Early Statin Treatment in Patients With Acute Coronary Syndrome

Demonstration of the Beneficial Effect on Atherosclerotic Lesions by Serial Volumetric Intravascular Ultrasound Analysis During Half a Year After Coronary Event: The ESTABLISH Study

Shinya Okazaki, MD; Takayuki Yokoyama, MD; Katsumi Miyauchi, MD; Kazunori Shimada, MD; Takeshi Kurata, MD; Hitoshi Sato, MD; Hiroyuki Daida, MD

Background—Recent clinical trials have demonstrated that aggressive lipid lowering by statins could prevent recurrent events after acute coronary syndrome (ACS). We hypothesized that this efficacy was caused by a significant reduction in plaque volume by aggressive LDL cholesterol (LCL-C) lowering. The present study investigated the effect of early statin treatment on plaque volume of a nonculprit lesion by serial volumetric intravascular ultrasound in patients with ACS.

Methods and Results—Seventy patients with ACS were enrolled. All patients underwent emergency coronary angiography and percutaneous coronary intervention (PCI). They were randomized to intensive lipid-lowering therapy (n = 35; atorvastatin 20 mg/d) or control (n = 35) groups after PCI. Volumetric intravascular ultrasound analyses were performed at baseline and 6-month follow-up for a non-PCI site in 48 patients (atorvastatin, n = 24; control, n = 24). LDL-C level was significantly decreased by 41.7% in the atorvastatin group compared with the control group, in which LDL-C was increased by 0.7% (P < 0.0001). Plaque volume was significantly reduced in the atorvastatin group (13.1 ± 12.8% decrease) compared with the control group (8.7 ± 14.9% increase; P < 0.0001). Percent change in plaque volume showed a significant positive correlation with follow-up LDL-C level (R = 0.456, P = 0.0011) and percent LDL-C reduction (R = 0.612, P < 0.0001), even in patients with baseline LDL-C <125 mg/dL.

Conclusions—Early aggressive lipid-lowering therapy by atorvastatin for 6 months significantly reduced the plaque volume in patients with ACS. Percent change in plaque volume showed a significant positive correlation with percent LDL-C reduction, even in patients with low baseline LDL-C. (Circulation. 2004;110:1061-1068.)

Key Words: atherosclerosis ▪ lipids ▪ plaque ▪ statins ▪ coronary disease

Recent large-scale lipid-lowering trials have suggested that statins can reduce recurrent ischemic coronary events in patients with hypercholesterolemia as well as in those with a normal cholesterol level.1–3 Previous angiographic studies have also demonstrated that intensive lipid lowering could retard the progression of coronary atherosclerosis.4–7 However, the degree of angiographic change did not correlate well with the clinical benefits demonstrated. Thus, the concept of plaque stabilization developed, with growing evidence from recent histopathological and vascular biology studies. More recently, early statin treatment in patients with acute coronary syndrome (ACS) showed a significant advantage in the short-term follow-up period.8–11 However, the detailed mechanism of this early statin efficacy is not fully understood. The aim of this study was to examine whether early aggressive lipid lowering with atorvastatin could induce a significant reduction in plaque volume by stabilizing vulnerable plaques in non–percutaneous coronary intervention (PCI) sites of the culprit vessel in patients with ACS.

Methods

Study Design

ESTABLISH is a prospective, open-label, randomized, single-center study to assess with serial volumetric IVUS analysis the effect of 6 months of treatment with atorvastatin to induce regression of atherosclerosis in non-PCI sites of the culprit vessel. Patients were randomized to receive intensive lipid-lowering therapy (atorvastatin 20 mg PO once daily) or usual care [lipid-lowering diet, and if LDL cholesterol (LDL-C) level was...
still high (>150 mg/dL) at the outpatient visit, a cholesterol 
sorption inhibitor was initiated) after PCI and intravascular 
ultrasound (IVUS) measurement were performed. Randomization 
was undertaken by minimization method controlling for a culprit 
vessel, baseline total cholesterol level, and presence of diabetes 
meillius. Follow-up visits were scheduled every month until 6 
months after PCI, when recatheterization was performed. At the 
6-month follow-up, repeated IVUS measurements in the culprit 
vessel were performed. This study was approved by the local 
medical ethics committee, and informed consent was obtained 
from each patient.

