Original Article

The Priority of Non-HDL-C Assessment to Predict New Lesions among Stable Angina Patients with Strong Statins

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Aim: In this study, we aim to examine the clinical meaning of low-density lipoprotein cholesterol (LDL-C) <70 mg/dL as assessed by Friedewald equation [LDL-C (F)] and Martin method [LDL-C (M)] and non-high-density lipoprotein cholesterol (HDL-C) <100 mg/dL on the occurrence of new lesions among Japanese patients with stable angina who underwent percutaneous coronary intervention (PCI) and were prescribed with strong statins.

Methods: Among the 537 consecutive stable angina patients who had underwent PCI and had been prescribed with strong statins, the association between the occurrence of new lesions with myocardial ischemia at the 9-month follow-up coronary angiography and ≤ 2 years after PCI and baseline characteristics were assessed.

Results: New lesions appeared 9 months and ≤ 2 years after PCI in 31 and 90 patients, respectively. Multivariate logistic regression analysis revealed diabetes mellitus (DM) was significantly associated with the occurrence of new lesions ≤ 2 years after PCI [odds ratio (OR) 1.71, 95 % confidence interval (CI) 1.06–2.83, $p=0.031$], and only non-HDL-C ≥ 100 mg/dL was associated with the occurrence of new lesions both at 9 months and ≤ 2 years after PCI [OR 1.80, 95 % CI 1.10–3.00, $p=0.021$ and OR 1.85, 95 % CI 1.13–3.07, $p=0.016$].

Conclusions: Non-HDL-C ≥ 100 mg/dL was determined to be the independent risk factor for the occurrence of new lesions 9 months and ≤ 2 years after PCI among stable angina patients with strong statins. Residual risk after PCI should be considered by assessing not only DM but also non-HDL-C beyond the scope of LDL-C-lowering therapy with strong statins.

Key words: Stable angina, Non-high-density lipoprotein cholesterol, New lesion, Percutaneous coronary intervention, Strong statin

Introduction

Coronary artery disease (CAD) has been identified as a major cause of cardiovascular deaths worldwide[1]. Percutaneous coronary intervention (PCI) has become a standard procedure for coronary revascularization among patients with CAD. Since the introduction of second-generation drug-eluting stents (second DES), the need for target lesion revascularization has decreased. However, despite recent clinical advances in PCI and medical therapies[2], cardiovascular events have remain to be a primary problem.

Dyslipidemia is known to be significantly associated with an increased risk of CAD, and the relationship between dyslipidemia and CAD has already been well established[3-5]. Since clinical trials have demonstrated that decreases in serum levels of low-density lipoprotein cholesterol (LDL-C) can reduce the rate of cardiovascular events[6, 7], lipid-lowering therapy represents an important strategy in primary and secondary prevention of CAD[8, 9]. In particular, LDL-C has been recommended as the main treatment target of lipid management in CAD patients[10-12]. Therefore, clinical practice guidelines

recommend a target LDL-C of <70 mg/dL for high-risk patients[9, 13]. In Japan, LDL-C <100 mg/dL is the secondary prevention target, and <70 mg/dL is recommended for high-risk patients[14], but there is still residual cardiovascular event risk even after achieving it.

LDL-C is generally measured by simply using Friedewald equation method, but this method bears disadvantage as it is not applicable to patients with triglycerides (TG) >400 mg/dL[15]. Martin *et al.* reported a novel method for estimating LDL-C that appears to provide more accurate measurements of LDL-C than values derived using Friedewald equation[16]. The LDL-C estimation by Martin method was calculated by applying an adjustable factor for the TG/very low-density lipoprotein cholesterol (VLDL-C) ratio based on TGs and non-high-density lipoprotein cholesterol (HDL-C) concentrations. In addition, non-HDL-C, which is easily calculated without using an estimate for measurement, is also reportedly associated with cardiovascular events as a numerical value representing remnants such as VLDL-C, which is considered as another arteriosclerotic factor alongside LDL-C.

It appears that there is yet no reports that have evaluated the effects of LDL-C as assessed using the Martin method [LDL-C (M)] or non-HDL-C on the occurrence of new lesions on coronary angiography among Japanese patients with stable angina receiving treatment with strong statins.

Aim

This study aims to investigate the clinical meaning of LDL-C <70 mg/dL as assessed using Friedewald equation (LDL-C (F)) and LDL-C (M) and non-HDL-C <100 mg/dL on the occurrence of new lesions in Japanese stable angina patients who had undergone PCI and had been prescribed with strong statins

Methods

Study Population

We evaluated a cohort study of 621 consecutive stable angina patients from a single center who had been receiving treatment with strong statins for >2 weeks on admission and who had successfully undergone elective PCI using second DES [durable polymer everolimus-eluting stent (DP-EES), Resolute zotarolimus-eluting stent (R-ZES), and biodegradable polymer biolimus-eluting stent (BP-BES)] and imaging modality (intravascular ultrasound or optical coherence tomography) for complete revascularization

at Kagoshima University Hospital between January 2010 and December 2018. These patients underwent 9-month follow-up coronary angiography after PCI. All patients were administered strong statin regardless of dyslipidemia and dual antiplatelet therapy (aspirin and thienopyridine, as either ticlopidine or clopidogrel) before the PCI. ST-segment elevation myocardial infarction (STEMI) patients, non-STEMI patients, unstable angina patients, and hemodialysis patients were excluded from this study. Of the 621 patients, 23 patients were excluded because of lacking sufficient blood test items on admission or a fasting serum TG level >400 mg/dL. Furthermore, 61 patients who could not be tracked after discharge were also excluded **(Fig. 1)**. Baseline demographic data and cardiovascular risk factors such as current smoker, diabetes mellitus (DM), and hypertension were recorded at the time of enrolment.

