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Original article

Clinical significance of non-culprit plaque regression following acute coronary syndrome: A serial intravascular ultrasound study

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A B S T R A C T

Background: The use of serial intravascular ultrasound (IVUS) for coronary atherosclerosis has offered valuable insight into plaque regression (PR) or progression. However, the beneficial effects of PR on the long-term clinical outcomes in patients with acute coronary syndrome (ACS) remain unclear. We aimed to evaluate the impact of coronary plaque change in patients following primary percutaneous coronary intervention.

Methods: We retrospectively analyzed data from 4 prospective clinical trials involving 173 patients with ACS who underwent serial IVUS of non-culprit lesions on statin treatment at baseline and at 6 or 8 months of follow-up. The relationship of the IVUS findings with the change in percent atheroma volume (PAV), on-treatment low-density lipoprotein cholesterol (LDL-C), and major adverse cardiac and cerebrovascular events (MACCE) were investigated.

Results: In our serial IVUS analysis, baseline plaque volume and PAV were 79.6 mm^3 and 46.0%, respectively. The overall change in PAV was −1.5% [interquartile range (IQR): −4.1% to 1.0%], and PR (i.e. PAV change from baseline <0) was observed in 67.1% of patients. They were followed up observationally for a mean of 3.5 years and a total of 37 MACCE occurred. The rate of MACCE tended to be lower in patients with PR than in those without PR (18.1% vs. 28.7%, p = 0.14). A multivariate Cox hazard model analysis demonstrated that achievement of both PR and on-treatment low LDL-C levels (<70 mg/dL) was the only significant independent predictor of MACCE (hazard ratio: 0.42, 95% confidence interval: 0.19–0.88; p = 0.02).

Conclusions: Achievement of both PR and sufficient lowering of the LDL-C was clinically important in post-ACS management.

Introduction

Pathologic studies have shown that the most common cause of myocardial infarction (MI) and death from cardiac cause is thrombotic coronary occlusion after rupture of a lipid-rich atheroma with a thin fibrous layer of intimal tissue covering the necrotic core (i.e. thin-cap fibroatheroma) [1–8]. Plaque stabilization may not only reduce the incidence of acute coronary syndrome (ACS), but it can also prevent the evolution of plaques to more stenotic lesions [9].

The ESTABLISH trial showed by serial volumetric intravascular ultrasound (IVUS) analysis that early atorvastatin therapy reduced the non-culprit atherosclerotic plaque volume in patients with ACS [10]. The ASTEROID investigators showed that high-intensity statin therapy led to significant plaque regression in patients with stable coronary artery disease (CAD) [11]. Moreover, statin therapy with the addition of non-statin agents, such as ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors, had a beneficial effect on plaque

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regression, which was brought about by progressive lowering of the low-density lipoprotein cholesterol (LDL-C) [12–15].

However, the prognostic impact of coronary atherosclerotic plaque changes on clinical outcomes remains unclear, especially in patients with ACS. Therefore, we aimed to investigate the prognostic value of non-culprit plaque regression in patients with ACS who underwent serial IVUS examination.

Materials and methods

Study design and population

This was an observational cohort study that included ACS patients who participated in 4 clinical prospective trials that evaluated the impact of serial IVUS findings at 6 or 8 months on coronary plaque burden. ACS was defined as unstable angina pectoris, non-ST-segment elevation MI (NSTEMI), or ST-segment elevation MI (STEMI). The details of the designs and inclusion/exclusion criteria of the 4 trials have been previously described. In brief, updated information on the survival status and date of last follow-up of the ACS patients who underwent serial IVUS measurements in these clinical trials were collected; these trials assessed early intensive lipid lowering with atorvastatin [10], combination of ezetimibe and statin [16], dipeptidyl peptidase-4 inhibitors [17], and cardiac rehabilitation [18]. Overall, 381 patients were treated with primary percutaneous coronary intervention (PCI) of the culprit lesion of ACS; in these patients, anon-culprit plaque atheroma in the culprit vessel was evaluated by IVUS. A non-culprit lesion segment was defined as any diseased but non-severe stenosis with having a percentage plaque area visually >20% by IVUS. In this study, we excluded patients who did not receive statin therapy for at least 1 month after the ACS onset (n = 59) and those without available data on follow-up IVUS examination (n = 150) (Fig. 1).

Based on the serial IVUS findings of the target segment relative to the baseline, plaque regression was defined as a decrease in the absolute change in the percent atheroma volume (PAV), whereas plaque progression was defined as an increase in the absolute change in the PAV. Upon the follow-up IVUS procedure, achievement of LDL-C targets for post-ACS management was defined as LDL-C < 70 mg/dL [19–21].