Patient Population
Patients were enrolled between November 2001 and August 2003. 
Patients were eligible for inclusion if they had ACS with 
significant stenosis on initial coronary angiography and received 
PCI. ACS was defined as high-risk unstable angina, non-ST-
elevated myocardial infarction (MI) or ST-elevated MI. MI was 
diagnosed by the rise (≥2 times) in serum creatine phosphokinase 
and positivity for troponin T. Exclusion criteria were failed PCI, 
predicted CABG, cardiogenic shock, and positivity for troponin T. 

TABLE 1. Baseline Characteristics of Patients and Additional 
Therapy During Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin (n=35)</th>
<th>Control (n=35)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (n=35)</td>
<td>61.3±10.1</td>
<td>62.5±11.2</td>
<td>0.647</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>30 (85.7)</td>
<td>30 (85.7)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.9±3.2</td>
<td>24.0±3.2</td>
<td>0.245</td>
</tr>
<tr>
<td>Prior CAD, n (%)</td>
<td>5 (14.3)</td>
<td>5 (14.3)</td>
<td>0.961</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>19 (54.3)</td>
<td>19 (54.3)</td>
<td>0.894</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>12 (34.3)</td>
<td>11 (31.4)</td>
<td>0.865</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>24 (68.6)</td>
<td>19 (54.2)</td>
<td>0.277</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>6 (17.1)</td>
<td>12 (34.3)</td>
<td>0.086</td>
</tr>
</tbody>
</table>

Classification of ACS, n (%)
- AMI: 22 (63) vs 26 (74)
- ST elevated: 17 vs 18
- Non-ST elevated: 5 vs 8
- Unstable angina: 13 (37) vs 9 (26)

New Q wave
- Yes: 8 vs 9
- No: 27 vs 26

Maximum CPK, IU/L
- 1499±1797 vs 1440±1646 (P=0.886)

Troponin T, ng/mL
- 1.25±2.25 vs 2.48±3.71 (P=0.100)

Use of ACE inhibitor, n (%) 14 (40) vs 14 (40)

Use of AT1 antagonist, n (%) 14 (40) vs 14 (40)

Use of β-blocker, n (%) 14 (40) vs 19 (54)

CAD indicates coronary artery disease; AMI, acute MI; CPK, creatine 
phosphokinase; and AT1, angiotensin receptor type 1. Values are mean±SD 
when appropriate. A χ² test was used for categorical data; unpaired Student’s 
test or Mann-Whitney rank-sum test was used for continuous data. Values of 
P<0.05 were considered statistically significant.

aspirin were administered during the procedures. After PCI, all patients 
received aspirin 100 mg once daily and ticlopidine 100 mg twice daily 
for >3 weeks and cilostazol 100 mg twice daily for 4 days.

IVUS Examination
For IVUS examinations, the same system (2.9 F, 40-MHz; Boston 
Scientific) was used at baseline and follow-up. All IVUS 
examinations were performed in the following manner. After intracoro-
mary administration of 0.2 mg nitroglycerin, the ultrasound 
catheter was positioned sufficiently distal (≥10 mm distal) to the 
PCI site. Pullback was performed automatically at 0.5 mm/s. IVUS 
measurements were recorded on super VHS videotape and 
sent to our IVUS laboratory for offline quantitative analysis.

IVUS Analysis
Plaque volume was assessed by volumetric analysis with a Netra 
3D IVUS system (ScImage). Baseline and follow-up IVUS 
images were reviewed side by side on a display, and the target 
segment was selected. One target segment was determined in a 
non-PCI site (>5 mm proximal or distal to the PCI site) with a 
reproducible index side branch. Segments with marked calcification 
or tortuosity were avoided. If a distal protection device was 
used in a patient, a non-PCI site was selected proximal to the PCI 
site to avoid the segment affected by balloon injury of distal 
occlusion. Quantitative analysis was performed by an independent 
selected blinded to the patient groups 
and to the angiographic result. IVUS analyses included the vessel 
volume, lumen volume, and plaque volume. Standard measure-
ments obtained included lesion length, vessel volume, and lumen

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when appropriate. A χ² test was used for categorical data; unpaired Student’s 
test or Mann-Whitney rank-sum test was used for continuous data. Values of 
P<0.05 were considered statistically significant.

RCA indicates right coronary artery; LAD, left anterior descending artery; 
LCx, left circumflex artery; and POBA, plain old balloon angioplasty. Values are 
mean±SD when appropriate. A χ² test was used for categorical data; unpaired 
Student’s t test or Mann-Whitney rank-sum test was used for continuous data. Values of 
P<0.05 were considered statistically significant.
volume. Plaque volume was calculated as vessel volume minus lumen volume. The percent change in plaque volume was defined as the change in plaque volume (follow-up minus baseline plaque volume) divided by the baseline plaque volume. The primary outcome was percent change in plaque volume; the secondary outcome was the correlation between percent change in plaque volume and follow-up LDL-C levels or percent LDL-C reduction.

