (10%)	0.76
Medication				
Beta-blockers	86 (45%)	75 (49%)	11 (29%)	0.028
ACE-inhibitors/ARBs	95 (50%)	75 (49%)	20 (53%)	0.66
Diuretics	31 (16%)	26 (17%)	5 (13%)	0.81
Aspirin	133 (69%)	110 (71%)	23 (61%)	0.19

Values are presented as mean ± SD or n (%).
ACE = angiotensin-converting enzyme; ARB = angiotensin-II-receptor blocker; CAD = coronary artery disease.

Table 2: Change in lipid profile between baseline and follow-up coronary CTA according to statin use.

		Statin use *				P-value
	Total (n = 202)	At baseline and follow-up (n = 91)	Only at baseline (n = 18)	Only at follow-up (n = 52)	No (n = 41)	
Lipid profile prior to baseline coronary CTA						
Total cholesterol (mg/dl)	186 ± 48	168 ± 44	172 ± 46	202 ± 44	211 ± 48	<0.001
LDL (mg/dl)	110 ± 41	94 ± 37	101 ± 41	124 ± 37	131 ± 40	<0.001
HDL (mg/dl)	51 ± 15	50 ± 16	53 ± 17	49 ± 13	56 ± 14	0.12
Triglycerides (mg/dl)	122 ± 63	120 ± 60	90 ± 47	143 ± 73	111 ± 52	0.015
Lipid profile prior to follow-up coronary CTA						
Total cholesterol (mg/dl)	176 ± 43	167 ± 39	223 ± 58	161 ± 30	195 ± 38	<0.001
LDL (mg/dl)	94 ± 40	84 ± 36	137 ± 51	82 ± 24	114 ± 38	<0.001
HDL (mg/dl)	55 ± 15	54 ± 15	58 ± 18	53 ± 13	56 ± 15	0.59
Triglycerides (mg/dl)	147 ± 95	161 ± 111	165 ± 138	125 ± 56	134 ± 66	0.10
Change in lipid profile between baseline and follow-up coronary CTA						
Total cholesterol (mg/dl)	-9 ± 52	0 ± 44	51 ± 67	-41 ± 43	-15 ± 42	<0.001
LDL (mg/dl)	-16 ± 46	-11 ± 40	35 ± 58	-42 ± 40	-18 ± 36	<0.001
HDL (mg/dl)	3 ± 12	4 ± 10	6 ± 16	4 ± 10	0 ± 14	0.14
Triglycerides (mg/dl)	24 ± 94	42 ± 99	89 ± 144	-24 ± 74	23 ± 53	<0.001

Values are presented as mean ± SD.
CTA = computed tomography angiography; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
***** Statin use at baseline and follow-up: statins were already used at the baseline coronary CTA and were continued during the interscan period.
Statin use only at baseline: statins were used at the baseline coronary CTA, but were discontinued during the interscan period.
Statin use only at follow-up: statins were not used at the baseline coronary CTA, but were initiated during the interscan period.
No statin use: statins were not used at the baseline coronary CTA or during the interscan period.

CAD progression for total group

The median annual plaque progression rate between patients with and without all coronary vessels analysed was not significantly different for total, calcified and non-calcified plaque (P = 0.16, P = 0.84 and P = 0.73, respectively) (Supplemental Figure 1). Per-patient total plaque volume change between the baseline and follow-up coronary CTA was 74.8 ± 100.8 mm^3, and the annual change in total plaque volume was 12.2 ± 15.8 mm^3 (Figure 2). The annual change in calcified and non-calcified plaque volume was 7.9 ± 11.8 mm^3 and 2.1 ± 15.7 mm^3, respectively. A detailed overview of the changes in plaque characteristics for the 558 detected plaques is provided in Table 3. There was a significant increase in mean

plaque burden, maximal plaque thickness, diameter stenosis, area stenosis and lesion length (all P <0.001), while minimal lumen diameter and minimal lumen area significantly decreased from baseline to follow-up (both P <0.001). The association between baseline plaque volume and plaque progression according to plaque composition is shown in Supplemental Figure 2.

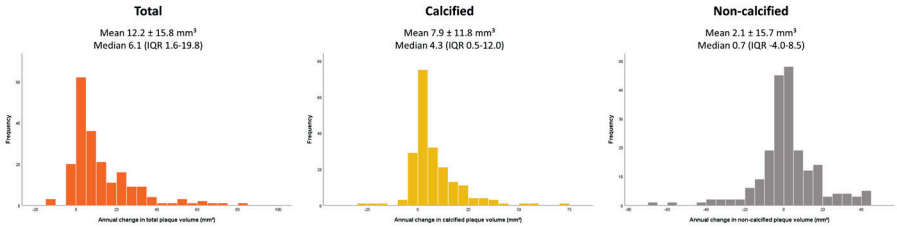

Figure 2: Per-patient annual changes in total, calcified and non-calcified plaque volume. On a per-patient basis, the mean annual change in total, calcified and non-calcified plaque volume was 12.2 ± 15.8 mm^3, 7.9 ± 11.8 mm^3 and 2.1 ± 15.7 mm^3, respectively. IQR = interquartile range.

CAD progression according to statin use

The per-patient total plaque volume at baseline was significantly higher in statin users compared to non-statin users (549 (IQR 232-1027) mm^3 vs. 298 (IQR 124-769) mm^3; P = 0.013). Also, statin users showed a higher calcified and non-calcified plaque volume at baseline compared to non-statin users (33 (IQR 10-77) mm^3 vs. 21 (IQR 6-38) mm^3; P = 0.051 and 479 (IQR 212-896) mm^3 vs. 284 (IQR 108-702) mm^3; P = 0.019, respectively). The per-patient annual increase in total plaque volume was not significantly different between statin and non-statin users (12.8 ± 16.2 mm^3 vs. 10.1 ± 13.9 mm^3; P = 0.33). Although the annual progression of non-calcified plaque was significantly reduced in statin users compared to non-statin users (1.0 ± 16.0 mm^3 vs. 6.4 ± 13.9 mm^3; P = 0.049), statin users showed a significant increase in calcified plaque progression (9.0 ± 12.2 mm^3 vs. 3.3 ± 8.6 mm^3; P = 0.001). A detailed overview of the per-plaque changes according to the use of statins is displayed in Table 3. In Figure 3, an example of quantitative CTA analysis is provided for a statin-taking patient. Although initially no coronary calcification was present at quantitative CTA analysis, extensive calcification had occurred after 8 years of follow-up. The annual change in calcified and non-calcified plaque volume according to the intensity of statin therapy at follow-up is shown in Supplemental Figure 3. Moreover, the change in % diameter stenosis between patients with and without statin use at baseline and/or follow-up is shown in Supplemental Figure 4.

