学位論文

The Residual Lipid-Rich Coronary Atheroma Behind the Implanted Newer-Generation Drug-Eluting Stent and Future Stent-Related Event Risks
（新世代薬剤溶出性ステント留置後にステント下に残存する脂質性プラークと、将来の心血管イベント発生リスクの関係解明研究）

邑井　洸太

Kota　Murai

熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学

指導教員

野口　暉夫　客員教授

熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学

2023 年 3 月

学　位　論　文

論文題名　：　**The Residual Lipid-Rich Coronary Atheroma Behind the Implanted Newer-Generation Drug-Eluting Stent and Future Stent-Related Event Risks**
（新世代薬剤溶出性ステント留置後にステント下に残存する脂質性プラークと、将来の心血管イベント発生リスクの関係解明研究）

著 者 名　：　邑井　洸太
Kota　Murai

指導教員名　：　熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学
野口　暉夫　客員教授

審査委員名　：　災害・救命医療学担当教授　笠岡　俊志
組織幹細胞学担当教授　小川　峰太郎
腎臓内科学担当教授　向山　政志
心臓発生学担当特任准教授　有馬　勇一郎

２０２３年３月

Canadian Journal of Cardiology 38 (2022) 1504–1515

Clinical Research

The Residual Lipid-Rich Coronary Atheroma Behind the Implanted Newer-Generation Drug-Eluting Stent and Future Stent-Related Event Risks

Kota Murai, MD,[a,b] Yu Kataoka, MD, PhD,[a,b] Stephen J. Nicholls, MBBS PhD,[c] Rishi Puri, MBBS, PhD,[d] Yuriko Nakaoku, MD, PhD,[e] Kunihiro Nishimura, MD, PhD, MPH,[e] Satoshi Kitahara, MD,[a,b] Takamasa Iwai, MD,[a] Kenichiro Sawada, MD,[a,b] Hideo Matama, MD,[a,b] Satoshi Honda, MD, PhD,[a] Masashi Fujino, MD, PhD,[a] Shuichi Yoneda, MD, PhD,[a] Kensuke Takagi, MD,[a] Kensaku Nishihira, MD, PhD,[f] Fumiyuki Otsuka, MD, PhD,[a] Yasuhide Asaumi, MD, PhD,[a] Kenichi Tsujita, MD, PhD,[g] and Teruo Noguchi, MD, PhD[a,b]

[a] *Department of Cardiovascular Medicine, National Cerebral & Cardiovascular Center, Suita, Osaka, Japan*

[b] *Department of Advanced Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan*

[c] *Victorian Heart Institute, Monash University, Clayton, Victoria, Australia*

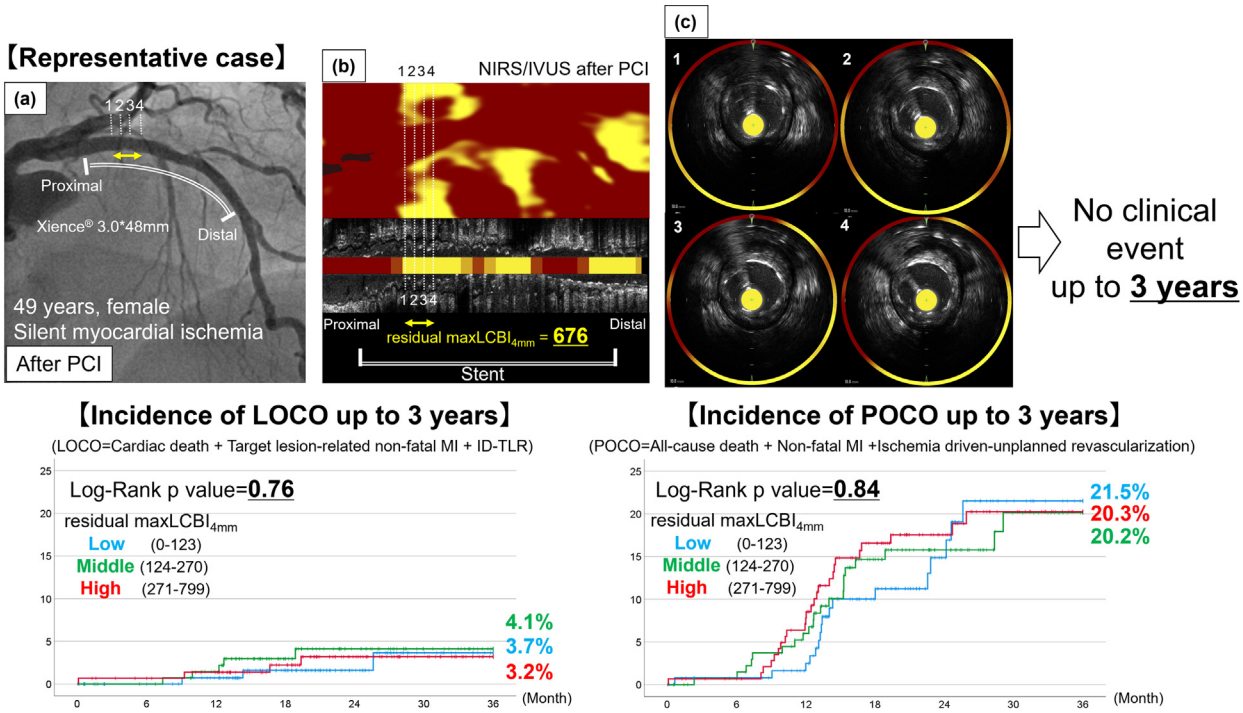
[d] *Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio, USA*

[e] *Department of Preventive Medicine and Epidemiology, National Cerebral & Cardiovascular Center, Suita, Osaka, Japan*

[f] *Department of Cardiology, Miyazaki Medical Association Hospital, Arita, Miyazaki, Japan*

[g] *Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan*

See editorial by Mintz et al., pages 1516-1517 of this issue.



https://doi.org/10.1016/j.cjca.2022.07.004

ABSTRACT

Background: Lipid-rich plaque is an important substrate that causes future coronary events. However, the clinical implications of underlying plaque characteristics in coronary lesions after newer-generation drug-eluting stent (DES) implantation remain unknown.

Methods: The current study analyzed 445 target lesions after newer-generation DES implantation in 416 patients with coronary artery disease (CAD) (chronic coronary syndrome/acute coronary syndrome = 264/181) from the REASSURE-NIRS multicentre registry. Near-infrared spectroscopy (NIRS) imaging was used to evaluate maximum lipid core burden index after stent implantation in target lesions (residual max$LCBI_{4mm}$). The primary and secondary outcomes were 3-year lesion-oriented clinical outcomes (LOCO): cardiac death, nonfatal target-lesion–related myocardial infarction (MI), or ischemia-driven target-lesion revascularization (ID-TLR) and patient-oriented clinical outcomes (POCO): all-cause death, nonfatal MI, or ID unplanned revascularization. Outcomes were compared by residual max$LCBI_{4mm}$ tertile.

Results: Median residual max$LCBI_{4mm}$ was 183; 16% of lesions had residual max$LCBI_{4mm}$ > 400. Higher residual max$LCBI_{4mm}$ was not associated with a greater likelihood of LOCO or POCO during the observational period (LOCO, log-rank $P = 0.76$; POCO, log-rank $P = 0.84$). Mixed-effects logistic regression demonstrated that residual max$LCBI_{4mm}$ does not predict LOCO (odds ratio [OR], 1.000; 95% confidence interval [CI], 0.997-1.003; $P = 0.95$). There was no significant relationship between residual max$LCBI_{4mm}$ and POCO (OR, 1.001; 95% CI, 0.999-1.002; $P = 0.30$).

Conclusions: Residual max$LCBI_{4mm}$ is not associated with LOCO or POCO in patients with CAD after newer-generation DES implantation. Our findings suggest that NIRS-derived underlying lipid-rich plaque is not associated with the risk of stent-related events and patient-based outcomes in patients with CAD who have received newer-generation DESs.

