Impact of Statins on Serial Coronary Calcification During Atheroma Progression and Regression

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ABSTRACT

BACKGROUND Statins can regress coronary atheroma and lower clinical events. Although pre-clinical studies suggest procalcific effects of statins in vitro, it remains unclear if statins can modulate coronary atheroma calcification in vivo.

OBJECTIVES This study compared changes in coronary atheroma volume and calcium indices (CaI) in patients receiving high-intensity statin therapy (HIST), low-intensity statin therapy (LIST), and no-statin therapy.

METHODS In a post-hoc patient-level analysis of 8 prospective randomized trials using serial coronary intravascular ultrasound, serial changes in coronary percent atheroma volume (PAV) and CaI were measured across matched coronary segments in patients with coronary artery disease.

RESULTS Following propensity-weighted adjustment for differences in baseline and changes in clinical, laboratory, and ultrasonic characteristics, HIST (n = 1,545) associated with PAV regression from baseline (−0.6 ± 0.1%; p < 0.001), whereas both LIST (n = 1,726) and no-statin therapy (n = 224) associated with PAV progression (±0.8 ± 0.1% and ±1.0 ± 0.1%; p < 0.001, respectively; p < 0.001 for both HIST vs. LIST and HIST vs. no-statin; p = 0.35 for LIST vs. no-statin). Significant increases in CaI from baseline were noted across all groups (median [interquartile range] HIST, ±0.044 [0.0–0.12]; LIST, ±0.038 [0.0–0.11]; no-statin, ±0.020 [0.0–0.10]; p < 0.001 for all), which could relate to statin intensity (p = 0.03 for LIST vs. no-statin; p = 0.007 for HIST vs. no-statin; p = 0.18 for HIST vs. LIST). No correlations were found between changes in CaI and on-treatment levels of atherogenic and antiatherogenic lipoproteins, and C-reactive protein, in either of the HIST groups or the no-statin group.

CONCLUSIONS Independent of their plaque-regressive effects, statins promote coronary atheroma calcification. These findings provide insight as to how statins may stabilize plaque beyond their effects on plaque regression. (J Am Coll Cardiol 2015;65:1273–82) © 2015 by the American College of Cardiology Foundation.
Statins are the cornerstone for treating atherosclerotic cardiovascular disease and can regress atherosclerosis (1,2) and lower cardiovascular event rates (3). The most recent U.S. guidelines now advocate high-intensity statin therapy (HIST) in all individuals with known atherosclerosis, regardless of baseline lipoprotein levels (4).

Coronary arterial calcification has been extensively evaluated, and the baseline extent of coronary calcium measured noninvasively strongly associates with incident cardiovascular events (5). Underlying this imaging approach is the presumption that coronary calcium scoring using computed tomography (CT) represents a reliable surrogate measure of coronary atheroma volume. Given the direct relationship between achieved low-density lipoprotein cholesterol (LDL-C) levels, serial measures of plaque burden, and cardiovascular events, it is therefore logical to deduce that the effects on both plaque and its calcific component following statin therapy might be concordant. However, prior serial CT evaluations of the effect of statins on coronary calcification yielded conflicting results (6–11).

Mechanistic studies have demonstrated the potential procalcific effects of statins in vitro (12). Coronary intravascular ultrasound (IVUS) has high imaging resolution for measuring atheroma volume, and techniques to measure plaque calcification on IVUS are well described (13). Moreover, serial coronary IVUS has been pivotal in elucidating factors promoting the progression and regression of coronary atheroma (14). Using serial coronary IVUS in patients with coronary artery disease, we tested the hypothesis that statin therapy would associate with concordant changes of both coronary atheroma volume and plaque calcification. We specifically compared these changes in patients receiving HIST, low-intensity statin therapy (LIST), and no-statin therapy.

