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Original article

Impact of baseline plaque characteristic on the development of neoatherosclerosis in the very late phase after stenting

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ABSTRACT

Background: Neoatherosclerosis (NA) is recognized as an important contributing factor to very late stent failure. The aim of this study was to investigate whether preprocedural underlying plaque morphology is associated with the development of NA using optical coherence tomography (OCT).

Methods: One-hundred thirteen stents [25 bare metal stents, 22 first-generation drug-eluting stents (DES), 66 second-generation DES] from 98 patients who underwent percutaneous coronary intervention with pre-percutaneous coronary intervention (PCI) OCT and very late OCT examination >3 years after stenting were retrospectively studied. In OCT analysis, NA was defined as a neointima with lipid or calcification. In-stent lipid volume index was defined as the in-stent averaged lipid arc multiplied by in-stent lipid length.

Results: In all, 28 stents were implanted to the culprit lesions of acute coronary syndrome (ACS) and 85 stents were in stable lesions. NA was observed in 29 stents (25.7%) and the median duration from PCI to remote OCT examination was 5.1 (4.0–6.1) years. Multivariable logistic regression analysis revealed that low-density lipoprotein cholesterol (LDL-C) at follow-up OCT [odds ratio (OR) 1.03, 95% confidence interval (CI) 1.01–1.04, $p < 0.001$], stent age (OR 2.13, 95% CI 1.36–3.31, $p = 0.001$), and thin-cap fibroatheroma (TCFA) at baseline culprit lesions (OR 14.2, 95% CI 4.6–43.8, $p < 0.001$) were independent predictors for the development of NA. In multiple linear regression analysis, in-stent lipid volume index was significantly correlated with LDL-C at follow-up OCT, stent age, the target lesion of ACS, and OCT-TCFA at baseline.

Conclusion: In addition to the known predictors, underlying plaque characteristics at the time of stenting was significantly associated with the development of NA at approximately 5 years after stent implantation.

Introduction

Percutaneous coronary interventions (PCIs) by using stents have been widely performed for the treatment of coronary artery disease. Recently, accumulating evidence has demonstrated the development of neoatherosclerosis (NA) inside both bare-metal stent (BMS) and drug-eluting stents (DES) [1–5]. Some of these studies have also suggested NA was related to poor prognosis including cardiac death, target-vessel revascularization, and very late stent thrombosis [1–3].

NA may occur in months to years following stent placement, whereas atherosclerosis in native coronary arteries develops over decades. The exact mechanisms underlying the rapid development of NA remain elusive. Histopathological studies revealed that NA is a frequent finding in 1st-generation DES and occurs earlier than in BMS [6]. Moreover, prevalence of the existence of NA was comparable in 1st-generation DES and 2nd-generation DES [7]. Although a histopathological study suggested that underlying plaque morphology (outside stent struts) was related to NA [6], the association between the baseline plaque characteristics before stenting and development of NA has not been fully elucidated.

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Optical coherence tomography (OCT) is an unprecedented high-resolution imaging modality for evaluating vascular structures, which enables in vivo assessment of the development of lipid-laden neointima inside the stents [8]. Therefore, we aimed to investigate whether preprocedural underlying plaque morphology is associated with the development of NA in the very late phase by using OCT.

Methods

Study population

Between November 2008 and May 2017, a total of 3553 patients with coronary artery disease (CAD) underwent PCI. Among them, 2678 (75.4%) patients with CAD underwent OCT analysis at the index PCI. The Tsuchiura Kyodo General Hospital Intravascular Imaging Registry is a single center registry of patients who undergo OCT imaging of the coronary arteries. Patients who underwent OCT examination in our institution were eligible for the registry. We also performed remote OCT imaging for the following reasons: (1) follow-up coronary angiography (CAG) and OCT imaging as a scheduled follow-up, and (2) OCT evaluation as a stent follow-up in case of PCI for other vessels. OCT examination is currently reimbursed in these situations in Japan. From a total of 2678 consecutive patients who were enrolled in the registry between November 2008 and May 2017, we identified 149 patients who underwent both OCT at the index PCI and remote OCT >3 years from the index stent implantation in our institution. The exclusion criteria included stents with poor OCT image quality, and stenting for in-stent restenosis. Patients who underwent any interventional procedure such as ballooning before OCT imaging were also excluded. Patients who underwent remote OCT imaging at the time of acute coronary syndrome (ACS) presentation were also excluded. Thus, the remaining 113 stents in 98 patients were included in the final analysis (Fig. 1). There were no significant differences regarding proportion of ACS through each stage in the study population. Although we also included in-stent restenosis (11 stents) without clinical symptoms, there were no cases of stent thrombosis in the study.