In the present study, patients were divided into 3 groups according to the plaque change during follow-up and on-treatment LDL-C; group 1 for plaque regression with on-treatment LDL-C <70 mg/dL; group 2 for plaque regression without on-treatment LDL-C <70 mg/dL; and group 3 for plaque progression with/without on-treatment LDL-C < 70 mg/dL.

The institutional review board and hospital ethics committee of Juntendo University Hospital approved this study (approval number was 17-171). Each patient provided written informed consent to participate in the follow-up. This study proceeded in accordance with the Declaration of Helsinki.

Intravascular ultrasound image acquisition and analysis

The acquisition and analysis of the IVUS measurements have been previously described in detail [10,16,17]. Briefly, a segment of a non-culprit lesion of the ACS culprit vessel (i.e. non-PCI site) was evaluated by serial IVUS measurements using 2 commercially available IVUS systems and catheters, including a mechanical rotating 40-MHz transducer (Atlantis Pro2, Boston Scientific Corporation, Natick, MA, USA and View It, Terumo Corporation, Tokyo, Japan). All IVUS examinations in the same patient were performed using the same system at baseline and follow-up. After intracoronary administration of 0.2 mg nitroglycerin, each IVUS catheter was advanced into the culprit vessel and was positioned as far distally and safely as possible. The IVUS data, including a reproducible index, such as side branches, were derived >5 mm proximal or distal to the deployed stent. Pullback was performed automatically at 0.5 mm/s. All measurements were fulfilled at the end of this study.

For the selection of the analyzed segment, culprit lesions of previous revascularization and prior MI were avoided; subsequently, the analyzed segment was determined by the proximal and distal side branches. When multiple (tandem) lesions were found in a culprit vessel, we selected and examined a single lesion suitable for analysis due to less calcification, better image quality, or location of side branches. Cross-sectional images that were spaced precisely at 1 mm apart were selected for measurement. The lumen and external elastic membrane were traced every 0.3-mm cross-section using manual planimetry, and the software automatically interpolated between the 2 manually traced images. On the basis of expert consensus [22], the PAV was calculated as the

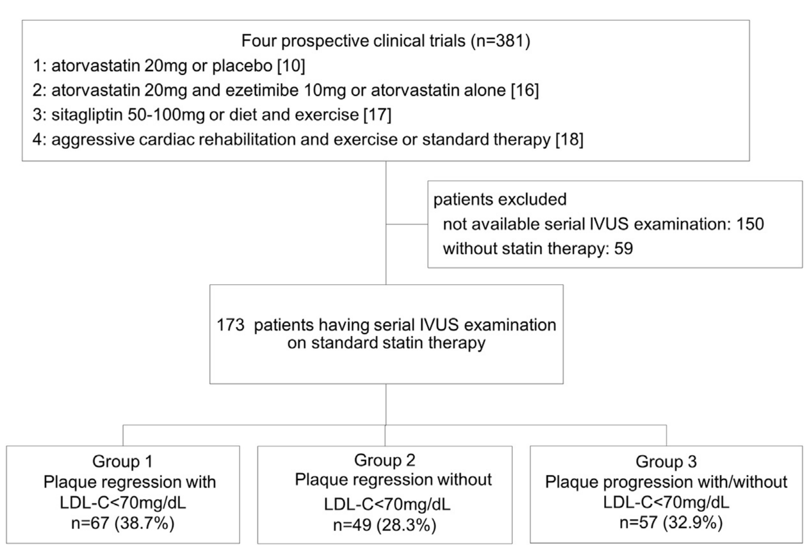

Fig. 1. Study flow chart of all subjects. IVUS, intravascular ultrasonography; LDL-C, low-density lipoprotein cholesterol.

proportion of the entire vessel wall that was occupied by the atherosclerotic plaque throughout the segment of interest, as follows:

$$\mathrm{PAV} = \frac{\sum(\mathrm{EEMarea} - \mathrm{Lumenarea})}{\sum \mathrm{EEMarea}}$$

All IVUS analyses were performed with Netra 3D IVUS system (ScImage, Los Altos, CA, USA) or VISIATRAS™ (Terumo, Tokyo, Japan) in an independent core laboratory (Juntendo University, Tokyo, Japan). The investigators for the IVUS analysis were unaware of the patient information and the timing of IVUS (baseline or follow-up) in order to eliminate any bias in the measurement of paired studies. The baseline and follow-up IVUS images were reviewed side by side on a display.