**METHODS**

**STUDY POPULATION.** The present analysis included patients participating in 8 clinical trials assessing the impact of medical therapies on serial changes in coronary atheroma burden using IVUS. Included in this analysis were trials assessing intensive lipid lowering with statins (REVERSAL [Reversal of Atherosclerosis With Aggressive Lipid Lowering] and SATURN [The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin]) (2,15), antihypertensive therapies (AQUARIUS [Aliskiren Quantitative Atherosclerosis Regression Intravascular Ultrasound Study] and NORMALIZE [Norvasc for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation]) (16,17), the antiatherosclerotic efficacy of acyl-coenzyme A:cholesterol ester transfer protein inhibition (ACTIVATE [ACAT Intravascular Atherosclerosis Treatment Evaluation]) (18), cholesteryl ester transfer protein inhibition (ILLUSTRATE [Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation]) (19), endocannabinoid receptor antagonism (STRADIVARIUS [Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant–The Intravascular Ultrasound Study]) (20), and the peroxisome proliferator-activated receptor-gamma agonism (PERISCOPE [Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation]) (21).

The ASTERIOD (A Study to Evaluate the Effect of Rouvastatin on Intravascular-Ultrasound Derived Indices of Coronary Atheroma Burden) study was not included in this analysis because smoking status and C-reactive protein (CRP) levels were not collected (1). From each of these trials, patients receiving HIST (n = 1,545), LIST (n = 1,726), or no-statin therapy (n = 224) were included in the present analysis. In the present analysis, HIST was defined as atorvastatin 80 mg or rosuvastatin 40 mg, whereas LIST was defined as atorvastatin dosing <40 mg, rosuvastatin <20 mg, simvastatin <40 mg, pravastatin <80 mg, lovastatin <20 mg, and fluvasatin dosing <40 mg. Hence, the present analysis comprises a patient-level analysis of 8 randomized trials in which patients were stratified on the basis of statin treatment (or no-statin treatment).

**ACQUISITION AND ANALYSIS OF SERIAL IVUS IMAGES.** The acquisition and serial analysis of IVUS images in each of these trials has been previously described in detail (1,2,15,17–22). Briefly, target vessels for imaging were selected if they contained no luminal stenosis >50% angiographic severity within a segment of at least 30 mm length. Imaging was performed within the same coronary artery at baseline and at study completion, which ranged from 18 to 24 months. Imaging in all trials was screened by the Atherosclerosis Imaging Core Laboratory of the Cleveland Clinic Coordinating Center for Clinical Research. Patients meeting pre-specified requirements for image quality were eligible for randomization. An anatomically matched segment was defined at the 2 time points on the basis of proximal and distal side branches (fiduciary points). Cross-sectional images spaced precisely 1 mm apart were selected for measurement. Leading

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edges of the lumen and external elastic membrane were traced by manual planimetry. Plaque area was defined as the area occupied between these leading edges. The accuracy and reproducibility of this method have been reported previously (23). The percent atheroma volume (PAV) was determined by calculating the proportion of the entire vessel wall occupied by atherosclerotic plaque, throughout the segment of interest as follows:

$$\text{PAV} = \frac{\sum (EEM_{\text{area}} - \text{Lumen}_{\text{area}})}{\sum EEM_{\text{area}}} \times 100$$

The total atheroma volume (TAV) was calculated by summing the plaque areas in all measured images. To account for heterogeneity of segment length in individual subjects, the TAV was normalized by multiplying the mean atheroma area in each pullback by the median segment length for the entire study cohort as follows:

$$\text{TAV}_{\text{Normalized}} = \frac{\sum (EEM_{\text{area}} - \text{Lumen}_{\text{area}})}{\text{Number of Images in Pullback}} \times \text{Median number of images in cohort}$$

Calcium was identified by an echogenic signal brighter than the adventitia with corresponding acoustic shadowing. A calcium grade was assigned for each analyzed image, reflecting the degree of acoustic shadowing (0 = no calcium; 1 = calcium with acoustic shadowing <90°; 2 = calcium with shadowing ≥90° but <180°; 3 = calcium with shadowing ≥180° but <270°; 4 = calcium ≥270°) (13,24). For images containing multiple calcium deposits, the grade represented the summation of all angles of acoustic shadowing. For each pullback, a calcium index (CaI) was thus calculated as follows (25):

$$\text{CaI} = \frac{\text{Total no. of analyzed frames with any Calcium}}{\text{Total no. of analyzed frames}} \times \frac{\text{Maximal arc of Calcium}}{4}$$

Change in CaI was defined as follow-up CaI minus baseline CaI.

