The role of detailed coronary atherosclerosis evaluation by CT in ischemic heart disease

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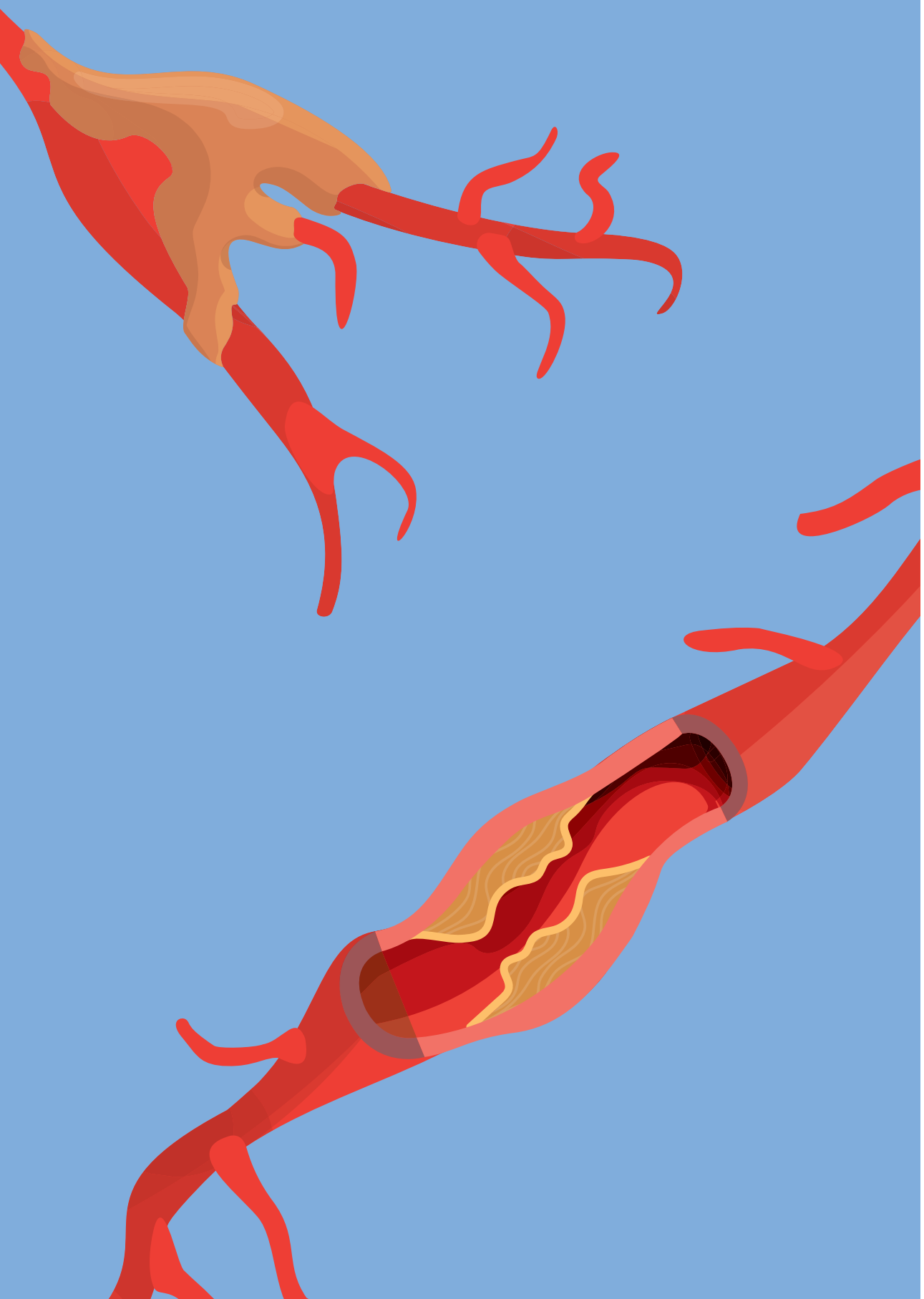

Chapter 9

Association of Statin Treatment on Progression of Coronary Atherosclerotic Plaque Composition

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Key points

Question: Atherosclerotic plaque progression**,** across a range of density measurements by coronary computed tomography angiography (CCTA), is understudied.

Findings: In serial CCTA, statin untreated coronary lesions progressed in volume of all 6 compositional plaque types (LAP (-30, 75 HU), fibro-fatty (76-130 HU), fibrous (131-350 HU), low-density calcium (351-700 HU), high-density calcium (701-1000 HU), and 1K plaque (>1000 HU), while statins were associated with reductions in LAP and fibro-fatty plaque, and larger progression of high-density calcium and 1K plaque. Statins were not associated with change in calcified plaque, but with a transformation towards more dense calcium, which was associated with slower overall plaque progression.

Meaning: The results suggest an association of statin use with greater rates of transformation of coronary atherosclerosis towards high-density calcium, supporting the concept of reduced atherosclerotic risk with increased densification of calcium.

Abstract

Importance: The density of atherosclerotic plaque forms the basis for categorizing calcified and noncalcified morphology of plaques.

Objective: We hypothesized that alterations in plaque – across a range of density measurements – provide a more detailed understanding of atherosclerotic disease progression.

Design, setting, and participants: We enrolled patients who underwent serial coronary computed tomography angiography (CCTA) two or more years apart at 13 sites in 7 countries, with quantitative measurement of coronary plaque of the entire coronary tree.

Exposures: Serial CCTA

Main outcomes and measures: The main outcome was progression of plaque composition of individual coronary plaques. Six plaque composition types were defined on a voxel-level basis according to the attenuation (expressed in Hounsfield Units, HU) of plaque: low-attenuation plaque (LAP, -30, 75 HU), fibro-fatty (76-130 HU), fibrous (131-350 HU), low-density calcium (351-700 HU), high-density calcium (701-1000 HU), and 1K plaque (>1000 HU). The progression rates of these 6 compositional plaque types were evaluated according to the interaction of statin use with baseline plaque volume, adjusted for risk factors and time interval between scans. Second, plaque progression was examined according to baseline calcium density. Analysis was performed among lesions matched at baseline and follow-up.

Results: A total of 2,458 coronary lesions in 857 patients (mean age 62.1 ± 8.7, 63.0% male; 63.9% on statins) were included. Untreated coronary lesions increased in volume of all six compositional types over time. Statin therapy was associated with reductions in LAP (β -0.018 [-0.028, -0.008], p=0.001) and fibro-fatty plaque (β -0.033 [-0.045, -0.020], p<0.001) and larger progression of high-density calcium (β 0.017 [0.008, 0.025], p<0.001) and 1K (β 0.020 [0.011, 0.029], p<0.001) plaque. When restricted to lesions without LAP or fibro-fatty plaque at baseline, statins were not associated with a change in overall calcified plaque (β -0.031 [-0.082, 0.021], p=0.241), but with a transformation towards more dense calcium. Interaction analysis between the baseline plaque volume and calcium density showed that the more dense coronary calcium associated with less plaque progression.

