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Effects of Statin Plus Ezetimibe on Coronary Plaques in Acute Coronary Syndrome Patients with Diabetes Mellitus: Sub-Analysis of PRECISE-IVUS Trial

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Aim: Coronary plaque regression is weak in acute coronary syndrome (ACS) patients with diabetes mellitus (DM). We evaluated whether dual lipid-lowering therapy (DLLT) with ezetimibe and atorvastatin attenuates coronary plaques in ACS patients with DM.

Methods: The prospective, randomized controlled, multicenter PRECISE-IVUS (Plaque Regression with Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound) trial assigned 246 patients undergoing percutaneous coronary intervention to DLLT or atorvastatin monotherapy and evaluated IVUS-derived changes in percent atheroma volume (ΔPAV), at baseline and 9–12-month follow-up, in 126 ACS cases, including 25 DM patients. The atorvastatin dose was up-titrated to achieve low-density lipoprotein cholesterol (LDL-C) <70 mg/dL.

Results: In DM patients, the monotherapy group (n=13) and the DLLT group (n=12) showed a similar prevalence of coronary risks and baseline lipid profiles. During the study, the change in LDL-C level was similar between DM and non-DM patients. Compared with non-DM patients, DM patients showed weaker regression of ΔPAV by DLLT than those who underwent monotherapy (DM: −2.77±3.47% vs. −0.77±2.51%, P=0.11; non-DM: −2.01±3.36% vs. −0.08±2.66%, P=0.008). The change in LDL-C level was not correlated with ΔPAV in non-DM patients, but there was significant correlation between the change in LDL-C level and ΔPAV in DM patients (r=0.52, P=0.008).

Conclusions: ACS patients with DM showed weaker coronary plaque regression than their counterparts. A significant correlation between the change in LDL-C level and ΔPAV in DM patients suggested that more intensive lipid-lowering therapy is required in ACS patients with DM.

Key words: Ezetimibe, Statins, Coronary plaque, Diabetes mellitus, Acute coronary syndrome

Introduction

Percutaneous coronary intervention (PCI) can improve prognoses in patients with acute coronary syndrome (ACS). However, despite developments in PCI technologies, diabetes mellitus (DM)[1] remains a critical cause of poor outcomes after ACS treatment[2]. Therefore, lifestyle changes or medication are important for secondary prevention in patients with ACS. Large studies have demonstrated that intensive, lipid-lowering therapy using statins can reduce the prevalence of cardiovascular events in patients with ACS[3-6]. European and American guidelines recommend early, intensive lipid-lowering therapy for ACS management[1, 7]. Studies using intravascular imaging modalities have shown that lipid-lowering therapy can improve the volume and vulnerability of coronary plaques[8-13]. However, Hiro and colleagues reported that coronary plaque regression is weaker in ACS patients with DM than in those without DM[14].

The randomized Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) demonstrated that dual lipid-lowering therapy (DLLT) using a combination of statin and ezetimibe could reduce the prevalence of cardiovascular events[15]. IMPROVE-IT showed that intensive therapy with ezetimibe to reduce levels of low-density lipoprotein cholesterol (LDL-C) was beneficial against ACS. Furthermore, we reported the benefits of DLLT on coronary plaque regression in the Plaque REgression with Cholesterol absorption Inhibition or Synthesis inhibitor Evaluated by IntraVascular UltraSound (PRECISE-IVUS) trial[16]. That trial evaluated the effects of an ezetimibe-atorvastatin combination on coronary plaques using intravascular ultrasound (IVUS) in Japanese patients with ACS and stable coronary disease who underwent PCI. In the PRECISE-IVUS trial, DLLT, using an ezetimibe-atorvastatin combination, significantly reduced LDL-C levels and coronary plaque volume. In that study, the lower level of LDL-C achieved also correlated with a reduction in the prevalence of cardiovascular events or a change in atheromatous plaque volume, thereby demonstrating "the lower, the better" concept by DLLT using a combination of statins and ezetimibe. However, DLLT's benefit on coronary plaques in ACS patients with DM has not been investigated.

We investigated whether DLLT, using an ezetimibe-atorvastatin combination, attenuated coronary plaque development in ACS patients with DM. In addition, several clinical factors, e.g., sex, hypertension, and obesity, are reportedly associated with coronary plaque development[17-19]. However, the determinant factors related to coronary plaque regression in ACS patients with DM are not known, a knowledge gap that we attempted to fill.

Methods

Design of the PRECISE-IVUS Trial

The present study is a sub-analysis of the PRECISE-IVUS trial. The detailed design of the PRECISE-IVUS trial has been published[16]. In brief, PRECISE-IVUS was a prospective, randomized, controlled, assessor-blind, multicenter trial to evaluate the benefit of an ezetimibe-atorvastatin combination on coronary plaque volume, measured by IVUS, in patients with coronary artery disease. Eligible patients (30–85 years of age and LDL-C level upon study enrollment >100 mg/dL) were assigned randomly to receive atorvastatin alone or an ezetimibe-atorvastatin combination at 10 mg every day (DLLT group) after having undergone successful IVUS-guided PCI to treat ACS or stable angina pectoris. The atorvastatin dose was up-titrated to achieve the target level of LDL-C (<70 mg/dL). Biomarkers, including lipid profiles, and periodic medical examination were measured 3, 6, and 9–12 months after enrollment. Serial volumetric IVUS was carried out at baseline and 9–12 months to evaluate coronary plaque changes. The PRECISE-IVUS trial enrolled 246 patients, and 126 patients were enrolled as the ACS cohort. This sub-study evaluated these 126 patients with ACS. The sub-study flowchart is shown in **Fig. 1**. An equal number of patients were assigned to the DLLT group and atorvastatin monotherapy group. Fourteen patients were excluded from the atorvastatin monotherapy group (2 patients withdrew consent, and 12 did not complete endpoint assessment) and 12 patients were excluded from the DLLT group (1 patient withdrew consent, and 11 did not complete endpoint assessment). Finally, 49 and 51 patients had full datasets for atorvastatin monotherapy and DLLT, respectively. The monotherapy group had 13 patients with DM, and the DLLT group contained 12 patients with DM.

