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Impact of the Low- to High-Density Lipoprotein Cholesterol Ratio on Composition of Angiographically Ambiguous Left Main Coronary Artery Plaque

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Background: A high low-density lipoprotein cholesterol (LDL-C) to a high-density lipoprotein cholesterol (HDL-C) ratio is associated with cardiac events, while the left main coronary artery (LMCA) is considered to be an important target of atherosclerotic plaque accumulation. This aim of the present study was to investigate the relationship between a LDL-C/HDL-C ratio and the characteristics of tissue components of LMCA plaque.

Methods and Results: One-hundred-twenty consecutive patients with stable angina pectoris who received chronic statin treatment underwent percutaneous coronary intervention for the left coronary artery. We prospectively performed integrated backscatter (IB) intravascular ultrasound (IVUS) to their LMCAs and evaluated the tissue characteristics. According to the median value of their LDL-C/HDL-C ratios (2.4), they were divided into 2 groups [high LDL-C/HDL-C ratio (>2.4) (n=60) or low LDL-C/HDL-C ratio (≤2.4) (n=60)]. There was no significant difference in the data analyzed using conventional IVUS between the 2 groups. In the IB-IVUS analysis, patients with a high LDL-C/HDL-C ratio had a larger lipid volume and a smaller fibrous volume compared to patients with a low LDL-C/HDL-C ratio (52±10% vs. 48±10%, P=0.014 and 45±9% vs. 50±10%, P=0.010).

Conclusions: A high LDL-C/HDL-C ratio was associated with a high percentage of lipid volume and a low percentage of fibrous volume in LMCA lesions. Our findings might well suggest the increased risk of cardiovascular events in patients with a high LDL-C/HDL-C ratio. (*Circ J* 2011; **75:** 1960–1967)

Key Words: Integrated backscatter intravascular ultrasound; Left main coronary artery; Low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio

It is well known that a coronary plaque rupture followed by thrombus formation causes acute coronary syndrome (ACS).[1,2] Coronary plaque with a large lipid-core is associated with plaque vulnerability, which directly relates to the risk of plaque rupture. Recently, tissue components of coronary plaques can be analyzed by an integrated backscatter (IB) intravascular ultrasound (IVUS).[3–5] In contrast, ACS of the left main coronary artery (LMCA) is associated with very poor prognosis because of severe pump failure and/or ventricular arrhythmia.[6,7] In such a situation, evaluation of LMCA might provide to be useful information.

The low-density lipoprotein cholesterol (LDL-C) to high-density lipoprotein cholesterol (HDL-C) ratio is a predictor of risk for coronary heart disease (CHD) and a surrogate marker of lipid-lowering therapies.[8] Meta-analysis data from 4 studies using conventional IVUS has indicated the positive liner correlation between achieved LDL/HDL ratio and percent volume changes of coronary plaque burden.[9–13] However, there are a few reports questioning whether a LDL-C/HDL-C ratio correlates with the characteristics of tissue components of LMCA plaques. Accordingly, in the present study, we tested our hypothesis of whether a high LDL-C/HDL-C ratio indicating a poor prognosis is related to a high percentage of the lipid volume of LMCA plaques detected by IB-IVUS in angiographically ambiguous LMCA lesions in patients with stable angina.

Methods

Study Population

We enrolled a total of 140 consecutive stable angina pectoris

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(AP) patients, who received statin treatment for at least 6 months, undergoing percutaneous coronary intervention (PCI) for de novo left anterior descending coronary artery or left circumflex coronary artery lesions with severe stenosis (defined as percent stenosis >50% diameter) as determined by quantitative coronary angiography (QCA) between August 2009 and July 2010 at Nagoya University. Exclusion criteria consisted of patients aged >80 years, who had end-stage renal disease and who were on maintenance hemodialysis, and/or a contraindication of aspirin treatment. Furthermore, patients were also excluded if they had severe stenotic LMCA lesions for which revascularization would be needed.

A blood sample was obtained from the peripheral vein prior to PCI following a 12-h overnight fast, and various data including lipid and glucose profiles were measured. An LDL-C/HDL-C ratio was defined as LDL-C calculated using Friedewald's formula[14]/measured HDL-C. An echocardiogram was administered on the day prior to PCI. Immediately prior to PCI, IVUS imagings were performed from the bifurcation of the left anterior descending or circumflex artery to the LMCA ostium in addition to the culprit lesion. We analyzed the whole LMCA, which had plaques with more than 30% of percent plaque volume at minimum luminal area detected using IVUS as previously reported.[15] The study protocol and chart reviews were approved by our institutional ethics committee. Written informed consent was given by all patients prior to the procedure.

Definition

Lesion types were divided according to the American Heart Association/American College of Cardiology classification.[16] Hypertension was defined as a systolic blood pressure >140 mmHg, a diastolic blood pressure >90 mmHg, and/or having received treatment for hypertension. Diabetes mellitus was confirmed if patients had hemoglobin A_{1c} levels ≥6.5%, a fasting plasma glucose concentration >126 mg/dl, and/or a history of any anti-hyperglycemic medication or previous diagnosis of diabetes.

