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Differential association between the progression of coronary artery calcium score and coronary plaque volume progression according to statins: The Progression of AtheRosclerotic PlAque Determined by Computed TomoGraphic Angiography Imaging (PARADIGM) study

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Abstract

**Aims:** Coronary artery calcium score (CACS) is a strong predictor of major adverse cardiac events (MACE). On the other hand, statins, which markedly reduce MACE risk, increase CACS. We explored whether CACS progression represents compositional plaque volume (PV) progression differently according to the presence of statin.

**Methods and Results:** From a prospective multinational registry of consecutive patients (n=2,252) who underwent serial coronary computed tomography angiography at a ≥2-year interval, 654 patients (61±10 years, 56% men, inter-scan interval 3.9±1.5 years, 246 statin-naïve and 408 statin-taking patients) who have both their CACS and coronary PVs (total, calcified, and non-calcified; sum of fibrous, fibro-fatty, and low-attenuation) analysed were included in the current analysis. CACS progression was defined as a change in square-rooted CACS > 2.5. In multivariate linear regression analyses, CACS increase was associated with both non-calcified (β=0.588, \( p=0.001 \)) and calcified PV increase (β=2.554, \( p<0.001 \)) in the statin-naïve group. However, in the statin-taking group, CACS increase was positively associated with calcified PV change (β=1.388, \( p<0.001 \)), but negatively associated with non-calcified PV change (β=-0.248, \( p<0.001 \)). Both non-calcified and calcified PV progression were independent risk factors for CACS progression (Odds ratio (OR): 1.028 and 1.161, respectively, all \( p<0.05 \)) in statin-naïve patients, but only calcified PV progression increased the risk of CACS progression in statin-taking patients (OR: 1.114, \( p=0.019 \)).

**Conclusion:** Under the effect of statins, increase in CACS reflects the does not necessarily imply the progression of coronary atherosclerosis burden differently. The result of serial CACS should be carefully interpreted according to the presence of statins.

**Keywords:** Coronary artery disease, coronary artery atherosclerosis, statins, coronary computed tomography angiography, coronary artery calcium score
Introduction

Coronary artery calcification (CAC) is one of the strongest predictors of major adverse cardiac events (MACE). Consequently, it has been hypothesized that an increase in CAC indicates increased MACE risk, and attempts have been made to implement the monitoring of CAC score (CACS) progression into a risk stratification tool in order to improve the identification of patients at greater risk. However, these attempts have yielded conflicting results, especially in patients who used statins.

Statins, which markedly reduce MACE as proven in previous randomized clinical trials, are also able to alter coronary plaque characteristics. Importantly, emerging evidence suggests that statins induce the calcification of coronary artery plaques and, thereby, increase CAC, which in general has been considered to be related with the increase risk of MACE. Further, others suggest that statins stabilize plaque through calcification and thus the increase in CACS would not be entirely related to the increased clinical risk and might be benign or even protective in patients treated with statins.

To explain this discrepancy between CAC progression and statins, alongside with the observed dissociation of CAC progression from increased clinical risk, a direct comparison between the changes in CACS or calcium volume score (CVS) and compositional change in plaque volume (PV) is required. However, the association between CACS progression and quantitative PV changes has been evaluated only recently, mainly owing to the fact that most CAC scan studies were conducted on low-risk screening populations, while studies that analysed PV changes with respect to statin use employed invasive imaging techniques, thereby, focusing on high-risk patients who did not undergo CAC scans.

Therefore, we explored whether the association between CAC progression and compositional PV progression differed between statin-naïve and statin-taking individuals, in a
subset of patients who underwent serial coronary computed tomography angiography (CCTA).

Methods

Study design and population

The Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging (PARADIGM) study is a dynamic multinational observational registry that prospectively collected clinical, procedural, and follow-up data on patients who underwent clinically indicated serial CCTA at an inter-scan interval of ≥2 years between 2003 and 2015. The study protocol complies with the Declaration of Helsinki and was approved by the institutional review boards of all participating centres.

For the current analysis, patients with CCTA uninterpretable for quantitative analysis (n=492), with CCTA not containing non-contrast images for CACS measurement (n=944), who received revascularization in the inter-scan period (n=53), and without information about statins (n=109) were excluded from the study (n=2,252), leaving 654 patients (Figure 1). Patients were divided into statin-naïve and statin-taking group.