The present study complied with the Declaration of Helsinki with respect to clinical investigations. The study protocol was approved by the Human Ethics

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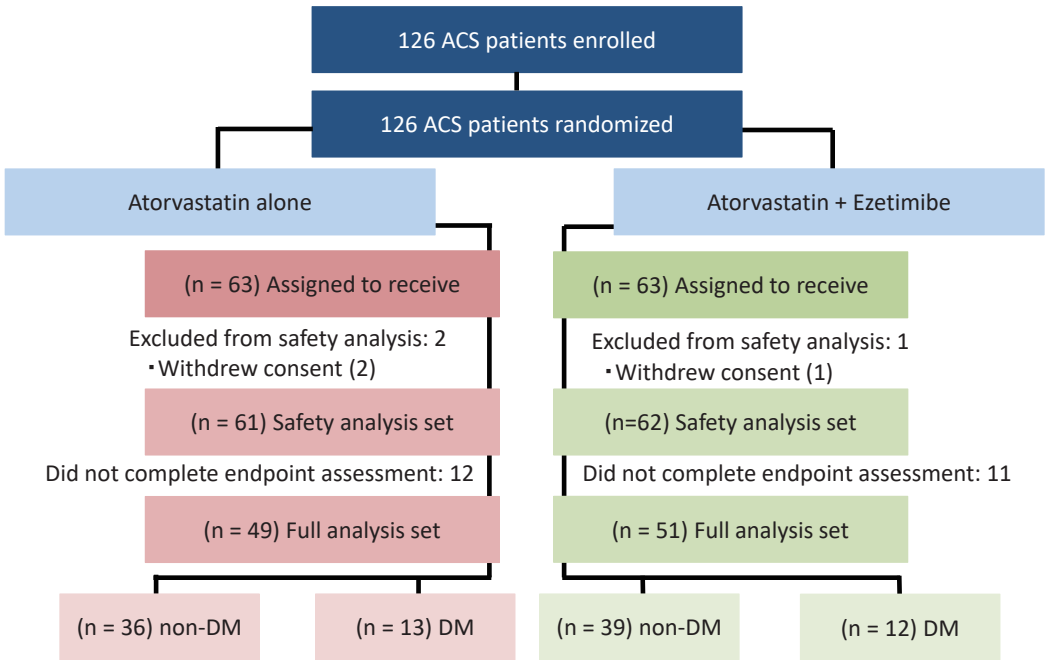

Fig. 1. Flowchart of the sub-study of the PRECISE-IVUS trial
ACS, acute coronary syndrome; DM, diabetes mellitus

Review Committee of Kumamoto University. The study was conducted in accordance with the guidelines of the participating institution's ethics committee. Written informed consent was obtained from all ACS patients until 24 h after PCI.

Definition of ACS

ACS was defined as ST-elevation myocardial infarction (STEMI), non-STEMI, or unstable angina pectoris. MI was diagnosed by increased levels of cardiac biomarkers in plasma (creatine kinase-MB or cardiac troponin) above the 99th percentile of the upper limit of the normal range, together with evidence of myocardial ischemia and at least one of the following symptoms: electrocardiographic changes (new ST-T changes, left bundle branch block, or pathologic Q wave) or imaging evidence of new viable myocardial loss or a new abnormality in regional wall motion[20]. Unstable angina pectoris was diagnosed by new or accelerating myocardial ischemia symptoms accompanied by new ischemic ST-T-wave changes.

Definition of DM

The diagnosis of DM was made according to the diagnostic criteria from the Japanese Diabetes Society. We defined DM when patients had a history of DM diagnoses or were taking any hypoglycemic medications. If this information were unavailable, the diagnosis of DM was made when "diabetic type" (fasting plasma glucose concentration ≥ 126 mg/dL, fasting plasma glucose concentration ≥ 126 mg/dL, 2-h plasma glucose concentration ≥ 200 mg/dL during a 75-g oral glucose tolerance test, casual plasma glucose concentration ≥ 200 mg/dL, or HbA1c ≥ 6.5%) was confirmed on two or more occasions examined on separate days; a single plasma glucose test meeting criteria for "diabetic type," when any of the following three conditions were met: (1) typical symptoms of diabetes (thirst, polydipsia, polyuria, and weight loss), (2) $HbA1_C \geq 6.5\%$, or (3) diabetic retinopathy.

IVUS Imaging for Coronary Plaque Analyses

Details of recording of IVUS images have been described[16]. An IVUS catheter was inserted into the target vessel for PCI as distal as possible to safely obtain the longest possible target segment for analyses. Then, it was pulled back at 0.5 mm/s automatically after intracoronary injection of nitroglycerin (0.1–0.2 mg). The target segment to be monitored was determined at a non-PCI site (>5 mm proximal or distal from the PCI site), with a reproducible fiduciary index (usually a side branch), as the beginning and ending of the segments to be analyzed. IVUS images were analyzed by two independent, experienced observers who were unaware of the treatment allocation and temporal sequence of paired images, as recommended by expert consensus[21]. Based on expert consensus, the primary endpoint was the absolute change in percent

atheroma volume (ΔPAV)[21].

Statistical Analyses

Data are the mean ± standard deviation for variables with a normal distribution. Data with skewed distributions are expressed as the median with interquartile range. Continuous variables among groups were compared using the unpaired Student's *t*-test or Mann–Whitney *U*-test, as appropriate. Continuous variables between baseline and follow-up were compared by one-sample Student's *t*-tests or the Wilcoxon signed rank test according to their distributions. Categorical variables were compared using the chi-square test or Fisher's exact test. The relationship between the absolute change in PAV and several biomarkers (including these for cholesterol absorption) was evaluated using a simple regression analysis. Pearson's correlation coefficient (r) was used to evaluate the association between PAV and biomarkers. Also, Spearman's rank correlation coefficient (ρ) was used if the variables did not have a normal distribution. $P<0.05$ was considered significant. Statistical analyses were carried out using SPSS v25 (IBM, Armonk, USA).

Results

Baseline Characteristics of Enrolled Patients

Table 1 shows the baseline characteristics of enrolled patients. In DM patients, the monotherapy group and DLLT group showed a similar prevalence of coronary risks, baseline lipid profiles, and medications. Forty-eight patients with ACS have been treated with statins; the statins were up-titrated according to the study protocol in all patients. Twelve-percent of the patients were receiving insulin. In non-DM patients, the percentage of current smokers was significantly higher in the monotherapy group than in the DLLT group. The baseline levels of campesterol and sitosterol (markers of cholesterol absorption) were significantly higher in the DLLT group than in the monotherapy group (non-DM: campesterol, 4.7 (3.6 to 6.4) vs. 3.4 (2.9 to 4.5) μg/dL, $P=0.04$; DM: sitosterol, 2.7 (1.9 to 3.3) vs. 1.8 (1.5 to 2.3) μg/dL, $P=0.01$).

