Effects of 4 Statins on Regression of Coronary Plaque in Acute Coronary Syndrome

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Background: There is no information on differences in the effects of moderate- and low-intensity statins on coronary plaque in patients with acute coronary syndrome (ACS). The aim of this study was to compare the effects of 4 different statins in patients with ACS, using intravascular ultrasound (IVUS).

Methods and Results: A total of 118 patients with ACS who underwent IVUS before percutaneous coronary intervention and who were found to have mild to moderate non-culprit coronary plaques were randomly assigned to receive either 20 mg/day atorvastatin or 4 mg/day pitavastatin (moderate-intensity statin therapy), or 10 mg/day pravastatin or 30 mg/day fluvastatin (low-intensity statin therapy). IVUS at baseline and at end of 10-month treatment was available in 102 patients. Mean percentage change in plaque volume (PV) was $-11.1\pm12.8\%$, $-8.1\pm16.9\%$, $0.4\pm16.0\%$, and $3.1\pm20.0\%$ in the atorvastatin, pitavastatin, pravastatin, and fluvastatin groups, respectively ($P=0.007$, ANOVA). Moderate-intensity statin therapy induced regression of PV, whereas low-intensity statin therapy produced insignificant progression ($9.6\%$ vs. $1.8\%$, $P<0.001$). On multivariate linear regression analysis, moderate-intensity statin therapy ($P=0.02$) and uric acid at baseline ($P=0.02$) were significant determinants of large percent PV reduction. LDL-C at follow-up did not correlate with percent PV change.

Conclusions: Moderate-intensity statin therapy induced regression of coronary PV, whereas low-intensity statin therapy resulted in slight progression of coronary PV in patients with ACS. (Circ J 2016; 80: 1634–1643)

Key Words: Acute coronary syndrome; Intravascular ultrasound; Plaque volume; Statin
ACS Treatment: 4 Different Statins

was registered at www.clinicaltrials.gov (NCT00549926) and conducted according to the Declaration of Helsinki. The study protocol was approved by the institutional human ethics review board and written informed consent was obtained from each patient.

Patient Enrollment and Randomization

Patients with ACS who underwent successful PCI under IVUS guidance were enrolled. ACS was defined as ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), or unstable angina pectoris. STEMI was defined as persistent (>20 min) ST-elevation on 2 contiguous leads (>0.2 mV in V1–V3, >0.1 mV in other leads) of 12-lead electrocardiogram (EKG) or a new (or presumably new) left-bundle-branch block. NSTEMI was diagnosed based on the presence of all the following changes: (1) new ST-segment depression >0.1 mm or T-wave inversion >0.4 mm in ≥2 contiguous EKG leads; (2) symptoms consistent with acute MI; and (3) high high-sensitivity troponin I (>0.04 ng/ml). Unstable angina was defined as an unstable pattern of chest pain (at rest, new onset, or crescendo angina) coinciding with objective evidence on coronary angiography of >50% coronary stenosis but without significant elevation in plasma troponin I (>0.04 ng/ml).

All patients had coronary plaque (>50 μm in thickness or percent plaque area ≥20%) in the culprit vessel ≥5 mm from the PCI-treated lesions. We excluded patients who had been treated with lipid-lowering drugs.

Patients were randomized within 72 h after PCI to receive 1 of 4 statins: 20 mg/day atorvastatin or 4 mg/day pitavastatin (moderate-intensity statin therapy); or 10 mg/day pravastatin or 30 mg/day fluvastatin (low-intensity statin therapy). The doses of 20 mg/day atorvastatin and 4 mg/day pitavastatin have been shown to cause equal regression of coronary PV in patients with ACS in the Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome (JAPAN-ACS) study. The doses of 10 mg/day of pravastatin and 30 mg/day of fluvastatin conformed to low-intensity statin therapy as defined in the American Heart Association (AHA) guideline in 2013.5 In patients treated with low-intensity statin therapy, doubling the dose or switching to moderate-intensity statin therapy was permitted in patients with persistently high low-density lipoprotein cholesterol (LDL-C; >100 mg/dl) after the commencement of statin therapy.

Blood lipid profile and measurements of various inflammatory markers were performed at baseline and after 10 months of continuous statin therapy.

Angiography

Coronary angiograms were reviewed separately by an independent observer unaware of all clinical data and IVUS findings. All cineangiograms were analyzed using CAAS 5.9 (Pie Medical Imaging, Maastricht, The Netherlands). Standard quantitative measurements7 were used to calibrate and measure coronary dimensions.

