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Elevated Lipoprotein(a) as a potential residual risk factor associated with lipid-rich coronary atheroma in patients with type 2 diabetes and coronary artery disease on statin treatment: Insights from the REASSURE-NIRS registry

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高リポ蛋白(a)血症と冠動脈内脂質プラークの関係の解明）

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Elevated Lipoprotein(a) as a potential residual risk factor associated with lipid-rich coronary atheroma in patients with type 2 diabetes and coronary artery disease on statin treatment: Insights from the REASSURE-NIRS registry

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ABSTRACT

Background and aims: The residual risk of atherosclerotic cardiovascular disease (ASCVD) in patients with diabetes on statin therapy warrants identification of other pro-atherogenic drivers. Lipoprotein(a) [Lp(a)] promotes the formation of necrotic cores within vessel walls. Given that patients with diabetes have an Lp(a)-associated ASCVD risk, Lp(a) might lead to plaque vulnerability in patients with diabetes on statin therapy.

Methods: We analyzed target lesions that underwent PCI in 312 patients with coronary artery disease (CAD) on statin treatment from the REASSURE-NIRS registry (NCT04864171). Maximum 4-mm lipid-core-burden index ($maxLCBI_{4mm}$) in target lesions was measured with near-infrared spectroscopy (NIRS) imaging. The relationship between Lp(a) levels and $maxLCBI_{4mm}$ was investigated in patients with and without diabetes.

Results: High-intensity statin use ($p = 0.49$) and on-treatment low-density lipoprotein cholesterol (LDL-C) ($p = 0.32$) and Lp(a) levels ($p = 0.09$) were comparable between patients with and without diabetes. Lp(a) levels were significantly associated with $maxLCBI_{4mm}$ in patients with diabetes ($p = 0.01$) but not in patients without diabetes ($p = 0.96$). Multivariate analysis showed that LDL-C levels ($p = 0.03$) predict $maxLCBI_{4mm}$ in patients without diabetes, but not Lp(a) levels ($p = 0.91$). Both LDL-C ($p = 0.01$) and Lp(a) ($p = 0.04$) levels were independent predictors of $maxLCBI_{4mm}$ in patients with diabetes. Even in patients with diabetes achieving LDL-C <1.8 mmol/L (70 mg/dL), Lp(a) levels remained associated with $maxLCBI_{4mm}$ ($p = 0.04$).

Conclusions: A significant relationship between Lp(a) and $maxLCBI_{4mm}$ exists in patients with diabetes and CAD on statin treatment, even with LDL-C <1.8 mmol/L (70 mg/dL). Lp(a) might be associated with more vulnerable coronary atheroma in patients with diabetes despite receiving statin therapy.

1. Introduction

Despite reductions in LDL-C levels with statin therapy, patient with type 2 diabetes mellitus still experience atherosclerotic cardiovascular disease (ASCVD) more frequently [1]. Pathophysiologically, coronary atherosclerosis in patients with diabetes is associated with lipidic plaque

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components [2]. Given that lipid-rich coronary atheroma is a vulnerable disease substrate that ultimately causes coronary events, there is a clinical need to understand the mechanisms promoting accumulation of lipidic plaque materials within vessel walls of patients with diabetes receiving statin therapy.

Lipoprotein(a) is an atherogenic cholesterol particle that consists of apolipoprotein B100 covalently bound to the glycoprotein apolipoprotein(a) [3,4]. A growing body of evidence suggests that Lp(a) is associated with ASCVD in primary and secondary prevention settings [5–8]. However, recent observational studies have shown inconsistent findings about the relationship between Lp(a) and ASCVD in patients with diabetes. While Waldeyer et al. have reported that cardiovascular risk associated with Lp(a) is significantly higher in patients with type 2 diabetes mellitus than in patients without diabetes [9], one recent UK BioBank study showed a greater Lp(a)-associated risk of ASCVD in patients without diabetes [10]. These observations suggest the need to further explore whether circulating Lp(a) could be an important driver of lipid-rich plaque formation in patients with diabetes. Since near-infrared spectroscopy imaging (NIRS) enables quantitative assessment of lipidic plaque burden *in vivo* [11,12], the current study employed this modality to investigate the association between Lp(a) and lipidic plaque components in patients with coronary artery disease (CAD) with or without diabetes, who are receiving LDL-C lowering statin therapy.