**Definition of Events and Follow-Up for Major Adverse Coronary Events**

Follow-up visits were scheduled every month. Cardiac events, consisting of death caused by cardiac causes, MI, recurrent angina related to the PCI vessel, or target vessel revascularization (repeated PCI or CABG), were reported. Angiographic follow-up

### TABLE 3. Blood Parameters of Patients at Baseline and Follow-Up

<table>
<thead>
<tr>
<th>Laboratory Parameters</th>
<th>Baseline</th>
<th></th>
<th></th>
<th></th>
<th>Follow-Up</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Atorvastatin (n=35)</td>
<td>Control (n=35)</td>
<td>P</td>
<td>Atorvastatin (n=33)</td>
<td>Control (n=32)</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>191.8±35.7</td>
<td>190.7±42.8</td>
<td>0.904</td>
<td>141.1±29.1*</td>
<td>190.9±29.7</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Reduction in TC, %</td>
<td></td>
<td></td>
<td></td>
<td>25.2±14.5*</td>
<td>−3.0±20.3</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>HDL-C, mg/dL</td>
<td>45.5±9.9</td>
<td>44.3±11.2</td>
<td>0.653</td>
<td>46.6±10.5</td>
<td>47.4±11.2</td>
<td>0.749</td>
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<tr>
<td>Triglyceride, mg/dL</td>
<td>108.7±76.3</td>
<td>112.3±54.5</td>
<td>0.825</td>
<td>122.5±63.8</td>
<td>120.4±49.0</td>
<td>0.882</td>
<td></td>
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<tr>
<td>LDL-C, mg/dL</td>
<td>124.6±34.5</td>
<td>123.9±35.3</td>
<td>0.933</td>
<td>70.0±25.0*</td>
<td>119.4±24.6</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>Reduction in LDL-C, %</td>
<td></td>
<td></td>
<td></td>
<td>41.7±19.9*</td>
<td>−0.7±4.1</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Lipoprotein(a), mg/L</td>
<td>20.7±12.6</td>
<td>24.5±14.6</td>
<td>0.261</td>
<td>22.8±20.1</td>
<td>25.8±17.9</td>
<td>0.525</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein A1, mg/dL</td>
<td>112.3±16.5</td>
<td>107.4±16.9</td>
<td>0.246</td>
<td>125.4±15.6</td>
<td>125.1±21.4</td>
<td>0.943</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein B, mg/dL</td>
<td>91.7±19.3</td>
<td>90.4±21.3</td>
<td>0.789</td>
<td>66.1±18.8</td>
<td>92.6±14.9</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein E, mg/dL</td>
<td>3.88±0.74</td>
<td>3.92±0.92</td>
<td>0.848</td>
<td>3.31±0.87*</td>
<td>4.34±1.30</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.7±1.1</td>
<td>5.7±1.2</td>
<td>0.936</td>
<td>5.6±0.8</td>
<td>5.5±0.7</td>
<td>0.320</td>
<td></td>
</tr>
<tr>
<td>Insulin, µU/mL</td>
<td>12.4±9.4</td>
<td>11.7±12.9</td>
<td>0.812</td>
<td>7.6±4.5</td>
<td>5.9±4.1</td>
<td>0.151</td>
<td></td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>98.4±88.0</td>
<td>142.1±194.0</td>
<td>0.981</td>
<td>41.0±50.8</td>
<td>77.9±214.8</td>
<td>0.773</td>
<td></td>
</tr>
<tr>
<td>hsCRP, mg/dL</td>
<td>0.90±2.84</td>
<td>0.69±1.24</td>
<td>0.972</td>
<td>0.09±0.10</td>
<td>0.14±0.24</td>
<td>0.681</td>
<td></td>
</tr>
</tbody>
</table>

TC indicates total cholesterol; BNP, brain natriuretic peptide; and hsCRP, high-sensitivity C-reactive protein. Values are mean±SD when appropriate. A χ² test was used for categorical data; unpaired Student’s t test or Mann-Whitney rank-sum test was used for continuous data. Values of P<0.05 were considered statistically significant.

*Baseline vs follow-up.

