Increased Serum Malondialdehyde-Modified Low-Density Lipoprotein and Coronary Angiographic Progression After Drug-Eluting Stent Implantation in Patients With Stable Angina

Masashi Yokoi, MD; Tsuyoshi Ito, MD; Hiroshi Fujita, MD;
Tomonori Sugiura, MD; Yoshihiro Seo, MD; Nobuyuki Ohte, MD

Background: Cardiac events can occur after drug-eluting stent (DES) implantation due to coronary plaque progression at non-stented sites. Malondialdehyde-modified low-density lipoprotein (MDA-LDL) is suggested to be an atherogenic marker. This study investigated the relationship between serum MDA-LDL and angiographic progression after DES implantation.

Methods and Results: In total, 207 patients who underwent percutaneous coronary intervention (PCI) using DES and follow-up coronary angiography were retrospectively analyzed. MDA-LDL was serially measured before PCI and at follow up. Persistent high MDA-LDL was defined as a MDA-LDL level more than the median value both before PCI and at follow up. Angiographic progression was assessed by serial analysis of quantitative coronary angiography. Angiographic progression occurred in 35 patients (16.9%). MDA-LDL before PCI was significantly higher in the progression group than the non-progression group in all patients (143.4 ± 35.8 U/L vs. 103.0 ± 33.5 U/L, $P < 0.001$) and in patients with controlled LDL-cholesterol (LDL-C < 100 mg/dL both before PCI and at follow up; 121.8 ± 32.7 U/L vs. 84.9 ± 24.9 U/L, $P < 0.001$). There were positive correlations between % diameter stenosis changes and serum MDA-LDL before PCI in all patients ($r = 0.33$, $P < 0.01$) and those with controlled LDL-C ($r = 0.23$, $P = 0.04$). In multivariate logistic regression analysis, persistent high MDA-LDL was an independent predictor of plaque progression.

Conclusions: Increased serum MDA-LDL was associated with angiographic progression after DES implantation.

Key Words: Angiographic progression; Coronary artery disease; Malondialdehyde-modified low-density lipoprotein; Quantitative coronary angiography

The appearance and development of drug-eluting stents (DES) have markedly reduced adverse cardiac events, including target lesion revascularization (TLR) after percutaneous coronary intervention (PCI).^{1,2} In addition, lipid-lowering pharmacological therapy has been established as a cornerstone of reducing the risk of coronary artery disease (CAD).^{3,4} However, cardiac events can occur even under adequate lipid-lowering therapy after PCI with DES, due to the development of new lesions at non-stented segments.⁵ Therefore, it is clinically important to predict and prevent CAD progression, as it is a strong predictor of future cardiac events.⁶ Although complex plaque morphology,⁷ enhanced inflammation,⁸ and impaired lipid profiles⁹ may be responsible for plaque progression, the underlying mechanisms are not fully elucidated.

Oxidative modification of low-density lipoprotein (LDL) plays a key role in the formation and acceleration of atherosclerosis.¹⁰ Malondialdehyde-modified LDL

(MDA-LDL), which is an epitope of oxidized LDL, was recently shown to be a marker of CAD severity¹¹ and plaque vulnerability,¹² as well as a predictor of acute coronary syndrome¹³ and adverse cardiac events after PCI using DES.¹⁴ However, it remains unclear whether abnormal serum MDA-LDL level contributes to angiographic plaque progression of non-PCI lesions.

The aim of this study was to clarify the relationship between serial serum MDA-LDL levels and angiographic progression at non-PCI target lesions in patients with stable angina undergoing lipid-lowering therapy after DES implantation.

