

# 学位論文

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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## 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.<sup>1,2</sup> Vulnerable plaques are characterized by a large, lipid-enriched necrotic core overlaid with a thin fibrous cap.<sup>3</sup> Pathological studies have revealed that the size of the lipid component of coronary plaques is strongly associated with their vulnerability.<sup>4,6</sup> 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.<sup>5,7–9</sup>

There are many risk factors for the development of CVD; hypertension, dyslipidemia, diabetes, obesity, and

cigarette smoking are traditional systemic risk factors,<sup>10</sup> and the low-density lipoprotein-cholesterol (LDL-C) level is a well-established molecular risk factor.<sup>11</sup> 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.<sup>12</sup> 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,<sup>7,13</sup> 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

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**Table 1. Baseline Clinical Characteristics of the Total Cohort and Subgroup of Patients With LDL-C <100 mg/dL**

Parameter	Total patients (n=104)	Patients with LDL-C <100 mg/dL (n=47)
Mean age (years)	68.4±10.0	69.1±9.4
Male	87 (83.7)	41 (87.2)
BMI (kg/m <sup>2</sup> )	23.9±3.6	23.8±3.7
<b>Clinical history</b>		
Hypertension	56 (53.8)	27 (57.4)
Diabetes	37 (35.6)	19 (40.4)
Smoking	35 (33.7)	19 (40.4)
<b>Target plaque location</b>		
LAD	52 (50.0)	23 (48.9)
LCX	19 (18.3)	8 (17.0)
RCA	33 (31.7)	16 (34.0)
<b>Medications</b>		
Statin	62 (59.6)	35 (74.5)
Antiplatelet agent	104 (100)	47 (100)
ARB/ACEI	49 (47.1)	19 (40.4)
β-blocker	24 (23.1)	13 (27.7)
CCB	27 (26.0)	14 (30.0)

Data are expressed as mean±standard deviation or number (%). ARB/ACEI, angiotensin II receptor blocker/angiotensin converting-enzyme inhibitor; BMI, body mass index; CCB, calcium-channel blocker; LAD, left anterior descending; LCX, left circumflex; LDL-C, low-density lipoprotein cholesterol; RCA, right coronary artery.

current study.

## Methods

### Study Population

We prospectively enrolled 141 consecutive patients who underwent successful percutaneous coronary intervention (PCI) after either ACS or stable angina pectoris (SAP) between January 2010 and July 2012 and in whom IB-IVUS at the same lesion could be performed twice. We investigated the serum lipid profiles and the percentage of the lipid component of coronary plaques by IB-IVUS at the time of the PCI and 6 months later. The exclusion criteria included residual stenosis (defined as >50% of the diameter) in the left main trunk (LMT) as determined by quantitative coronary angiography or a history of either coronary artery bypass grafting or malignant tumor. Additionally, patients who experienced coronary artery events within 3 months after PCI were excluded to avoid the influence of the PCI procedure or subacute thrombosis. Furthermore, patients were also excluded if they had difficulty undergoing IVUS or had >50% calcification of the coronary artery wall. After the first PCI, the follow-up and standard drug treatments were initiated in the outpatient clinic. The patients were carefully monitored during their recovery, and their blood samples were collected early in the morning after an overnight fast at least twice: prior to PCI and at the 6-month follow-up. The use of antidiabetic drugs was left to the judgment of the attending physician who set no particular restrictions, but we made efforts to achieve and/or maintain optimal lipid levels during the 6-month recovery after PCI. The Ethics Committee of KKR Takamatsu Hospital approved the study protocol, and all patients gave written informed consent prior to enrollment.