The study was approved by the local ethics committee and conformed to the Declaration of Helsinki statement on research involving human subjects. Informed consent for the institutional OCT database registration and potential future analysis of the data was provided by all participants after a complete explanation of the protocol and potential risks related to imaging before catheterization.

OCT image acquisition and analysis

The OCT images were acquired at the index PCI for lesions showing thrombolysis in myocardial infarction (TIMI) 3 flow without suspected angiographic thrombi; otherwise, thrombectomy was performed with an aspiration catheter (Eliminate, Terumo, Tokyo, Japan or Export Advance, Medtronic, Minneapolis, MN, USA) to obtain TIMI 3 flow before the OCT imaging. Either the time-domain (M2/M3 Cardiology Imaging System, LightLab Imaging, Inc., Westford, MA, USA) or the frequency-domain OCT system (C8-XRTM OCT Intravascular Imaging System, St. Jude Medical, St. Paul, MN, USA or LUNAWAVETM OFDI System, Terumo) was used in the present study. The technique of intracoronary OCT imaging is described elsewhere [9–11]. The OCT analysis at the index PCI included either the presence or absence of intraluminal thrombus, lipid-rich plaque and ruptured plaque, thin-capped fibroatheroma (TCFA), calcification, and macrophage infiltration according to consensus documents [9,12,13]. The lipid core on OCT was characterized by diffusely bordered, signal-poor regions with an overlaying, signal-rich band that represented the fibrous cap. The arc of the lipid and the thinnest fibrous cap thickness were measured; plaque with a lipid arc >90 degrees circumference was defined as fibroatheroma in the present study [14]. TCFA was defined as a fibroatheroma with a fibrous cap thickness <65 μm. A ruptured plaque was defined as a plaque showing disruption of the fibrous cap with or without cavity formation. We also evaluated neointima plaque morphology at remote OCT images including ruptured plaque, TCFA, and thrombus. Qualitative OCT assessment included the presence of lipid and calcification inside the stent. Lipid was defined as a diffusely bordered signal-poor region with rapid signal attenuation. Calcification was defined as a clearly delineated signal-poor region with low backscatter. The stent was considered to have NA when lipid-laden neointima or calcification was present. Cross-sectional remote OCT images were analyzed with an interval of 1.0 mm for quantitative and qualitative evaluation. Quantitative assessment was performed with the OCT off-line analysis software (LightLab Imaging Inc.). Representative cases of OCT images at the index PCI and at the follow-up are shown in Fig. 2. In-stent lipid volume index was defined as the in-stent averaged lipid arc multiplied by in-stent lipid length [15]. The stent and lumen areas were traced, and minimum, maximum, and mean neointimal thickness were semi-automatically determined.

Angiographic analysis

Baseline coronary angiograms obtained before the interventional procedures were analyzed off-line (QAngio XA 7.3, Medis,

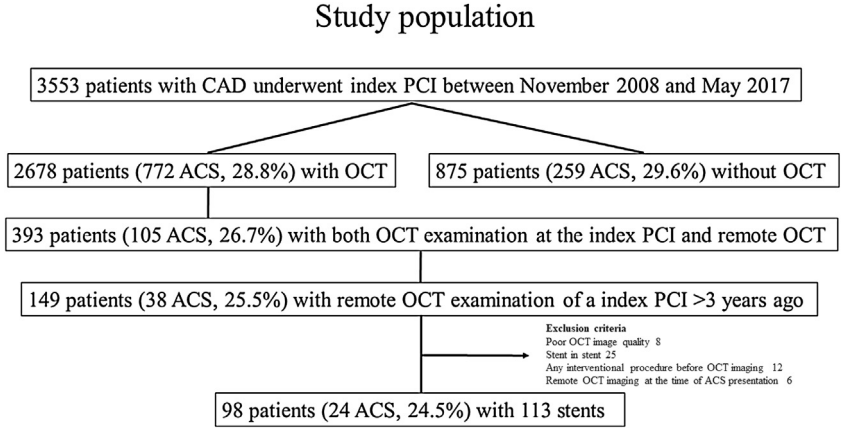

Fig. 1. Study flow diagram. CAD, coronary artery disease; PCI, percutaneous coronary intervention; OCT, optical coherence tomography; ACS, acute coronary syndrome.

