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Clinical Importance of the LDL-C/Apolipoprotein B Ratio for Neointimal Formation after Everolimus-Eluting Stent Implantations

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Aims: Smaller low-density lipoprotein (LDL) particle size has been suggested to result in the development of endothelial dysfunction, atherosclerosis, and in-stent restenosis (ISR); however, little is known regarding the impact of the LDL particle size on the neointima formation leading to ISR after everolimus-eluting stent (EES) implantation.

Methods: In this study, we have included 100 patients to examine the relationship between an LDL-C/apolipoprotein B (Apo B) ≤ 1.2, reportedly representing the LDL particle size, and the neointimal characteristics using optical coherence tomography (OCT) and coronary angioscopy (CAS) during the follow-up coronary angiography (CAG) period (8.8 ± 2.5 months) after EES implantation. We divided them into two groups: LDL-C/Apo B ≤ 1.2 group (low LDL-C/Apo B group, $n=53$) and LDL-C/Apo B > 1.2 group (high LDL-C/Apo B group, $n=47$).

Results: The low LDL-C/Apo B group had a significantly larger neointimal volume (12.8 ± 5.3 vs. 10.3 ± 4.9 mm^3, $p=0.021$) and lower incidence of a neointimal homogeneous pattern (71 vs. 89 %), higher incidence of a neointimal heterogeneous pattern (25 vs. 9 %) ($p=0.006$) and higher prevalence of macrophage accumulation (9 vs. 2 %) ($p=0.030$) as assessed via OCT, and, as per the CAS findings, a higher prevalence of yellow grade ≥ 2 (grade 2; adjusted residual: 2.94, grade 3; adjusted residual: 2.00, $p=0.017$) than the high LDL-C/Apo B group.

Conclusions: A low LDL-C/Apo B ratio was found to be strongly associated with neointimal proliferation and neointimal instability evidenced chronically by OCT and CAS. An LDL-C/Apo B ≤ 1.2 will be of aid in terms of identifying high-risk patients after EES implantation.

Key words: Low-Density Lipoprotein Cholesterol (LDL-C)/apolipoprotein B ratio, Neointimal volume, Neointimal grade, Yellow grade, Everolimus-eluting stent, Optical coherence tomography, Coronary angioscopy

1. Introduction

Low-density lipoprotein cholesterol (LDL-C) is a collection of broad lipoproteins with a specific gravity of 1.019 to 1.063 g/mL and has several subfractions with different particle sizes. Among the LDL-C subfractions, LDL-Cs with a small particle size and heavy gravity is defined as small dense LDL-C (sd-LDL-C). The sd-LDL-C has been often associated with atherosclerosis lipoproteins because of its low affinity for the LDL receptors, easy penetrance into the vessel walls, long blood half-life, and high oxidizability[1]. Numerous reports have suggested a relationship between sd-LDL-C and the onset of cardiovascular diseases (CVDs)[2-4], but a direct measurement of sd-LDL-C has not been widely used

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in clinical practice in Japan. The LDL-C/apolipoprotein B (Apo B) ratio has been reported to indirectly express the LDL particle size[5]. An LDL particle size of ≤ 25.5 nm is the cutoff value for the classification between a large buoyant LDL and sd-LDL. This cutoff value is suggested to correspond to an LDL-C/Apo B ratio of ≤ 1.2; therefore, it indicates a predominance of sd-LDL particles[6, 7]. On the other hand, coronary imaging modalities such as intravascular ultrasound (IVUS), optical coherence tomography (OCT), and coronary angioscopy (CAS) can assess the detailed characteristics of the neointimal tissues at the implanted stent site. Especially, the OCT-derived neointimal characteristics and CAS-derived yellow grade have been identified to be well-known markers for vulnerable plaque or neoatherosclerosis and future cardiovascular outcomes[8]. Therefore, the intravascular evaluation of the stent placement using multi-modalities during the follow-up coronary angiography (CAG) period might be vital for predicting the prognosis. Nonetheless, a few reports have already evaluated the relationship between the predominance of sd-LDL particles and detailed neointimal characteristics using both OCT and CAS during the follow-up CAG period after implantation of third-generation drug-eluting stents (DESs)[9, 10].

2. Aim

We, herein, evaluated the relationship between an LDL-C/Apo B ratio ≤ 1.2 (reflecting the predominance of the sd-LDL particles) and the future neointimal characteristics after third-generation everolimus-eluting stent (EES) implantation using OCT and CAS.

3. Methods

3.1 Study Population

The data analyzed in this study were retrospectively obtained from 465 consecutive patients who underwent elective percutaneous coronary intervention (PCI) from April 2016 to March 2019. The inclusion criteria were patients who underwent third-generation EES implantations for stable angina and with stenting site assessed by OCT and CAS during the follow-up CAG and those in whom the LDL-C and apolipoprotein B levels were measured. Among the 465 patients, the following were excluded from the study: 21 who had a history of coronary artery bypass grafting (CABG), 105 who had incomplete imaging studies (in terms of the imaging quality or timing), 39 with missing CAS data, 239 with missing OCT data, and 125 with missing Apo B data. As a result, the remaining 100 patients were included for analysis. We then divided them into two groups according to an LDL-C/Apo B level of 1.2 at the time of PCI: low LDL-C/Apo B ≤ 1.2 group [n=53] and high LDL-C/Apo B >1.2 group [n=47]. This study was a retrospective observational study; thus, it was carried out via opt-out method on our hospital websites. The study protocol was reviewed and approved by the Ethics Committee of Nihon University Itabashi Hospital.

3.2 Patient Characteristics, Laboratory and Procedural Parameters, and Clinical Outcomes

The patient characteristics at the time of PCI were obtained by reviewing their respective hospital charts. Blood samples were collected after about 10–12 hours of fasting in the early morning on the day of the PCI. The LDL-C serum level was measured using the Friedewald formula[11], and the serum Apo B level and malondialdehyde-modified LDL (MDA-LDL) level, which is a molecular species of oxidized LDL, were measured via turbidimetric latex agglutination assays (SRL).

3.3 Optical Coherence Tomography

OCT was performed during the follow-up CAG in the total study patients. The SJM FD-OCT imaging system (Abbott Medical Japan Co., Ltd. and LightLab Imaging, Inc., USA) and SJM FD-OCT Integrated imaging system (Abbott Medical Japan Co., Ltd., LightLab Imaging, Inc., USA, and St. Jude Medical, Atrial Fibrillation Division, Inc, USA) were used in this present study. The brief OCT method was described elsewhere[12]. The image analysis was performed using the SJM FD-OCT Integrated imaging system (Abbott Medical Japan Co., Ltd., LightLab Imaging, Inc., USA, and St. Jude Medical, Atrial Fibrillation Division, Inc, USA). As for the OCT assessment, the lumen and stent areas were traced automatically **(Fig. 1A)**. The neointimal area was defined and calculated as the stent area minus the lumen area[13], whereas the neointimal area (*) was measured every 1 mm from the distal to the proximal stent edge. The neointimal volume = the number of slices × neointimal area. For a qualitative analysis, the OCT signal patterns of the neointimal tissue were categorized into three patterns based on Gonzalo's classification[13]: homogeneous, heterogeneous, and layered patterns (as shown in **Fig. 1B**). An assessment of the tissue characteristics was carried out at the in-stent maximal lumen narrowing site, as determined by the agreement of two observers blinded to the clinical and procedural characteristics[14].