**Statistical Analysis.** Continuous variables were reported as mean ± SD if normally distributed and as median (interquartile range) if non-normally distributed. Demographics, baseline clinical characteristics, baseline medications, laboratory biochemical data, and baseline IVUS parameters were compared. Two-sample Student t tests were used for normally distributed continuous variables, Wilcoxon rank sum tests for non-normally distributed continuous variables, and chi-square tests (or exact tests) for categorical variables. Because of differences in various baseline characteristics across the treatment groups, a propensity score weighting method was applied. The multiple treatment propensity scores and corresponding inverse probability of treatment weight (the reciprocal of the propensity scores) were estimated by generalized boosted models using an iterative estimation procedure (26), using all the related baseline characteristics and medications as covariates. The balance of the pre-treatment covariates was assessed, and significant improvement in baseline balance was achieved following weighting.

All subsequent analyses were weighted by inverse probability of treatment weight, except the analysis of baseline CaI. Serial changes in IVUS measurements were analyzed by analysis of covariance, adjusting for their baseline counterparts, and are reported as least squares mean ± SE, and the causal effects of each therapy were examined using inverse probability of treatment weight weighted generalized linear regression models in the context of survey design controlling for baseline IVUS values. Such survey-weighted generalized linear models have robust design-based standard errors. Because the CaI (both baseline and change) had many zero values, a rank-transformation was performed, and the same strategy of survey-design generalized linear models was created using the rank-transformed CaI changes as

<table>
<thead>
<tr>
<th>TABLE 1 Baseline Demographics, Clinical Characteristics, and Medications</th>
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<tbody>
<tr>
<td><strong>High-Intensity Statin</strong> (n = 1,545)</td>
</tr>
<tr>
<td>Age, yrs</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Current smoker</td>
</tr>
<tr>
<td>History of MI</td>
</tr>
<tr>
<td>History of PCI</td>
</tr>
<tr>
<td>History of CABG</td>
</tr>
<tr>
<td>History of PAD</td>
</tr>
<tr>
<td>History of CVA</td>
</tr>
<tr>
<td>Prior statin use</td>
</tr>
<tr>
<td>Baseline aspirin</td>
</tr>
<tr>
<td>Baseline beta blockers</td>
</tr>
<tr>
<td>Baseline ACE inhibitor/ARB</td>
</tr>
<tr>
<td>Baseline nitrates</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%). Prior statin use was defined as statin use on any occasion prior to study enrollment.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; CVA = cerebrovascular accident; MI = myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention.
the outcome. Because calcium is a component of plaque, atheroma volume (PAV or TAV) was adjusted within the model for Cal. Clinical trial and baseline Cal were controlled for in the Cal model as well. Average treatment effects on IVUS and on Cal were compared in a pairwise fashion among the statin therapy groups. Given that each trial’s duration varied between 18 and 24 months, changes in PAV, TAV, and Cal were also interpolated at 1 year and thus reported as annualized changes. Because of the intrinsic relationships between plaque progression and calcification, changes in coronary atheroma volume and Cal were also compared according to plaque progression/nonprogression. A 2-sided probability value of 0.05 was considered statistically significant. Analyses were performed using SAS software version 9.2 (SAS Institute, Cary, North Carolina) and the twang package and survey package in (open-source) R software.

**RESULTS**

**CLINICAL CHARACTERISTICS OF THE STUDY POPULATION.** Table 1 describes baseline demographics, clinical characteristics, and medication use in each of the treatment groups. Significant trends for between-group differences were noted across certain baseline variables. The no-statin group was of older age, more likely female, had a higher body mass index, and had a higher incidence of diabetes mellitus, hypertension, peripheral arterial disease, and nitrate use compared with the HIST and LIST groups.