Methods

Study Population

From June 2009 to January 2014, a total of 604 patients with stable angina underwent PCI at our institute. Of

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Department of Cardiology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Mailing address: Tsuyoshi Ito, MD, Department of Cardiology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuhocho, Nagoya 467-8601, Japan. E-mail: tuyosiito@gmail.com

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Variables	All (n=207)	Progression (n=35)	Non-progression (n=172)	P value
Age (years)	71.1±8.4	68.7±9.0	71.5±8.3	0.07
Male	148 (71.5)	27 (77.1)	121 (70.3)	0.42
BMI (kg/m ²)	24.2±3.3	24.5±2.5	24.1±3.4	0.43
HT	184 (88.9)	32 (91.4)	152 (88.4)	0.77
DM	89 (43.0)	17 (48.6)	72 (41.9)	0.47
Smoking	54 (26.1)	9 (25.7)	45 (26.2)	0.96
Previous PCI	73 (35.3)	16 (45.7)	57 (33.1)	0.16
Previous CABG	13 (6.3)	1 (2.9)	12 (7.0)	0.70
MVD	89 (43.0)	20 (57.1)	69 (40.1)	0.06
CKD	66 (31.9)	8 (22.9)	58 (33.7)	0.21
History of MI	68 (32.9)	13 (37.1)	55 (32.0)	0.55
In-stent restenosis at follow up	31 (14.9)	9 (25.7)	22 (12.8)	0.05
ID-TLR at follow up	9 (4.3)	2 (5.7)	7 (4.1)	0.65
Follow-up period (months)	10.3±2.3	10.5±2.7	10.2±2.2	0.44
Reason for follow up				
Onset of ischemic symptom	22 (10.6)	5 (14.3)	17 (9.9)	
Objective signs of ischemia	4 (1.9)	0 (0)	4 (2.3)	
Follow-up examination	181 (87.4)	30 (85.7)	151 (87.8)	0.51
Non-target lesion maximum stenosis				
Mild (0–25%)	21 (10.1)	1 (2.9)	20 (11.6)	
Moderate (26–75%)	109 (52.7)	19 (54.3)	90 (52.3)	
Severe (76–100%)	77 (37.2)	15 (42.9)	62 (36.0)	0.27
SBP at PCI (mmHg)	136.5±18.6	135.2±17.9	136.8±18.8	0.65
DBP at PCI (mmHg)	73.1±10.7	72.5±11.9	73.3±10.5	0.71
SBP at follow up (mmHg)	136.1±16.9	131.6±13.8	137.1±17.3	0.08
DBP at follow up (mmHg)	66.7±10.8	65.5±9.2	67.0±11.1	0.46
Medications at PCI				
Statin	133 (64.3)	25 (71.4)	108 (62.8)	0.33
Antihypertensive agents	168 (81.2)	29 (82.9)	139 (80.8)	0.78
Antidiabetic agents				
None	134 (64.7)	22 (62.9)	112 (65.2)	
Oral	60 (29.0)	8 (22.9)	52 (30.2)	
Insulin	13 (6.3)	5 (14.3)	8 (4.7)	0.09
Medications at follow up				
Statin	194 (93.7)	34 (97.1)	160 (93.0)	0.70
Antihypertensive agents	182 (87.9)	31 (88.6)	151 (87.8)	0.90
Antidiabetic agents				
None	130 (62.8)	21 (60)	109 (63.4)	
Oral	63 (30.4)	9 (25.7)	54 (31.4)	
Insulin	14 (6.8)	5 (14.3)	9 (5.2)	0.14
Laboratory data at PCI				
MDA-LDL (U/L)	109.9±37.1	143.4±35.8	103.0±33.5	<0.01
LDL-C (mg/dL)	102.7±29.1	112.5±29.8	100.8±28.7	0.03
HDL-C (mg/dL)	47.8±13.7	44.2±12.1	48.5±13.9	0.09
TGs (mg/dL)	146.4±64.3	155.2±63.8	144.6±64.4	0.38
CRP (mg/dL)	0.09 (0.05–0.19)	0.13 (0.05–0.23)	0.09 (0.05–0.18)	0.27
HbA1c (%)	6.34±0.95	6.58±1.02	6.30±0.93	0.11
Laboratory data at follow up				
MDA-LDL (U/L)	105.8±32.5	134.5±36.0	100.0±28.4	<0.01
LDL-C (mg/dL)	95.0±26.7	106.0±31.6	92.8±25.1	<0.01
HDL-C (mg/dL)	49.8±13.3	45.5±11.1	50.6±13.5	0.04
TGs (mg/dL)	151.5±73.4	174.3±77.5	146.8±71.9	0.04
CRP (mg/dL)	0.08 (0.04–0.17)	0.09 (0.05–0.16)	0.07 (0.04–0.18)	0.69
HbA1c (%)	6.12±0.92	6.39±1.18	6.07±0.85	0.06