CACS and quantitative CCTA analysis protocol

All acquisition and analysis of CCTAs were performed in direct accordance with guidelines. Datasets from each participating site were transferred to a core laboratory for blinded image analysis by Level-III experienced readers.

Agatston CACS and CVS at both baseline (CCTA-1) and follow-up CCTAs (CCTA-2) were calculated on non-contrast images from each CCTA using a dedicated workstation (Vitrea v7.6; Vital Images Inc., Minnetonka, MN, USA). CACS and CVS progression at follow-up were defined as follows:
CACS progression: \[\sqrt{\text{CACS at CCTA-2}} - \sqrt{\text{CACS at CCTA-1}} > 2.5\]

CVS progression: \[\sqrt{\text{CVS at CCTA-2}} - \sqrt{\text{CVS at CCTA-1}} > 2.5 \text{ mm}^3\]

For quantitative CCTA analysis to determine the total and compositional PVs, coronary atherosclerosis was evaluated on multiplanar and cross-sectional CCTA images using semi-automated plaque analysis software (QAngioCT Research Edition v2.1.9.1; Medis Medical Imaging Systems, Leiden, the Netherlands) with manual correction (Supplemental Material Part IV). Briefly, all coronary segments with a diameter ≥2 mm were evaluated for every coronary artery and its branches using a modified 17-segment American Heart Association model. Segments with stents were excluded. A coronary atherosclerosis plaque was defined as any tissue ≥1 mm$^3$ within or adjacent to the lumen that could be discriminated from surrounding structures and identified in ≥2 planes. Total PV (mm$^3$) of all analysed segments were added up to generate a per-patient level PV.

PV was further sub-classified by composition using pre-defined Hounsfield units (HU) cut-off values: non-calcified (-30 to 350 HU) PV encompassing low-attenuation (-30 to 30 HU), fibro-fatty (30 to 130 HU), and fibrous (131 to 350 HU) PV; and calcified PV (≥351 HU). For longitudinal comparisons of CCTAs, coronary segments were co-registered between the CCTA-1 and CCTA-2 evaluations using branches and the distance from the ostium as landmarks.

**Statistical analysis**

Categorical variables are presented as absolute counts and percentages, and continuous variables are expressed as means ± standard deviations. Differences between continuous variables were analysed using the Student’s t-test, and the chi-square test or Fisher’s exact test was employed, as appropriate, for categorical variables.
To account for the difference in the analysed vessel length between patients, normalized PVs were calculated as [(absolute PV/the total length of analysed coronary arteries) multiplied by the mean total analysed vessel length of the study population].\textsuperscript{12,21} CACS and PV progressions were defined as the difference of each value between CCTA-1 and CCTA-2 annualized by dividing with the inter-scan interval.\textsuperscript{12}

The correlation of annual CACS or CVS change with annual PV change was analysed using Spearman’s correlation test. To explore whether the associations between (1) CACS change and PV change, and (2) CVS change and PV change differ according to statin treatment, multivariate linear regression models adjusted for age, sex, ethnicity, hypertension, diabetes mellitus, hyperlipidaemia, family history of coronary artery disease (CAD), smoking history, and baseline low-density lipoprotein level were constructed for each statin-naïve and statin-taking group. The differences between the beta coefficients (β) of models for each group were tested.

To explore if the impact of compositional PV changes on the CACS and CVS progression differ according to the presence of statin, multivariate logistic regression models adjusted for interval between two CCTAs, baseline CACS or CVS along with variables entered in the multivariate linear regression analyses were constructed for each group. The differences between the odds ratios (ORs) of PV changes from each group were compared.

A two-tailed \( p \)-value <0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study population and baseline characteristics

In the 654 patients included, there were 246 statin-naïve and 408 statin-taking patients (61±10 years old, 55.8% male, inter scan interval 3.9±1.5 years, Table 1). The referral reason
for CCTA was mainly cardiac symptoms for both CCTAs (98.8% and 84.2%, respectively). There were no differences in age and male sex, but statin-taking patients possessed more clinical risk factors for CAD including hypertension, diabetes mellitus, and hyperlipidaemia (all \( p<0.05 \)). The total cholesterol and low-density lipoprotein level were all higher in statin-taking patients than in statin-naïve patients at baseline (all \( p<0.05 \)) but became lower in statin-taking patients at the follow-up (all \( p>0.05 \)).