Table 3: Change in plaque characteristics between baseline and follow-up coronary CTA according to statin use.

				Statin use at baseline and/or follow-up					
	Total (n = 558)			Yes (n = 464)			No (n = 94)		
	Baseline	Follow-up	P-value	Baseline	Follow-up	P-value	Baseline	Follow-up	P-value
Total plaque volume (mm^3)	143.3 (68.4-308.4)	160.2 (82.6-333.3)	<0.001	144.2 (69.5-307.3)	164.0 (82.9-332.5)	<0.001	133.7 (57.7-309.1)	144.5 (78.8-352.9)	<0.001
Calcified plaque volume (mm^3)	7.7 (1.7-22.6)	19.3 (7.1-45.0)	<0.001	7.7 (1.8-23.4)	20.9 (7.8-46.3)	<0.001	8.6 (1.3-21.0)	12.2 (2.4-29.5)	<0.001
Non-calcified plaque volume (mm^3)	127.2 (58.7-274.3)	132.3 (66.2-278.3)	0.001	132.0 (62.2-275.2)	129.2 (66.2-279.7)	0.061	118.9 (47.8-262.2)	135.1 (70.5-268.3)	<0.001
Mean plaque burden (%) *	58.0 (51.8-62.9)	60.7 (54.0-65.9)	<0.001	58.1 (52.3-63.1)	60.7 (54.1-66.0)	<0.001	57.3 (50.5-62.6)	60.2 (53.3-65.5)	0.002
Maximal plaque thickness (mm)	1.75 (1.44-2.07)	1.97 (1.73-2.27)	<0.001	1.77 (1.47-2.11)	1.99 (1.73-2.30)	<0.001	1.68 (1.29-1.97)	1.94 (1.68-2.17)	<0.001
Diameter stenosis (%)	24.1 (14.6-32.9)	27.3 (19.4-37.3)	<0.001	24.3 (14.7-33.5)	27.5 (19.4-37.7)	<0.001	23.5 (13.3-31.2)	26.9 (17.7-33.1)	<0.001
Area stenosis (%)	42.4 (26.9-55.0)	47.2 (34.9-60.7)	<0.001	42.7 (27.0-55.8)	47.4 (35.0-61.2)	<0.001	41.5 (24.8-52.6)	46.5 (32.2-55.3)	<0.001
Minimal lumen diameter (mm)	2.3 (1.9-2.8)	2.1 (1.7-2.5)	<0.001	2.2 (1.9-2.7)	2.1 (1.7-2.5)	<0.001	2.4 (1.9-2.9)	2.2 (1.8-2.7)	<0.001
Minimal lumen area (mm^2)	5.0 (3.5-7.4)	4.4 (2.9-6.4)	<0.001	4.8 (3.4-7.3)	4.3 (2.9-6.3)	<0.001	5.5 (3.8-7.4)	4.4 (3.1-7.2)	0.001
Lesion length (mm)	13.6 (6.6-30.6)	14.4 (7.3-30.6)	<0.001	13.9 (6.6-30.8)	14.5 (7.4-30.7)	<0.001	11.8 (6.3-30.6)	14.1 (6.7-30.7)	<0.001

Values are presented as median (interquartile range).
CTA = computed tomography angiography.
* Mean plaque burden was defined as follows: The sum of ((vessel wall area – lumen area) / vessel wall area) per slice / total number of slices.

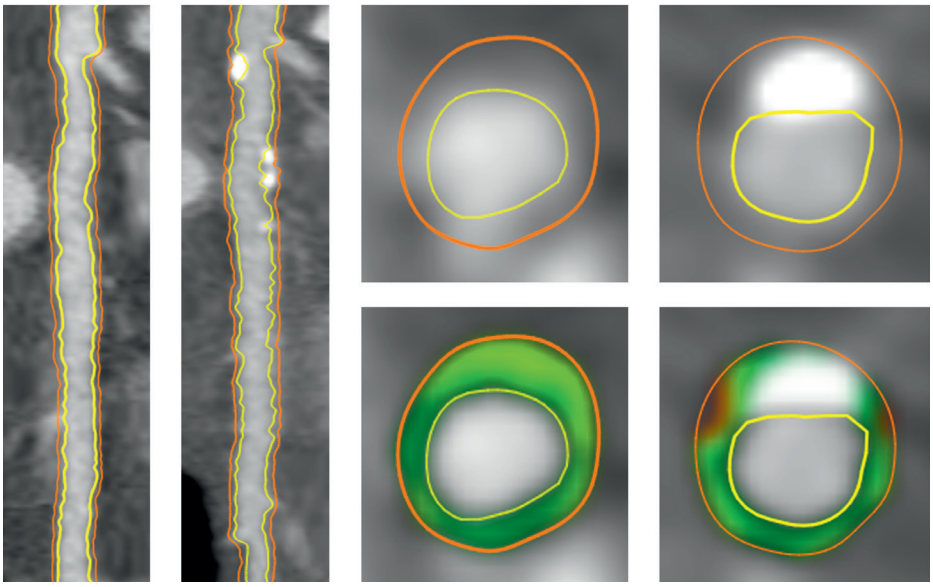

Figure 3: Example of quantitative CTA analysis for a statin-taking patient. Representative case showing the impact of statin use on CAD progression. Although initially no coronary calcification was present at quantitative CTA analysis, extensive calcification had occurred after 8 years of follow-up. Red indicates necrotic core tissue, light green indicates fibro-fatty tissue, dark green indicates fibrous tissue and white indicates dense calcium tissue. CAD = coronary artery disease; CTA = computed tomography angiography.