### 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 anti-hyperglycemic 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.<sup>7,9,14,15</sup> 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

**Table 2. Laboratory and Imaging Data for the Total Cohort and Subgroup of Patients With LDL-C <100 mg/dL at Baseline and 6-Month Follow-up**

Parameter	All patients (n=104)			Patients with LDL-C <100 mg/dL (n=47)		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value
<b>Laboratory data</b>						
Total-C (mg/dL)	186.0±40.6	167.8±31.2	<0.001	156.1±24.8	160.9±30.8	0.3095
LDL-C (mg/dL)	110.7±33.9	90.8±23.6	<0.0001	82.2±14.0	84.3±22.8	0.4871
HDL-C (mg/dL)	50.5±15.4	52.0±15.4	0.4959	47.0±12.4	50.1±13.5	0.0515
L/H ratio	2.3±0.8	1.9±0.6	<0.0001	1.8±0.5	1.8±0.6	0.3415
Non-HDL-C (mg/dL)	135.5±36.3	115.8±26.7	<0.0001	109.1±21.2	110.7±28.1	0.6800
TG (mg/dL)	135.0±69.8	149.6±77.1	0.1553	141.8±73.0	161.5±87.9	0.1099
HbA1c (%)	6.1±1.2	6.1±1.0	0.7244	6.1±1.1	6.1±0.9	0.8679
CRP (mg/dL)	0.23±0.49	0.19±0.51	0.5081	0.32±0.71	0.26±0.73	0.6981
<b>Conventional IVUS</b>						
Total vessel volume (mm <sup>3</sup> )	78.0±23.2	73.8±23.4	0.1984	74.3±21.5	70.3±22.3	0.0716
Total lumen volume (mm <sup>3</sup> )	43.3±20.3	39.8±19.3	0.2086	38.1±18.8	35.8±17.6	0.2372
TPV (mm <sup>3</sup> )	34.7±11.2	34.0±11.7	0.6590	36.3±10.5	34.5±12.3	0.1727
Plaque burden (%)	46.5±14.7	47.9±15.5	0.3204	51.1±15.2	50.2±14.6	0.6620
<b>IB-IVUS</b>						
TLV (mm <sup>3</sup> )	9.5±5.4	7.5±5.8	<0.05	9.0±5.3	7.5±5.6	0.1547
Percentage of lipid volume (%)	26.5±11.8	20.3±11.6	<0.001	23.8±11.2	20.3±12.1	0.1378
TFV (mm <sup>3</sup> )	23.3±7.8	24.1±7.6	0.4274	25.1±7.3	24.4±8.4	0.4852
Percentage of fibrous volume (%)	67.6±9.6	72.3±9.0	<0.001	70.1±9.2	71.8±9.8	0.4009

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.

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.<sup>16</sup> 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

the baseline and 6-month follow-up measurements were assessed with a paired t-test for continuous variables. We performed a univariate linear regression analysis to determine the relationship between the percentage of the lipid component of coronary plaques and each lipid profile. A multivariate linear regression analysis adjusted for age, BMI, hypertension, diabetes, the L/H ratio, and TG was performed to determine the relationship of these parameters to the lipid component of coronary plaques. In order to determine whether LDL-C or HDL-C modifies the associations of the L/H ratio with the percentage of the lipid component of coronary plaques, we included a baseline adjustment of LDL-C or HDL-C in the models. In this analysis, the L/H ratio was used as a continuous variable. A P-value <0.05 was considered to be statistically significant. All data were analyzed using SAS software version 9.1 (SAS Institute Inc., Cary, NC, USA).

## 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 68.4±10.0 years, and the majority of the patients were male. Of the

**Table 3. Univariate Linear Regression Analysis of the Percentage of the Lipid Component of Coronary Plaques and Each Lipid Parameter at Baseline**

	Regression coefficient	95% CI	t value	P value
L/H ratio	5.681	2.987–8.375	4.18	<0.0001
HDL-C	-0.212	-0.357–-0.067	-2.91	<0.01
Non-HDL-C	0.085	0.023–0.146	2.73	<0.01
LDL-C	0.072	0.005–0.139	2.12	<0.05
TC	0.037	-0.019–0.094	1.32	0.19
TG	0.035	0.002–0.067	2.11	<0.05

CI, confidence interval. Other abbreviations as in Table 2.