Conclusions and relevance: The results suggest an association of statin use with greater rates of transformation of coronary atherosclerosis towards high-density calcium. A pattern of slower overall plaque progression was observed with increasing density, all supporting the concept of reduced atherosclerotic risk with increased densification of calcium.

Keywords: Atherosclerosis, computed tomography, cardiac imaging, plaque progression

Introduction

The atherosclerotic plaque burden in the coronary tree is a strong predictor of future major cardiovascular events.[1] The larger the volume of atherosclerotic plaque, the higher the likelihood of plaque destabilization (rupture or erosion) leading to vascular thrombosis and occlusion of the coronary artery.[2] Atherosclerotic features associated with ruptured plaques are large necrotic cores with an inflamed and thin fibrous cap.[3] On the other hand, plaque features hypothesized to contribute to plaque stability are small necrotic cores that have been replaced by sheets of calcification.

Using intravascular ultrasound (IVUS) or coronary computed tomography angiography (CCTA), statins have been associated with a decrease in lipid rich plaque, and an increase in calcification.[4,5] While a large plaque burden corroborates with high future risk, it may be possible that atherosclerosis that is predominantly calcified may portend reduced risk. Using coronary artery calcium (CAC) scoring from non-contrast computed tomography (CT), indeed, higher density calcium was associated with a lower major event risk.[6] In line with this, we previously demonstrated lower rates of future acute coronary syndromes (ACS) for 1K plaque (very dense calcium >1000 Hounsfield Units).[7]

Calcium by CCTA is generally considered one compositional type, while its density is not considered separately. However, the two prior studies indicate that a more nuanced approach refining density ranges further may be necessary.[6,7] Low-density calcium may not portend the same low-risk status as higher density calcium, such as 1K plaque.[7] From the serial CCTA PARADIGM (Progression of Atherosclerotic Plaque DetermIned by Computed Tomographic Angiography Imaging) study, we hypothesized that alterations in plaque over time – across a range of density measurements – provide a more detailed understanding of atherosclerotic disease progression. First, changes in density subgroups of non-calcified and calcified plaque were examined according to statin use. Second, plaque progression over time was evaluated by baseline calcium density.

Methods

Patients

The PARADIGM study is dynamic, multinational observational registry that included patients who underwent clinically indicated serial CCTA.[8] The institutional review board approved the study protocol in all participating centers. From 13 sites in 7 countries, 2252 consecutive patients with suspected or known coronary artery disease undergoing serial CCTA ≥2 years apart were enrolled (eFigure 1). For the current study, patients with non-interpretable CCTA on 0.5 mm slice basis (N=492), patients without lesions present both at baseline and follow-up (N=431), patients initiating or stopping statin therapy after baseline CCTA (N=237) or unknown information regarding statin use at baseline or follow-up (N=235) were excluded. Further – to allow longitudinal assessment of plaque volume changes over time – tandem lesions at baseline which had confluenced at follow-up were also excluded. Statin therapy was defined as the use of statins at baseline and follow-up CCTA, whereas no statin use was defined as no statin use before both CCTAs. In a sensitivity analysis, a third group – patients who started statin therapy after baseline CCTA – was compared with statin naïve patients at both scans with results presented in the supplement. This group may be more similar in clinical risk profile with patients not using statins than the statin treated patients at both CT scans. The study protocol was approved by the institutional review boards of all centres, and, when required, patients provided written informed consent.

CCTA image analysis

CT scans were acquired in accordance with the Society of Cardiovascular Computed Tomography guidelines.[9] Baseline and follow-up CCTA DICOM files from each patient were transferred to a core laboratory for blinded image analysis. Coronary plaque was evaluated on multiplanar and cross-sectional images, and level-III experienced readers blinded to clinical data performed quantitative plaque analysis using dedicated semi-automated software with manual adjustments (QAngioCT Research Edition v2.1.9.1, Medis Medical Imaging Systems, Leiden, The Netherlands).

Plaque quantification methodology has been previously described.[5] In brief, all coronary arteries including side branches ≥2mm in diameter were evaluated. Atherosclerosis was defined as any tissue ≥1 mm^2 within or adjacent to the lumen, which could be discriminated from surrounding lumen, epicardial fat, and pericardial tissue, and was identified in ≥2 planes.[1] Coronary lesions were quantified for plaque volumes, and volumes of several composition types were derived based on fixed Hounsfield Unit (HU) thresholds, on voxel-level basis: low-attenuation plaque (LAP, -30 to 75 HU), fibro-fatty (76 to 130 HU), fibrous (131 to 350 HU), low-density calcium (351 to 700 HU), high-density calcium (701 to 1000 HU), and 1K plaque (>1000 HU). Ranges for LAP were defined according to histological comparisons with CCTA.[10] For longitudinal comparisons, coronary lesions at baseline and follow-up were co-registered using fiduciary landmarks, such as the distance from the ostium of the artery or side branches, as previously described. Changes in per-lesion plaque volumes (by composition) were calculated by subtracting volumes at baseline from follow-up. Core lab inter- and intra-observer variability for plaque volume and the several composition types were excellent (all ≥0.95).[5] Spotty calcification (SC), a commonly used high-risk plaque feature, was defined as a calcification <3 mm surrounded by non-calcified plaque. Compositional plaque volumes are provided according to the presence of SC.

Outcomes

Analysis are performed on a per-lesion level. First, progression or regression of LAP, fibro-fatty, fibrous, low-density calcium, high-density calcium, and 1K plaque according to statin use were evaluated by the interaction term between baseline plaque volume and statin use. Absolute changes in plaque volume over time are strongly dependent on the baseline plaque volume – hence – larger progression/regression rates by statin can be expected in larger baseline lesions. Analyses were also performed stratified by the median CT-interval. Second, to isolate the effect of statins on coronary calcium density, the interactions between baseline plaque volume and statin use were examined among coronary lesions without LAP or fibro-fatty plaque. Third, the influence of baseline calcium density on the progression of total plaque volume was evaluated by the interaction between baseline plaque volume and percentage of calcium being low-density, high-density, or 1K.

Statistical analysis

Continuous data were presented as mean ± standard deviation, regardless of distribution, for uniformity of presentation. The student T test or Mann-Whitney U test were used for comparison of continuous data; the Chi-square test for categorical data, as appropriate. Associations between statin use and change in plaque volume were performed using linear mixed models with random intercept to account for the within-patient clustering of coronary lesions. Interactions between statin use and baseline plaque volume were adjusted for the 2 main effects, age, sex, diabetes, hypertension, smoking status, body mass index (BMI), and the CT-interval, based

on clinical judgement. Positive interaction terms between baseline plaque volume and statin use can be interpreted that statins are associated with larger increase of the outcome when the baseline plaque volume is larger, and vice versa. For visual interpretation of the interaction terms, the estimated changes from the statistical models are plotted according to baseline plaque volume. Analyses were performed using SPSS software (version 25, SPSS IBM Corp., Armonk, New York, USA).