Data are expressed as n (%), mean±standard deviation, or median (interquartile range). BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; ID-TLR, ischemia driven target lesion revascularization; LDL-C, low-density lipoprotein cholesterol; MDA-LDL, malondialdehyde-modified low-density lipoprotein; MI, myocardial infarction; MVD, multi-vessel disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TGs, triglycerides.

Figure 1. Relationship between angiographic progression and serum malondialdehyde-modified low-density lipoprotein (MDA-LDL) level. LDL-C, low-density lipoprotein cholesterol.

these, 213 patients who were treated with DES had follow-up coronary angiography (CAG) at 6–18 months after PCI and serial MDA-LDL measurement before PCI and at the time of follow-up CAG. After hemodialysis patients ($n=6$) were excluded, 207 patients were retrospectively analyzed. The mean follow-up interval was 10.3 ± 2.3 months. The research protocol was approved by the Nagoya City University Graduate School of Medical Sciences and the Nagoya City University Hospital Institutional Review Board (Reference number: 60-19-0151).

The informed consent requirement was waived by the Board because we retrospectively accessed the database for analysis. All procedures performed in the present study involving human participants were in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki.

Blood Sampling and MDA-LDL Measurement

Venous blood samples were collected after the patients fasted overnight. MDA-LDL levels were determined using an enzyme-linked immunosorbent assay kit (Sekisui Medical Co, Tokyo, Japan).¹⁵ After blood samples were collected, sera were separated within 6 h. Samples were diluted 2000-fold in a dilution buffer containing 3.5 mmol/L sodium dodecyl sulfate (SDS). Duplicate 100 μ L portions of the samples were added to the wells of plates coated with a monoclonal antibody against MDA-LDL (ML25). MDA-derived epitopes that may be buried in the lipid shell of LDL were expressed and recognized by ML25 in a protein assay with SDS-containing samples. The reaction was allowed to stand for 2 h at room temperature, then the plates were washed. Next, β -galactosidase-conjugated monoclonal antibody against apoB (AB16) was added. After incubation for 1 h at room temperature, o-nitrophenyl-galactopyranoside was added. After 2 h, the reaction was stopped by adding 100 μ L of 0.2 mol/L sodium carbonate (pH 12). Absorbance at 415 nm was determined with a microplate reader. We tentatively defined 1 U/L MDA-LDL as the absorbance obtained with a primary standard concentration of 1 mg/L. A calibration curve was prepared by diluting a reference serum as a secondary standard from 300 to

9,600-fold with dilution buffer and calculating the amount of MDA-LDL in the samples. High-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), C-reactive protein (CRP), and hemoglobin A1c (HbA1c) were measured using standard laboratory procedures. LDL cholesterol (LDL-C) was measured using a direct homogenous assay (Kyowa Medex Co, Tokyo, Japan).¹⁶

Blood samples were drawn just before PCI and at the time of follow-up CAG, and the patients were classified into the following 4 groups according to the serial levels of MDA-LDL, LDL-C, HDL-C, TGs, and CRP: persistent low, increased, attenuated, and persistent high respectively. High status was defined as a level more than the median value at baseline measurement, and persistent high was defined as the presence of high levels at both baseline and follow up. Patients with baseline high and follow-up low levels were considered the attenuated group, those with baseline low and follow-up high levels were considered the increased group, and those with low levels at both baseline and follow up were defined as the persistent low group.