Impact of clinical characteristics and statin use on CAD progression

On a per-plaque basis, increasing age (β = 0.070; P = 0.058) and hypertension (β = 1.380; P = 0.075) were associated with annual total plaque progression, although no significant associations were found (Table 4). In addition, male gender (β = 1.676; P = 0.009), diabetes (β = 1.725; P = 0.012) and statin use (β = 1.498; P = 0.046) showed an independent association with annual progression of calcified plaque. While hypertension (β = 2.259; P = 0.015) was an independent determinant of non-calcified plaque progression, statin use (β = -2.178; P = 0.050) was borderline significantly associated with a reduced progression of non-calcified plaque. On a per-patient basis, similar results were found (Supplemental Table 2). Interestingly, patients who experienced a cardiac event (n = 12) during the interscan period showed a trend toward a more rapid progression of non-calcified plaque compared to patients without a cardiac event (n = 190) (P = 0.35) (Supplemental Figure 5).

Table 4: Association between clinical variables, statin use and annual increase in total, calcified and non-calcified plaque volume (per-plaque analysis).

Clinical variables	Total				Calcified				Non-calcified			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
	Estimate	P-value	Estimate	P-value	Estimate	P-value	Estimate	P-value	Estimate	P-value	Estimate	P-value
Age (years)	0.082	0.025	0.070	0.058	0.062	0.036	0.034	0.26	0.045	0.29	0.070	0.11
Male	1.221	0.12	1.089	0.17	1.642	0.009	1.676	0.009	-0.727	0.42	0.197	0.83
Family history of CAD	-0.460	0.52	0.141	0.84	-0.997	0.085	-0.416	0.46	1.045	0.21	1.182	0.16
Current smoker	0.316	0.74	0.981	0.29	-0.687	0.37	-0.626	0.40	0.642	0.56	1.006	0.36
Diabetes	1.746	0.036	1.198	0.15	1.964	0.003	1.725	0.012	-0.380	0.70	-0.023	0.98
Dyslipidemia	-0.012	0.99	-0.361	0.66	0.004	0.99	0.007	0.99	0.126	0.89	0.422	0.67
Hypertension	1.319	0.094	1.380	0.075	-0.288	0.66	-0.483	0.44	2.002	0.026	2.259	0.015
Obesity	0.497	0.58	-0.268	0.77	0.573	0.43	0.284	0.70	- 0.363	0.73	-0.720	0.51
Statin use at baseline and/or follow-up	0.105	0.91	-0.041	0.97	1.781	0.014	1.498	0.046	-2.402	0.021	-2.178	0.050
Absolute change in LDL-C (mg/dl)	-0.0150	0.052	-0.005	0.50	-0.011	0.071	-0.005	0.47	-0.001	0.89	-0.007	0.45
Plaque volume at baseline (mm^3) *	0.010	<0.001	0.010	<0.001	0.042	<0.001	0.039	<0.001	-0.004	0.001	-0.004	0.001

CAD = coronary artery disease; LDL-C = low-density lipoprotein cholesterol.

* Total, calcified or non-calcified plaque volume was used for the analysis depending on the outcome parameter.

DISCUSSION

The impact of clinical characteristics and statin use on coronary plaque progression was investigated using serial coronary CTA. Statin use was significantly associated with a more rapid progression of calcified plaque, whereas non-calcified plaque progression was reduced. While hypertension was the only clinical variable predictive of non-calcified plaque progression, diabetes and male gender were independent determinants of calcified plaque progression.

Impact of statin use on CAD progression

Statin use has frequently been shown to reduce the rate of major adverse cardiac events and to improve overall survival in patients with CAD.[19] The current study is the first to provide an insight on the long-term impact of statin use on coronary plaque progression in a low-risk patient population. To our knowledge, our study represents the longest interscan period to date for a serial coronary CTA study. In our study, statin use was associated with a slowed progression of non-calcified coronary plaque, whereas the progression of calcified coronary plaque was increased with the use of statins. Overall, this resulted in a similar overall progression of coronary plaque in statin and non-statin users.

Multiple other studies have addressed the impact of statin use on CAD progression. The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) registry is the largest study currently performed in patients who underwent serial coronary CTA.[15] In this study, the effect of statins on individual coronary atherosclerotic plaques was assessed during a mean interscan period of 3.8 years. In agreement with our results, the progression of non-calcified plaque was significantly reduced in statin users, whereas statin users demonstrated a more rapid progression of calcified plaque (both $P < 0.001$). Interestingly, statin use was also associated with a slower rate of overall plaque progression ($P = 0.002$). These conflicting results with regard to the effect of statins on overall plaque progression could be explained by many factors, including the enrollment of a patient population with a different background and follow-up duration. Possibly, the calcifying effect of statins on coronary plaques becomes more significant over time (i.e. comparable to the reduction in non-calcified plaque), thereby resulting in no net effect of statin use on overall plaque progression during long-term follow-up. Also after adjusting for risk factors in multivariable analysis, statin use did not impact overall plaque progression.

The pro-calcific effect of statins has also been demonstrated in other studies that used either serial non-invasive or invasive imaging modalities to assess coronary plaque progression. However, most serial imaging studies were hampered by a short follow-up

duration or retrospective design.[10-14] Most importantly, our study differs from previous studies in that the majority of statin-taking patients showed a negligible extent of calcified plaque at the baseline coronary CTA.

It could be hypothesized that the increase in coronary calcification represents a 'healing' mechanism of statins, whereby coronary plaques become increasingly stabilized through calcification of the necrotic core.[20] Although conceptually attractive, it remains to be determined whether this increased calcification is the underlying cause for the improved clinical outcome in statin-taking patients with confirmed CAD.

Clinical predictors of CAD progression

Increasing age, male gender, hypertension and diabetes were found to be non-significantly associated with overall CAD progression. Whereas diabetes mainly led to coronary plaque progression by an increase in calcified plaque, hypertension induced progression of non-calcified plaque.

Our findings are in line with previous research on coronary plaque progression and morphology in patients with hypertension or diabetes. Bayturan et al. evaluated 951 patients with very low LDL cholesterol levels (≤70 mg/dl) who underwent serial intravascular ultrasound to assess CAD progression.[21] The authors found that despite achieving very low LDL cholesterol levels, the presence of diabetes (P = 0.02) and an increase in systolic blood pressure (P = 0.001) were independently associated with CAD progression. The relationship between hypertension and incident CAD was further investigated in the CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry), a large multicenter registry including patients without known CAD who underwent a single coronary CTA.[22] In that study, it was found that non-calcified plaques, as well as calcified plaques, were significantly more prevalent in patients with hypertension compared to a matched cohort of patients without hypertension. More recently, the impact of diabetes and glycemic status on CAD progression was investigated in two substudies of the PARADIGM registry.[23, 24] In these studies, it was demonstrated that patients with diabetes experience greater overall CAD progression compared to patients without diabetes. Although diabetes was significantly associated with progression of all 4 coronary plaque subtypes (i.e. fibrous, fibro-fatty, necrotic core and dense calcium), the strongest association was found for progression of dense calcium plaque. Finally, diabetes was shown to be associated with an increased prevalence of total and calcified coronary plaque in multiple studies that included patients who underwent a single coronary CTA or coronary calcium score.[25-28]

Our study findings could yield the need for intensified preventive treatment of patients with diabetes and hypertension to slow and stabilize CAD progression and improve clinical outcome. Previous studies have demonstrated that good glycemic and blood pressure control could lead to lower CAD progression.[29-31] Moreover, the progression of different plaque types (i.e. calcified vs. non-calcified) in patients with diabetes and hypertension may suggest the presence of distinct pathophysiological mechanisms of coronary plaque progression.