2. Patients and methods

2.1. Study subjects

Study subjects were selected from the REASSURE-NIRS multi-center registry, which enrolled consecutive patients with CAD requiring percutaneous coronary intervention (PCI) under the guidance of NIRS/intravascular ultrasound (IVUS) imaging (NCT04864171). A total of 741 patients with CAD were enrolled in this registry from August 1, 2015 to August 31, 2020. Written informed consent was not obtained from each patient because this study consisted of an observational analysis of hospitalized patients. However, details about the current study were posted on our institution's website (https://www.ncvc.go.jp/hospital/pub/clinical-research/untersuchung/) to ensure that patients could refuse inclusion in the current analysis. When we contacted participants by mail or telephone, we explained the study and obtained informed consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. This study was approved by the institutional review board of the National Cerebral and Cardiovascular Center (M30-084) and the Miyazaki Medical Association Hospital (2020–43).

The following subjects were excluded: patients with no history of statin therapy (n = 125), patients with no Lp(a) data (n = 251), patients with in-stent restenosis (n = 49), and patients with a target lesion within a bypass graft (n = 4). Consequently, the current study included the remaining 312 patients with CAD who underwent PCI with NIRS/IVUS imaging guidance and lipid-lowering statin therapy (Supplemental Figure I). High-intensity statin was defined as atorvastatin ≥20 mg, rosuvastatin ≥10 mg, or pitavastatin ≥4 mg [13].

2.2. Acquisition and quantitative analysis of NIRS/IVUS imaging

The current study analyzed target lesions requiring PCI with NIRS/IVUS imaging. A target lesion was defined as a lesion for which PCI was performed. After intracoronary administration of nitroglycerin (100–300 μg), the imaging catheter (TVC Insight™ or Dualpro™, Infraredx, Bedford, MA, USA) was advanced into the target vessel prior to PCI, and then automatically withdrawn at a translation velocity of 0.5 mm/s and 960 rpm (TVC Insight™) or 2.0 mm/s and 1800 rpm (Dualpro™) [11,12]. The Makoto® system (Infraredx) was used to quantitatively analyze the chemogram data. This analysis was conducted by persons blinded to the clinical characteristics of the patients (HN, TI, KM, SK and YK). Quantitative measurements were conducted to evaluate the amount of lipidic plaque materials in target lesions. Throughout the raw spectra obtained, the probability of lipid core on NIRS imaging was automatically mapped on a red-to-yellow color scale. Next, maximum 4-mm lipid-core burden index ($maxLCBI_{4mm}$) was calculated as the number of yellow pixels within target lesions divided by the total number of pixels within the corresponding segment [11,12].

2.3. Quantitative coronary angiography analysis

Quantitative coronary angiography (QCA) analysis was performed at target lesions using off-line commercially available software (QAngio® XA, Medis, Leiden, the Netherlands). QCA analysis included measurement of reference vessel diameter, minimal lumen diameter, and percent diameter stenosis.

2.4. Lipid measurements

All lipid parameters were measured in the fasting state prior to PCI. Fasting serum levels of Lp(a), triglycerides, and high-density lipoprotein cholesterol were measured with enzymatic methods (Sekisui Medical, Tokyo, Japan) using an automated analyzer (Hitachi Labospect 008; Hitachi-Hitec, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula, except when triglyceride levels were >4.5 mmol/L (400 mg/dL) [14].

2.5. Statistical analysis

Results are reported as percentages for categorical variables and means ± standard deviation for continuous variables. When variables were not normally distributed, they were expressed as medians (interquartile range). Clinical characteristics were compared using the Wilcoxon rank-sum test for continuous variables as appropriate. Categorical variables were compared using Fisher's exact test or chi-square test, as appropriate. Lp(a) levels were log-transformed, and log-transformed Lp(a) was used in the current analysis. Multivariable linear mixed effects models were generated to evaluate the effect of clinical characteristics on $maxLCBI_{4mm}$. Multivariable models included age, gender, high-intensity statin use, and other clinical characteristics with $p \leq 0.10$ in univariate analyses. In patients with diabetes and LDL-C <1.8 mmol/L (70 mg/dL) during statin therapy, age, gender, high-intensity statin use, LDL-C level, and clinical characteristics with $p \leq 0.10$ in univariate analyses were included in the multivariate model. All statistical tests were two-sided, and $p < 0.05$ was regarded as statistically significant. Analyses were performed with JMP version 14.0.0 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Clinical demographics

Table 1 describes the clinical characteristics of patients with and without diabetes. Patients with diabetes were more likely to have a history of dyslipidemia (83.4% *vs.* 93.2%, $p = 0.007$). Over third-fourths of all subjects presented with stable CAD (84.1% *vs.* 77.6%, $p = 0.15$). Multivessel disease was more frequently observed in patients with diabetes (41.1% *vs.* 55.3%, $p = 0.01$) (Table 1).

