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The Effect of Lipid and Inflammatory Profiles on the Morphological Changes of Lipid-Rich Plaques in Patients With Non–ST-Segment Elevated Acute Coronary Syndrome

Follow-Up Study by Optical Coherence Tomography and Intravascular Ultrasound

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Objectives The aim of this study was to determine the relationship between the morphological changes of nonculprit lipid-rich plaques and several clinical profiles in patients with non–ST-segment elevated acute coronary syndrome (NSTEACS).

Background Identification of coronary lesion with morphological characteristics of rupture-prone plaques is still difficult.

Methods Eighty-two consecutive patients with NSTEACS who underwent percutaneous coronary intervention were enrolled. The changes in total atheroma volume (TAV) of residual nonculprit lipid-rich plaques and the changes in the corresponding fibrous cap thickness (FCT) were assessed by intravascular ultrasound and optical coherence tomography, respectively, at baseline and after 9 months.

Results The percentage changes in TAV (mm^3) of lipid-rich plaques and in the corresponding FCT (μm) over the 9-month follow-up period were 3.1 ± 11% and 15 ± 17%, respectively. There was no significant correlation between the changes in TAV and those in FCT. The change in TAV showed a significant correlation with reduction of the low-density lipoprotein/high-density lipoprotein (LDL/HDL) ratio ($r = 0.42$, $p < 0.01$). In contrast, the change in FCT showed no correlation with LDL/HDL ratio but had a significant positive correlation with changes in high-sensitivity C-reactive protein ($r = 0.44$, $p < 0.01$). Furthermore, in multivariate logistic analysis, statin use was an independent predictor of changes in well-stabilized plaques that showed both TAV reduction and FCT increase.

Conclusions The changes in TAV and FCT of coronary plaques over a 9-month observation period were related to 2 different independent factors (i.e., reduction of LDL-cholesterol and high-sensitivity C-reactive protein, respectively). Furthermore, lipid-lowering therapy with statin has the potential to stabilize these parameters by both plaque reduction and FCT. (J Am Coll Cardiol Intv 2010;3:766–72)

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The vulnerability of coronary plaques has been implicated in the pathogenesis of acute coronary syndrome. Plaques prone to rupture are characterized by a large necrotic core and a thin fibrous cap with macrophage infiltration into the cap (1,2). In the clinical setting, monitoring atheroma volume changes with serial intravascular ultrasound (IVUS) has been used to characterize the natural history of atherosclerosis and the effects of antiatherosclerotic therapeutic strategies (3–5).

Recently, intravascular optical coherence tomography (OCT) has been proposed as a high-resolution imaging method for plaque characterization. Optical coherence tomography might allow us to evaluate the micro structural characteristics of coronary plaques, including the fibrous cap thickness (FCT) in vitro and in vivo (6). The OCT and corresponding histological findings in postmortem studies showed good correlations regarding FCT, which is thought to be a major factor in the assessment of plaque vulnerability as well as the atherosclerotic plaque burden (7).

Analysis of lipid-rich plaques with both OCT and IVUS indicated that large lipid-rich plaques are not always sealed with a thin fibrous cap. Statin is believed to contribute to secondary prevention of cardiovascular events by reducing low-density lipoprotein (LDL) levels followed by regression of lipid-rich plaque. In addition, statin has been reported to significantly reduce the incidence of major cardiovascular events, even in subjects with normal cholesterol levels, with elevated high-sensitivity C-reactive protein (hs-CRP) (8). Therefore, we hypothesized that lipid profile and hs-CRP reflect different mechanisms of stabilization of vulnerable plaques.

In this study, the 9-month serial change of mild to moderate coronary atheroma was analyzed in patients with non–ST-segment elevated acute coronary syndrome (NSTEACS) with serial IVUS and OCT. We compared changes in total atheroma volume (TAV) and FCT of the plaques, both of which are thought to be the major factors influencing plaque vulnerability, in relation to hs-CRP and serum lipids. Furthermore, we also examined which factors have the potential to stabilize lipid-rich plaques.

