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ORIGINAL INVESTIGATIONS

2-Year Outcomes After Stenting of Lipid-Rich and Nonrich Coronary Plaques

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ABSTRACT

BACKGROUND Autopsy studies suggest that implanting stents in lipid-rich plaque (LRP) may be associated with adverse outcomes.

OBJECTIVES The purpose of this study was to evaluate the association between LRP detected by near-infrared spectroscopy (NIRS) and clinical outcomes in patients with coronary artery disease treated with contemporary drug-eluting stents.

METHODS In this prospective, multicenter registry, NIRS was performed in patients undergoing coronary angiography and possible percutaneous coronary intervention (PCI). Lipid core burden index (LCBI) was calculated as the fraction of pixels with the probability of LRP >0.6 within a region of interest. MaxLCBI$_{4mm}$ was defined as the maximum LCBI within any 4-mm-long segment. Major adverse cardiac events (MACE) included cardiac death, myocardial infarction, definite or probable stent thrombosis, or unplanned revascularization or rehospitalization for progressive angina or unstable angina. Events were subcategorized as culprit (treated) lesion–related, nonculprit (untreated) lesion–related, or indeterminate.

RESULTS Among 1,999 patients who were enrolled in the COLOR (Chemometric Observations of Lipid Core Plaques of Interest in Native Coronary Arteries Registry), PCI was performed in 1,621 patients and MACE occurred in 18.0% of patients, of which 8.3% were culprit lesion–related, 10.7% were nonculprit lesion–related, and 3.1% were indeterminate during 2-year follow-up. Complications from NIRS imaging occurred in 9 patients (0.45%), which resulted in 1 peri-procedural myocardial infarction and 1 emergent coronary bypass. Pre-PCI NIRS imaging was obtained in 1,189 patients, and the 2-year rate of culprit lesion–related MACE was not significantly associated with maxLCBI$_{4mm}$ (hazard ratio of maxLCBI$_{4mm}$ per 100: 1.06; 95% confidence interval: 0.96 to 1.17; p = 0.28) after adjusting clinical and procedural factors.

CONCLUSIONS Following PCI with contemporary drug-eluting stents, stent implantation in NIRS-defined LRPs was not associated with increased periprocedural or late adverse outcomes compared with those without significant lipid.
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ABBREVIATIONS AND ACRONYMS

DES = drug-eluting stents

IVUS = intravascular ultrasound

LCBI = lipid core burden index

LRP = lipid-rich plaque

MACE = major adverse cardiac events

MI = myocardial infarction

NIRS = near-infrared spectroscopy

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

Rupture of lipid-rich plaque (LRP) with thrombosis is responsible for approximately two-thirds of acute coronary events, including myocardial infarction and cardiac death (1). Pathological studies have raised concerns that treating LRP with stents may result in increased periprocedural adverse events due to distal embolization, and that drug-eluting stents (DES) may impair healing, resulting in late adverse outcomes (2). However, large randomized trials of patients with ST-segment elevation myocardial infarction (STEMI) have shown improved outcomes with primary percutaneous coronary intervention (PCI) using second-generation DES compared with bare-metal stents or balloon angioplasty (3–5).

SEE PAGE 1383

Near-infrared spectroscopy (NIRS) can differentiate LRP (fibroatheroma) from lipid-poor plaque using the absorption pattern of scattered light in the near-infrared range (6,7). We herein report the principal findings from the prospective, multicenter COLOR (Chemometric Observations of Lipid Core Plaques of Interest in Native Coronary Arteries Registry) that evaluated the association between NIRS findings of treated culprit lesions and culprit lesion-related clinical outcomes in patients with coronary artery disease undergoing PCI with DES.

METHODS

STUDY DESIGN AND PROTOCOL. Patients with a clinical indication for coronary angiography and possible revascularization with at least 1 NIRS chemogram obtained from a native coronary artery (either at baseline or post-PCI) were enrolled. Detailed inclusion and exclusion criteria are listed in Supplemental Table 1. Coronary angiography and PCI were performed per standard of care. After intracoronary administration of nitroglycerine, a NIRS catheter (Infraredx, Burlington, Massachusetts) was inserted distal to the lesion and pulled back at 0.5 mm/s to the aorto-ostium while acquiring raw spectroscopic information. In the first 709 patients, a 3.2-F NIRS-only catheter was used, and for the later 1,290 patients a 3.2-F combined NIRS/intravascular ultrasound (IVUS) catheter (TVC Imaging System, Infraredx) was used. The NIRS technology and chemogram imaging have been previously reported in detail (6,7). Timing of NIRS (pre-intervention, post-PCI, or both) were per operator discretion. All angiographic and NIRS/IVUS images were archived and sent to independent imaging core laboratories (Cardiovascular Research Foundation, New York, New York, and South Australian Health and Medical Research Institute, Adelaide, Australia) for offline analysis. The COLOR study organization and participating sites and investigators are shown in Supplemental Table 2.

Burlington, Massachusetts; [f]Monash Cardiovascular Research Centre, Monash University, Melbourne, Victoria, Australia; [s]Brigham and Women's Hospital, Boston, Massachusetts; and the [t]Montefiore Medical Center, Bronx, New York. Dr. Maehara has received grant support from Abbott Vascular and Boston Scientific; and has served as a consultant for Conavi Medical Inc. Dr. Stone has served as a consultant to and has equity in SpectraWave. Dr. Brilakis has received consulting/speaker honoraria from Abbott Vascular, American Heart Association (Associate Editor for *Circulation*), Biotronik, Boston Scientific, Cardiovascular Innovations Foundation (Board of Directors), CSI, Elsevier, GE Healthcare, InfraRedx, Medtronic, and Teleflex; has received research support from Regeneron and Siemens; and is a shareholder of MHI Ventures. Dr. Shunk has served as a consultant for Terumo, TransAortic Medical, and PercAssist Inc.; has equity in TransAortic Medical and PercAssist; and has received institutional grant support from Svelte, Siemens, CardioVascular Systems Inc., and Sanofi. Dr. Maini has served on the Advisory Board, received Speakers Bureau honoraria, and has served as consultant for Abbott Vascular, Medtronic, Boston Scientific, and Siemens; and has equity in East End Medical. Dr. Petersen has served on the Speakers Bureau of CSI, Inc.; has received research grants from CSI, Inc., Bristol-Myers Squibb/Pfizer, and National Institutes of Health SBIR sub-award from Veravanti; has received educational grants from Abbott Vascular, Boston Scientific, Phillips, Bristol-Myers Squibb/Pfizer, Janssen, Novartis, and AstraZeneca; has served as a research investigator/clinical trial participant for Keystone Heart, CSI Inc., Abbott Vascular, Boston Scientific, Abiomed, Svelte Medical, Niech Medical, and Novartis; and has stock/ownership in Veravanti. Dr. Généreux has received speaker fees from Abbott Vascular, Edwards Lifesciences, Medtronic, Tryton Medical Inc., Cardinal Health, and Cardiovascular Systems Inc.; has received consulting fees from Abbott Vascular, Boston Scientific, Cardiovascular Systems Inc., and Pi-Cardia; has received institutional research grants from Boston Scientific; and has equity in SIG.NUM, SoundBite Medical Solutions Inc., Saranas, and Pi-Cardia. Dr. Shah is an employee of InfraReDx. Dr. Nicholls has received research support from AstraZeneca, Amgen, Eli Lilly, Novartis, Resverlogix, InfraReDx, Sanofi-Regeneron, and Cerenis; and has served as a consultant for AstraZeneca, Amgen, Boehringer Ingelheim, CSL Behring, Akcea, Cerenis, Eli Lilly, Kowa, Novartis, Merck, Pfizer, Takeda, and Sanofi-Regeneron. Dr. Mintz has received honoraria from Boston Scientific/Philips. Dr. Muller has served as a consultant for SpectraWAVE, Inc. Dr. Weisz has served as an Advisory Board member for Corindus, Filterlex, and TriSol; and has received institutional grant support from Abbott, Ancora, Corindus, CSI, Shock Wave, Svelte, and V-Wave. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Steven E. Nissen, MD, served as Guest Associate Editor for this paper.