PCI Procedure and Clinical Follow up

PCI was performed using standard techniques. The procedural strategy was left to the operator's discretion. DES was used as the first-line choice. Intravascular ultrasound or optical coherence tomography was routinely used to support appropriate stent implantation. All patients were pretreated with aspirin plus ticlopidine or clopidogrel before stenting, and at least 1 year of dual antiplatelet therapy was recommended. After PCI, lipid-lowering therapy, mainly with statin, was conducted with a target level of LDL-C <100 mg/dL, as recommended by the Japan Atherosclerosis Society Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases (2012).¹⁷ Controlled LDL-C was defined as LDL-C <100 mg/dL both before PCI and at follow up. Smoking cessation, healthy diet, maintaining a healthy weight, and physical activity according to the patient's exercise capacity were recommended for each patient. Antihypertensive and antidiabetic drugs were prescribed at the discretion of

the attending physicians according to patient's age and other comorbidities. Follow-up CAG was performed for the onset of ischemic symptoms, objective signs of myocardial ischemia, or as a follow-up examination. Decision to perform and the timing of follow-up CAG were left to the discretion of the attending physician.

Analysis of CAG

CAG was performed with the standard Judkins technique, with intracoronary administration of 0.2 mg nitroglycerin after intravenous administration of 3,000 U heparin. Off-line quantitative CAG (QCA) was performed with an automated edge-detection program (Cardiovascular Measurement System; Medical Imaging Systems, Leiden, the Netherlands). The non-PCI target lesion was a de novo

Table 2. Patient Characteristics and QCA Analysis of Non-PCI Target Lesions According to MDA-LDL Type

Variables	MDA-LDL type				P value
	Persistent low (n=80)	Increased (n=23)	Attenuated (n=40)	Persistent high (n=64)	
Age (years)	71.4±8.4	71.0±7.5	74.0±6.3	68.8±9.5	0.022
Male	58 (72.5)	15 (65.2)	29 (72.5)	46 (71.9)	0.92
BMI (kg/m ²)	24.1±3.9	23.5±3.4	24.0±2.7	24.6±2.8	0.51
HT	75 (93.8)	18 (78.3)	35 (87.5)	56 (87.5)	0.19
DM	39 (48.8)	12 (52.2)	10 (25.0)	28 (43.8)	0.067
Smoking	20 (25.0)	5 (21.7)	12 (30.0)	17 (26.6)	0.90
LDL-C					
At PCI	87.7±26.1	94.1±17.8	115.3±28.7	116.8±26.3	<0.001
At follow up	83.6±21.9	100.5±25.0	84.5±18.7	113.9±26.3	<0.001
HDL-C					
At PCI	49.3±15.2	50.0±12.2	47.1±13.5	45.4±12.2	0.30
At follow up	51.6±14.2	53.0±12.9	48.8±12.5	47.0±12.3	0.12
TGs					
At PCI	130.2±59.4	168.0±79.4	153.7±67.6	154.3±58.8	0.026
At follow up	136.2±66.1	158.4±94.1	151.4±69.1	168.1±74.3	0.073
CRP					
At PCI	0.09 (0.05–0.15)	0.08 (0.06–0.14)	0.12 (0.05–0.18)	0.13 (0.05–0.25)	0.64
At follow up	0.08 (0.04–0.15)	0.07 (0.05–0.17)	0.09 (0.04–0.29)	0.07 (0.04–0.16)	0.61
HbA1c					
At PCI	6.31±0.88	6.37±0.88	6.01±0.60	6.59±1.16	0.023
At follow up	5.98±0.72	6.27±1.13	5.86±0.51	6.41±1.16	0.006
QCA at PCI					
Reference diameter (mm)	2.27±0.07	2.23±0.15	2.21±0.09	2.24±0.08	0.97
MLD (mm)	1.39±0.06	1.39±0.15	1.40±0.10	1.39±0.07	1.00
%DS	39.12±1.79	38.32±3.39	38.35±3.28	39.35±2.10	0.99
QCA at follow up					
Reference diameter (mm)	2.29±0.07	2.21±0.16	2.19±0.09	2.25±0.09	0.89
MLD (mm)	1.37±0.06	1.35±0.14	1.26±0.12	1.13±0.07	0.14
%DS	40.19±2.02	40.17±3.58	43.56±4.06	50.39±2.56	0.02
Change in MLD (mm)	−0.03±0.03	−0.04±0.09	−0.14±0.05	−0.25±0.05	<0.01
Change in %DS	1.07±1.03	1.86±2.39	5.22±2.53	11.04±1.88	<0.01

