Early Intervention With Rosuvastatin Decreases the Lipid Components of the Plaque in Acute Coronary Syndrome – Analysis Using Integrated Backscatter IVUS (ELAN Study) –

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Background: It has recently become possible to analyze coronary plaque characteristics by using integrated backscatter intravascular ultrasound (IB-IVUS). The aim of this study was to use this modality to evaluate the impact of early intervention with rosuvastatin on both the volume and tissue characteristics of non-culprit plaques in acute coronary syndrome (ACS).

Methods and Results: Patients with ACS underwent IB-IVUS after percutaneous coronary intervention procedure and were administered rosuvastatin. Follow-up IB-IVUS was recorded 6 months later. We analyzed the changes in plaque burden and tissue characteristics in these patients. Plaque components were classified as calcified, fibrous, and lipid according IB-IVUS. We comprehensively analyzed 20 ACS patients. The low-density lipoprotein-cholesterol levels decreased significantly from 117±34 mg/dl to 73±19 mg/dl (P<0.001) after statin therapy. Comparing the baseline images with the follow-up ones revealed a significant reduction in the plaque burden from 98.4±42.1 mm³/10 mm to 80.2±35.8 mm³/10 mm (P<0.001) and in the lipid volume from 44.1±29.6 mm³/10 mm to 28.6±17.8 mm³/10 mm (P<0.001). With respect to the % lipid volume, the reduction rate at follow-up showed a significant correlation with its baseline value (r=–0.498, P=0.024).

Conclusions: Early intervention with rosuvastatin in ACS patients enabled significant reduction of the non-culprit plaque during 6 months. This regression was mainly due to the decrease in the lipid component of the plaque.

(Circ J 2011; 75: 633–641)

Key Words: Atherosclerosis; IB-IVUS; Plaque; Statins

Large-scale lipid-lowering trials have shown an obvious reduction in adverse cardiovascular events in patients with coronary heart disease (CHD).1–3 More intensive therapy with HMG-CoA reductase inhibitors (statins) was reported to result in a greater reduction in cardiac events.4 Even in follow-up as short as 30 days, early intervention with a statin has shown beneficial effects for patients with acute coronary syndrome (ACS).5 Intravascular ultrasound (IVUS) enables tomographic imaging of the coronary artery, and recent serial IVUS trials with CHD patients have documented decreases in the coronary plaque burden after aggressive lipid-lowering therapy with statins.6,7 Regression of plaque burden is commonly considered to be related to regression or stabilization of coronary atherosclerosis.

Currently, several techniques for tissue characterization of plaque composition have been developed using IVUS imaging. Integrated backscatter (IB) IVUS and virtual histology (VH) IVUS are now commercially available. These techniques allow quantitative detection of plaque components that is comparable to pathohistologic quantification in vivo.8,9 The tissue characteristics of coronary atheroma in various clinical presentations of CHD have been analyzed. Several studies have shown that vulnerable plaques have a larger lipid pool and less fibrous components than stable plaques.10–14 Kawasaki et al have further demonstrated that statin therapy decreased the lipid component of the coronary plaques in patients with stable angina, but a reduction in the plaque volume was not observed.15
There are few data on the relationship between a decrease in plaque burden and the changes in tissue characteristics during aggressive lipid-lowering therapy for CHD, especially ACS. The purpose of the present study was to detect longitudinal changes in plaque volume and components for non-culprit lesions during early lipid-lowering therapy with rosuvastatin in ACS patients. Further, we sought to confirm a reduction in plaque volume accompanied by a depletion of the lipid component.

**Methods**

**Patients and Study Design**

This study was designed as a simple follow-up study in consecutive ACS patients who underwent IVUS observation, including tissue analysis with IB-IVUS, at the end of successful percutaneous coronary intervention (PCI). ACS was defined as unstable angina with severe coronary stenosis accompanied by crescendo chest oppression and acute myocardial infarction, and was diagnosed by an elevation of serum creatine phosphokinase levels (≥2-fold) and positive results for troponin T. Within 48 h of emergency or elective PCI procedure, patients were administered rosuvastatin (2.5 mg/day) regardless of their serum low-density lipoprotein cholesterol (LDL-C) level, and the rosuvastatin dose was increased up to 5.0 mg/day to reach the target level of LDL-C (<100 mg/dl). Patients were examined during scheduled hospital visits every 2 months and LDL-C, high-density lipoprotein cholesterol (HDL-C) and high-sensitivity C-reactive protein (hs-CRP) levels were determined during these visits. Follow-up angiography and IVUS examination, including tissue analysis, were performed 6 months after the initial procedure (Figure 1). Informed consent for the present study was given by each patient. Some were excluded from this trial because of cardiogenic shock, recommendation for coronary artery bypass grafting, side effects of rosuvastatin, and insufficient image quality of serial IVUS. This protocol was approved by the Ethical Review Board on Medical Research of Shinshu University School of Medicine. This study was not supported by any industry.