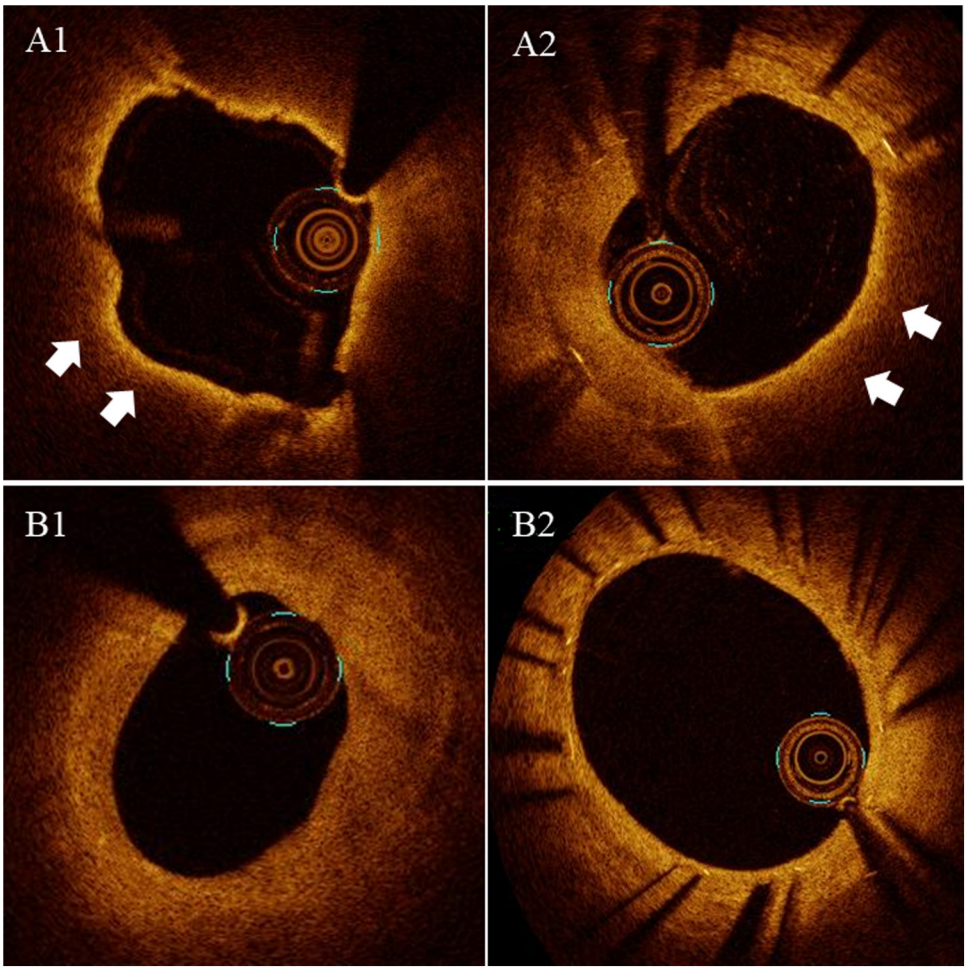

Fig. 2. Representative cases of OCT images at the index PCI and at the follow-up. (A1) A preprocedural OCT image at the index PCI. Thin-cap fibroatheroma was identified (white arrows). (A2) After 4 years, development of neoatherosclerosis was documented. Lipid-laden neointima was identified as a diffusely bordered signal-poor region with overlying signal rich homogenous band (white arrows). (B1) A preprocedural OCT image at the index PCI. (B2) After 4 years, neointimal hyperplasia without neoatherosclerosis was observed at the follow-up. OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

Leiden, The Netherlands). Angiographic lesion morphology was classified according to the American Heart Association/American College of Cardiology lesion classification [16].