IVUS Study Protocol

After IVUS-guided PCI of the ACS culprit lesion, IVUS was performed in the culprit vessel. Briefly, after 200 μg i.c. nitroglycerin, a 40-MHz, 2.6-Fr IVUS catheter (Atlantis SR Pro2, Boston Scientific, Natick, MA, USA) was advanced into the culprit vessel, and the transducer was positioned as far distally as could be advanced safely. This procedure was designed to select the longest possible vessel segment for analysis. The transducer of the IVUS catheter was pulled back at a rate of 0.5 mm/s by a motorized pullback device. The consoles used were Galaxy 2 systems (Boston Scientific). The same imaging system with the same type of IVUS catheter was used in both the baseline and follow-up examinations. After the 10-month treatment period, IVUS was repeated under conditions identical to those used at baseline.

Two independent experienced investigators who were unaware of the patient group allocation performed quantitative IVUS analysis. The target segment was determined at a non-PCI site (>5 mm proximal or distal to the PCI site) of the culprit vessel. Subsequently, every 11th image (1 mm apart)
which was calculated as follows: %Change=[PV (follow-up)– PV (baseline)]/PV (baseline)×100. The major secondary end-points were actual change in PV and actual change in percent PV (%PV). %PV was calculated using the following formula:

%PV = \frac{\sum (EEM CSA - LUMEN CSA)}{\sum EEM CSA} × 100.

Substantial plaque progression and regression were defined as >5% relative increase or decrease in PV, respectively. No change in PV was defined as PV change ≤5%.

The intra- and inter-observer intra-class correlation coefficients for the vessel, lumen, and plaque areas were 0.999 and 0.999; 0.996 and 0.993; and 0.993 and 0.991, respectively, as reported previously.

was manually traced using echoPlaque4 (INDEC systems, Santa Clara, CA, USA). The IVUS measurements were performed according to the standards of the American College of Cardiology and the European Society of Cardiology.

Coronary PV was calculated as the sum of the differences between the external elastic membrane (EEM) and the lumen area across all evaluated frames, using the equation: PV=\sum (EEM_{CSA} - LUMEN_{CSA}), where EEM_{CSA} is the EEM cross-sectional area and LUMEN_{CSA} is the lumen cross-sectional area. The primary endpoint was the percent change in coronary PV induced by moderate- and low-intensity statin therapy, which was calculated as follows: %Change=[PV (follow-up)– (baseline)/PV (baseline)]×100. The major secondary end-points were actual change in PV and actual change in percent PV (%PV). %PV was calculated using the following formula:

%PV = \frac{\sum (EEM_{CSA} - LUMEN_{CSA})}{\sum EEM_{CSA}} × 100.

Substantial plaque progression and regression were defined as >5% relative increase or decrease in PV, respectively. No change in PV was defined as PV change ≤5%.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All (n=102)</th>
<th>Atorvastatin (n=26)</th>
<th>Pitavastatin (n=26)</th>
<th>Pravastatin (n=25)</th>
<th>Fluvastatin (n=25)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>62.8±10.2</td>
<td>62.4±8.7</td>
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<td>24 (92)</td>
<td>22 (85)</td>
<td>18 (72)</td>
<td>18 (72)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>24.4±3.7</td>
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<td>25.8±4.6</td>
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<td>Hypertension</td>
<td>36 (35)</td>
<td>11 (42)</td>
<td>5 (19)</td>
<td>8 (32)</td>
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<td>CKD (eGFR &lt;60)</td>
<td>23 (23)</td>
<td>5 (19)</td>
<td>3 (12)</td>
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<td>14 (56)</td>
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<td>Family history of CAD</td>
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<td>8 (31)</td>
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<td>STEMI</td>
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<tr>
<td>NSTEMI</td>
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<td>9 (36)</td>
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<td>UAP</td>
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<td>Culprit vessel</td>
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<td>RCA</td>
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<td>9 (36)</td>
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<td>46 (45)</td>
<td>10 (38)</td>
<td>14 (54)</td>
<td>11 (44)</td>
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<td>LCX</td>
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<td>2 (8)</td>
<td>4 (15)</td>
<td>5 (20)</td>
<td>6 (24)</td>
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<td>Multivessel disease</td>
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<td>7 (27)</td>
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<td>9 (36)</td>
<td>8 (32)</td>
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<tr>
<td>Post-procedure QCA</td>
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<td>Minimum lumen diameter (mm)</td>
<td>2.9±0.5</td>
<td>3.0±0.5</td>
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<td>3.0±0.5</td>
<td>2.9±0.3</td>
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<td>%DS (%)</td>
<td>13±7</td>
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<td>13±9</td>
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<td>Procedure</td>
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<tr>
<td>Stent implantation (BMS)</td>
<td>82 (80)</td>
<td>21 (81)</td>
<td>22 (85)</td>
<td>19 (76)</td>
<td>20 (80)</td>
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<tr>
<td>Stent implantation (DES)</td>
<td>19 (19)</td>
<td>5 (19)</td>
<td>3 (12)</td>
<td>6 (24)</td>
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<tr>
<td>PES</td>
<td>10 (10)</td>
<td>5 (19)</td>
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<td>2 (8)</td>
<td>1 (4)</td>
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<tr>
<td>SES</td>
<td>9 (9)</td>
<td>0 (0)</td>
<td>2 (8)</td>
<td>3 (12)</td>
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<tr>
<td>Stent diameter (mm)</td>
<td>3.5±0.4</td>
<td>3.5±0.5</td>
<td>3.4±0.4</td>
<td>3.5±0.4</td>
<td>3.5±0.3</td>
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<td>Stent length (mm)</td>
<td>18±5</td>
<td>18±5</td>
<td>19±5</td>
<td>20±5</td>
<td>18±5</td>
<td>0.37</td>
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<tr>
<td>POBA</td>
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<td>1 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.40</td>
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</table>