**CCTA and CAC Scan findings at baseline and follow-up**

At baseline, both the CACS and CVS were greater in the statin-taking than in the statin-naïve group (146.2±381.7 vs. 58.8±231.4, and 128.9±311.5 mm\(^3\) vs. 54.1±204.4 mm\(^3\), respectively, all \( p<0.001 \)) (Table 2). Total PV and PVs by compositions were all greater in the statin-taking than in the statin-naïve group at baseline (all \( p<0.001 \), Table 2, Supplemental Table 3). When annualized, increase in CACS, CVS, and PV were all greater in the statin-taking than in the statin-naïve group. The rate of calcified PV progression was also significantly higher in the statin-taking group, but there was no difference in non-calcified PV progression between both groups.

**Association of PV changes with CACS and CVS changes according to statin use**

In the Spearman correlation analysis, annual total and calcified PV change were significantly associated with both CACS and CVS changes regardless of the presence of statin (Supplemental Figure 5 and 6). However, non-calcified PV progression had very weak correlation with CVS changes only in statin-naïve patients.

In multivariate linear regression analysis, the increase of CACS was associated with total PV increase in both the statin-naïve (\( \beta \) [95% confidence interval (CI)] 1.442 [1.233-1.651], \( p<0.001 \)) and statin-taking (\( \beta \) [95% CI]: 0.906 [0.753-1.060], \( p<0.001 \)) group (Table 9).
When stratified by plaque compositions, the increase of CACS was associated with both calcified PV increase and non-calcified PV increase in the statin-naïve group (β [95% CI]: 2.554 [2.266-2.842] and 0.588 [0.249-0.911], respectively, all \( p<0.05 \)). However, in the statin-taking group, while the increase of CACS was associated with increased calcified PV (β [95% CI]: 1.388 [1.240-1.535], \( p<0.001 \)), non-calcified PV change showed a negative association (β [95% CI]: -0.248 [-0.464 to -0.032], \( p<0.001 \)).

CVS increase was also associated with both calcified and non-calcified PV increases in statin-naïve group (β [95% CI]: 0.036 [0.031-0.041] and 0.006 [0.001-0.011], respectively, all \( p<0.05 \)). However, in statin-taking group, increase in CVS was associated with only calcified PV increase (β [95% CI]: 0.016 [0.013-0.019], \( p<0.001 \)), but not with non-calcified PV (\( p=0.760 \)).

**Differential impact of PV changes on CACS and CVS progression according to statins**

The impact of annual PV changes on the CACS and CVS progression was studied (Supplemental Table 5). In statin-naïve patients, both annual calcified and non-calcified PV progressions independently increased the risk of patients being a CACS progressor (OR [95% CI]: 1.150 [1.042-1.268] and 1.037 [1.011-1.064], respectively, all \( p<0.05 \)). However, only calcified PV progression was an independent risk factor for CACS progressor (OR [95% CI]: 1.114 [1.0074-1.157], \( p<0.001 \)), while non-calcified PV progression was not (\( p=0.857 \)).

Calcified and non-calcified PV progression were also an independent risk factor for CVS progression in statin-naïve patients (OR [95% CI]: 1.161 [1.045-1.289] and 1.028 [1.004-1.054], respectively, all \( p<0.05 \)), while only calcified PV progression was in statin-taking patients (OR [95% CI]: 1.092 [1.056-1.130], \( p<0.001 \)).
Discussion

In the analysis of this large prospective observational CCTA registry, the association between CACS progression and compositional PV changes differed according to the statin use. In statin-naïve patients, CACS progression reflected the progression of the overall coronary atherosclerotic burden, as observed in the multivariate analysis where CACS progression were associated with both calcified and non-calcified PV progression. In contrast, in statin-taking patients, CACS progression was associated only with calcified PV progression. Accordingly, the interpretation of CACS progression should differ according to statin treatment, as CAC progression in statin-taking patients does not equal entirely reflect with the overall progression of coronary atherosclerosis burden.

CACS has been employed for risk stratification of the primary preventive population as one of a screening modality because of its relative simplicity, both in acquisition and interpretation, and the relatively low exposure to radiation. Elevated CACS portends a worse prognosis and has been widely used as an effective tool for the prognostication of future MACE.