Results

Patients

Of the total 2252 patients, 857 patients (age 62.1 ± 8.7 years, 63.0% male) were included in the study, of whom 548 (63.9%) were on statin therapy. Inclusion and exclusion criteria are shown in eFigure 1. Statin treated patients were older, more often male, and presented more frequently with diabetes and hypertension (Table 1). Statin use was associated with lower low-density lipoprotein (LDL) cholesterol levels at baseline and follow-up: 107 mg/dl ± 40 vs 113 mg/dl ± 29, p=0.029 at baseline, and 88 mg/dl ± 31 vs 110 mg/dl ± 30, p<0.001 at follow-up.

Baseline compositional plaque volumes

A total of 2485 lesions were evaluated, of which 1658 (66.7%) were among patients on statin therapy. Mean compositional plaque volumes of the lesions are presented in eFigure 2. At baseline and follow-up, lesions in statin- versus no statin-treated patients had lower volume of LAP and higher volumes of all 3 calcium subtypes (eFigure 2). Spotty calcification (SC) lesions were composed of greater non-calcified plaque components and low-density calcium, but not more high-density calcium or 1K plaque, compared to non-SC lesions (eTable 1). With increasing density of plaque calcification, the proportion of LAP, fibrofatty plaque and fibrous plaque decreased (eTable 2).

Progression of plaque volume in statin versus no statin treated patients

Table 2 shows the adjusted interaction terms between baseline plaque volume and statin use for the change in LAP, fibro-fatty plaque, fibrous plaque, low-density calcium, high-density calcium, and 1K plaque, while changes in the volume of the 6 plaque components with and without statin treatment are shown in Figure 1. Statin therapy was associated with larger reductions in LAP and fibro-fatty plaque compared with no statin therapy (p-interaction = 0.001 and <0.001, respectively). Without statin therapy, LAP and fibro-fatty plaque volumes progressed with larger baseline plaque volumes. No significant interaction between baseline plaque volume and statin therapy was observed for changes in fibrous plaque and low-density calcium volume (p-interaction = 0.580 and 0.114, respectively). Statin therapy was associated with a larger increase in high-density calcium and 1K plaque volume, compared to no statin therapy (p-interaction <0.001 for both comparisons). When stratifying the analyses by the median CT-interval (3.2 years), significant associations of larger reductions in LAP and fibro-fatty plaque, and larger increases in high-density calcium and 1K plaque were only observed in lesions re-scanned in the longer CT-interval cohort (eTable 3).

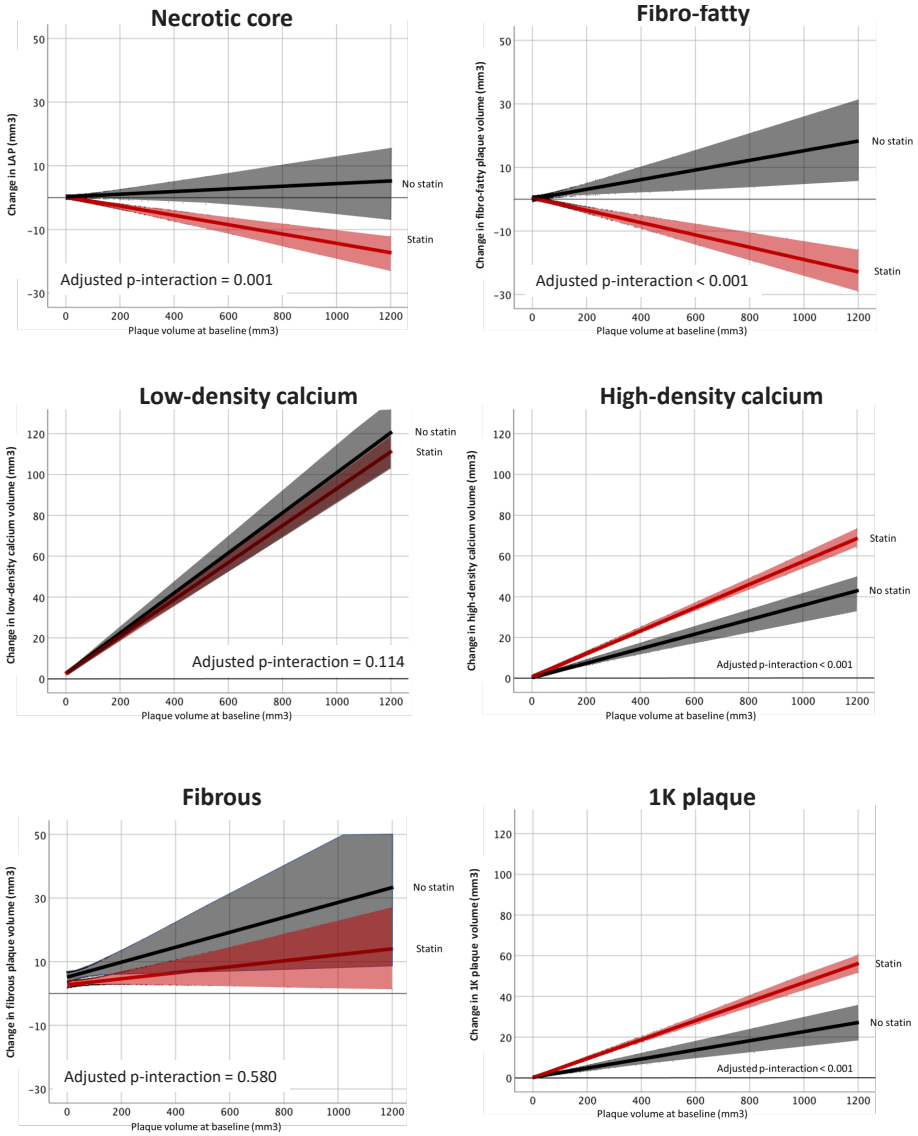

Figure 1. Compositional plaque changes according to baseline plaque volume and statin.
Predicted changes in LAP, fibro-fatty plaque, fibrous plaque, low-density and high-density calcium, and 1K plaque are presented according to baseline plaque volume and statin use. The predicted changes (bold lines), and 95% confidence intervals (shaded area) are derived from a generalized linear model including baseline plaque volume, statin use and the interaction term. The p-values for interaction are derived from Table 2. Without statins, increasing trends of all non-calcified and calcified density subgroups are observed, while with statins significant reductions in LAP and fibrofatty plaque and larger increases in high-density calcium and 1K plaque.

Effects of statins on calcium density

When restricting to 591 lesions – 400 (67.7%) among patients on statin therapy – without LAP or fibro-fatty plaque, statins were not associated with the change in overall calcium (>350 HU) volume (P-interaction = 0.241) (eTable 4). However, less progression of low-density calcium (351-700 HU) was observed with statin use (P-interaction <0.001), while the progression of higher density calcification (>700 HU) was greater (P-interaction <0.001) with statins (Figure 2). Examples of coronary plaques that evolve over time with and without statin therapy are shown in Figure 3.