Study endpoints

The primary endpoint was the first occurrence of major adverse cardiac and cerebrovascular events (MACCE), which was defined as all-cause death, non-fatal MI, target vessel revascularization (TVR), target lesion revascularization (TLR), non-target vessel revascularization (non-TVR), and ischemic stroke. Clinical follow-up included a review of medical charts, telephone contact, and questionnaires sent to the patients or their families. Mortality data and cause of death were collected from the medical records of patients who died or who were treated at the participating facilities.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or as median (interquartile range, IQR) and were compared using one-way analysis of variance or the Kruskal–Wallis test. Categorical variables were expressed as frequency (percentage) and were compared using the chi-square test. The absolute change between the baseline and follow-up data was compared by paired *t*-test or Wilcoxon signed rank test, according to their distributions. The relationships between the absolute change in the PAV and the change in LDL-C level were evaluated by linear regression analysis. Unadjusted cumulative event rates were estimated using Kaplan–Meier curves and were compared among the 3 groups. The prognostic effects of plaque change and on-treatment LDL-C levels on MACCE were determined using multivariate Cox proportional hazard regression analysis. The multivariate analyses included clinically important variables, such as achievement of plaque regression with on-treatment LDL-C target, age, diabetes mellitus, use of drug-eluting stents (DES), and STEMI. Values of $p < 0.05$ were considered to indicate statistical significance. All data were analyzed using JMP version 12.2 for Windows (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics and lipid profiles

The baseline clinical characteristics and medication use of the 173 patients included in this study are summarized in Table 1. Overall, the patients had a mean age of 62.1 ± 10.4 years; 86% were men; and had the classic risk factors of hypertension in 67%, diabetes mellitus in 46%, and dyslipidemia in 71%. The proportion of patients who had STEMI was 54% and who were treated with DES was 24%.

There were 67 (38.7%) patients in group 1, 49 (28.3%) patients in group 2, and 57 patients (32.9%) in group 3; there were no significant differences among the groups in terms of the baseline characteristics, except for the higher prevalence of dyslipidemia in group 2. Baseline laboratory findings and changes in lipid profile and IVUS findings are shown in Table 2. The mean baseline and follow-up LDL-C values were 117.6 ± 34.9 mg/dL and 71.8 ± 26.0 mg/dL, respectively. In the overall population, the absolute change in the LDL-C was −48.4 mg/dL (IQR: −70.2 mg/dL to −22.0 mg/dL) and the percent change in the LDL-C was −43.4% (IQR: −56.0% to −22.9%). At follow-up, 57% of the patients achieved LDL-C levels less than 70 mg/dL.

Table 1
Baseline clinical characteristics.

Variable	Entire cohort (*n* = 173)
Age, years	62.1 ± 10.4
Male, *n* (%)	149 (86.1)
BMI (kg/m^2)	24.5 ± 3.4
Hypertension, *n* (%)	114 (66.7)
Diabetes mellitus, *n* (%)	79 (45.7)
Dyslipidemia, *n* (%)	122 (70.9)
Smoking, *n* (%)	137 (82.0)
Family history, *n* (%)	49 (28.8)
STEMI, *n* (%)	93 (53.8)
Ejection fraction (%)	56.8 ± 12.0
Medication at discharge	
Aspirin, *n* (%)	173 (100)
Statin, *n* (%)	173 (100)
ACE-i/ARB, *n* (%)	134 (77.5)
β blocker, *n* (%)	104 (62.7)
OHA, *n* (%)	39 (37.1)

ACE-i, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; OHA, oral hypoglycemic agents; STEMI, ST segment elevation myocardial infarction.

Comparison of the 3 groups showed that group 2 had a significantly higher value of LDL-C at baseline, but it did not significantly differ in baseline high density lipoprotein cholesterol (HDL-C), triglycerides, and hemoglobin A1c; whereas group 1 had significantly higher absolute and percent changes in LDL-C for 6–8 months, but it did not significantly differ in the absolute and percent changes in the other risk factors.

Angiographic findings

Culprit lesions of ACS were identified in the left anterior descending artery (57.2%), left circumflex (12.7%), right coronary artery (29.5%), and left main trunk (0.2%). IVUS analysis regions were located proximal to the portion in these culprit lesions of 76.3%. Angiographical reference diameter was 2.98 mm (IQR; 2.71–3.60 mm). There was no significant difference in culprit vessel and reference diameter among the 3 groups. Patients in group 1 had a lower rate of DES use (14.9%) than that of group 2 (30.6%) and group 3 (29.8%) ($p = 0.06$), respectively.