RÉSUMÉ

Contexte : Les plaques d'athérome à haute teneur en lipides jouent un rôle important dans la survenue d'incidents coronariens subséquents. Toutefois, les implications cliniques des caractéristiques sous-jacentes dans les lésions coronariennes après la mise en place d'une endoprothèse médicamentée (EM) de nouvelle génération demeurent mal comprises.

Méthodologie : Dans le cadre de cette étude, nous avons analysé 445 lésions cibles après la mise en place d'une EM de nouvelle génération, chez 416 patients atteints d'une coronaropathie (syndrome coronarien chronique/syndrome coronarien aigu = 264/181) inscrits au registre multicentrique REASSURE-NIRS. La spectroscopie proche infrarouge (SPIR) a été utilisée pour déterminer la valeur maximale de l'indice du fardeau lié à la présence de plaques avec noyaux lipidiques (*lipid core burden index*) pour les lésions cibles après la mise en place de l'endoprothèse ($LCBI_{4\ mm}$ maximal résiduel). Le critère d'évaluation principal et le critère d'évaluation secondaire étaient respectivement les résultats cliniques liés aux lésions (LOCO, pour *lesion-oriented clinical outcomes*) après trois ans, c'est-à-dire les décès attribuables à des causes cardiaques, l'infarctus du myocarde (IM) non fatal lié à la lésion et la revascularisation de la lésion cible en raison d'une ischémie (RLC-CI), et les résultats cliniques liés aux patients (POCO, pour *patient-oriented clinical outcomes*), c'est-à-dire les décès toutes causes confondues, l'IM non fatal, et la revascularisation non planifiée en raison d'une ischémie. Les résultats cliniques ont été comparés selon le tertile de la valeur de $LCBI_{4\ mm}$ maximal résiduel.

Résultats : La valeur médiane du $LCBI_{4\ mm}$ maximal résiduel était de 183; 16 % des lésions ont obtenu un score de $LCBI_{4\ mm}$ maximal résiduel > 400. Les valeurs de $LCBI_{4mm}$ maximal résiduel plus élevées n'étaient pas associées à une probabilité supérieure de LOCO ou de POCO au cours de la période d'observation (LOCO, test du log-rank $P = 0{,}76$; POCO, test du log-rank $P = 0{,}84$). L'analyse par régression logistique à effets mixtes a démontré que le $LCBI_{4mm}$ maximal résiduel ne permettait pas de prédire les LOCO (rapport de cotes [RC], 1,000; intervalle de confiance [IC] à 95 % de 0,997 à 1,003; $P = 0{,}95$). Aucune association significative n'a été notée entre le $LCBI_{4\ mm}$ maximal résiduel et les POCO (RC, 1,001; IC à 95 % de 0,999 à 1,002; $P = 0{,}30$).

Conclusions : Les valeurs de $LCBI_{4\ mm}$ maximal résiduel ne sont associées ni aux LOCO ni aux POCO chez les patients atteints d'une coronaropathie après la mise en place d'une EM de nouvelle génération. Selon nos observations, la détection par SPIR des plaques d'athérome à haute teneur en lipides n'est pas associée au risque d'événements liés à l'endoprothèse ou aux résultats cliniques chez les patients atteints d'une coronaropathie pour lesquels une EM de nouvelle génération a été implantée.

The characteristics of residual plaques after stent implantation have been reported to be causal factors of late stent failure. The presence of yellow plaques on coronary angioscopy or thin-cap fibroatheroma on optical coherence tomography (OCT) imaging is associated with an increased risk of future cardiac events following percutaneous coronary intervention (PCI) with bare-metal stents (BMSs) or first-generation drug-eluting stents (DESs).[1,2] Mechanistically, a pathologic study found a greater frequency of residual unstable plaques containing necrotic cores behind the implanted BMS or first-generation DES that had a formation of neoatherosclerosis.[3] These neoatherosclerotic changes have been reported to still occur following newer-generation DES implantation.[4] This observation suggests that evaluation of plaque features after PCI could predict subsequent cardiac risk.

Near-infrared spectroscopy (NIRS) is an intravascular imaging modality that enables quantitative visualization of lipidic plaques in vivo. Recent studies have shown the potential of NIRS to detect vulnerable plaques and predict PCI-related

Received for publication February 1, 2022. Accepted July 7, 2022.

Address for correspondence: Dr Yu Kataoka, Department of Cardiovascular Medicine, National Cerebral & Cardiovascular Center, 6-1, Kishibe-shimmachi, Suita, Osaka, 564-8565, Japan. Tel.: +81-6-6170-1070.
E-mail: yu.kataoka@ncvc.go.jp

See page 1513 for disclosure information.

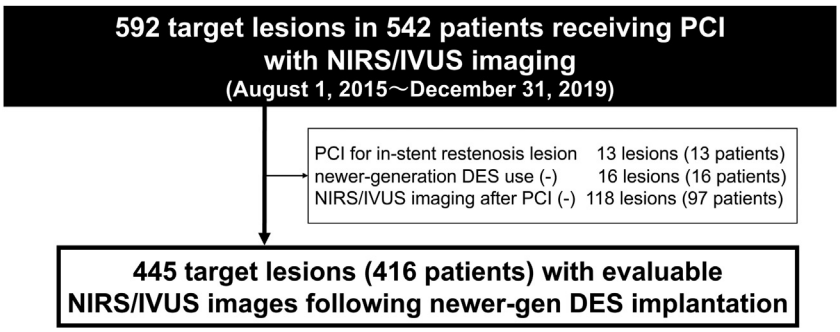


Figure 1. Patients' disposition: A total of 445 lesions in 416 patients with evaluable NIRS-IVUS images after the implantation of newer-generation DESs were included in the current analysis. IVUS, intravascular ultrasound; DES, drug-eluting stent; NIRS, near-infrared spectroscopy; PCI, percutaneous coronary intervention.

myocardial infarction.[5-7] NIRS has the potential to visualize lipidic signals behind the implanted stent in vivo.[8] We hypothesized that NIRS-derived lipidic parameters after PCI could identify lesions or patients associated with future cardiac events. Therefore, the current study investigated the ability of residual lipidic plaques after newer-generation DES implantation to predict future stent-related cardiac events in patients with coronary artery disease (CAD).

Material and Methods

Study subjects

Revelation of P**a**thophy**s**iological Phenotype**s** of V**u**lne**r**able Lipid-Rich Plaq**u**e on **N**ear-**I**nfra**r**ed **S**pectroscopy (REASSURE-NIRS) is an ongoing prospective multicentre registry in Japan (NCT04864171). It enrolls consecutive patients with CAD who undergo PCI with NIRS and intravascular ultrasound (IVUS) imaging. The current study is a subanalysis using this registry data. The following target lesions were excluded from the current analysis: in-stent restenosis lesions, lesions that were not treated with newer-generation DES, and lesions without post-PCI NIRS imaging.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. This study protocol was approved by the institutional review boards of the National Cerebral and Cardiovascular Center (M30-084-4) and Miyazaki Medical Association Hospital (2020-43).