Laboratory Data during the Study Period

Table 2 and Supplemental Table 1 show the percent change of laboratory data during the study period. HbA1c level did not change significantly between the monotherapy group and the DLLT group in DM and non-DM patients. The percent change in the LDL-C level is shown in **Table 2 and Fig. 2**. The serum level of LDL-C was reduced in all groups. In non-DM patients, the percent change in the LDL-C level significantly decreased in the DLLT group compared with that in the monotherapy group (DLLT group, −23.0 ± 23.2% vs. monotherapy group, −23.0 ± 23.2%, $P<0.001$). The percent change in the LDL-C level in DM patients tended to be reduced by DLLT, but it was not significant (DLLT group, −42.9 ± 13.8% vs. monotherapy group, −29.2 ± 30.6%, $P=0.16$) (**Fig. 2A**). The percent change in the apolipoprotein (Apo)A1/ApoB ratio was reduced significantly by DLLT in the non-DM and DM group. The levels of campesterol and sitosterol were increased by monotherapy in the non-DM and DM group but were reduced by DLLT. The level of lathosterol (marker of cholesterol synthesis) was reduced in all groups (**Table 2**).

ΔPAV

Compared with non-DM patients, DM patients showed weaker regression of ΔPAV in the DLLT group than in the monotherapy group (non-DM: DLLT group, −2.01 ± 3.36% vs. monotherapy group, −0.08 ± 2.66%, $P=0.008$; DM: DLLT group, −2.77 ± 3.47% vs. monotherapy group, −0.77 ± 2.51%, $P=0.11$) (**Table 2, Fig. 2B**). The total atheroma volume showed similar results between non-DM and DM patients (non-DM: DLLT group, −9.02 ± 14.71% vs. monotherapy group, 0.93 ± 8.67%, $P=0.001$; DM: DLLT group, −1.60 ± 14.62% vs. monotherapy group, −7.54 ± 7.04%, $P=0.20$). In patients with DM, vessel volume and lumen volume tended to be reduced in the monotherapy group; however, those were inhibited in the DLLT group, although they were not significant (**Table 2**).

Relationship between Coronary Plaque Regression and Biomarker Levels

Table 3 shows the relationship between lipid profiles and ΔPAV. There was no correlation between the percent change in the HbA1c level and ΔPAV (non-DM, $r=0.11$, $P=0.42$; DM, $r=0.14$, $P=0.51$, respectively) (**Fig. 3A, B**). The LDL-C level at 9–12-month follow-up was significantly correlated with ΔPAV in DM patients ($r=0.52$, $P=0.008$), but not in non-DM patients ($r=0.12$, $P=0.31$) (**Fig. 3A**). Furthermore, the percent change in the LDL-C level was significantly correlated with PAV in DM patients ($r=0.44$, $P=0.03$), but not in non-DM patients ($r=0.13$, $P=0.25$) (**Fig. 3B**). The percent change in the ApoB level and ApoB/ApoA1 ratio was significantly correlated with ΔPAV in DM patients ($\rho=0.41$, $P=0.04$, and $\rho=0.52$, $P=0.007$, respectively) (**Table 3**), but not in non-DM patients ($\rho=0.13$, $P=0.27$, and $\rho=0.012$, $P=0.92$, respectively) (**Table 3**). The percent change in the levels of campesterol and sitosterol was