LIMITATIONS

The present study has several limitations. First, the number of patients included was relatively low. This could be an important reason for the lack of statistical significance in the relationship between clinical variables and overall plaque progression after adjustment for potential confounders. Second, coronary CTA scanners from different vendors were used to assess CAD progression which could affect plaque volume measurements. However, all coronary CTAs at follow-up were performed according to a predefined standard operating procedure to reduce the difference in Hounsfield units (HU) between coronary CTAs from different vendors. Third, statin use at baseline and follow-up visits was used to define statin users, but no information was available on possible changes in treatment and dosages in the interscan period. Therefore, the effect of statin use on overall CAD progression could be underestimated if statin-taking patients at follow-up did not use statins during the entire interscan period. Fourth, quantitative CTA analysis was only performed for visually determined plaques at the baseline and follow-up coronary CTA. Therefore, patients without coronary plaques at the follow-up coronary CTA were excluded from the current study. Fifth, information on non-statin therapy and dietary pattern was not available and therefore its effect on coronary plaque progression could not be assessed. Sixth, high-risk plaque features (e.g. napkin-ring sign and spotty calcification) were not analysed in the current study and are therefore not available.

CONCLUSION

The current study demonstrated that statin use was associated with an increased progression of calcified coronary plaque and a reduced progression of non-calcified coronary plaque. Whereas hypertension was the only modifiable risk factor predictive of non-calcified plaque progression, diabetes mainly led to an increase in calcified plaque. Additional studies are required to study the effect of statin use and intensive control of cardiovascular risk factors on coronary plaque progression and its relationship to clinical outcome.

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Disclosures

None.

REFERENCES

1. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, Ahmed M, Aksut B, Alam T, Alam K, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J Am Coll Cardiol*. 2017;70:1-25.

2. Blankenhorn DH, Azen SP, Kramsch DM, Mack WJ, Cashin-Hemphill L, Hodis HN, DeBoer LW, Mahrer PR, Masteller MJ, Vailas LI, et al. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med*. 1993;119:969-76.

3. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2004;291:1071-80.

4. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA*. 2006;295:1556-65.

5. Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, Wolski K, Crowe T, Desai MY, Hazen SL, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA*. 2007;297:499-508.

6. Kini AS, Baber U, Kovacic JC, Limaye A, Ali ZA, Sweeny J, Maehara A, Mehran R, Dangas G, Mintz GS, et al. Changes in plaque lipid content after short-term intensive versus standard statin therapy: the YELLOW trial (reduction in yellow plaque by aggressive lipid-lowering therapy). *J Am Coll Cardiol*. 2013;62:21-9.

7. Knuuti J, Ballo H, Juarez-Orozco LE, Saraste A, Kolh P, Rutjes AWS, Juni P, Windecker S, Bax JJ and Wijns W. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. *Eur Heart J*. 2018;39:3322-3330.

8. Danad I, Szymonifka J, Twisk JWR, Norgaard BL, Zarins CK, Knaapen P and Min JK. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. *Eur Heart J*. 2017;38:991-998.

9. Gonzalez JA, Lipinski MJ, Flors L, Shaw PW, Kramer CM and Salerno M. Meta-Analysis of Diagnostic Performance of Coronary Computed Tomography Angiography, Computed Tomography Perfusion, and Computed Tomography-Fractional Flow Reserve in Functional Myocardial Ischemia Assessment Versus Invasive Fractional Flow Reserve. *Am J Cardiol*. 2015;116:1469-78.

10. Burgstahler C, Reimann A, Beck T, Kuettner A, Baumann D, Heuschmid M, Brodoefel H, Claussen CD, Kopp AF and Schroeder S. Influence of a lipid-lowering therapy on calcified and noncalcified coronary plaques monitored by multislice detector computed tomography: results of the New Age II Pilot Study. *Invest Radiol*. 2007;42:189-95.

11. Inoue K, Motoyama S, Sarai M, Sato T, Harigaya H, Hara T, Sanda Y, Anno H, Kondo T, Wong ND, et al. Serial coronary CT angiography-verified changes in plaque characteristics as an end point: evaluation of effect of statin intervention. *JACC Cardiovasc Imaging*. 2010;3:691-8.

12. Hoffmann H, Frieler K, Schlattmann P, Hamm B and Dewey M. Influence of statin treatment on coronary atherosclerosis visualised using multidetector computed tomography. *Eur Radiol*. 2010;20:2824-33.

13. Zeb I, Li D, Nasir K, Malpeso J, Batool A, Flores F, Dailing C, Karlsberg RP and Budoff M. Effect of statin treatment on coronary plaque progression - a serial coronary CT angiography study. *Atherosclerosis*. 2013;231:198-204.

14. Shin S, Park HB, Chang HJ, Arsanjani R, Min JK, Kim YJ, Lee BK, Choi JH, Hong GR and Chung N. Impact of Intensive LDL Cholesterol Lowering on Coronary Artery Atherosclerosis Progression: A Serial CT Angiography Study. *JACC Cardiovasc Imaging*. 2017;10:437-446.

15. Lee SE, Chang HJ, Sung JM, Park HB, Heo R, Rizvi A, Lin FY, Kumar A, Hadamitzky M, Kim YJ, et al. Effects of Statins on Coronary Atherosclerotic Plaques: The PARADIGM Study. *JACC Cardiovasc Imaging*. 2018;11:1475-1484.