Statistical analysis

Per-stent analysis was performed in the present study. Categorical values are presented as counts and proportions, and comparisons between groups were performed using the chi-square test or Fisher's exact test depending on the data. Continuous values showing a normal distribution are expressed as the mean value ± standard deviation, and Student's *t*-test was performed to compare groups. Non-normally distributed, continuous values are expressed as the median value (25–75th percentile), and the Mann–Whitney *U* test was used to compare groups.

Intra- and interobserver variability for the presence of NA, lipid-laden neointima, and calcification were estimated by means of the kappa coefficient (*k*). Multivariable logistic regression analyses were performed to determine the independent predictors for NA. Multivariable linear regression analyses were performed to determine the independent predictors for in-stent lipid volume index. We included patient characteristic and stent demographic factors into the multivariable model with $p < 0.05$. Receiver operating curve (ROC) analysis was performed to determine the predictability (sensitivity and specificity) of low-density lipoprotein cholesterol (LDL-C) and OCT-TCFA for the presence of NA. The Generalized Estimating Equations (GEE) approach was used to take into account the within-subject correlation due to multiple stents analyzed within a single patient. All statistical analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA) and R version 3.0.2 for 64-bit Windows. A value of $p < 0.05$ was considered statistically significant.

Results

Stent characteristics

Per-stent characteristics at remote OCT are summarized in Table 1. Median age was 68.0 years old and more than 80% of the stents were in male patients. About one fourth of the stents had the culprit lesions of acute coronary syndrome (ACS) at baseline. Stents included 25 BMS, 22 1st-generation DES, and 66 2nd-generation DES. NA was identified in 29 stents (25.7%) at remote OCT, and the median follow-up time from stent implantation to remote OCT was 5.1 (4.0–6.1) years. The incidence of NA in each stent type was 24.0%, 45.5%, and 19.1% ($p = 0.064$), respectively. Stent characteristics at remote OCT are summarized in Table 1. Comparisons of stent demographics analysis between the 2 groups are also shown in Table 1. The incidence of NA tended to be more frequently observed in 1st-generation DES. Time since stent implantation was significantly longer in stents with NA. In the NA stent group, time since stent implantation was significantly longer in BMS and 1st-generation DES

Table 1
Per-stent analysis.