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PCI was performed using standard techniques and adjunctive medications. Clinical follow-up was performed at 30 days, 6 months, 1 year, and 2 years. Clinical event adjudication was performed by an independent clinical event committee using original source documents.

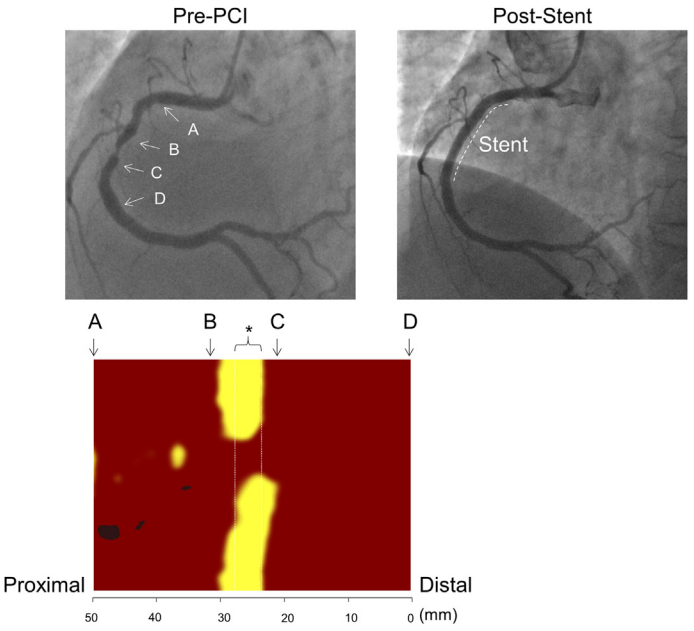
ENDPOINTS. The primary endpoint was a composite of major adverse cardiac events (MACE) including cardiac death, myocardial infarction (MI), definite or probable stent thrombosis, unplanned revascularization for progressive angina or unstable angina, or unplanned rehospitalization for progressive angina or unstable angina. Peri-procedural MI was defined according to the Society for Cardiovascular Angiography and Interventions definition (8). Definite or probable stent thrombosis was defined according to the Academic Research Consortium criteria (9).

By comparing the baseline and event-related coronary angiograms, each event was further subcategorized into either culprit lesion-related (initially treated), nonculprit lesion-related (i.e., related to a segment that was not treated), or indeterminate (10). The culprit lesion-related event was defined as the event arising from the PCI-treated segment during COLOR enrollment: ≥50% diameter stenosis at event angiography or new ulceration or thrombosis, clinical symptoms, or objective evidence of ischemia deemed related to the culprit lesion with or without revascularization. Objective evidence of ischemia was qualified by any of the following: new or transient ST-segment depression or elevation ≥0.1 mV or left bundle branch block or T-wave inversions; or a functional test (fractional flow reserve, echocardiographic, nuclear, magnetic resonance imaging, or electrocardiogram) consistent with stress-induced ischemia. Events were assigned as arising from a nonculprit lesion if any of the following were present: 1) either >20% progression of angiographic diameter stenosis from baseline to event or plaque rupture and/or thrombus by IVUS at the time of the event; 2) objective evidence of ischemia attributable to the lesion; 3) ≥50% angiographic diameter stenosis at the time of the event with or without revascularization; or 4) <50% angiographic diameter stenosis at the time of event with revascularization. For any event that cannot be attributed to a culprit or nonculprit lesion, such as an event with no angiography or no evidence of ischemia that can be localized to a specific lesion, mortality with no autopsy information was considered as indeterminate.

IMAGING ANALYSIS. Cine angiograms were analyzed with a computer-assisted, automated edge-detection algorithm (QCA-CMS, Medis Medical Imaging Systems, Leiden, the Netherlands) at an independent core laboratory using the conventional definition (11) without knowledge of patient characteristics and subsequent events.

NIRS raw spectroscopic data is used to automatically generate the chemogram, a color-coded distribution of the LRP probability with the x-axis corresponding to the pullback position (0.1 mm/pixel) and the y-axis corresponding to the circumferential position (1°/pixel). Low probability of lipid is shown as red and a high probability of lipid shown as yellow (7). Lipid core burden index (LCBI) is calculated as the fraction of pixels with the probability of LRP >0.6 divided by all pixels with sufficient spectroscopic information, within the region of interest, multiplied by 1,000. $MaxLCBI_{4mm}$ or $maxLCBI_{10mm}$ was defined as the maximum LCBI within any 4- or 10-mm-long segment, and lesion-LCBI was defined as the total LCBI throughout the entire lesion. NIRS analyses

FIGURE 1 Example From the COLOR Registry



A 57-year-old man presented with a non–ST-segment elevation myocardial infarction due to a severe stenosis in the mid right coronary artery. The pre-percutaneous coronary intervention (PCI) near-infrared spectroscopy (NIRS) image **(bottom color panel between A and D)** shows the lipid distribution corresponding to the angiographic segment (**upper left panel between A and D**). Nearly circumferential distribution of lipid-rich plaque was seen at the culprit lesion segment; the maximum lipid core burden index in 4-mm segment (*max lipid core burden index $[LCBI]_{4mm}$) measured 836. A zotarolimus slow-release drug-eluting stent of 3.5 mm in diameter and 38 mm in length was implanted successfully using 14 atmospheres. During the subsequent 2-year follow-up, there were no recurrent events.