16. Sakellarios A, Siogkas P, Georga E, Tachos N, Kigka V, Tsompou P, Andrikos I, Karanasiou GS, Rocchiccioli S, Correia J, et al. A Clinical Decision Support Platform for the Risk Stratification, Diagnosis, and Prediction of Coronary Artery Disease Evolution. *Conf Proc IEEE Eng Med Biol Soc*. 2018;2018:4556-4559.

17. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML and Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation*. 1975;51:5-40.

18. de Graaf MA, Broersen A, Kitslaar PH, Roos CJ, Dijkstra J, Lelieveldt BP, Jukema JW, Schalij MJ, Delgado V, Bax JJ, et al. Automatic quantification and characterization of coronary atherosclerosis with computed tomography coronary angiography: cross-correlation with intravascular ultrasound virtual histology. *Int J Cardiovasc Imaging*. 2013;29:1177-90.

19. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-9.

20. Mori H, Torii S, Kutyna M, Sakamoto A, Finn AV and Virmani R. Coronary Artery Calcification and its Progression: What Does it Really Mean? *JACC Cardiovasc Imaging*. 2018;11:127-142.

21. Bayturan O, Kapadia S, Nicholls SJ, Tuzcu EM, Shao M, Uno K, Shreevatsa A, Lavoie AJ, Wolski K, Schoenhagen, et al. Clinical predictors of plaque progression despite very low levels of low-density lipoprotein cholesterol. *J Am Coll Cardiol*. 2010;55:2736-42.

22. Nakanishi R, Baskaran L, Gransar H, Budoff MJ, Achenbach S, Al-Mallah M, Cademartiri F, Callister TQ, Chang HJ, Chinnaiyan K, et al. Relationship of Hypertension to Coronary Atherosclerosis and Cardiac Events in Patients With Coronary Computed Tomographic Angiography. *Hypertension*. 2017;70:293-299.

23. Kim U, Leipsic JA, Sellers SL, Shao M, Blanke P, Hadamitzky M, Kim YJ, Conte E, Andreini D, Pontone G, et al. Natural History of Diabetic Coronary Atherosclerosis by Quantitative Measurement of Serial Coronary Computed Tomographic Angiography: Results of the PARADIGM Study. *JACC Cardiovasc Imaging*. 2018;11:1461-1471.

24. Won KB, Lee SE, Lee BK, Park HB, Heo R, Rizvi A, Lin FY, Kumar A, Hadamitzky M, Kim YJ, et al. Longitudinal assessment of coronary plaque volume change related to glycemic status using serial coronary computed tomography angiography: A PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) substudy. *J Cardiovasc Comput Tomogr*. 2019;13:142-147.

25. Khazai B, Luo Y, Rosenberg S, Wingrove J and Budoff MJ. Coronary Atherosclerotic Plaque Detected by Computed Tomographic Angiography in Subjects with Diabetes Compared to Those without Diabetes. *PLoS One*. 2015;10:e0143187.

26. Chu ZG, Yang ZG, Dong ZH, Zhu ZY, Peng LQ, Shao H, He C, Deng W, Tang SS and Chen J. Characteristics of coronary artery disease in symptomatic type 2 diabetic patients: evaluation with CT angiography. *Cardiovasc Diabetol*. 2010;9:74.

27. Deseive S, Straub R, Kupke M, Broersen A, Kitslaar PH, Stocker TJ, Massberg S, Hadamitzky M and Hausleiter J. Impact of diabetes on coronary artery plaque volume by coronary CT angiography and subsequent adverse cardiac events. *J Cardiovasc Comput Tomogr*. 2019;13:31-37.

28. Rana JS, Dunning A, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng VY, Chinnaiyan K, et al. Differences in prevalence, extent, severity, and prognosis of coronary artery disease among patients with and without diabetes undergoing coronary computed tomography angiography: results from 10,110 individuals from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes): an InteRnational Multicenter Registry. *Diabetes Care*. 2012;35:1787-94.

29. Sipahi I, Tuzcu EM, Schoenhagen P, Wolski KE, Nicholls SJ, Balog C, Crowe TD and Nissen SE. Effects of normal, pre-hypertensive, and hypertensive blood pressure levels on progression of coronary atherosclerosis. *J Am Coll Cardiol*. 2006;48:833-8.

30. Kowall B, Lehmann N, Mahabadi AA, Moebus S, Budde T, Seibel R, Gronemeyer D, Erbel R, Jockel KH and Stang A. Progression of coronary artery calcification is stronger in poorly than in well controlled diabetes: Results from the Heinz Nixdorf Recall Study. *J Diabetes Complications*. 2017;31:234-240.

31. Chhatriwalla AK, Nicholls SJ, Wang TH, Wolski K, Sipahi I, Crowe T, Schoenhagen P, Kapadia S, Tuzcu EM and Nissen SE. Low levels of low-density lipoprotein cholesterol and blood pressure and progression of coronary atherosclerosis. *J Am Coll Cardiol*. 2009;53:1110-5.

SUPPLEMENTAL MATERIAL

Supplemental Methods

I. Full list of eligibility, inclusion, exclusion and exit criteria of SMARTool Clinical Study

Eligibility criteria:

A. Clinical history and lifestyle data records available at one-time point.
B. At least one previous CCTA examination performed for suspected CHD and of good quality to allow for: a) Non-invasive FFR-CT assessment b) Quantitative (automated) 17 segments (AHA) analysis and measurement with ≤10% error of MLA (mm^2), lumen area stenosis (%), mean plaque burden (mm^3), plaque burden at MLA (%), and remodeling index, c) Plaque phenotype assessment: HU based classification in calcified, non-calcified (LAP) and mixed plaques, napkin-ring sign, CAC score.
C. Previous blood and plasma sample available for retrospective analysis.

Inclusion criteria:

1) Male and female subjects.
2) Aged 45-82 years.
3) Caucasian population.
4) Submitted to CCTA for suspected CHD between 2009 and 2012 (in the context of EVINCI and ARTreat FPVII studies) at the hospitals reported in "SMARTool Clinical Center" document and satisfying the elegibility criteria reported above.
5) Submitted to clinical follow-up in the last 6 months with stable clinical conditions and documented CHD or persistent intermediate/high probability of CHD.
6) Signed informed consents (clinical and genetic).