**Table 4. Multivariate Linear Regression Analysis With Percentage of the Lipid Component of Coronary Plaques as the Dependent Variable at Baseline**

A	Regression coefficient	95% CI	Standardized partial regression coefficient	t value	P value
Age	-0.194	-0.422–0.034	-0.164	-1.69	0.095
BMI	-0.329	-0.952–0.294	-0.100	-1.05	0.297
Hypertension	-1.276	-5.737–3.185	-0.054	-0.57	0.572
Diabetes	3.058	-1.491–7.606	0.125	1.33	0.185
L/H ratio	6.842	2.937–10.748	0.461	3.48	<0.001
TG	0.028	-0.004–0.061	0.167	1.72	0.088
LDL-C	-0.044	-0.135–0.048	-0.126	-0.95	0.344
<b>B</b>					
Age	-0.186	-0.411–0.040	-0.157	-1.63	0.106
BMI	-0.341	-0.965–0.283	-0.104	-1.08	0.281
Hypertension	-1.373	-5.822–3.076	-0.058	-0.61	0.542
Diabetes	3.071	-1.483–7.624	0.125	1.34	0.184
L/H ratio	4.861	1.632–8.089	0.327	2.99	<0.01
TG	0.028	-0.005–0.061	0.166	1.69	0.093
HDL-C	-0.071	-0.235–0.093	-0.092	-0.86	0.395

Covariates: age, BMI, hypertension, diabetes, L/H ratio, TG at follow-up. Abbreviations as in Table 1–3.

**Table 5. Univariate Linear Regression Analysis of the Change in the Percentage of the Lipid Component of Coronary Plaque and Each Lipid Parameter in the Study Patients (n=104) at the 6-Month Follow-up**

	Regression coefficient	95% CI	t value	P value
L/H ratio	9.645	5.814–13.475	4.99	<0.0001
HDL-C	-0.461	-0.786–-0.136	-2.81	<0.01
Non-HDL-C	0.082	0.001–0.163	2.02	<0.05
LDL-C	0.088	0.002–0.175	2.02	<0.05
TC	0.045	-0.029–0.120	1.21	0.230
TG	-0.003	-0.047–0.041	-0.14	0.890

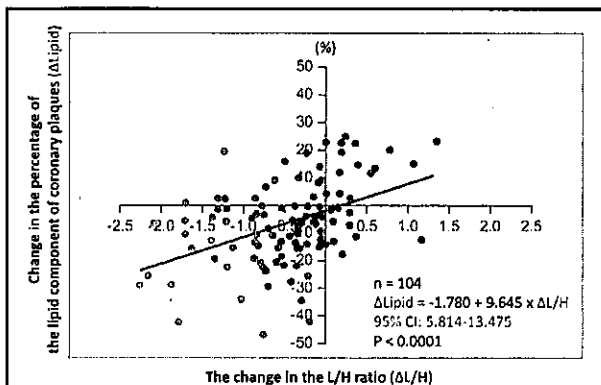
Abbreviations as in Tables 2,3.

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

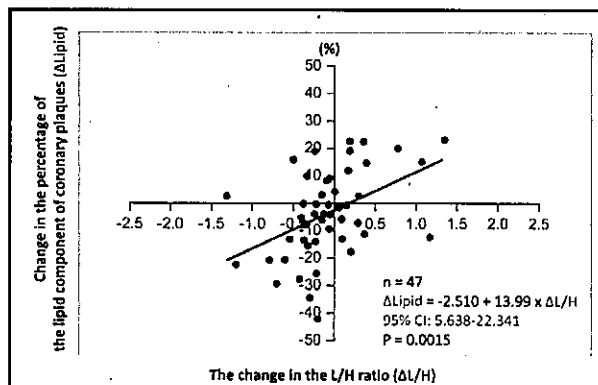
well as an elevated L/H ratio. In the conventional IVUS analysis, there were no significant differences in TPV and plaque burden at follow-up in any of the patients; however, TLV and the percentage of lipid volume were significantly decreased at follow-up in the IB-IVUS analysis.

#### 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)



**Figure 1.** Association between a change in the L/H ratio and a change in the percentage of the lipid component of coronary plaques at 6-month follow-up. There was a statistically significant fixed effect between the change in the L/H ratio and the change of the percentage of the lipid component of coronary plaques in all the patients enrolled in this study. L/H, low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio.



**Figure 2.** Assessment of 47 patients with LDL-C level < 100 mg/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 the 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 < 100 mg/dL (n=47) at the 6-Month Follow-up**

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

Abbreviations as in Tables 2,3.

had a statistically significant fixed effect with the percentage of the lipid component of coronary plaques at baseline. Among these parameters, the strongest association was observed between the L/H ratio and the percentage of the lipid component of coronary plaques (regression coefficient, 5.681; 95% confidence interval (95% CI): 2.987-8.375; P<0.0001) (Figure S1).