Data are expressed as n (%), mean±standard deviation, median (interquartile range), or mean±standard error. QCA, quantitative coronary angiography; MLD, minimal lumen diameter; %DS, percent diameter stenosis. Other abbreviations as in Table 1.

lesion that was not responsible for the ischemic symptoms or positive functional ischemic tests before PCI. All coronary sites that looked stenotic were visually screened at both baseline and follow up. When a patient had a single non-PCI target lesion, it was analyzed. When more than one measurable lesion was present, the lesion with the largest increase in percent diameter stenosis (%DS) between baseline and follow up was analyzed as the index lesion. In the case of a development of new stenosis in a normal segment at baseline, QCA at baseline was manually performed in the equal segment of new stenosis at follow-up angiography. To assess lesion progression, the same angiographic projections were analyzed at baseline and follow up, whereas coronary branches were used as markers to identify the coronary segments. As in a previous study,⁸ angiographic progression of a non-PCI target lesion was defined as any of the following based on QCA analysis: (1) ≥10% diameter reduction of a pre-existing stenosis ≥50%; (2) ≥30% diameter reduction of a pre-existing stenosis <50%; (3) development of a new stenosis ≥30% diameter reduction in a segment that was normal at the time of PCI; and (4) progression of any lesion to total occlusion at

follow-up CAG. We excluded lesions of grafted vessels and those within 20 mm of the anastomotic stenosis and the PCI target lesion. A stenosis >50% was considered angiographically significant, and multivessel disease (MVD) was defined as ≥2 vessels with angiographically significant stenosis. In-stent restenosis was defined as angiographic significant stenosis at the stented segment or its edges (5-mm segments adjacent to the stent). Coronary angiograms were reviewed separately by 2 independent observers.

Statistical Analysis

Continuous variables were compared using the Student's t-test, the Mann-Whitney U-test, and 1-way analysis of variance, as appropriate. The chi-squared test and Fisher's exact test were used to compare categorical variables. Receiver operating characteristic (ROC) curves were generated to assess the potential of MDA-LDL and LDL-C to predict angiographic progression of non-PCI target lesions. Comparison of areas under the curve (AUC) was performed with the chi-squared test. Correlations between serum MDA-LDL levels before PCI and changes in %DS were estimated with Pearson's correlation coefficients.