PCI procedure

PCI was performed with NIRS and IVUS imaging. All procedural decisions, including the selection of newer-generation DESs and other devices, use of a mechanical support system, and adjunctive pharmacotherapy, were made according to the discretion of the individual PCI operator. Newer-generation DESs consisted of Xience (Abbott Vascular, Santa Clara, California, USA), Synergy (Boston Scientific, Marlborough, Massachusetts, USA), Ultimaster (Terumo, Tokyo, Japan), Resolute (Medtronic, Dublin, Ireland), and Orsiro (BIOTRONIK, Bülach, Switzerland). Each PCI operator was encouraged to achieve optimal stent expansion defined as minimum stent area (MSA) > 5.0 mm^2 or larger than the distal reference lumen area on IVUS imaging; IVUS-derived plaque area < 50% at the proximal and distal edges of the stents; and no edge dissection, which involves media > 3 mm on IVUS imaging.[9]

NIRS and IVUS imaging

NIRS and IVUS imaging were performed before and after the completion of PCI. After intracoronary administration of nitroglycerin (100 μg to 300 μg), the imaging catheter (TVC Insight or Dualpro, Infraredx, Bedford, Massachusetts, USA) was automatically pulled back from more than 5-mm distal to the site of the implanted newer-generation DES at a speed of 0.5 mm per second and 960 revolutions per minute (rpm) (TVC Insight) or 2.0 mm per second and 1800 rpm (Dualpro).[6] QIvus (Medis, Leiden, The Netherlands) was used for quantitative analysis of the raw IVUS images. Chemogram data from NIRS imaging was analyzed with the Makoto system (Infraredx). Physicians blinded to the clinical characteristics of study participants conducted both types of analyses (K.M., S.K., T.I., and Y.K.).

Quantitative analysis of IVUS and NIRS images

Quantitative analysis of IVUS and NIRS images were conducted for target lesions with a newer-generation DES. Cross-sectional analysis for IVUS images was performed at 1-mm intervals. The leading edges of the stents were manually traced, and stent area was defined as the area within the edges.[10] Percent stent expansion was defined as MSA divided by the average of the proximal and distal reference lumen area.[11] With regard to NIRS imaging analysis, lipid core burden index (LCBI) was measured as the number of yellow pixels divided by the total number of pixels within the lesion of interest.[5] The maximum value of LCBI in any 4-mm segment within the target lesion before PCI (pre-PCI $maxLCBI_{4mm}$) and within the implanted newer-generation DES (residual $maxLCBI_{4mm}$) was analyzed.[12]

Quantitative coronary angiography analysis

The current study included quantitative coronary angiography (QCA) analysis at lesions with a newer-generation DES (QAngio XA, Medis). Variables analyzed included reference diameter, minimum lumen diameter (MLD), and percent diameter stenosis (% DS).[13]

Outcomes

The primary outcome was the occurrence of a lesion-oriented clinical outcome (LOCO), which was defined as the composite of cardiac death, target lesion-related nonfatal myocardial infarction (MI), and ischemia-driven target lesion revascularization (ID-TLR). The secondary outcome was patient-oriented clinical outcome (POCO), which included the composite of all-cause death, non-fatal MI, and ID unplanned revascularization. The followings are definitions of each component of LOCO. Cardiac death included sudden cardiac death; death caused by acute MI, heart failure, or cardiogenic shock; and other cardiovascular causes.[14] Target-lesion−related nonfatal MI was defined as the occurrence of MI attributable to in-stent restenosis-occlusion or stent thrombosis at target lesion. Diagnosis of MI was based on the rise of cardiac biomarkers (creatine kinase-muscle/brain or troponin) more than upper normal limit with at least 1 of the following fulfilled criteria: electrocardiographic changes indicative of new myocardial ischemia; development of pathological Q waves; angiographically documented graft or native coronary artery occlusion, or stenosis with thrombosis, or diminished epicardial flow; imaging evidence of new loss of viable myocardium or new regional wall-motion abnormality.[14] ID-TLR was defined as any repeat revascularization for target lesion causing myocardial ischemia or typical ischemic symptoms.[14] Target lesion was defined as coronary artery stenosis receiving newer-generation DESs.

With regard to each component of POCO, all-cause death included cardiac and noncardiac death and undetermined cause of death. Nonfatal MI was defined according to the aforementioned diagnosis criteria of MI.[14] ID unplanned revascularization was defined as any revascularization for target or nontarget lesion causing myocardial ischemia or typical ischemic symptoms. This revascularization was not staged but unscheduled one.

Study patients were followed in our institute's outpatient clinic, a local cardiology clinic, or both every 1 to 3 months. Testing to evaluate for myocardial ischemia following PCI was conducted according to each physician's discretion. Clinical follow-up data were collected from medical records from hospital discharge up to 3 years after PCI. All outcomes were adjudicated by independent physicians who were unaware of the clinical characteristics of study participants (K.M. and Y.K.).

Sample size

The sample size was calculated based on a previous study that analyzed the association between the residual maxLCBI$_{4mm}$ and a composite of cardiovascular death, target-vessel MI, and clinically driven TLR.[15] In this previous study, the rate of events at 5 years was 3.1% and 15.0% in lesions with a residual maxLCBI$_{4mm}$ < 200 and > 200, respectively. Based on these event rates, assuming power of 0.95 with a 2-sided α of 0.05, the sufficient sample size for each group was calculated to be 150.

Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation (SD). Non-normally distributed variables were expressed as medians (25th to 75th percentiles). Categorical data were expressed as numbers (%). Comparisons of normally distributed continuous variables were performed with Student's *t*-test or 1-way analysis of variance (ANOVA). Non-normally distributed variables were compared using the Mann−Whitney U test or Kruskal-Wallis test. Categorical variables were analyzed using the χ^2 test or Fisher's exact test, as appropriate. Correlations between pre-PCI maxLCBI$_{4mm}$ and residual maxLCBI$_{4mm}$ were analyzed with Spearman's correlation coefficients. Time-to-event was based on Kaplan-Meier estimates and was compared using the log-rank test between groups according to residual maxLCBI$_{4mm}$ tertile and residual maxLCBI$_{4mm}$ = 200, respectively.[15] Mixed-effects logistic regression with patient-specific random intercepts was used to estimate the association between residual maxLCBI$_{4mm}$ and LOCO. Logistic regression was used to evaluate the relationship between residual maxLCBI$_{4mm}$ and POCO. In the analysis of patient-based outcomes, the highest residual maxLCBI$_{4mm}$ was selected if the patient had multiple target lesions. Subgroup analyses were performed to analyze the effects of various clinical characteristics as well as the effects of their interaction with residual maxLCBI$_{4mm}$.[11,16-18] All statistical tests were 2-sided, and $P < 0.05$ was regarded as statistically significant. Analyses were performed with SPSS software, version 27 (IBM Corporation, Armonk, New York, USA) and STATA version 15 (StataCorp LP, College Station, Texas, USA).

Results

Baseline clinical demographics

A total of 592 target lesions in 542 patients have been enrolled between August 1, 2015 and December 31, 2019. We excluded 13 in-stent restenosis lesions (13 patients), 16 lesions (16 patients) of patients who did not receive implantation of newer-generation DESs, and 118 lesions (97 patients) without post-PCI NIRS imaging. The remaining 445 target lesions in 416 patients receiving newer-generation DES implantation with NIRS and IVUS imaging were included into the current analysis (Fig. 1). The study population was predominantly male (81%). There was a high prevalence of hypertension (75%), dyslipidemia (85%), and type 2 diabetes mellitus (43%). Fifty-nine percent of study patients presented with chronic coronary syndrome (CCS) and the remaining had acute coronary syndrome (ACS). Clinical demographics of study patients across tertiles of residual maxLCBI$_{4mm}$ (low tertile, 0 to 123; middle tertile, 124 to 270; high tertile, 271 to 799) were compared (Table 1). There were no significant differences in baseline clinical characteristics among the 3 groups (Table 1). Regarding medication use, a high frequency of guideline-recommended medical therapies, including dual-antiplatelet therapy, high-intensity statins ($P = 0.04$),