Accumulating evidences for CACS supporting its use in cardiovascular risk assessment also suggests that monitoring the increase in CACS would improve the prognostication ability, as the CACS progression indicates the increased risk of MACE. Generally, CACS progression is associated with increased cardiovascular events. However, in a recent study, increase in CACS yielded no additional benefit when added to the most recent CACS. In another study, while CVS was positively associated with MACE, CAC density was inversely associated with cardiovascular disease. Considering all existing evidence at this point, it is premature to conclude that an increase in CACS is indisputably related to an increased risk in all circumstances.
These remaining inconsistencies and the relatively weak association between the elevation of CACS and worsening of clinical outcome may be attributable to the fact that the impact of statins was not comprehensively considered in these studies. However, statins, statin became one of the cornerstones in both the primary and secondary prevention of cardiovascular disease based on its effect on reducing future MACE.\textsuperscript{7,8} have failed to attenuate the increase of CACS in previous studies.\textsuperscript{2,27} This discrepancy maybe could be explained by recent observations where the pro-calcific effect of statins on coronary atherosclerotic plaques have demonstrated in both invasive and non-invasive studies. More recently, the pro-calcific effect of statins on coronary atherosclerotic plaques have also been observed in both invasive and non-invasive imaging studies.\textsuperscript{28,29} Statins seem to reduce the risk of MACE while elevating CACS which is thought to be related to the increase of the risk.

The plausible hypothesis that can bridge these two conflicting observations would be that the increase in CACS represents changes in coronary atherosclerotic plaque differently, according to the presence of statin treatment. The progression of CACS in patients on statin treatment, at least in partially, may reflect the stabilization or even the attenuation of CAD, rather than the progression of atherosclerotic burden.\textsuperscript{11} To prove this hypothesis, evaluating the direct correlation between the change in CACS and the PV of the whole coronary arteries, instead of a specific target lesion, is mandatory as a first step, as the CAC scan reflects the atherosclerotic burden in the per-patient unit. In this regard, CCTA which enables the concurrent determination of CACS and PV of the whole coronary vasculature would be the most suitable imaging modality. This attempt was made only recently in a study which demonstrated a strong correlation between increases in CACS and PV.\textsuperscript{12}

In this study, we have expanded the observation by demonstrating that the correlation between CACS progression and the compositional change in PV progression differs
according to the use of statins. In the absence of statins, the elevation of CACS was associated with both annual calcified and non-calcified PV progression. Furthermore, the progressions of calcified and non-calcified PV were both an independent risk factor for patients being a CACS progressor at follow-up. In contrast, in the presence of statins, CACS progression was associated only with calcified PV progression, but not with non-calcified PV progression. These results suggest that CACS progression in statin-taking patients does not necessarily imply the pure progression of coronary atherosclerosis burden, especially the progression of the lipid component of a plaque – the determinants of plaque instability. These results are also in line with previous observations where statins were significantly associated with increased total and calcified PV progression, but failed to attenuate the increase of CACS.

In all, these results suggest that the presence of statins at each CACS scan should be considered when interpreting the changes in CACS. Interpretation of CACS progression should differ according to the use of statins. The application of CACS progression for risk stratification might be beneficial only in a population not indicated for statin treatment, while the direct assessment of compositional PVs would be more helpful once the patients start taking statins. Whether this differential association between CACS progression and compositional PV progression according to statin use will also have a different impact on clinical outcome, and whether the cut-off values for defining the clinically meaningful CACS progression should be also differ according to the use of statins are beyond the scope of the current analysis and remain to be proven. Based on current observations, future large-scale event-driven trials concurrently evaluating the impact of statins on both CACS and coronary atherosclerotic characteristics now seems warranted, to answer these questions.
and could be clarified in future large-scale event-driven trials concurrently evaluating the impact of statins on both CACS and coronary atherosclerotic characteristics.

The present study has some limitations. First, because of the observational design of the study, selection bias seems unavoidable, with respect to the enrolment of patients who underwent serial CCTAs. As described above, the PARADIGM registry was specifically designed to describe the natural course of CAD in the low-risk population using non-invasive imaging. Based on the study design, it is plausible that high-risk patients subjected to invasive studies or revascularizations were omitted from the registry, as reflected by the low incidence of the observed hard event. Because no consensus currently exists regarding the use of serial CCTA for CAD monitoring, an observational study like PARADIGM provides a unique opportunity to evaluate the correlation between CACS progression assessed by CAC scan and plaque burden change. Second, we could not stratify the association between CACS and PVs according to the intensity of statin treatment. However, the impact of statins on calcifying the coronary atherosclerotic plaques are in line with previous studies and the coherence with prior observations supports the validity of our findings.