Table 3. Predictors of Angiographic Progression

Variables	Univariate analysis		Multivariate analysis					
	OR (95% CI)	P value	Model 1 OR (95% CI)	P value	Model 2 OR (95% CI)	P value	Model 3 OR (95% CI)	P value
Persistent high MDA-LDL	7.20 (3.25–15.97)	<0.01	6.49 (2.89–14.54)	<0.01	–	–	6.25 (2.78–14.09)	<0.01
Persistent low HDL-C	2.24 (1.07–4.69)	0.03	1.81 (0.81–4.02)	0.15	1.96 (0.92–4.17)	0.08	–	–
Persistent high LDL-C	2.13 (0.99–4.56)	0.05	–	–	2.01 (0.93–4.38)	0.08	–	–
Persistent high TGs	2.12 (1.01–4.43)	0.05	–	–	–	–	1.73 (0.78–3.87)	0.18
MVD	1.99 (0.95–4.15)	0.07	1.48 (0.67–3.29)	0.34	1.80 (0.85–3.83)	0.13	1.65 (0.74–3.66)	0.22
Age (years)	0.96 (0.92–1.00)	0.07	–	–	–	–	–	–
Persistent high CRP	1.81 (0.87–3.77)	0.11	–	–	–	–	–	–
Previous PCI	1.70 (0.81–3.55)	0.16	–	–	–	–	–	–
CKD	0.58 (0.25–1.36)	0.21	–	–	–	–	–	–
DM	1.31 (0.63–2.72)	0.47	–	–	–	–	–	–
HT	1.40 (0.39–5.01)	0.60	–	–	–	–	–	–
Smoking	0.98 (0.43–2.24)	0.96	–	–	–	–	–	–

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

Logistic regression analysis was performed to identify potential predictors related to angiographic progression of non-PCI target lesions. Variables of patient characteristics with P values <0.10 in the univariate model were used in the multivariate model. Covariates in univariate analysis for the prediction were persistent high MDA-LDL, persistent low HDL-C, persistent high LDL-C, persistent high TGs, MVD, age, persistent high CRP, previous PCI, chronic kidney disease, diabetes mellitus, hypertension, and smoking. The variables included in the multivariate analyses were as follows: (Model 1) persistent high MDA-LDL, persistent low HDL-C, and MVD; (Model 2) persistent low HDL-C, persistent high LDL-C, and MVD; and (Model 3) persistent high MDA-LDL, persistent high TGs, and MVD. A P value <0.05 was considered statistically significant. SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

Patients' clinical, angiographic, and biochemical data are summarized in **Table 1**. Angiographic progression of the non-culprit lesion was observed in 35 (16.9%) patients. Of these, 19 patients had ≥10% reduction in the diameter of a pre-existing ≥50% stenosis, 9 patients had ≥30% reduction in the diameter of a pre-existing <50% stenosis, 2 patients had a new ≥30% stenosis in a previously normal lesion, and 5 patients had progression to total occlusion at follow-up angiography. Regarding the clinical and angiographic parameters, there were no significant differences between the 2 groups, with the exception that the rate of MVD and angiographic in-stent restenosis at follow up tended to be

higher in the progression group. In the biochemical data, the progression group presented with significantly higher MDA-LDL and LDL-C levels compared with the non-progression group before PCI and at follow-up measurements. TGs levels were higher and HDL-C levels were lower in the progression group at follow up. **Figure 1** showed comparisons of MDA-LDL level before PCI between the progression and the non-progression group. Even in patients with controlled LDL-C, the progression group had a significantly higher MDA-LDL level than the non-progression group (121.8 ± 32.7 U/L vs. 84.9 ± 24.9 U/L, $P < 0.001$). ROC curve analyses revealed that the difference in AUCs between MDA-LDL and LDL-C before PCI was statistically significant and that the MDA-LDL level before PCI could be a better predictor of angiographic progression than LDL-C level (**Figure 2A**). The MDA-LDL cut-off value before PCI for predicting angiographic progression was 126.5 U/L (sensitivity of 0.74; specificity of 0.80). Also, in the patients with controlled LDL-C, MDA-LDL before PCI could be a determinant of angiographic progression (cut-off value of 105 U/L, sensitivity of 0.77; specificity of 0.80) (**Figure 2B**). There was positive correlation between %DS changes and serum MDA-LDL levels before PCI not only in all patients but also in those with controlled LDL-C (**Figure 3**).