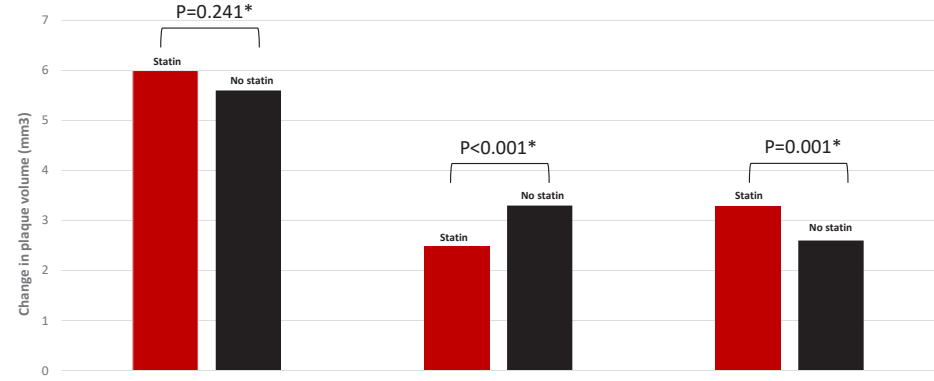

Figure 2. Calcium densification with statin therapy.
Estimated changes in overall calcium, low-density calcium, and higher density calcium according to statin therapy. Estimated changes in plaque volume are shown for the mean baseline plaque volume, the mean of other continuous variables and the geometric mean of categorical variables.
*P-values represent the interaction between plaque volume and statin use, adjusted for age, sex, diabetes, hypertension, smoking status, BMI, and CT-interval, derived from linear mixed models.

Plaque progression rates according to calcium density

Lesions with a higher proportion of calcium exhibited less overall plaque progression, either statin treated or not (p-interaction between baseline plaque volume and calcified proportion of plaque <0.001 and <0.001) (see eTable 5). In statin treated patients, a higher proportion of both high-density calcium and 1K plaque were associated with less plaque progression (P-interaction <0.001, and <0.001). In patients not using statins, only 1K plaque was associated with less plaque progression (P-interaction 0.013). When restricted to coronary lesions with high-density calcium or 1K plaque, 1K plaque was associated with the lowest plaque progression, (P-interaction <0.001 with statin and P-interaction 0.073 without statin).

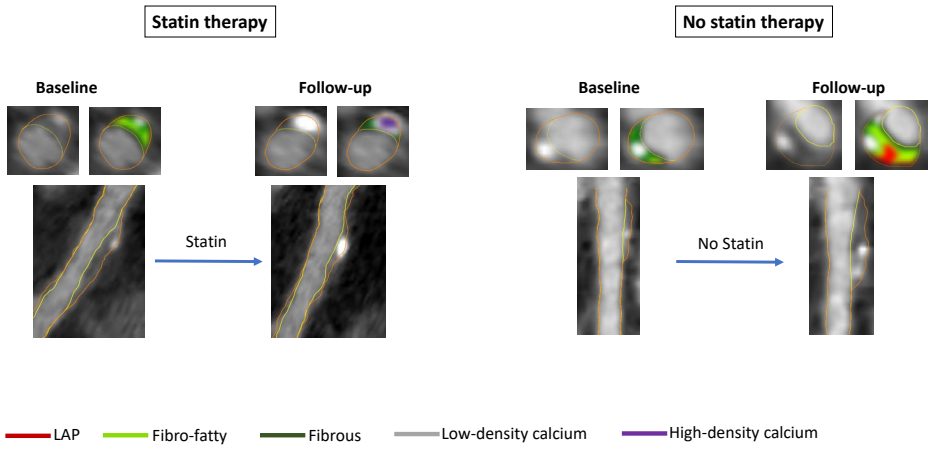

Figure 3. Coronary atherosclerosis progression with and without statin therapy.
Progression of plaque over time in coronary lesions in patients treated with and without statins. For each of the four time points, one multiplanar reconstruction is provided with two cross-sectional views, taken at the same site at baseline and follow-up. In the left panel, statin therapy is associated with reduction of fibro-fatty (light green) plaque together with a densification of the calcification (from low-density [grey] to high-density calcium [purple]). In the right panel, plaque expansion of both non-calcified and calcified plaque is observed.

Patients starting treatment with statins after the baseline CCTA

In the sensitivity analysis of patients who were begun on statins after the baseline CCTA, baseline age, sex, and prevalence of diabetes and hypertension were comparable to patients not on statins (eTable 6). LDL cholesterol levels were higher at baseline, but lower at follow-up in those starting on statins. Baseline plaque volumes of low- and high-density calcium were higher for patients that started on statins (eTable 7). Newly initiated statin therapy was associated with larger reductions in LAP and fibro-fatty plaque (p-interaction <0.001 for both comparisons), and larger progression of the 3 calcium subtypes (p-interaction: 0.001, <0.001, and <0.001, respectively), eFigure 3. When restricting to lesions without LAP or fibro-fatty plaque ,the association between statin therapy and low-density calcium progression was non-significant (P-interaction: 0.615), while larger progression was observed of calcium >700 HU (P-interaction <0.001), eFigure 4.

Table 1. Baseline patient characteristics

	Statin N=548	No statin N=309	p-value
Demographics			
Age, years	62.6 ± 8.7	61.1 ± 8.7	0.011
Male, n	359 (65.5)	181 (58.6)	0.044
Body mass index, kg/m^2	25.6 ± 3.4	25.7 ± 3.3	0.564
CT-interval, years			0.149
2-4	362 (66.1)	223 (72.2)	
4-6	141 (25.3)	62 (20.1)	
>6	45 (8.2)	24 (7.8)	
Location			0.220
Korea	376 (68.6)	245 (79.2)	
Canada	17 (3.1)	10 (3.2)	
Europe	145 (26.5)	45 (14.6)	
Brazil	10 (1.8)	9 (2.9)	
Risk factors			
Diabetes, n	161 (29.4)	62 (20.1)	0.003
Hypertension, n	350 (64.1)	156 (50.5)	<.001
Family history for CAD, n	135 (24.6)	67 (21.7)	0.328
Currently smoking, n	100 (18.3)	54 (17.5)	0.775
Medication use at baseline			
Aspirin, n	359 (65.5)	101 (32.7)	<.001
ACE inhibitor or ARB, n	230 (42.2)	79 (25.7)	<.001
Beta blocker, n	237 (43.3)	63 (20.5)	<.001
Lipid profile at baseline			
Total cholesterol, mg/dl	180 ± 44	186 ± 35	0.051
LDL cholesterol, mg/dl	107 ± 40	113 ± 29	0.029
HDL cholesterol, mg/dl	49 ± 13	50 ± 13	0.716
Lipid profile at follow-up			
Total cholesterol, mg/dl	159 ± 37	181 ± 34	<.001
LDL cholesterol, mg/dl	88 ± 31	110 ± 30	<.001
HDL cholesterol, mg/dl	49 ± 13	49 ± 12	0.509

Data is shown as mean ± SD, or counts (percentage).
CT, computed tomography; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; LDL, low-density lipoprotein; HDL, high-density lipoprotein

Table 2. Baseline plaque volume and statin use associated with compositional volumetric plaque change
Positive interaction terms between baseline plaque volume and statin use can be interpreted that statins are associated with larger increase of the specific plaque composition, and vice versa