Table 1. Baseline patients' clinical characteristics

		Residual $maxLCBI_{4mm}$			
	Overall n = 416*	Low tertile (0-123) n = 127*	Middle tertile (124-270) n = 142*	High tertile (271-799) n = 147*	*P* value
Age, y	70 ± 11	70 ± 11	69 ± 11	70 ± 11	0.67
Male, n (%)	335 (81)	102 (80)	114 (80)	119 (81)	0.99
BMI, kg/m^2	23.9 ± 3.4	23.7 ± 3.6	23.9 ± 3.0	24.0 ± 3.6	0.70
Hypertension, n (%)	311 (75)	96 (76)	110 (78)	105 (71)	0.48
Dyslipidemia, n (%)	352 (85)	103 (81)	120 (85)	129 (88)	0.31
T2DM, n (%)	179 (43)	56 (44)	67 (47)	56 (38)	0.28
Smoking, n (%)	95 (23)	33 (26)	27 (19)	35 (24)	0.37
Previous MI, n (%)	69 (17)	25 (20)	16 (11)	28 (19)	0.11
Previous CABG, n (%)	15 (4)	6 (5)	4 (3)	5 (3)	0.69
Hemodialysis, n (%)	14 (3)	5 (4)	5 (4)	4 (3)	0.85
LVEF, %	54 ± 11	55 ± 11	55 ± 9	53 ± 12	0.18
Clinical diagnosis					
CCS, n (%)	247 (59)	81 (64)	87 (61)	79 (54)	0.21
ACS, n (%)	169 (41)	46 (36)	55 (39)	68 (46)	
Medication use after PCI					
Aspirin, n (%)	415 (99)	127 (100)	141 (99)	147 (100)	0.38
$P2Y_{12}$ inhibitor, n (%)	416 (100)	127 (100)	142 (100)	147 (100)	-
DAPT, n (%)	416 (100)	127 (100)	142 (100)	147 (100)	-
DAPT duration, days	366 ± 240	359 ± 237	367 ± 238	371 ± 246	0.91
Statin, n (%)	398 (96)	120 (95)	136 (96)	142 (97)	0.69
HIS†, n (%)	151 (36)	54 (43)	55 (39)	42 (29)	0.04
Ezetimibe, n (%)	134 (32)	38 (30)	44 (31)	52 (35)	0.58
β-blocker, n (%)	266 (64)	76 (60)	89 (63)	101 (69)	0.29
ACE-I/ARB, n (%)	265 (64)	78 (61)	92 (65)	95 (65)	0.81
Biochemistry data					
LDL-C, mmol/L	1.76 ± 0.50	1.74 ± 0.46	1.74 ± 0.54	1.79 ± 0.49	0.60
HDL-C, mmol/L	1.24 ± 0.36	1.20 ± 0.38	1.26 ± 0.35	1.25 ± 0.34	0.35
HbA1c, %	6.3 ± 0.9	6.3 ± 0.9	6.3 ± 0.9	6.3 ± 0.9	0.76
eGFR, mL/min/1.73m^2	60.2 ± 19.3	61.0 ± 19.4	59.4 ± 17.7	60.5 ± 20.8	0.78

ACE-I, angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HIS, high intensity statin; LCBI, lipid core burden index; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; T2DM, type 2 diabetes mellitus.

*Patients who received PCI in multiple lesions were categorized into the groups including the highest residual $maxLCBI_{4mm}$ value.

†High-intensity statin is defined as any of the following: rosuvastatin ≥ 10 mg, atorvastatin ≥ 20 mg, pitavastatin ≥ 4 mg.

β-blockers ($P = 0.29$), and angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers ($P = 0.81$) was observed in each group (Table 1). The degree of risk factor control was similar across the 3 groups (Table 1).

Characteristics of $maxLCBI_{4mm}$ before and after newer-generation DES implantation

Mean pre-PCI $maxLCBI_{4mm}$ of the target lesion was 494 ± 249. Reduction in pre-PCI $maxLCBI_{4mm}$ was observed in 91% of target lesions after newer-generation DES implantation. Thus, residual $maxLCBI_{4mm}$ was 183 (79 to 338); 16% of target lesions had residual $maxLCBI_{4mm} > 400$. The comparison of pre-PCI $maxLCBI_{4mm}$ and residual $maxLCBI_{4mm}$ in patients with ACS vs CCS is summarized in Supplemental Table S1. Figure 2 illustrates the distribution of pre-PCI $maxLCBI_{4mm}$ and residual $maxLCBI_{4mm}$ for target lesions. There was a significant correlation between pre-PCI $maxLCBI_{4mm}$ and residual $maxLCBI_{4mm}$ ($\rho = 0.52$, $P < 0.01$) (Supplemental Fig. S1).

Characteristics of analyzed target lesions and implanted newer-generation DESs

Table 2 summarizes the characteristics of target lesions. Target lesions with higher residual $maxLCBI_{4mm}$ were likely to be located in the left anterior descending artery ($P = 0.06$) and accompanied by a more severe form of disease including smaller MLD ($P = 0.03$) and larger % DS ($P = 0.04$) (Table 2). In addition, multiple newer-generation DESs were more frequently implanted in target lesions with higher residual $maxLCBI_{4mm}$ ($P = 0.03$), resulting in a significantly longer total stent length ($P < 0.001$) (Table 2). The type of newer-generation DES implanted was similar across the 3 groups ($P = 0.20$) (Table 2).

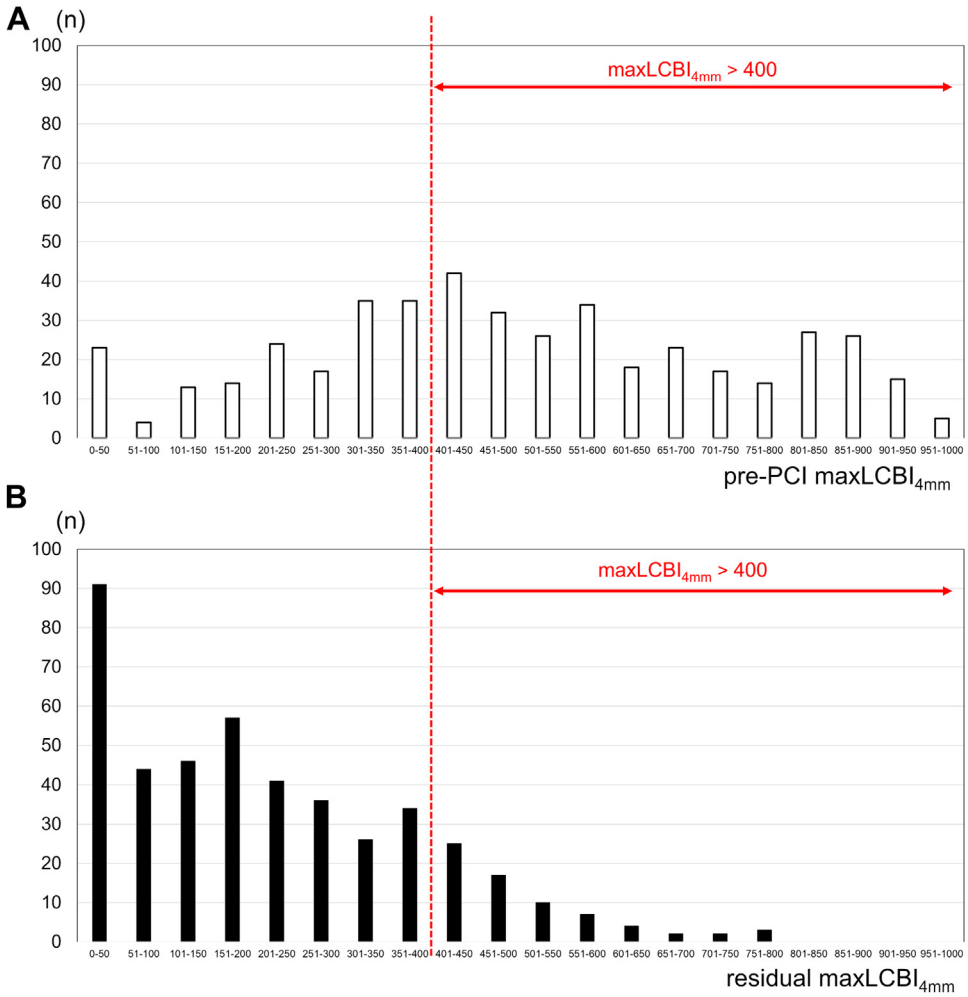


Figure 2. Distribution of pre-PCI maxLCBI$_{4mm}$ and residual maxLCBI$_{4mm}$. (**A**) pre-PCI maxLCBI$_{4mm}$. (**B**) Residual maxLCBI$_{4mm}$. The **red** frame highlights the population of maxLCBI$_{4mm}$ > 400. Residual maxLCBI$_{4mm}$ > 400 was observed in 16% of study subjects. LCBI, lipid core burden index; PCI, percutaneous coronary intervention.