TABLE 1 2-Year Outcomes After PCI (n = 1,621)

	All Events	Culprit Lesion-Related Events	Nonculprit Lesion-Related Events	Indeterminate Events
Major adverse cardiac events*	18.0 (278)	8.3 (127)	10.7 (161)	3.1 (46)
Cardiac death or myocardial infarction	5.8 (90)	2.1 (34)	0.9 (14)	4.6 (69)
Cardiac death	2.7 (41)	0.4 (6)	0.0 (0)	2.3 (35)
Noncardiac death	1.5 (23)	0.0 (0)	0.0 (0)	1.5 (23)
Myocardial infarction	3.4 (53)	1.9 (31)	0.9 (14)	0.7 (11)
Periprocedural	1.2 (20)	1.1 (18)	0.0 (0)	0.1 (2)
Spontaneous	2.2 (34)	0.9 (14)	0.9 (14)	0.6 (9)
Definite/probable stent thrombosis	1.0 (16)	0.7 (11)	0.3 (5)	0.0 (0)
Definite	1.0 (15)	0.6 (10)	0.3 (5)	0.0 (0)
Probable	0.1 (2)	0.1 (2)	0.0 (0)	0.0 (0)
Unplanned rehospitalization due to progressive or unstable angina	15.2 (230)	6.9 (105)	10.6 (160)	0.7 (10)
Unplanned revascularization due to progressive or unstable angina	12.0 (183)	6.6 (100)	7.9 (120)	0.0 (0)

Rates are shown as Kaplan-Meier estimates at 2 years as % (n events). *Major adverse cardiac events were cardiac death, myocardial infarction, stent thrombosis, or unscheduled rehospitalization or revascularization due to progressive angina or unstable angina.

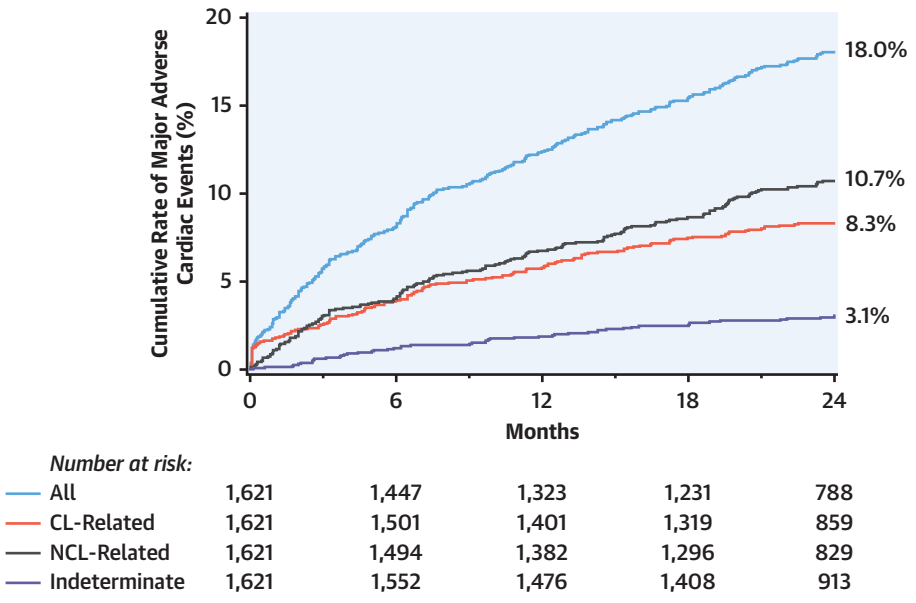
PCI = percutaneous coronary intervention.

were performed offline using Matlab-based software programmed at the Cardiovascular Research Foundation (New York, New York) (12). A representative case is shown in Figure 1.

Pre-intervention and post-PCI angiograms, IVUS images, and chemograms were coregistered using fiduciary anatomic markers (e.g., side branches). In cases with NIRS without IVUS imaging, the culprit segment was confirmed by comparing coronary angiography and the operator's annotation of the NIRS image such as the stent edge, side branch, and guiding catheter position.

In each NIRS/IVUS pullback, the slice with the minimum lumen area and the maximum LRP area was identified, and lumen and vessel area were measured. LRP burden was calculated as the area of the

FIGURE 2 Kaplan-Meier Curves for the Cumulative Rate of Major Adverse Cardiac Events



CL = culprit lesion; NCL = nonculprit lesion

TABLE 2 Demographic and Clinical Characteristics in Patients Undergoing PCI

	All Patients (N = 1,621)	Patients With Culprit Lesion-Related Events* (n = 127)	Patients Without Culprit Lesion-Related Events* (n = 1,494)	p Value
Age, yrs	63.9 ± 10.7	61.7 ± 9.1	64.1 ± 10.8	0.02
Male	1,262 (77.9)	101 (79.5)	1,161 (77.7)	0.64
Diabetes mellitus	637/1,616 (39.4)	61 (48.0)	576/1,489 (38.7)	0.05
Insulin-treated	96/1,616 (5.9)	10 (7.9)	86/1,489 (5.8)	0.33
Current smoking	337/1,563 (21.6)	34/122 (27.9)	303/1,441 (21.0)	0.09
Hypertension	1,469/1,618 (90.8)	122 (96.1)	1,347/1,491 (90.3)	0.04
Dyslipidemia	1,472/1,612 (91.3)	119 (93.7)	1,353/1,485 (91.1)	0.41
Renal insufficiency†	317/1,547 (20.5)	19/124 (15.3)	298/1,423 (20.9)	0.16
Prior myocardial infarction	491/1,611 (30.5)	46 (36.2)	445/1,484 (30.0)	0.16
Prior PCI	858/1,618 (53.0)	81 (63.8)	777/1,491 (52.1)	0.01
Prior coronary bypass surgery	158 (9.7)	23 (18.1)	135 (9.0)	0.0009
Prior heart failure	177/1,611 (11.0)	16 (12.6)	161/1,484 (10.8)	0.55
Peripheral vascular disease	159/1,606 (9.9)	19 (15.0)	140/1,479 (9.5)	0.06
Clinical presentation				
ST-segment elevation MI	31/1,617 (1.9)	1 (0.8)	30/1,490 (2.0)	0.51
Non-ST-segment elevation MI	167/1,617 (10.3)	14 (11.0)	153/1,490 (10.3)	0.76
Unstable angina	835/1,617 (51.6)	63 (49.6)	772/1,490 (51.8)	0.64
Stable coronary artery disease	584/1,617 (36.1)	49 (38.6)	535/1,490 (35.9)	0.56
Body mass index, kg/m^2	29.9 ± 5.7	30.5 ± 6.0	29.9 ± 5.7	0.23
Low-density lipoprotein, mg/dl	85.5 ± 35.7	85.8 ± 35.0	85.4 ± 35.8	0.92
High-density lipoprotein, mg/dl	39.6 ± 11.9	39.2 ± 12.4	39.6 ± 11.9	0.75
Medication at admission				
Statin	1,266 (78.1)	113 (89.0)	1,153 (77.2)	0.002
Aspirin	1,345/1,596 (84.3)	111/126 (88.1)	1,234/1,470 (83.9)	0.25
$P2Y_{12}$ inhibitor	736 (45.4)	71 (55.9)	665 (44.5)	0.01
Medication at discharge				
Statin	1,508 (93.0)	116 (91.3)	1,392 (93.2)	0.44
Aspirin	1,596 (98.5)	122 (96.1)	1,474 (98.7)	0.04
$P2Y_{12}$ inhibitor	1,587 (97.9)	121 (95.3)	1,466 (98.1)	0.04