QCA and IVUS Analyses

All patients had oral aspirin (100 mg) for ≥14 days prior to PCI. A bolus of 10,000 IU heparin was administered from the arterial sheath immediately prior to the procedure. An intracoronary infusion of 5 mg isosorbide dinitrate was administered immediately prior to angiography for QCA and IVUS.

QCA

Coronary angiograms were obtained prior to PCI. The projection showing the worst view (the maximal degree of stenosis) was adapted for QCA. A contour-detection minimum-cost algorithm (QCA-CMS Version 3.0, MEDIS, Leiden, The Netherlands) was used for QCA analysis. The reference segment diameter was averaged from 5-mm long angiographically normal segments proximal to the lesion; if a normal proximal segment could not be identified, a distal angiographically normal segment was analyzed as previously described.[17]

Conventional IVUS

A commercially available imaging system (Clear View, Boston Scientific, Natick, Massachusetts for imaging and SCIMED, Freemont, California for a motored pull-back device) and a 40 MHz IVUS catheter were used for conventional IVUS analysis. According to the American College of Cardiology guidelines,[18] the external elastic membrane (EEM) and lumen were traced by manual planimetry. The cross-sectional area (CSA) of the EEM was determined by tracing the leading edge of the adventitia. Plaque plus media (P&M) CSA was defined as (EEM CSA − lumen CSA). The percent plaque area was calculated as P&M CSA/EEM CSA×100 (%). Conventional 3-dimensional IVUS image analysis was performed to assess the vessel volume, lumen volume, and total-plaque volume (sum of EEM, lumen, and plaque plus media CSA at 1-mm axial intervals for the analysis segments). The percent plaque area (volume) (%) was calculated as P&M area (volume)/vessel area (volume)×100.

IB-IVUS

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 an average power of the ultrasound backscattered signal from a small volume of tissue using a fast Fourier transform, which was measured in decibels. The definition of the IB value was classified for each of 3 histological categories: fibrous, lipid, and high-signal area, indicated as green, blue, and red, respectively. The analyses for 3-dimensional IVUS images including lipid volume, fibrous volume, and high-signal volume were determined as the sum of fibrous, lipid, and high-signal areas in each CSA at 1-mm axis intervals, respectively. The percentages of fibrous area (volume) [fibrous area (volume)/P&M area (volume)×100], lipid area (volume) [lipid area (volume)/P&M area (volume)×100] and high-signal area (volume) [high-signal area (volume)/P&M area (volume)×100] were automatically calculated.

Statistical Analysis

SPSS version 18 (SPSS, Chicago, IL, USA) was used for all statistical analyses. Continuous variables were presented as mean±standard deviations, and differences between the 2 groups were evaluated by the Student unpaired t-test or the Mann–Whitney U-test if distribution was abnormal. Triglyceride levels were logarithmically transformed. Categorical variables were presented as numbers (percentages), and comparisons across the 2 groups were performed by the chi-squared test or Fisher's exact test. We performed a simple linear regression analysis to test the relationship between tissue characterizations of LMCA plaque and the obtained metabolic profiles. A multiple regression analysis was performed to adjust for various factors, which might relate to plaque characteristics (gender, age, body mass index, current smoking, hypertension, diabetes, hemoglobin $A1_c$, and LDL-C/HDL-C ratio). A P value of <0.05 was considered significant.

Results

Of 140 patients, 18 (age >80 years, 11; end-stage renal disease on maintenance hemodialysis, 6; and severe stenotic LMCA lesions, 1) met the exclusion criteria. We tried to perform IVUS imaging immediately prior to PCI for 122 patients. However, IVUS catheters could not be placed appropriately within the coronary artery in 2 patients, leaving 120 patients who were eligible for this study. A total of 30 randomly selected LMCA images were measured for the evaluation of inter- and intra-observer agreement. The inter- and intra-observer variability of EEM volume and plaque volume in a quantitative measurement of IVUS images were well correlated [r=0.94 (P<0.001) and r=0.96 (P<0.001), r=0.96 (P<0.001) and r=0.93 (P<0.001), respectively]. The inter- and intra-observer variability of lipid volume and fibrous volume in 3-dimensional IVUS images were also well correlated [r=0.98 (P<0.001) and r=0.96