Exclusion criteria:

1) Severe multivessel disease (3 vessel and/or LM disease with >90% stenosis).
2) Severe coronary calcification (CAC score > 600).
3) Having undergone surgical procedures related to heart diseases (valve replacement, CRT treatment, any surgery of the heart or arteries).
4) Documented MACE at history (myocardial infarction, severe heart failure, recurrent angina) in the last 6 months with/without revascularization.
5) Documented severe peripheral vascular disease (carotid, femoral).
6) Surgery of carotid and/or peripheral arteries or cerebral ischemic attack.
7) History/surgery of Abdominal Aortic Aneurysm (AAA).
8) Severe heart failure (NYHA Class III-IV).
9) LV dysfunction (left ventricular EF <40%).

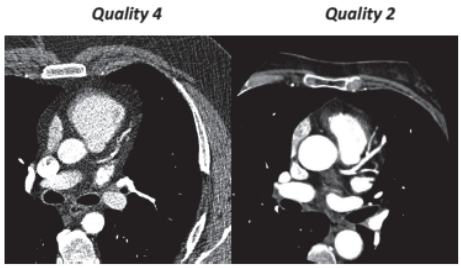
10) Atrial fibrillation.
11) Lack of written informed consent (clinical consent and/or genetic consent).
12) Pregnancy (evaluated by urine test) and breastfeeding.
13) Active cancer.
14) Asthma.
15) Cardiomyopathy or congenital heart disease.
16) Significant valvular disease (hemodynamically significant valvular stenosis or insufficiency by echo Doppler).
17) Renal dysfunction (creatinine > 1.3 mg/dL).
18) Chronic Kidney Disease (eGFR < 30 ml/min/1.73 m^2).
19) Hepatic failure (at least 3 of the following: albumin < 3.5 g/dL; prolonged prothrombin time (PT); jaundice; ascites).
20) Waldenström disease.
21) Multiple myeloma.
22) Autoimmune/Acute inflammatory disease.
23) Previous severe adverse reaction to iodine contrast agent.
24) Positivity at blood tests for HIV, Hepatitis B and C (CRF number 1-clinical evaluation).

Exit Criteria:

A) Informed consent retired by the patient (genetic or clinical).
B) Adverse events to contrast medium during CCTA.

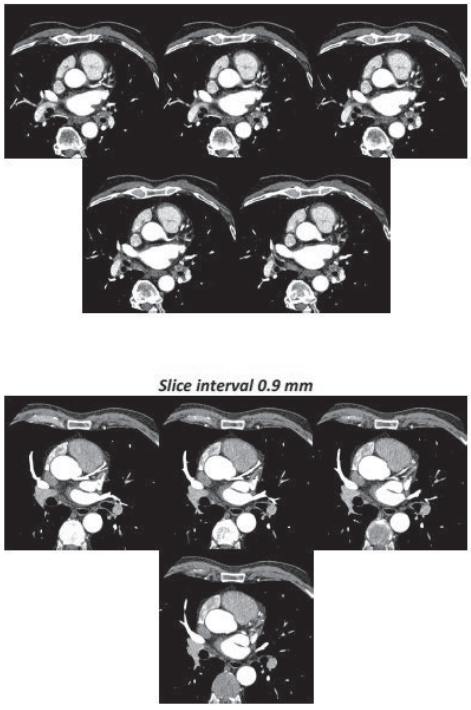
II. Standard operating procedure (SOP) for coronary CTA in SMARTool

✓ The CT image quality in the majority of cases should be preferably 2.



✓ Absence of motion or other artifacts in the acquired image; heart rate less than 65 beats/min and optimally less than 60 beats/min.
✓ Please administer nitroglycerin prior to the CTA acquisition.
✓ Optimized reconstruction of the most suitable cardiac cycle (i.e. diastole at 70-80% of the R-R interval).

- ✓ Please send multiple cardiac phases so we may choose different phases for different coronary segments if needed.
- ✓ kV, mA and contrast protocol should be preferably the same for the first and second scan. However, changes in patient body composition and local acquisition protocols should guide decision making.
- ✓ The reconstructed field of view should be reduced to maximize number of pixels devoted to depiction of the heart, usually field of view of 200-250 mm for coronary CTA studies of native coronary arteries.



III. Complete workflow of quantitative CTA analysis

A 3-dimensional coronary tree was extracted from the coronary CTA data set and straightened multiplanar reconstructions were created of each coronary artery. Subsequently, the lumen and vessel wall contours were automatically detected and these were manually adjusted if needed. Each atherosclerotic lesion was detected based on the lumen and vessel wall contours and the corresponding references lines, which indicate the normal tapering of the coronary artery. For each coronary lesion, stenosis parameters were calculated at the level of the minimal lumen area. In addition, total plaque volume and plaque volume according to the plaque composition were determined using predefined intensity cut-off values in Hounsfield units (HU): -30 to 75 HU for necrotic core plaque, 75

to 130 HU for fibro-fatty plaque, 130 to 350 HU for fibrous plaque and >350 HU for dense calcium plaque. Non-calcified plaque was defined as necrotic core, fibro-fatty and fibrous plaque combined (-30 to 350 HU).

IV. Definitions of clinical variables

Diabetes was defined as physician-diagnosed diabetes or current treatment with antidiabetic medication. Dyslipidemia was defined as physician-diagnosed dyslipidemia or current treatment with lipid-lowering medication. Hypertension was defined as physician-diagnosed hypertension or current treatment with antihypertensive medication. Obesity was defined as a body mass index greater or equal to 30. Patients were considered as current smoker if currently smoking or quit within the last 3 months. Family history of CAD was based on patient self-report. In addition, lipid profiles, including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides, were obtained at baseline and follow-up.

SUPPLEMENTAL TABLES

Supplemental Table 1: Baseline characteristics of excluded patients without (visually assessed) atherosclerosis development at follow-up.

	Without atherosclerosis at FU (n = 36)	With atherosclerosis at FU (n = 202)
Age (years)	56 ± 8	61 ± 9
Male	8 (22%)	140 (69%)
Family history of CAD	19 (56%)	94 (49%)
Current smoker	4 (12%)	33 (17%)
Diabetes	4 (12%)	41 (21%)
Dyslipidemia	22 (65%)	134 (70%)
Hypertension	16 (47%)	131 (68%)
Obesity	6 (18%)	38 (20%)

Values are presented as mean ± SD or n (%).
CAD = coronary artery disease; FU = follow-up.