Figure 1A: Representative intravascular optical coherence tomography signal patterns

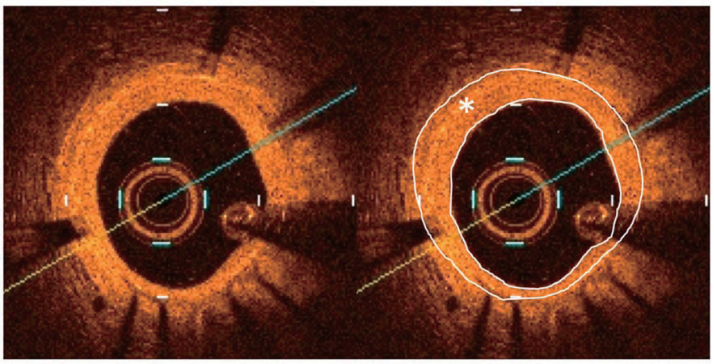


Figure 1B: OCT signal patterns of the neointimal tissue

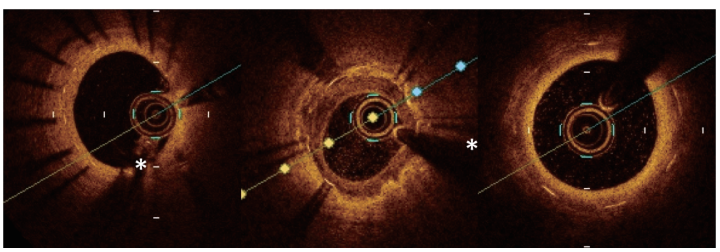


Figure 1C: OCT signal pattern of the macrophage accumulation

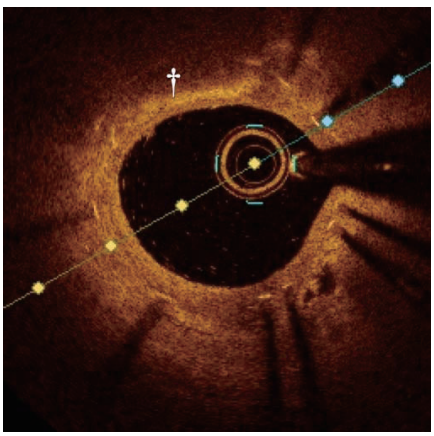
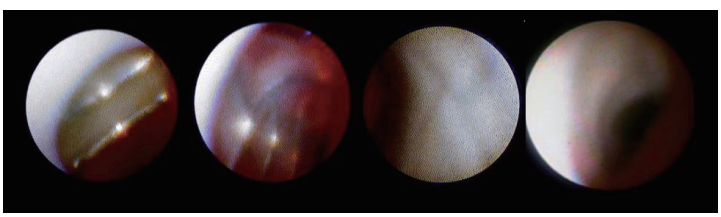
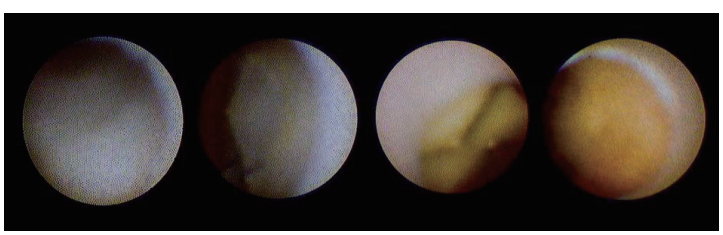


Figure 1D: CAS neointimal coverage grade



grade0 grade1 grade2 grade3

Figure 1E: CAS yellow grade



grade0 grade1 grade2 grade3

Fig. 1. Representative image of the assessment of the intravascular OCT volume (A), OCT signal patterns of the neointimal tissue (B) and an OCT signal pattern of the macrophage

(A) The stent strut and lumen border (indicated by white outlines) were automatically detected. (B) A homogeneous pattern is defined by the uniform optical properties with a mature neointima composed of collagen fibers and proteoglycans (left panel). A heterogeneous pattern is defined by focally-changing neointimal optical properties and various backscattering patterns with an immature tissue centered on the extracellular matrix (middle panel). A layered pattern is defined by the presence of concentric layers with an abluminal high-scattered layer and abluminal low-scattered layer (right panel). *Guide-wire artifact. (C) Macrophage accumulation† was defined as signal-rich, distinct, or confluent punctate that exceeded the intensity of the background speckle noise. Representative images used to classify the neointimal coverage grade (D) and that of the yellow grade (E) assessed by CAS. The details are shown in the text. CAS, coronary angioscopy; OCT, optical coherence tomography.

We have also examined the accumulation of macrophages. Macrophage accumulation was defined as signal-rich, distinct, or confluent punctate that exceeded the intensity of the background speckle noise (Fig. 1C). At least, one macrophage accumulation was noted every 1 mm from the distal to the proximal stent edge and was defined as the presence of macrophage accumulation.

3.4 Coronary Angioscopy

During the follow-up CAG, all patients underwent CAS to evaluate the yellow grade (maximum grade) and neointimal coverage grade (minimum grade) at the proximal, mid, and distal sites of each stent. CAS was performed using a VISIBLE fiber imaging catheter (FiberTech Co. Ltd., Japan) and i-Light endoscope system (iHeart Medical Co. Ltd., Japan). The outer section of a 4F probing catheter (Medikit, Japan) was used to guide for the insertion of the optical fiber into the coronary artery. While the angioscopic observations were carried out, blood was removed from the view by injecting 10% dextran through the probing catheter as previously reported[15, 16]. The angioscopy images were recorded on a digital recorder.

The neointimal grade on the stent struts and yellow grade of the plaque, which reportedly indicate plaque vulnerability, were assessed by classifying them into four grades as previously described[9]. The neointimal grades were as follows: grade 0, complete exposure of the stent struts; grade 1, dull light reflection from the stent struts; grade 2, no light reflection from the stent struts with slightly visible struts; and grade 3, complete coverage (Fig. 1D). The yellow grade was classified as either of the following: grade 0, white; grade 1, light yellow; grade 2, yellow; or grade 3, bright yellow (Fig. 1E)[17]. The CAS evaluations were made by two independent coronary intervention specialists and angioscopy by those blinded to the patients' clinical status. In case of disagreement, the plaque color was reevaluated. If the reevaluations remained discordant, the disagreement was resolved through discussion until a consensus was reached.

3.5 Statistical Analysis

Data are expressed as means ± standard deviation (SD) or numbers (%). Data that did not have a normal distribution are expressed as medians (interquartile range). The mean values between the two groups were tested using the Student's *t*-test and Mann-Whitney *U* test as appropriate. Comparisons of the mean values or categorical variables during different time periods were analyzed using chi-square test and Fisher's exact test as appropriate. Four-group differences were analyzed via ANOVA, followed by Bonferroni post-hoc adjustment or Kruskal-Walls and then Steel-Dwass post-hoc adjustment as appropriate. Correlations between two categories were analyzed via Spearman's rank correlation coefficient. A single regression analysis was conducted to identify the contribution of each lipid parameter to the neointimal volume, neointimal grade, and yellow grade. Meanwhile, a multiple regression analysis was conducted to identify the neointimal volume and grade and yellow grade. Several lipid profile and high-sensitivity CRP values were determined to have a skewed distribution; thus, those values were log-transformed. The significant variables determined via univariate analysis were entered into this model. We considered $p<0.05$ to be statistically significant. All data were analyzed using EZR (Easy R) software, which is based on R and R commander[18].