**PCI Procedure and IVUS Examination**

Before PCI, the patient was premedicated with oral aspirin (200 mg) and ticlopidine (200 mg) or clopidogrel (75 mg or 300 mg), and intravenous heparin (100 U/kg) was administered. In all the patients, coronary stents were successfully implanted in the culprit lesions in a standard manner without distal protection systems. The selection of the deployed stents was at the operator’s discretion. We used a commercially available IVUS system (2.9 F, 40 MHz; Boston Scientific Corp, Natick, MA, USA) with an auto-pullback system (0.5 mm/s). At the end of the PCI procedure, a final IVUS observation was performed to confirm stent expansion and to observe the non-culprit lesions after intracoronary administration of 0.2 mg nitroglycerin. The radiofrequency signal output at every 0.5 mm of the IVUS images was captured simultane-
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IVUS Analysis
IVUS observation of the nearly normal segment was performed by angiography at a distance >5 mm proximal or distal to the implanted stent edges. The most diseased segments more than 10 mm long, as detected by IVUS, were designated as target segments for serial volumetric and tissue analysis. Baseline and follow-up IVUS images were reviewed side by side. The distance from the stent edges and side branches was considered as a reference point for matching the target segments. Quantitative volumetric analysis of IVUS images was performed using a computerized planimetry system (EchoPlaque2; Indec Systems, Mountain View, CA, USA) by an independent experienced observer who was unaware of the clinical data. The areas of the external elastic membrane (EEM), lumen, and plaque were measured in each frame of the IVUS images, and volumetric analysis was performed according to Simpson’s rule. These volumetric parameters were corrected for a longitudinal length of 10 mm (corrected volume, mm$^3$/10 mm) because of the differences in the lengths of the target segments.

For analysis of tissue characterization, IVUS images, including color-coded maps of IB values, were acquired consecutively at 0.5-mm intervals. The internal border of the tunica media (the internal elastic membrane) and intimal reading edge were manually traced using custom software for IB-IVUS, as described in previous studies. In each frame of IB-IVUS, the percent areas of calcified, fibrous (fibrosis + dense fibrosis), and lipid components of atherosclerotic plaques were determined by an independent experienced observer.

Table. Patients’ and Lesion Characteristics

| n (patients) | 20 |
| Age, years   | 70.5±8.9 |
| STEMI, n (%) | 16 (80%) |
| Clinical history, n (%) | |
| Hypertension | 12 (60%) |
| Dyslipidemia | 7 (35%) |
| Diabetes mellitus | 7 (35%) |
| Smoking | 15 (75%) |
| Medications before initial hospitalization, n (%) | |
| Statins | 1 (5%) |
| Medications after PCI procedure, n (%) | |
| Aspirin | 20 (100%) |
| Ticlopidine/clopidogrel | 20 (100%) |
| ACEI/ARB | 16 (80%) |
| β-blockers | 7 (35%) |
| CCB | 6 (30%) |
| OHA | 5 (25%) |
| Insulin | 0 (0%) |
| Length of the target segments | 12.4±4.8 mm |
| LAD | 12 (60%) |
| LCX | 1 (5%) |
| RCA | 7 (35%) |

STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-2 receptor blocker; CCB, calcium-channel blocker; OHA, oral hypoglycemic agent; LAD, left anterior descending; LCX, left circumflex artery; RCA, right coronary artery.

Figure 2. Change in LDL-C and HDL-C levels in each case. LDL-C level showed a significant decrease during the follow up period, but the HDL-C level showed no significant change during statin therapy. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
plaque were analyzed automatically. The average percent area of each component throughout the target segment was calculated and multiplied by the corrected plaque volume (mm\(^3/10\) mm) to estimate the volume of each component. The serial volumetric changes in these components were determined from the baseline and follow-up studies.