**BASELINE AND CHANGES IN LABORATORY MEASURES.** Table 2 describes baseline, follow-up, and changes in laboratory biochemical measures within each treatment group. Significant trends for between-group differences were noted across various baseline laboratory variables. Patients receiving HIST had the highest baseline LDL-C levels (119.5 ± 34 mg/dl) but the lowest CRP levels (1.8 mg/l). The no-statin group had the lowest baseline high-density lipoprotein cholesterol levels (41.7 ± 14 mg/dl) but the highest triglyceride levels (158 [106 to 228] mg/dl) and CRP levels (3.1 [1.4 to 6.4] mg/l). At follow-up, patients receiving HIST had the lowest levels of LDL-C, non-high-density lipoprotein cholesterol, triglycerides, and CRP compared with the LIST and no-statin groups (LDL-C, 70.8 ± 26 mg/dl vs. 89.1 ± 25 mg/dl vs. 107.2 ± 31 mg/dl, respectively; non-high-density lipoprotein cholesterol, 96.6 ± 29 mg/dl vs. 117.2 ± 30 mg/dl, respectively; triglycerides, 28.1 [11.0 to 44.0] mg/dl vs. 34.3 [17.1 to 54.4] mg/dl vs. 41.7 [29.1 to 53.4] mg/dl, respectively; CRP, 1.1 [0.6-4.3] mg/l vs. 1.8 [1.1-5.1] mg/l vs. 3.1 [1.4-6.4] mg/l, respectively).

**BASELINE AND CHANGES IN CORONARYATHEROMA VOLUME ACCORDING TO THERAPY.** Table 3 describes baseline and changes in PAV and TAV of each treatment group, and pairwise comparisons for changes in atheroma volume following propensity-weighting. Baseline PAV was 36.9 ± 8.9%, 38.0 ± 9.0%, and 37.2 ± 9.0% in the HIST, LIST, and no-statin groups, respectively. The HIST group had significantly lower

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**TABLE 2 Laboratory Findings**

<table>
<thead>
<tr>
<th></th>
<th>High-Intensity Statin (n = 1,545)</th>
<th>Low-Intensity Statin (n = 1,726)</th>
<th>No-Statin (n = 224)</th>
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<tbody>
<tr>
<td>Baseline</td>
<td></td>
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<tr>
<td>LDL-C</td>
<td>119.5 ± 33.8</td>
<td>96.3 ± 33.9</td>
<td>110.0 ± 36.2</td>
</tr>
<tr>
<td>HDL-C</td>
<td>43.9 ± 11.0</td>
<td>44.0 ± 12.0</td>
<td>41.7 ± 14.2</td>
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<tr>
<td>Non-HDL-C</td>
<td>149.8 ± 39.5</td>
<td>126.6 ± 40.1</td>
<td>141.9 ± 39.2</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>137.5 (97-190)</td>
<td>135 (97-193)</td>
<td>157.7 (106-228)</td>
</tr>
<tr>
<td>apoB</td>
<td>110.3 ± 30.8</td>
<td>91.3 ± 35.7</td>
<td>96.2 ± 28.3</td>
</tr>
<tr>
<td>apoA-1</td>
<td>126.0 ± 24.5</td>
<td>127.9 ± 28.0</td>
<td>133.3 ± 33.6</td>
</tr>
<tr>
<td>apoB:apoA-1</td>
<td>0.83 ± 0.24</td>
<td>0.64 ± 0.22</td>
<td>0.78 ± 0.45</td>
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<tr>
<td>CRP</td>
<td>1.8 (0.9-4.3)</td>
<td>2.4 (1.1-5.4)</td>
<td>3.1 (1.4-6.4)</td>
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<tr>
<td>Follow-up</td>
<td></td>
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<tr>
<td>LDL-C</td>
<td>70.8 ± 25.5</td>
<td>89.1 ± 25.0</td>
<td>107.2 ± 30.9</td>
</tr>
<tr>
<td>HDL-C</td>
<td>48.0 ± 12.2</td>
<td>50.7 ± 17.1</td>
<td>43.5 ± 14.9</td>
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<tr>
<td>Non-HDL-C</td>
<td>96.6 ± 29.0</td>
<td>117.2 ± 30.8</td>
<td>138.8 ± 34.3</td>
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<tr>
<td>Triglycerides</td>
<td>117.7 (90.4-158.5)</td>
<td>129.6 (94.0-177.4)</td>
<td>150.7 (105.2-216.3)</td>
</tr>
<tr>
<td>apoB</td>
<td>76.8 ± 21.5</td>
<td>82.9 ± 27.6</td>
<td>93.5 ± 27.2</td>
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<tr>
<td>apoA-1</td>
<td>140.5 ± 24.6</td>
<td>138.9 ± 29.9</td>
<td>135.3 ± 28.1</td>
</tr>
<tr>
<td>apoB:apoA-1</td>
<td>0.55 ± 0.17</td>
<td>0.57 ± 0.20</td>
<td>0.72 ± 0.25</td>
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<tr>
<td>CRP</td>
<td>1.1 (0.6-2.8)</td>
<td>2.0 (0.9-4.4)</td>
<td>2.6 (1.1-5.1)</td>
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</table>