IVUS imaging analysis

The IVUS findings are shown in Table 2. Baseline plaque volume and PAV were similar among the 3 groups. Overall, the absolute changes in the plaque volume and PAV were −5.0 mm^3 (IQR: −11.5 mm^3 to − 0.2 mm^3, $p < 0.001$) and −1.5% (IQR: −4.1% to 1.0%, $p < 0.001$), respectively. Across the three groups, the absolute change in the PAV decreased by −3.2% (IQR: −6.8% to −1.5%) in group 1; by −3.4% (IQR: −5.2% to −1.4%) in group 2; and by 2.6% (IQR: 1.0% to 4.5%) in group 3. The overall absolute change in the PAV had a weak correlation with the absolute change in the LDL-C ($r = 0.15$, $p = 0.051$). Interestingly, there was a significant correlation between the absolute change in the PAV and the absolute change in the LDL-C in patients with STEMI, whereas it was not

Table 2
Baseline laboratory findings and changes in lipid profile and IVUS findings.

Variable	Entire cohort N = 173	Plaque regression with LDL-C < 70 mg/dL n = 67 (38.7%)	Plaque regression without LDL-C <70 mg/dL n = 49 (28.3%)	Plaque progression with/without LDL-C <70 mg/dL n = 57 (32.9%)	p
Baseline					
LDL-C (mg/dL)	117.6 ± 34.9	112.4 ± 27.9	129.6 ± 43.6	113.6 ± 32.0	0.017
HDL-C (mg/dL)	45.9 ± 12.8	46.4 ± 9.6	42.9 ± 10.6	47.7 ± 17.0	0.15
TG (mg/dL)	125.0 ± 74.0	113.2 ± 67.7	136.3 ± 73.3	129.2 ± 80.8	0.22
HbA1c (%)	6.3 ± 0.9	6.4 ± 1.1	6.2 ± 0.8	6.3 ± 1.0	0.54
eGFR (ml/min/1.73 m^2)	81.0 ± 19.3	79.2 ± 20.6	84.7 ± 19.4	80.1 ± 17.5	0.29
BNP (pg/mL)	52.3 (19.9, 138.4)	50.8 (22.0, 129.3)	43.9 (15.8, 143.5)	58.2 (20.1, 188.7)	0.36
Max CPK (mg/dL)	1407 (563, 4439)	1214 (560, 3766)	1477 (342, 5740)	1926 (678, 5589)	0.84
Follow-up					
LDL-C (mg/dL)	71.8 ± 26.0	54.8 ± 10.7	93.0 ± 16.1	73.5 ± 31.4	<0.001
HDL-C (mg/dL)	46.1 ± 13.8	46.6 ± 10.3	45.2 ± 17.7	46.4 ± 13.8	0.86
TG (mg/dL)	128.6 ± 61.9	114.1 ± 62.6	150.2 ± 55.6	127.0 ± 61.9	0.0073
Change from baseline					
LDL-C					
Absolute change (mg/dL)	−48.4 (−70.2, -22.0)	−60.0 (−78.0, −42.0)	−25.4 (−72.2, 0.2)	−42.6 (−64.5, −25.0)	<0.001
Percent change (%)	−43.4 (−56.0, −22.9)	−53.2 (−59.8, −38.5)	−23.0 (−44.0, −0.41)	−39.2 (−52.7, −23.4)	<0.001
p-Value for change	<0.001	<0.001	<0.001	<0.001	
HDL-C					
Absolute change (mg/dL)	0.0 (−6.0, 5.0)	0.0 (−6.0, 6.0)	0.0 (−6.0, 3.0)	0.0 (−7.5, 6.0)	0.54
Percent change (%)	0.0 (−14.0, 12.7)	0.0 (−13.2, 12.9)	0.0 (−14.3, 7.1)	0.0 (−16.7, 15.5)	0.66
p-Value for change	0.26	0.91	0.46	0.36	
TG					
Absolute change (mg/dL)	5.0 (−27.0, 40.0)	0.0 (−24.0, 36.0)	18.0 (−20.5, 56.0)	0.0 (−30.0, 33.0)	0.19
Percentage change (%)	5.0 (−23.4, 51.7)	0.0 (−21.2, 52.4)	17.9 (−14.0, 57.7)	0.0 (−28.4, 34.6)	0.20
p-Value for change	0.20	0.91	0.16	0.78	
IVUS measurements					
Analysis length (mm)					
Baseline	10.0 (8.85, 15.0)	10.0 (8.0, 15.0)	10.0 (9.6, 15.0)	10.0 (8.8, 14.0)	0.57
Follow-up	10.0 (9.03, 15.0)	10.0 (8.0, 15.0)	10.4 (9.5, 15.0)	10.0 (9.0, 14.3)	0.62
Vessel volume (mm^3)					
Baseline	163.4 (100.0, 248.2)	152.4 (102.5, 241.9)	178.0 (104.2, 255.0)	162.7 (91.7, 231.4)	0.64
Follow-up	156.0 (94.2, 235.1)	146.5 (93.5, 241.1)	168.3 (116.3, 236.1)	150.5 (85.6, 205.7)	0.41
Change from baseline	−5.71 ± 22.2	−5.65 ± 26.3	−3.31 ± 16.6	−7.86 ± 21.3	0.58
p-Value for change	<0.001	0.083	0.17	0.0073	
Plaque volume (mm^3)					
Baseline	79.6 (41.8, 117.3)	77.8 (41.7, 115.4)	90.0 (47.4, 127.5)	71.4 (38.7, 110.6)	0.49
Follow-up	73.3 (40.0, 109.9)	59.8 (35.9, 105.8)	81.8 (41.7, 116.5)	73.5 (41.9, 112.1)	0.41
Change from baseline	−5.03 (−11.5, −0.15)	−9.18 (−15.7, −2.99)	−8.93 (−13.9, −2.23)	−0.11 (−4.39, 5.89)	<0.001
p-Value for change	<0.001	<0.001	<0.001	0.49	
PAV (%)					
Baseline	46.0 (39.8, 53.0)	46.0 (39.7, 52.3)	46.0 (40.7, 53.8)	45.5 (37.7, 54.8)	0.92
Follow-up	44.3 (36.1, 52.9)	42.3 (34.7, 47.5)	42.6 (36.2, 50.2)	51.2 (41.1, 58.8)	<0.001
Change from baseline	−1.53 (−4.12, 1.03)	−3.23 (−6.84, −1.53)	−3.37 (−5.22, −1.40)	2.64 (1.03, 4.51)	<0.001
p-Value for change	<0.001	<0.001	<0.001	<0.001	