Table 1. Patient Characteristics

	All (n=120)	High LDL-C/HDL-C ratio (n=60)	Low LDL-C/HDL-C ratio (n=60)	P value
Age (years)	67.6±7.0	66.6±7.6	68.6±9.2	0.195
Male	95 (79)	50 (83)	45 (75)	0.261
Body mass index (kg/m^2)	24.3±2.8	24.7±3.1	24.0±3.5	0.233
Clinical history				
Hypertension	90 (75)	43 (72)	47 (78)	0.399
Diabetes	57 (48)	33 (55)	24 (40)	0.100
Current smoker	27 (23)	13 (22)	14 (23)	0.866
Previous angioplasty	39 (33)	21 (35)	18 (30)	0.559
Previous bypass surgery	9 (8)	2 (3)	7 (12)	0.081
Previous myocardial infarction	23 (19)	14 (23)	9 (15)	0.284
Multiple vessel disease	69 (58)	37 (62)	32 (53)	0.620
Familial history of CHD	13 (11)	4 (7)	9 (15)	0.110
Estimated GFR (ml·min^{-1}·1.73 m^{-2})	64.3±16.3	62.5±19.9	65.0±22.0	0.516
Total cholesterol (mg/dl)	184.0±28.5	199.6±30.6	173.7±31.8	<0.001
LDL-C (mg/dl)	112.3±29.2	128.8±24.2	95.8±24.2	<0.001
HDL-C (mg/dl)	46.3±9.7	40.2±8.9	52.5±12.7	<0.001
LDL-C/HDL-C ratio	2.6±0.9	3.3±0.7	1.9±0.4	<0.001
Logarithmic transformed TG (mg/dl)	2.1±0.2	2.2±0.2	2.0±0.2	0.043
Hemoglobin A$_{1c}$ (%)	6.2±0.9	6.3±1.2	6.0±1.0	0.120
LVEF (%)	65±9	63±14	67±8	0.115
Culprit location				
Left anterior descending	81 (68)	40 (67)	41 (68)	0.845
Left circumflex	39 (33)	20 (33)	19 (32)	0.845
AHA/ACC type				
A	21 (18)	10 (17)	11 (18)	0.810
B$_1$	36 (30)	21 (35)	15 (25)	0.232
B$_2$	39 (33)	16 (27)	23 (38)	0.172
C	24 (20)	13 (22)	11 (18)	0.648
Medication				
ARB or ACE-I	71 (59)	38 (63)	33 (55)	0.431
β-blockers	35 (29)	16 (27)	19 (32)	0.521
Statins	120 (100)	60 (100)	60 (100)	
Rosuvastatin	39 (33)	16 (27)	23 (38)	0.172
Atorvastatin	23 (19)	11 (18)	12 (20)	0.817
Pitavastatin	23 (19)	10 (17)	13 (22)	0.487
Fluvastatin	17 (14)	11 (18)	6 (10)	0.191
Pravastatin	18 (15)	12 (20)	6 (10)	0.125
Eicosapentanoic acid	11 (9)	6 (10)	5 (8)	0.580
Insulin	7 (6)	5 (8)	2 (3)	0.219
Pioglitazone	4 (3)	2 (3)	2 (3)	0.691
Sulfonylurea	13 (11)	8 (13)	5 (8)	0.378
Other diabetes medications	17 (14)	8 (13)	9 (15)	0.793

Values are mean±SD or number (%).
LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CHD, coronary heart disease; GFR, glomerular filtration rate; TG, triglyceride; LVEF, left ventricular ejection fraction measured by echocardiogram; AHA/ACC, American Heart Association/American College of Cardiology.

(P<0.001), and r=0.96 (P<0.001) and r=0.97 (P<0.001), respectively].

According to the median value of obtained LDL-C/HDL-C ratios, that is, 2.4, they were divided into 2 groups [high LDL-C/HDL-C ratio (>2.4) group (n=60) or low LDL-C/HDL-C ratio (≤2.4) group (n=60)]. Table 1 shows the clinical characteristics of the enrolled patients. Of 120 patients with a mean age of 68±7 years, 95 (79%) were males. Lipid profiles obtained in patients with a high LDL-C/HDL-C ratio were worse than those with a low LDL-C/HDL-C ratio (total cholesterol levels, 199.6±30.6 mg/dl vs. 173.7±31.8 mg/dl, P<0.001; LDL-C levels, 128.8±24.2 mg/dl vs. 95.8±24.2 mg/dl, P<0.001; HDL-C levels, 40.2±8.9 mg/dl vs. 52.5±12.7 mg/dl, P<0.001; LDL-C/HDL-C ratio, 3.3±0.7 vs. 1.9±0.4, P<0.001; logarithmically transformed trtiglyceride levels, 2.2±0.2 mg/dl vs. 2.0±0.2 mg/dl, P=0.043).