3.2. Medication use and risk factor control

The use of anti-atherosclerotic medications and degree of risk factor control are shown in Table 2. Approximately 25% of study patients received high-intensity statin therapy (24.0% *vs.* 28.0%, $p = 0.49$) and approximately 18% received ezetimibe (18.5% *vs.* 18.1%, $p = 0.92$) at the time of the index PCI. There were no significant differences in the use of other guideline-recommended medical therapies (angiotensin-

Table 1
Baseline characteristics.

	Patients without diabetes (n = 151)	Patients with diabetes (n = 161)	*p* value
Age (years)	69.4 ± 11.3	69.5 ± 10.8	0.98
Male, n (%)	124 (82.1)	138 (85.7)	0.38
BMI (kg/m^2)	23.7 ± 3.2	24.3 ± 3.7	0.12
Hypertension, n (%)	117 (77.5)	120 (74.5)	0.54
Systolic BP (mmHg)	129.6 ± 16.6	129.6 ± 18.6	0.98
Diastolic BP (mmHg)	73.3 ± 11.6	71.9 ± 13.6	0.34
Dyslipidemia, n (%)	126 (83.4)	150 (93.2)	0.007
Smoking, n (%)	28 (18.5)	40 (25.2)	0.16
CKD (eGFR <60), n (%)	65 (43.0)	83 (51.6)	0.13
A history of myocardial infarction, n (%)	35 (23.2)	53 (32.9)	0.06
Clinical presentation			
Stable CAD, n (%)	127 (84.1)	125 (77.6)	0.15
ACS, n (%)	24 (15.9)	36 (22.4)	0.15
STEMI, n (%)	9 (6.0)	14 (8.7)	0.35
NSTEMI, n (%)	5 (3.3)	10 (6.2)	0.23
uAP, n (%)	10 (6.6)	12 (7.4)	0.77
Multivessel disease, n (%)	62 (41.1)	89 (55.3)	0.01

ACS = acute coronary syndrome, BMI = body mass index, BP = blood pressure, CAD = coronary artery disease, CKD = chronic kidney disease, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, NSTEMI = non-ST-segment elevation myocardial infarction, STEMI = ST-segment elevation myocardial infarction, uAP = unstable angina pectoris.

converting enzyme inhibitors or angiotensin II receptor blockers: 51.7% *vs.* 59.4%, $p = 0.17$; β-blockers: 58.3% *vs.* 67.1%, $p = 0.11$) (Table 2). With regard to glucose-lowering agents, 23.0% of patients with diabetes were treated with metformin, 42.2% were treated with a dipeptidyl peptidase-4 inhibitor, and 7.4% were treated with a glucose cotransporter 2 inhibitor (Table 2). With these anti-atherosclerotic medical therapies, on-treatment LDL-C (2.1 ± 0.8 *vs.* 2.0 ± 0.7 mmol/L; 81.0 ± 30.0 *vs.* 77.7 ± 28.6 mg/dL, $p = 0.32$) and the proportion of patients who achieved LDL-C <1.8 mmol/L (70 mg/dL) (39.7% *vs.* 45.9%, $p = 0.27$) were similar between the two groups. Although Lp(a) levels did not differ between the two groups [14.6 (6.5, 28.6) *vs.* 12.9 (7.2, 35.2) mg/dL, $p = 0.56$], a greater proportion of patients with diabetes had Lp (a) ≥30 mg/dL (21.8% *vs.* 34.2%, $p = 0.01$). The guideline-recommended goal of HbA1c <7.0% was achieved in 41.1% of patients with diabetes (Table 2).

