Role of the Low-Density Lipoprotein-Cholesterol/High-Density Lipoprotein-Cholesterol Ratio in Predicting Serial Changes in the Lipid Component of Coronary Plaque

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Background: The lipid component of coronary plaques is associated with their vulnerability. The aim of this study was to investigate which coronary risk factors were relevant in predicting serial changes in the lipid component of coronary plaques as evaluated by integrated backscatter intravascular ultrasound (IB-IVUS).

Methods and Results: We enrolled 104 patients who underwent IB-IVUS-guided percutaneous coronary intervention (PCI) and were followed up with repeat IB-IVUS 6 months later. We investigated the serial changes in the plasma lipoprotein levels and the percentage of the lipid component of coronary plaques on IB-IVUS. In the multivariate linear regression analysis, the low-density lipoprotein-cholesterol/high-density lipoprotein-cholesterol (L/H) ratio independently had a significant fixed effect with the percentage of the lipid component of coronary plaques at the time of PCI. In addition, the change in the L/H ratio at the 6-month follow-up was significantly associated with that in the lipid component of coronary plaques (regression coefficient, 9.645; 95% CI: 5.814–13.475; P<0.0001); furthermore, this change was also observed in patients with an LDL-C <100 mg/dL.

Conclusions: The L/H ratio was the most relevant parameter in predicting the lipid component of coronary plaques. Furthermore, strict management of the L/H ratio may reduce this lipid component, even in patients with an LDL-C <100 mg/dL.

Key Words: Hypercholesterolemia; Intravascular ultrasound; Lipoproteins; Vulnerable plaque

In the past decade, cardiovascular disease (CVD) has emerged as the leading cause of death worldwide. Most cases of acute coronary syndrome (ACS), which is one of the most traumatic events in CVD, are triggered by the rupture of a vulnerable plaque followed by thrombosis formation at the rupture site.1,2 Vulnerable plaques are characterized by a large, lipid-enriched necrotic core overlaid with a thin fibrous cap.3 Pathological studies have revealed that the size of the lipid component of coronary plaques is strongly associated with their vulnerability.4,5 Integrated backscatter intravascular ultrasound (IB-IVUS) is capable of assessing the lipid component of coronary plaques and can evaluate serial changes in the lipid component during drug interventions.5,6,7

There are many risk factors for the development of CVD; hypertension, dyslipidemia, diabetes, obesity, and cigarette smoking are traditional systemic risk factors,8 and the low-density lipoprotein-cholesterol (LDL-C) level is a well-established molecular risk factor.8 A meta-analysis of 4 randomized trials using conventional IVUS revealed that a decrease in both the LDL-C level and the LDL-C/high-density lipoprotein-cholesterol (HDL-C) ratio (L/H ratio) after statin treatment was associated with regression of the total atheroma volume in patients with CVD.9,10 Although the lipid component of coronary plaques as evaluated by IB-IVUS more precisely reflects the vulnerability of coronary plaques and predicts clinical outcomes compared with evaluation of the atheroma volume using conventional IVUS,7,11 it has not been determined which coronary risk factors are associated with the serial changes in the lipid component of coronary plaques evaluated by IB-IVUS. Accordingly, we sought to investigate this in the...
Definitions
The demographic and clinical data, including age, sex, body mass index (BMI), coronary risk factors (hypertension, diabetes, and smoking history), blood parameters (LDL-C calculated using direct methods, HDL-C, total cholesterol [TC], triglycerides [TG], hemoglobin A1c [HbA1c], and C-reactive protein [CRP, calculated using the Schwartz formula]), and medication use were retrospectively collected from the institution’s database. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, and/or an active regimen of oral antihypertensive drugs. Diabetes mellitus was confirmed if patients had an HbA1c level ≥6.5%, a history of any antihyperglycemic medication or a previous diagnosis of diabetes.