As shown in Table 4A and Table 4B, we found that the L/H ratio independently had a significant increasing effect (regression coefficient, 6.842; 95% CI: 2.937-10.748; P<0.001) for the percentage of the lipid component of coronary plaques using a multivariate linear regression analysis adjusting for TG, confounding factors (age and BMI), coronary risk factors, and LDL-C. Adjusting for HDL-C with the same explanatory variables, the L/H ratio had the same increasing effect (regression coefficient, 4.861; 95% CI: 1.632-8.089; P<0.01). LDL-C and HDL-C, as baseline adjustments in the models, were not statistically significant. Thus, based on the multivariate analysis results we could not confirm whether either of these variables had an effect.

**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 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.<sup>17</sup> Therefore, we selected 47 patients with LDL-C < 100 mg/dL at baseline and analyzed their data to examine the relationship between changes in the L/H ratio and the percentage of the lipid component of coronary plaques. Baseline clinical characteristics and the laboratory values and measurement of the conventional and IB-IVUS parameters are summarized in Table 1 and Table 2. Although these patients had higher levels of TC, LDL-C, non-HDL-C, TLV and the percentage of lipid volume, as well as an elevated L/H ratio at baseline, there were no significant differences in these parameters between baseline and follow-up for these patients with LDL-C < 100 mg/dL. Based on these results, the number of patients with increased change in the percentage of the lipid component of coro-

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.<sup>18–20</sup> 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.<sup>9</sup> 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.<sup>21</sup> 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,<sup>22,23</sup> 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.<sup>17,24–26</sup> Plaque regression in the coronary artery as evaluated by conventional IVUS is associated with a decrease in LDL-C levels.<sup>12</sup> 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.<sup>27</sup> 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 CVD.<sup>28,29</sup> We recently showed that a high L/H ratio can affect the clinical outcome of patients after PCI.<sup>30</sup> Furthermore, an

elevated L/H ratio is associated with a high lipid component of coronary plaques in patients with SAP in the LMT.<sup>31</sup> 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,<sup>31</sup> 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 not 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.<sup>32–35</sup> 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.<sup>36</sup> 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 artery 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.

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### Disclosures

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### 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

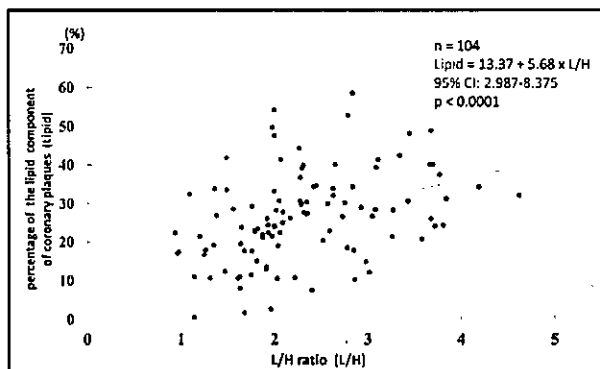
Please find supplementary file(s);  
<http://dx.doi.org/10.1253/circj.CJ-16-1209>



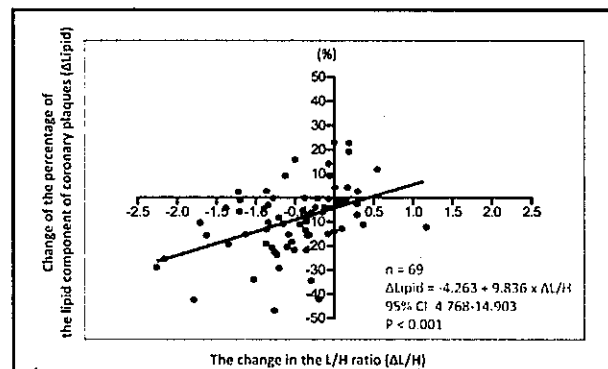
## Role of the Low-Density Lipoprotein-Cholesterol/ High-Density Lipoprotein-Cholesterol Ratio in Predicting Serial Changes in the Lipid Component of Coronary Plaque

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### 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. L/H ratio, low-density lipoprotein-cholesterol (LDL-C)/high-density lipoprotein-cholesterol (HDL-C) ratio.