4. Results

4.1 Baseline Patient, Lipid Profile, and Procedural Characteristics

The patients and lesion characteristics at the time of PCI per study group in the total patients are presented in Table 1. In brief, no differences were noted in terms of age, height, or body weight, the prevalence of male sex, medication use, hemoglobin A1c level, and the high-sensitivity CRP levels. The proportion of hypertension cases in the "Low LDL-C/Apo B" group was higher than that in the "High LDL-C/Apo B" group (70 vs. 45 %, $p=0.011$). No definitive difference was noted in the stent sites between the two groups. The PCI procedural characteristics between the "Low LDL-C/Apo B" and "High LDL-C/Apo B" groups are shown in Table 1. The stent profiles and the predilatation and postdilatation balloon profiles were observed to not significantly differ between the two groups.

4.2 Findings of Intracoronary Imaging in the Follow-Up CAG in the "Low LDL-C/Apo B" and "High LDL-C/Apo B" Groups

The follow-up CAG was performed at 8.9 ± 2.8 months after the initial PCI for the "Low LDL-C/Apo B" group and 8.6 ± 2.1 months for the "High LDL-C/Apo B" group ($p=0.57$). A representative example of the OCT-derived neointimal volume obtained during the follow-up CAG between the two groups is shown in Fig. 2A. Among those patients, the OCT-derived neointimal volume was significantly larger (12.8 ± 5.3 vs. 10.3 ± 4.9 mm^3, $p=0.021$), and lumen volume in the "Low LDL-C/Apo B" group was smaller than that

Table 1. Patient characteristics at the time of PCI per study group

	Low LDL-C/Apo B group ($n=53$)	High LDL-C/Apo B group ($n=47$)	p value*
Age (years)	65.6 ± 11.8	64.6 ± 13.8	0.71
Male sex	45 (85)	39 (83)	0.79
Height (cm)	164.7 ± 9.4	163.8 ± 9.3	0.66
Weight (kg)	66.7 ± 14.4	65.6 ± 14.4	0.70
Body mass index (kg/m^2)	24.4 ± 3.6	24.3 ± 3.4	0.85
Medication use			
DAPT	53 (100)	47 (100)	0.99
ACE-I/ARB	38 (72)	37 (79)	0.42
βblockers	25 (47)	28 (60)	0.21
Statins	50 (94)	43 (91)	0.58
Maximum dose of any statin	12 (24)	6 (14)	0.22
Comorbidities			
Hypertension	37 (70)	21 (45)	0.011
Diabetes	16 (30)	9 (19)	0.20
Hemodialysis	2 (4)	2 (4)	0.90
Laboratory examination			
Hemoglobin A1c (NGSP) (%)	6.3 ± 0.8	6.4 ± 0.9	0.76
High-sense CRP (mg/dL)	0.132 (0.068-0.679)	0.103 (0.027-0.273)	0.11
eGFR(mL/min/1.73mm^2)	61.8 ± 24.4	71.9 ± 28.7	0.19
Coronary features			
Stented vessels			
LMT	0 (0)	0 (0)	>0.99
LAD	34 (64)	32 (68)	0.34
LCX	9 (17)	6 (13)	0.56
RCA	10 (19)	9 (19)	0.97
Stent profiles			
Diameter (mm)	3.2 ± 0.5	3.0 ± 0.5	0.20
Length (mm)	25.6 ± 7.2	27.9 ± 8.3	0.14
Predilatation (%)	45 (82)	42 (88)	0.51
Diameter (mm)	2.3 ± 0.5	2.3 ± 0.3	0.41
Length (mm)	13.3 ± 1.7	13.6 ± 1.6	0.43
Scoring balloon (n)	12 (27)	8 (19)	0.40
Postdilatation (%)	42 (79)	36 (77)	0.75
Diameter (mm)	3.2 ± 0.5	3.1 ± 0.6	0.22
Length (mm)	12.1 ± 2.9	11.6 ± 1.6	0.35

Values are the mean ± SD, median (interquartile ranges), or n (%). Abbreviations: ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker; DAPT, dual antiplatelet therapy; eGFR, estimated-glomerular filtration rate; high-sense CRP, high-sense C-reactive protein; NGSP, national glycohemoglobin standardization program; LMT, left main trunk; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery *by a Student-t test, Mann-Whitney U test, chi-square test, or Fisher exact test as appropriate.

in the "High LDL-C/Apo B" group (47.9 ± 21.0 vs. 56.9 ± 22.9 mm^3, $p=0.044$) **(Fig. 2B)**. With regard to the neointimal properties, the homogeneous pattern in the "Low LDL-C/Apo B" group had a significantly lower proportion than predicted, as compared to the "High LDL-C/Apo B" group (71% vs. 89%, adjusted residual: −2.01). Furthermore, the heterogeneous pattern in the "Low LDL-C/Apo B" group had a significantly higher proportion than predicted as compared to the "High LDL-C/Apo B" group (25 % vs. 9 %, adjusted residual: 3.88) (chi-square test: $p=0.006$) **(Fig. 2C)**. Regarding the macrophage accumulation, the "Low LDL-C/Apo B" group had a significantly higher proportion than predicted as compared to the "High LDL-C/Apo B" group (9 % [5/53] vs. 2 % [1/47], chi-square test: $p=0.030$, adjusted residual: 6.54).