**Change from baseline**

<table>
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<tr>
<th></th>
<th>% change</th>
<th>p value†</th>
<th>% change</th>
<th>p value†</th>
<th>% change</th>
<th>p value†</th>
<th>% change</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>-36.2 ± 29.5</td>
<td>&lt;0.001</td>
<td>-2.2 ± 28.5</td>
<td>0.002</td>
<td>2.8 ± 24.6</td>
<td>0.10</td>
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<tr>
<td>HDL-C</td>
<td>11.0 ± 20.1</td>
<td>&lt;0.001</td>
<td>16.4 ± 27.9</td>
<td>0.001</td>
<td>10.3 ± 73.5</td>
<td>0.04</td>
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<tr>
<td>Non-HDL-C</td>
<td>-31.9 ± 25.5</td>
<td>&lt;0.001</td>
<td>-3.7 ± 23.5</td>
<td>0.001</td>
<td>-0.6 ± 18.8</td>
<td>0.66</td>
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<tr>
<td>Triglycerides</td>
<td>-12.8</td>
<td>&lt;0.001</td>
<td>-5.2</td>
<td>&lt;0.001</td>
<td>-3.6</td>
<td>0.72</td>
<td></td>
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<tr>
<td>apoB</td>
<td>-27.6 ± 21.7</td>
<td>&lt;0.001</td>
<td>-4.8 ± 28.7</td>
<td>&lt;0.001</td>
<td>-0.02 ± 26.3</td>
<td>0.99</td>
<td></td>
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</tr>
<tr>
<td>apoA-1</td>
<td>13.2 ± 18.6</td>
<td>&lt;0.001</td>
<td>11.8 ± 37.0</td>
<td>&lt;0.001</td>
<td>7.4 ± 45.8</td>
<td>0.052</td>
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</tr>
<tr>
<td>apoB:apoA-1</td>
<td>-32.3 ± 19.6</td>
<td>&lt;0.001</td>
<td>-8.7 ± 27.5</td>
<td>&lt;0.001</td>
<td>-2.0 ± 24.0</td>
<td>0.30</td>
<td></td>
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</tr>
<tr>
<td>CRP</td>
<td>-33.3</td>
<td>&lt;0.001</td>
<td>-17.6</td>
<td>&lt;0.001</td>
<td>-19.6</td>
<td>0.52</td>
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<td></td>
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</table>

Values are mean ± SD or median (95% confidence interval). *Unless otherwise noted, laboratory values obtained during treatment are the time-weighted averages of all post-baseline values. †P value for test of % change = 0. ‡P value for signed rank test. All lipoprotein measurements are in mg/dl. CRP measurements are in mg/l.

apoB = apolipoprotein B; apoA-1 = apolipoprotein A-1; apoB = apolipoprotein B; CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
PAV at baseline compared with the LIST group (p = 0.002). At follow-up, the HIST group demonstrated significant PAV regression from baseline (−0.6 ± 0.1%; p < 0.001), whereas both the LIST and no-statin groups each demonstrated significant PAV progression (±0.8 ± 0.1% and ±1.0 ± 0.1%; p < 0.001 from baseline, respectively). These changes in PAV differed significantly for pairwise comparisons between the HIST versus LIST (p < 0.001) and the HIST versus no-statin groups (p < 0.001) (Figure 1A).

Baseline TAV was similar across all treatment groups, with no significant between-group differences. At follow-up, both the HIST and LIST groups demonstrated significant TAV regression from baseline (−6.6 ± 0.6 mm³ and −2.1 ± 0.6 mm³; p < 0.001 from baseline, respectively), whereas the no-statin group demonstrated significant TAV progression (+3.0 ± 0.7 mm³; p < 0.001). Differences in the magnitude of TAV regression were significant for pairwise comparisons among the HIST versus LIST (p < 0.001), HIST versus no-statin (p < 0.001), and LIST versus no-statin (p = 0.006) groups (Figure 1B).