Methods

Study population. The study population was drawn from 160 consecutive NSTEACS patients admitted to Wakayama Medical University Hospital between January 2006 and November 2007. Subjects who had significant left main coronary artery disease (n = 3), congestive heart failure (n = 6), renal insufficiency with baseline serum creatinine >1.5 mg/dl (n = 8), or previous or current use of lipid-lowering therapy (n = 12) were excluded. The IVUS and OCT studies of entire culprit vessels were performed in a residual 110 patients with NSTEACS. Of 110 patients, 82 who gave consent to undergo follow-up study by both IVUS and OCT were enrolled in this study.

Clinical and biochemical parameters. Blood samples were collected at baseline (at the day of discharge) and at the end of the 9-month follow-up period from all subjects. The criteria for several coronary risk factors at baseline were defined as follows: hypertension: blood pressure >140/90 mm Hg or a history antihypertensive drug prescription; diabetes mellitus: fasting plasma glucose >126 mg/dl, and casual plasma glucose >200 mg/dl; and hyperlipidemia: total cholesterol level >220 mg/dl or triglyceride >150 mg/dl. Percentage change of each parameters (LDL, HDL, LDL/HDL, hs-CRP) was calculated as: (follow-up − baseline)/baseline.

This protocol was approved by the Wakayama Medical University Ethics Committee, and all patients provided informed consent before initial coronary angiography.

Baseline catheterization. Oral aspirin (162 mg) and intravenous heparin (100 U/kg) were administered before percutaneous coronary intervention (PCI). Cardiac catheterization was performed via the femoral approach with a 6-F sheath and catheters. The culprit lesion was identified on the basis of coronary angiography findings as well as those of electrocardiography and echocardiography. After PCI for the culprit lesion of acute coronary syndromes, IVUS and OCT examinations of the target vessels were performed entirely. The target plaques in this study were lipid-rich plaques with a fibrous cap of various thickness, which were angiographically mild or moderate lesions (30% to 70% stenosis) located >10 mm from the culprit site of NSTEACS. When more than 2 plaques were recognized in 1 vessel, those with the thinnest fibrous cap were selected as target plaques in this study. After a 9-month follow-up period, IVUS and OCT examinations were performed after coronary angiography. The operator placed each IVUS and OCT catheter in the vessel originally investigated and positioned it distal to the target plaque, which was carefully identified on the basis of the distance from the reproducible landmarks such as major branches, spotty calcification, side vein, and stent edge.

An automatic pullback was repeated under conditions identical to those in the baseline study. Interobserver and intraobserver variabilities of IVUS and OCT analyses were assessed by the evaluation of all images by 2 independent

Abbreviations and Acronyms

CI = confidence interval
FCT = fibrous-cap thickness
HDL = high-density lipoprotein
hs-CRP = high-sensitivity C-reactive protein
IVUS = intravascular ultrasound
LDL = low-density lipoprotein
NSTEACS = non–ST-segment elevated acute coronary syndrome
OCT = optical coherence tomography
OR = odds ratio
PCI = percutaneous coronary intervention
TAV = total atheroma volume

investigators and by the same reader at 2 separate time points, respectively.

OCT examination and analysis. Intravascular OCT imaging was performed according to the previous description (6). Briefly, after administration of 100 to 300 μg of intracoronary nitroglycerin, a 0.016-inch OCT catheter (ImageWire, LightLab Imaging, Inc., Westford, Massachusetts) was advanced through a 3-F occlusion balloon catheter to the distal site of the culprit branch.

The OCT images were analyzed with proprietary offline software provided by LightLab Imaging, Inc. The targets were initially defined as lipid-rich plaques, which were observed as plaques with lipid in 2 or more quadrants (9,10) and with a recognizable image of a fibrous cap on OCT analysis. The FCT of each lipid-rich plaque was defined as the minimum distance from the coronary artery lumen to the inner border of the necrotic core.