This study was approved by the Research and Ethics Committee at Kagoshima University Hospital and was carried out in accordance with the ethical principles stated in the 1975 Declaration of Helsinki. All patients provided written informed consent prior to enrolment.

Measurements

In this study, blood tests and echocardiograms were conducted prior to PCI. Blood samples were drawn after 12 h of fasting. Thereafter, concentrations of hemoglobin, high-sensitivity C-reactive protein (hs-CRP), fasting plasma glucose (FPG), total cholesterol (TC), HDL-C, TG, uric acid, and creatinine were measured. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation with coefficients modified for Japanese patients, as follows: eGFR $(ml/min/1.73\ m^2) = 194 \times$ serum Cr $(mg/dL)^{-1.094} \times$ age $(years)^{-0.287}$ ($\times 0.739$ for female subjects)[17]. Meanwhile, LDL-C (F) was calculated using the Friedewald equation as follows: (TC – HDL-C – TG/5)[15]. LDL-C (M) was calculated as reported by Martin *et al.*[16] using the equation TC – HDL-C – TG/adjustable factor, where the adjustable factor was determined from strata-specific median TG/VLDL-C ratios derived from a dataset of 900,605 individuals in the United States. Non-HDL-C was calculated using the equation TC – HDL-C.

Definitions

Body mass index was calculated as body weight divided by height squared (kg/m²). Hypertension was defined based on the following criteria: systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the use of antihypertensive medications.
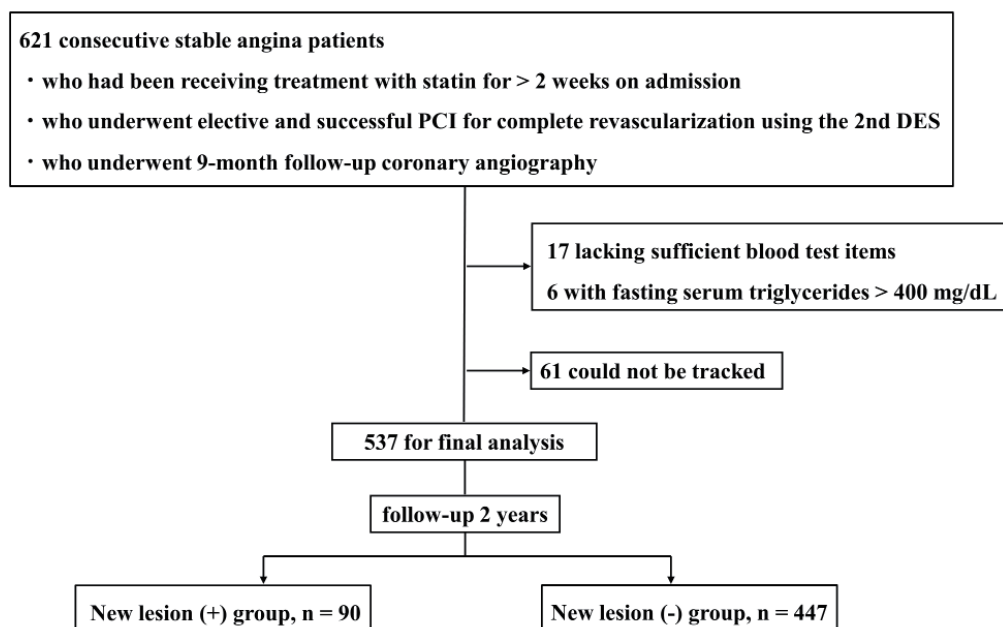
Fig. 1. Study flowchart

In all, 537 patients (New lesion (+) group, *n*=90; New lesion (–) group, *n*=447) fulfilled the study criteria.
PCI, percutaneous coronary intervention; DES, drug-eluting stents

DM was defined based on the following criteria: FPG >126 mg/dL, HbA1c ≥ 6.5 % (in accordance with the National Glycohemoglobin Standardization Program), or the use of antihyperglycemic medications. Dyslipidemia was defined as LDL-C (F) ≥ 140 mg/dL, TG ≥ 150 mg/dL, HDL-C< 40 mg/dL, or the use of antidyslipidemic medications. Current smokers were defined as those who were actively smoking at the time of admission.

As per the findings of the PATROL trial[18], it was determined that the efficacy and safety of atorvastatin (10 mg/day), rosuvastatin (2.5 mg/day), and pitavastatin (2 mg/day) are the same in Japanese. Therefore, strong statins were defined as doses of atorvastatin (10 mg/day) or rosuvastatin (2.5 mg/day) or pitavastatin (2 mg/day) or more than these doses in this study.

The clinical practice guideline of Japan Atherosclerosis Society has recommended that LDL-C <70 mg/dL is the secondary prevention target for familial hypercholesterolemia, acute coronary syndrome, or DM with high-risk factors for CAD recurrence[14]. In this study, we used the cut-off level of LDL-C <70 mg/dL, as DM patients with chronic kidney disease, metabolic syndrome, or overlap of major risk factors or who are smokers were 58 %, and all patients underwent PCI. In addition, current recommendations set the goal of non-HDL-C as 30 mg/dL higher than the corresponding LDL-C goals[19-20].