Values are mean ± SD, n (%), or n/N (%). *During follow-up. †Creatinine clearance <60 ml/min/1.73 m^2 by Modification of Diet in Renal Disease formula.
MI = myocardial infarction; PCI = percutaneous coronary intervention.

plaque-containing lipid (i.e., LRP) within an orange, tan, or yellow circumferential arc (corresponding to a lipid core probability of >0.6) divided by total vessel area. Calcified plaque was defined as superficial hyperechoic tissue with acoustic shadowing. Attenuated plaque was defined as noncalcified plaque with signal attenuation. LRP was defined as max$LCBI_{4mm}$ >400. NIRS/IVUS plaque phenotype was classified as: 1) LRP with superficial attenuation; 2) LRP without superficial attenuation; 3) LRP with superficial calcium; 4) calcified non-LRP; or 5) no LRP. If 2 different types coexisted, the primary plaque phenotype was chosen based on a stated hierarchy (1 to 5) (Supplemental Figure 1).

STATISTICAL ANALYSIS. Continuous variables are summarized by mean ± SD and were compared by the Student's *t*-test, unless non-normally distributed ($p < 0.05$ per Shapiro-Wilk test), then compared by Wilcoxon rank sum test. Categorical variables are shown as counts and frequency and compared using the chi-square or Fisher exact test, as appropriate. Time-to event variables are presented as Kaplan-Meier estimates and were compared by the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) are estimated by Cox proportional hazards regression. Lesion level analyses are performed using the Wei-Lin-Weissfeld method to handle clustered data (within-patient correlations). The predictive utility of LCBI for events is summarized by the area under the receiver-operating characteristic curve.

Baseline and angiographic variables that were considered clinically relevant based on their historically proven relationship with adverse cardiovascular outcomes were entered multivariable Cox

TABLE 3 Angiographic, QCA, and Procedural Findings of the PCI-Treated Lesions

	All Culprit Lesions (N = 2,281)	Culprit Lesions With Events* (n = 138)	Culprit Lesions Without Events* (n = 2,143)	p Value
Number of culprit lesions (per patient)	1.4 ± 0.7	1.7 ± 1.0	1.4 ± 0.7	<0.0001
1	112 (68.7)	72 (56.7)	1,040 (69.8)	0.004
2	384 (23.7)	36 (28.3)	348 (23.3)	0.23
≥3	122 (7.5)	384 (23.7)	1,112 (68.7)	0.001
Culprit vessel				
Left main	18 (0.8)	1 (0.7)	17 (0.8)	0.92
Left anterior descending artery	965 (42.3)	65 (47.1)	900 (42.0)	0.32
Left circumflex	583 (25.6)	34 (24.6)	549 (25.6)	0.86
Right	691 (30.3)	35 (25.4)	656 (30.6)	0.19
Bypass graft	24 (1.1)	3 (2.2)	19 (0.9)	0.58
Pre-PCI				
Reference vessel diameter, mm	2.64 ± 0.67	2.56 ± 0.73	2.64 ± 0.67	0.26
Minimum lumen diameter, mm	1.10 ± 0.51	1.03 ± 0.49	1.10 ± 0.51	0.15
Diameter stenosis, %	58.3 ± 16.7	59.9 ± 15.6	58.2 ± 16.8	0.24
Lesion length, mm	15.5 ± 11.1	17.6 ± 12.6	15.4 ± 10.9	0.054
Calcification moderate/severe	312/2,167 (14.4)	20/136 (14.7)	292/2,031 (14.4)	0.52
True bifurcation lesion	211/2,178 (9.7)	25/138 (18.1)	186/2,040 (9.1)	0.0009
Ostial lesion	114/2,178 (5.2)	10/138 (7.2)	104/2,040 (5.1)	0.27
In-stent restenosis lesion	306/2,022 (15.1)	35/136 (25.7)	271/1,886 (14.4)	0.002
Post-PCI				
Minimum lumen diameter, mm				
In-segment	2.06 ± 0.56	1.99 ± 0.55	2.07 ± 0.56	0.14
In-stent	2.45 ± 0.53	2.33 ± 0.56	2.46 ± 0.53	0.02
Diameter stenosis, %				
In-segment	22.9 ± 13.0	22.6 ± 12.8	22.9 ± 13.0	0.77
In-stent	13.9 ± 8.1	14.7 ± 9.1	13.9 ± 8.0	0.42
Maximum device diameter, mm†	3.2 ± 0.6	3.2 ± 0.7	3.2 ± 0.6	0.96
Maximum balloon pressure, atm	16.4 ± 4.0	17.1 ± 4.0	16.3 ± 4.0	0.02
Cutting or scoring balloon use	323 (14.2)	29 (21.0)	294 (13.7)	0.01
Atherectomy use	52 (2.3)	3 (2.2)	49 (2.3)	0.89
Any stent implanted	2,145 (94.0)	119 (86.2)	2,026 (94.5)	<0.0001
Drug-eluting stent	1,974/2,279 (86.6)	109 (79.0)	1,865/2,141 (87.1)	0.02
Second-generation	1,800 (78.9)	96 (69.6)	1,704 (79.5)	0.02
Bare-metal stent	136 (6.0)	6 (4.3)	130 (6.1)	0.41
Total stent length, mm	29.9 ± 19.0	37.0 ± 25.6	29.5 ± 18.5	0.001

Values are mean ± SD, n (%), or n/N (%). The p values are adjusted for clustering by generalized estimating equation. *During follow-up. †Either stent balloon or balloon.
PCI = percutaneous coronary intervention.