Table 1. Baseline characteristics of enrolled patients

	non-DM			DM		
	Monotherapy (*n* = 36)	DLLT (*n* = 39)	*P*	Monotherapy (*n* = 13)	DLLT (*n* = 12)	*P*
Age, years	63.8 ± 10.2	64.2 ± 11.8	0.87	67.9 ± 7.1	65.1 ± 9.2	0.40
Male, n (%)	32 (89)	30 (77)	0.23	9 (69)	11 (92)	0.32
Body mass index, kg/m^2	24.6 ± 3.0	24.9 ± 3.6	0.74	25.1 ± 3.3	25.2 ± 3.2	0.98
Hypertension, *n* (%)	20 (56)	30 (77)	0.09	8 (62)	9 (75)	0.67
Dyslipidemia, *n* (%)	28 (78)	23 (59)	0.09	9 (69)	10 (88)	0.65
Current smoking,h *n* (%)	20 (56)	10 (26)	0.01	2 (15)	3 (25)	0.65
History of MI, *n* (%)	3 (8)	2 (5)	0.67	1 (8)	2 (17)	0.59
History of stroke, *n* (%)	1 (3)	3 (8)	0.62	0 (0)	1 (8)	0.48
History of PAD, *n* (%)	1 (3)	1 (3)	1.00	0 (0)	0 (0)	-
Medication						
Aspirin, *n* (%)	36 (100)	39 (100)	-	13 (100)	12 (100)	-
Thienopyridines, *n* (%)	34 (94)	39 (100)	1.00	11 (85)	11 (92)	0.48
Cilostazol, *n* (%)	0 (0)	0 (0)	0.48	0 (0)	0 (0)	-
Sarpogrelate, *n* (%)	1 (3)	0 (0)	-	0 (0)	1 (1)	0.48
Warfarin, *n* (%)	0 (0)	3 (8)	0.24	0 (0)	1 (1)	0.24
Nitrates, *n* (%)	2 (6)	5 (13)	0.43	1 (8)	0 (0)	0.43
Beta blockers, *n* (%)	22 (61)	19 (49)	0.36	7 (54)	8 (67)	0.36
Calcium-channel blockers, *n* (%)	7 (19)	15 (4)	0.08	4 (31)	5 (42)	0.08
ACE inhibitors or ARBs, *n* (%)	26 (72)	31 (79)	0.59	6 (46)	9 (75)	0.23
Hypoglycemic agents, n (%)	0 (0)	0 (0)	-	9 (69)	7 (58)	0.61
Statins, *n* (%)	20 (56)	15 (38)	0.17	6 (46)	7 (58)	0.70
TC, mg/dL	165.7 ± 32.5	178.6 ± 28.5	0.07	178.9 ± 26.8	165.0 ± 28.2	0.22
HDL-C, mg/dL	37.5 ± 10.5	40.9 ± 9.5	0.15	40.4 ± 8.3	37.9 ± 8.4	0.47
LDL-C, mg/dL	107.1 ± 28.4	114.9 ± 27.6	0.24	109.7 ± 24.3	102.9 ± 19.9	0.46
Triglycerides, mg/dL	107.0 (88.0 to 153.0)	106.0 (72.0 to 135.0)	0.90	115.0 (84.0 to 195.5)	115. 0 (81.0 to 140.3)	1.00
Hs-CRP, mg/L	5.6 (2.4 to 14.2)	6.1 (1.4 to 17.9)	0.67	5.2 (3.7 to 18.0)	11.2 (3.3 to 54.1)	0.69
Lipoprotein (a), mg/dL	20.0 (12.0 to 38.5)	21.0 (12.5 to 38.5)	1.00	11.0 (9.0 to 17.0)	25.5 (15.0 to 36.5)	0.12
Apolipoprotein A1, mg/dL	99.0 (93.5 to 117.5)	107.0 (97.5 to 116.5)	0.64	116.0 (104.0 to 130.0)	102.0 (87.5 to 111.5)	0.05
Apolipoprotein B, mg/dL	90.0 (78.0 to 104.5)	97.0 (87.5 to 110.0)	0.24	100.0 (91.0 to 103.0)	91.0 (80.5 to 102.0)	0.11
ApoB/ApoA1	0.86 (0.75 to 1.02)	0.88 (0.77 to 1.09)	0.35	0.82 (0.75 to 1.04)	0.96 (0.84 to 1.03)	0.12
Free fatty acid, μEq/L	438.0 (291.0 to 715.5)	357.0 (276.5 to 632.5)	0.16	560.0 (325.0 to 724.0)	508.0 (380.0 to 648.0)	1.00
RLP-C, mg/dL	3.6 (2.7 to 4.7)	3.3 (2.7 to 4.4)	0.83	3.3 (2.6 to 5.1)	3.4 (2.7 to 4.2)	1.00
sdLDL-C, mg/dL	27.9 (21.8 to 34.8)	25.4 (22.5 to 41.4)	0.83	34.2 (25.0 to 37.9)	23.7 (21.3 to 30.0)	0.05
Adiponectin, μg/mL	4.1 (2.6 to 6.0)	4.9 (3.0 to 6.9)	0.15	3.3 (2.7 to 5.1)	4.9 (4.1 to 5.7)	0.17
HbA1c, %	5.4 (5.1 to 5.8)	5.2 (5.0 to 5.4)	0.53	6.4 (6.25 to 7.25)	6.9 (6.2 to 8.2)	0.43
Lathosterol, mg/dL	1.1 (0.7 to 1.9)	1.0 (0.7 to 2.4)	0.75	1.6 (0.9 to 2.1)	1.0 (0.7 to 1.5)	0.43
Campesterol, μg/dL	3.4 (2.9 to 4.5)	4.7 (3.6 to 6.4)	0.04	3.9 (2.8 to 5.1)	3.4 (2.5 to 4.1)	0.70
Sitosterol, μg/dL	1.8 (1.5 to 2.3)	2.7 (1.9 to 3.3)	0.01	2.1 (1.8 to 2.6)	1.8 (1.1 to 2.3)	0.43
Lathosterol, mg/100 mg TC	0.6 (0.4 to 1.0)	0.6 (0.4 to 1.2)	1.00	0.9 (0.5 to 1.1)	0.8 (0.4 to 0.9)	0.70
Campesterol, mg/100 mg TC	2.1 (1.6 to 2.6)	2.8 (2.2 to 3.5)	0.02	2.0 (1.6 to 2.9)	2.0 (1.6 to 2.8)	1.00
Sitosterol, mg/100 mg TC	1.0 (0.9 to 1.4)	1.5 (1.1 to 1.8)	0.02	1.1 (1.0 to 1.6)	1.0 (0.6 to 1.4)	0.70
Campesterol/lathosterol	2.9 (2.1 to 4.3)	3.6 (2.4 to 7.7)	0.56	2.6 (1.9 to 3.6)	3.3 (1.5 to 6.1)	0.43
Plaque volume, mm^3	84.5 (44.3 to 128.2)	76.2 (38.9 to 110.2)	0.73	82.0 (46.2 to 144.2)	92.1 (65.3 to 150.2)	1.00
PAV, %	51.5 ± 11.1	50.3 ± 12.5	0.66	52.1 ± 14.4	58.0 ± 7.5	0.21
TAV, mm^3	91.9 ± 36.4	90.2 ± 39.0	0.84	116.9 ± 63.7	106.9 ± 40.0	0.65
Vessel volume, mm^3	174.6 ± 98.5	160.9 ± 92.3	0.54	190.6 ± 134.7	178.0 ± 108.2	0.80
Lumen volume, mm^3	85.0 ± 51.4	81.1 ± 51.3	0.74	86.1 ± 55.6	74.2 ± 47.3	0.57
Lesion length, mm	12.3 ± 6.4	10.6 ± 5.3	0.20	10.3 ± 4.6	11.6 ± 5.7	0.52

Data are the *n* (%), mean ± SD, or median (IQR). DM, diabetes mellitus; DLLT, dual lipid-lowering therapy with atorvastatin and ezetimibe; MI, myocardial infarction; PAD, peripheral artery disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Hs-CRP, high sensitive C-reactive protein; RLP-C, remnant like particle-cholesterol; sdLDL-C, small dense low-density lipoprotein-cholesterol; PAV, percent atheroma volume; TAV, total atheroma volume.