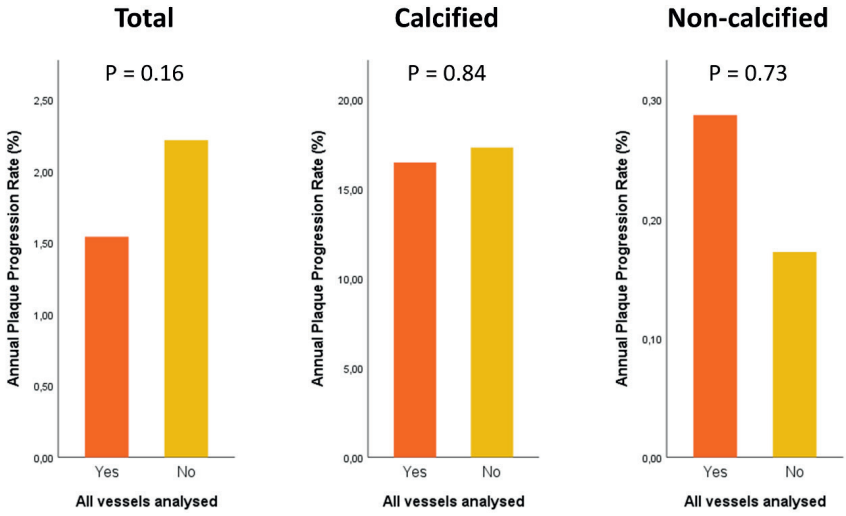
Supplemental Table 2: Association between clinical variables, statin use and annual increase in total, calcified and non-calcified plaque volume (per-patient analysis).

Clinical variables	Total				Calcified				Non-calcified			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
Age (years)	0.235	0.052	0.202	0.083	0.167	0.066	0.141	0.12	0.151	0.21	0.226	0.088
Male	6.328	0.008	4.295	0.073	6.145	0.001	6.852	<0.001	-1.093	0.65	2.144	0.43
Family history of CAD	-0.338	0.88	1.288	0.54	-2.021	0.24	-0.013	0.99	2.897	0.21	3.656	0.13
Current smoker	0.161	0.96	2.330	0.39	-2.951	0.20	-3.365	0.11	2.455	0.42	3.555	0.26
Diabetes	8.714	0.002	4.797	0.076	8.386	<0.001	7.686	<0.001	-0.558	0.84	0.767	0.80
Dyslipidemia	1.418	0.58	-0.899	0.71	0.778	0.68	0.168	0.93	1.195	0.63	1.663	0.55
Hypertension	5.670	0.022	4.107	0.070	0.313	0.87	-0.823	0.64	6.035	0.014	6.886	0.008
Obesity	2.542	0.38	-0.662	0.81	2.478	0.25	0.043	0.98	-0.601	0.84	-2.118	0.50
Statin use at baseline and/or follow-up	2.720	0.33	0.349	0.90	5.745	0.005	4.472	0.032	-5.394	0.049	-5.482	0.073
Absolute change in LDL-C (mg/dl)	-0.042	0.088	-0.005	0.84	-0.033	0.070	-0.015	0.41	0.001	0.98	-0.009	0.74
Plaque volume at baseline (mm^3) *	0.014	<0.001	0.012	<0.001	0.034	<0.001	0.023	0.007	-0.002	0.30	-0.003	0.17

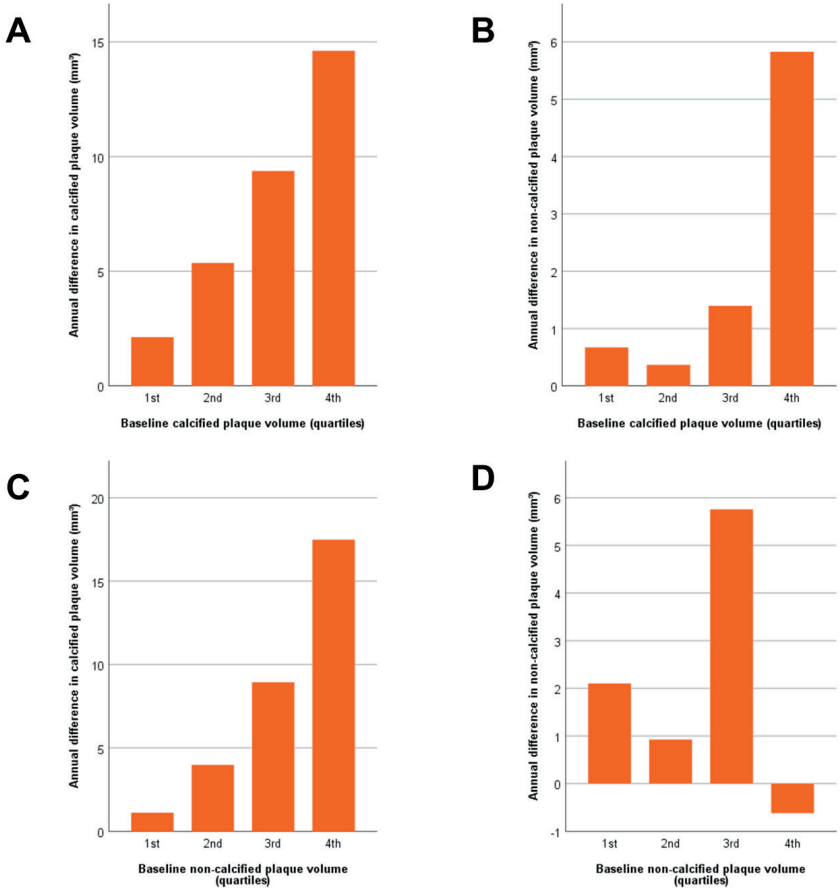
CAD = coronary artery disease; LDL-C = low-density lipoprotein cholesterol.

* Total, calcified or non-calcified plaque volume was used for the analysis depending on the outcome parameter.