BNP, brain natriuretic peptide; CPK, creatine phosphokinase; EEM, external elastic membrane; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IVUS, intravascular ultrasonography; LDL-C, low-density lipoprotein cholesterol; PAV, percent atheroma volume; TG, triglycerides.

significant in non-ST-segment elevation ACS (STEMI: $r = 0.21$, $p = 0.04$, NSTE-ACS: $r = 0.10$, $p = 0.40$).

Relationship of plaque regression and on-treatment LDL-C with the clinical outcomes

After a mean follow-up period of 3.5 ± 1.8 years, a total of 37 clinical events were identified, including death ($n = 5$), non-fatal MI ($n = 2$), any revascularization ($n = 28$), and ischemic stroke ($n = 2$). Details of MACCE during the follow-up period are shown in Table 3. A total 71% of revascularizations (TVR + non-TV revascularization, 20/28) were recognized as non-culprit lesion-related revascularization. Furthermore, change in percent atheroma volume and clinical outcomes stratified by 4 clinical prospective trials are shown in Supplementary Table 1. An unadjusted analysis showed that the rate of MACCE tended to be lower in patients with plaque regression than in those without plaque regression (18.1% vs. 28.7%, $p = 0.14$). Among the 3 groups, as shown in Fig. 2, group 1 had a tendency to have a lower cumulative incidence of MACCE (log-rank, $p = 0.12$).

Univariate Cox proportional hazard analysis (Table 4) showed that the development of MACCE was not significantly associated with the achievement of either plaque regression (HR, 0.63; 95% CI, 0.33–1.22; $p = 0.17$) or low on-treatment LDL-C (HR, 0.60; 95% CI, 0.31–1.15; $p = 0.13$) alone, but the incidence of MACCE significantly decreased after achieving both plaque regression and low on-treatment LDL-C (HR, 0.47; 95% CI, 0.21–0.96; $p = 0.04$). In the multivariate model, after adjusting for the important clinical variables, the only independent predictors of MACCE were plaque regression with low on-treatment LDL-C (HR, 0.42; 95% CI, 0.19–0.87; $p = 0.02$).

Discussion

The major findings of this study were as follows: (1) among ACS patients on statin therapy, 67% achieved plaque regression of the non-culprit lesion and 57% reached a relatively low target LDL-C (<70 mg/dL) at 6 or 8 months after the ACS onset; (2) there was a weak correlation between the change in PAV and the change in LDL-C; and (3) achieving both plaque regression and low on-

Table 3
Details of major adverse cardiac and cerebrovascular events during the follow-up period.

Variable, *n* (%)	Entire cohort *N* = 173	Plaque regression with LDL-C < 70 mg/dL *n* = 67 (38.7%)	Plaque regression without LDL-C <70 mg/dL *n* = 49 (28.3%)	Plaque progression with/without LDL-C <70 mg/dL *n* = 57 (32.9%)	*p*
MACCE	37 (21.4)	9 (13.4)	12 (24.5)	16 (28.1)	0.11
All-cause death	5 (2.9)	2 (2.9)	1 (2.0)	2 (3.5)	
Non-fatal MI	2 (1.2)	0 (0.0)	1 (2.0)	1 (1.8)	
TVR	14 (8.1)	2 (2.9)	6 (12.2)	6 (10.5)	
TLR	8 (4.6)	2 (2.9)	2 (4.1)	4 (7.0)	
Non-TVR	6 (3.5)	2 (2.9)	2 (4.1)	2 (3.5)	
Ischemic stroke	2 (1.2)	1 (1.5)	0 (0.0)	1 (1.8)	

LDL-C, low-density lipoprotein cholesterol; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction, TLR; target lesion revascularization; TVR; target vessel revascularization.