	Delta necrotic core		Delta fibro-fatty plaque		Delta fibrous plaque	
Variable	**Adjusted beta-coefficient (95% CI)***	**P-value**	**Adjusted beta-coefficient (95% CI)***	**P-value**	**Adjusted beta-coefficient (95% CI)***	**P-value**
Model:						
Plaque volume at baseline, mm³	0.003 (-0.006, 0.012)	0.471	0.014 (0.003, 0.026)	0.013	0.014 (-0.007, 0.036)	0.189
Statin use, n	-0.266 (-1.26, 0.724)	0.598	0.086 (-1.15, 1.33)	0.892	-2.51 (-4.79, -0.238)	0.030
Plaque volume at baseline * statin use	-0.018 (-0.028, -0.008)	0.001	-0.033 (-0.045, -0.020)	<0.001	-0.007 (-0.031, 0.017)	0.580
	Delta low-density calcium		**Delta high-density calcium**		**Delta 1K plaque volume**	
Model:						
Plaque volume at baseline, mm³	0.103 (0.088, 0.119)	<0.001	0.039 (0.031, 0.046)	<0.001	0.025 (0.017, 0.033)	<0.001
Statin use, n	0.309 (-1.20, 1.81)	0.687	0.338 (-0.417, 1.09)	0.380	0.030 (-0.712, 0.772)	0.937
Plaque volume at baseline * statin use	-0.014 (-0.031, 0.003)	0.114	0.017 (0.008, 0.025)	<0.001	0.020 (0.011, 0.029)	<0.001

Generalized linear mixed models with random intercept
*adjusted for age, sex, diabetes, hypertension, smoking status, BMI, and CT-interval

Discussion

Our analysis provides insight into the magnitude and directionality of coronary atherosclerotic disease progression including observations following intercurrent preventive therapy. We observed a natural trend towards progression of both non-calcified and calcified plaque of atherosclerosis. This trend appeared to be modified with statin therapy to a decrease in LAP and fibrofatty plaque along with larger increases of high-density calcium and 1K plaque compared to plaques in patients not treated with statins. These findings are seemingly attributable to a see-saw effect whereby plaque transforms toward higher density calcification. Specifically, statins were not associated with overall progression, but with a transformation toward more dense calcium. Finally, distinct differences in the overall plaque progression rates were observed according to calcium density, with the slowest progression for lesions with the densest calcium (1K plaque).

Natural history of plaque transformation over time

Serial CCTA and IVUS studies have shown a natural trend of coronary atherosclerosis to progress over time.[4,5,11,12] Puri et al., evaluated in 224 patients not treated with statins undergoing serial IVUS 18 months apart, and observed an increase in total atheroma volume. This also included a significant increase in calcified plaque, which was evaluated by a calcification index based on the number of slices with calcium and calcification arc. Similar findings of increased non-calcified and calcified plaque progression without statin therapy have been reported with serial CCTA.[5,11,13,14] These observations reflect the natural disease progression of atherosclerosis. When plaques evolve, macrophages and smooth muscles cells within the necrotic core die, resulting in release of free calcium and phosphate that will crystalize and form microcalcifications. Microcalcifications confluence to speckled fragments, which may further evolve into larger sheets of dense calcium, which are detected by CCTA as dense calcified plaque.[15]

The current study extents prior findings of our group by examinating atherosclerosis progression according to the volume of non-calcified and calcified plaque and density of calcified plaque. Lee et al showed that CAC progressed in patients using statins associated with a reduction in non-calcified plaque, while both calcified and non-calcified plaque progressed in patients not treated with statin.[14]

Without statins, all subgroups of non-calcified and calcified plaque showed increasing trends in our study. With the use of statins, the volume of LAP and fibrofatty plaque decreased while that of high-density calcium and 1K calcium

increased. Also, statins were not associated with an increase in calcified plaque, but an apparent transformation of calcium towards higher-density.

Recent literature has highlighted the importance of coronary calcium density related to altered patterns of risk.[6,7] Criqui et al., examined individuals from MESA (Multi-Ethnic Study of Atherosclerosis) and observed that higher calcium density on non-contrast CT images was associated with reduced risk for future major vascular events.[6] We previously demonstrated that very dense calcium from CCTA images (1K plaque) was associated with reduced risk for ACS.[7]

The contradictory behavior of low-density and higher density calcium may be reflective of different stages in the calcification cascade. Microcalcifications (0.5-15 um) represent the earliest form of calcification and are commonly seen in the deeper area of necrotic core, as the results of dying smooth muscle cells and macrophages.[16,17] Microcalcifications coalesce into larger masses over time and form speckles and fragments of calcifications and later dense sheets. Due to resolution, microcalcifications cannot be reliably detected with CT, but larger calcifications will be detected with increasing attenuation (Hounsfield Units). Our results suggest that low-density calcium represents calcification early in the evolutionary cascade towards stable dense calcific sheets. Plaques with low-density calcium only (lacking higher density calcium) were predominantly non-calcified, while 1K plaques were predominantly calcified. The observation of reduced volume of low-density calcium with statin therapy may be explained by a concomitant reduction in surrounding necrotic core and coalescing calcium fragments into larger masses resulting in a shift towards greater volume of higher attenuation calcium. Explanations for accelerated calcification with statins remain speculative, but recent research suggests this may be partly due to modulation of the macrophage Rac1–IL1β signaling axis.[18]

The current study builds on our prior analysis concerning calcium density groups and risk for future ACS. In that study, 189 patients who did versus 189 patient who did not experience ACS after baseline CCTA imaging were matched based on age, sex, cardiovascular risk factors, and coronary disease severity.[7,19] While low-density calcium was similar between groups (57.1 ± 73.6 mm^3 vs 66.8 ± 99.1 mm^3, p=0.61), ACS patients had fewer 1K plaque: 3.9 ± 8.3 mm^3 vs 9.4 ± 23.2 mm^3, P=0.02. Also, baseline CCTA culprit precursor lesions had fewer 1K plaque than the respective control lesions.

The findings of the current study provide insight in the compositional changes associated with statins, which may (partially) explain the effects on major vascular event reduction, and could have implications for interpretation of plaque progression

on serial CCTA. Volumetric progression of calcium >700 HU may have protective implications, but this hypothesis requires further study. As a corollary, the prognostic power of CAC and CAC progression may lie not in its correlation of stable calcification to underlying plaque volume, but in its direct visualization of low-density calcium that is dynamically generated despite statins and calcium densification.

Three prior trials - two that randomized patients to different statin intensity groups and one placebo-controlled trial - did not find differences in calcified volume or Agatston score progression on serial non-contrast CT scanning.[20-22] In light of the current study findings, there can be multiple explanations for these negative trial results. Despite similar increase in volume of calcified plaque, the calcium density may have increased within the highest intensity statin arms, but this was not evaluated. Further, the potential of statins to reduce new plaque formation may have been offset by accelerated calcification of non-calcified plaque eventually resulting in a null effect. Indeed, LDL cholesterol levels were effectively lowered in the most intensive treatment arms. The current study aimed to limit this latter effect by examining interactions of statin use with baseline plaque, given the largest changes with statin can be expected within the largest plaques.