3.3. Coronary angiographic and NIRS-derived features of analyzed lesions

Supplemental Table I summarizes the characteristics of the analyzed lesions in the two groups. The analyzed lesions in patients with diabetes were more frequently located in the left circumflex artery compared with patients without diabetes (15.9% *vs.* 17.4%), but this difference was not statistically significant ($p = 0.06$). There were no significant

Table 2
Medication use and risk factor control.

	Patients without diabetes (n = 151)	Patients with diabetes (n = 161)	*p* value
Medication use			
Statin, n (%)	151 (100.0)	161 (100.0)	1.00
High-intensity statin, n (%)[a]	37 (24.0)	45 (28.0)	0.49
Ezetimibe, n (%)	28 (18.5)	29 (18.1)	0.92
PCSK9-inihibitor	2 (1.3)	1 (0.6)	0.52
ACE-I/ARB, n (%)	78 (51.7)	95 (59.4)	0.17
β-blocker, n (%)	88 (58.3)	108 (67.1)	0.11
Metformin, n (%)	-	37 (23.0)	-
DPP-4, n (%)	-	68 (42.2)	-
SGLT2, n (%)	-	12 (7.4)	-
Insulin, n (%)	-	27 (16.8)	-
Risk factor control			
LDL-C (mmol/l	2.1 ± 0.8	2.0 ± 0.7	0.32
LDL-C (mg/dL)	81.0 ± 30.0	77.7 ± 28.6	
LDL-C <1.8 mmol/l, n (%)	60 (39.7)	74 (45.9)	0.27
HDL-C (mmol/l)	1.2 ± 0.3	1.2 ± 0.3	0.06
HDL-C (mg/dL)	48.2 ± 10.8	45.7 ± 12.9	
Triglyceride (mmol/l)[b]	1.3 (0.9, 1.8)	1.5 (1.0, 2.0)	0.62
Triglyceride (mg/dL)[b]	112 (84, 158)	134 (91, 181)	
Lp(a) (mg/dL)[b]	14.6 (6.5, 28.6)	12.9 (7.2, 35.2)	0.56
Lp(a) > 30 mg/dL, n (%)	33 (21.8)	55 (34.2)	0.01
HbA1c (%)	5.8 ± 0.4	7.1 ± 0.9	<0.001
HbA1c <7.0%, n (%)	-	60 (41.1)	-
eGFR (ml/min/1.73 m^2)	61.4 ± 18.0	58.8 ± 23.8	0.28

ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin II blocker, DM = diabetes mellitus, DPP-4 = dipeptidyl peptidase-4 inhibitor, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, Lp(a) = lipoprotein(a), PCSK9 = proprotein convertase subtilisin/kexin 9, SGLT2 = sodium glucose cotransporter 2 inhibitor.

[a] Atorvastatin ≧ 20 mg, rosuvastatin ≧ 10 mg and pitavastatin ≧ 4 mg.

[b] Median (interquartile range).