Measurement of Conventional and IB-IVUS Parameters
Several previous reports have already established the reliability and utility of IB-IVUS.7,9,14,15 To prevent coronary spasm, we administered an optimal dose of intracoronary isosorbide dinitrate before obtaining the measurements. The catheter was attached to an IVUS imaging system (VISIWAVE, Terumo, Japan) with automatic pullback at 0.5 mm/s. Candidate plaques for imaging were selected from the proximal site of the main branch where the last 5 mm from the stent edge was excluded. Imaging was performed at the site of the same lesion 6 months after PCI. For the purpose of minimizing measurement errors, data collection from both conventional IVUS and IB-IVUS was performed by a single skilled medical engineer. A total of 10 cross-sectional images precisely spaced 0.5 mm apart were selected for measurement. The leading edge of the lumen and the external elastic membrane were traced using manual planimetry and the plaque area was defined as the area between these leading edges. Because the cross-sectional images were obtained at 0.5-mm intervals, the total plaque volume (TPV) could be calculated using the Simpson method.
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<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (n=104)</th>
<th>Patients with LDL-C &lt;100 mg/dL at Baseline and 6-Month Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total-C (mg/dL)</td>
<td>186.0±40.6</td>
<td>156.1±42.8</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>110.7±33.9</td>
<td>82.2±14.0</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>50.5±15.4</td>
<td>47.0±12.4</td>
</tr>
<tr>
<td>L/H ratio</td>
<td>2.3±0.8</td>
<td>1.8±0.5</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>135.5±36.3</td>
<td>109.1±21.2</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>135.0±69.8</td>
<td>141.8±73.0</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.1±1.2</td>
<td>6.1±1.1</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.23±0.49</td>
<td>0.32±0.71</td>
</tr>
<tr>
<td>Conventional IVUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total vessel volume (mm³)</td>
<td>78.0±23.2</td>
<td>74.3±21.5</td>
</tr>
<tr>
<td>Total lumen volume (mm³)</td>
<td>43.3±20.3</td>
<td>38.1±18.8</td>
</tr>
<tr>
<td>TPV (mm³)</td>
<td>34.7±11.2</td>
<td>36.3±10.5</td>
</tr>
<tr>
<td>Plaque burden (%)</td>
<td>46.5±14.7</td>
<td>51.1±15.2</td>
</tr>
<tr>
<td>IB-IVUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLV (mm³)</td>
<td>9.5±5.4</td>
<td>9.0±5.3</td>
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<tr>
<td>Percentage of lipid volume (%)</td>
<td>26.5±11.8</td>
<td>23.8±11.2</td>
</tr>
<tr>
<td>TFV (mm³)</td>
<td>23.7±7.8</td>
<td>25.1±7.3</td>
</tr>
<tr>
<td>Percentage of fibrous volume (%)</td>
<td>67.6±9.6</td>
<td>70.1±9.2</td>
</tr>
</tbody>
</table>

Data are expressed as mean±standard deviation or number (%). CRP, C-reactive protein; HDL-C, high-density lipoprotein-cholesterol; IB, integrated backscatter; IVUS, intravascular ultrasound; LDL-C, low-density lipoprotein-cholesterol; L/H ratio, LDL-C/HDL-C ratio; TC, total cholesterol; TFV, total fibrous volume; TG, triglycerides; TLV, total lipid volume; TPV, total plaque volume.

Results

Patients’ Characteristics

Of the 141 patients initially considered, 15 met the exclusion criteria (residual stenosis in LMT, 4; history of coronary artery bypass grafting, 4; malignant tumor, 7). Two patients were excluded because of coronary artery events within 3 months after PCI. We attempted to perform IVUS imaging in the remaining 124 patients prior to PCI, but 15 patients had difficulty with the use of the IVUS catheter, and 5 patients had >50% calcification of their coronary artery wall; the remaining 104 patients were eligible for this study.