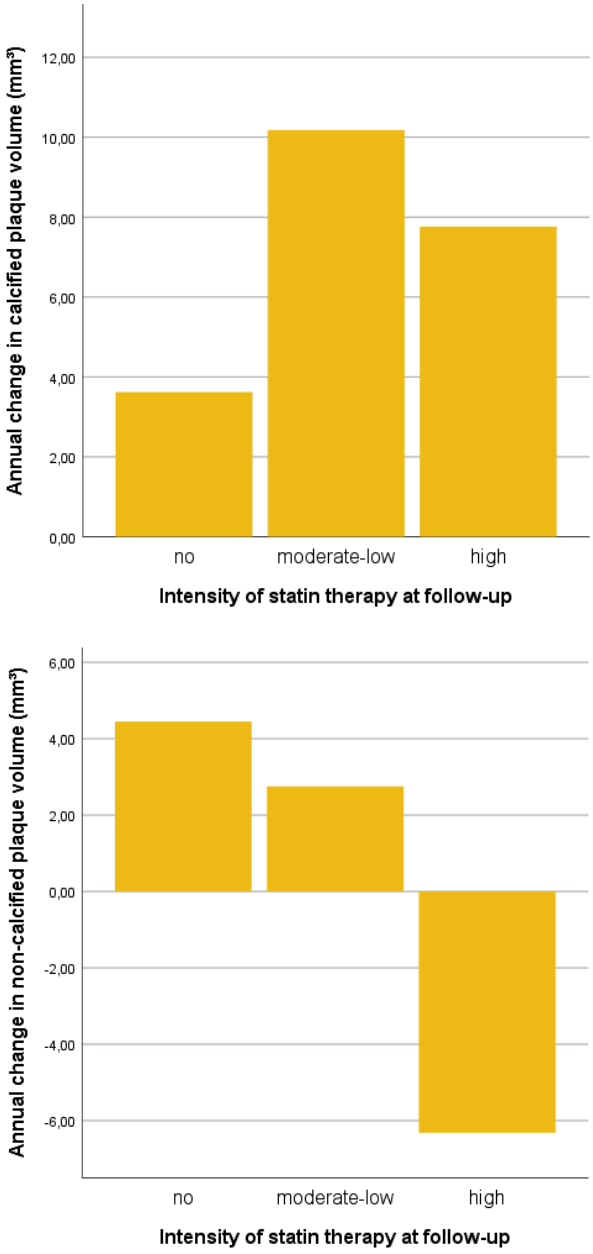
SUPPLEMENTAL FIGURES



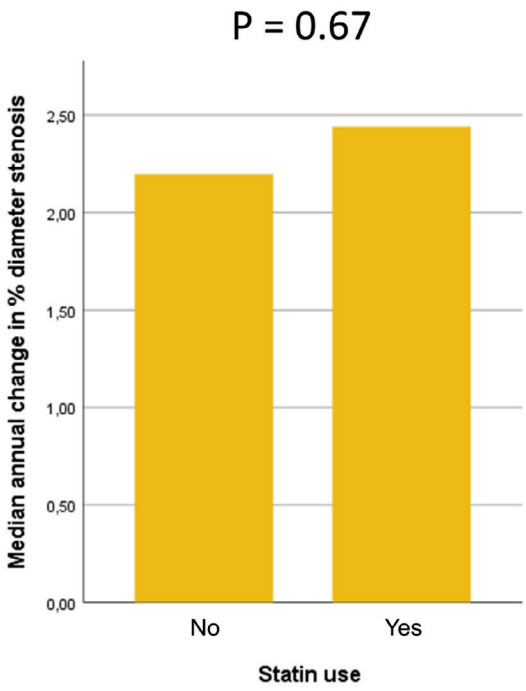
Supplemental Figure 1: Median annual plaque progression rate in patients with and without all coronary vessels analysed by quantitative CTA analysis. The median annual plaque progression rate between patients with and without all coronary vessels analysed was not significantly different for total, calcified and non-calcified plaque. CTA = computed tomography angiography.



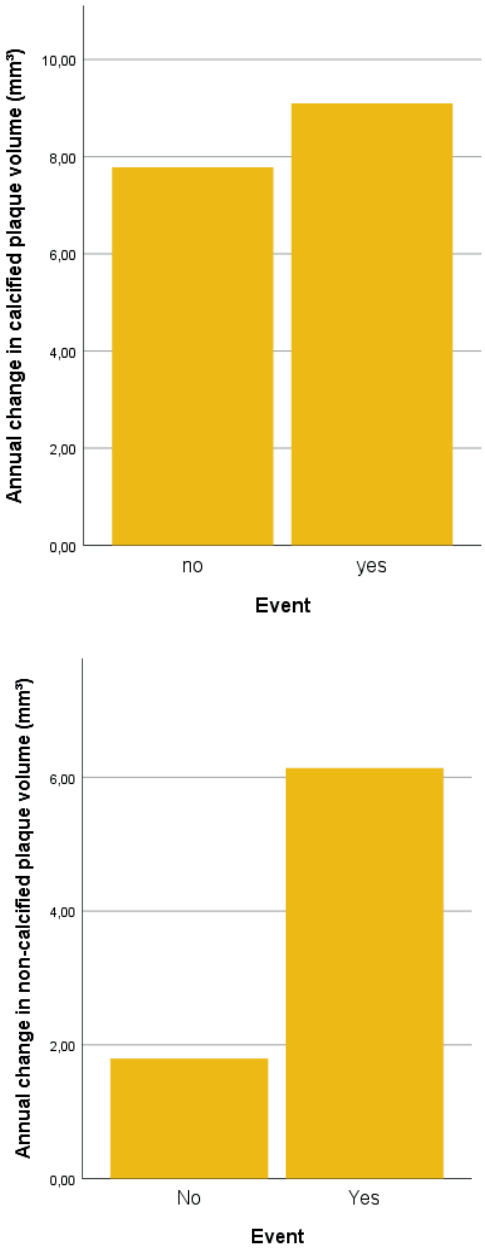
Supplemental Figure 2: Association between baseline plaque volume and plaque progression according to plaque composition. A higher calcified plaque volume at baseline was associated with progression of both calcified and non-calcified plaque. However, a higher non-calcified plaque volume at baseline was only associated with progression of calcified plaque progression.



Supplemental Figure 3: Annual change in calcified and non-calcified plaque volume according to the intensity of statin therapy at follow-up. The intensity of statin therapy was classified according to the ACC 2018 Guideline on the Management of Blood Cholesterol based on dosage and type.



Supplemental Figure 4: Change in % diameter stenosis between patients with and without statin use at baseline and/or follow-up. The increase in % diameter stenosis was comparable between patients with and without statin use at baseline and/or follow-up.



Supplemental Figure 5: Annual change in calcified and non-calcified plaque volume according to the occurrence of a cardiac event (defined as acute myocardial infarction or unstable angina). Patients who experienced a cardiac event (n = 12) during the interscan period showed a trend toward a more rapid progression of non-calcified plaque compared to patients without a cardiac event (n = 190) (P = 0.35).