IVUS and NIRS measures

IVUS and NIRS measures in target lesions are shown in Table 3. On IVUS imaging, smaller final MSA after PCI was observed in target lesions with higher residual maxLCBI$_{4mm}$ ($P = 0.02$) (Table 3). Lesions with higher residual maxLCBI$_{4mm}$ were more likely to have smaller percent stent expansion ($P = 0.09$), and a lower proportion fulfilled the 3 post-IVUS criteria ($P = 0.05$). Following PCI with newer-generation DES implantation, maxLCBI$_{4mm}$ decreased. The degree of the decrease was smaller in target lesions with higher residual maxLCBI$_{4mm}$ ($P < 0.001$). As a consequence, the frequency of residual maxLCBI$_{4mm}$ ≥400 was highest in the high residual maxLCBI$_{4mm}$ tertile ($P < 0.001$) (Table 3).

Residual maxLCBI$_{4mm}$ and the occurrence of LOCO and POCO

During the observational period with a median follow-up of 679 (481 to 997) days, there were 12 LOCOs in target lesions (Supplemental Table S2A). Only 1 cardiac death (0.2%) occurred during the observational period. Nonfatal MI occurred at the implanted newer-generation DES in 1.0% of target lesions. ID-TLR was required in 2.8% of lesions analyzed (Supplemental Table S2A). The occurrence of POCO was observed in 20.2% of the entire study population. The prevalence of all-cause death, nonfatal MI, and ID-TLR was 1.8%, 2.4%, and 18.1%, respectively (Supplemental Table S2B).

Kaplan-Meier analysis showed that the incidence of LOCO was not significantly different across residual maxLCBI$_{4mm}$ tertiles (log-rank $P = 0.76$) (Fig. 3A). There were no significant associations between residual maxLCBI$_{4mm}$ tertile and cardiac death (log-rank $P = 0.37$), target lesion-related nonfatal MI (log-rank $P = 0.99$) or ID-TLR (log-rank $P = 0.46$) (Supplemental Fig.S2A-C). The incidence of LOCO for each type of newer-generation DES is summarized in Supplemental Table S3. The clinical characteristics of subjects who had LOCO during the observational period are summarized in Supplemental Table S4. Furthermore, residual maxLCBI$_{4mm}$ was not associated with the

Table 2. Characteristics of target lesions and implanted newer-generation DESs

	Residual $maxLCBI_{4mm}$			
	Low tertile (0-123) n = 148	Middle tertile (124-270) n = 149	High tertile (271-799) n = 148	*P* value
Target vessel				
LMT, n (%)	5 (3)	3 (2)	0 (0)	0.06
LAD, n (%)	74 (50)	93 (62)	89 (60)	
LCX, n (%)	21 (14)	21 (14)	26 (18)	
RCA, n (%)	48 (32)	32 (22)	33 (22)	
QCA data				
Pre-PCI measures				
Reference diameter, mm	3.2 ± 0.6	3.2 ± 0.5	3.1 ± 0.6	0.21
Pre-PCI MLD, mm	0.7 (0.4-1.0)	0.7 (0.4-1.0)	0.6 (0.2-0.8)	0.03
Pre-PCI %DS, %	77 (62-90)	78 (66-89)	81 (71-94)	0.04
Post-PCI measures				
Post-PCI MLD, mm	2.9 ± 0.6	2.9 ± 0.5	2.8 ± 0.5	0.24
Post-PCI % DS, %	7 (3-13)	7 (2-14)	7 (1-14)	0.76
Implanted newer-generation DESs				
Averaged stent diameter, mm	3.4 ± 0 .6	3.3 ± 0.6	3.3 ± 0.5	0.48
Total stent length, mm	25.5 ± 10.8	31.2 ± 14.7	32.6 ± 15.4	< 0.001
Multiple stent use, n (%)	11 (7)	23 (15)	26 (18)	0.03
Maximum inflation pressure, atm	16 ± 3	17 ± 3	16 ± 4	0.01
Types of implanted newer-generation DES				
Xience, n (%)	75 (51)	92 (62)	95 (64)	0.20
Synergy, n (%)	29 (20)	28 (19)	15 (10)	
Ultimaster, n (%)	29 (20)	20 (13)	26 (18)	
Resolute, n (%)	11 (7)	6 (4)	9 (6)	
Orsiro, n (%)	4 (3)	3 (2)	3 (2)	

atm, standard atmosphere; DES, drug-eluting stent; LAD, left anterior descending artery; LCBI, lipid core burden index; LCX, left circumflex artery; LMT, left main coronary trunk; MLD, minimum lumen diameter; PCI, percutaneous coronary intervention; % DS, percent diameter stenosis; QCA, quantitative coronary angiography; RCA, right coronary artery.

occurrence of POCO (log-rank $P = 0.84$) (Fig. 3B) or each of its components (Supplemental Fig. S3A-C). Supplemental Figure S4 illustrates the occurrence of LOCO and POCO in lesions and patients stratified according to the residual $maxLCBI_{4mm} \leq$ and $>$ 200, respectively (Supplemental Fig. S4A and B).

Mixed-effects logistic regression showed that residual $maxLCBI_{4mm}$ does not predict the occurrence of LOCO, target-lesion−related nonfatal MI, or ID-TLR (Table 4). There was no significant relationship between residual $maxLCBI_{4mm}$ and the incidence of POCO, all-cause death, nonfatal MI, or ischemia-driven unplanned revascularization (Table 5). Figure 4 shows the ability of residual $maxLCBI_{4mm}$ to predict LOCO in a variety of subgroups. There was no evidence of statistical heterogeneity to suggest a differential effect of residual $maxLCBI_{4mm}$ across subgroups (Fig. 4).

Discussion

Despite the established safety and efficacy of newer-generation DESs, stent failure still occurs, partly because of underlying plaque characteristics. In the current study, lesions containing a greater amount of lipidic materials on NIRS had higher residual $maxLCBI_{4mm}$ following newer-generation DES implantation. However, residual $maxLCBI_{4mm}$ was not necessarily associated with lesion-related or patient-related clinical events over a 3-year observational period. The current findings suggest that NIRS-derived lipidic plaque features behind implanted newer-generation DESs are not associated with either lesion-based or patient-based cardiac outcomes.

$maxLCBI_{4mm}$ is a histologically validated measure that corresponds to lipidic plaque in vivo.[5,19] The clinical implication of this NIRS-derived measure has been evaluated in published studies. Goldstein et al. showed that $maxLCBI_{4mm}$ of culprit lesions was associated with an elevated risk of periprocedural MI after PCI.[7] In addition, several observational studies have found an association between $maxLCBI_{4mm}$ in nonculprit segments and cardiovascular events.[20,21] In contrast, the COLOR registry, which included 1621 patients with CAD, reported that $maxLCBI_{4mm}$ in the culprit segment does not predict future events.[22] These inconsistent findings suggest that there is uncertainty about the role of $maxLCBI_{4mm}$ in the clinical setting. The current analysis explored whether $maxLCBI_{4mm}$ in target lesions after stent implantation could help with risk stratification for cardiovascular events. Residual $maxLCBI_{4mm}$ was not a significant predictor of LOCO or POCO after PCI with newer-generation DES implantation. These observations indicate that the clinical implications of $maxLCBI_{4mm}$ behind the implanted newer-generation DES in culprit lesions and de novo nonculprit lesions might be different.