IVUS examination and analysis. After re-administration of 100 to 300 μg of intracoronary nitroglycerin, a 2.9-F 20-MHz IVUS catheter (Eagle-Eye, Volcano Therapeutics, Inc., Rancho Cordova, California) was inserted >10 mm distal to the target plaque decided by OCT examination and subsequently pulled back with a motorized pullback system at a rate of 0.5 mm/s. It was confirmed that the target plaque was identical to that for which FCT was measured by OCT. The TAV was calculated as: Σ (EEM_{CSA} − $LUMEN_{CSA}$), where EEM_{CSA} is the external elastic membrane cross-sectional area and $LUMEN_{CSA}$ is the luminal cross sectional area in the most diseased 10-mm segment with the largest plaque at each baseline and follow-up period. The percentage change in TAV was defined as: (follow-up − baseline TAV)/baseline TAV.

Statistical analysis. Statistical analysis was performed with StatView, version 5.0.1 (SAS Institute, Cary, North Carolina). Continuous variables are shown as mean ± SD. Comparison between baseline and follow-up was performed with the paired *t* test. Correlation between continuous variables was estimated with Pearson correlation coefficient. A value of $p < 0.05$ was considered statistically significant. A multivariate logistic analysis was used to determine the significant factors indicating the "well-stabilized plaque." After univariate screening, any candidate variables with a value of $p < 0.10$ were entered into a multivariate model that then identified independent predictors of outcome defined by a multivariate value of $p < 0.05$.

Results

Clinical characteristics. A total of 82 plaques (82 patients) were evaluated with OCT and IVUS at baseline and at 9-month follow-up. Patients with NSTEACS were treated with antithrombotic therapy and underwent PCI within 48 h of admission. Baseline clinical characteristics and concomitant medical therapy during the 9-month follow-up period are also listed in Table 1. The mean LDL/HDL ratio was 2.6 ± 0.8, and 58 patients (71%) received statins during the follow-up period.

Table 1. Baseline Characteristics of 82 Patients

Age, yrs	66 ± 14
Male	62 (76)
Cardiovascular factors	
Prior CAD	8 (10)
Hypertension	61 (76)
Diabetes	18 (23)
Dyslipidemia	62 (75)
Smoker	22 (28)
Culprit vessel	
LAD	50 (61)
LCX	10 (12)
RCA	22 (27)
Therapy during 9 months	
Aspirin	82 (100)
ACE inhibitor or ARB	73 (89)
Beta blocker	74 (90)
Statin	58 (71)
Nitrates	25 (30)

Values are n (%) or mean ± SD.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCX = left circumflex artery; RCA = right coronary artery.

Changes in plaque morphology. There were no procedure-related complications associated with the use of IVUS or OCT.

Figure 1 shows representative IVUS and OCT images obtained at the same position near a major side branch in NSTEACS patients with statin treatment during the 9-month follow-up period. Slight regression of plaque burden was observed by IVUS from 63.4 mm^3 at baseline to 60.4 mm^3 at the 9-month follow-up. Furthermore, OCT revealed a significant increase in FCT at 9 months (310 μm) in comparison with the baseline value (90 μm).

The serial changes in plaque burden assessed by IVUS and changes in FCT assessed by OCT are shown in Table 2. The TAV did not change significantly (74 ± 44 mm^3 to 76 ± 45 mm^3, p = NS) during the 9-month follow-up, although the FCT increased significantly (95 ± 32 μm to 112 ± 45 μm, $p < 0.05$).