Table 2. Percent change in laboratory data during the study period

	non-DM			DM		
Percent change (%)	Monotherapy ($n=36$)	DLLT ($n=39$)	P	Monotherapy ($n=13$)	DLLT ($n=12$)	P
TC	−12.7 ± 18.6	−26.1 ± 16.7	0.002	−20.9 ± 20.0	−25.8 ± 11.9	0.46
HDL-C	16.0 ± 22.4	11.5 ± 29.5	0.47	4.2 ± 36.2	18.5 ± 13.0	0.20
LDL-C	−23.0 ± 23.2	−41.6 ± 18.8	<0.001	−29.2 ± 30.6	−42.9 ± 13.8	0.16
Triglycerides	1.0 (-25.5 to 38.6)	−4.2 (−21.9 to 73.5)	0.32	−0.7 (−41.8 to 18.1)	−17.3 (−46.0 to 3.3)	0.35
Hs-CRP	−90.1 (−96.4 to −79.0)	−90.1 (−96.9 to −68.0)	0.92	−91.3 (−98.0 to −85.7)	−93.4 (−98.5 to −86.7)	0.89
Lipoprotein (a)	−24.5 (−50.0 to −8.3)	−5.3 (−53.8 to 20.0)	0.57	−32.4 (−67.5 to 120)	−18.9 (−34.3 to 5.7)	0.94
Apolipoprotein A1	16.5 (8.5 to 25.0)	14.4 (3.6 to 25.2)	0.29	11.0 (−6.0 to 30.7)	25.2 (−17.5 to 29.2)	0.04
Apolipoprotein B	−23.1 (−37.0 to −8.3)	−33.7 (−46.2 to −24.7)	0.002	−33.8 (−47.6 to −4.7)	−40.6 (−44.9 to −33.0)	0.44
ApoB/ApoA1	−32.8 (−46.2 to −24.7)	−43.6 (−52.0 to −34.1)	0.008	−36.5 (−55.7 to −8.6)	−51.5 (−58.1 to −43.0)	0.02
Free fatty acid	21.1 (−53.8 to 65.3)	6.2 (−49.2 to 95.6)	0.84	−41.3 (−66.6 to 42.3)	6.3 (−29.7 to 44.8)	0.47
RLP-C	−7.6 (−36.6 to 43.2)	−18.8 (−32.6 to 19.2)	0.22	2.0 (−54.0 to 53.6)	−20.0 (−36.4 to −0.4)	0.93
sdLDL-C	−25.0 (−41.7 to 13.9)	−30.3 (−49.0 to −5.6)	0.04	−17.2 (−46.3 to 7.1)	−31.0 (−38.3 to −26.4)	0.69
Adiponectin	15.6 (−1.4 to 58.2)	21.3 (−4.6 to 59.5)	0.85	4.7 (−0.9 to 21.2)	31.9 (−1.6 to 57.9)	0.33
HbA1c	2.6 ± 9.1	3.9 ± 6.6	0.52	−4.3 ± 9.5	−9.0 ± 17.3	0.41
Lathosterol	−50.0 (−68.8 to 44.4)	−27.3 (−48.9 to 25.0)	0.15	−44.4 (−67.7 to 5.3)	−14.3 (−44.3 to −70.1)	0.06
Campesterol	41.4 (11.9 to 76.2)	−44.9 (−61.7 to −29.9)	<0.001	44.0 (0.9 to 83.7)	−38.9 (−47.1 to −25.0)	<0.001
Sitosterol	51.1 (19.4 to 71.8)	−36.4 (−52.6 to −6.3)	<0.001	25.4 (−21.9 to 99.5)	−30.0 (−39.7 to −1.7)	0.07
Lathosterol/TC	−34.8 (−57.3 to 46.4)	2.7 (−32.0 to 55.6)	0.03	−24.7 (−52.6 to 9.7)	49.5 (−21.4 to 102.8)	0.03
Campesterol/TC	72.1 (30.7 to 111.4)	−29.9 (−37.1 to −12.5)	<0.001	77.6 (52.2 to 102.5)	−15.2 (−29.8 to −2.3)	<0.001
Sitosterol/TC	61.2 (33.8 to 115.4)	−10.7 (−27.5 to 9.7)	<0.001	63.4 (10.1 to 125.7)	−5.8 (−29.9 to 41.1)	0.05
Campesterol/lathosterol	161.1 (25.0 to 437.8)	−32.1 (−62.9 to 20.0)	<0.001	211.7 (61.1 to 285.8)	−35.7 (−64.4 to 17.2)	0.001
Plaque volume	0.98 ± 9.5	−6.21 ± 3.4	0.18	−4.54 ± 9.54	−3.80 ± 12.5	0.87
PAV	−0.08 ± 2.66	−2.01 ± 3.36	0.008	−0.77 ± 2.51	−2.77 ± 3.47	0.11
TAV	0.93 ± 8.67	−9.02 ± 14.7	0.001	−7.54 ± 7.04	−1.60 ± 14.6	0.20
Vessel volume	1.46 ± 11.15	−2.82 ± 30.7	0.43	−3.71 ± 9.03	1.09 ± 13.5	0.30
Lumen volume	1.59 ± 14.9	1.28 ± 36.9	0.96	−1.48 ± 11.1	8.41 ± 18.1	0.11

See Table 1 for abbreviations.

significantly correlated with ΔPAV in non-DM patients ($\rho=0.34$, $P=0.004$, and $\rho=0.31$, $P=0.009$, respectively), but not in DM patients. The baseline levels of campesterol and sitosterol were not correlated with ΔPAV.

Discussion

This sub-study of the PRECISE-IVUS trial showed that coronary plaque tended to be reduced by intensive lipid-lowering therapy, but it was significantly weak in ACS patients with DM even if they underwent DLLT. ΔPAV seemed to be reduced in the DM-DLLT group compared with non-DM monotherapy group. However, there was no statistical difference between non-DM monotherapy and DM-DLLT ($P=0.06$) by one-way analysis of variance with repeated measures followed by a Bonferroni multiple comparison adjustment. This result suggests that DLLT could be more effective to attenuate ΔPAV than monotherapy even in DM patients, but this might not be enough for LDL-C management in DM patients. Baseline characteristics, coronary plaque volume, vessel size, and lesion length were similar between the monotherapy group and DLLT group in ACS patients with DM. The reduction in the LDL-C level was similar between patients with and without DM. In patients with DM, DLLT reduced the LDL-C level <70 mg/dL, as recommended in guidelines. The HbA1c level did not increase through the follow-up period. Therefore, poor control of LDL-C or glucose levels was not related to weaker regression of coronary plaques in patients with DM.

Our study revealed other important results. Although ΔPAV in patients with DM was not significantly different between the monotherapy group and DLLT group, a significant correlation between the percent change in the LDL-C level and ΔPAV was observed in DM patients, but not in non-DM patients. Baseline characteristics were similar between