Based on the cut-off levels of 70 mg/dL, 70 mg/dL and 100 mg/dL for LDL-C (F), LDL-C (M), and non-HDL-C, respectively, patients were then divided.

The new lesions at 9-month follow-up coronary angiography were defined as the lesion showing ≥ 75 % stenosis on angiography; moreover, there had myocardial ischemia estimated by fractional flow reserve or myocardial perfusion single-photon emission computed tomography. Furthermore, the occurrence of new lesions ≤ 2 years after PCI was defined as the incidences of clinically driven non-target lesion revascularization after PCI including new lesions on 9-month follow-up coronary angiography.

All patients were followed up at our hospital or by their physician; they continued to take strong statins during follow-up. In this study, we examined the relationship between the occurrence of new lesions leading to myocardial ischemia and the baseline characteristics of patients.

Statistical Analysis

Quantitative data are presented as mean ± standard deviation for data showing normal distributions, while median and interquartile range (IQR) was utilized for data showing non-normal distributions. Fisher's exact test was then used to compare the incidence of categorical variables, with the latter expressed as percentages. Continuous variables were compared between the New lesion (+)

and New lesion (–) groups using Student's t-test (normal distribution) or the Wilcoxon rank-sum test (non-normal distribution). Logistic regression analysis was also performed to analyze the relationship between the New lesion (+) group and background factors, with the results expressed as odds ratios (OR) and 95 % confidence intervals (CIs). Independent associations between the New lesion (+) group and baseline characteristics were assessed by multivariate logistic regression modeling using relevant factors. Variables with $p<0.05$ on univariate analysis were used in the multivariate analysis model. Values of $p<0.05$ were considered indicative of statistical significance. Statistical analyses were performed using SAS software (JMP version 14.0).

Results

Baseline Characteristics

Median follow-up duration was 1160 days. Baseline patient clinical characteristics have been provided in **Table 1**. The median values of TC, LDL-C (F), LDL-C (M), HDL-C, non-HDL-C, and TG were 155 (136–181) mg/dL, 80 (63–100) mg/dL, 82 (67–105) mg/dL, 47 (40–58) mg/dL, 103 (86–128) mg/dL, and 109 (82–155) mg/dL, respectively.

Comparing the Baseline Characteristics of Study Patients according to Occurrence of New Lesions 9 Months and ≤ 2 Years after PCI

The comparison of baseline characteristics of study patients according to the occurrence of new lesions 9 months and ≤ 2 years after PCI is shown in **Table 2**. Thirty-one patients (6 %) were determined to have new lesions at 9-month follow-up coronary angiography after PCI. Furthermore, of the 537 patients recruited, 90 patients (17 %) showed new lesions and were taken as the New lesion (+) group, with the remaining 447 patients (83 %) taken as having no new lesions [New lesion (–) group] ≤ 2 years after PCI. There were 45 (8 %) patients with in-stent restenosis.

The rate of history of smoking and the use of β-blockers were significantly higher in the New lesion (+) 9-month group than that in the New lesion (–) 9-month group (58 % vs. 12 %; $p<0.001$ and 66 % vs. 33 %; $p<0.001$). Frequencies of LDL-C (F) ≥ 70 mg/dL, LDL-C (M) ≥ 70 mg/dL, and non-HDL-C ≥ 100 mg/dL were significantly higher in the New lesion (+) 9-month group compared with the New lesion (–) 9-month group [LDL-C (F) ≥ 70 mg/dL, 81 % vs. 64 %, $p=0.040$; LDL-C (M) ≥ 70 mg/dL, 84 % vs. 68 %, $p=0.048$; non-HDL-C ≥ 100 mg/dL, 74 % vs. 55 %, $p=0.030$, respectively]

Table 1. Baseline characteristics of study patients at PCI

Variables	Overall ($n=537$)
Age, years	69 [64–76]
Sex: male, n (%)	392 (73)
Body mass index, kg/m^2	23.8 [21.5–26.2]
Risk factors, n (%)	
Hypertension	438 (82)
Diabetes mellitus	313 (58)
Dyslipidemia	408 (76)
Current smoker	63 (12)
History of smoking	81 (15)
Medication, n (%)	
Oral anticoagulation	65 (12)
Calcium-channel blocker	229 (43)
ACEI	101 (19)
ARB	225 (42)
β-blocker	185 (34)
Ezetimibe	40 (7)
Nitrates	50 (9)
Proton pump inhibitor	262 (49)
Laboratory data	
Hemoglobin, g/dL	12.9 ± 0.1
hs-CRP, mg/L	1.2 [0.4–3.2]
TC, mg/dL	155 [136–181]
LDL-C (F) ≥ 70 mg/dL, n (%)	348 (65)
LDL-C (M) ≥ 70 mg/dL, n (%)	372 (69)
HDL-C < 40 mg/dL, n (%)	133 (25)
Non-HDL-C ≥ 100 mg/dL, n (%)	304 (57)
TG ≥ 150 mg/dL, n (%)	141 (26)
Uric acid, mg/dL	5.9 [4.9–6.8]
FPG, mg/dL	110 [96–133]
eGFR, mL/min/1.73 m^2	61.4 [47.5–75.2]
LVEF, 50%	58.3 [48.7–66.2]

Values are shown as number and percentage or median with interquartile range.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; TC, Total cholesterol; TG, Triglyceride.