The sensitivity analysis included patients who started on statins after baseline CCTA, and the results were confirmatory to the main study findings. The patients were more comparable in clinical risk profile to the statin non-users than patients using statins at both CT scans

Plaque progression according to calcium density

Calcified plaque was associated with slower plaque progression, similar to findings of serial IVUS, [23] with the slowest progression for 1K plaque. Lesions with 1K plaque had few non-calcified plaque, similar to end-stage fibrocalcific plaques, which may explain the absence of plaque expansion in these lesions.

Interestingly, SC (considered a high-risk plaque feature that has been associated with future ACS) was characterized by large volumes of non-calcified plaque and low-density calcification, but not high-density or 1K plaque. This less favorable plaque phenotype may explain its prognostic value, but also highlight that any independent prognostic value of SC needs more study.[24]

Limitations

The observational design of the study represents a limitation including non-randomized allocation of statin therapy. This resulted in differences in clinical risk

profile and baseline plaque volume; this was adjusted for in multivariable models, but unknown confounders may still exist. Also, causality between statin use and compositional plaque changes cannot be inferred. Follow-up CCTA was only performed when clinically indicated and not, ideally, performed systematically as was done by Smit et al.[13] This will have introduced selection bias since patients with more rapid plaque progression eventually experiencing an event may not have been indicated for follow-up CCTA, whereas other patients who were clinically stable were not referred for follow-up CCTA. Hence, generalizability to higher-risk and lower-risk patients is not possible. The CT interval between baseline and follow-up CT was not standardized. Chronic total occlusions and lesions that had confluenced at follow-up were not evaluated, which may further limit generalizability. Prognostic implications of compositional plaque changes were not investigated, because the few number of hard event points, and should be further studied. Further, fixed Hounsfield Unit thresholds were applied, and the luminal contrast attenuation or provided kilovolt are known to influence this.

Conclusion

The current study provides insight into the magnitude and directionality of coronary atherosclerotic disease progression, including reductions in LAP and fibrofatty plaque along with concomitant increases high-density calcium and 1K plaque with statin use. These findings are seemingly attributable to a see-saw effect whereby plaque transforms toward higher density atherosclerotic plaque. Specifically, statins were not associated with overall progression, but a transformation toward more dense calcium. Finally, distinct differences in the overall plaque progression rates were observed according to calcium density, with the slowest progression for lesions with the most dense calcium (1K plaque).

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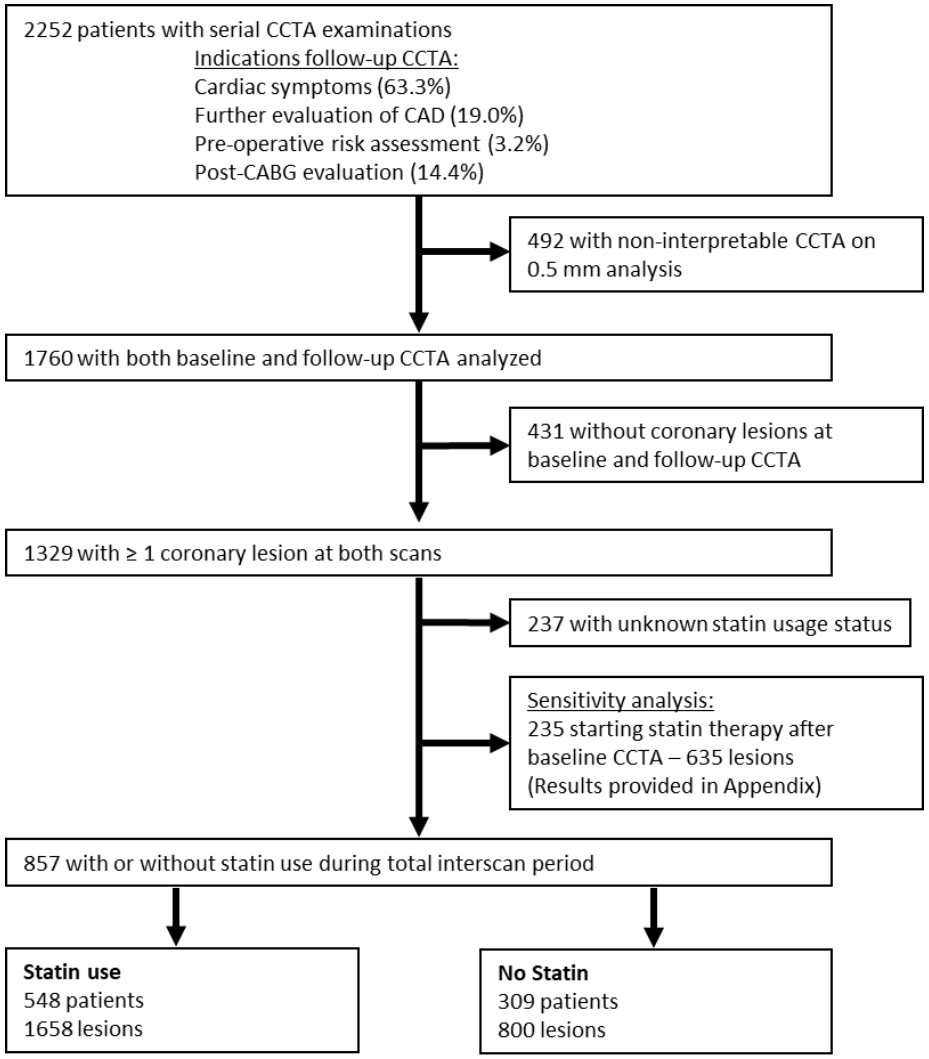
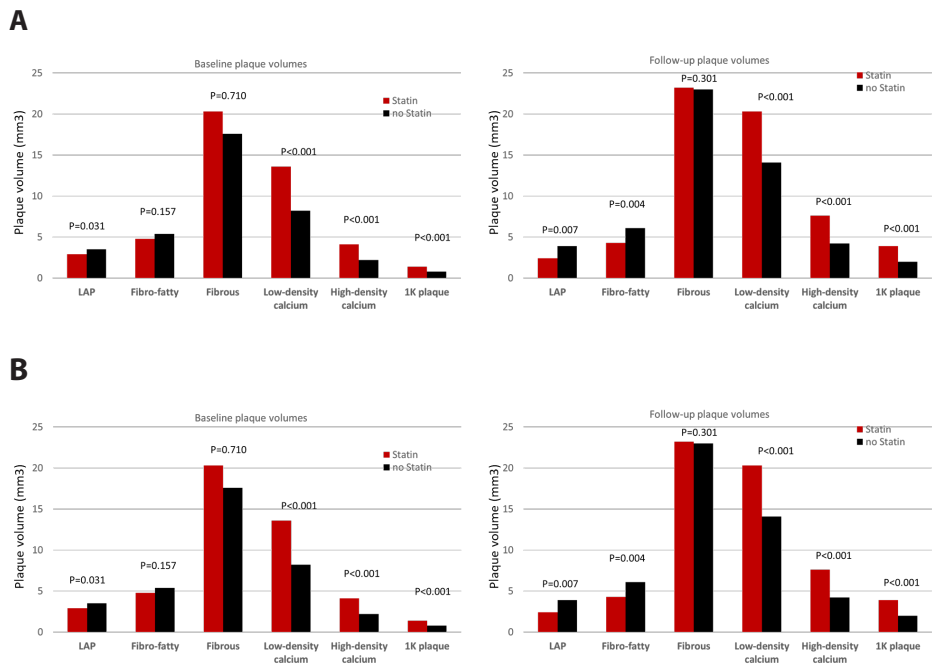
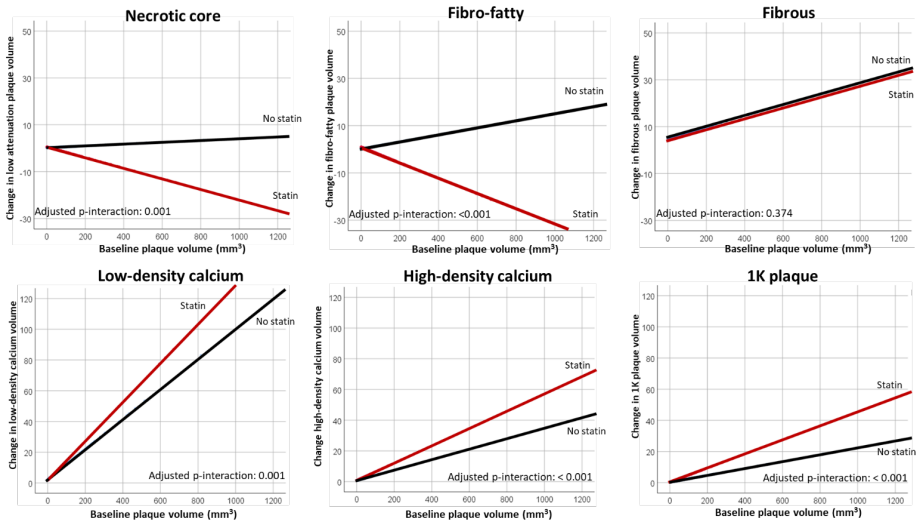