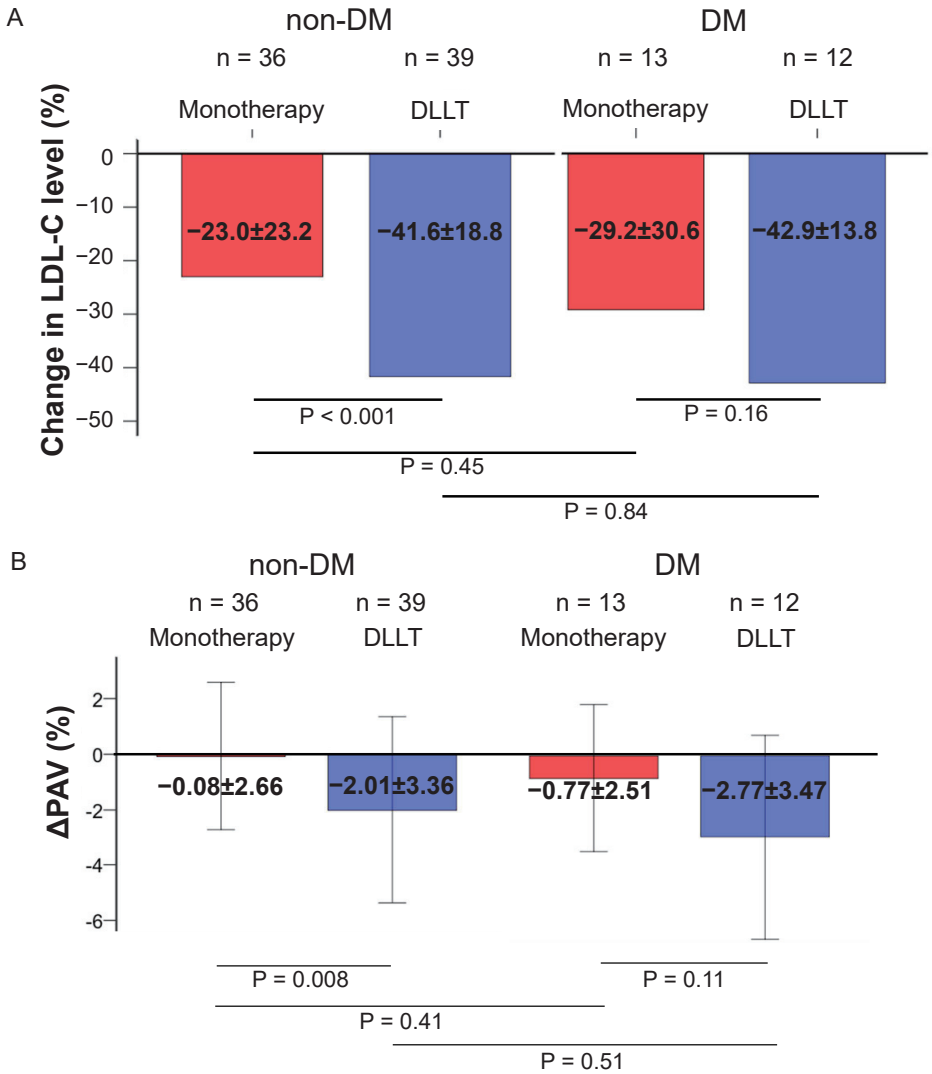

Fig. 2. Percent change in levels of hemoglobin A1c, low-density lipoprotein cholesterol, and percent coronary plaque volume between the monotherapy group and dual lipid-lowering group in ACS patients with and without diabetes mellitus

In non-DM[1] patients, the percent change in the LDL-C level was reduced significantly in the dual lipid-lowering-therapy (DLLT) group compared with the monotherapy group (A). The percent change in the LDL-C level in DM patients tended to be reduced by DLLT, but this reduction was not significant (A). Compared with non-DM patients, DM patients showed weaker regression of the change in the percent atheroma volume (ΔPAV) (B).

DM and non-DM patients with ACS except for the baseline levels of campesterol and sitosterol, which are cholesterol absorption markers. In non-DM patients, markers of cholesterol absorption were associated with ΔPAV. Strandberg *et al.* associated that higher cholesterol absorption with a higher prevalence of cardiovascular events[22]. Statins increase cholesterol absorption[23], which could be associated with accelerated atherosclerosis[24]. Therefore, increased levels of cholesterol absorption markers may have attenuated the benefit of the reduced LDL-C level on ΔPAV in our study, but this phenomenon was not observed in DM patients. It has been reported that cholesterol metabolism is disturbed so that cholesterol synthesis is elevated, while cholesterol absorption efficiency is reduced in patients with DM[22]. Ezetimibe's efficacy might be reduced under the condition of decreased cholesterol absorption. Furthermore, the percent change of lathosterol/TC ratio, which is the cholesterol synthesis marker, was increased in the DLLT group in DM patients compared with non-DM patients ($P<0.001$). Therefore, our observation of cholesterol metabolism markers may suggest a different plaque regression mechanism between DM and

Table 3. Relationship between lipid profiles and ΔPAV

	non-DM		DM	
Percent change during follow-up	*r*	*P*	*r*	*P*
HbA1c, %	0.11	0.42	0.14	0.51
LDL-C, %	0.13	0.25	0.44	0.03
	ρ	*P*	ρ	*P*
Lipoprotein (a), %	–0.07	0.59	0.09	0.71
ApoA1, %	0.05	0.68	–0.11	0.62
ApoB, %	0.13	0.27	0.41	0.04
ApoB/ApoA1, %	0.012	0.92	0.52	0.007
RLP-C, %	0.15	0.22	0.12	0.57
sdLDL-C, %	0.18	0.13	0.30	0.15
Lathosterol/TC, %	-0.067	0.58	-0.18	0.38
Campesterol/TC, %	0.34	0.004	0.23	0.27
Sitosterol/TC, %	0.31	0.009	0.29	0.15

See Table 1 for abbreviations.

Furthermore, the percent change in the LDL-C level was significantly correlated with PAV in patients with DM ($r=0.04$, $P=0.03$), but not in non-DM patients ($r=0.13$, $P=0.25$, Fig. 3A, B).