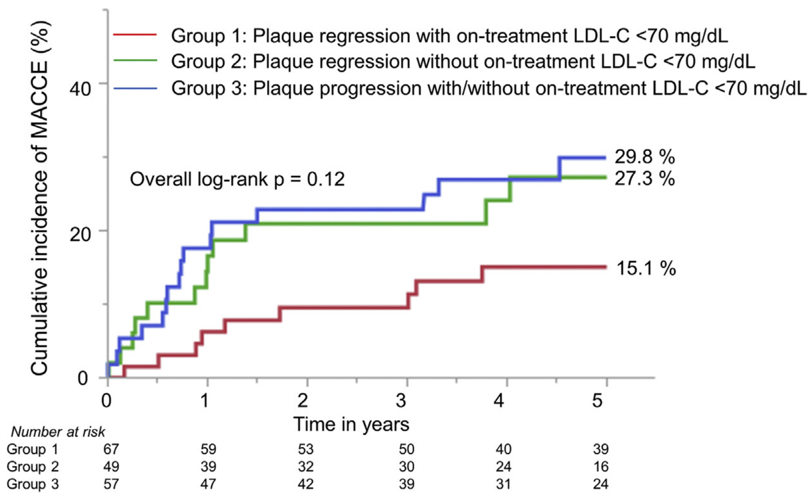

Figure 2. Time-to-event curves for MACCE according to non-culprit plaque change determined by IVUS and low on-treatment LDL-C level (<70 mg/dL). Patients in group 1 had a lower incidence of MACCE (log-rank, $p = 0.12$). IVUS, intravascular ultrasonography; LDL-C, low-density lipoprotein cholesterol; MACCE, major adverse cardiac and cerebrovascular events.

Table 4
Multivariable Cox proportional hazard model for MACCE.

	Unadjusted			Adjusted		
	HR	95% CI	*p*	HR	95% CI	*p*
Plaque regression with on-treatment low LDL-C	0.47	0.21–0.96	0.037	0.42	0.19–0.88	0.020
Age, 1-year increase	1.03	0.99–1.06	0.13	1.03	0.99–1.07	0.073
Diabetes mellitus	1.11	0.58–2.11	0.76	1.20	0.62–2.33	0.59
Use of drug-eluting stents	0.79	0.32–1.72	0.58	0.58	0.23–1.30	0.20
STEMI	0.85	0.44–1.63	0.62	0.84	0.44–1.62	0.60

LDL-C, low-density lipoprotein cholesterol; MACCE, major adverse cardiac and cerebrovascular event; STEMI, ST segment elevation myocardial infarction; CI, confidence interval; HR, hazard ratio.

treatment LDL-C after ACS was a significant predictor of a relatively low risk of MACCE. We, therefore, believe that stabilization of the non-culprit coronary plaque with sufficient LDL-C lowering therapy could lead to better clinical outcomes post-ACS management.

LDL-Cis a causal factor in the pathophysiology of CAD [23]. Previous randomized controlled trials have demonstrated that intensive LDL-C lowering with statin therapy reduced cardiac and cerebrovascular events in patients with CAD [5,24,25]. In the 2016 ESC/EAS guidelines, achievement of specific goals was recommended (LDL-C <70 mg/dL) for patients with CAD because of the very high risk of developing ACS [20]. In addition, the recent guidelines of the Japan Atherosclerosis Society suggested that the objective in high-risk patients should be to optimally reduce the LDL cholesterol level to below 70 mg/dL [19]. Importantly, the LDL-C threshold of 70 mg/dL after ACS management is close to the theoretical point of conversion from coronary atherosclerosis progression to regression [11]. Therefore, our results confirmed that sufficient LDL-C lowering (<70 mg/dL) with statin is clinically important in Japanese patients with ACS.