**Figure S2.** We assessed 69 patients without smoking. The univariate linear regression analysis showed a statistically significant fixed effect between the change in the L/H ratio and the change of the percentage of the lipid component of coronary plaques at the 6-month follow-up in those patients.

**Table S1. Data for Conventional IVUS and IB-IVUS Parameters at Baseline and 6-Month Follow-up of Patients With and Without ACS**

Parameter	ACS (n=24)	Without ACS (n=80)	P value
<b>Conventional IVUS</b>			
Total vessel volume (mm <sup>3</sup> )			
Baseline	79.3±23.9	77.6±23.0	0.7462
Follow-up	75.6±25.5	73.26±22.7	0.6745
Total lumen volume (mm <sup>3</sup> )			
Baseline	42.8±21.0	43.5±20.0	0.8800
Follow-up	39.0±21.0	40.1±18.8	0.8141
TPV (mm <sup>3</sup> )			
Baseline	36.6±11.2	34.1±11.1	0.3443
Follow-up	36.6±12.1	33.2±11.4	0.2161
Plaque burden (%)			
Baseline	48.1±13.5	46.0±15.1	0.5499
Follow-up	51.1±16.6	46.9±15.0	0.2523
<b>IB-IVUS</b>			
TLV (mm <sup>3</sup> )			
Baseline	9.2±5.0	9.6±5.5	0.7301
Follow-up	8.3±7.0	7.3±5.4	0.4465
Percentage of lipid volume (%)			
Baseline	23.8±8.2	27.3±12.5	0.1987
Follow-up	20.8±11.4	20.1±11.6	0.8017
TFV (mm <sup>3</sup> )			
Baseline	25.3±7.5	22.6±7.8	0.1483
Follow-up	25.6±6.9	23.7±7.8	0.2854
Percentage of fibrous volume (%)			
Baseline	69.7±7.2	67.0±10.2	0.2210
Follow-up	71.9±9.0	72.4±9.0	0.8105

Data are expressed as mean±standard deviation or number (%). ACS, acute coronary syndrome; IB, integrated backscatter; IVUS, intravascular ultrasound; TFV, total fibrous volume; TLV, total lipid volume; TPV, total plaque volume.

**Table S2. Baseline Clinical Characteristics of Patients With Decreased or Increased Change in the Percentage of the Lipid Component of Coronary Plaque**

Parameter	Decrease group (n=74)	Increase group (n=30)	t value	P value
Mean age (years)	68.0±9.9	69.5±10.3	0.684	0.4955
Male	61 (82.4)	26 (86.7)	0.525	0.6010
BMI (kg/m <sup>2</sup> )	24.1±3.8	23.6±3.0	-0.523	0.6018
<b>Clinical history</b>				
Hypertension	41 (55.4)	15 (50.0)	-0.497	0.6205
Diabetes	24 (32.4)	13 (43.3)	1.047	0.2974
Smoking	19 (25.7)	16 (53.3)	2.778	<0.01
<b>Target plaque location</b>				
LAD	40 (54.1)	12 (40.0)	-1.297	0.1977
LCX	13 (17.6)	6 (20.0)	0.288	0.7738
RCA	21 (28.4)	12 (40.0)	1.150	0.2529
<b>Medications</b>				
Statin	46 (62.2)	15 (50.0)	-1.137	0.2581
Antiplatelet agent	74 (100)	30 (100)	-	-
ARB/ACEI	36 (48.6)	13 (43.3)	-0.488	0.6267
β-blocker	17 (23.0)	7 (23.3)	0.039	0.9689
CCB	19 (25.7)	8 (26.7)	0.103	0.9178

Data are expressed as mean±standard deviation or number (%). ARB/ACEI, angiotensin II receptor blocker/angiotensin converting-enzyme inhibitor; BMI, body mass index; CCB, calcium-channel blocker; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