Patient characteristics and QCA analysis of non-PCI target lesions according to MDA-LDL type are shown in **Table 2**. Median values of MDA-LDL, LDL-C, HDL-C, TGs, and CRP before PCI were 107 U/L, 100 mg/dL, 45 mg/dL, 133 mg/dL, and 0.09 mg/dL, respectively. In the persistent high MDA-LDL group, patients were younger. Furthermore, LDL-C and HbA1c were significantly higher

compared to other groups. Although not statistically significant, TGs were higher and HDL-C was lower in the persistent high MDA-LDL group. The changes in minimal lesion diameter and %DS were significantly different among the MDA-LDL groups. Univariate logistic regression analysis showed that persistent high MDA-LDL and persistent low HDL-C had significant association with angiographic progression of the non-PCI target lesion. Multivariate analysis revealed that persistent high MDA-LDL was an independent predictor regardless of the model (Table 3).

Discussion

To the best of our knowledge, this is the first report showing that MDA-LDL may be a potential marker of angiographic progression of non-PCI target coronary lesions in stable angina patients who were treated with DES and lipid-lowering therapy. Our main finding was that serum MDA-LDL level, in particular MDA-LDL before PCI, was strongly associated with angiographic progression. This association remained true even in the patients with controlled LDL-C. Furthermore, persistent high MDA-LDL was an independent predictor of angiographic progression.

Disease Progression After PCI in the DES Era

Since the appearance and development of DESs, the restenosis rate after PCI has markedly improved, resulting in a great reduction in the incidence of TLR.^{1,2} The development of current-generation DES, in conjunction with the advancement of intravascular imaging modalities to optimize stent deployment, has enabled safe and effective treatment, even in cases with complex lesions such as left main disease.¹⁸ In our study, all DESs were implanted under intravascular imaging guidance. Although angiographic in-stent restenosis, which may potentially reflect in-stent atherosclerotic progression (neoatherosclerosis),¹⁹ was relatively frequently observed in the progression group, the rate of TLR was acceptably low. In contrast, there is little evidence that PCI for stable CAD can reduce cardiac death or myocardial infarction compared with optimal medical therapy.²⁰ PCI is considered a “local treatment” for symptom relief and cannot prevent the development of new coronary atherosclerotic lesions at the non-stented segment that affects long-term prognosis after DES implantation. In line with a previous study showing that new coronary lesion development is common,²¹ this study demonstrated the high incidence of non-PCI target lesion progression, which has a potentially large effect on adverse cardiac events.⁶ Therefore, preventing new lesion progression has become an important therapeutic target to improve long-term clinical outcomes in CAD patients after DES implantation.

Role of Oxidative Stress in CAD Progression

Despite increased attention to the importance of CAD progression, the underlying mechanism is still not fully understood. The theory that oxidative stress triggers lipid oxidation and that oxidized LDL plays a crucial role in coronary atherogenesis has been suggested.²² Uptake of oxidized LDL leads to notable cholesterol deposition, converting macrophages to foam cells and promoting the development of atherosclerotic plaques.¹⁰ In addition, oxidized LDL induces various inflammatory activities includ-

ing recruitment of monocytes, activation of lymphocytes, and secretion of cytokines and growth factors with accelerated smooth muscle cell proliferation and necrotic core formation.²³ Although it is difficult to quantify intracoronary oxidative stress in daily clinical practice, we focused on MDA-LDL, a potential alternative marker to oxidative stress, to investigate the relationship with coronary plaque progression at non-stented sites. We showed that increased MDA-LDL was significantly associated with coronary plaque progression, supporting the hypothesis that exposure to oxidative stress may be associated with coronary atherosclerotic plaque progression.