In conclusion, an increase in CACS indicates changes in coronary plaque burden and its composition, differently, based on the use of statins. The progression of CACS should be carefully interpreted according to the presence of statins. Application of CACS progression monitoring as a surrogate marker of CAD progression and for risk-stratification should be limited to patients naïve to statins, while the direct assessment of compositional PVs and plaque characteristics might be more beneficial in patients on statin treatment.
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References


Figure legends

Figure 1. Flow chart of the study

2,252 patients with repeated (≥2) CCTA examinations
  492 patients with non-interpretable CCTA on 0.5-mm analysis
  944 patients with ≥1 CCTA without non-contrast image for CACS measurement
  53 patients received revascularization in inter-scan period
  109 patients without information about statins

654 patients with both baseline and follow-up CCTA analyzed for CACS and plaque volume
  246 statin-naïve patients
  408 statin-taking patients

CACS, coronary artery calcium score; CCTA, coronary computed tomography angiography
Progression in coronary artery calcification score represents coronary atherosclerotic plaque burden progression differently according to the statin use.

Coronary artery calcification score progression was annualized. PV progression was normalized and annualized. Multivariate linear regression analysis adjusted with age, sex, race, hypertension, diabetes mellitus, dyslipidaemia, smoking, family history of coronary artery disease, body mass index, and baseline low-density lipoprotein level.

CACS, coronary artery calcium score; CI, confidence interval; PV, plaque volume
<table>
<thead>
<tr>
<th></th>
<th>Total (n=654)</th>
<th>Statin-naïve group (n=246)</th>
<th>Statin-taking group (n=408)</th>
<th>P between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCTA inter-scan interval, years</td>
<td>3.9±1.5</td>
<td>3.8±1.4</td>
<td>3.9±1.5</td>
<td>0.557</td>
</tr>
<tr>
<td>Age, years</td>
<td>61.0±9.9</td>
<td>60.2±10.4</td>
<td>61.4±9.4</td>
<td>0.150</td>
</tr>
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<td>Male gender, n (%)</td>
<td>365 (55.8)</td>
<td>147 (59.8)</td>
<td>218 (53.4)</td>
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<td>Body mass index, kg/m²</td>
<td>24.8±3.1</td>
<td>24.8±3.2</td>
<td>24.8±3.1</td>
<td>0.919</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>371 (56.9)</td>
<td>124 (50.4)</td>
<td>247 (60.8)</td>
<td>0.009</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>157 (24.0)</td>
<td>47 (19.1)</td>
<td>110 (27.0)</td>
<td>0.022</td>
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<tr>
<td>Hyperlipidemia, n (%)</td>
<td>157 (24.0)</td>
<td>24 (9.8)</td>
<td>133 (32.6)</td>
<td>&lt;.001</td>
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<td>Family history of CAD, n (%)</td>
<td>162 (24.8)</td>
<td>62 (25.2)</td>
<td>100 (24.5)</td>
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</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>238 (36.4)</td>
<td>94 (38.2)</td>
<td>144 (35.3)</td>
<td>0.467</td>
</tr>
</tbody>
</table>

**Lipid profile at baseline**

<table>
<thead>
<tr>
<th></th>
<th>Total cholesterol, mg/dL</th>
<th>Low density lipoprotein, mg/dL</th>
<th>High density lipoprotein, mg/dL</th>
<th>Triglycerides, mg/dL</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>183.9±37.3</td>
<td>114.7±34.5</td>
<td>48.4±13.4</td>
<td>143.7±82.2</td>
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<tr>
<td></td>
<td>177.7±30.2</td>
<td>111.2±27.5</td>
<td>48.6±14.4</td>
<td>136.3±90.2</td>
</tr>
<tr>
<td></td>
<td>187.7±40.6</td>
<td>116.8±38.0</td>
<td>48.2±12.7</td>
<td>148.1±76.8</td>
</tr>
<tr>
<td></td>
<td>&lt;.001</td>
<td>0.033</td>
<td>0.716</td>
<td>0.093</td>
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**Lipid profile at follow-up**