Data given as n (%) or mean ± SD. ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin-receptor blockers; BMI, body mass index; BMS, bare metal stent; CAD, coronary artery disease; CKD, chronic kidney disease; DES, drug-eluting stent; DS, diameter stenosis; eGFR, estimated glomerular filtration rate; LAD, left anterior descending artery; LCX, left circumflex artery; NSTEMI, non-ST-segment elevation myocardial infarction; PES, paclitaxel-eluting stent; POBA, plain old balloon angioplasty; QCA, quantitative coronary angiography; RCA, right coronary artery; SES, sirolimus-eluting stent; STEMI, ST-segment elevation myocardial infarction; UAP, unstable angina pectoris.
Circulation Journal Vol.80, July 2016

**Table 2. Laboratory Results**

<table>
<thead>
<tr>
<th></th>
<th>All (n=102)</th>
<th>Atorvastatin (n=26)</th>
<th>Pitavastatin (n=26)</th>
<th>Pravastatin (n=25)</th>
<th>Fluvastatin (n=25)</th>
<th>P-value</th>
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<tr>
<td>Baseline</td>
<td></td>
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<tr>
<td>TC (mg/dl)</td>
<td>211±35</td>
<td>204±25</td>
<td>209±36</td>
<td>223±32</td>
<td>209±44</td>
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<tr>
<td>LDL-C (mg/dl)</td>
<td>141±27</td>
<td>135±27</td>
<td>140±20</td>
<td>152±30</td>
<td>139±29</td>
<td>0.14</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>48±13</td>
<td>43±10</td>
<td>50±13</td>
<td>51±12</td>
<td>48±16</td>
<td>0.17</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>124 (77–200)</td>
<td>153 (77–218)</td>
<td>136 (108–266)</td>
<td>111 (62–156)</td>
<td>104 (78–201)</td>
<td>0.26</td>
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<tr>
<td>Non-HDL-C (mg/dl)</td>
<td>160 (140–186)</td>
<td>155 (139–178)</td>
<td>162 (141–187)</td>
<td>173 (154–187)</td>
<td>143 (137–188)</td>
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</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>3±1.0</td>
<td>3.3±1.0</td>
<td>3.0±0.9</td>
<td>3.1±0.9</td>
<td>3.1±1.0</td>
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</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.7 (5.2–6.6)</td>
<td>5.7 (5.3–6.6)</td>
<td>5.6 (5.2–6.2)</td>
<td>5.4 (5.2–6.4)</td>
<td>5.8 (5.4–7.7)</td>
<td>0.31</td>
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<tr>
<td>hs-CRP (mg/L)</td>
<td>0.12 (0.07–0.29)</td>
<td>0.11 (0.09–0.24)</td>
<td>0.11 (0.05–0.25)</td>
<td>0.15 (0.06–0.46)</td>
<td>0.14 (0.08–0.37)</td>
<td>0.77</td>
</tr>
<tr>
<td>UA (mg/dl)</td>
<td>5.9±1.3</td>
<td>5.9±1.1</td>
<td>5.6±1.3</td>
<td>5.7±1.5</td>
<td>6.2±1.1</td>
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**Follow-up**