Table 2 shows the QCA and IVUS data. QCA and conventional IVUS analysis showed no significant difference in the characteristics of LMCA plaques between the 2 groups. In the IB-IVUS assessment, at the section of the minimum lumen

Table 2. Data on QCA and Intravascular Imaging of Left Main Coronary Artery

	High LDL-C/HDL-C ratio (n=60)	Low LDL-C/HDL-C ratio (n=60)	P value
QCA			
Reference vessel diameter (mm)	5.1±0.8	4.9±0.8	0.084
Minimum lumen diameter (mm)	4.2±0.7	4.0±0.6	0.110
Diameter stenosis (%)	27±17	27±18	0.969
Lesion length (mm)	8.6±1.1	8.5±1.7	0.633
Conventional IVUS			
EEM area of MLA (mm^2)	23.6±5.7	23.3±6.2	0.842
Plaque area of MLA (mm^2)	10.0±2.9	10.1±4.1	0.897
Percent plaque area of MLA (%)	44±13	43±15	0.835
EEM volume (mm^3)	151.3±90.3	135.3±69.2	0.278
Plaque volume (mm^3)	59.5±33.7	53.1±33.0	0.302
Percent plaque volume (%)	41±10	39±11	0.345
IB-IVUS			
Lipid area of MLA (%)	51±10	55±12	0.206
Fibrous area of MLA (%)	45±10	42±12	0.426
High signal area of MLA (%)	1±1	1±1	0.061
Lipid volume (%)	52±10	48±10	0.014
Fibrous volume (%)	45±9	50±10	0.010
High signal volume (%)	1±1	1±2	0.301

Values are mean±SD.
QCA, quantitative coronary angiography; IVUS, intravascular ultrasound; EEM, external elastic membrane; MLA, minimum luminal area; IB, integrated backscatter. Other abbreviations see in Table 1.

Table 3. Univariate Linear Regression Analyses

	Percent lipid volume		Percent fibrous volume	
	Regression coefficient	P value	Regression coefficient	P value
Body mass index	0.230	0.012	–0.203	0.027
Diabetes	0.052	0.574	–0.036	0.695
LDL-C	0.142	0.122	–0.129	0.160
HDL-C	–0.254	0.005	0.258	0.005
LDL-C/HDL-C ratio	0.275	0.002	–0.261	0.004
Total cholesterol	–0.119	0.194	0.132	0.150
Logarithmic transformed TG	–0.056	0.544	0.049	0.600
Hemoglobin A_{1c}	0.105	0.262	–0.710	0.451

Abbreviations see in Table 1.

Table 4. Multiple Linear Regression Analyses

	Percent lipid volume			Percent fibrous volume		
	Regression coefficient	β coefficient	P value	Regression coefficient	β coefficient	P value
Male	1.470	0.060	0.548	–1.729	–0.074	0.460
Age	–0.670	–0.137	0.153	0.165	0.143	0.140
Body mass index	0.576	0.183	0.071	–0.492	–0.164	0.107
Current smoker	2.994	0.125	0.179	–2.451	–0.108	0.250
Hypertension	1.347	0.058	0.540	–1.315	–0.059	0.532
Diabetes	–1.077	–0.053	0.659	0.612	0.032	0.793
Hemoglobin A_{1c}	0.489	0.055	0.663	–0.184	–0.022	0.864
LDL-C/HDL-C ratio	2.890	0.252	0.010	–2.669	–0.245	0.012

Abbreviations see in Table 1.