<table>
<thead>
<tr>
<th></th>
<th>Total cholesterol, mg/dL</th>
<th>Low density lipoprotein, mg/dL</th>
<th>High density lipoprotein, mg/dL</th>
<th>Triglycerides, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>168.3±35.8</td>
<td>94.5±30.2</td>
<td>48.0±11.7</td>
<td>128.8±73.1</td>
</tr>
<tr>
<td></td>
<td>178.2±30.3</td>
<td>104.0±25.7</td>
<td>47.9±11.2</td>
<td>133.2±80.6</td>
</tr>
<tr>
<td></td>
<td>162.3±37.6</td>
<td>88.8±31.3</td>
<td>48.1±12.1</td>
<td>126.2±68.2</td>
</tr>
<tr>
<td></td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>0.799</td>
<td>0.246</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; CCTA, coronary computed tomography angiography; HDL, high-density lipoprotein; LDL, low-density lipoprotein
**Table 2.** Coronary computed tomography angiography findings at baseline and follow-up

<table>
<thead>
<tr>
<th></th>
<th>Statin-naïve group (n=246)</th>
<th>Statin-taking group (n=408)</th>
<th><em>P</em> between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>FU</td>
<td>Baseline</td>
</tr>
<tr>
<td><strong>Coronary artery calcium scan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Agatston CACS</td>
<td>58.8±231.4</td>
<td>115.2±426.2</td>
<td>146.2±381.7</td>
</tr>
<tr>
<td>Agatston CACS category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, n (%)</td>
<td>132 (53.7)</td>
<td>106 (43.1)</td>
<td>138 (33.8)</td>
</tr>
<tr>
<td>1-99, n (%)</td>
<td>82 (33.3)</td>
<td>92 (37.4)</td>
<td>153 (37.5)</td>
</tr>
<tr>
<td>100-399, n (%)</td>
<td>26 (10.6)</td>
<td>33 (13.4)</td>
<td>79 (19.4)</td>
</tr>
<tr>
<td>≥400, n (%)</td>
<td>6 (2.4)</td>
<td>15 (6.1)</td>
<td>38 (9.3)</td>
</tr>
<tr>
<td>CVS, mm³</td>
<td>54.1±204.4</td>
<td>103.2±368.7</td>
<td>128.9±311.5</td>
</tr>
<tr>
<td><strong>Quantitative CCTA analysis – Normalized PVs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PV, mm³</td>
<td>70.0±141.6</td>
<td>115.4±206.4</td>
<td>142.3±237.1</td>
</tr>
<tr>
<td>Calcified PV, mm³</td>
<td>20.2±68.6</td>
<td>42.5±109.4</td>
<td>51.0±131.6</td>
</tr>
<tr>
<td>Non-calcified PV, mm³</td>
<td>49.8±89.2</td>
<td>73.0±122.7</td>
<td>91.3±139.4</td>
</tr>
<tr>
<td>Fibrous PV, mm³</td>
<td>31.7±61.9</td>
<td>50.1±84.6</td>
<td>62.5±105.3</td>
</tr>
<tr>
<td>Fibrous-fatty PV, mm³</td>
<td>16.2±32.2</td>
<td>20.3±42.8</td>
<td>25.3±40.8</td>
</tr>
<tr>
<td>Low-attenuation PV, mm³</td>
<td>1.9±4.9</td>
<td>2.6±7.5</td>
<td>3.6±8.3</td>
</tr>
<tr>
<td><strong>Annualized change in coronary artery calcium scan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agatston CACS, /year</td>
<td>14.6±44.0</td>
<td>27.5±50.8</td>
<td></td>
</tr>
<tr>
<td>CVS, mm³/year</td>
<td>12.8±37.3</td>
<td>24.2±41.9</td>
<td></td>
</tr>
<tr>
<td><strong>Annualized change in normalized PVs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PV, mm³/year</td>
<td>13.0±21.7</td>
<td>20.2±29.1</td>
<td></td>
</tr>
<tr>
<td>Calcified PV, mm³/year</td>
<td>6.0±12.9</td>
<td>13.8±25.7</td>
<td></td>
</tr>
<tr>
<td>Non-calcified PV, mm³/year</td>
<td>7.0±17.3</td>
<td>6.4±22.8</td>
<td></td>
</tr>
<tr>
<td>Fibrous PV, mm³/year</td>
<td>5.5±11.9</td>
<td>6.2±16.6</td>
<td></td>
</tr>
<tr>
<td>Fibrous-fatty PV, mm³/year</td>
<td>1.3±8.4</td>
<td>0.3±9.5</td>
<td></td>
</tr>
<tr>
<td>Low-attenuation PV, mm³/year</td>
<td>0.2±1.8</td>
<td>-0.06±2.06</td>
<td></td>
</tr>
</tbody>
</table>