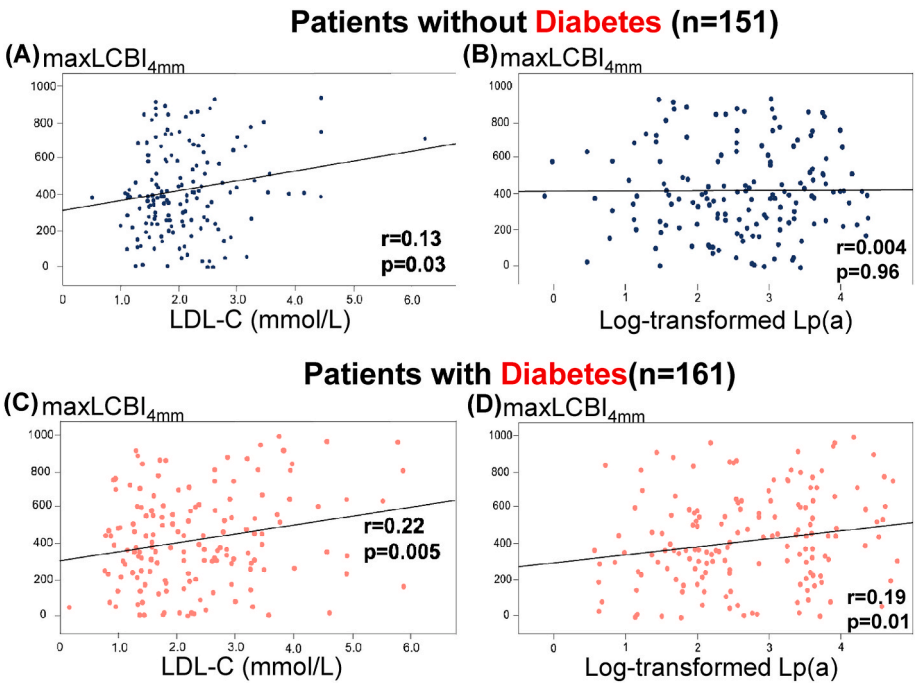

Fig. 1. The associations of lipid parameters with $maxLCBI_{4mm}$ at target lesions.
(A) LDL-C in patients without diabetes, (B) Lp(a) in patients without diabetes, (C) LDL-C in patients with diabetes, (D) Lp(a) in patients with diabetes. LDL-C = low-density lipoprotein cholesterol, Lp(a) = lipoprotein(a), $maxLCBI_{4mm}$ = maximum 4-mm lipid-core burden index.

differences in QCA measures between the two groups (Supplemental Table I). On NIRS imaging, average $maxLCBI_{4mm}$ in target lesions in both groups was >400 with statin therapy (418.2 ± 239.5 *vs.* 414.8 ± 252.0, $p = 0.90$). In addition, over 45% of subjects had $maxLCBI_{4mm} \geq 400$ in target lesions (47.7% *vs.* 46.6%, $p = 0.85$) (Supplemental Table I).

3.4. Associations among LDL-C, Lp(a), and $maxLCBI_{4mm}$

Fig. 1 illustrates the associations between LDL-C levels or Lp(a) levels and $maxLCBI_{4mm}$ in target lesions in patients with and without diabetes.

In patients without diabetes, LDL-C levels were positively associated with $maxLCBI_{4mm}$ (r = 0.13, $p = 0.03$). There were no significant relationships between Lp(a) levels and $maxLCBI_{4mm}$ (r = 0.004, $p = 0.96$) in patients without diabetes (Fig. 1A and B). In contrast, there were significant relationships between LDL-C levels (r = 0.22, $p = 0.005$) and $maxLCBI_{4mm}$ and between Lp(a) levels and $maxLCBI_{4mm}$ (r = 0.19, $p = 0.01$) in patients with diabetes (Fig. 1C and D). Univariate and multivariate analyses were conducted to elucidate factors associated with $maxLCBI_{4mm}$ in target lesions. In patients without diabetes, univariate analysis identified that LDL-C levels were associated with $maxLCBI_{4mm}$

Table 3
Uni- and multivariate linear mixed model analysis for $maxLCBI_{4mm}$ in patients (A) without diabetes and (B) with diabetes.

(A)	Univariate analysis			Multivariate analysis		
	β correlation coefficient	95% CI	*p* value	β correlation coefficient	95% CI	*p* value
Age	0.037	−2.65 - 4.21	0.65	0.028	−3.00 - 4.19	0.74
Male	−0.107	−33.82 - 166.72	0.19	0.035	−87.82 - 131.72	0.69
eGFR	0.002	−2.13 - 2.18	0.98	-	-	-
Acute coronary syndrome	0.106	−35.84 - 174.35	0.19	-	-	-
High-intensity statin[a]	0.124	−20.09 - 158.21	0.13	0.149	−8.46 - 173.36	0.08
LDL-C	0.173	0.11 - 2.65	0.03	0.182	0.11 - 2.78	0.03
HDL-C	−0.125	−6.34 - 0.78	0.12	-	-	-
Log-transformed Lp(a)	0.004	−38.71 – 40.50	0.96	-	-	-
HbA1c	−0.102	−177.2 - 39.8	0.21	-	-	-
(B)	Univariate analysis β correlation coefficient	Multivariate analysis 95% CI	*p* value	β correlation coefficient	95% CI	*p* value
Age	0.026	−3.03 - 4.25	0.74	0.065	−2.15 - 5.26	0.41
Male	−0.026	−93.89 - 130.90	0.74	0.014	−113.29 - 113.74	0.99
eGFR	0.026	−1.38 - 1.93	0.74	-	-	-
Acute coronary syndrome	0.174	12.19–198.15	0.02	0.042	−79.49 - 133.26	0.62
High-intensity statin[a]	0.079	−43.21 - 131.58	0.32	0.101	−27.15 - 147.79	0.17
LDL-C	0.218	0.57 - 3.26	0.005	0.219	0.41 - 3.57	0.02
HDL-C	−0.123	−5.42 - 0.62	0.11	-	-	-
Log-transformed Lp(a)	0.192	9.39–80.28	0.01	0.165	2.20–74.34	0.04
HbA1c	0.071	−23.07 - 61.56	0.37	-		-

eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, HDL-C = high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol, Lp(a) = lipoprotein(a), $maxLCBI_{4mm}$ = maximum 4-mm lipid core burden index.
[a] Atorvastatin ≧ 20 mg, rosuvastatin ≧ 10 mg and pitavastatin ≧ 4 mg.

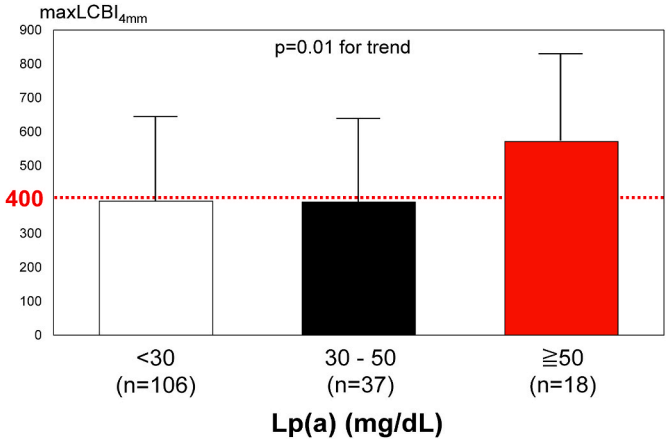

Fig. 2. Comparison of maxLCBI$_{4mm}$ in patients with diabetes stratified according to Lp(a) levels.
Lp(a) = lipoprotein(a), maxLCBI$_{4mm}$ = maximum 4-mm lipid-core burden index.

(β correlation coefficient = 0.173, p = 0.03) but not Lp(a) levels (β correlation coefficient = 0.004, p = 0.96). After adjustment for age, gender, and high-intensity statin use, LDL-C levels remained independently associated with maxLCBI$_{4mm}$ (β correlation coefficient = 0.182, p = 0.03) (Table 3A). In patients with diabetes, significant contributors to maxLCBI$_{4mm}$ included acute coronary syndrome (β correlation coefficient = 0.174, p = 0.02), LDL-C levels (β correlation coefficient = 0.218, p = 0.005), and Lp(a) levels (β correlation coefficient = 0.192, p = 0.01) (Table 3B). Even after for adjusting age, gender and high-intensity statin use, both LDL-C (β correlation coefficient = 0.219, p = 0.02) and Lp(a) levels (β correlation coefficient = 0.165, p = 0.04) remained associated with maxLCBI$_{4mm}$ in patients with diabetes (Table 3B). Fig. 2 shows maxLCBI$_{4mm}$ in diabetic subjects stratified by Lp(a) levels. Higher maxLCBI$_{4mm}$ was observed in patients with Lp(a) ≥50 mg/dL (p = 0.01 for trend), whereas maxLCBI$_{4mm}$ values were <400 in subjects with Lp(a) < 30 mg/dL and between 30 and 50 mg/dL, respectively (Fig. 2). Supplemental Figure II illustrates the relationship between Lp(a) levels and maxLCBI$_{4mm}$ in patients with stable CAD and acute coronary syndrome (ACS), respectively, by diabetes status.

The association between LDL-C or Lp(a) levels and maxLCBI$_{4mm}$ in subjects with on-treatment LDL-C <1.8 mmol/L (70 mg/dL) was further analyzed (Supplemental Table II). In patients without diabetes, multivariate analysis revealed that high-intensity statin use (β correlation coefficient = 0.291, p = 0.02) and LDL-C levels (β correlation coefficient = 0.265, p = 0.03) were significantly associated with maxLCBI$_{4mm}$ but not Lp(a) levels (β correlation coefficient = −0.081, p = 0.51) (Supplemental Table IIA). In contrast, multivariate analysis in patients with diabetes showed that Lp(a) is an independent lipid parameter which elevated maxLCBI$_{4mm}$ in target lesions (β correlation coefficient = 0.245, p = 0.03), but not LDL-C (β correlation coefficient = 0.196, p = 0.10) (Supplemental Table IIB). Supplemental Figure III illustrates one patient without diabetes and two patients with diabetes.