**Figure 1 Statins and Coronary Plaque Calcification: Changes in Coronary Atheroma Volume and Calcium Indices According to Therapy**

(A) Percent atheroma volume (PAV) adjusted model, depicting corresponding changes in PAV and calcium index (Cal). (B) Total atheroma volume (TAV) adjusted model depicting corresponding changes in TAV and Cal. Changes in PAV and TAV (blue boxes) are reported as least squares mean ± standard error of the mean, whereas the changes in Cal (salmon boxes) are reported as median (interquartile range). CI = confidence interval; HIST = high-intensity statin therapy; LIST = low-intensity statin therapy.
for baseline CaI. However, the TAV-adjusted model yielded significantly greater baseline CaI for the LIST versus no-statin (p = 0.002) and HIST versus no-statin (p = 0.001) pairwise comparisons.

All treatment groups demonstrated significant progression of coronary calcium from baseline, measured as a change in CaI (HIST, +0.044 [0.0 to 0.12]; LIST, +0.038 [0.0 to 0.11]; no-statin, +0.02 [0.0 to 0.10]; p < 0.001 for all treatment groups). In a PAV-adjusted model, pairwise comparisons demonstrated that the change in CaI was significantly greater in the LIST versus no-statin groups (p = 0.03) and the HIST versus no-statin groups (p = 0.007), but not for the HIST versus LIST comparison (p = 0.18) (Figure 1A). In a TAV-adjusted model, similar results were found, with pairwise comparisons demonstrating the change in CaI to be significantly greater in the LIST versus no-statin groups (p = 0.01) and the HIST versus no-statin groups (p = 0.004), but not for the HIST versus LIST comparison (p = 0.35) (Figure 1B).

CHANGES IN CORONARYATHEROMA VOLUME AND CaI ACCORDING TO PLAQUE PROGRESSION/REGRESSION. Table 5 describes changes in plaque volume and CaI stratified according to whether patients exhibited plaque progression (defined as change in PAV or TAV >0) or nonprogression/regression (change in PAV or TAV ≤0). Those with plaque progression demonstrated an overall +2.7 ± 0.05% and +7.5 ± 0.5 mm³ change in PAV and TAV, respectively, whereas nonprogressors/regressors demonstrated an overall −2.2 ± 0.06% and −13.1 ± 0.5 mm³ change in PAV and TAV, respectively. Changes in CaI were significantly greater in those with plaque progression compared with those with nonprogression/regression irrespective of whether adjusted for by changes in PAV (0.045 [0.00 to 0.12] vs. 0.034 [0.00 to 0.11]; p = 0.002) or changes in TAV (0.045 [0.00 to 0.12] vs. 0.034 [0.00 to 0.11]; p < 0.001).

RELATIONSHIPS BETWEEN CHANGES IN CaI AND ON-TREATMENT LIPOPROTEINS AND CRP. Table 6 describes correlations between changes in CaI and average on-treatment lipoprotein and CRP levels among patients receiving HIST and no-statin therapy. No significant correlations were found between HIST-mediated changes in lipoprotein or CRP levels and changes in CaI. Similarly, no significant associations were found between changes in lipoprotein and CRP levels and changes in CaI in those patients receiving no-statin therapy.

DISCUSSION

In this post-hoc propensity-weighted analysis of patients with coronary artery disease undergoing serial
coronary IVUS, we demonstrate the significant pro-
calcific effects of both high- and low-intensity statins,
and the calcific nature of coronary atheroma pro-
gression in statin-naive patients during follow-up.
The novel finding of this analysis was the dominant
influence of statins on changes in plaque calcification,
irrespective of net plaque progression or regression.
The greatest increases in calcium were evident
in patients receiving HIST to coincide with signifi-
cant plaque regression, and statin-naive patients
demonstrated the smallest increase in plaque calci-
fication over time, despite profound atheroma pro-
gression. Despite both the LIST and no-statin groups
each demonstrating comparable degrees of serial
plaque progression, the increases in Cal within the
LIST group were double that of the no-statin group.
These findings point to possible procalcific effects
of statins, which are consistent with possible plaque-
stabilizing effects of statins beyond simply their
effects on atheroma volume.