Residual Risk After Optimal Secondary Prevention Therapy

Based on accumulating evidence from lipid-lowering pharmacological therapy for the prevention of plaque progression²⁴ and cardiovascular events,³ current guidelines strongly recommend statin use for CAD patients as a secondary prevention.²⁵ However, a certain proportion of patients undergoing lipid-lowering therapy experience plaque progression, despite having well-controlled LDL-C.²⁶ LDL particles are heterogeneous in terms of composition both in size and density.²⁷ It has been reported that small dense LDL (sdLDL) is associated with increased risk for cardiovascular disease²⁸ because of easy absorption into the arterial wall, lower binding affinity for the LDL receptor, a prolonged plasma half-time and greater susceptibility to oxidation.²⁹ The concentration of sdLDL is increased in individuals with high TGs, dysglycemia and the metabolic syndrome.³⁰ In our study, high TGs and HbA1c, and low HDL-C were observed in patients with a high level of MDA-LDL. It may imply that potentially high sdLDL levels in patients with high MDA-LDL could lead to coronary atherosclerotic progression. One prior study referred to the relevance of hypertension and diabetes mellitus to plaque progression,²⁶ whereas another indicated residual inflammatory risk³¹ in patients undergoing lipid-lowering therapy. These data suggest that plaque progression is a multifactorial phenomenon and decreasing the LDL-C level alone may be insufficient to prevent it. Therefore, it is important to comprehensively manage other risk factors such as smoking, body weight, blood pressure, TGs, diabetes, and metabolic syndrome by implementing healthy behaviors and pharmacotherapy. In our study population, most patients who exhibited plaque progression had been managed with standard treatment, with lifestyle education and medication including statin therapy. Still, little is known about the residual risk under adequate secondary prevention after DES-PCI. Useful markers to identify high-residual-risk populations and practical methods to intervene should be established.

Clinical Implication

The major clinical implication of this study is that MDA-LDL at PCI and a sustained increase in MDA-LDL may be useful markers for risk stratification in patients after DES-PCI. The present study found that the MDA-LDL level before PCI was higher in patients with angiographic progression and correlated to angiographic %DS change, and that these findings are in line with a previous report that found that the pre-PCI MDA-LDL level is a predictor of cardiovascular events.¹⁴ In addition, the MDA-LDL level before PCI was significantly associated with coronary plaque progression, even under LDL-C control. By assessing MDA-LDL before PCI, high-risk patients may be

identified in advance. Furthermore, in this study, serial assessment of MDA-LDL demonstrated that persistent high MDA-LDL could have an effect on angiographic progression. By measuring MDA-LDL not only before PCI but also during follow up, high-risk patients could be more accurately identified. Although our findings are hypothesis-generating and larger prospective studies are required to confirm the effectiveness of MDL-LDL-lowering therapy and MDA-LDL-guided pharmacotherapy, high MDA-LDL may be a target to treat in patients after DES-PCI.

Study Limitations

This study had several limitations. First, it was a retrospective observational study with a relatively low number of Japanese patients recruited at a single center. In addition, indication of follow-up CAG was decided by the attending physician without strict criteria, and patients being treated with hemodialysis were excluded from the analysis because follow-up CAG in dialysis patients was performed only in cases with strongly suspected CAD recurrence and/or progression. Therefore, the population was highly biased. Further prospective studies are needed with larger populations. Second, lipid-lowering therapy was administered according to a 2012 Japanese guideline, and the target LDL-C level differed from that of current standard guidelines. Third, the relationship between MDA-LDL and LDL particle size is not clarified. More detailed evaluation of the lipid profile such as apolipoprotein B and sdLDL is required. Fourth, CAG is only a lumenogram and we did not incorporate intravascular imaging analysis in this study, so data on plaque burden and/or vulnerability were lacking. Fifth, although frequent in-stent restenosis in the progression group may suggest that MDA-LDL could be also related to in-stent neoatherosclerosis, it should be confirmed by further intravascular imaging and histopathological studies. Finally, angiographic progression is a surrogate marker for cardiovascular events. Clinical outcome data with longer follow up are needed.

Conclusions

Increased serum MDA-LDL was associated with angiographic plaque progression after DES implantation.

Disclosures

All authors received no support from sponsors and have no conflicts of interest to declare. N.O. is a member of *Circulation Journal* Editorial Team.

Data Availability

The deidentified participant data will not be shared.

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