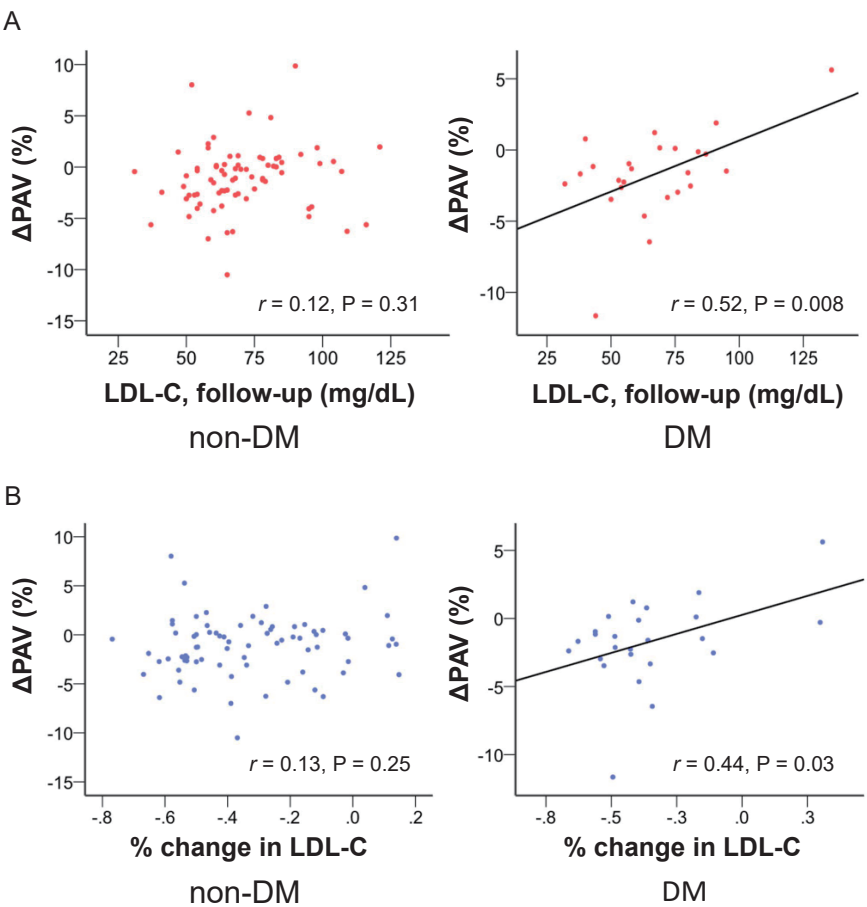

Fig. 3. Relationship between the level of low-density lipoprotein cholesterol and change in percent atheroma volume

Relationship between change in low-density lipoprotein cholesterol (LDL-C) level at follow-up (A), percent change in the level of LDL-C (B), and change in percent atheroma volume (ΔPAV) in ACS patients with and without DM.

non-DM patients. Furthermore, vessel volume and lumen volume tended to be reduced in the monotherapy group in patients with DM, but these features tended to be increased in the DLLT group; these changes were not observed in non-DM patients. These results suggest that people with DM and individuals not suffering from DM may have different coronary plaque characteristics and pathologic mechanisms in coronary plaque regression.

Scholars using IVUS have reported that ACS patients with DM have greater coronary plaque burden and necrotic core volume than those without DM[25, 26]. Pathology studies have also shown that the coronary plaques of patients with DM have large necrotic cores and accumulate macrophages and T cells, which reflect increased inflammation and which are associated with atherosclerosis progression and coronary plaque vulnerability in DM[27, 28]. Those studies supported our hypothesis of different coronary plaque characteristics.

A systematic review by Williams *et al.* postulated a coronary plaque regression mechanism. They stated that extensive lowering of the ApoB level can activate reverse lipid transportation from atheromatous plaques toward the liver[29]. Possible mechanisms for plaque regression which Williams *et al.* suggested are decreased retention of ApoB-containing lipoprotein within the arterial wall, efflux of cholesterol and other toxic lipids from plaques, emigration of foam cells out of the arterial wall, and migration of healthy phagocytes that remove necrotic debris. Reduction of the necrotic core and the number of inflammatory cells within atheromatous plaques are crucial for regression of coronary plaques in patients with DM. For this to occur, more intensive lowering of levels of ApoB and cholesterol would be required. Further basic and clinical evaluation is required to explain these mechanisms.

Hiro *et al.* reported similar results when evaluating coronary plaque changes using IVUS in 252 ACS patients treated with pitavastatin or atorvastatin[14]. In their study, coronary plaque regression was weaker in DM patients than in non-DM patients. In DM patients with baseline HbA1c ≥ 7.0%, there were significant correlations between the coronary plaque volume and LDL-C level at 8–12-month follow-up and the percent change of this parameter during the study period; such effects were not observed in DM patients with baseline HbA1c <7.0%. They suggested that glycemic control might be essential for coronary plaque regression in ACS patients with DM. Furthermore, they reported significant correlations between ΔPAV and the percent changes of other lipid parameters (e.g., total cholesterol, remnant-like particle cholesterol, non-high-density lipoprotein cholesterol, ApoB) in DM patients, but not in non-DM patients.

In our study, the change in the HbA1c level was not correlated with ΔPAV. LDL-C dependency, rather than glycemic control, seemed to be important. In addition, the percent change in the ApoB level and ApoB/ApoA1 ratio was significantly correlated with Δ PAV in DM patients, but not in non-DM patients. ApoB is a main component of chylomicron and very-low-density lipoprotein. Catabolism of chylomicron and very-low-density lipoprotein is attenuated in DM, so atherogenic lipoproteins tend to accumulate. This effect can lead to the development of more lipid-rich coronary plaques in patients with DM. Regression of the lipid-rich components in coronary plaques could depend on reduced LDL-C and ApoB levels in patients with DM. Therefore, more intensive therapy to reduce LDL-C and ApoB levels would be required in patients with DM.

Limitations

Our study had two main limitations. First, this sub-study was a retrospective analysis, and the baseline characteristics were not matched completely, primarily because of the small sample size (especially for DM patients). Although there was no statistical difference in ΔPAV in DM patients, absolute regression appears to be similar between DM and non-DM patients in **Fig. 2B**. Patients with DM might not have a significant difference due to small sample size, so the results should be interpreted carefully. Second, DM was mainly diagnosed according to medical history or laboratory data upon hospital admission. The glucose tolerance test was not carried out in some patients, so DM screening was suboptimal. Therefore, a larger prospective, randomized control trial would be required to confirm our results.

Conclusions

ACS patients with DM showed weaker regression of coronary plaques than non-DM patients. However, the percent change in levels of LDL-C and ApoB was correlated significantly to ΔPAV in DM patients, suggesting that more intensive lipid-lowering therapy with an ezetimibe-statin combination would be beneficial in ACS patients with DM.

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Conflicts of Interests

KS has received significant research grant support from Daiichi-Sankyo, Co., Ltd. Japan, outside the submitted work. KK has received significant research grant support from Bayer, Yakuhin, Ltd., Daiichi Sankyo Co., Ltd., Novartis Pharma AG., and SBI, Pharma Co., Ltd., and has received Honoraria from Bayer Yakuhin, Ltd. and Daiichi Sankyo Co., Ltd., outside the submitted work. HO has received grants from Astellas Pharma Incorporated, personal fees from Astra Zeneca Kabushiki Kaisha, grants and personal fees from Bayer Yakuhin, Limited, personal fees from Boehringer Ingelheim Japan, grants and personal fees from Bristol-Myers Squibb Company, grants and personal fees from Daiichi Sankyo Company, Limited, grants from Dainippon Sumitomo Pharma Company, Limited, grants and personal fees from Eisai Company, Limited, personal fees from Kowa Company, Limited, personal fees from Kyowa Hakko Kirin Company, Limited, grants and personal fees from Mitsubishi Tanabe Pharma, grants and personal fees from MSD Kabushiki Kaisha, grants from Novartis Pharma Kabushiki Kaisha, grants from Otsuka Pharmaceutical Company, Limited, grants and personal fees from Pfizer Japan Incorporated, grants and personal fees from Sanofi Kabushiki Kaisha, grants from Shionogi Company, Limited, grants and personal fees from Takeda Pharmaceutical Company, Limited, grants and personal fees from Teijin Pharma Company Limited, grants from Genzyme Japan Kabushiki Kaisha, grants from Kissei Pharmaceutical Company Limited, grants from Abbott Vascular Japan, grants from Boston Scientific Japan Kabushiki Kaisya, grants from Fukuda Denshi Company, Limited, grants from Johnson & Johnson, grants from Medtronic Japan Company Limited, grants from Nihon Kohden, and grants from Terumo, outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Supplemental Table 1. The absolute values of laboratory data at follow-up