The New lesion (+) ≤ 2 years group was significantly younger compared to the New lesion (–) ≤ 2 years group (median, 66 years, IQR 59–75 years vs. median, 70 years, IQR 64–77 years; $p=0.006$). Frequency of DM was determined to be significantly higher in the New lesion (+) ≤ 2 years group compared with the New lesion (–) ≤ 2 years group (69 % vs. 56 %; $p=0.025$). Furthermore, frequencies of LDL-C (F) ≥ 70 mg/dL, LDL-C (M) ≥ 70 mg/dL, and non-HDL-C ≥ 100 mg/dL were found to be significantly

Table 2. Comparison of baseline characteristics of study patients according to occurrence of new lesions 9-month and ≤ 2 years after PCI

Variables	New lesion (+) 9-month			New lesion (+) ≤ 2 years		
	New lesion (+) group ($n = 31$)	New lesion (-) group ($n = 506$)	*p* value	New lesion (+) group ($n = 90$)	New lesion (-) group ($n = 447$)	*p* value
Age, years	67 [60–76]	70 [64–77]	0.58	66 [59–75]	70 [64–77]	0.006
Sex: male, *n* (%)	22 (71)	370 (73)	0.83	67 (74)	325 (73)	0.73
Body mass index, kg/m^2	24.3 [20.9–25.9]	23.8 [21.5–26.1]	0.78	23.8 [21.6–26.3]	23.9 [21.5–26.1]	0.52
Risk factors, *n* (%)						
Hypertension	26 (84)	412 (81)	0.71	73 (81)	365 (82)	0.90
Diabetes mellitus	19 (61)	294 (58)	0.85	62 (69)	251 (56)	0.025
Dyslipidemia	22 (71)	386 (76)	0.52	68 (76)	340 (76)	0.92
Current smoker	2 (6)	61 (12)	0.36	13 (14)	50 (11)	0.36
History of smoking	18 (58)	63 (12)	<0.001	18 (20)	63 (14)	0.20
Medication, *n* (%)						
Oral anticoagulation	6 (19)	59 (12)	0.25	13 (14)	52 (12)	0.46
Calcium-channel blocker	18 (58)	211 (42)	0.98	42 (47)	187 (42)	0.40
ACEI	4 (13)	97 (19)	0.48	14 (16)	87 (19)	0.39
ARB	18 (58)	207 (41)	0.064	39 (43)	186 (42)	0.76
β-blocker	20 (66)	165 (33)	<0.001	31 (34)	154 (34)	0.99
Ezetimibe	1 (3)	39 (8)	0.72	6 (7)	34 (8)	0.99
Nitrates	4 (13)	46 (9)	0.52	7 (8)	43 (10)	0.69
Proton pump inhibitor	18 (58)	257 (51)	0.46	48 (53)	214 (48)	0.34
Laboratory data						
Hemoglobin, g/dL	12.9 ± 1.8	13.0 ± 2.0	0.47	13.2 ± 1.8	12.9 ± 2.0	0.179
hs-CRP, mg/L	1.6 [0.6–2.4]	1.2 [0.4–3.3]	0.65	1.7 [0.6–3.7]	1.1 [0.4–3.1]	0.159
TC, mg/dL	174 [141–196]	154 [135–178]	0.028	168 [140–197]	153 [135–176]	0.001
LDL-C (F) ≥ 70 mg/dL, *n* (%)	25 (81)	323 (64)	0.040	68 (76)	280 (63)	0.019
LDL-C (M) ≥ 70 mg/dL, *n* (%)	26 (84)	346 (68)	0.048	71 (79)	301 (67)	0.030
HDL-C <40 mg/dL, *n* (%)	7 (23)	126 (25)	0.68	25 (28)	108 (24)	0.47
Non-HDL-C ≥ 100 mg/dL, *n* (%)	23 (74)	281 (56)	0.030	63 (70)	241 (54)	0.005
TG ≥ 150 mg/dL, *n* (%)	8 (26)	133 (26)	0.99	25 (28)	116 (26)	0.69
Uric acid, mg/dL	6.2 [4.7–6.6]	5.9 [5.0–6.8]	0.70	6.1 [4.8–6.7]	5.9 [5.0–6.8]	0.99
FPG, mg/dL	106 [91–129]	111 [96–134]	0.108	116 [95–135]	109 [96–133]	0.31
eGFR, mL/min/1.73 m^2	65.4 [56.5–76.9]	61.1 [47.2–74.7]	0.135	64.9 [50.9–77.8]	59.7 [47.2–74.1]	0.065
LVEF, %	59 [50–66]	58 [49–66]	0.94	57.7 [50.8–66.2]	58.3 [47.9–66.2]	0.76

Abbreviations are as in Table 1

higher in the New lesion (+) ≤ 2 years group than those in the New lesion (–) ≤ 2 years group [LDL-C (F) ≥ 70 mg/dL, 76 % vs. 63 %, *p*=0.019; LDL-C (M) ≥ 70 mg/dL, 79 % vs. 67 %, *p*=0.030; non-HDL-C ≥ 100 mg/dL, 70 % vs. 54 %, *p*=0.005, respectively].