**Statistical Analysis**

Statistical analysis was performed using SPSS, version 11.0 for Windows (SPSS Inc, Chicago, IL, USA). Serial changes in continuous variables between baseline and follow-up were assessed using paired Student’s t-test for laboratory and ultrasound parameters. Quantitative data are expressed as mean ± standard deviation. Linear regression analysis was performed to assess the relationship between quantitative plaque characteristics. Differences were considered as significant at P<0.05.

**Results**

**Patients’ and Lesion Characteristics**

From April 2006 to May 2008, 33 ACS patients were prospectively enrolled into the present program. These patients were not consecutive because it was difficult to perform IB-IVUS for ACS patients who attended the hospital during the night or while on holiday. In total, 13 patients dropped out from this study during the follow-up period because of (1) cardiogenic shock (2 patients), (2) discontinuation of rosuvastatin for some reason (4 patients), (3) refusing follow-up IVUS examination (2 patients), and (4) inadequate quality of IVUS images (5 patients) (Figure 1). Finally, we were able to analyze the conventional and IB-IVUS images of 20 patients in this serial analysis, of whom 19 were men (95%). The mean age of the studied patients was 70.5±8.9 years. Follow-up angiography and IVUS examination were performed 6.2±1.2 months after the initial procedure. At initial admission, only 1 patient had received a statin (fluvastatin, 10 mg); however, this patient’s LDL-C level was 180 mg/dl, and his treatment dose was changed to 2.5 mg of rosuvastatin. Other patients had not received any lipid-lowering therapies before their ACS episodes. After PCI, angiotensin-converting enzyme inhibitors or angiotensin 2-receptor blockers were given to 16 (80%), calcium-channel blockers to 6 (30%), and \( \beta \)-blockers to 7 (35%) of the studied patients. The average length of the target segments was 12.4±4.8 mm, and 18 of these segments were located proximal to the stent-delivery sites. The target lesions were located in the left anterior descending artery in 12 patients (60%) (Table).

**Laboratory Outcome**

As expected, the mean LDL-C level decreased from 116.9±33.5 mg/dl at baseline to 73.2±19.3 mg/dl at follow-up; 19 patients (95%) achieved an LDL-C level <100 mg/dl and 10 (50%) patients reached a level <70 mg/dl. The average reduction in LDL-C level was 34.8±18.4% from the baseline. Furthermore, the mean high-sensitivity C-reactive protein level decreased significantly from 6.86±16.03 mg/L to 0.93±0.91 mg/L (P=0.007). The mean HDL-C level showed no significant changes during the therapy (49.7±16.3 mg/dl at baseline, 52.2±16.6 mg/dl at follow-up); however, 14 (70%) patients showed an increase in high-density lipoprotein-cholesterol level (Figure 2).
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Volumetric Analysis of Serial Conventional IVUS Measurements

Figure 3 shows the volumetric analysis of the conventional IVUS measurements at baseline and follow-up. With regard to EEM volume, no significant change was observed during the follow-up period (from 183.0±67.4 mm/10 mm to 176.2±66.0 mm/10 mm; P=0.15). The lumen volume increased significantly from 84.7±30.0 mm/10 mm to 95.6±38.5 mm/10 mm (P=0.02) and the percent change in lumen volume was +12.7±24.7%. Plaque volume decreased significantly from 98.4±42.1 mm/10 mm to 80.2±35.8 mm/10 mm (P<0.001) and the reduction rate was 18.4±13.3%.

Changes in Tissue Characteristics

In all 20 patients, IB-IVUS images were evaluated by 2 observers for interobserver agreement and 95% limits of agreement were determined using the Bland-Altman approach. The mean difference in volume was 0.002±1.58 (mm³), the limits of agreement were –3.1 and +3.1 (mm³), and there was a good correlation between the lipid measurements by the 2 observers (r>0.999, P<0.001). During the follow-up, there were no significant changes in the volume of the calcified (from 1.4±1.3 mm/10 mm to 1.9±1.3 mm/10 mm; P=0.06) or fibrous component (from 52.8±16.8 mm/10 mm to 49.8±19.3 mm/10 mm; P=0.38). On the other hand, the lipid volume showed a significant reduction from 44.1±29.6 mm/10 mm to 28.6±17.8 mm/10 mm (P<0.001) during this period (Figure 4).