	non-DM			DM		
	Monotherapy $n=36$	DLLT $n=39$	P value	Monotherapy $n=13$	DLLT $n=12$	P value
TC, mg/dL	141.9 ± 23.8	129.2 ± 21.3	0.18	139.8 ± 32.1	121.2 ± 21.4	0.10
HDL-C, mg/dL	42.2 ± 9.5	44.5 ± 12.8	0.39	41.0 ± 13.5	44.8 ± 10.0	0.44
LDL-C, mg/dL	77.6 ± 17.4	63.7 ± 16.2	0.001	74.2 ± 25.6	58.3 ± 16.0	0.08
Triglycerides, mg/dL	116.0 (87.0 to 144.5)	97.0 (78.0 to 118.0)	0.12	97.0 (84.5 to 153.0)	71.5 (66.3 to 96.3)	0.07
Hs-CRP, mg/L	0.39 (0.21 to 0.66)	0.48 (0.14 to 1.63)	0.78	0.35 (0.14 to 0.52)	0.38 (0.22 to 0.65)	0.85
Lipoprotein (a), mg/dL	16.0 (7.8 to 42.3)	15.0 (7.0 to 36.0)	0.57	10.0 (4.0 to 20.0)	26.0 (8.0 to 30.8)	0.94
Apolipoprotein A1, mg/dL	119.0 (106.5 to 109.0)	123.0 (109.0 to 134)	0.29	112.0 (102.0 to 131.0)	119.5 (108.5 to 129.5)	0.04
Apolipoprotein B, mg/dL	68.5 (58.8 to 82.3)	62.0 (54.0 to 70.0)	0.02	74.0 (56.0 to 91.0)	56.0 (49.0 to 68.3)	0.44
ApoB/ApoA1	0.55 (0.48 to 0.77)	0.52 (0.41 to 0.59)	0.05	0.63 (0.47 to 0.77)	0.46 (0.42 to 0.53)	0.02
Free fatty acid, μEq/L	417.0 (282.0 to 657.0)	378.0 (257.5 to 551.0)	0.49	380.0 (182.0 to 580.5)	484.5 (338.0 to 650.5)	0.27
RLP-C, mg/dL	3.4 (2.7 to 5.2)	2.7 (2.1 to 3.5)	0.22	3.3 (2.3 to 4.5)	2.2 (1.7 to 2.9)	0.93
sdLDL-C, mg/dL	20.5 (15.6 to 29.0)	19.9 (13.7 to 25.9)	0.19	22.9 (14.1 to 31.5)	15.1 (11.4 to 24.7)	0.15
Adiponectin, μg/mL	5.2 (3.3 to 6.9)	5.3 (3.7 to 8.0)	0.70	4.2 (3.6 to 5.9)	5.9 (3.8 to 7.2)	0.23
HbA1c, %	5.6 ± 0.4	5.4 ± 0.4	0.15	6.3 ± 0.7	6.5 ± 0.9	0.54
Lathosterol, mg/dL	0.7 (0.4 to 1.2)	0.9 (0.7 to 1.4)	0.15	0.6 (0.5 to 1.0)	0.9 (0.6 to 1.5)	0.06
Campesterol, μg/dL	5.0 (3.3 to 6.6)	2.5 (2.2 to 3.3)	< 0.001	4.7 (3.5 to 7.2)	2.0 (1.6 to 2.4)	< 0.001
Sitosterol, μg/dL	2.5 (1.8 to 3.2)	1.6 (1.2 to 2.1)	< 0.001	2.3 (1.7 to 3.4)	1.2 (0.9 to 1.8)	0.07
Lathosterol, mg/100 mg TC	0.5 (0.3 to 0.8)	0.7 (0.5 to 1.1)	0.03	0.5 (0.3 to 0.7)	0.8 (0.6 to 1.1)	0.03
Campesterol, mg/100 mg TC	3.6 (2.4 to 4.3)	2.1 (1.7 to 2.7)	< 0.001	3.6 (2.4 to 5.6)	1.6 (1.2 to 2.1)	< 0.001
Sitosterol, mg/100 mg TC	1.9 (1.3 to 2.7)	1.3 (1.0 to 1.6)	< 0.001	1.6 (1.2 to 3.0)	0.9 (0.8 to 1.6)	0.05
Campesterol/Lathosterol	7.3 (3.5 to 14.1)	2.6 (1.9 to 4.5)	< 0.001	5.6 (4.2 to 18.4)	1.8 (1.3 to 3.7)	< 0.001
Plaque volume, mm^3	81.5 (40.0 to 133.6)	70.0 (36.4 to 92.1)	0.16	82.6 (44.2 to 120.9)	87.5 (63.6 to 145.2)	0.65
PAV, %	51.4 ± 11.44	48.3 ± 11.6	0.24	51.4 ± 13.5	55.2 ± 7.5	0.38
TAV, mm^3	92.8 ± 37.6	81.2 ± 32.2	0.15	109.4 ± 58.9	105.3 ± 43.2	0.85
Vessel volume, mm^3	176.1 ± 103.5	145.9 ± 85.8	0.17	185.3 ± 152.3	179.7 ± 111.5	0.92
Lumen volume, mm^3	85.6 ± 52.5	76.3 ± 49.5	0.43	85.4 ± 65.8	77.7 ± 47.2	0.74
Lesion length, mm	12.3 ± 6.5	10.3 ± 5.3	0.16	10.3 ± 4.7	11.8 ± 5.9	0.47

Data are the n (%), mean ± SD, or median (IQR). DM, diabetes mellitus; DLLT, dual lipid-lowering therapy with atorvastatin and ezetimibe; MI, myocardial infarction; PAD, peripheral artery disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Hs-CRP, high sensitive C-reactive protein; RLP-C, remnant like particle-cholesterol; sdLDL-C, small dense low-density lipoprotein-cholesterol; PAV, percent atheroma volume; TAV, total atheroma volume.