	Overall (*N* = 113)	NA (*N* = 29)	Non-NA (*N* = 84)	*p*-Value
Age, year	68.0 (62.0–74.0)	66.0 (59.0–72.0)	68.5 (64.8–75.0)	0.131
Male	100 (88.5%)	28 (96.6%)	72 (85.7%)	0.178
Hypertension	70 (62.0%)	21 (72.4%)	49 (58.3%)	0.193
Dyslipidemia	76 (67.3%)	18 (62.1%)	58 (69.0%)	0.645
Diabetes mellitus	50 (44.3%)	17 (58.6%)	33 (39.3%)	0.112
Current smoker	20 (17.7%)	6 (20.7%)	14 (16.7%)	0.836
Prior MI	49 (43.4%)	15 (51.7%)	34 (40.5%)	0.403
LDL cholesterol, mg/dl	92.0 (74.3–111.8)	100.5 (91.8–119.0)	89.0 (72.0–108.3)	<0.001
HDL cholesterol, mg/dl	47.0 (41.0–55.0)	47.0 (43.0–50.0)	50.0 (41.0–56.0)	0.210
eGFR, ml/min/1.73 m^2	69.0 (55.0–79.8)	70.0 (59.4–86.2)	67.6 (54.9–78.7)	0.303
Medication				
Antiplatelet therapy				
Aspirin only	36 (31.9%)	8 (27.6%)	28 (33.3%)	0.694
Clopidogrel only	12 (10.6%)	2 (6.9%)	10 (11.9%)	
Aspirin + clopidogrel	63 (55.8%)	18 (62.1%)	45 (53.6%)	
Statin	91 (80.5%)	18 (62.1%)	73 (86.9%)	0.006
ACE/ARB	72 (63.7%)	16 (55.2%)	56 (66.7%)	0.376
Baseline target lesion status				
Acute coronary syndrome	28 (24.8%)	13 (44.8%)	15 (17.9%)	0.008
Stable angina	85 (75.2%)	16 (55.2%)	69 (82.1%)	
Angiographic and procedural findings at pre-PCI				
Reference diameter, mm	2.59 (2.32–2.96)	2.72 (2.46–2.96)	2.52 (2.31–2.97)	0.311
Minimum lumen diameter, mm	1.13 (0.91–1.35)	1.04 (0.91–1.27)	1.13 (0.91–1.37)	0.459
Diameter stenosis, %	57.0 (49.6–63.8)	57.1 (52.5–66.8)	56.2 (49.4–61.2)	0.396
Lesion length, mm	16.5 (11.5–23.1)	16.7 (11.5–22.8)	16.1 (11.2–24.3)	0.767
ACC/AHA classification (B2/C)	52 (46.0%)	15 (51.7%)	37 (44.0%)	0.620
Lesion location				
RCA	30 (26.6%)	10 (34.5%)	20 (23.8%)	0.123
LAD	69 (61.1%)	18 (62.1%)	51 (60.7%)	
LCX	14 (12.4%)	1 (3.4%)	13 (15.5%)	
Stent size, mm	3.5(3.0–3.5)	3.5 (3.0–3.5)	3.5 (3.0–3.5)	0.535
Stent length, mm	23.0(18.0–31.0)	23.4 (19.5–29.4)	21.8 (17.3–27.4)	0.287
Stent type				
Bare metal stent	25 (22.1%)	6 (20.7%)	19 (65.5%)	1.000
1st generation DES	22 (19.5%)	10 (34.5%)	12 (14.3%)	0.036
2nd generation DES	66 (58.4%)	13 (44.8%)	53 (63.1%)	0.133
Stent age	5.08 (4.02–6.13)	5.87 (4.97–6.95)	4.85 (3.99–5.97)	0.003
Malaposition	9 (8.0%)	3 (10.3%)	6 (7.1%)	0.692
Evagination	7 (6.2%)	0 (0%)	7 (8.3%)	0.188
Angiographic findings at post-PCI				
Reference diameter, mm	2.94 (2.59–3.24)	2.85 (2.54–3.23)	2.97 (2.62–3.23)	0.795
Minimum lumen diameter, mm	2.57 (2.11–2.90)	2.29 (1.93–2.81)	2.62 (2.19–2.90)	0.115
Diameter stenosis, %	11.1 (8.2–15.7)	12.7 (8.5–20.2)	10.7 (8.0–14.9)	0.178
Angiographic findings at remote CAG				
Reference diameter, mm	3.26 (3.00–3.58)	3.23 (3.05–3.45)	3.29 (3.00–3.66)	0.547
Minimum lumen diameter, mm	3.00 (2.69–3.33)	2.96 (2.77–3.21)	3.03 (2.69–3.33)	0.579
Diameter stenosis, %	7.96 (5.89–10.63)	7.61 (6.65)	8.18 (5.79–10.38)	0.755
Remote OCT measurement				
Minimum NIH thickness (mm)	0.13 (0.07–0.22)	0.14 (0.08–0.23)	0.12 (0.07–0.21)	0.177
Mean NIH thickness (mm)	0.29 (0.21–0.44)	0.38 (0.25–0.52)	0.27 (0.18–0.39)	0.008
Maximum NIH thickness (mm)	0.49 (0.36–0.69)	0.69 (0.48–0.84)	0.44 (0.33–0.58)	<0.001

Data are presented as *n* (%), mean standard deviation, or median (interquartile range).
NA, neoatherosclerosis; DES, drug-eluting stent; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AHA, American Heart Association; ACC, American College of Cardiology; eGFR, estimated glomerular filtration rate; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker, CAG, coronary angiography; OCT, optical coherence tomography; NIH, neointimal hyperplasia.

as compared with 2nd-generation DES. There were no significant differences in quantitative analysis of angiograms at the index PCI and at remote OCT (Table 1).

Risk factors of NA

There was no significant difference in age, sex, prevalence of hypertension, hyperlipidemia, and diabetes mellitus between the two groups (Table 1). Baseline target lesion status of ACS was significantly higher in stents with NA. LDL-C level at follow-up OCT was significantly higher and the use of statin was less frequent in stents with NA. ROC curve analysis showed that the optimal cut-off value of LDL-C for the presence of NA was 82 mg/dl [area under the curve (AUC): 0.71, 95% CI: 0.61–0.81, sensitivity 78.6%, specificity 54.9%, and accuracy 62.8%].