The current findings are inconsistent with findings from recent published studies. Madder et al. reported that higher

Table 3. IVUS and NIRS measures

	Residual $maxLCBI_{4mm}$			
	Low tertile (0-123) n = 148	Middle tertile (124-270) n = 149	High tertile (271-799) n = 148	*P* value
Post-PCI IVUS measures				
Reference lumen area, mm^2	8.1 ± 3.0	7.7 ± 2.6	7.4 ± 2.3	0.06
Final MSA, mm^2	6.4 ± 2.2	5.9 ± 2.2	5.7 ± 2.0	0.02
% Stent expansion, %	80 ± 12	77 ± 13	77 ± 13	0.09
The number of achieved post-IVUS criteria*				
3, n (%)	108 (78)	93 (62)	89 (60)	0.05
2, n (%)	40 (27)	56 (38)	59 (40)	
0 or 1, n (%)	0 (0)	0 (0)	0 (0)	
NIRS measures				
Pre-PCI measure				
Pre-PCI $maxLCBI_{4mm}$	349 ± 218	497 ± 230	633 ± 213	< 0.001
Post-PCI measure				
Residual $maxLCBI_{4mm}$	35 (6-79)	183 (154-226)	395 (340-478)	< 0.001
Residual $maxLCBI_{4mm} \geq 400$, n (%)	0 (0)	0 (0)	71 (48)	< 0.001
Absolute change in $maxLCBI_{4mm}$ after PCI	306 ± 215	306 ± 226	215 ± 200	< 0.001

IVUS, intravascular ultrasound; LCBI, lipid core burden index; MSA, minimum stent area; NIRS, near-infrared spectroscopy; PCI, percutaneous coronary intervention.

* Post-IVUS criteria is defined as follows: final MSA > 5.0 mm^2 or larger than distal reference lumen area; plaque area at the proximal and distal edge of the stent < 50%; no edge dissection, which involves media with a length > 3 mm.

residual $maxLCBI_{4mm}$ predicts a composite of cardiovascular death, target-vessel MI, and clinically driven TLR in 202 patients with CAD.[15] In that study, a BMS was used in more than one-fourth of patients, and more than 95% of patients had ACS, including cardiogenic shock or cardiac arrest. In addition, a composite outcome of the aforementioned cardiac events mainly occurred within 6 months according to Kaplan-Meier analysis of lesions with residual $maxLCBI_{4mm} > 200$. A greater proportion of patients who were acutely ill with ACS who underwent BMS implantation could have resulted in a greater occurrence of the composite outcome, including cardiovascular death and TLR within 6 months. Another study based on coronary angioscopy reported a higher rate of cardiac events in patients with yellow plaques behind the implanted stent in 360 patients with CAD.[23] More than 85% of patients were treated with first-generation DESs. There was a lower frequency of statin use (74%) in the study. Given that incomplete and dysfunctional endothelial coverage after first-generation DES implantation[24] could allow interaction between circulating lipoproteins, monocytes, and underlying plaques, this potential mechanism could cause DES-related neoatherosclerosis, which can account for the association between yellow plaques in the stented segment with cardiac events in patients after first-generation DES implantation.[4,25]

A lower LOCO rate, even in lesions with higher residual $maxLCBI_{4mm}$, might explain favourable vascular responses to newer-generation DESs reported in recent pathophysiological studies. Implantation of a cobalt-chromium everolimus-eluting stent has been shown to induce better strut coverage with less fibrin deposition and a smaller inflammatory response compared with first-generation DESs.[26] In addition, serial OCT has revealed vascular healing during the very early phase after implantation of a bioresorbable polymer sirolimus-eluting stent (Ultimaster),[27] biodegradable polymer everolimus-eluting stent (Synergy),[28] and durable polymer zotarolimus-eluting stent (Resolute).[29] Thus, adequate neointimal coverage after newer-generation DES implantation could mitigate the entry of proinflammatory materials into the underlying plaque to some extent, which might potentially account for a lower event rate even with higher residual $maxLCBI_{4mm}$.

Low-density lipoprotein cholesterol (LDL-C) has been reported to be an independent predictor of formation of neoatherosclerosis following stent implantation. Two OCT studies have shown that LDL-C levels above 1.81 or 2.12 mmol/L, respectively, are associated with a greater frequency of OCT-defined neoatherosclerosis in patients with CAD.[2,30] In the current study, according to the recent cholesterol guidelines, high-intensity statin therapy was frequently used, resulting in LDL-C ≤ 1.8 mmol/L. The adoption of this intensive lipid-lowering therapy might induce less influx of atherogenic lipoproteins into underlying plaques, which may result in a lower risk of formation of neoatherosclerosis and thereby ultimately prevent stent-related events. Whether lowering LDL-C levels could prevent neoatherosclerotic changes within an implanted stent warrants further investigation.

Another intriguing observation from the current analysis is that 91% of target lesions had some reduction of pre-PCI $maxLCBI_{4mm}$ after newer-generation DES implantation. There are several mechanisms hypothesized to explain this observation. Compression of a plaque with balloon angioplasty, stent implantation, or both could cause a greater distance between the NIRS catheter and the plaque surface. Because of shallow penetration of near-infrared light, existing lipid plaques farther from the catheter might not be adequately detected. Embolization of lipidic plaque materials after PCI might also potentially reduce $maxLCBI_{4mm}$. The

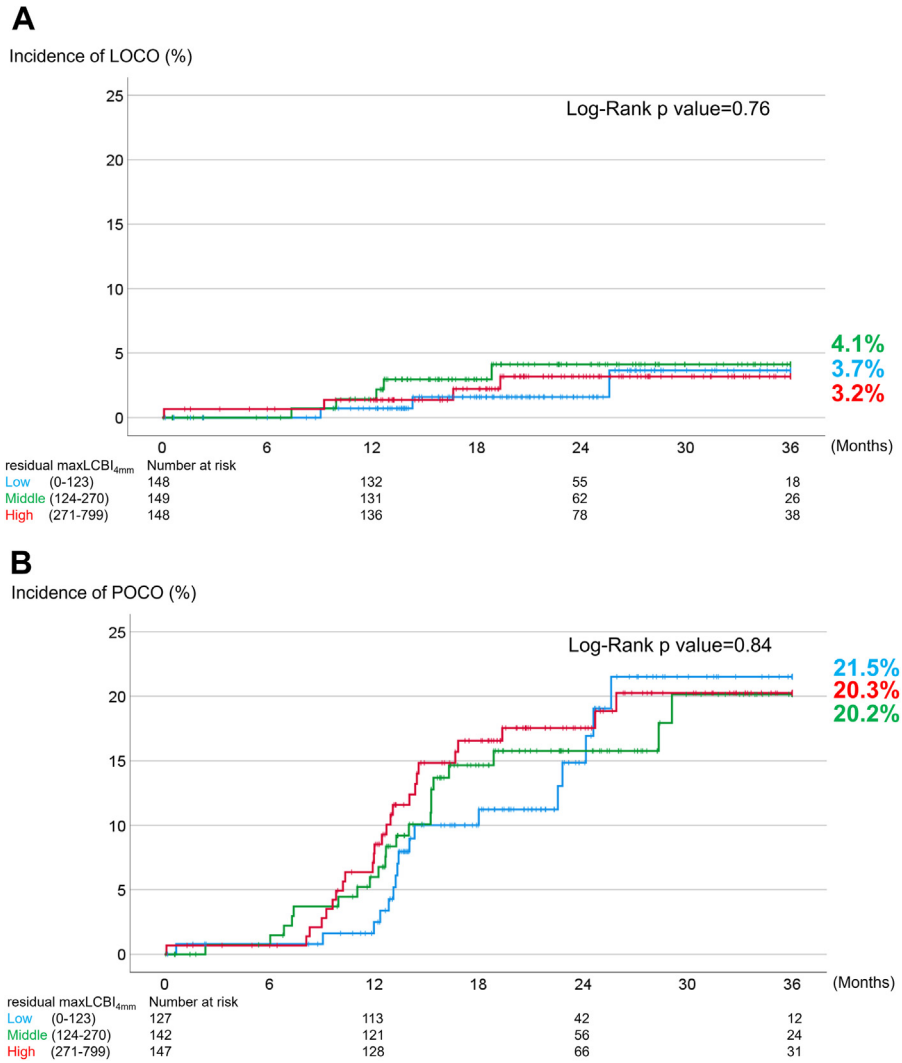


Figure 3. Comparison of outcomes in subjects stratified according to tertile of residual maxLCBI$_{4mm}$. (**A**) LOCO. (**B**) POCO. LOCO, lesion-oriented clinical outcome; LCBI, lipid core burden index; POCO, patient-oriented clinical outcome

struts of implanted stents overlying plaques might affect the absorbance and deflection of near-infrared light, which could cause lower maxLCBI$_{4mm}$ after DES implantation.