Cumulative volumes of each component at baseline and follow-up are shown in Figure 5. Moreover, there was a significant linear correlation between the percent lipid volume at baseline and the rate of reduction of the percent lipid volume during the follow-up (Figure 6A). In contrast,

Figure 4. Volumetric changes in the calcified, fibrous, and lipid components of plaque in each case. During follow-up, there were no significant changes in the volumes of the calcified and fibrous components, but the lipid volume showed a significant reduction.

Figure 5. Volumetric changes in plaque components with stacked column at baseline and follow-up. The decrease in the whole plaque burden during follow-up was mainly due to the reduction in the lipid component.
Figure 6. Correlation between (A) the percent lipid volume at baseline and the rate of reduction of the percent lipid volume and (B) change in the LDL-C level and the rate of reduction of the lipid volume during the follow-up. There was a significant linear correlation between the rate of reduction of the percent lipid volume and its baseline value. On the other hand, no significant correlation was shown between the change in LDL-C level and the rate of reduction of lipid volume. LDL-C, low-density lipoprotein cholesterol.

Figure 7. Serial integrated backscatter intravascular ultrasound images at 0.5 mm intervals from baseline (Upper) and follow-up (Lower). Color-coded maps show the calcified (red), fibrous (yellow and green), and lipid (blue) areas. The remarkable reduction in the lipid component is obvious by visual estimation. LDL-C, low-density lipoprotein cholesterol.
the regression of lipid volume was not associated with the percent reduction in the LDL-C level (Figure 6B). Moreover, none of the other laboratory data correlated with the percent change in plaque volume.

Figure 7 shows representative color-coded IB-IVUS images of the most diseased slices of the target segments. During follow-up, the percent lipid volume decreased and the remarkable reduction in the lipid component was obvious by visual estimation. In this case, regression of the plaque burden accompanying the reduction in the lipid component was observed after rosuvastatin therapy.

**Discussion**

The present study demonstrated a significant simultaneous reduction in plaque volume and lipid component in the non-culprit segments of ACS patients after rosuvastatin therapy. The obvious change in the cumulative volumes of each component showed that the decrease in whole plaque burden during follow-up was mainly due to the reduction in the lipid component. Moreover, these changes were remarkable in lipid-rich plaques during a relatively short period such as 6 months.

Mega-trials of lipid-lowering therapy have reported a decrease in cardiovascular events in CHD patients. The endpoints of these trials included revascularization of coronary arteries, ACS events, including acute myocardial infarction, and cardiovascular death. Therefore, lipid-lowering therapy seems to have a 2-pronged effect: retardation of luminal narrowing caused by increasing plaque burden, and inhibition of the growth or rupture of vulnerable atheroma.

Trials of serial IVUS examination of stable CHD patients have documented that lipid-lowering therapy inhibited increasing plaque volume in vivo. Moreover, the ASTEROID and COSMOS trials have recently showed that intensive statin therapy significantly decreased the average plaque volume in stable coronary plaques. The decrease in plaque burden is thought to be associated with plaque stabilization, even in patients with stable angina. However, changes in plaque burden should be related primarily to the degree of coronary stenosis and not directly to plaque vulnerability. To ascertain this relationship, serial analysis of plaque volume, as well as tissue characterization, of lipid-rich plaque or vulnerable plaque is necessary during aggressive lipid-lowering therapy.

Techniques for the tissue characterization of plaque using IVUS signals (i.e., IB-IVUS and VH-IVUS) have been developed and recently become commercially available. With these modalities, plaque composition in various clinical presentations can be compared among several investigators. Researchers using VH-IVUS have reported that vulnerable plaque has a larger necrotic core than stable plaque, and with IB-IVUS, it has been documented that a larger lipid component is present in patients with ACS lesions than in those with stable angina. With respect to serial observation of tissue characteristics, Schartl et al used conventional IVUS during statin therapy and reported changes in plaque echogenicity, although they did not observe a simultaneous reduction in the plaque burden.