proportional hazards regression models. The covariates entered in these models included $MaxLCBI_{4mm}$, presentation of acute coronary syndrome (STEMI, non-STEMI, or unstable angina), diabetes mellitus, use of second-generation DES versus others, in-stent restenotic lesion, and core laboratory-assessed quantitative angiographic parameters including lesion length, reference vessel diameter, and moderate or severe lesion calcification. Lesion-level multivariable models were adjusted for patient-level effects by means of the marginal Cox model. All tests were 2-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Between February 23, 2009, and February 7, 2014, a total of 1,999 patients were enrolled at 22 U.S. sites. A total of 9 patients (0.45%) had complications that were attributed to the NIRS or NIRS/IVUS imaging procedure (4 dissections, 3 episodes of ventricular tachycardia, 1 case of worsening congestive heart failure, 1 transient slow flow). These complications resulted in periprocedural MI in 1 patient and

TABLE 4 Baseline Near-Infrared Spectroscopy and Intravascular Ultrasound Findings Prior to PCI

	All Culprit Lesions	Culprit Lesions With Events*	Culprit Lesions Without Events*	p Value
NIRS	1,283	83	1,200	
MaxLCBI$_{4mm}$	332 ± 237	366 ± 273	329 ± 234	0.18
MaxLCBI$_{10mm}$	224 ± 181	247 ± 210	222 ± 178	0.26
Lesion LCBI	121 ± 108	128 ± 114	121 ± 108	0.36
Lesion length, mm	26.6 ± 14.2	31.7 ± 19.5	26.2 ± 13.7	0.009
IVUS	850	43	807	
Minimum lumen area, mm^2	2.8 ± 1.1	2.8 ± 1.1	2.8 ± 1.1	0.92
Vessel area at minimum lumen area site, mm^2	12.5 ± 5.2	12.9 ± 4.9	12.5 ± 5.3	0.59
Plaque burden at minimum lumen area site, %	74.8 ± 11.6	76.5 ± 10.0	74.7 ± 11.7	0.26
LRP burden at minimum lumen area site, %	22.6 ± 23.0	16.2 ± 23.0	22.9 ± 22.9	0.06
Maximum LRP burden, %	33.6 ± 23.2	29.9 ± 20.8	33.8 ± 23.3	0.23
Number of lesions with NIRS/IVUS	815	40	775	
Plaque type (LRP is defined as maxLCBI$_{4mm}$ >400)				
LRP with superficial attenuated plaque	152 (18.7)	6 (15.0)	146 (18.8)	0.54
LRP without superficial attenuated plaque	47 (5.8)	3 (7.5)	44 (5.7)	0.50
LRP with superficial calcified plaque	81 (9.9)	3 (7.5)	78 (10.1)	0.62
No LRP	381 (46.7)	18 (45.0)	363 (46.8)	0.84
Calcified no LRP	154 (18.9)	10 (25.0)	144 (18.6)	0.31

Values are n, mean ± SD, or n (%). *During follow-up.
IVUS = intravascular ultrasound; LCBI = lipid core burden index; LRP = lipid-rich plaque; NIRS = near-infrared spectroscopy.

emergent coronary artery bypass grafting in another patient (imaging-related MACE rate of 0.1%). For the current analysis, 378 patients were excluded due to prior heart transplant or no PCI at the time of enrollment. In the remaining 1,621 patients, PCI was performed on 2,281 lesions. A total of 1,189 patients had pre-culprit NIRS imaging of 1,283 lesions prior to PCI, representing the current study population (Supplemental Figure 2). Mean patient age was 63.9 years, 77.9% were men, and 39.4% had diabetes mellitus. The median follow-up was 732 days (interquartile range: 714 to 748 days). Within 2 years, MACE occurred in 18.0% of patients overall, of which 8.3% were culprit lesions-related events, 10.7% were non-culprit lesion-related events, and 3.1% were indeterminate (**Table 1, Figure 2**).

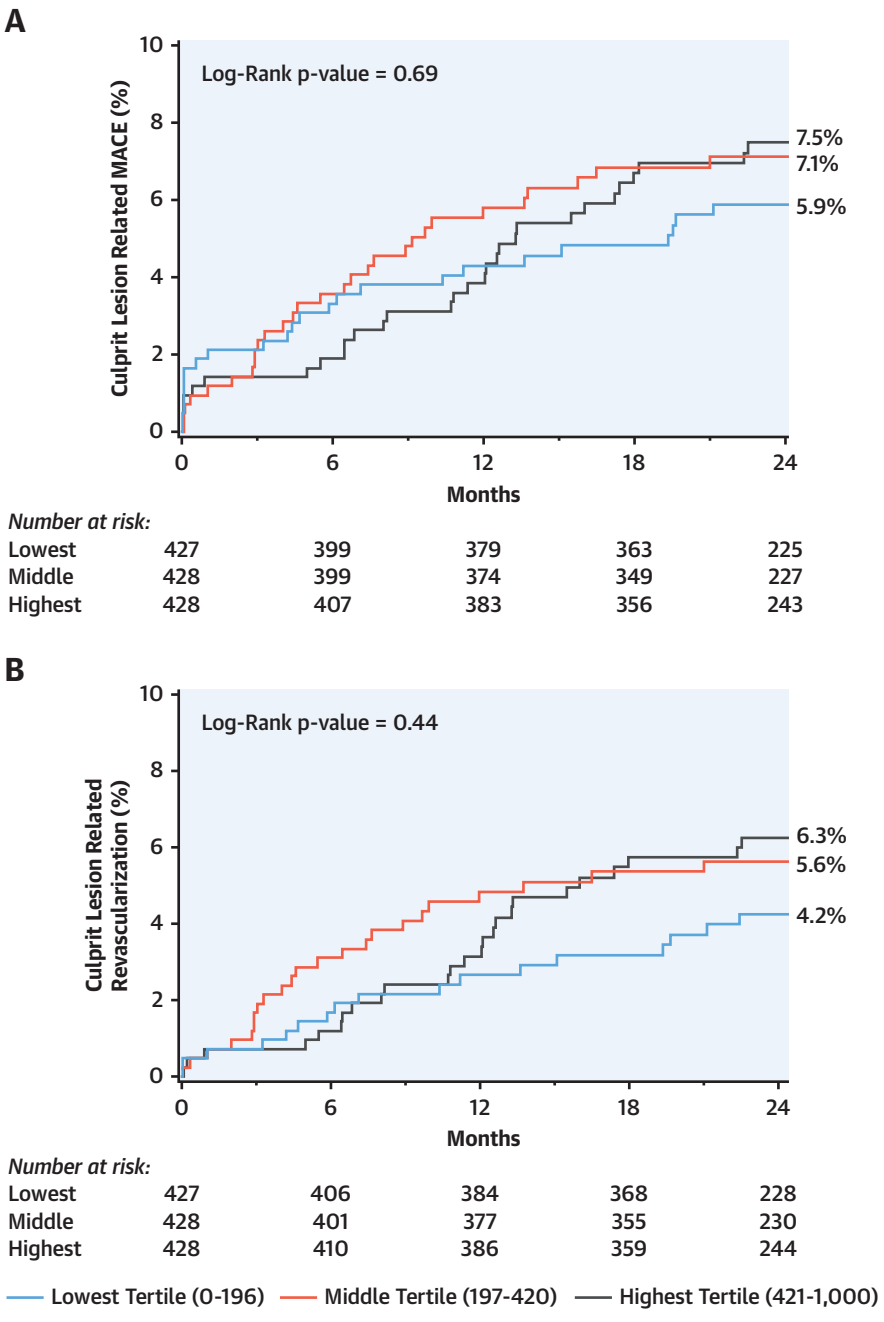
Patients having culprit lesion-related MACE were younger and had a higher prevalence of diabetes mellitus and a history of prior PCI or coronary bypass surgery compared with those without MACE (**Table 2**). Patients with MACE more often used statins and P2Y$_{12}$ inhibitors on admission. **Table 3** shows angiographic and procedural findings of the culprit lesions. Culprit lesions associated with MACE at 2-year follow-up had more complex lesion morphology (longer lesions treated with longer stents and more true bifurcation or in-stent restenosis lesions) and smaller final in-stent minimum lumen diameter compared with those not associated with MACE. The use of DES, especially second-generation DES, was less frequent in culprit lesions associated with MACE.