Correlation between plaque morphology and laboratory outcomes. Figure 2 shows that there was no significant correlation between the change in TAV assessed by IVUS and the change in FCT assessed by OCT ($r = 0.14$, $p = 0.62$). The change in TAV was significantly correlated with the change in LDL/HDL ratio ($r = 0.42$, $p < 0.01$), although no correlation was observed with change in hs-CRP ($r = 0.22$, $p = 0.06$). In contrast, change in FCT was significantly correlated with the change in hs-CRP ($r = 0.44$, $p < 0.01$) but not with that in LDL/HDL ratio (r =

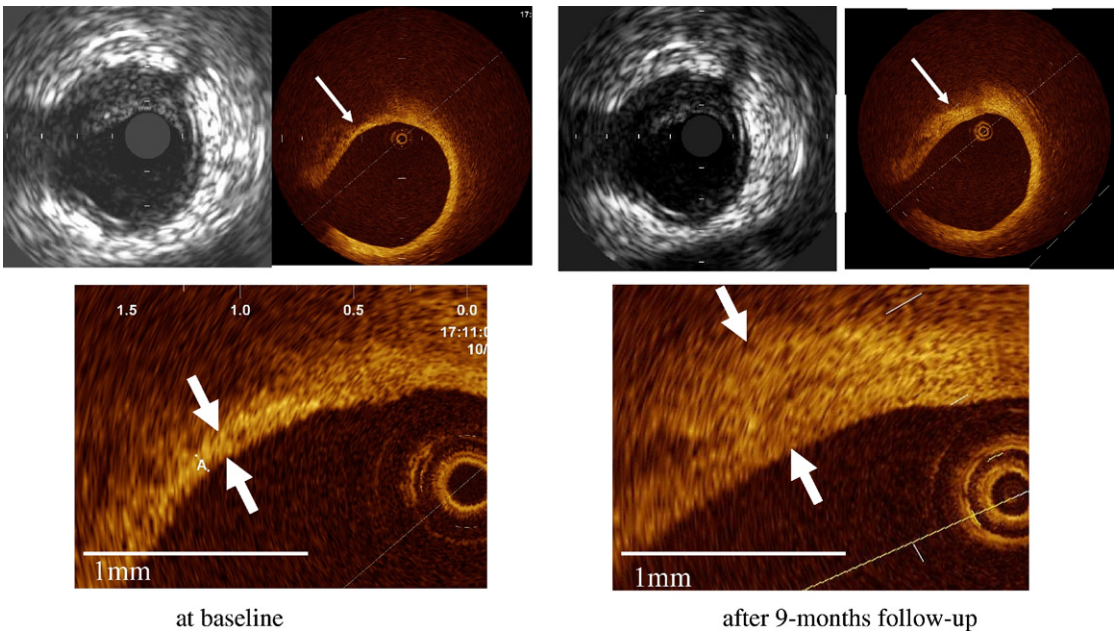

Figure 1. Representative Case of Well-Stabilized Plaques

The **left 3 panels** illustrate the appearance of the same cross-section with intravascular ultrasound and optical coherence tomography at baseline, whereas the **right 3 panels** show the same cross-section after 9-month follow-up periods. Atheroma volume was reduced from 63.2 mm^3 to 60.9 mm^3, and the thickness of fibrous cap was increased from 90 to 310 μm; **arrows** delineate the fibrous cap.

0.08, p = 0.31) (Fig. 3). Meanwhile, absolute values (LDL, HDL, hs-CRP) at both baseline and follow-up could not have any association with the change in plaque morphology (data not shown).

Predictors of well-stabilized plaques. Plaques with both a decrease in TAV and increase in FCT at the 9-month follow-up were defined as well-stabilized plaques, and the present study included 31 such plaques (39%). The results of univariate logistic regression analysis indicated that hypertension (odds ratio [OR]: 0.43; 95% confidence interval [CI]: 0.17 to 1.1, p = 0.075) and diabetes mellitus (OR: 0.36; 95% CI: 0.14 to 0.97, p = 0.042) were negative predictive factors and statin use during the 9-month follow-up period (OR: 4.6; 95% CI: 1.7 to 13, p = 0.0033) was a positive predictor of "well-stabilized plaque." Multivariate logistic regression analysis demonstrated that statin-use (OR: 3.5; 95% CI: 1.1 to 11, p = 0.032) was an independent predictive factor of "well-stabilized plaque."