The CAS assessment of the neointimal grade

Figure 2A: Representative OCT images

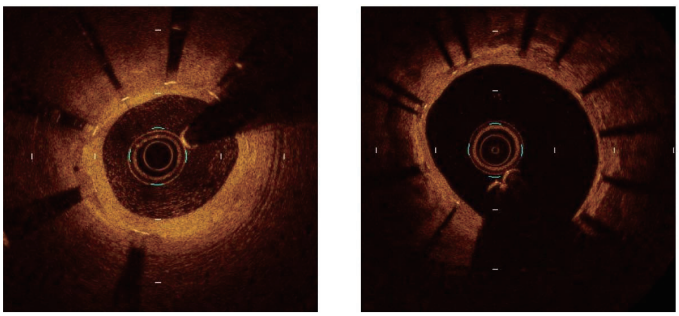


Figure 2B: OCT volumes

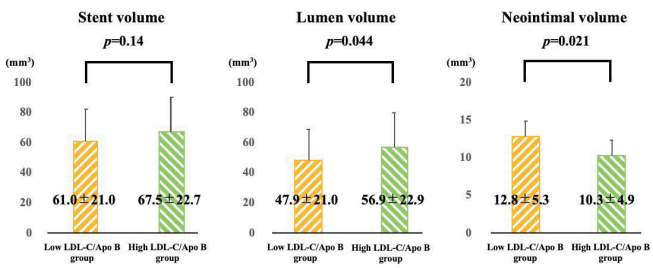


Figure 2C: Proportion of neointimal properties

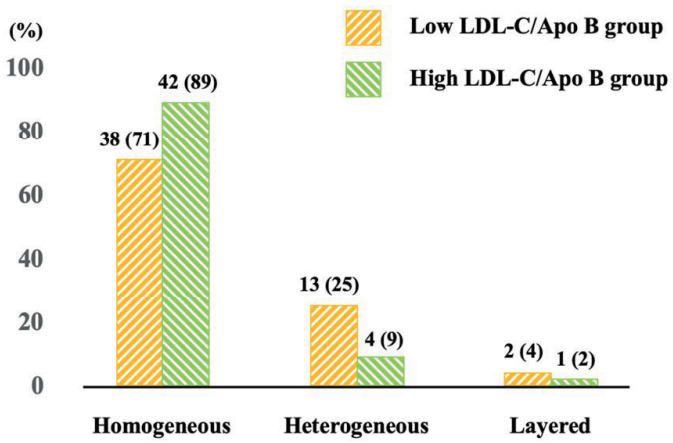


Figure 2D: Distribution of the neointimal coverage grade

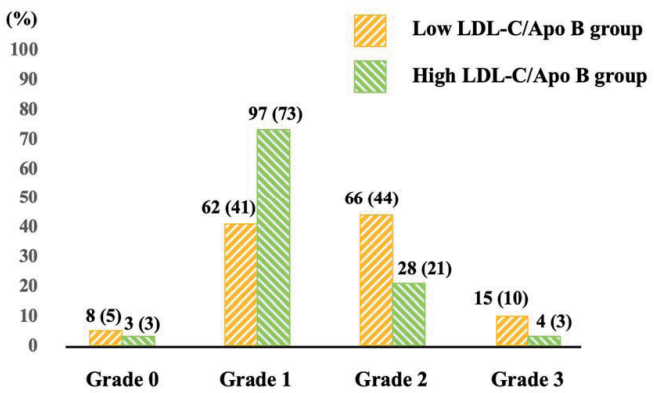


Figure 2E: Distribution of the yellow grade

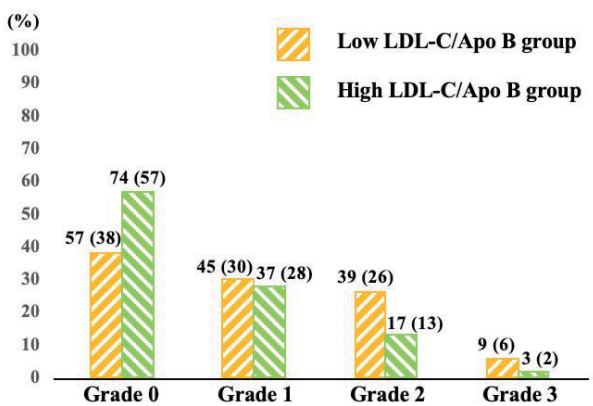


Fig. 2. Representative images of the (A), stent, lumen, and neointimal volume (B), and proportion of neointimal properties (C) by OCT

The left image is from a "Low LDL-C/Apo B" group case, and right image from a "High LDL-C/Apo B" group case (A). The distribution of the neointimal coverage grade (D) and yellow grade ratings (E) assessed by CAS between the "Low LDL-C/Apo B" and "High LDL-C/Apo B" groups. The details are shown in the text. Apo B, Apolipoprotein B; CAS, coronary angioscopy; OCT, optical coherence tomography.

revealed that a neointimal grade ≥ 2 in the "Low LDL-C/Apo B" group has exhibited significantly higher proportions than predicted as compared with the "High LDL-C/Apo B" group (54 % vs. 24 %, chi-square test: $p<0.001$) (adjusted residual; grade 2: 4.03, grade 3: 2.74) (Fig. 2D). Higher proportions were also observed than predicted of yellow grade ≥ 2 in the "Low LDL-C/Apo B" group than in the "High LDL-C/Apo B" group (32 % vs. 15 %, chi-square test: $p=0.017$) (adjusted residual; grade 2: 2.94, grade

Table 2. Factors of the neointimal volume on OCT and neointimal grade and yellow grade on CAS adjusted by the significant variables

	Neointimal volume		Neointimal grade		Yellow grade	
Variables	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	0.99 (0.96-1.03)	0.77	1.02 (0.98-1.06)	0.26	1.05 (0.99-1.08)	0.08
Sex	0.63 (0.17-2.30)	0.49	0.82 (0.23-3.01)	0.77	1.29 (0.69-9.51)	0.24
DM	1.62 (0.56-4.69)	0.38	1.48 (0.50-4.32)	0.49	1.34 (0.38-3.54)	0.41
LDL-C	1.01 (0.99-1.03)	0.24	0.99 (0.97-1.01)	0.23	1.04 (0.96-1.08)	0.25
HDL-C	0.99 (0.96-1.04)	0.85	1.02 (0.97-1.06)	0.50	0.99 (0.96-1.03)	0.59
Log-transformed TG	3.31 (0.41-7.96)	0.20	1.26 (0.09-17.8)	0.86	1.17 (0.51-5.65)	0.48
Log-transformed MDA-LDL	16.3 (0.59-452)	0.09	7.21 (0.24-217)	0.26	1.44 (0.64-6.33)	0.47
Log-transformed Apo B	1.06 (0.04-2.98)	0.42	6.61 (0.06-212)	0.29	13.4 (0.96-198)	0.56
LDL-C/Apo B ≤ 1.2 (vs. >1.2)	4.62 (1.53-14.0)	0.006	2.98 (1.58-8.96)	0.013	3.57 (1.71-12.6)	0.024
Log-transformed hs-CRP	2.12 (0.96-4.68)	0.06	2.07 (0.85-5.00)	0.11	1.21 (0.49-6.43)	0.80

Abbreviations: Apo B, apolipoprotein B; CAS, coronary angioscopy; CI, confidence interval; HDL-C, high-density lipoprotein-cholesterol; hs-CRP; high-sensitivity C-relative protein; LDL-C, low-density lipoprotein-cholesterol; MDA-LDL, Malondialdehyde-modified low-density lipoprotein; NA, not applicable; OCT, optical coherence tomography; OR, odds ratio; TG, triglyceride.

3: 2.00) **(Fig. 2E)**.

4.3 Contributive Factors for the OCT-Derived Neointimal Volume and CAS-Derived Neointimal and Yellow Grades

There are already a number of reported lipid parameters that are possibly associated with sd-LDL-C (TG, MDA-LDL, non-HDL, Apo B, LDL-C/HDL-C ratio, TG/HDL-C ratio, and non-HDL-C/HDL-C ratio); thus, we evaluated the contribution of each lipid parameter to the neointimal volume, neointimal grade, and yellow grade using a single regression analysis **(Supplemental Table 1)**. Among each lipid parameter, the LDL-C/Apo B ratio was noted to have the highest proportion of the contribution to the neointimal volume (R^2: 0.05, $p=0.021$), neointimal grade (R^2: 0.10, $p=0.001$), and yellow grade (R^2: 0.09, $p=0.003$).

Table 2 shows the multiple regression analysis evaluating the factors of the neointimal volume and neointimal and yellow grades. In the multivariate analysis, an LDL-C/Apo B ratio ≤ 1.2 remained an independent factor for the neointimal volume (odds ratio [OR]: 4.62 [95 % confidence interval (CI) 1.53–14.0], $p=0.006$) and neointimal grade (OR: 2.98 [95 % CI 1.58–8.96], $p=0.013$). In terms of the yellow grade, the LDL-C/Apo B ratio (OR: 3.57 [95 % CI, 1.71–12.6], $p=0.024$) remained an independent factor for the yellow grade.