Table 4 shows the corresponding pre-PCI NIRS and IVUS. Culprit lesions associated with MACE at 2-year follow-up were similar as those without MACE except for longer lesion length. The baseline LCBI was not associated with culprit lesion-related MACE either as a continuous variable, when analyzed in tertiles of maxLCBI$_{4mm}$ (**Figure 3**) or by receiver-operating characteristic curve analysis (**Figure 4**). Multivariable Cox proportional hazard models to predict culprit lesion-related MACE at 30 days, between 31 days to 2 years, and overall through 2 years demonstrated an almost neutral effect of maxLCBI$_{4mm}$ (**Table 5**, Supplemental Table 3). Lesion length and in-stent restenosis lesion were predictive of long-term adverse events. Using the same covariates but assessing individual endpoints as well as maxLCBI$_{4mm}$, maxLCBI$_{10mm}$, and lesion LCBI (**Table 6**, Supplemental Table 4), there were no associations between NIRS LRP measures and culprit lesion-related MACE, cardiac death, MI, stent thrombosis, revascularization, or rehospitalization.

DISCUSSION

The major results from the present PCI cohort of the large-scale multicenter COLOR registry are: 1) there was no association between the presence or severity

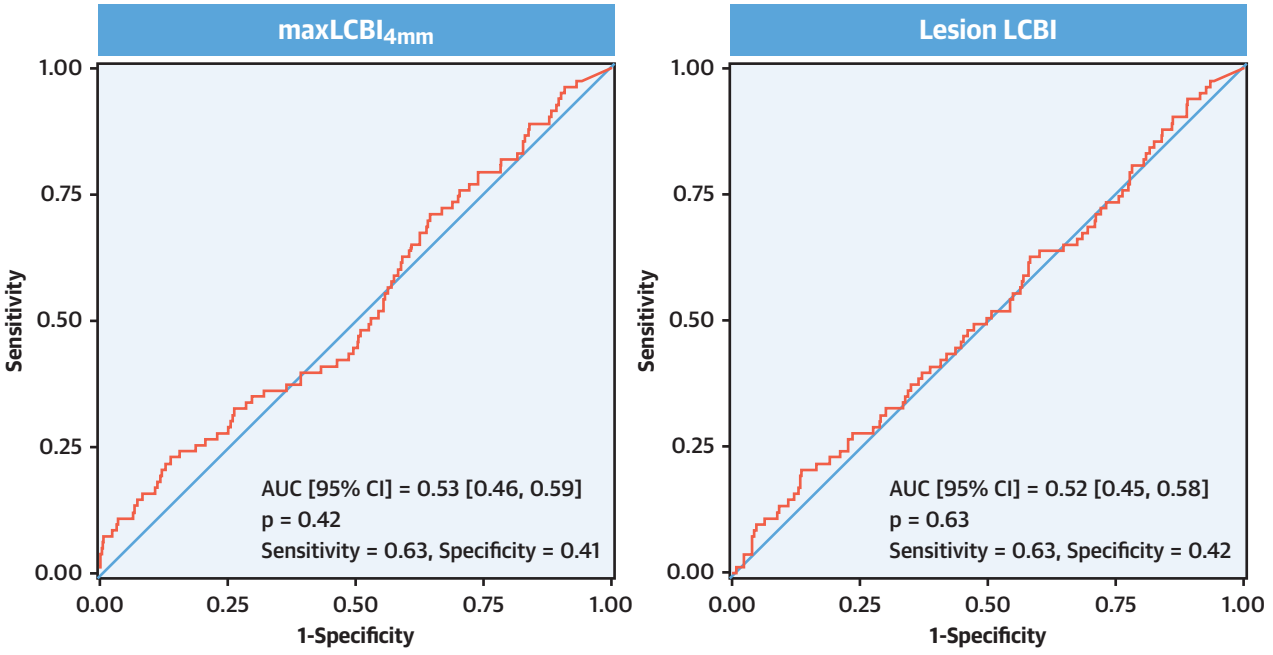
FIGURE 3 Kaplan-Meier Curves for 2-Year Culprit Lesion-Related Major Adverse Cardiac Events Stratified by Tertile of maxLCBI4$_{mm}$ in Culprit Lesions



(A) Major adverse cardiac events (MACE); **(B)** revascularization.

of culprit lesion LRP as assessed by pre-PCI NIRS and subsequent 2-year culprit lesion-related events (**Central Illustration**); and 2) MACE within 2 years of DES implantation occurred in 18.0% of patients. Nonculprit lesion-related events (10.7%) were slightly more common than culprit lesion-related events post-PCI (8.3%). Thus, with contemporary PCI devices and techniques, stenting a NIRS-detected LRP did not

FIGURE 4 Receiver-Operating Characteristics of MaxLCBI$_{4mm}$ and Total Lesion LCBI to Discriminate the Occurrence of 2-Year Culprit-Lesion-Related Major Adverse Cardiac Events



AUC = area under the curve; CI = confidence interval; LCBI = lipid core burden index.

increase adverse outcomes compared with a plaque that did not contain a LRP.