**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**

Parameter	Decrease group (n=74)			Increase group (n=30)		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value
<b>Laboratory data</b>						
TC (mg/dL)	189.0±43.6	166.5±31.6	<0.0001	178.9±32.5	171.0±31.0	0.1682
LDL-C (mg/dL)	114.9±36.4	90.3±22.8	<0.0001	100.1±24.1	92.3±26.2	0.1401
HDL-C (mg/dL)	49.2±15.4	51.3±14.8	0.0572	53.7±15.3	53.6±17.2	0.9436
L/H ratio	2.4±0.8	1.8±0.5	<0.0001	2.0±0.7	1.9±0.8	0.5092
Non-HDL-C (mg/dL)	139.7±37.7	115.2±26.5	<0.0001	125.2±31.8	117.4±28.0	0.1754
TG (mg/dL)	137.2±68.8	155.9±84.6	0.0223	129.4±73.2	133.8±54.2	0.7134
HbA1c (%)	6.1±1.2	6.1±1.1	0.8763	6.2±1.3	6.0±0.8	0.3568
CRP (mg/dL)	0.24±0.57	0.13±0.16	0.1150	0.21±0.20	0.32±0.92	0.5117
<b>Conventional IVUS</b>						
Total vessel volume (mm <sup>3</sup> )	79.7±24.3	75.5±25.2	<0.05	73.7±20.3	69.6±18.2	<0.05
Total lumen volume (mm <sup>3</sup> )	45.4±20.7	41.2±20.3	<0.05	38.2±19.0	36.4±16.8	0.4007
TPV (mm <sup>3</sup> )	34.3±12.2	34.3±12.4	0.9698	35.5±8.7	33.1±9.8	0.1578
Plaque burden (%)	44.9±14.8	47.4±16.0	0.1301	50.6±14.2	49.2±14.6	0.6083
<b>IB-IVUS</b>						
TLV (mm <sup>3</sup> )	10.3±5.7	5.7±4.0	<0.0001	6.4±3.5	10.4±5.9	<0.0001
Percentage of lipid volume (%)	29.7±11.3	16.1±8.2	<0.0001	18.4±8.8	30.5±12.5	<0.0001
TFV (mm <sup>3</sup> )	22.4±8.4	25.8±9.3	<0.0001	26.2±8.1	21.0±6.6	<0.01
Percentage of fibrous volume (%)	65.4±9.5	75.6±6.0	<0.0001	73.1±8.0	64.2±10.2	<0.001

Data are expressed as mean±standard deviation or number (%). CRP, C-reactive protein; LDL-C, low-density lipoprotein-cholesterol; L/H ratio, LDL-C/HDL-C ratio; HDL-C, high-density lipoprotein-cholesterol; IB, integrated backscatter; TC, total cholesterol; TG, triglycerides; TLV, total lipid volume. Other abbreviations as in Table S1.

**Table S4. Clinical Characteristics of the Smoking and Nonsmoking Patients at Baseline**

Parameter	Smoker (n=35)	Nonsmoker (n=69)	t value	P value
Mean age (years)	66.1±9.9	69.6±9.9	1.711	0.0901
Male	34 (97.1)	53 (76.8)	-2.717	<0.01
BMI (kg/m <sup>2</sup> )	23.9±2.7	23.9±4.0	0.018	0.9858
<b>Clinical history</b>				
Hypertension	20 (60.0)	35 (50.7)	-0.891	0.3748
Diabetes	12 (34.3)	25 (36.2)	0.194	0.8465
Smoking	35 (100)	0 (0)	-2.18e+8	<0.0001
<b>Target plaque location</b>				
LAD	12 (34.3)	40 (58.0)	2.320	<0.05
LCX	9 (25.7)	10 (14.5)	-1.399	0.1648
RCA	14 (40.0)	19 (27.5)	-1.288	0.2005
<b>Medications</b>				
Statin	22 (62.9)	40 (58.0)	-0.476	0.6353
Antiplatelet agent	35 (100)	69 (100)	-	-
ARB/ACEI	15 (42.9)	34 (49.3)	0.615	0.5401
β-blocker	10 (28.6)	14 (20.3)	-0.942	0.3484
CCB	8 (22.9)	19 (27.5)	0.510	0.6112

Data are expressed as mean±standard deviation or number (%). Abbreviations as in Tables S2,S3.