4.4 Lipid Profile Changes under Statin Treatments from the Initial PCI to the Follow-Up CAG and its Association to the OCT-Derived Neointimal Volume and CAS-Derived Neointimal and Yellow Grades

In the "Low LDL-C/Apo B" group at the time of PCI ($n=53$), majority of the cases (36 [67.9 %]) maintained an LDL-C/Apo B ratio of ≤ 1.2 during the follow-up (categorized as the L-to-L group), while the remaining 17 (32.1 %) had an increased LDL-C/Apo B ratio of >1.2 during the follow-up (L-to-H group). Among the 47 cases in the "High LDL-C/Apo B" group, 24 (51.1 %) had an LDL-C/Apo B ratio of >1.2 during the follow-up (H-to-H group), while the remaining 23 (48.9 %) had a decreased LDL-C/Apo B ratio of ≤ 1.2 during the follow-up (H-to-L group). No differences were noted in terms of age, body mass index, comorbidities, and medication use including statins; however, the L-to-H group had the highest rate of maximum dose of any statin (29 %, $p=0.010$, adjusted residual: 2.99) among the four groups **(Table 3)**. The stent profiles, that is, the predilatation and postdilatation balloon profiles, did not significantly differ among the four groups. The lipid profile changes under the statin treatment from the time of PCI to the follow-up CAG period are presented in **Table 4**. A greater decrease in TG from the time of PCI to the follow-up CAG was observed in the L-to-H and H-to-H groups than in the L-to-L and H-to-L groups ($p<0.001$). Also, a greater reduction in the Apo B as compared to the LDL-C was observed in the L-to-H and H-to-H groups compared to the other two groups (despite no statistical difference [$p=0.28$]). The OCT-derived stent, lumen, and neointimal volumes and the CAS-derived neointimal and yellow grades obtained during the follow-up CAG among the four groups are shown in **Fig. 3**. The neointimal volume was significantly larger in the L-to-L group and tended to be larger in the L-to-H and H-to-L groups than that in the H-to-H group

Table 3. Patients characteristics at the time of PCI among the groups of the 4 types of changes in the LDL-C/Apo B ratio

	Low-Low group ($n=36$)	Low-High group ($n=17$)	High-Low group ($n=23$)	High-High group ($n=24$)	p value
Age (years)	68.1 ± 10.4	60.0 ± 12.5	67.5 ± 12.4	61.8 ± 14.4	0.06
Male sex	31 (82)	14 (82)	19 (83)	20 (83)	0.50
Height (cm)	165.0 ± 9.8	164.7 ± 8.7	163.9 ± 9.8	163.8 ± 8.8	0.95
Weight (kg)	65.1 ± 13.7	70.8 ± 14.9	67.2 ± 13.7	64.1 ± 14.9	0.47
Body mass index (kg/m^2)	23.7 ± 3.5	25.9 ± 3.3	24.9 ± 4.2	23.6 ± 4.0	0.18
Medication use					
DAPT	36 (100)	17 (100)	23 (100)	24 (100)	0.99
ACE-I/ARB	25 (69)	13 (76)	19 (79)	17 (71)	0.69
βblockers	16 (44)	11 (65)	15 (65)	13 (54)	0.36
Statins	34 (94)	16 (94)	22 (96)	23 (96)	0.99
Maximum dose of any statin	7 (19)	5 (29)	3 (13)	3 (13)	0.010
Comorbidities					
Hypertension	22 (61)	13 (76)	9 (39)	12 (50)	0.09
Diabetes	9 (25)	2 (12)	6 (26)	8 (33)	0.48
Hemodialysis	2 (6)	0 (0)	0 (0)	2 (8)	0.38
Laboratory examination					
Hemoglobin A1c (NGSP) (%)	6.2 ± 0.8	6.1 ± 0.6	6.2 ± 0.7	6.3 ± 0.7	0.83
eGFR(mL/min/1.73mm^2)	60.3 ± 18.8	63.7 ± 15.3	66.6 ± 11.9	72.4 ± 28.1	0.15
High-sense CRP (mg/dL)	0.153 (0.093-0.227)	0.095 (0.019-0.636)	0.151 (0.027-0.327)	0.099 (0.024-0.381)	0.54
Coronary features					
Stented vessels					
LMT	0 (0)	0 (0)	0 (0)	0 (0)	0.99
LAD	22 (61)	6 (35)	17 (74)	18 (75)	0.040
LCX	6 (17)	3 (18)	2 (9)	1 (4)	0.41
RCA	8 (22)	8 (47)	4 (17)	5 (21)	0.14
Stent profiles					
Diameter (mm)	3.1 ± 0.4	3.3 ± 0.5	3.1 ± 0.4	3.0 ± 0.5	0.13
Length (mm)	25.7 ± 7.5	25.4 ± 6.7	28.5 ± 7.4	27.3 ± 9.0	0.49
Predilatation (%)	30 (83)	15 (88)	21 (91)	21 (88)	0.84
Diameter (mm)	2.3 ± 0.4	2.4 ± 0.5	2.2 ± 0.3	2.3 ± 0.3	0.67
Length (mm)	13.5 ± 1.6	12.9 ± 1.9	13.6 ± 1.7	13.6 ± 1.5	0.66
Scoring balloon (n)	6 (20)	2 (13)	2 (10)	3 (14)	0.67
Postdilatation (%)	31 (86)	11 (65)	16 (70)	21 (88)	0.14
Diameter (mm)	2.3 ± 0.4	2.4 ± 0.5	2.2 ± 0.3	2.3 ± 0.3	0.18
Length (mm)	13.5 ± 1.6	12.9 ± 1.9	13.6 ± 1.7	13.6 ± 1.5	0.32

Values are the mean ± SD, median (interquartile ranges), or n (%). Abbreviations: ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker; DAPT, dual antiplatelet therapy; eGFR, estimated-glomerular filtration rate; high-sense CRP, high-sense C-reactive protein; NGSP, national glycohemoglobin standardization program; LMT, left main trunk; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery *by a Student-t test, Mann-Whitney U test, chi-square test, Fisher exact test, an ANOVA, and Kruskal-Walls test as appropriate

(13.1 ± 5.5, 10.7 ± 3.1, and 11.8 ± 5.7 vs. 8.9 ± 3.5 mm^3, $p=0.009$). Also, the lumen volume in the L-to-L group was significantly smaller than that in the H-to-H group (44.6 ± 18.0 vs. 60.3 ± 25.0 mm^3, $p=0.045$ by Bonferroni post-hoc adjustment). With regard to the accumulation of macrophages, macrophages were found in three cases (8%) in the L-to-L group, two cases (9%) in the H-to-L group, one case (6%) in the L-to-H group, and zero cases (0%) in the H-to-H group. The H-to-H group was determined to have a significantly lower proportion than predicted as compared to the other three groups ($p=0.038$, adjusted residual: −10.36). The neointimal grade was significantly higher in the L-to-L and H-to-L groups than that of the L-to-H and the H-to-H groups (grade 1.66 ± 0.56 and 1.47 ± 0.58 vs. 1.15 ± 0.45, and 1.03 ± 0.15, $p<0.001$). The yellow grade was significantly higher in the L-to-L group and

Table 4. Lipid profile changes under statin treatments from the time of PCI to the follow-up CAG period among the groups of the 4 types of changes in the LDL-C/Apo B ratio