OCT measurement of underlying plaque morphology before index PCI

Underlying plaque morphology by OCT at the time of index PCI are summarized in Table 2. The prevalence of TCFA and plaque rupture was more frequent in stents with NA. Although there was no significant difference in the prevalence of fibroatheroma, fibrous cap thickness was significantly thinner and max lipid arc was significantly greater in stents with NA.

Table 2
Underlying plaque morphology by OCT before index PCI.

	Overall (*N* = 113)	NA (*N* = 29)	Non-NA (*N* = 84)	*p*-Value
Thrombus	24 (21.2%)	10 (35.7%)	14 (16.7%)	0.063
TCFA	27 (23.9%)	17 (58.6%)	10 (11.9%)	<0.001
Plaque rupture	25 (22.1%)	11 (37.9%)	14 (16.7%)	0.034
Fibroatheroma	96 (85.0%)	28 (96.6%)	68 (81.0%)	0.067
Calcified plaque	54 (47.8%)	12 (41.4%)	42 (50.0%)	0.558
Microchannel	29 (25.7%)	9 (34.6%)	20 (24.7%)	0.461
Macrophage	37(32.7%)	11 (37.9%)	26 (31.3%)	0.673
Fibrous cap thickness (μm)	110 (67–150)	63 (57–116)	120 (80–168)	<0.001
Max lipid arc (°)	197.2 (118.9–286.1)	266 (204–360)	168 (93–272)	0.004

Data are presented as *n* (%), mean SD, or median (interquartile range).
NA, neoatherosclerosis; PCI, percutaneous coronary intervention; TCFA, thin-cap fibroatheroma; OCT, optical coherence tomography.

Table 3
Neointima plaque morphology at remote optical coherence tomography.

	Overall (*N* = 113)	NA (*N* = 29)	Non-NA (*N* = 84)	*p*-Value
Lipid plaque	28 (24.8%)	28 (96.6%)	0	<0.001
Calcium plaque	3 (2.7%)	3 (10.3%)	0	0.016
Thrombus	3 (2.7%)	2 (6.9%)	1 (11.9%)	0.161
Ruptured plaque	1 (0.9%)	1 (3.4%)	0	0.257
TCFA	10 (8.8%)	10 (34.5%)	0	<0.001
Malaposition	9 (8.0%)	3 (10.3%)	6 (7.1%)	0.692
Evagination	7 (6.2%)	0	7 (8.3%)	0.188
Minimum NIH thickness (mm)	0.13 (0.07–0.22)	0.14	0.12	0.177
Mean NIH thickness (mm)	0.29 (0.21–0.44)	0.38	0.27	0.008
Maximum NIH thickness (mm)	0.49 (0.36–0.69)	0.69	0.44	<0.001

Data are presented as *n* (%), mean SD, or median (interquartile range).
NA, neoatherosclerosis; TCFA, thin-cap fibroatheroma; NIH, neointimal hyperplasia.

Table 4
Univariable and multivariable logistic regression analysis for predictors of neoatherosclerosis.

	Univariable analysis			Multivariable analysis		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Baseline clinical presentation						
Acute coronary syndrome	3.74	1.49–9.38	0.005			
1st generation DES	3.16	1.19–8.41	0.021			
OCT-TCFA	10.50	3.89–28.20	<0.001	14.2	4.61–43.77	<0.001
OCT-PR	3.06	1.19–7.86	0.028			
OCT-Fibroatheroma	6.59	0.83–52.10	0.074			
Stent age	1.66	1.19–2.31	0.003	2.13	1.36–3.31	0.001
LDL cholesterol	1.02	1.01–1.04	0.010	1.03	1.01–1.04	<0.001
Statin use	0.25	0.09–0.66	0.005			

DES, drug-eluting stent; TCFA, thin-cap fibroatheroma; OCT, optical coherence tomography; PR, plaque rupture; LDL, low-density lipoprotein; OR, odds ratio; CI, confidence interval.

Table 5
Univariable and multivariable linear regression analysis to predict in-stent lipid volume index.