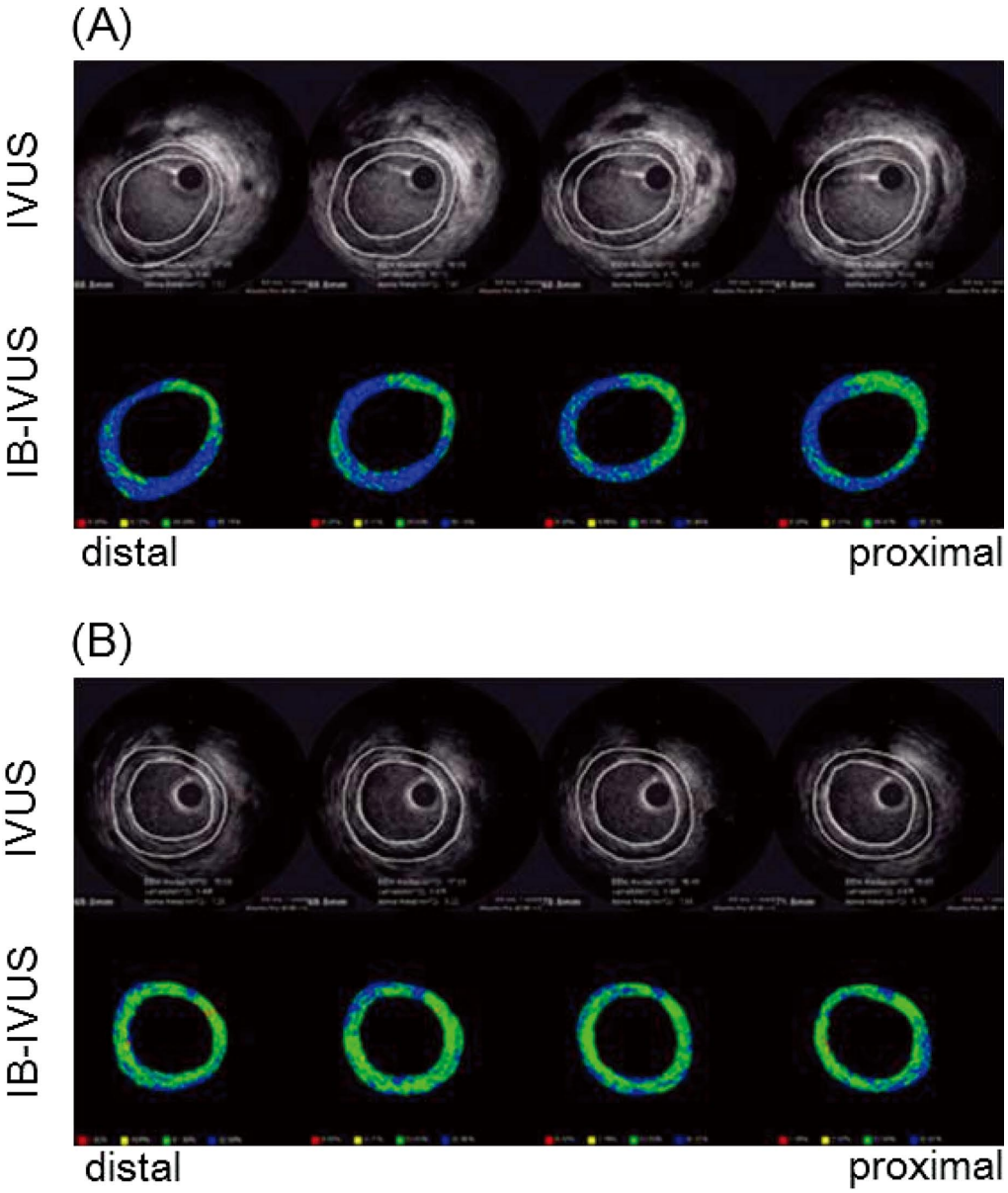

Figure. Representative images of serial conventional and integrated backscatter (IB) intravascular images. (**A**) A patient with a low- to high-density cholesterol (LDL-C/HDL-C) ratio of 3.47 (high LDL-C/HDL-C group).The percentages of lipid volume and of fibrous volume were 59% and 40%, respectively. (**B**) A patient with a LDL-C/HDL-C ratio of 1.24 (low LDL-C/HDL-C group). The percentages of lipid volume and of fibrous volume were 35% and 61%, respectively. IVUS, intravascular ultrasound.

area, no significant difference was observed as to the percent lipid area and fibrous area (51±10% vs. 55±12%, P=0.206 and 45±10% vs. 42±12%, P=0.426) However, in the volumetric analysis, patients with a high LDL-C/HDL-C ratio had a significantly higher percentage of lipid volume and a significantly lower percentage of fibrous volume of LMCA plaques compared to patients with a low LDL-C/HDL-C ratio (52±10% vs. 48±10%, P=0.014 and 45±9% vs. 50±10%, P=0.010).

The simple correlation coefficients between lipid or fibrous volume and obtained data of metabolic profiles are shown in Table 3. Body mass index and an LDL-C/HDL-C ratio had a mildly positive correlation with lipid volume (r=0.230, P=0.012 and r=0.275, P=0.002) and a mildly negative correlation with fibrous volume (r=–0.203, P=0.027 and r=–0.261, P=0.004). HDL-C levels had a mildly negative correlation with lipid volume and a mildly positive correlation with fibrous volume (r=–0.254, P=0.005 and r=0.258, P=0.005). In contrast, no significant correlation was observed between diabetes, LDL-C, hemoglobin A_{1c} levels, logarithmically transformed triglyceride and tissue components of LMCA plaques. Using multivariate linear regression analysis after adjustment for the above-mentioned confounding factors, a LDL-C/HDL-C ratio had a significantly positive correlation with lipid volume and had a significantly negative correlation with fibrous volume in coronary plaques (β=0.252, P=0.01 and β=–0.245, P=0.012) (Table 4).

Discussion

In the present study, we showed that stable AP patients with a high LDL-C/HDL-C ratio had a higher percentage of lipid volume and a lower percentage of fibrous volume of LMCA plaques compared to patients with a low LDL-C/HDL-C ratio. On multivariate linear regression analysis, after adjustment for various confounding factors, the LDL-C/HDL-C ratio remained an independent predictor for characteristics of tissue components of LMCA plaque.