Influence of Baseline Characteristics on New Lesions

Univariate logistic regression analysis was performed to examine the impact of background factors on the occurrence of new lesions 9 months and ≤ 2 years after PCI **(Table 3)**. These analyses revealed

that history of smoking, usage of *β*-blocker, and non-HDL-C ≥ 100 mg/dL were associated with the New lesion (+) 9-month group [history of smoking: OR 9.71, 95 % CI 4.57–21.20, *p*<0.001; using of *β*-blocker: OR 3.75, 95 % CI 1.78–8.29, *p*<0.001; non-HDL-C ≥ 100 mg/dL: OR 2.30, 95 % CI 1.05–5.58, *p*=0.047]. Furthermore, age, DM, LDL-C (F) ≥ 70 mg/dL, LDL-C (M) ≥ 70 mg/dL, and non-HDL-C ≥ 100 mg/dL were determined to be associated with the New lesion (+) ≤ 2 years group [age: OR 0.97, 95 % CI 0.95–0.99, *p*=0.020; DM: OR 1.73, 95 % CI 1.08–2.84, *p*=0.027; LDL-C (F) ≥ 70 mg/dL: OR 1.84, 95 % CI 1.11–3.15, *p*=0.021; LDL-C (M) ≥ 70

Table 3. Univariate logistic analysis for the occurrence of new lesions 9-month and ≤ 2 years after PCI

	New lesion (+) 9-month N (%) = 31 (6)			New lesion (+) ≤ 2 years N (%) = 90 (17)		
	OR	95%CI	p value	OR	95%CI	p value
Age, years	0.98	0.95–1.02	0.39	0.97	0.95–0.99	0.020
Sex: male	1.11	0.48–2.40	0.79	1.09	0.66–1.86	0.73
Body mass index, kg/m²	0.99	0.90–1.09	0.94	1.04	0.98–1.10	0.20
Risk factors						
Hypertension	1.18	0.48–3.52	0.73	0.96	0.55–1.77	0.90
Diabetes mellitus	1.14	0.55–2.47	0.73	1.73	1.08–2.84	0.027
Dyslipidemia	1.31	0.56–2.84	0.50	1.02	0.58–1.71	0.92
Current smoker	1.99	0.58–12.51	0.35	1.36	0.68–2.55	0.36
History of smoking	9.71	4.57–21.20	<0.001	1.52	0.83–2.67	0.16
Medication						
Oral anticoagulation	1.81	0.65–4.35	0.21	1.28	0.64–2.40	0.45
Calcium-channel blocker	1.93	0.93–4.11	0.08	1.22	0.77–1.92	0.40
ACEI	0.62	0.18–1.64	0.39	0.76	0.40–1.37	0.39
ARB	2.00	0.96–4.25	0.06	1.07	0.68–1.69	0.76
β-blocker	3.75	1.78–8.29	<0.001	1.00	0.61–1.60	0.99
Ezetimibe	0.39	0.02–1.94	0.37	0.86	0.32–1.98	0.75
Nitrates	0.67	0.25–2.36	0.48	0.79	0.32–1.71	0.58
Proton pump inhibitor	0.74	0.35–1.54	0.43	0.80	0.50–1.26	0.35
Laboratory data						
Hemoglobin, g/dL	0.98	0.81–1.18	0.81	1.08	0.96–1.22	0.192
hs-CRP, mg/L	0.98	0.92–1.01	0.37	0.99	0.98–1.01	0.51
TC, mg/dL	1.01	0.99–1.02	0.054	1.01	1.00–1.02	0.003
LDL-C (F) ≥ 70 mg/dL	2.36	1.01–6.44	0.064	1.84	1.11–3.15	0.021
LDL-C (M) ≥ 70 mg/dL	2.40	0.98–7.21	0.078	1.81	1.07–3.19	0.032
HDL-C < 40 mg/dL	1.13	0.50–2.91	0.77	1.21	0.72–1.99	0.47
Non-HDL-C ≥ 100 mg/dL	2.30	1.05–5.58	0.047	1.99	1.24–3.29	0.006
TG ≥ 150 mg/dL	0.95	0.39–2.10	0.91	1.11	0.66–1.83	0.69
Uric acid, mg/dL	0.91	0.71–1.17	0.49	0.99	0.84–1.16	0.89
FPG, mg/dL	0.99	0.98–1.00	0.20	1.00	0.99–1.00	0.26
eGFR, mL/min/1.73 m²	1.01	0.99–1.02	0.21	1.01	0.99–1.02	0.102
LVEF, %	1.00	0.98–1.03	0.90	1.01	0.98–1.02	0.56

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

mg/dL: OR 1.81, 95 % CI 1.07–3.19, p=0.032; non-HDL-C ≥ 100 mg/dL: OR 1.99, 95 % CI 1.24–3.29, p=0.006] **(Table 3)**.

We then performed multivariate logistic regression analysis **(Tables 4, 5)**. Non-HDL-C ≥ 100 mg/dL was found to be an independent risk factor for the occurrence of new lesions 9 months after PCI (non-HDL-C ≥ 100 mg/dL: OR 1.80, 95 % CI 1.10–3.0, p=0.021) **(Table 4)**. In Model 1 including LDL-C (F) ≥ 70 mg/dL and Model 2 including LDL-C (M) ≥ 70 mg/dL, DM was the only independent risk factor for the occurrence of new lesions (DM: Model 1, OR 1.70, 95 % CI 1.06–2.81, p=0.032,

Model 2, OR 1.70, 95 % CI 1.05–2.79, p=0.034). On the other hand, in Model 3 including non-HDL-C ≥ 100 mg/dL, both DM and non-HDL-C ≥ 100 mg/dL were independent risk factors for the occurrence of new lesions ≤ 2 years after PCI (DM: OR 1.71, 95 % CI 1.06–2.83, p=0.031; non-HDL-C ≥ 100 mg/dL: OR 1.85, 95 %CI 1.13–3.07, p=0.016) **(Table 5)**.