The baseline clinical characteristics of all the study patients are shown in Table 1. The mean age was 68±10.0 years, and the majority of the patients were male. Of the method as the mean plaque area multiplied by the pullback length in millimeters. IB signals were obtained using a commercially available system connected to the IVUS imaging system (IB-IVUS, YD Co., Ltd., Nara, Japan) and a 40-MHz IVUS catheter. The IB values for each tissue component were defined as the average power of the backscattered ultrasound signal. The IB values were classified into 4 color maps for each histological category: fibrosis, dense fibrosis, lipid, and calcification area, indicated as green, yellow, blue, and red, respectively. The percentages of each colored area were automatically calculated, and the total lipid volume (TLV) and total fibrous volume (TFV) were determined as the sum of the lipid and fibrous areas, respectively, in each cross-sectional area at 0.5-mm axis intervals. The percentage of the lipid component was calculated as TLV/TPV. The distribution of the lesions might depend on the distance from main branches and the diameter of the coronary artery. To prevent extraneous measurement of coronary compliance, we first selected the proximal site of the main branch and performed a volumetric analysis to assess the plaque characteristics. Second, all measurements were performed 3–5 min after the administration of isosorbide dinitrate because the nitroglycerin-induced effect on coronary distensibility lasts for at least 2 min.16 Additionally, IB-IVUS cannot determine the tissue components underlying any calcification because the ultrasound signal cannot penetrate calcium, which is why we excluded patients with severely calcified lesions. Therefore, our results cannot be extrapolated to patients with heavily calcified coronary plaques.

Statistical Analysis

The data are expressed as the mean±standard deviation for continuous variables. Differences in volume between
104 patients, 62 (59.6%) were treated with statins at baseline, and 89 (85.6%) patients were taking statins at the time of the 6-month follow-up exam. The primary reason why patients were not on a statin regimen at baseline was that they were previous ACS patients and had not visited the hospital for their medical concerns. The laboratory values and measurement of the conventional IVUS and IB-IVUS parameters from the enrolled patients at baseline and at follow-up are summarized in Table 2. All patients at baseline had higher levels of TC, LDL-C, and non-HDL-C as well as an elevated L/H ratio. In the conventional IVUS analysis, there were no significant differences in TPV and plaque burden at follow-up in any of the patients; however, TLV and the percentage of lipid volume were significantly decreased at follow-up in the IB-IVUS analysis.

**Factors Associated With the Percentage of the Lipid Component at Baseline**

As shown in Table 3, the univariate linear regression analysis showed that all of the lipid parameters (except TC)
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Changes in the Lipid Profile and the Percentage of the Lipid Component at the 6-Month Follow-up

We repeated the same examinations 6 months after PCI and evaluated the association of the absolute change in each lipid profile with the percentage of the lipid component of coronary plaques. As shown in Table 5, the univariate linear regression analysis showed a statistically significant fixed effect between changes in the L/H ratio and the percentage of the lipid component of coronary plaques at the 6-month follow-up in these patients. L/H, low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio.

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We repeated the same examinations 6 months after PCI and evaluated the association of the absolute change in each lipid profile with the percentage of the lipid component of coronary plaques. As shown in Table 5, the univariate linear regression analysis showed a statistically significant fixed effect between changes in all of the lipid parameters (except TC and TG) and the percentage of the lipid component of coronary plaques. Among the parameters, the strongest association was observed between changes in the L/H ratio and the percentage of the lipid component of coronary plaques (regression coefficient, 9.645; 95% CI: 5.814–13.475; P<0.0001) (Figure 1).

Furthermore, previous studies have reported that reducing the LDL-C level lowers the risk of CVD-related adverse events. Therefore, we selected 47 patients with LDL-C level <100mg/dL at baseline. Univariate linear regression analysis showed a statistically significant fixed effect between a change in the L/H ratio and a change of the percentage of the lipid component of coronary plaques at 6-month follow-up in these patients. L/H, low-density lipoprotein cholesterol (LDL-C)/high-density lipoprotein cholesterol ratio.

Table 6. Univariate Linear Regression Analysis of the Change in the Percentage of the Lipid Component of Coronary Plaques and Each Lipid Parameter in Subgroup of Patients With LDL-C <100mg/dL (n=47) at the 6-Month Follow-up