**Table S5. Laboratory Data for the Smoking and Nonsmoking Patients at Baseline**

Parameter	Smoker (n=35)	Nonsmoker (n=69)	t value	P value
TC (mg/dL)	186.4±38.9	185.8±42.0	-0.069	0.9451
LDL-C (mg/dL)	109.5±32.8	111.2±34.7	0.243	0.8084
HDL-C (mg/dL)	49.1±11.4	51.2±17.1	0.665	0.5078
L/H ratio	2.3±0.8	2.3±0.8	-0.093	0.9257
Non-HDL-C (mg/dL)	137.3±35.0	134.6±37.5	-0.357	0.7216
TG (mg/dL)	137.2±75.2	133.8±67.4	-0.2328	0.8164
HbA1c (%)	6.2±1.3	6.1±1.2	-0.402	0.6888
CRP (mg/dL)	0.31±0.77	0.20±0.27	-1.076	0.2845

Data are expressed as mean±standard deviation or number (%). Abbreviations as in Table S3.

**Table S6. Laboratory and Imaging Data at Baseline and 6-Month Follow-up for the Smoking and Nonsmoking Patients**

Parameter	Smoker (n=35)			Nonsmoker (n=69)		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value
<b>Laboratory data</b>						
TC (mg/dL)	186.4±38.9	173.8±30.1	0.0625	185.8±42.0	164.7±31.8	<0.0001
LDL-C (mg/dL)	109.5±32.8	92.1±25.6	<0.01	111.2±34.7	90.2±22.8	<0.0001
HDL-C (mg/dL)	49.1±11.4	50.4±11.0	0.4041	51.2±17.1	52.8±17.3	0.1521
L/H ratio	2.3±0.8	1.9±0.6	<0.01	2.3±0.8	1.8±0.6	<0.0001
Non-HDL-C (mg/dL)	137.3±35.0	123.4±29.2	<0.05	134.6±37.5	112.0±24.9	<0.0001
TG (mg/dL)	137.2±75.2	156.5±93.3	0.1719	133.8±67.4	146.0±68.6	0.0970
HbA1c (%)	6.2±1.3	6.0±1.1	0.4384	6.1±1.2	6.1±1.0	0.7840
CRP (mg/dL)	0.31±0.77	0.12±0.14	0.1785	0.20±0.27	0.22±0.62	0.7719
<b>Conventional IVUS</b>						
Total vessel volume (mm <sup>3</sup> )	74.0±22.0	73.4±23.4	0.8433	80.0±23.8	74.0±23.7	<0.001
Total lumen volume (mm <sup>3</sup> )	39.2±19.6	38.8±20.0	0.8707	45.4±20.6	40.4±19.4	<0.01
TPV (mm <sup>3</sup> )	34.8±10.8	34.6±12.6	0.9013	34.6±11.6	33.6±11.3	0.3172
Plaque burden (%)	49.6±15.5	48.5±16.0	0.8470	45.0±14.3	47.6±15.5	0.1259
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TLV (mm <sup>3</sup> )	8.8±4.7	8.7±5.9	0.9825	9.5±5.8	6.2±4.4	<0.0001
Percentage of lipid volume (%)	24.8±10.0	24.1±13.6	0.8125	27.4±12.6	18.3±10.0	<0.0001
TFV (mm <sup>3</sup> )	24.2±7.7	23.8±9.2	0.7516	23.1±8.9	24.8±8.7	0.0756
Percentage of fibrous volume (%)	69.8±8.0	69.4±10.9	0.8355	66.5±10.3	73.8±7.7	<0.0001

Data are expressed as mean±standard deviation or number (%). Abbreviations as in Tables S1,S3.

**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**

	Regression coefficient	95% CI	t value	P value
L/H ratio	9.836	4.768-14.903	3.87	<0.001
Non-HDL-C	0.092	-0.003-0.187	1.94	0.057
TG	0.055	-0.002-0.112	1.92	0.059
LDL-C	0.080	-0.024-0.183	1.53	0.131
HDL-C	-0.292	-0.687-0.104	-1.47	0.146
TC	0.060	-0.026-0.146	1.39	0.169

CI, confidence interval. Other abbreviations as in Table S3.