eFigure 1. Flow-chart



eFigure 2. Plaque volumes by compositional type at baseline (A) and follow-up CCTA (B).



eFigure 3. Compositional plaque changes according to baseline plaque volume in patients begun on statin treatment after baseline CCTA.

Comparison between lesions in patients started statins after baseline CCTA compared to those not treated with statins at both CCTAs. Predicted changes in LAP, fibro-fatty plaque, fibrous plaque, low-density and high-density calcium, and 1K plaque are presented according to baseline plaque volume and statin use. The predicted changes (bold lines) are derived from a generalized linear model including baseline plaque volume, statin use and the interaction term. The p-values for interaction are derived from a linear mixed model, and adjusted for adjusted for age, sex, diabetes, hypertension, smoking status, BMI, and CT-interval . Without statins, increasing trends of all non-calcified and calcified density subgroups are observed, while with statins significant reductions in LAP and fibrofatty plaque and larger increases in low- density, high-density calcium and 1K plaque.

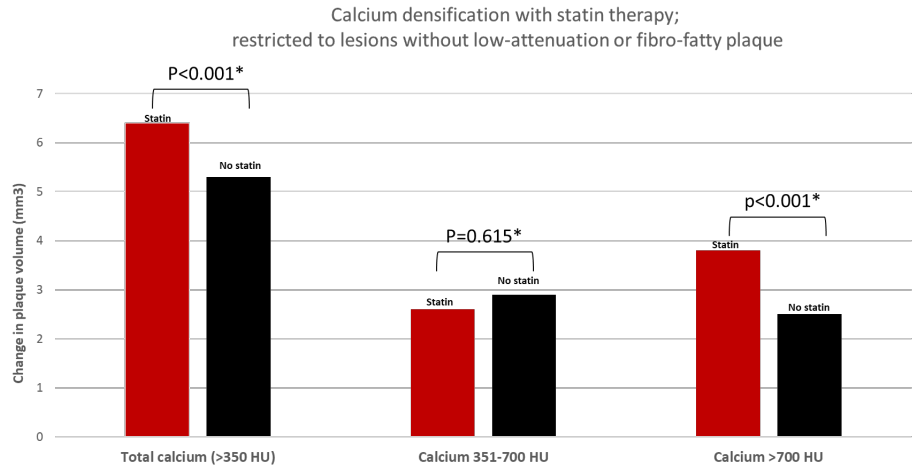


Figure 4. Calcium densification with statin therapy.

Comparison between lesions with newly started statins after baseline CCTA versus lesions not treated with statins at both CCTA's. Estimated changes in overall calcium, low-density calcium, and higher density calcium according to statin therapy. Estimated changes in plaque volume are shown for the mean baseline plaque volume, the mean of other continuous variables and the geometric mean of categorical variables.

* P-values represent the interaction between plaque volume and statin use, adjusted for age, sex, diabetes, hypertension, smoking status, BMI, and CT-interval, derived from linear mixed models.

eTable 1. Atherosclerotic profile per coronary lesions at baseline

	Statin N=1658	No statin N=800	p-value	Spotty calcification N=273	No spotty calcification N=2185	p-value
Baseline						
Necrotic core, mm^3	2.9 ± 8.7	3.5 ± 10.2	0.031	6.3 ± 12.5	2.7 ± 8.7	<.001
Fibro-fatty plaque, mm^3	4.8 ± 10.5	5.4 ± 11.4	0.157	10.4 ± 15.3	4.3 ± 9.9	<.001
Fibrous plaque, mm^3	20.3 ± 35.4	17.6 ± 30.2	0.710	37.8 ± 47.9	17.1 ± 30.8	<.001
Low-density calcium, mm^3	13.6 ± 29.8	8.2 ± 16.9	<.001	16.1 ± 28.5	11.3 ± 26.1	<.001
High-density calcium, mm^3	4.1 ± 11.7	2.2 ± 6.7	<.001	3.5 ± 9.0	3.5 ± 10.5	0.162
1K plaque, mm^3	1.4 ± 6.6	0.79 ± 4.1	<.001	0.91 ± 3.6	1.3 ± 6.1	0.558

eTable 2. Plaque composition proportions according the presence of low-density, high-density calcium, or 1K plaque

	Lesions with low-density calcium only N=990	Lesions with low- and high-density calcium N=608	p-value	Lesions with low-, high-density calcium, and 1K plaque N=572	p-value
Composition[†]					
Necrotic core, %	3.6 ± 7.6	2.4 ± 5.7		2.0 ± 4.3	0.033
Fibro-fatty plaque, %	8.6 ± 10.3	5.3 ± 7.8		4.4 ± 6.3	<0.001
Fibrous plaque, %	62.2 ± 18.7	41.9 ± 18.3		31.9 ± 16.3	<0.001
low-density calcium, %	25.8 ± 22.5	44.8 ± 21.1		38.8 ± 13.5	<0.001
High-density calcium, %	0	5.8 ± 7.3		17.2 ± 10.1	<0.001
1K plaque, %	0	0		5.7 ± 6.8	<0.001