	Univariable analysis			Multivariable analysis		
	β	95% CI	*p*-Value	β	95% CI	*p*-Value
Baseline clinical presentation						
Acute coronary syndrome	233.2	129.1–337.3	<0.001	147.9	35.1–260.7	0.010
1st generation DES	144.7	24.6–264.9	0.019			
OCT-TCFA	295.1	195.1–395.1	<0.001	253.9	128.2–379.6	<0.001
Stent age	58.7	24.7–92.8	<0.001	50.2	22.6–77.8	<0.001
LDL cholesterol	2.13	0.36–3.91	0.019	1.37	0.06–2.69	0.040
Statin use	−186.5	−304.6 to −68.4	0.002			

DES, drug-eluting stent; TCFA, thin-cap fibroatheroma; OCT, optical coherence tomography; LDL, low-density lipoprotein; CI, confidence interval.

Remote OCT measurements

Remote OCT measurements are summarized in Table 3. Remote OCT measurements showed significantly greater mean and maximum neointimal hyperplasia thickness in stents with NA compared with those in non-NA stents. There were no significant differences in ruptured plaque, TCFA, thrombus, mal-apposition, and evagination between the two groups.

OCT measurement after index PCI

There were no OCT data immediately after index PCI in 27 patients due to specific reasons in individual cases. All available OCT findings of the index PCI were compared and showed no significant differences between two groups (Supplemental Table 1).

Predictors for NA and in-stent lipid volume index

Univariate and multivariate logistic regression analyses were performed to determine the predictors for NA (Table 4). In the final model evaluated by GEE, stent age, LDL-C, and OCT-TCFA were independent predictors for NA. Univariate and multivariate linear regression analyses were performed to determine the predictors for in-stent lipid volume index (Table 5). In the final model evaluated by GEE, the culprit lesions of ACS at baseline, stent age, LDL-C, and OCT-TCFA were independent predictors for greater lipid volume index.

Intra- and inter-observer variability

The inter-observer κ coefficients for the presence of OCT-PR, OCT-TCFA at baseline, and NA at remote OCT were 0.85, 0.82, and 0.88, respectively. The intra-observer κ coefficients for the presence of OCT-PR, OCT-TCFA at baseline, and NA at remote OCT were 0.87, 0.84, and 0.89, respectively.

Discussion

To the best of our knowledge, this is the first OCT study demonstrating preprocedural underlying plaque morphology is associated with the development of NA after stent implantation. Preprocedural OCT-defined TCFA were related to progression of NA at approximately 5 years after stent implantation. Similar to previous studies [3,5,17], the present study showed longer stent age and high LDL-C were also important predictive factors for NA. Of note, even considering these factors, multivariable logistic regression analysis revealed that OCT-TCFA was the only independent predictor of underlying plaque morphology for the presence of NA and the volume of in-stent lipid. Accumulating evidence from the observational studies including recent reports [1–3] indicated that the presence of NA was related to stent failure and cardiovascular events. Our study further added to the body of evidence that OCT-TCFA at the index PCI and high LDL-C were associated with NA at long-term follow-up (median 5.1 years after implantation). Pre-PCI OCT findings might identify the patients at high risk for future NA development. Recent studies have reported differential morphological characteristics of in-stent neointimal tissue assessed by OCT and the presence of NA was independently associated with future cardiac events [3]. Ueda et al. also reported in-stent atherosclerosis of yellow plaque after DES implantation was associated with future events of very late stent failure [18]. Predictors of NA provide important information and may help guide patient management for secondary prevention after stent implantation. Previous studies reported that stent age, stent type, current smoking, chronic kidney disease, LDL-C at follow-up, and the use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockade, were associated with the presence of NA [5,17,19]. Consistent with these findings, our study demonstrated that longer stent age and higher LDL-C levels at follow-up were independent predictors of NA. Few previous studies investigated the association between pre-PCI plaque characteristics and NA progression at long-term follow-up by using OCT. The impact of underlying plaque morphology at the index procedure evaluated by intracoronary imaging on future in-stent neointimal tissue at long-term follow-up remains unknown. A histopathological study supported that stent implantation in unstable lesions may be prone to greater delay in vascular healing compared with those implanted in stable lesions and suggested an increased risk of future thrombotic complications and development of NA [6,20]. Our results demonstrated, in line with these previous studies, that underlying plaque morphology at the time of the index PCI showed a significant impact on long-term NA progression. In comparison with 2nd-generation DES, the stent age of 1st-generation DES and BMS were significantly longer in our study. Probably as the confounding variables with longer stent age, univariable analysis showed that the use of 1st-generation DES was a significant predictor of NA. Previous studies indicated stent type was an important factor for NA [17,21]. Drug effect of 1st-generation DES and/or the difference in durable polymer may cause dysfunctional endothelium, leading to the development of NA and very-late stent failure. Other OCT studies demonstrated NA in BMS was only observed after extended follow up (>5 years) [22] and also indicated 2nd-generation everolimus-eluting stents (EES) showed a similar rate of NA compared with BMS at 5 years [23]. However, multivariable analysis showed the use of 1st-generation DES was not a significant predictor of NA in the current study. This might be probably because of the relatively small number of 1st-generation DES and lack of long-term follow-up data of 2nd-generation DES. In accordance with a prior study, both the use of statin and LDL-C values were important factors for NA. Although ROC analysis showed LDL-C has an acceptable diagnostic accuracy for predicting NA, adding the feature of OCT-TCFA significantly increased the accuracy for finding NA (LDL-C vs. LDL-C + OCT-TCFA, AUC 0.71 vs. 0.83, p-value = 0.007) (Fig. 3). Unless patients including those with OCT-TCFA are equally treated with optimal medical therapy, including statins, NA will occur with high