<table>
<thead>
<tr>
<th>Regression coefficient</th>
<th>95% CI</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/H ratio 13.990</td>
<td>5.638–22.341</td>
<td>3.37</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-C −0.631</td>
<td>−1.036–−0.227</td>
<td>−3.14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TC −0.093</td>
<td>−0.242–−0.056</td>
<td>−1.26</td>
<td>0.215</td>
</tr>
<tr>
<td>TG −0.021</td>
<td>−0.078–−0.037</td>
<td>−0.72</td>
<td>0.477</td>
</tr>
<tr>
<td>Non-HDL-C −0.029</td>
<td>−0.208–−0.150</td>
<td>−0.32</td>
<td>0.749</td>
</tr>
<tr>
<td>LDL-C −0.017</td>
<td>−0.252–−0.217</td>
<td>−0.15</td>
<td>0.883</td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 2,3.
nary plaques was relatively greater among the patients with LDL-C <100 mg/dL rather than among all patients (Figures 1, 2). Despite these findings, similar to the results for the entire cohort, there was a statistically significant fixed effect between changes in the L/H ratio and the percentage of the lipid component of coronary plaques (regression coefficient, 13.990; 95% CI: 5.638–22.341; P<0.01) (Table 6, Figure 2).

**Discussion**

Among the lipid parameters tested, the L/H ratio was most strongly associated at both baseline and the 6-month follow-up with the percentage of the lipid component of coronary plaques in patients with coronary artery disease (CAD). After adjusting for various coronary risk factors, multivariate linear regression analysis showed that the L/H ratio at baseline remained independently associated with the percentage of the lipid component of coronary plaques. In addition, the changes in the L/H ratio and the percentage of the lipid component of coronary plaques during follow-up were positively associated; furthermore, this association was also observed in patients with LDL-C <100 mg/dL. These findings suggested that the L/H ratio had predictive relevance for serial changes in the lipid component of coronary plaques.

Several studies have revealed that disruption of plaque might play a central role in the development of ACS and that plaques with a rich lipid component are more likely to be highly vulnerable to disruption. Okubo et al previously reported that tissue characterization by IB-IVUS had high sensitivity (90–95%) and specificity (92–99%) for histologically identifying the components of plaque. Furthermore, IB-IVUS imaging of lipid-rich plaque in non-culprit lesions might be a surrogate marker for the development and progression of atherosclerosis and future ischemic events in patients with ACS and SAP. In this study, we evaluated the lipid component of non-culprit lesions in patients with ACS and SAP. Although some studies have reported that non-culprit lesions in ACS patients had more characteristics of vulnerable plaque and were at higher risk for future adverse events compared with plaques in non-ACS patients, in the present study, the percentage of the lipid component of coronary plaques at baseline, as well as any changes in this percentage at follow-up, did not differ between patients with and without ACS (Table S1). Therefore, we evaluated the relationship between the serum lipid profiles and the lipid component of non-culprit lesions in patients with and without ACS.

Abundant clinical evidence has established that elevated levels of LDL-C constitute a strong predictor of CAD and that LDL-C-lowering therapy is one of the most effective strategies for preventing CVD. Plaque regression in the coronary artery as evaluated by conventional IVUS is associated with a decrease in LDL-C levels. Soeda et al reported that a 45.7% reduction in LDL-C was accompanied by a 11.3% decrease in plaque volume, with a concomitant significant decrease in the ratio of the lipid core volume to plaque volume as evaluated by dual-source computed tomography. Importantly, several epidemiological and clinical studies have reported that the L/H ratio rather than individual assessment of LDL-C and HDL-C is more closely associated with the development of CAD. We recently showed that a high L/H ratio can affect the clinical outcome of patients after PCI. Furthermore, an elevated L/H ratio is associated with a high lipid component of coronary plaques in patients with SAP in the LMT. Consistent with this, the present study also confirmed that a high L/H ratio is associated with the percentage of the lipid component of coronary plaques (Figure S1, Table 3).

