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Clinical Significance of Lipid-Rich Plaque Detected by Optical Coherence Tomography

A 4-Year Follow-Up Study

Lei Xing, MD, PhD,[a,b] Takumi Higuma, MD, PhD,[b] Zhao Wang, PhD,[c] Aaron D. Aguirre, MD, PhD,[b] Kyoichi Mizuno, MD, PhD,[d] Masamichi Takano, MD, PhD,[e] Harold L. Dauerman, MD,[f] Seung-Jung Park, MD, PhD,[g] Yangsoo Jang, MD, PhD,[h] Chong-Jin Kim, MD, PhD,[i] Soo-Joong Kim, MD, PhD,[i] So-Yeon Choi, MD, PhD,[j] Tomonori Itoh, MD, PhD,[k] Shiro Uemura, MD, PhD,[l] Harry Lowe, MD, PhD,[m] Darren L. Walters, MD, PhD,[n] Peter Barlis, MD, PhD,[o] Stephen Lee, MD, PhD,[p] Amir Lerman, MD,[q] Catalin Toma, MD,[r] Jack Wei Chieh Tan, MD,[s] Erika Yamamoto, MD, PhD,[b] Krzysztof Bryniarski, MB,[b] Jiannan Dai, MB,[b] Thomas Zanchin, MD,[b] Shaosong Zhang, MD, PhD,[a] Bo Yu, MD, PhD,[a] Hang Lee, PhD,[t] James Fujimoto, PhD,[c] Valentin Fuster, MD, PhD,[u] Ik-Kyung Jang, MD, PhD[b,i]

ABSTRACT

BACKGROUND Lipid-rich plaque (LRP) is thought to be a precursor to cardiac events. However, its clinical significance in coronary arteries has never been systematically investigated.

OBJECTIVES This study investigated the prevalence and clinical significance of LRP in the nonculprit region of the target vessel in patients undergoing percutaneous coronary intervention (PCI).

METHODS The study included 1,474 patients from 20 sites across 6 countries undergoing PCI, who had optical coherence tomography (OCT) imaging of the target vessel. Major adverse cardiac events (MACE) were defined as a composite of cardiac death, acute myocardial infarction, and ischemia-driven revascularization. Patients were followed for up to 4 years (median of 2 years).

RESULTS Lipid-rich plaque was detected in nonculprit regions of the target vessel in 33.6% of patients. The cumulative rate of nonculprit lesion-related MACE (NC-MACE) over 48 months in patients with LRP was higher than in those without LRP (7.2% vs. 2.6%, respectively; $p = 0.033$). Acute coronary syndrome at index presentation (risk ratio: 2.538; 95% confidence interval [CI]: 1.246 to 5.173; $p = 0.010$), interruption of statin use ≥1 year (risk ratio: 4.517; 95% CI: 1.923 to 10.610; $p = 0.001$), and LRP in nonculprit regions (risk ratio: 2.061; 95% CI: 1.050 to 4.044; $p = 0.036$) were independently associated with increased NC-MACE. Optical coherence tomography findings revealed that LRP in patients with NC-MACE had longer lipid lengths ($p < 0.001$), wider maximal lipid arcs ($p = 0.023$), and smaller minimal lumen areas ($p = 0.003$) than LRPs in patients without MACE.

CONCLUSIONS Presence of LRP in the nonculprit regions of the target vessel by OCT predicts increased risk for future NC-MACE, which is primarily driven by revascularization for recurrent ischemia. Lipid-rich plaque with longer lipid length, wider lipid arc, and higher degree of stenosis identified patients at higher risk of future cardiac events. (The Massachusetts General Hospital Optical Coherence Tomography Registry; NCT01110538)
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From the [a]Department of Cardiology, the Second Affiliated Hospital of Harbin Medical University, and the Key Laboratory of Myocardial Ischemia, Chinese Ministry of Education, Harbin, China; [b]Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [c]The Research Laboratory of Electronics, Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Cambridge, Massachusetts; [d]Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan; [e]Division of Cardiology, Nippon Medical School Chiba-Hokusoh Hospital, Chiba, Japan; [f]Department of Medicine, University of Vermont College of Medicine, Burlington, Vermont; [g]Department of Cardiology,

Despite advances in pharmacological therapy and percutaneous coronary intervention (PCI), recurrent major adverse cardiac events (MACE) still occur in patients with coronary artery disease (1,2). Lipid-rich plaque (LRP) is thought to be responsible for most cases of MACE (3). In recent years, research has been focused on the detection of LRP, under the premise that local treatment of LRP may prevent future MACE. However, the clinical significance and natural history of LRP have not been systematically investigated. Optical coherence tomography (OCT) is a promising intravascular imaging modality used to detect LRP. The aim of this study was to investigate the prevalence and clinical significance of LRP in the nonculprit regions of the target vessel in patients undergoing PCI and to determine morphological characteristics of LRP-related MACE during 4 years of follow-up.