The present study demonstrated that the IVUS finding of non-culprit plaque regression could be a surrogate marker of prognosis for ACS, even at the early stage. Stone et al. reported that approximately 20% of ACS patients who were successfully treated with PCI developed cardiovascular events within 3 years, with adverse events that were equally attributable to recurrence at the originally treated culprit lesions and to the previously untreated non-culprit coronary plaque segments [26]. Coronary artery calcium progression on serial computed tomography has been shown to add value to baseline calcium score, demographics, and cardiovascular risk factors in predicting all-cause mortality [27]. Nicholls et al. reported a direct relationship of the IVUS findings of coronary atheroma burden with its progression and adverse cardiovascular events [28]. In addition, Puri et al. reported that patients who had a relatively large baseline coronary atheroma volume had a higher risk for cardiac events after 2 years of follow-up, despite the achievement of very low on-treatment LDL-C levels [29]. By serial IVUS measurements, the extended-ESTABLISH study showed that coronary plaque regression over a period of 6 months was associated with a lower rate of cardiovascular events during a 5-year follow-up [30]. On the other hand, the extended JAPAN-ACS study demonstrated that coronary plaque regression did not predict future cardiovascular events [31]. Consequently, our results suggested that targeting both plaque regression and sufficient LDL-C lowering after an ACS might play an important role in reducing clinical events in the long-term follow-up.

In the present study, 33% of patients had plaque progression for 6–8 months regardless of the outcome of PCI and contemporary medical treatment. These results suggested that mechanisms beyond LDL-C contributed significantly to the atherosclerosis development and progression in a non-negligible proportion of patients. The residual cardiovascular risk after ACS is multifactorial; the well-known risk factors, such as smoking, diabetes, and hypertension, have to be well-controlled according to the guideline recommendations, with a fully comprehensive approach to cardiovascular health and prevention [20]. Several studies had shown that a relatively low level of HDL-C was associated with a poor prognosis, even in patients with LDL-C levels that are well-controlled by statins [32,33]. Furthermore, hypertriglyceridemia is related to coronary adverse events [34,35]. However, in our study, plaque regression/progression had no significant relationship with the lipid profiles, except for the LDL-C, biomarkers related to diabetes. Ridker et al. recently reported that canakinumab, which is a monoclonal antibody that targets interleukin-1β, decreased the levels of high-sensitivity C-reactive protein and reduced the incidence of adverse cardiovascular events in patients with previous CAD [36]. Pemafibrate, which is a novel selective peroxisome proliferator-activated receptor modulator, had a stronger triglyceride-lowering effect than that of the existing fibrates, such as fenofibrate [37]. Consequently, evidence on the use of novel non-statin agents for plaque regression and stabilization is expected to increase. In addition, the impact of combining LDL-C lowering agents with the other class of agents that target plaque biology should be directly assessed by future imaging studies, including quantification of plaque lipid content and inflammation, to better measure the response to lipid-lowering treatment.

This study had several limitations. First, only 173 patients with ACS participated. Although our data were useful because we evaluated the prognosis from a novel viewpoint, further large-scale studies are warranted. Second, in this study, we used the two different IVUS systems and catheters even though the same IVUS system is used for the patient. This might affect our results. However, a previous report showed quantitative measurements by the two different, currently available IVUS systems that we used in this study were accurate and comparable [38]. Third, we assessed only volumetric IVUS measurements and limited segments in the culprit vessel, in which the median value of analyzed length was only 10 mm. Fourth, in our combined data analysis from several clinical trials, other medical interventions beside lipid-lowering therapy might have influenced coronary plaque dynamics after ACS and clinical outcomes. Future studies should evaluate the value of the information generated from novel imaging techniques.

Conclusion

This study suggested that targeting both plaque regression and sufficient LDL-C lowering is clinically important in post-ACS management.

Conflict of interests

Dr Daida has received speakers' Bureau/Honoraria from Amgen Astellas BioPharma K.K., Astellas Pharma Inc., AstraZeneca plc., GlaxoSmithKline K.K., Sanofi-Aventis K.K., Shionogi & Co., Daiichi Sankyo Company, Takeda Pharmaceutical Co., Terumo Corporation, Nippon Boehringer Ingelheim Co., Medtronic Japan, Bayer Yakuhin, and MSD K.K., as well as research funds or grants from Abbott Medical Japan, Astellas Pharma Inc., Daiichi Sankyo Company, and Kowa Pharmaceutical Company that are unrelated to this project.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2018.12.023.

References

[1] Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. J Am Coll Cardiol 2006;47:C13–8.
[2] Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient. Circulation 2003;108: 1664–1672.
[3] Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000; 20:1262–75.
[4] Kolodgie FD, Narula J, Burke AP, Haider N, Farb A, Hui-Liang Y, et al. Localization of apoptotic macrophages at the site of plaque rupture in sudden coronary death. Am J Pathol 2000;157:1259–68.
[5] van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation 1994;89:36–44.
[6] Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992;326:242–50.
[7] Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989;79:733–43.
[8] Davies MJ, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. N Engl J Med 1984;310:1137–40.
[9] Lee RT, Libby P. The unstable atheroma. Arterioscler Thromb Vasc Biol 1997;17:1859–67.
[10] Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, et al. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. Circulation 2004;110:1061–8.
[11] 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;295:1556–65.
[12] Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. JAMA 2016;316:2373–84.
[13] Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K, et al. Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: the multicenter randomized controlled PRECISE-IVUS trial. J Am Coll Cardiol 2015;66:495–507.
[14] Bohula EA, Giugliano RP, Cannon CP, Zhou J, Murphy SA, White JA, et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to