<table>
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<tr>
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<th>All (n=102)</th>
<th>Atorvastatin (n=26)</th>
<th>Pitavastatin (n=26)</th>
<th>Pravastatin (n=25)</th>
<th>Fluvastatin (n=25)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>TC (mg/dl)</td>
<td>160±32*†</td>
<td>142±26*†‡‡</td>
<td>146±20*†‡‡</td>
<td>179±30*†</td>
<td>175±34*†</td>
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<td>LDL-C (mg/dl)</td>
<td>90±27*†</td>
<td>72±22*†‡‡</td>
<td>78±13*†‡‡</td>
<td>107±23*†</td>
<td>103±29*†</td>
<td>&lt;0.001</td>
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<tr>
<td>HDL-C (mg/dl)</td>
<td>50±14*†</td>
<td>48±15*†</td>
<td>50±13</td>
<td>54±12</td>
<td>50±15</td>
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<tr>
<td>TG (mg/dl)</td>
<td>128 (93–189)</td>
<td>125 (102–239)</td>
<td>121 (89–191)</td>
<td>128 (83–155)</td>
<td>148 (109–202)</td>
<td>0.40</td>
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<tr>
<td>Non-HDL-C (mg/dl)</td>
<td>108 (95–125)*†</td>
<td>97 (76–109)*†</td>
<td>97 (86–108)*†‡‡</td>
<td>122 (110–139)*‡</td>
<td>121 (101–140)*‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>1.9±0.7*†</td>
<td>1.7±0.8*†‡‡</td>
<td>1.7±0.5*†‡‡</td>
<td>2.1±0.6*†</td>
<td>2.2±0.6*†</td>
<td>&lt;0.001</td>
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<tr>
<td>HbA1c (%)</td>
<td>5.7 (5.3–6.2)</td>
<td>5.8 (5.4–6.4)</td>
<td>5.6 (5.5–5.9)</td>
<td>5.5 (5.1–6.4)</td>
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<tr>
<td>hs-CRP (mg/L)</td>
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<td>0.06</td>
<td>0.09</td>
<td>0.06</td>
<td>0.07</td>
<td>0.27</td>
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<tr>
<td>UA (mg/dl)</td>
<td>5.8±1.4</td>
<td>5.6±1.4</td>
<td>5.6±1.3</td>
<td>5.9±1.5</td>
<td>6.2±1.6</td>
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**Percent change**

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<th>All (n=102)</th>
<th>Atorvastatin (n=26)</th>
<th>Pitavastatin (n=26)</th>
<th>Pravastatin (n=25)</th>
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<tr>
<td>TC (%)</td>
<td>−22±19*†</td>
<td>−30±13*†‡‡</td>
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<td>−19±17*†</td>
<td>−14±14*†</td>
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<td>LDL-C (%)</td>
<td>−36±20*†</td>
<td>−50±18*†‡‡</td>
<td>−43±13*†‡‡</td>
<td>−28±19*†</td>
<td>−24±24*†</td>
<td>&lt;0.001</td>
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<tr>
<td>HDL-C (%)</td>
<td>7±20*†</td>
<td>10±15*†</td>
<td>1±13</td>
<td>8±29</td>
<td>7±18</td>
<td>0.36</td>
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<tr>
<td>TG (%)</td>
<td>−1 (−33 to 81)</td>
<td>−7 (−33 to 42)</td>
<td>−15 (−57 to 30)</td>
<td>3 (−31 to 107)</td>
<td>25 (−4 to 146)*†</td>
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<td>Non-HDL-C (%)</td>
<td>−32</td>
<td>−43</td>
<td>−43</td>
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<td>&lt;0.001</td>
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<td>LDL-C/HDL-C (%)</td>
<td>−39±19*†</td>
<td>−51±12*†‡‡</td>
<td>−43±13*†‡‡</td>
<td>−32±16*†</td>
<td>−28±22*†</td>
<td>&lt;0.001</td>
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<td>HbA1c (%)</td>
<td>0 (−4.5 to 4.1)</td>
<td>0 (−4.3 to 5.9)</td>
<td>1.9 (−3.3 to 3.7)</td>
<td>−1.9 (−6.6 to 4.9)</td>
<td>0 (−7.3 to 4.4)</td>
<td>0.76</td>
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<td>hs-CRP (%)</td>
<td>−44</td>
<td>−60</td>
<td>−39</td>
<td>−61</td>
<td>−25</td>
<td>0.16</td>
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<tr>
<td>UA (%)</td>
<td>−1±22</td>
<td>−8±27</td>
<td>3±24</td>
<td>4±16</td>
<td>−1±19</td>
<td>0.18</td>
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</table>

Data given as mean±SD or median (IQR). *P<0.05 (vs. baseline, †atorvastatin vs. pravastatin, ‡atorvastatin vs. fluvastatin, ††pitavastatin vs. pravastatin, †pitavastatin vs. fluvastatin). Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; UA, uric acid.