4. Discussion

The residual cardiovascular risk in patients with diabetes despite statin therapy underscores the need to identify other atherogenic drivers to improve risk stratification and develop additive novel therapies. In the current study of patients with CAD receiving a statin that involved NIRS imaging, circulating Lp(a) levels were independently associated with maxLCBI$_{4mm}$ in patients with diabetes but not in patients without diabetes. Of note, higher Lp(a) levels still predicted higher maxLCBI$_{4mm}$, even in patients with diabetes who achieved on-treatment LDL-C <1.8 mmol/L (70 mg/dL). The current findings indicate that Lp(a) is an important contributor to a vulnerable feature of coronary atheroma in patients with diabetes.

The current study demonstrates that Lp(a) has a distinct role in vulnerability of coronary atherosclerosis in patients with diabetes. Pathophysiologically, diabetes-related enhanced oxidative stress might account for the association between Lp(a) and lipid-rich plaque in patients with diabetes. In general, increased oxidative stress in patients with diabetes was thought to induce more oxidation of LDL particles, which causes more production of oxidative phospholipids [15–18]. Given that oxidative phospholipids preferentially bind to circulating Lp(a) and have pro-inflammatory properties [19], the oxidation-mediated atherogenicity of Lp(a) might promote influx of lipidic materials into the vessel wall, which ultimately results in the formation of a lipid-rich coronary atheroma in patients with diabetes. Non-enzymatic glycation of Lp(a) might be another mechanism that accounts for the association between Lp(a) and maxLCBI$_{4mm}$ in patients with diabetes. *In vivo* and *in vitro* studies have demonstrated that glycation of apoB-100 occurs in Lp(a) particles and patients with diabetes have glycated Lp(a) more frequently than patients without diabetes [20]. In addition, Lp(a) glycation has been reported to enhance its atherogenicity via greater production of plasminogen activator inhibitor-1 [21,22]. These glycation-mediated effects might also contribute to more vulnerable plaques in patients with diabetes who have higher Lp(a) levels.

Recent studies and guidelines highlight that Lp(a) ≥50 mg/dL is an important cut-off value to stratify risk of future ASCVD and progression of calcific aortic valve stenosis [23–26]. Of note, another study analyzing 5143 patients with suspected CAD reported that the risk of a cardiovascular event was higher in patients with diabetes and Lp(a) ≥50 mg/dL than in patients without diabetes or patients with pre-diabetes [27]. In addition to this evidence, our analysis based on NIRS imaging showed higher maxLCBI$_{4mm}$ in target lesions in patients with diabetes with Lp(a) ≥50 mg/dL, whereas patients with Lp(a) < 30 mg/dL or 30–50 mg/dL had less lipidic coronary atheroma, reflected by maxLCBI$_{4mm}$ < 400. Since maxLCBI$_{4mm}$ has been shown to be an important predictor of coronary events [28–30], the current findings also support a cut-off value of Lp(a) ≥50 mg/dL for identifying high-risk patients with diabetes who require intensified preventive management.

Accumulating evidence suggests that an elevated Lp(a) level is a potential therapeutic target to further mitigate cardiovascular risks under statin-mediated LDL-C control [31–33]. In the current study, despite achieving LDL-C <1.8 mmol/L (70 mg/dL) with a statin, target lesions in patients with diabetes are more likely to harbor more lipidic atheroma burden in association with circulating Lp(a) levels. This finding shows that modulating Lp(a) levels might be beneficial for stabilizing lipid-rich plaques, which potentially leads to the prevention of subsequent cardiovascular events in patients with diabetes and CAD. This potential therapeutic benefit is supported by a recent sub-analysis of the FOURIER study, which demonstrated a significant reduction in ASCVD among patients with a greater absolute Lp(a) reduction or achieved lower Lp(a) levels [34]. Proprotein convertase subxilisin/kexin type 9 inhibitors, niacin, and mipomersen decrease Lp(a) levels by 20–30% [35–37]. This robust reduction has been reported by antisense oligonucleotides that inhibit apolipoprotein(a) synthesis [38]. Whether emerging therapies specifically lowering circulating Lp(a) levels could reduce the risk of ASCVD in patients with diabetes will be elucidated by dedicated ongoing clinical trials.