At first glance, the significant increase in coronary
calcification following HIST seems paradoxical to the
demonstrated net plaque regression in these patients.
Prior investigations testing the serial effects of statins
on coronary calcium have largely been undertaken
via calcium scoring using CT, and findings across
those studies were inconsistent (6–11). Common to
most of those studies was the comparatively shorter
follow-up period and smaller sample sizes. Achieved
LDL-C levels were often >100 mg/dl following the
use of mild statin regimens, not reflective of current
practice guidelines for patients with atherosclerotic
cardiovascular disease (4). Moreover, the lack of
plaque volume measurement in those studies limited
their ability to truly ascertain statin-mediated effects
on the vessel wall. It is important to note, however,
that calcium-scoring via CT also has a much lower
resolution compared with IVUS, with CT capable
of detecting only relatively large calcium deposits
(1.03 to 1.37 mm²) (27). Conversely, the higher reso-
lution of IVUS in the present analysis was sensitive
enough to elucidate subtle, yet significant, changes
in atheroma calcification, in addition to changes in pla-
que volume. Hence, it remains unclear how the find-
ings of the present analysis relate to the measured
effects of statins on CT scanning. Nevertheless, the
current analysis is the first to simultaneously describe,
in a large number of patients, the evolution of both
coronary calcium and atheroma volume following
mild and potent statin regimens, as well as in patients
with coronary artery disease remaining statin-naive.

Findings of the present analysis are supported
by several prior clinical and pre-clinical observations.
In individuals with diabetes, statin use independently

| TABLE 6 | Relationships of Change in Cal With Average Follow-Up Lipoprotein and CRP Levels in Patients Receiving High-Intensity Statins or No-Statins* |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| LDL-C | apoB | HDL-C | apoA-1 | apoB/apoA-1 | CRP | Triglycerides |
| R | p Value | R | p Value | R | p Value | R | p Value | R | p Value |
| High-intensity statin therapy | | | | | | | | | |
| ΔCal | -0.02 | 0.41 | -0.003 | 0.90 | 0.02 | 0.39 | 0.04 | 0.16 | -0.04 | 0.21 | 0.02 | 0.43 | 0.01 | 0.59 |
| ΔCal | -0.003 | 0.92 | 0.005 | 0.85 | 0.02 | 0.44 | 0.04 | 0.19 | -0.02 | 0.39 | 0.03 | 0.29 | 0.01 | 0.62 |
| No-statin therapy | | | | | | | | | |
| ΔCal | 0.04 | 0.54 | 0.10 | 0.21 | 0.10 | 0.12 | 0.11 | 0.19 | 0.03 | 0.68 | 0.04 | 0.62 | 0.005 | 0.94 |
| ΔCal | 0.03 | 0.69 | 0.09 | 0.24 | 0.10 | 0.15 | 0.13 | 0.11 | 0.02 | 0.80 | 0.02 | 0.73 | 0.02 | 0.81 |

Baseline and change in Cal were rank transformed. Average follow-up CRP and triglycerides values were log transformed. *Pearson correlation coefficient (R) between average follow-up lipid parameters and the residuals of change in calcium index using rank analysis of variance, controlling for baseline Cal, baseline plaque burden, change in plaque burden, and clinical trial. †Plaque variable that was adjusted in the model was PAV. ‡Plaque variable that was adjusted in the model was TAV.

Abbreviations as in Tables 3 and 4.
associated with progressive coronary atheroma calci-

ification (28,29), with similar observations on CT noted

in nondiabetic individuals receiving statins from

MESA (Multi-Ethnic Study of Atherosclerosis) (30).

A trend toward increasing atheroma calci-

fication following statins was also reported by several other

investigators (11,31–33). Although lacking a placebo-

controlled arm, serial coronary plaque compositional

analyses via interrogation of the ultrasonic radio-

frequency IVUS backscatter signal were consistent in
demonstrating progressive coronary calci-

fication following aggressive statin therapy (34,35). Serial
ultrasonic carotid evaluation also revealed intensive
statin therapy to cause greater increases in plaque

echogenicity compared with a less intensive statin

regimen (36,37). Importantly, changes in plaque
echogenicity correlated inversely with changes in
levels of serum inhibitors of vascular calcification
(osteopontin and osteoprotegerin), which were inde-
pendent of alterations of lipid profile. Our analysis
also failed to demonstrate associations between changes in CaI with on-treatment lipoprotein or
CRP levels during statin treatment, suggesting that
the procalcific effects of statins are possibly mediated
by pleiotropic mechanisms unrelated to lipoprotein
metabolism.