**Definition of Major Adverse Cardiac Events (MACE)**

MACE were defined as a composite of death, MI, or any repeat revascularization during the study period.

**Statistical Analysis**

Background data are expressed as mean±SD or median (IQR). One-way analysis of variance (ANOVA) test was used to analyze continuous variables with a normal distribution, with pairwise post-hoc comparisons adjusted using the Tukey-Kramer method. For continuous variables with skewed distribution, Kruskal-Wallis test was used to examine differences in medians, with pairwise post-hoc comparisons with the Steel-Dwass test. Discrete variables are presented as percentages and frequencies; comparisons were based on the chi-squared test. We used general linear models to assess the relationship between percent change in coronary PV and LDL-C at 10 months. To determine the optimal threshold of LDL-C for the prediction of PV regression, receiver operating characteristics curve analysis was used. The cut-off point was defined as the greatest sum of the sensitivity and specificity estimates. Univariate and multivariate linear regression analysis was performed to identify independent predictors of the percent change in coronary PV. Variables with P<0.1 on simple regression analysis and various risk factors known to be involved in the development of ACS (age, male gender, current smoking, hypertension, diabetes mellitus, family history of coronary artery disease [CAD], angiotensin-converting enzyme inhibitor use at follow-up, and β-blocker use at follow-up) were included in multivariate linear regression analysis. P<0.05 indicated statistically significant difference. Interim analyses were not planned. All analyses were performed using JMP 9 (SAS Institute, Cary, NC, USA).

**Results**

**Patients**

Between March 2006 and October 2009, 118 consecutive patients were randomized to the 4 statin groups. Among these,
both baseline and follow-up IVUS data were available for 102 patients (86%; Figure 1). Mean time between baseline and follow-up examinations was 10.3±1.2 months. Table 1 lists the clinical characteristics of the entire group and the 4 statin groups. There were no significant differences in baseline demographics or clinical characteristics among the 4 groups. Overall, 80% of patients were men, 35% had diabetes, 66% had STEMI, and drug-eluting stents were used in 19% and bare-metal stents in 80%. Approximately 1% of the patients had undergone plain old balloon angioplasty before enrolment and 7 patients had been switched to moderate-intensity statin therapy by follow-up.

Effects of Statin Therapy on Laboratory Results
After 10 months of treatment, all 4 statins used in the present study significantly reduced LDL-C, with the largest changes on moderate-intensity statin therapy by follow-up. At follow-up comprised 92% and 40% of the moderate- and low-intensity statin groups, respectively (P<0.001). Moderate-intensity statin therapy induced a significantly greater reduction in LDL-C compared with low-intensity statins (–45% vs. –25%, P<0.001). Interestingly, atorvastatin, but not the other 3 statins, significantly increased high-density lipoprotein cholesterol (HDL-C) from 43±10 mg/dl at baseline to 48±15 mg/dl (P=0.007), but triglycerides, high-sensitivity CRP (hs-CRP), hemoglobin A1c and uric acid were similar among the 4 groups.

Effects of Statin Therapy on IVUS Parameters
The percent decrease in coronary PV was significant in the atorvastatin group (–11.1±12.8%, P<0.001) and in the pitavastatin group (–8.1±16.9%, P<0.001), whereas non-significant plaque progression was observed in the pravastatin group (0.4±16.0%, P=0.90) and in the fluvastatin group (3.1±20.0%, P=0.43; Table 3). Moderate-intensity statin therapy induced a significantly greater reduction in PV compared with low-intensity statin therapy (–9.6±14.9% vs. 1.8±17.9%, respectively, P<0.001; Figure 2).

Change in PV vs. Lipid Profile
The percent change in LDL-C did not correlate with the percent change in PV (r=0.172, P=0.08; Figure 3A), but LDL-C at the end of the study correlated significantly with percent change in PV (r=0.220, P=0.02; Figure 3B). The best cut-off for LDL-C at follow-up to predict PV regression was 95 mg/dl (area under the curve, 0.55; sensitivity, 44.7%; specificity, 72.0%). The patients who achieved LDL-C≤95 mg/dl at follow-up comprised 92% and 40% of the moderate- and low-intensity statin groups, respectively (P<0.001). Moderate-intensity statin therapy induced a significantly greater reduction in PV compared with low-intensity statin therapy in patients with LDL-C≤95 mg/dl at follow-up (–9.2±14.8% vs. –1.0±14.3%, P=0.04). In addition, there was no significant correlation between baseline hs-CRP or that at the end of the study and percent change in PV.