simvastatin and associated with better outcomes in IMPROVE-IT CLINICAL PERSPECTIVES. Circulation 2015;132:1224–33.
[15] Fujisue K, Tsujita K. Current status of lipid management in acute coronary syndrome. J Cardiol 2017;70:101–6.
[16] Nakajima N, Miyauchi K, Yokoyama T, Ogita M, Miyazaki T, Tamura H, et al. Effect of combination of ezetimibe and a statin on coronary plaque regression in patients with acute coronary syndrome: ZEUS trial (eZEtimibe Ultrasound Study). IJC Metabol Endocr 2014;3:8–13.
[17] Kuramitsu S, Miyauchi K, Yokoi H, Suwa S, Nishizaki Y, Yokoyama T, et al. Effect of sitagliptin on plaque changes in coronary artery following acute coronary syndrome in diabetic patients: the ESPECIAL-ACS study. J Cardiol 2017;69:369–76.
[18] Nishitani-Yokoyama M, Miyauchi K, Shimada K, Yokoyama T, Ouchi S, Aikawa T, et al. Impact of physical activity on coronary plaque volume and components in acute coronary syndrome patients after early phase II cardiac rehabilitation. Circ J 2018;83:101–9.
[19] Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, et al. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. J Atheroscler Thromb 2018;25:846–984.
[20] Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315.
[21] Stone NJ, Robinson JG, Lichtenstein AH, Merz CNB, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889–934.
[22] Mintz GS, Garcia-Garcia HM, Nicholls SJ, Weissman NJ, Bruining N, Crowe T, et al. Clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound regression/progression studies. EuroIntervention 2011;6(9):1123–30.
[23] Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017;38:2459–72.
[24] Tonkin A, Aylward P, Colquhoun D, Glasziou P, Harris P, MacMahon S, et al. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349–57.
[25] Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001–9.
[26] Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.
[27] Budoff MJ, Hokanson JE, Nasir K, Shaw LJ, Kinney GL, Chow D, et al. Progression of coronary artery calcium predicts all-cause mortality. JACC Cardiovasc Imaging 2010;3:1229–36.
[28] 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;55:2399–407.
[29] Puri R, Nissen SE, Shao M, Ballantyne CM, Barter PJ, Chapman MJ, et al. Coronary atheroma volume and cardiovascular events during maximally intensive statin therapy. Eur Heart J 2013;34:3182–90.
[30] Dohi T, Miyauchi K, Okazaki S, Yokoyama T, Yanagisawa N, Tamura H, et al. Plaque regression determined by intravascular ultrasound predicts long-term outcomes of patients with acute coronary syndrome. J Atheroscler Thromb 2011;18:231–9.
[31] Miyauchi K, Daida H, Morimoto T, Hiro T, Kimura T, Nakagawa Y, et al. Reverse vessel remodeling but not coronary plaque regression could predict future cardiovascular events in ACS patients with intensive statin therapy. Circ J 2012;76:825–32.
[32] Hagström E, Roe MT, Hafley G, Neely ML, Sidhu MS, Winters KJ, et al. Association between very low levels of high density lipoprotein cholesterol and long term outcomes of patients with acute coronary syndrome treated without revascularization: insights from the TRILOGY ACS Trial. Clin Cardiol 2016;39:329–37.
[33] Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med 2007;357:1301–10.
[34] Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, et al. Triglycerides and the risk of coronary heart disease: 10 158 incident cases among 262 525 participants in 29 Western prospective studies. Circulation 2007;115:450–8.
[35] Patel A, Barzi F, Jamrozik K, Lam TH, Ueshima H, Whitlock G, et al. Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. Circulation 2004;110:2678–86.
[36] Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet 2018;391:319–28.
[37] Ishibashi S, Arai H, Yokote K, Araki E, Suganami H, Yamashita S. Efficacy and safety of pemafibrate (K-877), a selective peroxisome proliferator-activated receptor α modulator, in patients with dyslipidemia: results from a 24-week, randomized, double blind, active-controlled, phase 3 trial. J Clin Lipidol 2018;12:173–84.
[38] Yamada R, Okura H, Kume T, Hayashida A, Neishi Y, Kawamoto T, et al. Comparison of quantitative measurements between two different intravascular ultrasound systems: in vitro and in vivo studies. J Cardiol 2013;61:201–5.