	Low-Low group (n = 36)	Low-High group (n = 17)	High-Low group (n = 23)	High-High group (n = 24)	p value
Total cholesterol (mg/dL)					
Time of PCI	157.0 (140.0-184.0)	148.0 (140.0-179.5)	185.0 (157.0-210.0)	188.0 (158.5-234.0)	0.002
Follow-up CAG	155.0 (140.8-167.3)	157.0 (139.0-170.5)	140.0 (129.0-156.0)	168.5 (144.3-185.0)	0.014
Δ (%)	-1.2	+6.2	-24.9	-10.4	< 0.001
LDL-C (mg/dL)					
Time of PCI	88.7 ± 22.8	84.5 ± 26.6	118.0 ± 32.6	118.8 ± 38.8	< 0.001
Follow-up CAG	79.2 ± 18.8	89.2 ± 16.6	72.5 ± 18.9	94.3 ± 23.5	0.001
Δ (%)	-10.8	+5.5	-38.5	-20.6	< 0.001
HDL-C (mg/dL)					
Time of PCI	44.1 ± 12.1	44.1 ± 13.2	44.0 ± 9.0	49.1 ± 14.6	0.41
Follow-up CAG	45.9 ± 14.1	47.8 ± 10.2	42.7 ± 8.4	53.9 ± 12.0	0.014
Δ (%)	+4.1	+8.4	-2.9	+9.8	0.05
Triglyceride (mg/dL)					
Time of PCI	132.5 (90.0-185.0)	144.0 (116.5-189.5)	106.0 (76.0-154.0)	120.5 (82.8-164.8)	0.11
Follow-up CAG	145.5 (114.3-203.3)	101.0 (81.0-151.3)	96.0 (79.0-124.0)	84.0 (68.0-101.5)	< 0.001
Δ (%)	+9.8	-29.9	-9.4	-30.2	< 0.001
Non-HDL-C (mg/dL)					
Time of PCI	126.0 (106.5-139.8)	103.0 (93.0-137.8)	151.0 (111.0-168.0)	141.5 (102.5-171.8)	0.009
Follow-up CAG	111.0 (96.0-128.5)	108.0 (89.0-122.3)	101.0 (84.0-118.0)	119.0 (93.3-133.0)	0.35
Δ (%)	-11.9	+4.8	-33.1	-15.9	< 0.001
Apo B (mg/dL)					
Time of PCI	98.0 (71.0- 105.0)	92.0 (72.0-110.5)	79.0 (64.0-93.5)	93.0 (80.0- 109.0)	0.13
Follow-up CAG	79.0 (64.0-94.8)	67.0 (60.5-73.0)	74.0 (56.0-87.0)	71.0 (54.0-88.8)	0.15
Δ (%)	-13.2	-24.4	-5.2	-23.7	0.28
MDA-LDL (U/L)					
Time of PCI	111.0 (81.5-145.0)	95.0 (76.0-146.3)	118.0 (91.0-140.0)	126.0 (79.0-176.3)	0.73
Follow-up CAG	120.0 (76.0-120.0)	71.5 (58.0-96.0)	75.5 (59.0-90.0)	84.0 (70.0-94.0)	0.038
Δ (%)	+10.0	-24.7	-36.0	-33.3	0.025
LDL-C/ApoB ratio					
Time of PCI	1.01 (0.75-1.11)	0.97 (0.83-1.11)	1.38 (1.33-1.49)	1.40 (1.36-1.50)	< 0.001
Follow-up CAG	1.02 (0.97-1.10)	1.30 (1.25-1.45)	1.04 (0.90-1.11)	1.30 (1.25-1.37)	< 0.001
Δ (%)	+0.1	+34.0	-24.6	-7.1	< 0.001
LDL-C/HDL-C ratio					
Time of PCI	2.11 (1.71-2.33)	1.69 (1.44-2.32)	3.11 (2.07-3.41)	2.40 (1.78-3.24)	0.029
Follow-up CAG	1.79 (1.40-2.13)	1.84 (1.41-2.46)	1.84 (1.21-2.21)	1.88 (1.36-2.31)	0.89
Δ (%)	-15.1	+8.8	-40.8	-21.6	0.001

Values are the mean ± SD median (interquartile ranges), or n (%). Abbreviations: Apo B, apolipoprotein B; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MDA-LDL, malondialdehyde-modified low-density lipoprotein-cholesterol; Δ, rate of change from at the time of PCI to the follow-up CAG; * an ANOVA and Kruskal-Walls test as appropriate

tended to be higher in the H-to-L group than the L-to-H and H-to-H groups (grade 1.06 ± 0.70 and 0.93 ± 0.74 vs. 0.63 ± 0.44 and 0.38 ± 0.32, p < 0.001).

4.5 The Correlation between LDL-C/Apo B and Other Lipid Profiles

As per our findings, the LDL-C/Apo B ratio during the follow-up period was determined to have a significant negative correlation with triglyceride (TG) concentration (Spearman's rank correlation coefficient; r = –0.28, p = 0.004). Further, the LDL-C/Apo B ratio also had a significant negative correlation with TG/HDL-C, which predicted the quantity of the sd-LDL-C (r = –0.40, p < 0.001) **(Fig. 4)**.

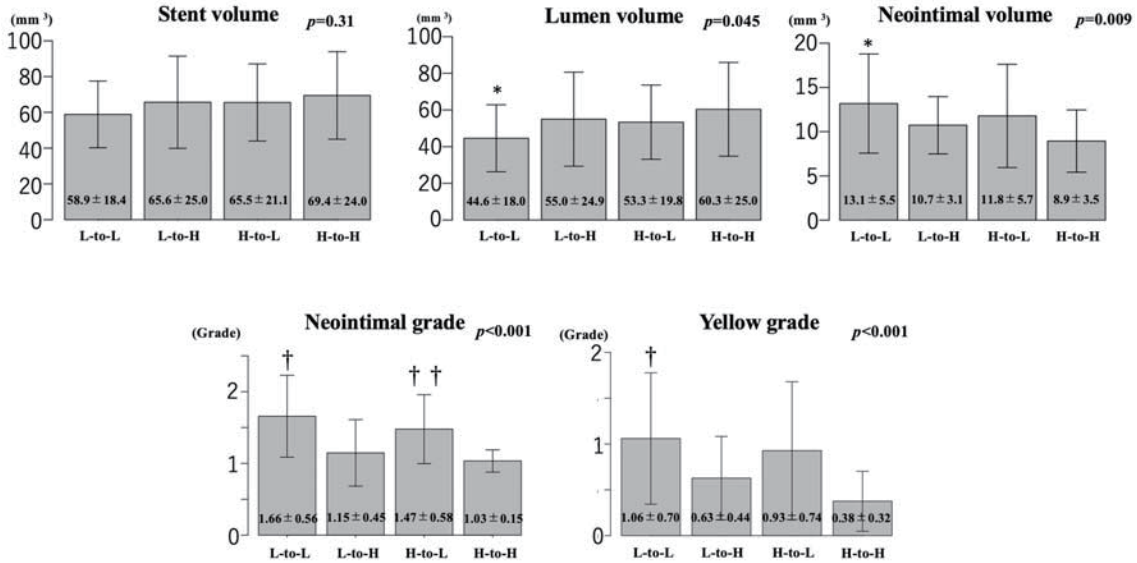


Fig. 3. OCT and CAS imaging findings between the 4 LDL/Apo B categorical groups according to the change in the LDL-C/Apo B ratio from the time of PCI to the follow-up CAG period

The L-to-L group indicates the patients in whom the LDL-C/Apo B ratio was ≤ 1.2 at both the time of PCI and follow-up CAG. The L-to-H group indicates the patients in whom the LDL-C/Apo B ratio was ≤ 1.2 at the time of PCI, but >1.2 during the follow-up CAG, the H-to-L group indicates the patients in whom the LDL-C/Apo B ratio was >1.2 at the time of PCI, but ≤ 1.2 during the follow-up CAG, and the H-to-H group indicates the patients in whom the LDL-C/Apo B ratio is >1.2 at both the time of PCI and follow-up CAG. *$p<0.05$ vs. H-to-H by Bonferroni post-hoc adjustment. †$p<0.05$ vs. H-to-H and L-to-H by Steel-Dwass post-hoc adjustment. ††$p<0.05$ vs. H-to-H by Steel-Dwass post-hoc adjustment. The details are shown in the text.