Predictive Values of LDL-C (F), LDL-C (M), and Non-HDL-C for the Occurrence of New Lesions

These results show that DM and non-HDL-C ≥ 100 mg/dL were potent independent risk factors of

Table 4. Predictive value of the occurrence of new lesions 9-month after PCI as determined by multivariate logistic analysis

	OR	95%CI	*p* value
Age, years	0.98	0.96–1.00	0.085
History of smoking	1.35	0.72–2.43	0.33
β-blocker	0.98	0.59–1.60	0.95
Non-HDL-C ≥ 100	1.80	1.10–3.00	0.021

Abbreviations are as in Tables 1, 2 and 3.

Table 5. Predictive value of the occurrence of new lesions ≤ 2 years after PCI as determined by multivariate logistic analysis modeling

	Model 1			Model 2			Model 3		
	OR	95%CI	*p* value	OR	95%CI	*p* value	OR	95%CI	*p* value
Age, years	0.98	0.96–1.00	0.086	0.98	0.96–1.00	0.075	0.98	0.96–1.00	0.086
Sex: male	1.02	0.61–1.76	0.94	1.05	0.61–1.77	0.92	1.01	0.60–1.75	0.96
Diabetes mellitus	1.70	1.06–2.81	0.032	1.70	1.05–2.79	0.034	1.71	1.06–2.83	0.031
LDL-C (F) ≥ 70	1.67	0.99–2.89	0.060	-	-	-	-	-	-
LDL-C (M) ≥ 70	-	-	-	1.62	0.94–2.89	0.091	-	-	-
Non-HDL-C ≥ 100	-	-	-	-	-	-	1.85	1.13–3.07	0.016

Abbreviations are as in Tables 1, 2 and 3.
Model 1, adjusted for age, sex (male), diabetes mellitus and LDL-C (F) ≥ 70 mg/dL
Model 2, adjusted for age, sex (male), diabetes mellitus and LDL-C (M) ≥ 70 mg/dL
Model 3, adjusted for age, sex (male), diabetes mellitus and non-HDL-C ≥ 100 mg/dL

the occurrence of new lesions ≤ 2 years after PCI. We further performed a receiver operating characteristic (ROC) curve analysis in order to evaluate the discriminatory capacity of LDL-C (F), LDL-C (M), and non-HDL-C levels in predicting the occurrence of new lesions 9 months **(Fig. 2)** and ≤ 2 years after PCI **(Fig. 3)**.

The ROC cut-off values for the LDL-C (F), LDL-C (M), and non-HDL-C levels in predicting the occurrence of new lesions at 9 months were 82 mg/dL, 89 mg/dL, and 107 mg/dL, respectively [area under the curve (AUC) = 0.63, *p* = 0.041, AUC = 0.63, *p* = 0.038 and AUC = 0.63, *p* = 0.041]. Comparisons of ROC curves to predict the occurrence of new lesions 9 months after PCI showed that there were no significant differences in the AUC for the LDL-C (F), LDL-C (M), and non-HDL-C levels (*p* = 0.39) **(Fig. 2)**.

In addition, the ROC cut-off values for the LDL-C (F), LDL-C (M), and non-HDL-C levels in predicting the occurrence of new lesions ≤ 2 years were 88 mg/dL, 107 mg/dL, and 129 mg/dL, respectively [AUC = 0.62, *p* = 0.001, AUC = 0.62, *p* < 0.001 and AUC = 0.63, *p* < 0.001]. Comparisons of ROC curves for predicting the occurrence of new lesions ≤ 2 years

after PCI also showed that there were no significant differences in the AUC for the LDL-C (F), LDL-C (M), and non-HDL-C levels (*p* = 0.39) **(Fig. 3)**.

Discussion

This current study has demonstrated that non-HDL-C ≥ 100 mg/dL, but not LDL-C (F) ≥ 70 mg/dL or LDL-C (M) ≥ 70 mg/dL, was an independent risk factor for the occurrence of new lesions 9 months and ≤ 2 years after PCI for stable angina patients on strong statins.