Although previous reports have shown that the L/H ratio has a profound effect on the lipid component of coronary plaques, it remains unknown whether treatment directed at improving the L/H ratio is associated with a diminishing lipid component of coronary plaques. In the present study, we performed serial observations of IB-IVUS at baseline and at 6-month follow-up and found that the changes in the L/H ratio were closely associated with the absolute changes in the percentage of the lipid component of coronary plaques. Furthermore, in order to extend our evaluation of the change in the lipid component of coronary plaques, additional analyses were performed in patients with either decreased or increased changes in the percentage of the lipid component of coronary plaques. Although there were no significant differences (except for smoking) in the baseline clinical characteristics of the 2 groups (Table S2), the percentage of both lipid and fibrous volume showed significant changes during follow-up in both groups as expected (Table S3). Similarly, TC, LDL-C, and non-HDL-C, as well as an elevated L/H ratio, at baseline had significantly improved during follow-up in the patients in the decrease group. These findings collectively reflected our main data. Moreover, as there was a significant difference in smoking incidence (Table S2), we performed additional analysis regarding smoking. As shown in Table S4 and Table S5, there were no significant differences (except in the percentage of LAD lesions) between the smokers and non-smokers. Although the baseline levels of HDL-C in the patients who smoked tend to be lower than those in patients who were non-smokers, there were no significant changes in HDL-C levels during follow-up in both groups of patients (Table S6). Similar to the results for the entire cohort, our findings showed that changes in the L/H ratio showed a significant fixed effect with changes in the lipid component of coronary plaque in nonsmoking patients (regression coefficient, 9.836; 95% CI: 4.768–14.903; P<0.001) (Table S7, Figure S2). Thus, our findings suggested that monitoring changes in the L/H ratio would predict changes in the percentage of the lipid component of coronary plaques, which is indicative of plaque vulnerability.

The target of lipid treatment has not been established in patients with CAD. Some guidelines recommended that LDL-C should be lower than 2.5 mmol/L (100 mg/dL) for patients with a history of CAD. Recently, a meta-analysis using individual patient data from 8 randomized controlled trials of statin therapy revealed that patients who achieved very low LDL-C levels had a lower risk for major cardiovascular events than did those achieving moderately low levels. Therefore, additional guidelines also suggest that for patients at high risk for CVD, the level of LDL-C should be strictly lower than 1.8 mmol/L (70 mg/dL). In agreement with these data, among the present patients with LDL-C levels <100 mg/dL, we demonstrated a significant fixed effect between changes in the L/H ratio and the percentage of the lipid component of coronary plaques (Table 6, Figure 2). Therefore, careful monitoring of the L/H ratio, even in patients with an LDL-C <100 mg/dL, is recommended.
Study Limitations
There are several potential limitations to note. This study was a post hoc analysis of observational data, which cannot be extrapolated to treatment recommendations. Also, it included a relatively small number of patients at a single center. There are also limitations regarding the implementation of serial IVUS, such as matching the lesions at baseline and 6 months later, non-uniform rotational distortion or a difference in the ultrasound intensity related to the IVUS catheter position. However, we minimized the selection bias by reevaluating the same patients 6 months later and studying only the proximal site of the main branches. Because there may have been circumstances that might introduce bias into the results, additional larger studies are required to validate our findings.

Conclusions
Our study revealed that the L/H ratio was the most relevant factor in predicting the extent of and changes in the lipid component of coronary plaques. Furthermore, patients with a small reduction in the L/H ratio should be carefully monitored, even if their LDL-C levels are lower than 100 mg/dL.

Acknowledgments
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Disclosures
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Funding Source
None.

References


**Supplementary Files**

**Supplementary File 1**

**Figure S1.** The association between the L/H ratio and the percentage of the lipid component of coronary plaques at baseline shows a statistically significant fixed effect.

**Figure S2.** We assessed 69 patients without smoking.

**Table S1.** Data for conventional IVUS and IB-IVUS parameters at baseline and 6-month follow-up of patients with and without ACS

**Table S2.** Baseline clinical characteristics of patients with decreased or increased change in the percentage of the lipid component of coronary plaque

**Table S3.** Laboratory and imaging data at baseline and follow-up among patients with decreased or increased change in the percentage of the lipid component of coronary plaque

**Table S4.** Clinical characteristics of the smoking and nonsmoking patients at baseline

**Table S5.** Laboratory data for the smoking and nonsmoking patients at baseline

**Table S6.** Laboratory and imaging data at baseline and 6-month follow-up for the smoking and nonsmoking patients

**Table S7.** Univariate linear regression analysis of the change in the percentage of the lipid component of coronary plaque and each lipid parameter in the nonsmoking patients (n=69) at the 6-month follow-up

Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-16-1209