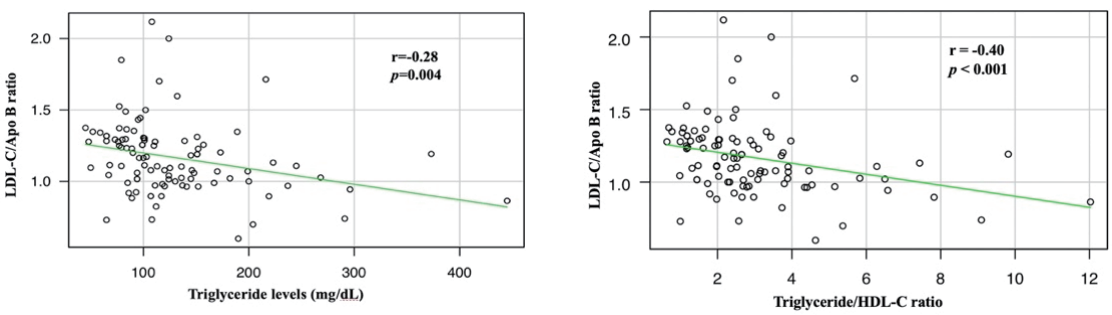


Fig. 4. The correlation between the LDL-C/Apo B ratio and triglyceride concentration and triglyceride/HDL-C

Apo B, Apolipoprotein B.

5. Discussion

This study has examined the association between the neointimal characteristics and LDL-C/Apo B ratio, which is an indicator for LDL particle size, using OCT and CAS imaging. There were four main findings of this study. First, despite the similar prevalence of male sex, coronary risk factors, and body weight, the "Low LDL-C/Apo B" ratio patients had a smaller rate of change in terms of TG, MDA-LDL, LDL-C, and Apo B concentration levels compared to that in the "High LDL-C/Apo B" ratio patients. Second, via OCT, the neointimal volume was determined to be significantly larger; meanwhile, via CAS, the neointimal properties were found to have lesser homogeneous pattern, greater heterogeneous pattern, higher prevalence of macrophage accumulation, and higher proportion of neointimal and yellow grades in the "Low LDL-C/Apo B" ratio patients than in the "High LDL-C/Apo B" ratio patients. Third, after the multivariate adjustment, the OCT-derived neointimal volume, neointimal grade, and high yellow grade observed via CAS were all independently associated with low LDL-C/Apo B ratio. Fourth, the patients with persistent "Low LDL-C/Apo B" ratio at the time of PCI to the

follow-up CAG (L-to-L group) had the greater neointimal instability and plaque progression.

5.1 The Role of the LDL-C/Apo B Ratio as an Indicator for the Predominance of sd-LDL Particles on Neointimal Proliferation

The sd-LDL-C has been recognized as a substance that strongly promotes endothelial dysfunction, atherosclerosis, and ISR; thus, it has been considered as a significant factor in the development of CVD[2-4]. There are various pathways to produce sd-LDL-C. The most powerful factor that prescribes the LDL particle size is the TG concentration[19, 20]. In hypertriglyceridemia, TG-rich large very low-density lipoprotein 1 (VLDL1) is catabolized in a slow blood clearance pool. During this catabolism, the TG-rich HDL transfers TG from VLDL1, passes the TG to the LDL, extracts the cholesterol from the LDL, and eventually produces sd-LDL[21, 22]. In our study, the LDL-C/Apo B ratio and TG were determined to have a mild negative correlation, which would partially support the possibility that the LDL-C/Apo B ratio could be a possible indicator of the predominance of sd-LDL particles. After the LDL infiltrates the neointima, the LDL-C becomes an oxidized LDL, which then subendothelially expresses the adhesion of monocyte molecules. Those monocytes become macrophages and change into foam cells uptaking the oxidized LDL, eventually producing cytokines such as midkine (associated with anti-apoptosis, cell migration ability, inflammatory cytokine induction, and angiogenesis) and growth factors, which have been determined to cause smooth muscle cell proliferation and subsequent neointimal hyperplasia during the early phase (a few months) after a DES implantation[23-27]. On the other hand, foamy macrophages promoted by oxidized LDL also constitute atherosclerotic plaque called neoatherosclerosis during the late phase after the DES implantation. It has been reported that neoatherosclerosis with DESs is recognized at a median of about 14 months[28]. As such, it is possible that a large predominance of sd-LDL particles contributes to not only neointimal hyperplasia, but also possibly neoatherosclerosis after stent implantations. There have been many lipid parameters that can predict the quantity or predominance of sd-LDL such as the TG, non-HDL-C, Apo B, TG/HDL-C ratio, or LDL-C/Apo B ratio[29]. An LDL-C/Apo B ratio of ≤ 1.2 has been reported to indicate the predominance of sd-LDL particles[6, 7], but what parameter is the strongest for the sd-LDL-C remains to be uncertain. This study found that the LDL-C/Apo B ratio was the strongest contributor for predicting a large neointimal volume, high neointimal grade, and yellow grade among those reported lipid parameters. This finding has strongly supported the clinical significance of the LDL-C/Apo B ratio as an indicator for the predominance of sd-LDL particles, promoting neointimal hyperplasia and plaque progression.

5.2 Effect of the "Low LDL-C/Apo B Ratio" on the Neointimal Characteristics Observed by OCT and CAS after Third-Generation DES Implantations

We found a heterogeneous neointimal pattern in the "Low LDL-C/Apo B" group more frequently than in the "High LDL-C/Apo B" group. A heterogeneous pattern is often associated with vascular inflammation induced by the stent with smooth cells in a rich extracellular matrix, whereas a layered pattern is correlated with a healed neointimal erosion and rupture and peri-strut neovascularization with smooth muscle cells in a rich extracellular matrix[30]. Therefore, those non-homogeneous patterns are often identified among the ISR lesions associated with DESs[31]. Normally, neointimal tissue gradually becomes mature and homogeneous via early vascular reaction such as thrombus formation and acute inflammation around the strut after stent implantations. In a previous report, the rate of homogeneous pattern rate had increased to 7 1% after 6 months after second-generation DES implantations[32]. Despite the use of third-generation DES implantations with a longer follow-up period of 8.8 months, a lower homogeneous pattern rate and higher macrophage accumulation rate in the "Low LDL-C/Apo B" group than in the "High LDL-C/Apo B" group suggested greater immature neointimal tissue.

In our study, the neointimal volume observed by OCT was found to be significantly larger, and the proportion of the neointimal coverage grade and yellow grade observed by CAS was also observed to be higher in the "Low LDL-C/Apo B" group than in the "High LDL-C/Apo B" group. Further, even after adjusting for the age, sex, and cholesterol profiles, the neointimal volume using OCT and neointimal and yellow grades using CAS has remained associated with low LDL-C/Apo B values.