PCI using second DES has become the standard procedure for coronary revascularization among patients with CAD, and many clinical trials using statins to lower LDL-C have shown substantial reductions in major cardiovascular events. However, residual risk is present even in patients with well-controlled LDL-C levels. Five-year outcomes of the j-Cypher Registry showed that the cumulative incidences of non-target lesion revascularization after PCI at 1 and 5 years were 16.1 % and 31.2 %, respectively[21]. In a study by Stone *et al.*, it was found that among patients presenting with acute coronary syndrome who underwent PCI, major adverse
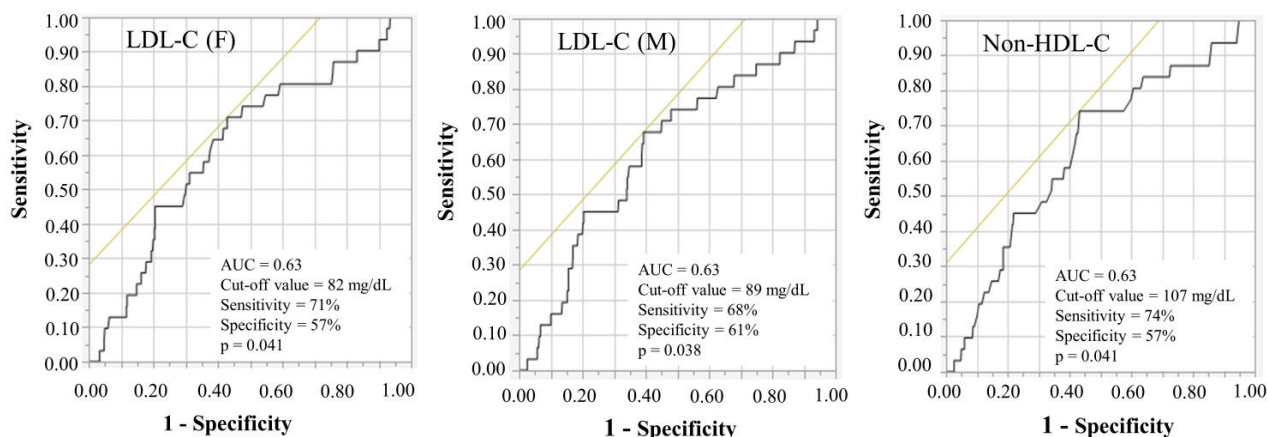
Fig. 2. Receiver operating characteristics curves for predicting the occurrence of new lesions 9 months after PCI

AUC, area under the curve; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention.

Fig. 3. Receiver operating characteristics curves for predicting the occurrence of new lesions ≤ 2 years after PCI

AUC, area under the curve; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention.
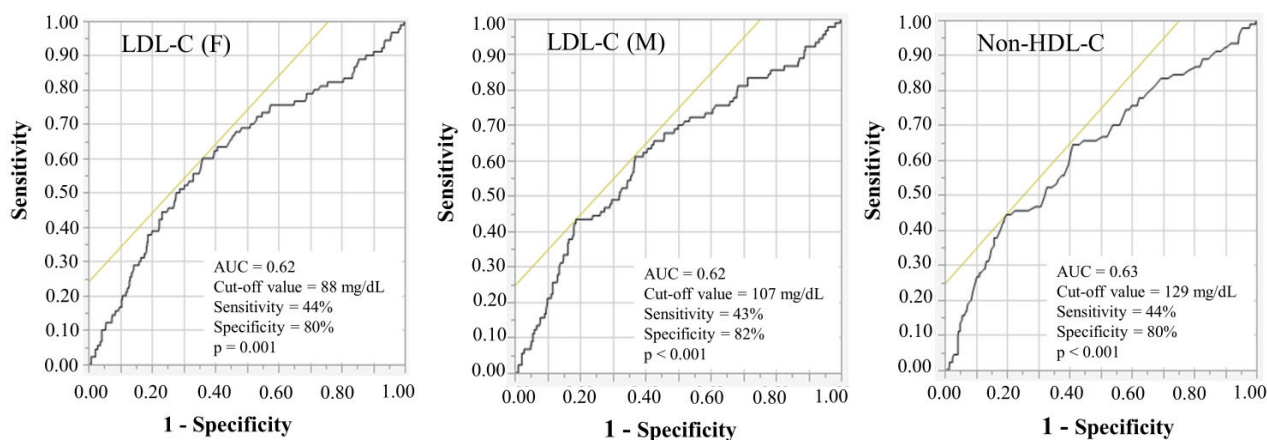
cardiovascular events occurring during 3-year follow-up were equally attributable to the recurrence at the site of culprit lesions (12.9 %) and non-culprit lesions (11.6 %)[22]. PCI has been deemed suitable for revascularization of culprit lesions; however, it is ineffective for suppressing new lesions. Suppressing the occurrence of new lesions after PCI is thus a significant issue for the prognosis of patients with CAD. Recently, the A Prospective Natural-History Study has demonstrated that predictors of non-culprit lesion-related major adverse cardiovascular events included insulin-requiring DM, baseline plaque burden ≥ 70 %, minimal luminal area ≤ 4.0 mm², and the presence of thin-cap fibroatheroma[22].

DM patients show approximately two to four times the risk of developing CAD compared to patients without DM[23, 24]. In addition, DM patients often suffer from a higher risk of adverse outcomes following PCI[25-28]. Thus, identification of factors that may increase CAD risk in DM patients following PCI is clinically important. DM patients can have an increased prevalence of lipid abnormalities, and dyslipidemia in DM patients is characterized by hypercholesterolemia, hypertriglyceridemia, low HDL-C levels, and small dense LDL particles[29]. DM is thus one of the substantial residual risks for CAD despite statin therapy[30]. These results seem to support our result that DM was strongly associated with the occurrence of new lesions after PCI despite strong statin therapy.

Lipid-lowering therapy has been identified to be vital in the primary and secondary prevention of CAD[8, 9]. Many clinical trials using statins have revealed that lowering LDL-C was significantly associated with substantial reductions in major cardiovascular events[31-34]. The Friedewald equation using a fixed TG/VLDL-C ratio of 5 is the standard method for estimating LDL-C (F) levels, but this equation is not recommended for use in patients with TG >400 mg/dL, and underestimation of LDL-C levels has been reported at both low LDL-C levels and high TG levels[15]. Martin *et al.* have recently reported a novel method for estimating LDL-C using an adjustable factor instead of a fixed factor of 5 [16]. Furthermore, we have demonstrated that in Japanese CAD patients receiving strong statins, LDL-C (M) was more accurate compared to LDL-C (F), particularly in patients with LDL-C <70 mg/dL[35]. In addition, we reported that LDL-C (M) was more useful than LDL-C (F) among Japanese patients with type 2 DM[36]. Thus, LDL-C (M) seems to be more useful for predicting for major cardiovascular events than LDL-C (F). However, both LDL-C (F) and LDL-C (M) levels are estimates from calculation formulas and thus do not evaluate remnant cholesterol, which remains a risk factor for arteriosclerosis along with LDL-C.