CACS, coronary artery calcium score; CCTA, coronary computed tomography angiography; 

CVS, calcium volume score; FU, follow-up; PV, plaque volume
Table 3. Multivariate linear regression analysis of the association between annual changes in CACS and CVS with annual PV changes† according to the statin treatment

<table>
<thead>
<tr>
<th></th>
<th>Statin-naive group (n=246)</th>
<th></th>
<th>Statin-taking group (n=408)</th>
<th></th>
<th>P vs. groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI)</td>
<td>SE</td>
<td>P</td>
<td>β (95% CI)</td>
<td>SE</td>
</tr>
<tr>
<td>Association with annual change of Agatston CACS*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PV</td>
<td>1.442 (1.233, 1.651)</td>
<td>0.107</td>
<td>&lt;.001</td>
<td>0.906 (0.753, 1.060)</td>
<td>0.078</td>
</tr>
<tr>
<td>Calcified PV</td>
<td>2.554 (2.266, 2.842)</td>
<td>0.147</td>
<td>&lt;.001</td>
<td>1.388 (1.240, 1.535)</td>
<td>0.075</td>
</tr>
<tr>
<td>Non-calcified PV</td>
<td>0.588 (0.258, 0.918)</td>
<td>0.169</td>
<td>0.001</td>
<td>-0.248 (-0.464, -0.032)</td>
<td>0.110</td>
</tr>
<tr>
<td>Fibrous PV</td>
<td>0.871 (0.364, 1.378)</td>
<td>0.259</td>
<td>0.001</td>
<td>-0.196 (-0.492, 0.101)</td>
<td>0.151</td>
</tr>
<tr>
<td>Fibro-fatty PV</td>
<td>0.605 (-0.034, 1.244)</td>
<td>0.326</td>
<td>0.065</td>
<td>-0.717 (-1.226, -0.208)</td>
<td>0.260</td>
</tr>
<tr>
<td>Low-attenuation PV</td>
<td>3.950 (0.972, 6.928)</td>
<td>1.519</td>
<td>0.010</td>
<td>-1.655 (-4.002, 0.692)</td>
<td>1.198</td>
</tr>
<tr>
<td>Association with annual change of CVS*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PV</td>
<td>1.241 (1.066, 1.417)</td>
<td>0.090</td>
<td>&lt;.001</td>
<td>0.734 (0.589, 0.879)</td>
<td>0.074</td>
</tr>
<tr>
<td>Calcified PV</td>
<td>2.170 (1.925, 2.415)</td>
<td>0.125</td>
<td>&lt;.001</td>
<td>1.179 (1.044, 1.315)</td>
<td>0.069</td>
</tr>
<tr>
<td>Non-calcified PV</td>
<td>0.524 (0.244, 0.804)</td>
<td>0.143</td>
<td>&lt;.001</td>
<td>-0.178 (-0.392, 0.037)</td>
<td>0.109</td>
</tr>
<tr>
<td>Fibrous PV</td>
<td>0.779 (0.350, 1.209)</td>
<td>0.219</td>
<td>0.001</td>
<td>-0.193 (-0.496, 0.110)</td>
<td>0.154</td>
</tr>
<tr>
<td>Fibro-fatty PV</td>
<td>0.541 (-0.001, 1.084)</td>
<td>0.277</td>
<td>0.052</td>
<td>-0.383 (-0.865, 0.099)</td>
<td>0.246</td>
</tr>
<tr>
<td>Low-attenuation PV</td>
<td>3.362 (0.832, 5.892)</td>
<td>1.291</td>
<td>0.010</td>
<td>-0.611 (-3.044, 1.822)</td>
<td>1.241</td>
</tr>
</tbody>
</table>

†PV progression was normalized and annualized.

*Changes in CACS and CVS were annualized.

Adjusted for age, sex, ethnicity, hypertension, diabetes mellitus, dyslipidaemia, smoking, family history of coronary artery disease, body mass index, and baseline low-density lipoprotein level

CACS, coronary artery calcium score; CI, confidence interval; CVS, calcium volume score; PV, plaque volume; SE, standard error