Clinical evidence to demonstrate the ability of maxLCBI$_{4mm}$ for predicting lesion-related hard cardiac events is still limited. Although the **L**ipid-**R**ich **P**laque (LRP) study reported the association of maxLCBI$_{4mm}$ with cardiovascular events, this study does not have enough statistical power to show the predictive ability of maxLCBI$_{4mm}$ for lesion-related hard cardiac events because of its low frequency.[20] In the current study, target lesion related nonfatal MI occurred in only 1% of analyzed lesions, and only 1 cardiac death occurred during the observational period. Further studies are required to investigate whether residual maxLCBI$_{4mm}$ could

Table 4. The association of residual maxLCBI$_{4mm}$ with clinical outcome: 3-year LOCO on mixed-effects logistic regression model analyses

	Odds ratio	95% CI	*P* value
Composite events	1.000	0.997-1.003	0.95
Cardiac death*	-	-	-
Target lesion related nonfatal MI	0.997	0.986-1.007	0.52
ID-TLR	1.000	0.996-1.004	0.95

CI, confidence interval; ID-TLR, ischemia-drive target lesion revascularization; LCBI, lipid core burden index; LOCO, lesion-oriented clinical outcome; MI, myocardial infarction.

*Owing to the small number of cardiac deaths, mixed-effects logistic regression model analysis was not conducted.

Table 5. 3-year POCO on logistic regression model analyses

	Odds ratio	95% CI	*P* value
Composite events	1.001	0.999-1.002	0.30
All-cause death	1.001	0.997-1.006	0.50
Nonfatal MI	0.998	0.993-1.003	0.48
Ischemia-driven unplanned revascularization	1.001	0.999-1.002	0.47

CI, confidence interval; MI, myocardial infarction; POCO, patient-oriented clinical outcome.

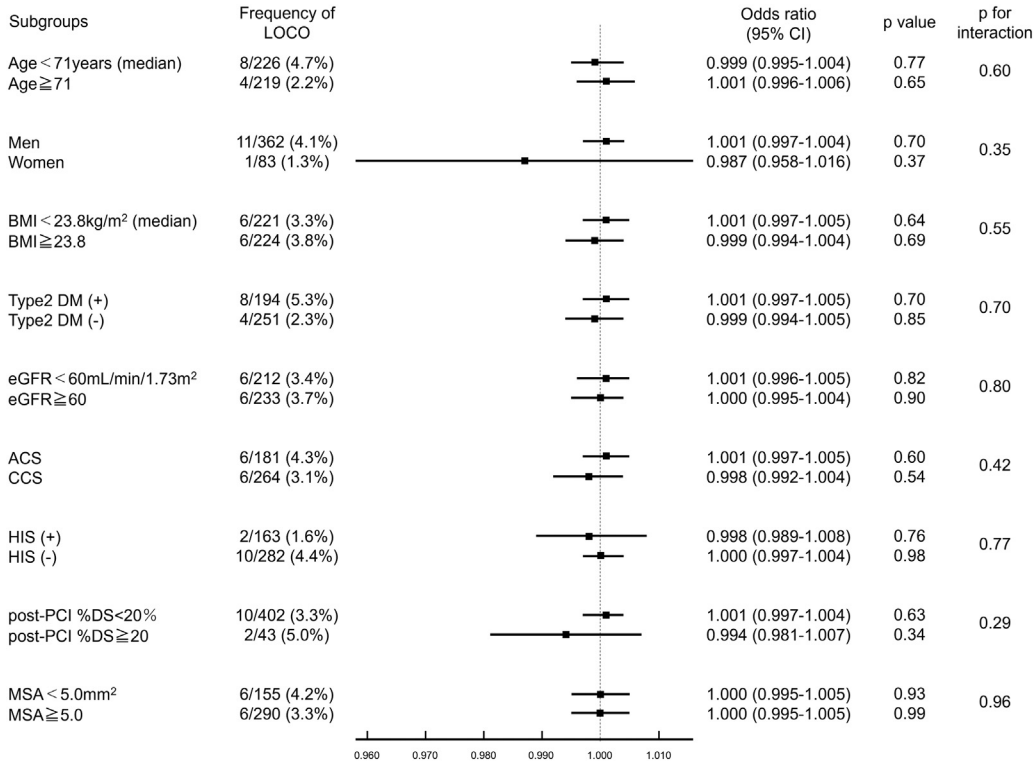


Figure 4. Subgroup analyses about the association of residual $maxLCBI_{4mm}$ with LOCO. Each event rates were Kaplan-Meier estimates at 3 years. ACS, acute coronary syndrome; BMI, body mass index; CCS, chronic coronary syndrome; CI, confidence interval, DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HIS, high-intensity statin; LOCO, lesion-oriented clinical outcome; LCBI, lipid core burden index; MSA, minimum stent area; PCI, percutaneous coronary intervention; % DS, percent diameter stenosis.

predict the risk of lesion-related hard cardiac events in a large study population with adequate statistical power.

Several caveats should be considered when interpreting the current findings. First, this was an observational study that included a relatively small number of cardiac events. Second, the procedural strategy and type of newer-generation DES were decided by each PCI operator. These characteristics might bias PCI outcomes. However, MSA, a predictor of stent-related events, was larger than the cutoff value of 5.0 mm^2 in all 3 residual $maxLCBI_{4mm}$ tertiles.[11] Third, the observational period was 679 days, which might have been too short to detect stent-related events. Fourth, histologic validation of the ability of NIRS to detect lipids under the implanted stent has not been performed yet.

Conclusions

$maxLCBI_{4mm}$ of the target lesion decreased after newer-generation DES implantation. During an observational period of up to 3 years, residual $maxLCBI_{4mm}$ was not associated with lesion-related or patient-related cardiac events. Our findings suggest that underlying lipid-rich plaques identified by NIRS do not invariably elevate the risk of stent-related events and patient-based outcomes in patients with CAD after newer-generation DES implantation.

Acknowledgements

We would like to acknowledge cardiology medical fellows and co-medical staffs (Sayaka Watanabe, Shintaro Kobayashi, Tomoyu Kondo) for their support in conducting NIRS/IVUS imaging during PCI. We thank Yuko Yoshioka and Emi Kanai for their excellent assistance.

Funding Sources

No funding was provided for this article.