In patients with mild to moderate hypertriglyceridemia and associated cardiometabolic disorders such as DM, obesity, and metabolic syndrome, discordance can occur due to small dense LDL, and LDL-C may not accurately reflect LDL particle concentrations or their effects on CAD[37, 38]. Furthermore, dyslipidemia with DM is often characterized by high serum TG concentrations, low HDL-C concentrations, and increased concentrations of small dense LDL-C particles. Non-HDL-C can be simply and accurately calculated as non-HDL-C=TC – HDL-C, regardless of a fasting or non-fasting state, and represents the cholesterol mass contained in all atherogenic lipoproteins, including LDL and VLDL, intermediate-density lipoprotein, chylomicrons, and their TG-rich lipoprotein remnants. Several lines of evidence suggest that VLDL could contribute to the pathogenesis of atherosclerosis through increased expression of proinflammatory cytokines and induction of endothelial cell apoptosis[39-43]. The residual risk beyond the scope of LDL-C-lowering therapies may reflect the aspects of atherogenesis not captured by LDL-C, including the effects of VLDLs. We, therefore, considered non-HDL-C as a superior marker to LDL-C, given the inclusion of all lipoproteins that are considered to be causes of arteriosclerosis, including VLDL-C. Several recent reports have also suggested non-HDL-C as a more important target for predicting cardiovascular events than LDL-C[44-46]. These results seem to support our result that non-HDL-C was strongly associated with the occurrence of new lesions after PCI despite strong statin therapy.

Furthermore, our study has demonstrated that there were no significant differences in ROC curves for predicting the occurrence of new lesions at 9 months and ≤ 2 years after PCI in the LDL-C (F), LDL-C (M), and non-HDL-C levels. However, the cut-off values for the LDL-C (F) and LDL-C (M) for predicting the occurrence of new lesions 9 months and ≤ 2 years after PCI were quite different. It may be derived from the difference in calculation formulas between LDL-C (F) and LDL-C (M).

In addition, a significant residual risk was also noted for the occurrence of new lesions after PCI despite aggressive lipid-lowering therapy. In Japan, LDL-C <100 mg/dL is the secondary prevention target, while <70 mg/dL is recommended for high-risk patients[14], but there is still residual cardiovascular event risk even after achieving it. Furthermore, many trials about the efficacy of lipid-lowering therapy have shown that the cardiovascular benefits of statins which have "pleiotropic effects" such as contributing to plaque stabilization may go beyond their influence on LDL-C levels.

In this study, non-HDL-C ≥ 100 mg/dL was determined to be independently associated with the occurrence of new lesions both at 9 months and ≤ 2 years after PCI in stable angina patients prescribed with strong statins. Non-HDL-C ≥ 100 mg/dL was the important risk factor as well as LDL-C (F) ≥ 70 mg/dL, or LDL-C (M) ≥ 70 mg /dL. The assessment using the non-HDL-C which can be simply and accurately calculated, regardless of a fasting or non-fasting state, and represents the cholesterol mass contained in all atherogenic lipoproteins, was thought to be more important than LDL-C. Therefore, the priority of non-HDL-C assessment to predict occurrence of new lesions after PCI in stable angina patients prescribed with strong statins should be ahead of LDL-C.

Our study demonstrated that the New lesion (+) ≤ 2 years group was significantly younger than the New lesion (−) ≤ 2 years group ($p=0.006$). However, the difference in ages between the New lesion (+) 9-month group and the New lesion (−) 9-month group was not significant ($p=0.58$). The reason for the difference in age effects on the new lesion occurrence between 9 months and ≤ 2 years is yet to be determined. We speculate that age is a risk factor for atherosclerosis, but risk factor other than age may

be involved in short-term new lesions, and age may be involved in long-term new lesions.

Limitations

Several limitations to this study merit consideration when interpreting the results. First, this present study contained a relatively small number of patients. In the future, we need to assess the effects of non-HDL-C on new lesions over a longer period after PCI in a large-scale prospective study. Second, although we were able to demonstrate an independent association between non-HDL-C ≥ 100 mg/dL and the presence of new lesions in stable angina patients treated with strong statins who underwent PCI, we failed to examine the associations between the occurrence of new lesions and patients with TG >400 mg/dL, because of the limits to the use of Friedewald equation. Third, only patients with stable angina were recruited to this study. The impact of non-HDL-C on the presence of new lesions after PCI in patients with acute coronary syndrome should thus be investigated. Fourth, although all patients were administered strong statin, the kinds and doses of statin were different in each patient.

Conclusions

Non-HDL-C ≥ 100 mg/dL was the independent risk factor for the occurrence of new lesions both at 9 months and ≤ 2 years after PCI in stable angina patients with strong statins. Residual risk after PCI should be considered by assessing not only DM but also non-HDL-C beyond the scope of LDL-C-lowering therapy with strong statins.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

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