Coronary plaque with a high percentage of lipid volume and a low percentage of fibrous volume is associated with plaque vulnerability. Reports have suggested that rupture of vulnerable coronary plaque, which evolves most frequently from mild to moderate stenosis, causes ACS including sudden cardiac death.[19] Although, in a clinical setting, the incidence of ACS due to LMCA plaque rupture is rare,[20] when it occurs, the prognosis is usually highly unfavorable because of the danger of severe pump failure and/or ventricular arrhythmias, except in cases with substantial pre-existing intero collaterals and/or rapidly complete reperfusion.[6,7] A plaque rupture might not necessarily cause ACS. A study which investigated the relationship between the clinical and angiographic observation with plaque rupture, detected by IVUS, has demonstrated that 22% of coronary plaque ruptured even in patients with stable angina or asymptomatic patients.[21] Significant clinical results might depend on other conditions (eg, original or coexisting stenosis, thrombus formation). The incidence of plaque rupture of LMCA itself is also relatively rare. Among 225 plaque ruptures in 223 patients, 10 (4%)/77 (34%)/28 (12%)/110 (49%) were reportedly located in LMCA/LAD/LCX/RCA, respectively.[21] In contrast, some angiographic studies have shown that patients with a more complex lesion or thrombus indicating plaque rupture or erosion tend to have a sudden progression of plaques.[22] Pathologically, plaque progression is associated with subclinical plaque rupture.[23] Detailed LMCA plaque observation might contribute to elucidate the advancement and mechanisms of arteriosclerosis, as well as sudden cardiac death. Therefore we used LMCA lesions as a target of this study. Appropriate risk stratification and early intervention for this disease is considered essential. For the detection of a lipid-rich plaque, in vivo detection of the tissue components of coronary plaque is required. Recently, IB-IVUS has added to perform analysis of the tissue components of coronary plaque in vivo,[3] and studies using this technique have revealed that patients with coronary risk factors including high insulin levels, metabolic syndrome, diabetes, and/or chronic kidney disease have a high prevalence of lipid-rich coronary plaque.[24,25]

It is well established that high serum levels of LDL-C constitute a strong predictor of CHD, and that LDL-C-lowering therapy reduces CHD.[26] The LDL-C/HDL-C ratio was found to be a more accurate in determining CHD risk, compared to LDL-C or HDL-C alone.[8,27] Several studies have demonstrated that a 1-unit increase in the LDL-C/HDL-C ratio is equivalent to a 53–75% increase in the risk of myocardial infarction.[9] The LDL-C/HDL-C ratio is also an excellent surrogate marker of lipid-lowering therapies.[8] Based on data from clinical trials using conventional IVUS (REVERSAL, CAMEROT, ACTIVATE, and ASTEROID),[9–13,28] a high LDL-C/HDL-C ratio is associated with coronary plaque progression, while a low LDL-C/HDL-C ratio achieved by pharmacological intervention is associated with coronary plaque regression. In the present study, a high LDL-C/HDL-C ratio was related to a high percentage of lipid volume in LMCA plaques, suggesting that patients with a high LDL-C/HDL-C ratio might be at a higher risk for LMCA plaque rupture, as well as a progression of coronary plaque, compared with those with a low LDL-C/HDL-C ratio. We speculated that AP patients with a high LDL-C/HDL-C ratio should undergo intensive treatment to reduce that ratio, including lifestyle modification and pharmacological intervention for the purpose of a secondary prevention.

It has been reported that in the analysis of severe stenotic (culprit) coronary plaques, including only as little as 2% of an LMCA lesion, an elevated LDL-C/HDL-C ratio is a positive predictor for lipid-rich coronary plaque in patients with chronic CHD.[29] Tyczynski et al have shown that plaque rupture tends to occur in the distal part of an LMCA.[30] This differs from a left anterior descending, left circumflex, and right coronary artery, in which plaque ruptures tend to occur within the proximal one third.[31] In addition, LMCA is histologically dissimilar to the 3 major coronary arteries in its abundance of elastic tissue. Thus, we considered that it is important to evaluate LMCA lesions separately from the other 3 major vessels. Patients with a LMCA that has an angiographically >50% diameter stenosis have a poor prognosis, although surgical treatment improves their survival.[17,32] However, there are only a few studies regarding the prognosis or treatment of patients with LMCA that is <50% in diameter for stenosis. Moreover, to assess an LMCA lesion angiographically (especially one that is mildly diseased) is often difficult and unreliable, although coronary angiography is adopted as the gold standard to evaluate coronary artery stenosis.[33] To determine the prognosis of patients who had an angiographically ambiguous LMCA lesion, as well as to more accurately evaluate LMCA lesions, clinical studies have reported the use of several modalities including conventional IVUS, fractional flow reserve, and multidetector computed tomography.[34–36] In the present study, characteristics of the tissue components of LMCA plaques detected using IB-IVUS were associated with the LDL-C/HDL-C ratio, which is a potent predictor of future cardiovascular events. Therefore, we speculated that the characteristics of those tissue components might be able to predict a patient's prognosis. However, because there were so few reports on the matter, further investigations are warranted. Subsequent clinical data might contribute to determining a highly stratified treatment strategy for LMCA lesions.

