

Supplementary Online Content

van Rosendaal AR, van den Hoogen IJ, Gianni U, et al. Association of statin treatment with progression of coronary atherosclerotic plaque composition. *JAMA Cardiol*. Published online August 18, 2021. doi:10.1001/jamacardio.2021.3055

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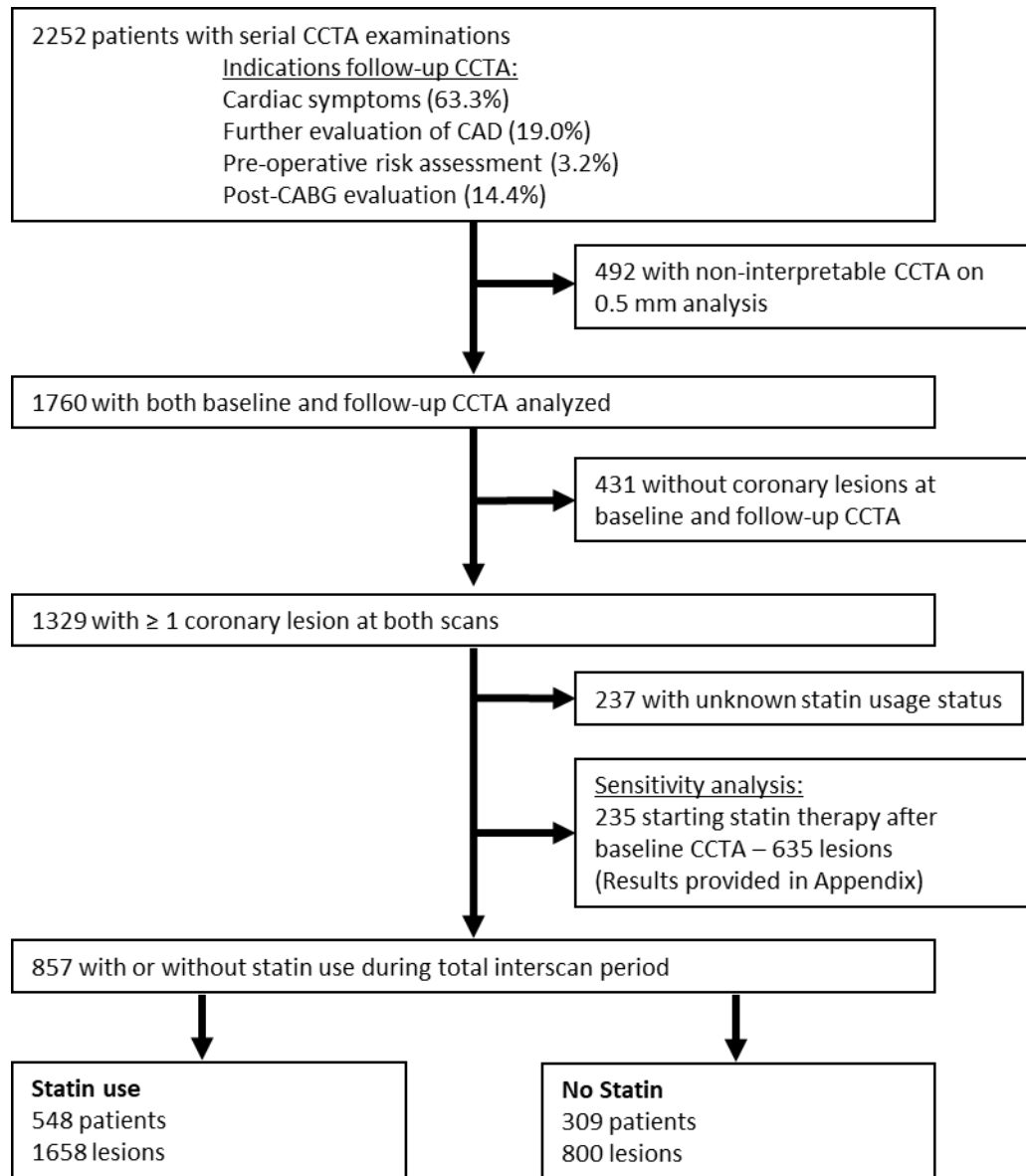
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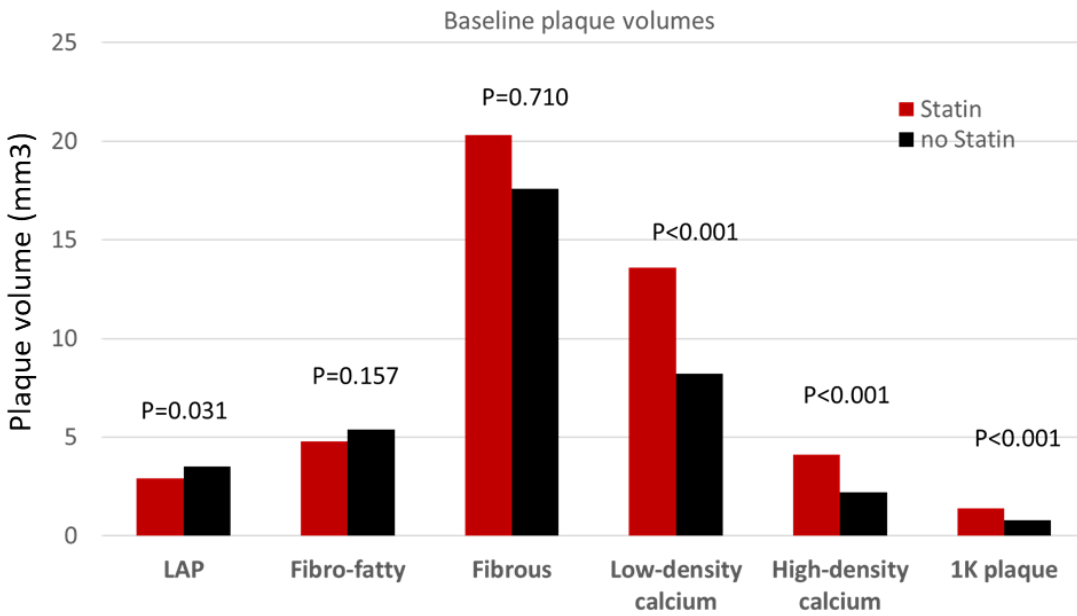
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Flowchart