Laboratory Results vs. Response Status
No significant differences in lipid profile were observed between patients with plaques showing progression, no change, and regression (Table 4). The percent change in each parameter was also not significantly different between the 3 groups. LDL-C and the ratio of LDL-C to HDL-C decreased

### Table 3. IVUS-Based Volume Parameters: Baseline and Follow-up

<table>
<thead>
<tr>
<th></th>
<th>All  (n=102)</th>
<th>Atorvastatin (n=26)</th>
<th>Pitavastatin (n=25)</th>
<th>Pravastatin (n=25)</th>
<th>Fluvastatin (n=25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV (mm³)</td>
<td>65.9±29.8</td>
<td>70.3±5.8</td>
<td>62.5±5.8</td>
<td>74.5±5.9</td>
<td>56.2±5.9</td>
<td>0.13</td>
</tr>
<tr>
<td>Percent PV (%)</td>
<td>46.3±11.6</td>
<td>50.2±2.3</td>
<td>44.1±2.3</td>
<td>46.0±2.3</td>
<td>44.7±2.3</td>
<td>0.23</td>
</tr>
<tr>
<td>EEM volume (mm³)</td>
<td>141.6±55.8</td>
<td>145.7±47.8</td>
<td>137.4±65.6</td>
<td>161.2±48.9</td>
<td>121.9±54.9</td>
<td>0.09</td>
</tr>
<tr>
<td>Lumen volume (mm³)</td>
<td>75.7±35.1</td>
<td>75.4±37.0</td>
<td>74.9±38.4</td>
<td>86.7±33.0</td>
<td>65.7±29.8</td>
<td>0.21</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV (mm³)</td>
<td>62.8±30.6</td>
<td>63.0±22.7</td>
<td>57.4±36.4</td>
<td>75.7±33.1</td>
<td>55.0±25.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Percent PV (%)</td>
<td>45.1±13.0</td>
<td>46.6±12.6</td>
<td>41.2±14.5</td>
<td>47.5±13.8</td>
<td>45.1±10.8</td>
<td>0.32</td>
</tr>
<tr>
<td>EEM volume (mm³)</td>
<td>137.3±51.6</td>
<td>138.5±42.8</td>
<td>132.8±57.6</td>
<td>157.4±51.1</td>
<td>120.9±50.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Lumen volume (mm³)</td>
<td>74.5±34.2</td>
<td>75.6±33.6</td>
<td>75.0±35.7</td>
<td>81.7±36.9</td>
<td>65.9±30.4</td>
<td>0.44</td>
</tr>
<tr>
<td>Actual change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV (mm³)</td>
<td>–3.2±11.7*†</td>
<td>–7.3±8.5*†</td>
<td>–5.1±11.2*†</td>
<td>1.2±14.2</td>
<td>–1.2±11.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Percent PV (%)</td>
<td>–1.2±7.0*†</td>
<td>–3.6±5.1*†</td>
<td>–2.9±5.2*†</td>
<td>1.5±9.9</td>
<td>0.4±5.8</td>
<td>0.02</td>
</tr>
<tr>
<td>EEM volume (mm³)</td>
<td>–4.3±17.4*†</td>
<td>–7.2±17.1*†</td>
<td>–5.0±18.0</td>
<td>–3.8±20.9</td>
<td>–1.0±13.3</td>
<td>0.65</td>
</tr>
<tr>
<td>Lumen volume (mm³)</td>
<td>–1.1±17.1</td>
<td>0.2±13.5</td>
<td>0.1±12.3</td>
<td>–5.0±27.6</td>
<td>0.1±9.8</td>
<td>0.64</td>
</tr>
<tr>
<td>Percent change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV (%)</td>
<td>–4.0±17.4*†</td>
<td>–11.1±12.8*†</td>
<td>–8.1±16.9*†</td>
<td>0.4±16.0</td>
<td>3.1±20.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Percent PV (%)</td>
<td>–2.6±16.4</td>
<td>–7.3±11.0*†</td>
<td>–7.6±11.8*†</td>
<td>4.0±24.0</td>
<td>1.1±13.3</td>
<td>0.02</td>
</tr>
<tr>
<td>EEM volume (%)</td>
<td>–1.2±10.2</td>
<td>–3.9±10.0</td>
<td>–0.6±13.0</td>
<td>–2.0±11.3</td>
<td>1.9±13.4</td>
<td>0.37</td>
</tr>
<tr>
<td>Lumen volume (%)</td>
<td>1.6±18.8</td>
<td>4.2±16.9</td>
<td>4.1±17.1</td>
<td>–3.4±23.7</td>
<td>1.4±16.5</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Data given as mean±SD. *P<0.05 (†vs. baseline, ‡atorvastatin vs. pravastatin, §atorvastatin vs. fluvastatin, ¶pitavastatin vs. pravastatin). EEM, external elastic membrane; IVUS, intravascular ultrasound; PV, plaque volume.
There was no differences in percent change in PV between the 3 groups (1.1±18.4% vs. –8.2±14.9% vs. –4.5±17.9%; P=0.09, ANOVA). LDL-C at follow-up was highest in the high LDL-C group and lowest in the low LDL-C group (100±24 mg/dl vs. 89±24 mg/dl vs. 80±30 mg/dl; P=0.009, ANOVA). Percent change significantly in all 3 plaque groups. Total cholesterol, non-HDL-C, and hs-CRP decreased significantly in both the no-change group and regression groups. HDL-C increased significantly in only the regression group.