Limitations of the present study need to be addressed. First, this study consisted of a relatively low number of patients from a single center. The current patients were primarily referred for issues involving revascularization. In addition, patients with a severe stenotic lesion at the LMCA or right coronary were excluded. Second, only patients with a stable angina were evaluated. Thus, the prevalence of plaques in patients who had exclusion criteria in the present study should be evaluated in any future study. Third, we were unable to accurately assess the period of statin treatment. To resolve this matter, patients with newly prescribed statin treatment within 6 months before the procedure were certainly excluded. However, further changes might occur with statin treatment that was given for over 6 months. Thus, an uncertain duration of statin treatment was one of the limitations of the present study. Finally, calcification perfectly reflects ultrasound, causing the acoustic shadowing typically observed in IVUS images.[37] Therefore, an accurate evaluation of the tissue components behind calcification was difficult, although a calculation for it was performed in the present study. Furthermore, minor injury to the surface of coronary plaques might occur during a simple IVUS passage; an occurrence that might introduce a bias into the results, thus limiting the generalizability of our findings.

In conclusion, a high LDL-C/HDL-C ratio was associated with a higher percent of lipid volume and a lower percent of fibrous volume of angiographically ambiguous LMCA lesions. As revealed by a multivariate linear regression analysis after adjustment for confounding factors, an LDL-C/HDL-C ratio had a significantly positive correlation with lipid volume and a significantly negative correlation with fibrous volume in LMCA plaques.

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Disclosures

None to declare.