Prior studies of NIRS, optical coherence tomography, and IVUS have shown that STEMI culprit lesions have larger lipid burden compared with non-STEMI or stable patients, and culprit lesions in patients with acute coronary syndromes have a larger lipid burden compared to nonculprit lesions (13–15). Moreover, several NIRS studies reported a relationship between the presence of LRP in nonculprit segments and future patient-level events (16–19). In the recent Lipid-Rich Plaque study, in which 5,743 30-mm length nonculprit segments in 1,271 patients were imaged by NIRS, the presence and severity of LRP predicted nonculprit lesion-related MACE (cardiac death/arrest, MI, acute coronary syndromes, revascularization, rehospitalization for progressive angina with >20% stenosis progression) during 2-year follow-up. MaxLCBI$_{4mm}$ >400 was associated with an 89% increase in MACE (HR: 1.89; 95% CI: 1.26 to 2.83) at the

TABLE 5 Multivariable Cox Proportional Hazard Model to Predict 2-Year Culprit Lesion-Related Major Adverse Cardiac Events

	Hazard Ratio (95% CI)	Adjusted p Value
MaxLCBI$_{4mm}$, per 100	1.06 (0.96–1.17)	0.28
Lesion length, per 10 mm	1.25 (1.08–1.45)	0.003
Reference vessel diameter, mm	0.68 (0.44–1.04)	0.07
Calcification moderate/severe	1.32 (0.74–2.34)	0.34
In-stent restenosis lesion	1.47 (0.87–2.47)	0.15
Second-generation drug-eluting stent	0.75 (0.43–1.31)	0.31
Diabetes mellitus	1.36 (0.87–2.13)	0.18
STEMI or NSTEMI presentation	0.89 (0.43–1.84)	0.76

CI = confidence interval; LCBI = lipid core burden index; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

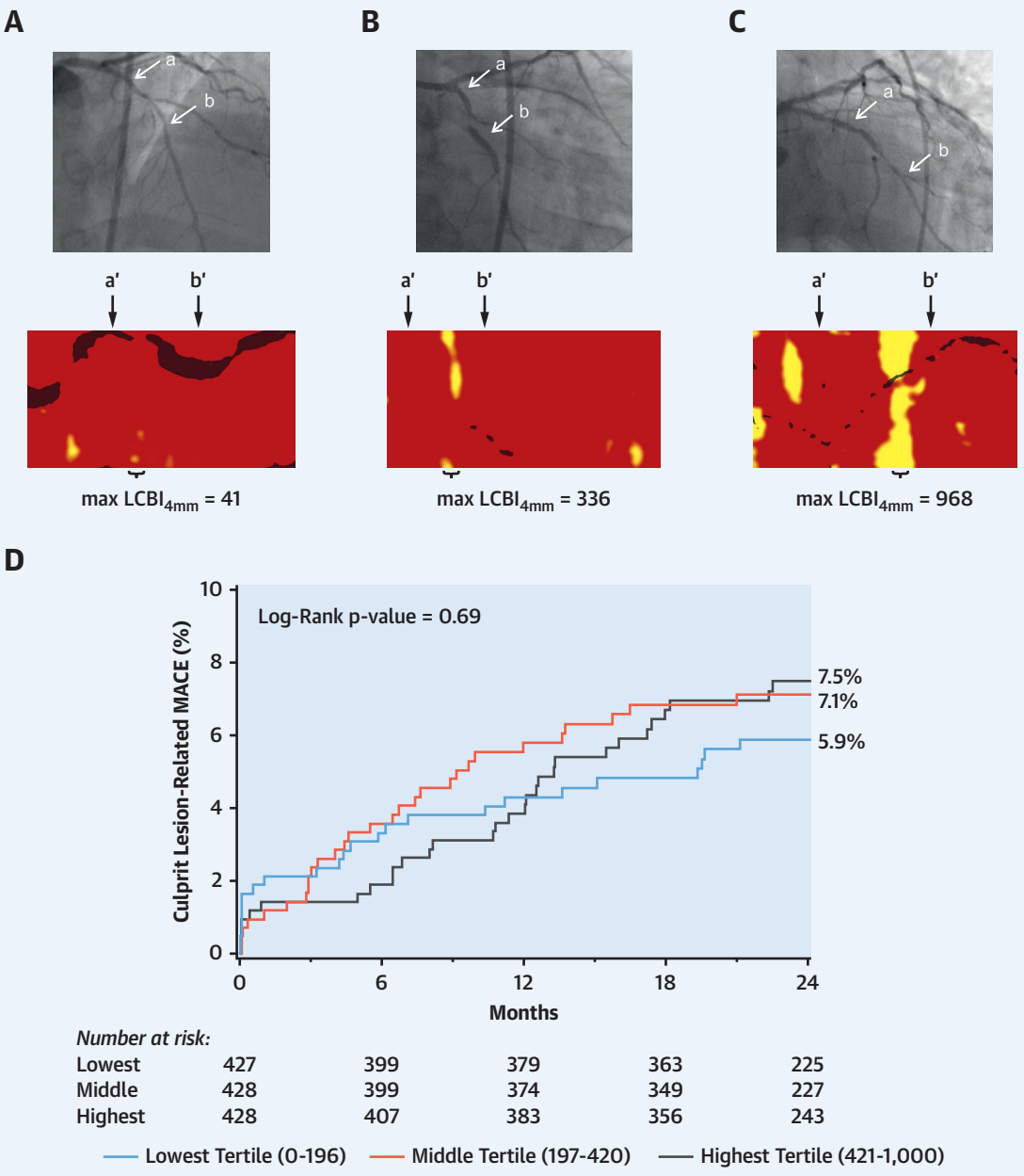
TABLE 6 Prediction of maxLCBI$_{4mm}$ for 2-Year Culprit Lesion-Related Major Adverse Cardiac Events in Multivariable Cox Proportional Hazard Models

	Hazard Ratio (95% CI)	Adjusted p Value
Major adverse cardiac events	1.06 (0.96–1.17)	0.28
Cardiac death	1.08 (0.58–2.03)	0.81
Myocardial infarction	1.00 (0.80–1.24)	0.98
Definite/probable stent thrombosis	1.28 (0.86–1.90)	0.22
Revascularization	1.09 (0.97–1.22)	0.16
Re-hospitalization	1.06 (0.96–1.18)	0.25

Adjusted covariates were same as in Table 5.
Abbreviations as in Table 5.

CENTRAL ILLUSTRATION **Representative Pre-Intervention Near-Infrared Spectroscopy of Lesions in the Lowest, Middle, and Highest Tertiles of MaxLCBI$_{4mm}$**

Baseline Max LCBI$_{4mm}$ was Not Associated with Culprit Lesion-Related MACE



Yamamoto, M.H. et al. J Am Coll Cardiol. 2020;75(12):1371-82.