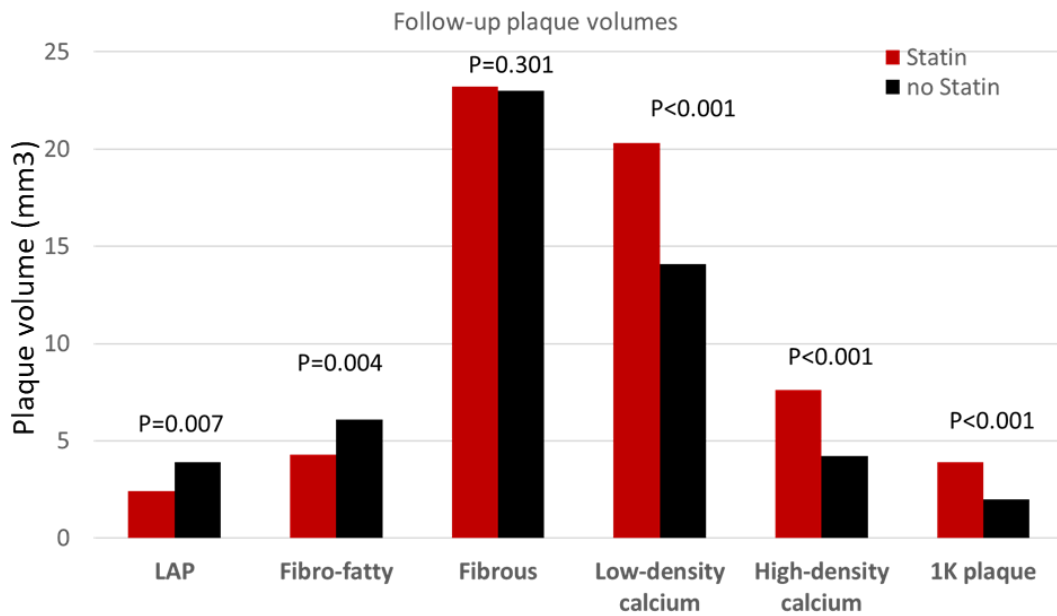


eFigure 2. Plaque Volumes by Compositional Type at Baseline and Follow-up CCTA

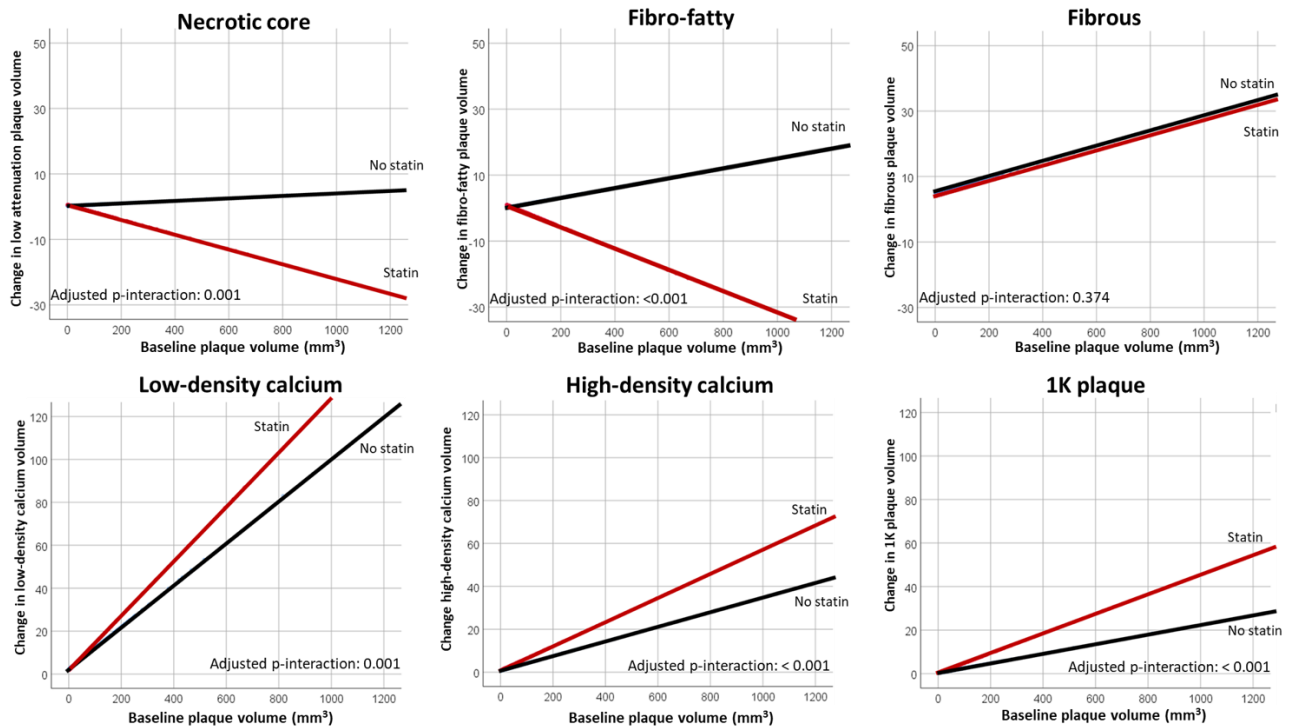
A



B

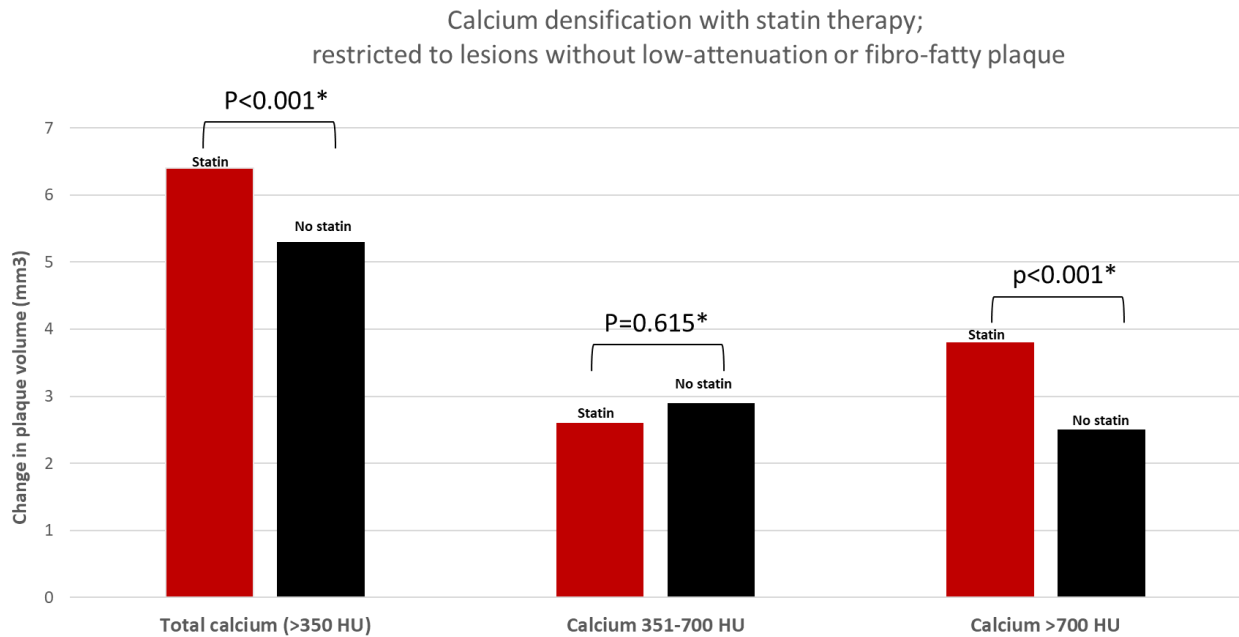


eFigure 3. Compositional Plaque Changes According to Baseline Plaque Volume in Patients Begun on Statin Treatment After Baseline CCTA



Comparison between lesions in patients started statins after baseline CCTA compared to those versus 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 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.

eFigure 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	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 Statin With Compositional Plaque Change, Stratified by the Median CT Interval

	<u>Delta necrotic core</u>		<u>Delta fibro-fatty plaque</u>		<u>Delta fibrous plaque</u>	
	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
	<u>Delta low-density calcium</u>		<u>Delta high-density calcium</u>		<u>Delta 1K plaque volume</u>	
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
<p>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</p> <p>Generalized linear mixed models with random intercept</p> <p>*adjusted for age, sex, diabetes, hypertension, smoking status, BMI, CT-interval and the main effects</p>						

eTable 5. Plaque Progression According to Calcium and Calcium Density Subgroups

	<u>Statin use</u>		<u>No statin</u>	
	<u>Delta total plaque volume (N=1658)</u>		<u>delta total plaque volume (N=800)</u>	
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
<p>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</p> <p>*adjusted for age, sex, diabetes, hypertension, CT-interval, and the main effects of the interaction term</p> <p>† calculated as calcium density subgroup / total calcium volume * 100%</p>				

eTable 6. Baseline Characteristics of Patients Who Began 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 are 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

	Statin started after baseline CT N=635	No statin at both CT scans N=800	p-value
<u>Baseline</u>			
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 are shown as mean ± SD, or counts (percentage). CT: computed tomography			