Discussion

In the present study, we investigated the morphological factors involved in stabilizing lipid-rich plaque. The results presented here indicate that the changes in FCT and lipid-rich plaque volume were determined by different factors (i.e., changes in hs-CRP and in LDL/HDL, respectively). Furthermore, administration of statin was confirmed to be a suitable form of therapy to stabilize vulnerable

Table 2. Lipid, Inflammatory Marker, and Morphological Profile Compared at Baseline and After 9-Month Follow-Up Period

	Baseline	Follow-Up	Percentage Change	p Value
LDL (mg/dl)	122 ± 38	103 ± 21	−16 ± 4	<0.010
HDL (mg/dl)	44 ± 10	45 ± 11	2.0 ± 0.8	0.087
LDL/HDL	2.6 ± 0.8	2.1 ± 0.8	−12 ± 20	0.032
hs-CRP (mg/dl)	0.72 ± 2.64	0.60 ± 2.52	−16 ± 24	0.010
Total atheroma volume (mm^3)	74 ± 44	76 ± 45	3.1 ± 11	0.120
Fibrous cap thickness (μm)	95 ± 32	112 ± 45	15 ± 17	<0.001

Values presented as mean ± SD unless otherwise indicated.
HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein.

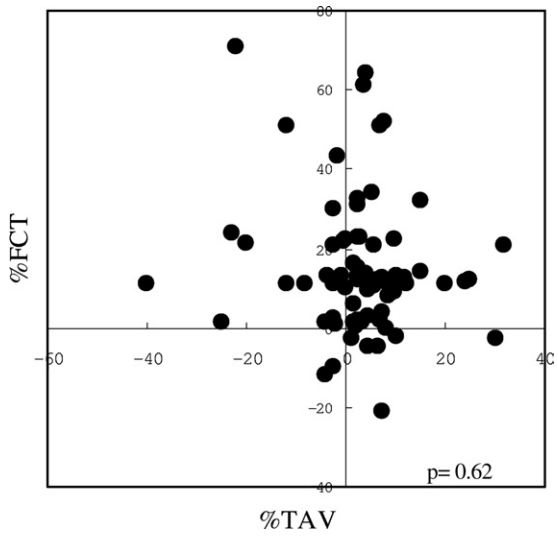

Figure 2. Correlation Between Percentage Change of FCT and TAV

The change in total atheroma volume (TAV) assessed by intravascular ultrasound and the change in fibrous cap thickness (FCT) assessed by optical coherence tomography had no correlation with each other ($r = 0.14$, $p = 0.62$).

lipid-rich plaques in terms of morphological assessment (Table 3).

There has been a great deal of research interest regarding the relationships among lipids, inflammation, and their effects on the arterial wall (11). Intravascular ultrasound has been used clinically as a representative imaging modality to evaluate the coronary arterial wall and plaque morphology, including quantification of plaque burden, but it is not possible to determine the thickness of the cap with this method, due to its poor resolution. In contrast, the high resolution of OCT makes it an ideal imaging modality for microstructural evaluation, such as determination of FCT (12,13), although this method is not suitable for evaluation of plaque burden due to its poor penetration depth. Therefore, assessment with a combination of both IVUS and OCT has the potential to allow detailed assessment of changes in plaque morphology.

The pathological features of the most common form of vulnerable plaque include a large lipid pool within the plaque, a thin fibrous cap, and macrophage accumulation within the cap, resulting in the expression of a proteolytic enzyme that weakens the fibrous cap and ultimately promotes plaque disruption (14). The ideal changes from vulnerable to stable plaque are an increase in FCT and a decrease in TAV. Pathological studies have also shown that ruptured plaques contain a large lipid core underlying a thin fibrous cap poor in smooth muscle cells and collagen (15). Especially, collagen is believed to be the main component of the fibrous cap responsible for its tensile strength (16). One of the main factors responsible for triggering of most acute coronary events seems to be the balance between collagen production and degradation (17).