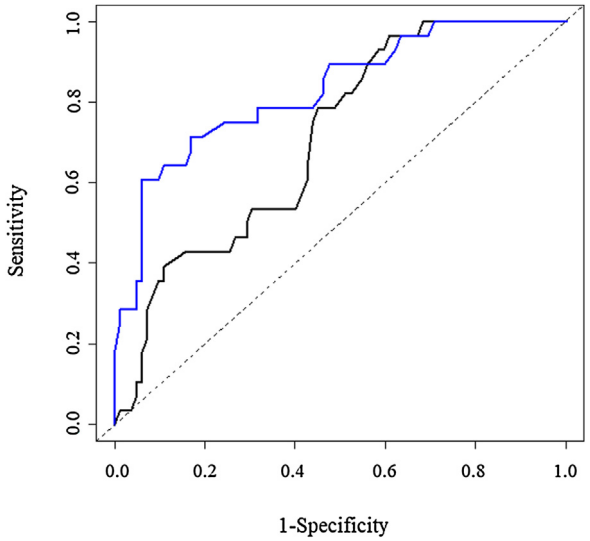

Fig. 3. Importance of LDL-C and OCT-TCFA. Receiver operating curve for finding NA. Black line indicates diagnostic performance of LDL-C. Blue line indicates diagnostic performance of LDL-C and OCT-TCFA. NA, neoatherosclerosis; OCT, optical coherence tomography; LDL-C, low-density lipoprotein cholesterol; TCFA, thin-cap fibroatheroma.

probability and may lead to poor prognosis. Further studies are needed to assess the effect of long-term optimal medical therapy including intensive LDL-C lowering management and its efficacy for reducing very late stent failure.

Limitations

This was a retrospective observational study; therefore, selection bias may have influenced the results. Second, we excluded patients with OCT examination <3 years after stent implantation, because the majority of NA progression (especially in BMS) occurs >3 years after stenting [22]. Third, five types of DESs, including sirolimus-eluting stent, paclitaxel-eluting stent, zotarolimus-eluting stent, biolimus-eluting stent, and EES, were included in the present study. Fourth, because of the relatively small number of each DES subtype and lack of long-term follow-up data of 2nd-generation DES, the time interval from stent implantation to follow-up was significantly different among each stent type. Therefore, an intensive subgroup analysis of the association between each stent type and follow-up OCT findings was suboptimal and probably underpowered. Further studies are needed for evaluating the relationship between each stent type and long-term follow-up OCT findings. Fifth, neointimal calcification was detected in only three cases, which precluded the meaningful statistical analysis regarding neointimal calcification. Sixth, because of few events, evaluation for prognosis was beyond the scope of the present study.

Conclusions

Underlying plaque characteristics at the time of stenting was significantly associated with the development of NA at approximately 5 years after stent implantation. Our results, demonstrating that higher LDL-C values at follow-up and longer stent age were also independent predictors of NA progression, suggest that patients treated with stenting for culprit lesions with OCT-TCFA particularly need to be recommended watchful observation and treated with long-term optimal medical therapy including intensive LDL-C lowering management.

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Conflict of interest

The authors state that there are no relationships with industry.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.01.002.

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