[†]calculated as percentage of total plaque volume

eTable 3. Interaction baseline plaque volume and newly started statin with compositional plaque change, stratified by the median CT interval

	Delta necrotic core		Delta fibro-fatty plaque		Delta fibrous plaque	
	Adjusted beta-coefficient (95% CI)*	P-value	Adjusted beta-coefficient (95% CI)*	P-value	Adjusted beta-coefficient (95% CI)*	P-value
Plaque volume at baseline * statin use						
CT-interval < median	0.005 (-0.006, 0.016)	0.353	-0.001 (-0.016, 0.013)	0.858	-0.070 (-0.099, -0.041)	<0.001
CT-interval > median	-0.038 (-0.055, -0.020)	<0.001	-0.059 (-0.080, -0.038)	<0.001	0.044 (0.006, 0.082)	0.023
	Delta low-density calcium		**Delta high-density calcium**		**Delta 1K plaque volume**	
Plaque volume at baseline * statin use						
CT-interval < median	-0.024 (-0.045, -0.004)	0.020	0.001 (-0.009, 0.011)	0.899	0.003 (-0.008, 0.013)	0.614
CT-interval > median	-0.005 (-0.031, 0.022)	0.740	0.030 (0.018, 0.043)	<0.001	0.034 (0.020, 0.047)	<0.001

Generalized linear mixed models with random intercept

*adjusted for age, sex, diabetes, hypertension, body mass index, smoking status, CT-interval, and the two main effects of the interaction term

CT intervals are defined by the median: 3.2 years

eTable 4. Statin use and progression of calcium density subgroups, restricted to lesions without necrotic core or fibro-fatty plaque

	Delta total calcium >350 HU		Delta calcium 350-700 HU		Delta calcium ≥700	
	Adjusted beta-coefficient (95% CI)*	P-value	Adjusted beta-coefficient (95% CI)*	P-value	Adjusted beta-coefficient (95% CI)*	P-value
Variable						
Plaque volume at baseline * statin use	-0.031 (-0.082, 0.021)	0.241	-0.077 (-0.120, -0.034)	<0.001	0.057 (0.023, 0.091)	0.001

Analyses in lesions without necrotic core or fibro-fatty plaque. Positive interaction terms between baseline plaque volume and statin use can be interpreted that statins are associated with larger increase of the specific plaque composition, and vice versa

Generalized linear mixed models with random intercept

*adjusted for age, sex, diabetes, hypertension, smoking status, BMI, CT-interval and the main effects

eTable 5. Plaque progression according to calcium and calcium density subgroups

	Statin use Delta total plaque volume (N=1658)		No statin delta total plaque volume (N=800)	
Plaque volume at baseline *	**Adjusted beta-coefficient (95% CI)***	**P-value**	**Adjusted beta-coefficient (95% CI)***	
All lesions				
Percentage calcium	-0.003 (-0.004, -0.002)	<.001	-0.003 (-0.005, -0.002)	<.001
Lesions with calcium†				
Percentage low-density calcium	0.003 (0.002, 0.005)	<.001	0.003 (0.000, 0.006)	0.020
Percentage high-density calcium	-0.005 (-0.007, -0.003)	<.001	-0.004 (-0.008, 0.001)	0.088
Percentage 1K plaque	-0.007 (-0.009, -0.005)	<.001	-0.008 (-0.013, -0.002)	0.013
Lesions with high-density calcium or 1K plaque†				
Percentage 1K plaque	-0.006 (-0.009, 0.003)	<.001	-0.007 (-0.015, 0.001)	0.073

Generalized linear mixed models with random intercept. Positive interaction terms between baseline plaque volume and the percentage of calcium density can be interpreted that a higher percentage of plaque being low-density, high-density, or 1K plaque is associated with larger increase in total plaque volume, and vice versa

*adjusted for age, sex, diabetes, hypertension, CT-interval, and the main effects of the interaction term

† calculated as calcium density subgroup / total calcium volume * 100%

eTable 6. Baseline characteristics of patients who begun on statins after baseline CCTA and patients not on statins

	Newly started statin N=235	No statin N=309	p-value
Demographics			
Age, years	60.9 ± 8.5	61.1 ± 8.7	0.859
Male, n	150 (63.8)	181 (58.6)	0.178
Body mass index, kg/m^2	24.7 ± 3.3	25.7 ± 3.3	0.003
CT-interval, years			<0.001
2-4	135 (57.4)	223 (72.2)	
4-6	63 (26.8)	62 (20.1)	
>6	37 (15.7)	24 (7.8)	
Location			0.121
Korea	167 (71.1)	245 (79.2)	
Canada	17 (7.2)	10 (3.2)	
Europe	42 (17.9)	45 (14.6)	
Brazil	9 (3.8)	9 (2.9)	
Risk factors			
Diabetes, n	61 (26.0)	62 (20.1)	0.073
Hypertension, n	136 (57.9)	156 (50.5)	0.054
Family history for CAD, n	77 (32.8)	67 (21.7)	0.004
Currently smoking, n	43 (18.3)	54 (17.5)	0.694
Medication use at baseline			
Aspirin, n	88 (37.4)	101 (32.7)	0.270
ACE inhibitor or ARB, n	59 (25.1)	79 (25.7)	0.870
Beta blocker, n	58 (24.7)	63 (20.5)	0.211
Lipid profile at baseline			
Total cholesterol, mg/dl	197 ± 37	186 ± 35	0.001
LDL cholesterol, mg/dl	122 ± 30	113 ± 29	0.001
HDL cholesterol, mg/dl	50 ± 15	50 ± 13	0.501
Lipid profile at follow-up			
Total cholesterol, mg/dl	162 ± 37	181 ± 34	<.001
LDL cholesterol, mg/dl	94 ± 34	110 ± 30	<.001
HDL cholesterol, mg/dl	50 ± 14	49 ± 12	0.555

Data is shown as mean ± SD, or counts (percentage).

CT, computed tomography; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; LDL, low-density lipoprotein; HDL, high-density lipoprotein

eTable 7 Baseline plaque volumes according to newly started statin and no statin use at both CT scans

	Statin started after baseline CT N=635	No statin at both CT scans N=800	p-value
Baseline			
Necrotic core, mm^3	4.1 ± 12.7	3.5 ± 10.2	0.450
Fibro-fatty plaque, mm^3	5.9 ± 12.8	5.4 ± 11.4	0.517
Fibrous plaque, mm^3	20.2 ± 32.9	17.6 ± 30.2	0.286
Low-density calcium, mm^3	10.5 ± 22.2	8.2 ± 16.9	0.011
High-density calcium, mm^3	3.0 ± 9.8	2.2 ± 6.7	0.001
1K plaque, mm^3	1.2 ± 6.8	0.79 ± 4.1	0.098

Data is shown as mean ± SD, or counts (percentage).
CT: computed tomography