In previous reports, the yellow grade in the stent was considered to decrease due to the stent being covered by neointimal proliferation during the chronic phase[33-35]. However, the neointimal hyperplasia is clinically problematic because it is strongly related to endothelial dysfunction and vascular inflammation, leading to early occurrence of ISR[36, 37]. In a prior study regarding the CAS characteristics of second-generation DESs, a neointimal coverage grade ≥ 2 was

43 % and yellow grade ≥ 2 was 26%, respectively[38]. A study comparing the CAS findings of the second- vs. third-generation DESs showed a significantly increased neointimal coverage grade but decreased yellow grade in the third-generation DESs[10]. The rate of neointimal grade ≥ 2 in the "Low LDL-C/Apo B" group was 54 %, which was slightly higher than that in the second-generation DESs reported previously[38], whereas in the "High LDL-C/Apo B" group, that rate was only 24 %. In terms of the yellow grade associated with advanced neoatherosclerosis[8], the rate of yellow grade ≥ 2 in the "Low LDL-C/Apo B" group was higher (32 %) in the third-generation DESs than that in the second-generation DESs[38]; however, in the "High LDL-C/Apo B" group, the rate was much lower (only 15 %). The increased neointimal coverage and high yellow grade in the "Low LDL/Apo B" patients may be explained by the baseline patient background (promoting atherosclerosis such as aging, a family history, or lifestyle habit) in which the high yellow grade plaque that originally coexisted or delayed vascular healing caused by incomplete or immature endothelization both generated neointimal instability, hyperplasia, and neoatherosclerosis. Through those processes, the low LDL-C/Apo B ratio indicating the predominance of sd-LDL particles may have lessened (or outweigh) the favorable effects of the third-generation DESs on the neointimal tissue as compared to the first- or second-generation DESs or BMSs. In fact, in the L-to-L group (the persistence of a "Low LDL-C/Apo B" level from the time of PCI to the follow-up), the statin treatment did not reduce the TG and MDA-LDL levels, resulting in significantly higher TG and MDA-LDL levels than in the other three groups **(Table 3)**. This group had the largest neointimal volume, highest grade of neointima and yellow plaque, and highest macrophage accumulation rate on the OCT and CAS. The MDA-LDL level was considered a major form of an oxidized LDL[39]; thus, those observations suggested that, in the L-to-L group, the persistent accumulation of TG-rich lipoproteins such as remnant lipoproteins and/or sd-LDL-C was resistive to the standard statin treatment, which may have contributed to the neointimal instability and plaque progression.

5.3 Clinical Implications

This study found an interesting finding regarding the effects of the change in the lipid profile on the neointimal characteristics, i.e., the L-to-L and H-to-L groups had a higher neointimal volume and grade and yellow grade during the follow-up CAG as compared to the L-to-H and H-to-H groups. These results provided suggestive evidence that maintaining and/or increasing the LDL-C/Apo B ratio >1.2 is essential to suppress excessive neointimal proliferation and reduce the yellow grade and neointimal instability. Therefore, once the patients have an LDL-C/Apo B ratio ≤ 1.2 from the time of PCI to the follow-up period, a more aggressive therapy for hyperlipidemia by using a strong statin plus ezetimibe, fibrates, or proprotein convertase subtilisin/lexin type 9 inhibitor (PCSK9i) injections should be used. On contrary, scintigraphy or coronary computed tomography may stratify high-risk patients from those in whom an LDL-C/Apo B ratio ≤ 1.2 persists during the follow-up.

5.4 Limitations

This study has some limitations. First, this was the retrospective cross-sectional study, and this study only included a small population for analysis; however, it should be noted that spontaneous assessment with OCT and CAS at the time of the stent implantation and follow-up CAG in all patients is clinically difficult considering the medical cost. Second, we have only evaluated stable angina patients after EES implantations in this study. In this cohort, it may be needed to include high-risk patients, as it might not be possible to generalize the results to other stents implanted in acute coronary syndrome patients. Finally, the weakness of this study was that we did not directly measure the sd-LDL-C. For example, there was a concern that the neointimal instability might contribute to a greater LDL-C reduction (as compared to that of the Apo B) with statin therapy rather than an LDL-C/Apo B ≤ 1.2 as with the predominance of sd-LDL particles. This was not a fact because the LDL-C reduction with statins was correlated with reduced neointimal volume, and decreased grades of neointima and yellow plaque (neointimal stability) (supplemental table). Therefore, our data supported the hypothesis that the neointimal instability after PCI may be partially caused by an LDL-C/Apo B ≤ 1.2 as with the predominance of sd-LDL particles.

6. Conclusion

A low ratio of the LDL-C/Apo B, which is known to be a marker for a predominance of smaller LDL particle size, has been strongly associated with neointimal proliferation and neointimal instability, as confirmed via OCT and CAS. Therefore, a ratio of LDL-C/Apo B of ≤ 1.2 will help in identifying high-risk patients after EES implantations in the future.

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Supplemental Table 1. Contribution of each lipid parameter to the neointimal volume, neointimal grade, and yellow grade

	Neointimal volume			Neointimal grade			Yellow grade		
	Correlation coefficient (R)	Contribution (R^2)	*p* value	Correlation coefficient (R)	Contribution (R^2)	*p* value	Correlation coefficient (R)	Contribution (R^2)	*p* value
Total cholesterol	-0.20	0.04	0.044	-0.29	0.08	0.003	-0.21	0.04	0.037
ΔTotal cholesterol	-0.04	<0.01	0.68	-0.18	0.03	0.029	-0.15	0.02	0.14
LDL-C	0.11	0.01	0.26	0.19	0.03	0.07	0.24	0.05	0.018
Δ LDL-C	-0.19	0.03	0.07	-0.29	0.08	0.002	-0.27	0.08	0.003
HDL-C	-0.18	0.03	0.08	-0.09	0.01	0.34	-0.01	<0.01	0.95
Δ HDL-C	0.20	0.04	0.044	0.17	0.03	-0.10	<0.01	<0.01	0.98
Triglyceride	0.13	0.02	0.18	-0.07	<0.01	0.47	-0.02	<0.01	0.88
Δ Triglyceride	0.02	<0.01	0.83	-0.31	0.09	0.002	-0.05	<0.01	0.59
Apolipoprotein B	0.12	0.02	0.22	0.10	0.01	0.30	0.02	<0.01	0.87
Δ Apolipoprotein B	0.04	<0.01	0.69	-0.04	<0.01	0.71	-0.08	0.01	0.43
MDA-LDL	0.09	0.01	0.40	0.09	0.01	0.39	0.03	<0.01	0.74
Δ MDA-LDL	-0.06	<0.01	0.56	-0.21	0.04	0.036	-0.25	0.06	0.011
Non-HDL-C	-0.16	0.02	0.14	0.09	0.01	0.38	0.18	0.03	0.08
Δ Non-HDL-C	-0.17	0.03	0.07	-0.26	0.06	0.008	-0.15	0.02	0.15
LDL-C/Apo B ratio	-0.23	0.05	0.021	-0.32	0.10	0.001	-0.30	0.09	0.003
Δ LDL-C/Apo B ratio	0.22	0.05	0.022	0.21	0.04	0.031	0.13	0.02	0.21
LDL-C/HDL-C ratio	0.03	<0.01	0.79	0.22	0.05	0.003	-0.16	0.03	0.10
Δ LDL-C/HDL-C ratio	-0.03	<0.01	0.76	-0.23	0.05	0.002	-0.24	0.06	0.02
Triglyceride/HDL-C ratio	0.18	0.03	0.07	-0.08	0.01	0.41	-0.02	<0.01	0.87
Δ Triglyceride/HDL-C ratio	0.09	0.01	0.36	-0.31	0.09	0.002	-0.01	<0.01	0.87
Non-HDL-C/HDL-C ratio	-0.01	<0.01	0.94	0.27	0.07	0.006	0.09	0.01	0.39
Δ Non-HDL-C/HDL-C ratio	-<0.01	<0.01	0.94	-0.27	0.07	0.007	-0.09	0.01	0.38

Abbreviations: Apo B, apolipoprotein B; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MDA-LDL, Malondialdehyde-modified low-density lipoprotein, Δ, each lipid profile value from the time of PCI to the follow-up CAG.