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### TABLE 4. Volume Parameters From IVUS Measurements

<table>
<thead>
<tr>
<th>Analysis segment, n</th>
<th>Atorvastatin (n=24)</th>
<th>Control (n=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal</td>
<td>14</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Distal</td>
<td>10</td>
<td>11</td>
<td>0.959</td>
</tr>
<tr>
<td>Average length, mm</td>
<td>8.89±2.45</td>
<td>8.63±1.97</td>
<td>0.69</td>
</tr>
<tr>
<td>Vessel volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mm³</td>
<td>151.4±78.2</td>
<td>130.4±58.7</td>
<td>0.31</td>
</tr>
<tr>
<td>After 6 mo, mm³</td>
<td>148.4±76.3</td>
<td>131.0±56.9</td>
<td>0.38</td>
</tr>
<tr>
<td>Change in vessel volume, mm³</td>
<td>−2.9±15.2</td>
<td>0.5±13.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Percent change in vessel volume</td>
<td>−0.97±9.8</td>
<td>1.6±12.0</td>
<td>0.42</td>
</tr>
<tr>
<td>Lumen volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mm³</td>
<td>81.7±36.4</td>
<td>71.0±27.9</td>
<td>0.27</td>
</tr>
<tr>
<td>After 6 mo, mm³</td>
<td>87.0±43.3</td>
<td>67.3±25.9</td>
<td>0.07</td>
</tr>
<tr>
<td>Change in lumen volume, mm³</td>
<td>5.3±13.7</td>
<td>−3.7±10.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Percent change in lumen volume</td>
<td>5.8±15.5</td>
<td>−3.3±14.7</td>
<td>0.045</td>
</tr>
<tr>
<td>Plaque volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mm³</td>
<td>69.6±49.0</td>
<td>59.5±38.6</td>
<td>0.44</td>
</tr>
<tr>
<td>After 6 mo, mm³</td>
<td>61.4±44.9</td>
<td>63.7±40.1</td>
<td>0.86</td>
</tr>
<tr>
<td>Change in plaque volume, mm³</td>
<td>−8.3±9.0</td>
<td>4.2±8.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percent change in plaque volume</td>
<td>−13.1±12.8</td>
<td>8.7±14.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean±SD. Unpaired Student’s t test or Mann-Whitney rank-sum test was used for statistical analysis. Values of P<0.05 were considered statistically significant.
was scheduled for all patients 6 months after PCI. Recurrent angina was defined as the presence of ischemia, either the recurrence of typical symptoms of angina or a positive exercise stress test related to the PCI vessel.

**Statistical Analysis**

Statistical analysis was performed with Stat View 5.0 MDSU statistical software (SAS Institute). Quantitative data are presented as mean±SD. Differences between the 2 groups with or without statin treatments were assessed with χ² test for categorical variables and with unpaired Student’s t test or the Mann-Whitney rank-sum test for continuous data. Correlations between percent change in plaque volume and lipid values or changes were analyzed by linear regression analysis. Event-free survival was assessed with the Kaplan-Meier method. A value of \( P < 0.05 \) was considered statistically significant. For the sample size calculation, no information was available for the volumetric IVUS trial in patients with ACS. A total of 50 patients seemed appropriate to investigate the efficacy of LDL-C lowering on plaque volume and correlation between the percent change in plaque volume and LDL-C levels.

**Results**

**Baseline Characteristics and Procedural Data**

This study consisted of 70 patients: 35 randomized to atorvastatin and 35 control subject. The mean patient age was 61.9±10.6 years; 60 patients (85.7%) were men; and 10 patients (14.3%) had prior coronary artery disease. There were 38 hypertensive patients (54.3%) and 23 diabetics (32.9%). The 2 groups had similar demographic characteristics, including use of β-blockers, ACE inhibitors, and angiotensin type 1 antagonists (Table 1). There were no significant differences between the 2 groups in lesion characteristics and PCI procedural data (Table 2). During this study period, 1 noncardiac death (malignant lymphoma) occurred in the control group. Two patients in the atorvastatin group and 1 patient in the control group were withdrawn because they refused follow-up angiography or follow-up IVUS. One patient in the control group could not be followed up because of a change of address. Thus, the study protocol was completed in 65 patients (atorvastatin, \( n=33 \); control, \( n=32 \)). For IVUS analysis, volumetric analysis was performed if (1) there was no more than moderate calcification because it prevents accurate assessment of plaque volume as a result of difficulty in identifying the external elastic lumina and measuring vessel dimensions and (2) there was no marked tortuosity or artifact interfering with reliable volumetric IVUS analyses. Thus, both baseline and follow-up volumetric IVUS analyses met the above conditions in 48 patients (24 patients for each group).
Follow-Up Data and Lipid Profile
Three patients in the control group received a cholesterol absorption inhibitor. No patient was withdrawn for any adverse effects in the atorvastatin group. At 6 months, LDL-C level was significantly decreased by 41.7% in the atorvastatin group compared with an increase of 0.7% in the control group (P<0.0001). HDL-C and triglyceride levels showed no significant differences in the 2 groups at baseline and follow-up (Table 3).