**Baseline LDL-C and Percent Change in PV**

We divided the patients into 3 groups according to baseline LDL-C tertile (high LDL-C group, >151 mg/dl; intermediate LDL-C group, 130–151 mg/dl; low LDL-C group, <130 mg/dl). There was no differences in percent change in PV between the 3 groups (1.1±18.4% vs. –8.2±14.9% vs. –4.5±17.9%; P=0.09, ANOVA). LDL-C at follow-up was highest in the high LDL-C group and lowest in the low LDL-C group (100±24 mg/dl vs. 89±24 mg/dl vs. 80±30 mg/dl; P=0.009, ANOVA). Percent change significantly in all 3 plaque groups. Total cholesterol, non-HDL-C, and hs-CRP decreased significantly in both the no-change group and regression groups. HDL-C increased significantly in only the regression group.
Multivariate linear regression analysis was performed to identify possible indicators of coronary plaque regression. Conventional coronary risk factors (age, male gender, current risk factors, past medical history, and medical therapy) were added to the baseline model to identify other potential factors associated with plaque regression.

### Table 5. Indicators of Percent PV Change in ACS Patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate linear regression</th>
<th>Multivariate linear regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta )</td>
<td>SE</td>
</tr>
<tr>
<td>Age</td>
<td>0.11</td>
<td>0.17</td>
</tr>
<tr>
<td>Male gender</td>
<td>-0.99</td>
<td>4.35</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.88</td>
<td>3.44</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.36</td>
<td>3.61</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.14</td>
<td>3.46</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>3.21</td>
<td>3.65</td>
</tr>
<tr>
<td>LDL-C at follow-up</td>
<td>0.15</td>
<td>0.06</td>
</tr>
<tr>
<td>UA at baseline</td>
<td>3.38</td>
<td>1.32</td>
</tr>
<tr>
<td>Moderate-intensity statin</td>
<td>-11.422</td>
<td>3.26</td>
</tr>
<tr>
<td>ACEI use at follow-up</td>
<td>3.18</td>
<td>3.71</td>
</tr>
<tr>
<td>( \beta )-blocker use at follow-up</td>
<td>5.65</td>
<td>4.60</td>
</tr>
<tr>
<td>PV before intervention</td>
<td>-0.06</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1–3.

### Change in PV

Change in PV was similar in the 3 groups for both moderate-intensity statin therapy (\(-7.1\pm15.8\% \text{ vs. } -15.5\pm12.4\% \text{ vs. } -5.2\pm15.2, \text{P}=0.08\)) and low-intensity statin therapy (\(6.7\pm18.3\% \text{ vs. } 1.4\pm12.4\% \text{ vs. } -3.7\pm21.1\%, \text{P}=0.23\)).
smoker, diabetes mellitus, hypertension, family history of CAD) and statin (moderate- or low-intensity statin therapy), angiotensin-converting enzyme inhibitor, β-blocker uric acid, and PV before intervention were included. Moderate-intensity statin therapy (P=0.02) and baseline serum uric acid (P=0.02) were significant determinants of percent regression in PV (Table S1).