References

1. Fuster V, Lewis A. Conner Memorial Lecture: Mechanisms leading to myocardial infarction: Insights from studies of vascular biology. *Circulation* 1994; **90:** 2126–2146.
2. Schoenhagen P, Tuzcu EM, Ellis SG. Plaque vulnerability, plaque rupture, and acute coronary syndromes: (Multi)-focal manifestation of a systemic disease process. *Circulation* 2002; **106:** 760–762.
3. Kawasaki M, Takatsu H, Noda T, Sano K, Ito Y, Hayakawa K, et al. In vivo quantitative tissue characterization of human coronary arterial plaques by use of integrated backscatter intravascular ultrasound and comparison with angioscopic findings. *Circulation* 2002; **105:** 2487–2492.
4. Sano K, Kawasaki M, Ishihara Y, Okubo M, Tsuchiya K, Nishigaki K, et al. Assessment of vulnerable plaques causing acute coronary syndrome using integrated backscatter intravascular ultrasound. *J Am Coll Cardiol* 2006; **47:** 734–741.
5. Miyagi M, Ishii H, Murakami R, Isobe S, Hayashi M, Amano T, et al. Impact of chronic statin therapy on coronary plaque composition at angiographically severe lesions: A non-randomized study focused on history of chronic statin treatment before coronary angioplasty. *Clin Ther* 2009; **31:** 64–73.
6. Spiecker M, Erbel R, Rupprecht HJ, Meyer J. Emergency angioplasty of totally occluded left main coronary artery in acute myocardial infarction and unstable angina pectoris: Institutional experience and literature review. *Eur Heart J* 1994; **15:** 602–607.
7. Yoshikawa D, Isobe S, Umeda H, Kawai T, Shimizu T, Yamashita K, et al. Three-year prognosis of Japanese patients with ST-elevation myocardial infarction treated with sirolimus-eluting stents. *Coron Artery Dis* 2009; **20:** 422–427.
8. Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Mänttäri M, Heinonen OP, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: Implications for treatment. *Circulation* 1992; **85:** 37–45.
9. Schoenhagen P, Tuzcu EM, Apperson-Hansen C, Wang C, Wolski K, Lin S, et al. Determinants of arterial wall remodeling during lipid-lowering therapy: Serial intravascular ultrasound observations from the Reversal of Atherosclerosis with Aggressive Lipid Lowering Therapy (REVERSAL) trial. *Circulation* 2006; **113:** 2826–2834.
10. Brener SJ, Ivanc TB, Poliszczuk R, Chen M, Tuzcu EM, Hu T, et al. Antihypertensive therapy and regression of coronary artery disease: Insights from the Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) and Norvasc for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation (NORMALISE) trials. *Am Heart J* 2006; **152:** 1059–1063.
11. Nissen SE, Tuzcu EM, Brewer HB, Sipahi I, Nicholls SJ, Ganz P, et al. Effect of ACAT inhibition on the progression of coronary atherosclerosis. *N Engl J Med* 2006; **354:** 1253–1263.
12. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: The ASTEROID trial. *JAMA* 2006; **295:** 1556–1565.
13. Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA* 2007; **297:** 499–508.
14. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density-lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18:** 499–502.
15. Ricciardi MJ, Meyers S, Choi K, Pang JL, Goodreau L, Davidson CJ. Angiographically silent left main disease detected by intravascular ultrasound: A marker for future adverse cardiac events. *Am Heart J* 2003; **146:** 507–512.
16. Ryan TJ, Bauman WB, Kennedy JW, Kereiakes DJ, King SB 3rd, McCallister BD, et al. Guidelines for percutaneous transluminal coronary angioplasty: A report of the American Heart Association/American College of Cardiology Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Percutaneous Transluminal Coronary Angioplasty). *Circulation* 1993; **88:** 2987–3007.
17. European Coronary Surgery Study Group. Long-term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris. *Lancet* 1982; **2:** 1173–1180.
18. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, et al. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS): A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2001; **37:** 1478–1492.
19. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995; **92:** 657–671.
20. Erbel R, Meinertz T, Wessler I, Meyer J, Seybold-Epting W. Recanalization of occluded left main coronary artery in unstable angina pectoris. *Am J Cardiol* 1984; **53:** 1725–1727.
21. Maehara A, Mintz GS, Bui AB, Walter OR, Castagna MT, Canos D, et al. Morphologic and angiographic features of coronary plaque rupture detected by intravascular ultrasound. *J Am Coll Cardiol* 2002; **40:** 904–910.
22. Yokoya K, Takatsu H, Suzuki T, Hosokawa H, Ojio S, Matsubara T, et al. Process of progression of coronary artery lesions from mild or moderate stenosis to moderate or severe stenosis: A study based on four serial coronary arteriograms per year. *Circulation* 1999; **100:** 903–909.
23. Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J, et al. Healed plaque ruptures and sudden coronary death: Evidence that subclinical rupture has a role in plaque progression. *Circulation* 2001; **103:** 934–940.
24. Amano T, Matsubara T, Uetani T, Nanki M, Marui N, Kato M, et al. Abnormal glucose regulation is associated with lipid-rich coronary plaque: Relationship to insulin resistance. *JACC Cardiovasc Imaging* 2008; **1:** 39–45.
25. Miyagi M, Ishii H, Murakami R, Isobe S, Hayashi M, Amano T, et al. Impact of renal function on coronary plaque composition. *Nephrol Dial Transplant* 2010; **25:** 175–181.
26. Sakamoto T, Ogawa H. "Just make it lower" is an alternative strategy of lipid-lowering therapy with statins in Japanese patients: LDL-cholesterol: The lower, the better; is it true for Asians? (Con) *Circ J* 2010; **74:** 1731–1741.
27. Kannel WB. Lipids, diabetes, and coronary heart disease: Insights from the Framingham Study. *Am Heart J* 1985; **110:** 1100–1107.
28. Takayama T, Hiro T, Yamagishi M, Daida H, Hirayama A, Saito S, et al. Effect of rosuvastatin on coronary atheroma in stable coronary artery disease: Multicenter coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese subjects (COSMOS). *Circ J* 2009; **73:** 2110–2117.
29. Kimura T, Itoh T, Fusazaki T, Matsui H, Sugawara S, Ogino Y, et al. Low-density lipoprotein-cholesterol/high-density lipoprotein-cholesterol ratio predicts lipid-rich coronary plaque in patients with coronary artery disease: Integrated-backscatter intravascular ultrasound study. *Circ J* 2010; **74:** 1392–1398.
30. Tyczynski P, Pregowski J, Mintz GS, Witkowski A, Kim SW, Waksman R, et al. Intravascular ultrasound assessment of ruptured atherosclerotic plaques in left main coronary arteries. *Am J Cardiol* 2005; **96:** 794–798.
31. Hong MK, Mintz GS, Lee CW, Lee BK, Yang TH, Kim YH, et al. The site of plaque rupture in native coronary arteries: A three-vessel intravascular ultrasound analysis. *J Am Coll Cardiol* 2005; **46:** 261–265.
32. Taylor HA, Deumite NJ, Chaitman BR, Davis KB, Killip T, Rogers WJ. Asymptomatic left main coronary artery disease in the Coronary Artery Surgery Study (CASS) registry. *Circulation* 1989; **79:** 1171–1179.
33. Bergelson BA, Tommaso CL. Left main coronary artery disease: Assessment, diagnosis, and therapy. *Am Heart J* 1995; **129:** 350–359.
34. Jasti V, Ivan E, Yalamanchili V, Wongpraparut N, Leesar MA. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis.

Circulation 2004; **110:** 2831–2836.
35. Abizaid AS, Mintz GS, Abizaid A, Mehran R, Lansky AJ, Pichard AD, et al. One-year follow-up after intravascular ultrasound assessment of moderate left main coronary artery disease in patients with ambiguous angiograms. *J Am Coll Cardiol* 1999; **34:** 707–715.
36. Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. *J Am Coll Cardiol* 2010; **55:** 2399–2407.
37. Friedrich GJ, Moes NY, Mühlberger VA, Gabl C, Mikuz G, Hausmann D, et al. Detection of intralesional calcium by intracoronary ultrasound depends on the histologic pattern. *Am Heart J* 1994; **128:** 435–441.