ACS is considered to be a thrombotic event in coronary artery disease, and is caused by rupture or erosion of vulnerable plaque. Pathologic and angioscopic observations of ACS patients have revealed multiple vulnerable plaques other than the culprit lesion in their coronary arteries, some appearing to be nearly ruptured and others with an already ruptured morphology. Early intervention with statins for ACS patients resulted in a decrease in adverse cardiovascular events within 16 weeks in the MIRACL trial and within 30 days in the PROVE IT-TIMI 22 trial. Aggressive statin therapy in ACS patients may stabilize vulnerable plaques, including the culprit and non-culprit lesions, during a short time period. Using serial IVUS in ACS patients, the ESTABLISH trial showed that early intervention with a statin induced a reduction in plaque volume (13.1% decrease during 6 months) in the non-culprit lesions, but simultaneous analysis of tissue characteristics was not performed. A longitudinal study using magnetic resonance imaging has also documented regression of coronary plaques in ACS patients after 6 months of statin therapy. By using coronary angiography and IVUS, Hirayama et al have demonstrated simultaneous early loss of the yellow color in plaques and reduction in the plaque burden (~17.8% during 80 weeks) with aggressive statin therapy. The recent JAPAN-ACS study has shown a relatively large regression in plaque volume in ACS patients (~16.3% and ~18.1% in the pitavastatin and atorvastatin groups, respectively). Using VH-IVUS, Toi et al reported a reduction in plaque burden and the fibrofatty component in ACS patients after statin therapy. We also documented a decrease in plaque volume accompanied by depletion of the lipid component according to IB-IVUS in ACS patients. Our results are consistent with earlier trials of early intervention with statins for ACS patients, and may confirm the relationship between reducing plaque volume and stabilizing vulnerable atheroma after statin therapy.

In our results, the more lipid-rich the plaque, the greater the tendency to depletion of the lipid component during lipid-lowering therapy. Heterogeneous vascular responses to statin therapy were observed in the target segments, a phenomenon that might be explained by differences in patient characteristics, including coronary risk factors and differences in the characteristics of the lesions in the target segments. In the clinical setting, several atheromas are usually observed in the culprit and non-culprit coronary arteries of ACS patients, and not all of them have the simple morphology of de novo vulnerable plaque. A pathological study of patients suffering from sudden coronary death has documented that previously ruptured atheromas were overlaid with fibrous tissue and multiple layering within the plaques was frequently observed in the coronary arteries. In the present study, some of the target segments may have contained these complex layered structures, and therefore the response to statin therapy would be different in each case.

Furthermore, the percent reduction in either the whole plaque or lipid volume of the plaque did not correlate with the percent reduction in the LDL-C level. Interestingly, no relationship between the rate of reduction of LDL-C and of plaque volume was also reported in the JAPAN-ACS and COSMOS trials. These consistent findings suggest that in the present study the reduction in plaque volume was not dependent on the reduction in the LDL-C level, but was mediated by other beneficial effects of rosuvastatin and the properties of each plaque at baseline.

**Study Limitations**

This study had only 20 patients and no control group. In earlier studies of serial IVUS observation, progression of plaque volume has been detected in control groups not given statin and in groups administered moderate lipid-lowering therapy. Due to ethical issues, it has recently been difficult to set up a control group who are not administered lipid-lowering therapy after ACS. And it was relatively hard work to...
match serial IVUS images of adequate quality and enough volume, including IB-IVUS, in cases of emergency ACS. The follow-up period of only 6 months may not be sufficient to conclude the long-term effect of statin therapy for ACS patients. Therefore, long-term and large-scale randomized studies are needed to confirm our results. With regard to tissue characterization, it is difficult to deny completely the existence of thrombus attached to the walls of the target segments, which would considerably impact our results for tissue characterization by IB-IVUS. For analysis in the present study, we selected coronary segments that had almost normal findings during angiography after PCI and that were more than 5 mm from the stent’s edges. Therefore, we believe that thrombus of the vascular wall would have had little effect on our results.

The vessel size at the distal segment of the culprit lesion can be underestimated in the acute phase of ACS, because less blood flow and increased vessel tonus can reduce it. Although similar results were observed for both the proximal and distal segments in this study, analyses of the distal segments should be carefully performed with close attention to initial vessel size.

Just after the PCI procedure, the study patients started rosuvastatin (2.5 mg/day) and other medicines such as antiplatelet drugs, calcium antagonists, angiotensin-converting enzyme inhibitors, and \( \beta \)-blockers. Administration of these drugs may comprehensively affect the stabilization of coronary plaques in ACS patients.

**Conclusion**

The present study demonstrated a reduction in the volume of non-culprit lesions in ACS patients after 6 months of statin therapy. The decrease in plaque burden during follow-up consisted mainly of a reduction in the lipid component, as estimated using IB-IVUS. Our results may have confirmed the relationship between the decrease in plaque volume and depletion of the lipid component, and we have documented the stabilizing effects of early intervention with statins on vulnerable plaques in ACS patients.

**References**


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