Volumetric IVUS Analysis
For the target segment selection, a distal segment was selected in 10 patients in the atorvastatin group and in 11 in the control group; a proximal segment was chosen in 14 patients in the atorvastatin group and in 13 in the control group. Table 4 shows the baseline and 6-month follow-up data of volumetric IVUS analysis at the target segment. Plaque volume was significantly reduced in the atorvastatin group (13.1±12.8% decrease; P<0.0001 for baseline versus follow-up). On the other hand, it was significantly increased by 8.7±14.9% in the control group (P=0.0276 for baseline versus follow-up, P<0.0001 for atorvastatin versus control at follow-up). Figure 1 shows the percent change in cholesterol level and volumetric IVUS analysis parameters in each group. In the atorvastatin group, significant percent changes in both plaque volume and lumen volume were observed. Figure 2 shows that percent change in plaque volume had a significant positive correlation with follow-up LDL-C level (R=0.456, P=0.0011) and percent LDL-C reduction (R=0.612, P<0.0001) but no correlation with percent HDL-C gain (R=0.206, P=0.160) and baseline LDL-C level (R=0.154, P=0.295). When the patients were divided into 2 subgroups by a baseline serum LDL-C level of 125 mg/dL (median LDL-C level), plaque volume was significantly reduced in the atorvastatin group in either the LDL-C <125 mg/dL (14.7±13.2% decrease; P=0.0027 for baseline versus follow-up) or the LDL-C >125 mg/dL (10.8±11.8% decrease; P=0.043 for baseline versus follow-up) subgroup. Percent change in plaque volume showed a more significant positive correlation with percent LDL-C reduction in patients with a low baseline LDL-C (<125 mg/dL) than in those with a high baseline LDL-C (>125 mg/dL) (R=0.685, P=0.0002; R=0.462, P=0.0231, respectively; Figure 3). Figure 4 shows a representative patient from each group. Baseline and follow-up IVUS images are presented side by side. Marked enlargement of the lumen and a reduction in plaque are clearly observed in an atorvastatin patient at the non-PCI site after only 6 months of pharmacological intervention, whereas a significant reduction in the lumen and an increase in plaque area are observed in a control patient.

Major Adverse Coronary Events
The prevalence of major adverse coronary events during 6 months of follow-up showed no significant difference between the 2 groups (8 patients each in both groups; P=0.8471). There was no case of cardiac death or target vessel–related MI. All cases of major adverse coronary events consisted of target vessel revascularization performed for restenosis with recurrent angina in 24.2% (8 of 33) of the atorvastatin group and 25.0% (8 of 32) in the control group.

Discussion
The present study demonstrated that early aggressive lipid-lowering by atorvastatin induced a significant reduction in coronary plaque volume assessed by volumetric IVUS analysis at 6 months after the onset of ACS. Moreover, the degree of plaque volume reduction was positively correlated with the percent LDL-C reduction, even in patients with low baseline LDL-C (<125 mg/dL).

Several serial IVUS studies have indicated that cholesterol lowering could retard the progression of atherosclerosis; however, they did not demonstrate significant plaque regression in patients with stable coronary artery disease.12,13 In a recent study in stable angina, the plaque volume reduction by statin treatment was not significant compared with control, although this study showed a 4-fold-greater increase in plaque hyperechogenicity.13 In contrast, the present study demonstrated plaque regression by aggressive lipid lowering over a relatively short period of time after ACS. This early regression in ACS may be explained by the difference in target plaque characteristics between ACS and stable coronary artery disease. Previous large-scale intervention trials suggest that they have very different clinical processes. It was reported that in ACS the rate of death or nonfatal MI was 10.4% among patients.
who received immediate invasive treatment with medical treatment and 14.1% among patients who received medical therapy alone.\textsuperscript{14} In contrast, stable angina patients were found to have a better clinical outcome. In SAPAT, the rate of death or nonfatal MI was \(<2\%\).\textsuperscript{15} This substantial prognostic difference suggests that patients with ACS have vulnerable plaques leading to recurrent clinical events; on the other hand, patients with stable angina have rather stable plaques. Indeed, previous clinical studies have demonstrated that patients with ACS had vulnerable plaque at the culprit lesion and in other branches of the coronary tree. An angiographic study showed that most MI occurs at sites at which only mild to moderate luminal stenosis previously existed.\textsuperscript{16} Those infarct-related lesions usually showed complex morphology that was histologically vulnerable.\textsuperscript{17} These studies suggest that coronary plaques in ACS have vulnerable morphology that is prone to regression by aggressive lipid lowering, as indicated in the present study.