Disclosures

Dr Murai has received honoraria from Abbott, TERUMO, Amgen, and ZEON MEDICAL and support for attending meetings from OrbusNeich. Dr Kataoka has received research support from Nipro and Abbott and honoraria from Nipro, Abbott, Kowa, Amgen, Sanofi, Astellas, Takeda, and Daiichi-Sankyo. Dr 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. Dr Puri has received speaker fees from Amgen and

Sanofi and has served as a consultant for Cerenis, Medtronic, Philips, Boston Scientific, and Shockwave and on advisory boards for Centerline Biomedical, Medtronic, Bioventrix; and holds minor equity in Centerline Biomedical. Dr Otsuka has received grant-in-aid for scientific research from the Japan Society for the Promotion of Science and honoraria from Abbott, Amgen Astellas Biopharma, Bayer, Boston Scientific, Bristol-Meyers, Daiichi-Sankyo, Kowa, Nipro, Novartis, Otsuka, Pfizer, Sanofi, Takeda, and TERUMO. Dr Tsujita has received grants from AstraZeneca, Sugi Bee Garden, Japan Medical Device Technology, Linical, TEIJIN, Cardinal Health, MSD, ITI, Astellas, Abbott Vascular, Eisai, KANEKA, Goodman, Sanofi, GM MEDICAL, St. Jude Medical, TERUMO, Novartis, Bayer, Pfizer, Fides-One, Bristol-Myers, Boston Scientific, Shionogi, Otsuka, Daichi-Sankyo, Chugai, Mitsubishi Tanabe, Boehringer, Medtronic, Japan Lifeline, and Takeda and honoraria from MSD, Amgen Astellas Biopharma, Sanofi, Bayer, Kowa, Otsuka, Daiichi-Sankyo, and Takeda. The other authors have no conflicts of interest to disclose.

References

1. Yamamoto M, Okamatsu K, Inami S, et al. Relationship between neointimal coverage of sirolimus-eluting stents and lesion characteristics: a study with serial coronary angioscopy. Am Heart J 2009;158:99-104.

2. Hoshino M, Yonetsu T, Kanaji Y, et al. Impact of baseline plaque characteristic on the development of neoatherosclerosis in the very late phase after stenting. J Cardiol 2019;74:67-73.

3. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol 2011;57:1314-22.

4. Otsuka F, Byrne RA, Yahagi K, et al. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. Eur Heart J 2015;36:2147-59.

5. Gardner CM, Tan H, Hull EL, et al. Detection of lipid core coronary plaques in autopsy specimens with a novel catheter-based near-infrared spectroscopy system. JACC Cardiovasc Imaging 2008;1:638-48.

6. Kataoka Y, Puri R, Andrews J, et al. In vivo visualization of lipid coronary atheroma with intravascular near-infrared spectroscopy. Expert Rev Cardiovasc Ther 2017;15:775-85.

7. Goldstein JA, Maini B, Dixon SR, et al. Detection of lipid-core plaques by intracoronary near-infrared spectroscopy identifies high risk of periprocedural myocardial infarction. Circ Cardiovasc Interv 2011;4:429-37.

8. Nishihira K, Otsuka F, Kataoka Y, et al. Embolization of neoatherosclerosis after percutaneous coronary intervention: insights from near-infrared spectroscopy imaging and histopathological analysis. Circ Cardiovasc Interv 2018;11:e006175.

9. Zhang J, Gao X, Kan J, et al. Intravascular ultrasound versus angiography-guided drug-eluting stent implantation: the ULTIMATE trial. J Am Coll Cardiol 2018;72:3126-37.

10. Nicholls SJ, Tuzcu EM, Sipahi I, Schoenhagen P, Nissen SE. Intravascular ultrasound in cardiovascular medicine. Circulation 2006;114:e55-9.

11. Sonoda S, Morino Y, Ako J, et al. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the sirius trial. J Am Coll Cardiol 2004;43:1959-63.

12. Murai K, Kataoka Y, Nakaoku Y, et al. The association between the extent of lipidic burden and delta-fractional flow reserve: analysis from coronary physiological and near-infrared spectroscopic measures. Cardiovasc Diagn Ther 2021;11:362-72.

13. Suzuki N, Asano T, Nakazawa G, et al. Clinical expert consensus document on quantitative coronary angiography from the Japanese Association of Cardiovascular Intervention and Therapeutics. Cardiovasc Interv Ther 2020;35:105-16.

14. Stone GW, Sabik JF, Serruys PW, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. N Engl J Med 2016;375:2223-35.

15. Madder RD, Kubo T, Ino Y, et al. Target lesion lipid content detected by near-infrared spectroscopy after stenting and the risk of subsequent target lesion failure. Arterioscler Thromb Vasc Biol 2021;41:2181-9.

16. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation 2008;118:1138-45.

17. Kataoka Y, Yasuda S, Miyamoto Y, et al. Clinical predictors of atheroma progression despite optimal glycemic control in early-stage diabetic patients with coronary artery disease: insight from the DIANA study. J Atheroscler Thromb 2014;21:509-18.

18. Watanabe H, Morimoto T, Shiomi H, et al. Impact of angiographic residual stenosis on clinical outcomes after new-generation drug-eluting stents implantation: insights from a pooled analysis of the RESET and NEXT trials. J Am Heart Assoc 2018;7.

19. Moreno PR, Lodder RA, Purushothaman KR, Charash WE, O'Connor WN, Muller JE. Detection of lipid pool, thin fibrous cap, and inflammatory cells in human aortic atherosclerotic plaques by near-infrared spectroscopy. Circulation 2002;105:923-7.

20. Waksman R, Di Mario C, Torguson R, et al. Identification of patients and plaques vulnerable to future coronary events with near-infrared spectroscopy intravascular ultrasound imaging: a prospective, cohort study. Lancet 2019;394:1629-37.

21. Erlinge D, Maehara A, Ben-Yehuda O, et al. Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study. Lancet 2021;397:985-95.

22. Yamamoto MH, Maehara A, Stone GW, et al. 2-Year outcomes after stenting of lipid-rich and nonrich coronary plaques. J Am Coll Cardiol 2020;75:1371-82.

23. Ueda Y, Matsuo K, Nishimoto Y, et al. In-stent yellow plaque at 1 year after implantation is associated with future event of very late stent failure: the DESNOTE Study (Detect the Event of Very late Stent Failure From the Drug-Eluting Stent Not Well Covered by Neointima Determined by Angioscopy). JACC Cardiovasc Interv 2015;8:814-21.

24. Nakazawa G, Nakano M, Otsuka F, et al. Evaluation of polymer-based comparator drug-eluting stents using a rabbit model of iliac artery atherosclerosis. Circ Cardiovasc Interv 2011;4:38-46.

25. Otsuka F, Finn AV, Yazdani SK, Nakano M, Kolodgie FD, Virmani R. The importance of the endothelium in atherothrombosis and coronary stenting. Nat Rev Cardiol 2012;9:439-53.

26. Otsuka F, Vorpahl M, Nakano M, et al. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. Circulation 2014;129:211-23.

27. Kuramitsu S, Kazuno Y, Sonoda S, et al. Vascular response to bioresorbable polymer sirolimus-eluting stent vs. permanent polymer everolimus-eluting stent at 9-month follow-up: an optical coherence

tomography sub-study from the CENTURY II trial. Eur Heart J Cardiovasc Imaging 2016;17:34-40.

28. Chevalier B, Smits PC, Carrie D, et al. Serial assessment of strut coverage of biodegradable polymer drug-eluting stent at 1, 2, and 3 months after stent implantation by optical frequency domain imaging: The DISCOVERY 1TO3 study (Evaluation With OFDI of Strut Coverage of Terumo New Drug Eluting Stent With Biodegradable Polymer at 1, 2, and 3 Months). Circ Cardiovasc Interv 2017;10.

29. Guagliumi G, Shimamura K, Sirbu V, et al. Temporal course of vascular healing and neoatherosclerosis after implantation of durable- or biodegradable-polymer drug-eluting stents. Eur Heart J 2018;39:2448-56.

30. Lee SY, Hur SH, Lee SG, et al. Optical coherence tomographic observation of in-stent neoatherosclerosis in lesions with more than 50% neointimal area stenosis after second-generation drug-eluting stent implantation. Circ Cardiovasc Interv 2015;8:e001878.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2022.07.004.