Several caveats should be considered when interpreting the current findings. First, this is a retrospective observational study from a multicenter registry database. The decision to use of lipid-lowering therapies and NIRS imaging for PCI guidance was based on the discretion of each physician. In addition, we excluded 251 subjects due to missing Lp(a) data (Supplemental Figure I). Therefore, potential selection bias could not be excluded. Second, the definition of high-intensity statin in Japan is different from the definition in Europe and the United States [13]. It remains unknown whether Lp(a) still associates with maxLCBI$_{4mm}$ in those receiving high-intensity statin with a greater dose than

the Japanese one. Third, the proportion of patients receiving a high-intensity statin was relatively small, which made difficult to analyze the association between Lp(a) levels and NIRS-derived measures with high-intensity statin use. Fourth, the current study involved cross-sectional imaging analysis, not serial analysis. This approach does not allow for detailed evaluation of phenotypic changes in coronary plaques, over time. Finally, NIRS imaging was conducted within the target coronary artery requiring PCI, not in all three vessels. The current study does not have any data about the relationship of Lp(a) with $maxLCBI_{4mm}$ at non-target vessels.

4.1. Conclusions

In conclusion, the current NIRS imaging analysis demonstrated that circulating Lp(a) levels are associated with $maxLCBI_{4mm}$ in target lesions in patients with diabetes and CAD on statin therapy, but not in those without diabetes. In particular, patients with diabetes and Lp(a) $\geq$50 mg/dL are more likely to have lipid-rich plaques, as reflected by $maxLCBI_{4mm} > 400$. Even in patients with diabetes who achieved LDL-C $<$1.8 mmol/L (70 mg/dL) with a statin, Lp(a) levels remained associated with $maxLCBI_{4mm}$. These findings reveal that circulating Lp(a) is an important promoter of plaque vulnerability in patients with diabetes. In addition, this lipoprotein might be a therapeutic target for modulating the lipidic component of their coronary atheroma in the context of statin therapy.

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CRediT authorship contribution statement

Hayato Nakamura: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Yu Kataoka:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Stephen J. Nicholls:** Writing – review & editing. **Rishi Puri:** Writing – review & editing. **Satoshi Kitahara:** Resources, Writing – review & editing. **Kota Murai:** Writing – review & editing, Resources. **Kenichiro Sawada:** Writing – review & editing, Resources. **Hideo Matama:** Resources, Writing – review & editing. **Takamasa Iwai:** Resources, Writing – review & editing. **Satoshi Honda:** Resources, Writing – review & editing. **Masashi Fujino:** Resources, Writing – review & editing. **Kensuke Takagi:** Resources, Writing – review & editing. **Shuichi Yoneda:** Resources, Writing – review & editing. **Fumiyuki Otsuka:** Resources, Writing – review & editing. **Kensaku Nishihira:** Resources, Writing – review & editing. **Yasuhide Asaumi:** Resources, Writing – review & editing. **Kenichi Tsujita:** Writing – review & editing. **Teruo Noguchi:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yu Kataoka has received research support from Nipro and Abbott, and honoraria from Nipro, Abbott, Kowa, Amgen, Sanofi, Astellas, Takeda and Daiichi-Sankyo. Stephen J. Nicholls is a recipient of a Principal Research Fellowship from the National Health and Medical Research Council of Australia and has received research support from AstraZeneca, Amgen, Anthera, CSL Behring, Cerenis, Eli Lilly, Esperion, Resverlogix, Novartis, InfraReDx and Sanofi-Regeneron and is a consultant for Amgen, Akcea, AstraZeneca, Boehringer Ingelheim, CSL Behring, Eli Lilly, Esperion, Kowa, Merck, Takeda, Pfizer, Sanofi-Regeneron and Novo Nordisk. Rishi Puri has received speaker fees from Amgen and Sanofi, served as a consultant for Cerenis, Medtronic, Philips, Boston Scientific, Shockwave and on advisory boards for Centerline Biomedical, Medtronic, Bioventrix and holds minor equity in Centerline Biomedical. Kota Murai has received honoraria from Abbot, Terumo, Amgen and Zeon Medical, and support for attending meetings from OrbusNeich. Other authors have nothing to disclose.

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Appendix A. Supplementary data

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