Pre-clinical studies testing the modulatory effects
of statins on vascular smooth muscle cells have also
yielded conflicting results; however, this may depend
on the nature of calcification-induction method
performed in vitro. Following an inflammation-
induced calcification model, statins inhibited vas-
cular smooth muscle cells calcification, consistent
with their known anti-inflammatory pleiotropic ef-
effec
ts (38). However, using a noninflammatory organic
phosphate model of in vitro calcification, statins dose-
dependently stimulated vascular smooth muscle cells
apoptosis and subsequent calcification (12). Despite
these paradoxical findings, such mechanistic observ-
ations are consistent with pathological observations
pointing to a central role of vascular smooth muscle cells and macrophage apoptosis driving plaque calcification in humans (39,40). The finding of progressive atheroma calcification in the no-statin group, who demonstrated marked atheroma progression, is also consistent with pathological observations of microcalcifications within plaque lipid pools (41), which can coalesce into speckles and fragments during atheroma progression (Central Illustration) (40). Aside from lipid regression within plaques following long-term potent statin therapies (35), statin-mediated atheroma calcification may improve plaque stability. Microcalcifications are commonly found within an overlying fibrous cap, and were once thought to enhance the risk of plaque rupture (42). However, more recent research suggests that a very low proportion of plaques containing microcalcification actually rupture (43), and that if statins rendered plaque microcalcifications more confluent and dense, then vessel wall stresses might fall considerably, contributing to plaque stability (44). The current analysis provides supportive evidence for the possible plaque-stabilizing effects of statins via inducing microcalcification.

STUDY LIMITATIONS. Despite a rigorous statistical approach to account for the differences of baseline characteristics and trial effect, we cannot exclude the possibility of unmeasured confounding variables biasing our results. However, inclusion/exclusion criteria for all these trials were relatively uniform, and all analysis was performed within a single core laboratory using standardized analytical techniques. The exact reasons for 224 patients with demonstrable coronary disease not to be prescribed statins during an 18- to 24-month trial period are unclear. However, these patients pose as an extremely unique population exhibiting the true phenotype of untreated, progressive coronary atherosclerosis, unlike ever to be formally prospectively investigated in a plaque imaging study again. Depth analysis of calcium is not a standard component of our core laboratory’s IVUS imaging protocol, and the degree of calcium was ultimately coded semiquantitatively. Therefore, we cannot comment on the precise nature or phenotype of statin versus non-statin-induced serial coronary calcification. However, unique to the present analysis is the accurate and concomitant assessment of serial changes in coronary atheroma volume across the entire length (median length of 50 mm) of the imaged vessel. Furthermore, we sampled a single epicardial coronary artery as a broad representation of the coronary vasculature. Therefore, findings of the present analysis do not apply to patients with pre-existing extensive coronary calcification, nor are such findings directly applicable to angiographically severe or hemodynamically significant lesions. Serum osteopontin and osteoprotegerin were not measured, therefore we can only speculate on mechanisms promoting statin-induced plaque calcification. Lastly, none of these serial IVUS trials were powered for detecting differences in clinical events, and therefore no specific association to clinical event rates can be drawn from the present analysis. Nevertheless the plaque-stabilizing effects and mortality benefit of statins in patients with atherosclerosis are well described (3).

CONCLUSIONS

The present analysis provides unique insight into the procalcific effects of prolonged statin therapy on coronary atheroma in vivo, potentially underscoring the plaque-stabilizing effects of statins.

REFERENCES


PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Serial analysis of coronary atheroma in vivo demonstrates that despite the association with plaque regression, statins possess procalcific effects related to the intensity of therapy.

TRANSLATIONAL OUTLOOK: Further research should be directed toward understanding the mechanisms responsible for plaque calcification that occurs during statin therapy and identifying those that concurrently stabilize coronary atheroma.


KEY WORDS atherosclerosis, calcium, intravascular ultrasound, statins