Nabata et al. (18) reported that CRP directly mediates production of matrix metalloproteinase-9, which destroys collagen through induction of tumor necrosis factor-alpha and interleukin-1-beta in vitro, suggesting an active role of CRP in destabilization of the fibrous cap leading to progression of plaque rupture.

The results of the present study indicated that changes in FCT are not correlated with changes in LDL-C but with changes in hs-CRP, which is consistent with the in vitro results of Nabata et al. (18). In contrast, Nissen et al. (3) proposed that the decrease in CRP level was independently and significantly correlated with plaque progression after adjustment for reduction of these lipid levels. Although this did not agree with our observations, the whole population in their study received moderate or intensive statin treatment, in contrast to the rate of 71% of patients in the present study. The relationship between changes in CRP and TAV observed in the REVERSAL (REVERSing Atherosclerosis with Aggressive Lipid Lowering) study was not found when the data were combined with those of the ACTIVATE (ACAT IntraVascular Atherosclerosis Treatment Evaluation) study, in which statin therapy was not an active experimental therapy (19).

In the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) study of 3,745 patients with acute coronary syndromes, Ridker et al. (20) reported that those with LDL-C <70 mg/dl or CRP <2 mg/l after statin therapy had a lower rate of recurrent coronary events, compared with those with LDL-C or CRP that remained higher than these levels. Furthermore, rosuvastatin significantly reduced the incidence of major cardiovascular events even in healthy subjects without hyperlipidemia but with elevated hs-CRP (21). In the present study, we found that statin therapy was an independent predictive factor of plaques that have caused both plaque reduction and fibrous cap thickening involved in stabilizing lipid-rich plaque. Therefore, it is reasonable to assume that the results of the present study might be relevant to the mechanism by which statin therapy reduces the rate of recurrent coronary events even in patients without hyperlipidemia.

Study limitations. First, the study population was relatively small, and the possibility of selection bias cannot be excluded, although consecutive subjects who were eligible and consented to participate in the study were selected. High-risk patients, such as those with cardiogenic shock and fatal arrhythmia, were excluded, because the observations with OCT required balloon occlusion of the coronary flow and flushing with lactated Ringer's solution to avoid red blood cell interference to allow visualization of the vessel wall.