The analyzed target segments in the present study in which significant regression was observed were nonculprit lesions proximal or distal to the culprit lesion. Goldstein et al.\textsuperscript{18} reported the presence of additional multiple complex angiographic lesions in 39.5\% of ACS patients, and these
lesions were associated with increased incidence of recurrent ACS. Rioufol et al. observed all 3 coronary trees in patients with ACS by IVUS. They found ≥2 ruptured plaques in 79% of patients. These studies suggest that ACS seems to be associated with the overall coronary instability that is responsible for the frequent recurrence rate even after acute treatment of the culprit lesions. Thus, the beneficial effect of aggressive lipid lowering on the nonculprit lesions in the present study may contribute to prevention of recurrent events. Indeed, recent statin trials indicated that early statin treatment in patients with ACS could produce a significant advantage in short-term follow-up.8–11 The MIRACL study investigated the efficacy of early statin treatment on recurrent coronary events within 16 weeks and found a significant 16% reduction in events.9

The mechanisms of the beneficial effect of acute statin treatment in ACS are not fully understood. Because efficacy was observed as early as 16 weeks, instead of the LDL-C-lowering effect, direct effects of statins, including recovery of impaired endothelial function and/or an anti-inflammatory effect and/or an antithrombotic effect, have been proposed. In the present study, we documented significant plaque regression in the atorvastatin group, with a significant positive correlation between percent LDL-C reduction and follow-up LDL-C level and percent change in plaque volume during only a 6-month period. Thus, aggressive LDL-C lowering itself should be an important mechanism for event reduction by early statin treatment after ACS. In a recent observational study, Von Birgelen et al.20 documented a positive correlation between baseline LDL-C level and annual change in plaque size of the left main trunk during ≥12 months of follow-up in cross-sectional analysis of IVUS measurements. Although the study demonstrated significant enlargement of the lumen area in the low baseline LDL-C (120 mg/dL) group, regression of plaque area was not observed, and only retardation of the progression was found. Similar correlation was not found between baseline LDL-C and percent change in plaque volume in the present study because pharmacological intervention modified the lipid profile. A significant correlation was observed between percent LDL-C reduction and follow-up LDL-C level and percent change in plaque volume. Moreover, this correlation was found even in patients with a low baseline LDL-C level (<125 mg/dL). Thus, plaque regression by aggressive LDL-C lowering could be attributable to the acute effect of statins in ACS, independent of the baseline LDL-C level.

**Study Limitations**

This study consisted of only 48 ACS patients with volumetric IVUS analysis; however, high-quality IVUS images in both the acute phase of ACS and follow-up allowed us to identify a significant difference in plaque volume between the atorvastatin and control groups in a short period. We could not perform tissue characterization in this study. Future study should address the detailed mechanisms of acute plaque stabilization by statins in patients with ACS.

**Conclusions**

Our study demonstrated that early aggressive lipid-lowering therapy by atorvastatin for 6 months significantly reduced the plaque volume in patients with ACS. Percent change in plaque volume showed a significant positive correlation with percent LDL-C reduction, even in patients with a low baseline LDL-C (<125 mg/dL). Thus, aggressive lipid lowering by statins immediately after ACS onset may be an attractive treatment strategy, regardless of the baseline serum LDL-C level.

**References**


14. Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive...


Early Statin Treatment in Patients With Acute Coronary Syndrome: Demonstration of the Beneficial Effect on Atherosclerotic Lesions by Serial Volumetric Intravascular Ultrasound Analysis During Half a Year After Coronary Event: The ESTABLISH Study
Shinya Okazaki, Takayuki Yokoyama, Katsumi Miyauchi, Kazunori Shimada, Takeshi Kurata, Hitoshi Sato and Hiroyuki Daida

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