(A) Lowest, **(B)** middle, and **(C)** highest tertiles of MaxLCBI$_{4mm}$. Each near-infrared spectroscopy segment (between **a** and **b**) shows the lipid distribution corresponding to the angiographic segment (between **a** and **b**). **(D)** Culprit-lesion-related MACE were not different among lesions with lowest, middle, and highest tertiles of maxLCBI$_{4mm}$. maxLCBI$_{4mm}$ = maximum lipid core burden index in 4-mm segment.

patient level and 339% increase in MACE (HR: 3.39; 95% CI: 1.85 to 6.20) at the lesion level (16).

In contrast to these results in nonculprit lesions, prior to the present study, few data have been reported on the risk associated with LRP and consequent PCI complications or long-term outcomes. In autopsy case report studies, treatment of lesions with a large necrotic core and a ruptured fibrous cap in acute MI with first-generation DES was associated with delayed arterial healing and increased late stent thrombosis (2). Small studies suggested an association between the presence of LRP and PCI complications (12,20,21), but no data was available on the long-term risks after PCI of an LRP lesion. The current COLOR registry is the largest study to evaluate outcomes after stenting LRP-containing coronary lesions. We found no differences in the short- or long-term culprit lesion-related outcomes after stenting LRP compared with non-LRP lesions. These findings suggest that DES treatment of LRP should not be withheld in LRP based solely on this morphological consideration.

In the current COLOR registry, the 2-year rate of culprit-lesion-related MACE was lower than in the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study (8.3% vs. 11.4%) (10). Acknowledging the uncertainties in cross-study comparisons, this difference may be related to 2 factors. First, a majority of patients in the COLOR registry had stable coronary artery disease, whereas all patients in PROSPECT presented with acute coronary syndromes. Second, COLOR enrolled patients a decade after PROSPECT, and ~80% of COLOR patients were treated with second-generation DES. Similar findings were recently reported from the Lipid-Rich Plaque study (9% 2-year culprit lesion-related MACE rate) (16). Conversely, nonculprit-related MACE at 2 years occurred with similar or greater frequency in COLOR (10.7%) than PROSPECT (9.4%).

STUDY LIMITATIONS. First, although the protocol allowed for enrollment of any patient, potential selection bias was possible especially because timing of NIRS assessment (pre- or post-PCI) was left to the operator's discretion. Second, operators were not blinded to NIRS/IVUS imaging, which may have affected treatment strategy. Third, imaging was not done routinely post-PCI. Finally, despite multivariable adjustment, we cannot rule out the presence of unmeasured confounders. In this cohort, a positive troponin at the time of clinical presentation was seen in 12.2%. Because acute coronary syndrome is associated with ischemic events at follow-up compared with stable coronary artery disease, we may underestimate the impact of LRP on the outcome.

CONCLUSIONS

In the present large-scale, multicenter registry, stent implantation in NIRS-defined LRPs was not associated with increased periprocedural or late adverse outcomes compared with stenting of lesions without significant lipid. Following PCI with contemporary DES, nonculprit lesion-related events were slightly more common during 2-year follow-up than culprit lesion-related events. Complications from NIRS imaging occurred in 9 patients (0.45%), which resulted in 1 periprocedural MI and 1 emergent coronary bypass grafting.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Stent implantation in lipid-rich coronary plaques is not associated with more adverse peri-procedural or later outcomes compared with stenting of nonrich lesions.

TRANSLATIONAL OUTLOOK: Further studies are needed to fully assess the safety and efficacy of various methods for stenting lipid-rich coronary plaques.

REFERENCES

1. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. J Am Coll Cardiol 2006;47:C13-8.

2. 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.

3. Bangalore S, Amoroso N, Fusaro M, Kumar S, Feit F. Outcomes with various drug-eluting or bare metal stents in patients with ST-segment-elevation myocardial infarction: a mixed treatment comparison analysis of trial level data from 34 068 patient-years of follow-up from randomized trials. Circ Cardiovasc Interv 2013;6:378-90.

4. Raber L, Kelbaek H, Ostojic M, et al. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction:

the COMFORTABLE AMI randomized trial. JAMA 2012;308:777–87.

5. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002;346:957–66.

6. 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.

7. 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. J Am Coll Cardiol Img 2008;1:638–48.

8. Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). J Am Coll Cardiol 2013;62:1563–70.

9. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

10. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.

11. Popma J, Almonacid A. Qualitative and quantitative coronary angiography. In: Topol EJ, Teirstein P, editors. Textbook of Interventional Cardiology. 6th edition. Philadelphia, PA: Saunders, 2011:757–75.

12. Stone GW, Maehara A, Muller JE, et al. Plaque characterization to inform the prediction and prevention of periprocedural myocardial infarction during percutaneous coronary intervention: the CANARY trial (Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow). J Am Coll Cardiol Intv 2015;8:927–36.

13. Dong L, Mintz GS, Witzenbichler B, et al. Comparison of plaque characteristics in narrowings with ST-elevation myocardial infarction (STEMI), non-STEMI/unstable angina pectoris and stable coronary artery disease (from the ADAPT-DES IVUS Substudy). Am J Cardiol 2015;115:860–6.

14. Kato K, Yonetsu T, Kim SJ, et al. Nonculprit plaques in patients with acute coronary syndromes have more vulnerable features compared with those with non-acute coronary syndromes: a 3-vessel optical coherence tomography study. Circ Cardiovasc Imaging 2012;5:433–40.

15. Madder RD, Puri R, Muller JE, et al. Confirmation of the intracoronary near-infrared spectroscopy threshold of lipid-rich plaques that underlie ST-segment-elevation myocardial infarction. Arterioscler Thromb Vasc Biol 2016;36:1010–5.

16. 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.

17. Madder RD, Husaini M, Davis AT, et al. Large lipid-rich coronary plaques detected by near-infrared spectroscopy at non-stented sites in the target artery identify patients likely to experience future major adverse cardiovascular events. Eur Heart J Cardiovasc Imaging 2016;17:393–9.

18. Danek BA, Karatasakis A, Karacsonyi J, et al. Long-term follow-up after near-infrared spectroscopy coronary imaging: Insights from the lipid cORe plaque association with CLinical events (ORACLE-NIRS) registry. Cardiovasc Revasc Med 2017;18:177–81.

19. Schuurman AS, Vroegindewey M, Kardys I, et al. Near-infrared spectroscopy-derived lipid core burden index predicts adverse cardiovascular outcome in patients with coronary artery disease during long-term follow-up. Eur Heart J 2018;39:295–302.

20. 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.

21. Brilakis ES, Abdel-Karim AR, Papayannis AC, et al. Embolic protection device utilization during stenting of native coronary artery lesions with large lipid core plaques as detected by near-infrared spectroscopy. Catheter Cardiovasc Interv 2012;80:1157–62.

KEY WORDS intravascular ultrasound, lipid-rich plaque, near-infrared spectroscopy, stent

APPENDIX For supplemental tables and figures, please see the online version of this paper.