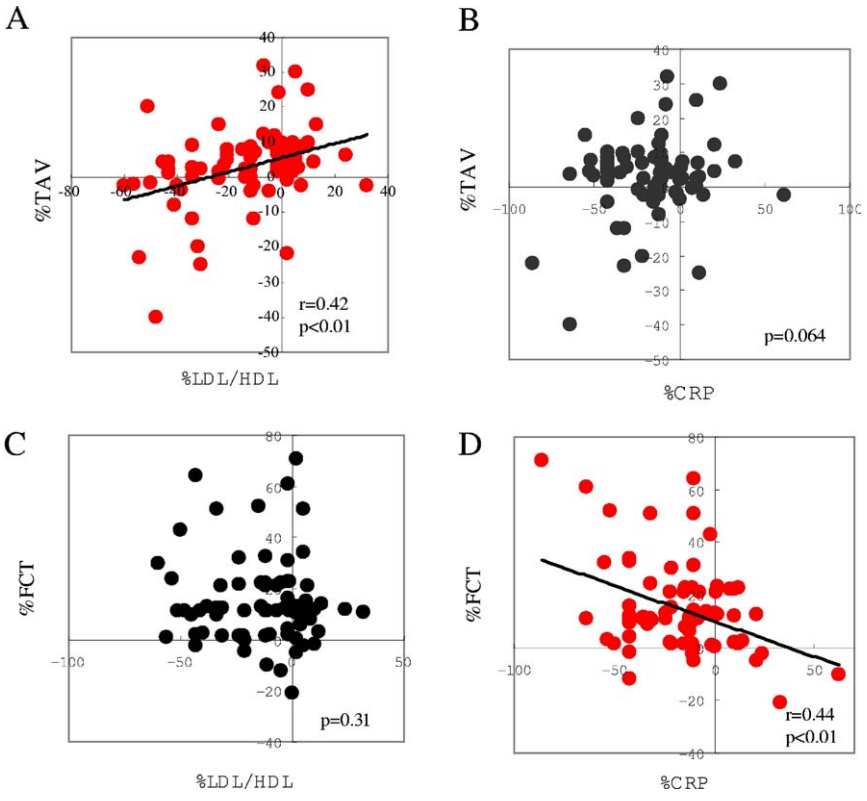

Figure 3. The Correlation Between the Lipid Profile and Percentage Change of FCT and TAV

Scatter plots of **(A)** % total atheroma volume (TAV) to % low-density lipoprotein/high-density lipoprotein (LDL/HDL), **(B)** %TAV to % C-reactive protein (CRP), **(C)** % fibrous-cap thickness (FCT) to %LDL/HDL, and **(D)** %FCT to %CRP. Pearson's correlation coefficient (r) and the p value are depicted in the insert.

Furthermore, we assessed the change of only 1 plaque morphology in a culprit vessel in this study, because it requires repeated balloon occlusion and much greater amount of lactate Ringer's solution for the assessment of the multiple plaques in 3-vessel coronary trees. In the near future, a new-generation OCT system (frequency-domain OCT), which needs no occlusion balloon and less flush with its faster pullback speed, will be expected to assess the natural course of all coronary plaques in entire coronary trees.

Second, this study was a cross-sectional study and thus could not assess the question of whether the change of plaque morphology holds great significance in clinical settings. Future longitudinal and prospective studies are needed to determine whether the change of plaque morphology is relevant to the risk of future cardiovascular events in our subjects.

Third, the percentage of subjects who were prescribed statins in this study was 71%, which might be small compared with prescription rates worldwide. In Japan, the prescribed

Table 3. Univariate and Multivariate Logistic Regression Analyses as Predictors of Well-Stabilized Plaques

	Univariate Analysis OR (95% CI)	p Value	Multivariate Analysis OR (95% CI)	p Value
Age, yrs	0.98 (0.93–1.04)	0.60	—	—
Sex	1.6 (0.46–5.4)	0.47	—	—
Hyperlipidemia	0.91 (0.33–2.5)	0.86	—	—
Hypertension	0.43 (0.17–1.1)	0.075	0.58 (0.21–1.6)	0.300
Diabetes mellitus	0.36 (0.14–0.97)	0.042	0.68 (0.22–2.1)	0.500
Statin	4.6 (1.7–13.0)	0.0033	3.5 (1.1–11.0)	0.032

The plaques that both the total atheroma volume decreased and the fibrous cap thickness increased were defined as a "well-stabilized plaque."
CI = confidence interval; OR = odds ratio.

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initiation of statins was recommended for patients whose LDL-cholesterol was below 100 mg/dl according to the guidelines published by the Japan Atherosclerosis Society (22).

Lastly, we used only the hs-CRP level in the peripheral blood as the main proinflammatory biomarker, although other biomarkers such as interleukin-6 and lipoprotein-associated phospholipase A2 might affect plaque morphology.

Conclusions

The changes in atheroma volume and FCT were related to different independent factors involved in stabilizing lipid-rich plaques (i.e., changes in LDL/HDL and hs-CRP, respectively). Furthermore, statin treatment seems to be a suitable form of therapy for stabilizing vulnerable plaques by both decreasing the amount of lipid-rich plaque and increasing the FCT.

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