Adverse Events
As expected in this relatively small study, there were no significant differences in the frequency of MACE or other adverse events among the 4 statin groups (Table S1). LDL-C at follow-up and percent change in PV were not significantly different between patients with MACE and without MACE (93±31 mg/dl vs. 87±26 mg/dl, P=0.49; and −1.3±21% vs. −4.6±16%, P=0.45).

Discussion
In the present study, moderate-intensity statin therapy with either 4 mg/day pitavastatin or 20 mg/day atorvastatin achieved significant regression of coronary PV compared with low-intensity statin therapy with either 10 mg/day pravastatin or 30 mg/day fluvastatin. To the best of our knowledge, this is the first clinical IVUS study to compare the effects of moderate-intensity statin therapy and low-intensity statin therapy on non-culprit intermediate coronary plaque in patients with ACS.

Statin therapy was recommended to lower cardiovascular events by reducing the synthesis and increasing the uptake of cholesterol from the blood. It has been reported that statin treatment after the onset of ACS has the potential to improve clinical outcome and to facilitate PV regression. Previous studies also showed that coronary plaque regression induced by statin therapy appeared to be more predominant in ACS patients than in non-ACS patients. This may be related to the underlying differences in coronary plaque composition in patients with ACS compared with those with stable angina pectoris. In pathology and imaging studies, ACS patients have a larger percentage of lipid-laden plaque with inflammatory cells, compared with a higher percentage of fibrocalcific plaque in patients with chronic stable lesions. Statin therapy has been reported to reduce the plaque lipid component, which may translate into entire plaque regression. Therefore, it can be argued that coronary plaque in ACS patients is more susceptible to plaque regression.

Previous studies also noted the presence of a significant relationship between reduction in LDL-C and PV regression. The JAPAN-ACS trial reported that the use of pitavastatin or atorvastatin by patients with ACS resulted in significant regression of coronary PV, with no correlation between LDL-C and PV regression. Previous studies also showed that coronary plaque regression induced by statin therapy appeared to be more predominant in ACS patients than in non-ACS patients. This may be related to the underlying differences in coronary plaque composition in patients with ACS compared with those with stable angina pectoris. In pathology and imaging studies, ACS patients have a larger percentage of lipid-laden plaque with inflammatory cells, compared with a higher percentage of fibrocalcific plaque in patients with chronic stable lesions. Statin therapy has been reported to reduce the plaque lipid component, which may translate into entire plaque regression. Therefore, it can be argued that coronary plaque in ACS patients is more susceptible to plaque regression.

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Experimental studies suggest possible lipid accumulation in the intima via the vasa vasorum penetrating from the adventitia through the vessel wall. Another recent report suggested that moderate-high-intensity statin therapy reduced the density of vasa vasorum around the human carotid artery, and this finding could be identified in the coronary arteries. Statins also lessen intra-plaque inflammation, which is mainly due to inhibition of interleukin (IL)-1, interferon-γ, IL-6, and plasminogen activator-inhibitor-1 as well as improve endothelial function by enhancing nitric oxide production. High-intensity statins possess not only potent LDL-C-lowering properties but also significant anti-inflammatory and antioxidant effects, which may have led to greater plaque regression in patients with moderate-intensity compared with low-intensity statin treatment in the present study.

The present study also identified high serum uric acid as a significant independent risk factor associated with increased coronary PV. Hyperuricemia is an independent predictor of 1-year mortality in ACS patients treated with PCI. Further studies are necessary to evaluate the role of hyperuricemia in...
subclinical atherosclerosis and the development of cardiovascular events.

The present study had certain limitations. First, it was performed in a single center and included a small number of patients with a relatively short treatment duration, which may have reduced the power to detect relevant differences in clinical endpoints. Second, IVUS was performed on the culprit vessel for the assessment of non-culprit plaque because IVUS of non-culprit vessel in ACS patients is ethically unacceptable under certain circumstances. Examination of the culprit vessel may not represent the pan-coronary nature of plaque. Mechanical interventions could have altered the progression or regression of the measured plaque, especially in the culprit vessel. To confirm the results of this part of the study, a prospective study needs to be conducted in a larger group of patients.

Conclusions

Among patients treated with statin to prevent future ACS, randomization to moderate-intensity statin treatment was associated with significant plaque regression compared with low-intensity statin therapy, independent of serum LDL-C at follow-up. The intensity of statin therapy rather than LDL-C level during statin treatment is more important for the regression of coronary atherosclerosis.

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Disclosures

The authors declare no conflict of interest.

References