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METHODS

STUDY POPULATION. Study patients were retrospectively selected from the Massachusetts General Hospital (MGH) OCT Registry (NCT01110538), which is an international multicenter registry of patients who have underwent OCT of the coronary arteries, and involves 20 sites across 6 countries. The registry was approved by the institutional review board at each participating site. Written informed consent was obtained from all patients before enrollment. Patients were followed longitudinally for up to 4 years.

From August 2010 to May 2015, the MGH OCT registry enrolled 2,714 patients. Among them, we identified 2,084 patients who had at least 1 year of follow-up. Of those patients, 588 patients were excluded because of incomplete imaging of the nonculprit regions. An additional 22 patients were excluded because of poor image quality. Finally, 1,474 patients were included in the analysis (**Figure 1**). For this study, all patients had OCT imaging performed in the nonculprit regions of the target vessel (Online Figure 1). The patients were followed annually, with a median follow-up period of 24 months. The primary outcome measurement was MACE, which was defined as a composite of cardiac death; acute myocardial infarction (AMI), defined as ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction by American College of Cardiology/American Heart Association guidelines (4); and ischemia-driven revascularization. Ischemia-driven revascularization was defined as a repeat PCI or bypass surgery of the lesions with either: AMI, unstable angina, stable angina, or documented silent ischemia. On the basis of follow-up angiography, MACE was further adjudicated as culprit (previous PCI site) lesion-related MACE and lesion-related nonculprit-MACE (NC-MACE) (previously untreated segment in any 1 of 3 coronary arteries). If follow-up angiography was not performed, the site associated with the event was classified as indeterminate. Culprit lesion-related, NC-, or indeterminate MACE, whichever occurred first in the patient, was set as the endpoint. More than 1 event recorded for the same patient at the same time point was attributed as 1 composite cardiac event for further statistical analysis.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AMI = acute myocardial infarction

LRP = lipid-rich plaque

MACE = major adverse cardiac event(s)

NC-MACE = nonculprit lesion-related major adverse cardiac events

OCT = optical coherence tomography

PCI = percutaneous coronary intervention

Heart Institute, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [h]Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [i]Division of Cardiology, Department of Internal Medicine, KyungHee University Hospital, Seoul, Republic of Korea; [j]Department of Cardiology, Ajou University School of Medicine, Suwon, Republic of Korea; [k]Division of Cardiology, Department of Internal Medicine, Iwate Medical University School of Medicine, Morioka, Japan; [l]Department of Cardiology, Kawasaki Medical School, Matsushima, Japan; [m]Cardiology Department, Concord Repatriation General Hospital, University of Sydney, Sydney, New South Wales, Australia; [n]Department of Cardiology, Prince Charles Hospital, University of Queensland, Brisbane, Queensland, Australia; [o]Cardiology Department, Northern Hospital and Department of Medicine, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville, Victoria, Australia; [p]Department of Medicine, Queen Mary Hospital, Hong Kong University, Hong Kong, China; [q]Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic and College of Medicine, Rochester, Minnesota; [r]Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [s]Department of Cardiology, National Heart Centre Singapore, Singapore; [t]Biostatistics Center, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; and the [u]Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York. Dr. Jang is supported by Mr. and Mrs. Michael and Kathryn Park and by Mrs. and Mr. Gill and Allan Gray. Dr. Aguirre is supported by American Heart Association grant 14FTF20380185. Mr. Fujimoto is supported by National Institutes of Health grant R01-CA075289-18; and holds royalties from IP owned by MIT and licensed to St. Jude Medical. Dr. Ik-Kyung Jang has received grants and consulting fees from St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Deepak L. Bhatt, MD, MPH, served as Guest Editor-in-Chief for this paper.

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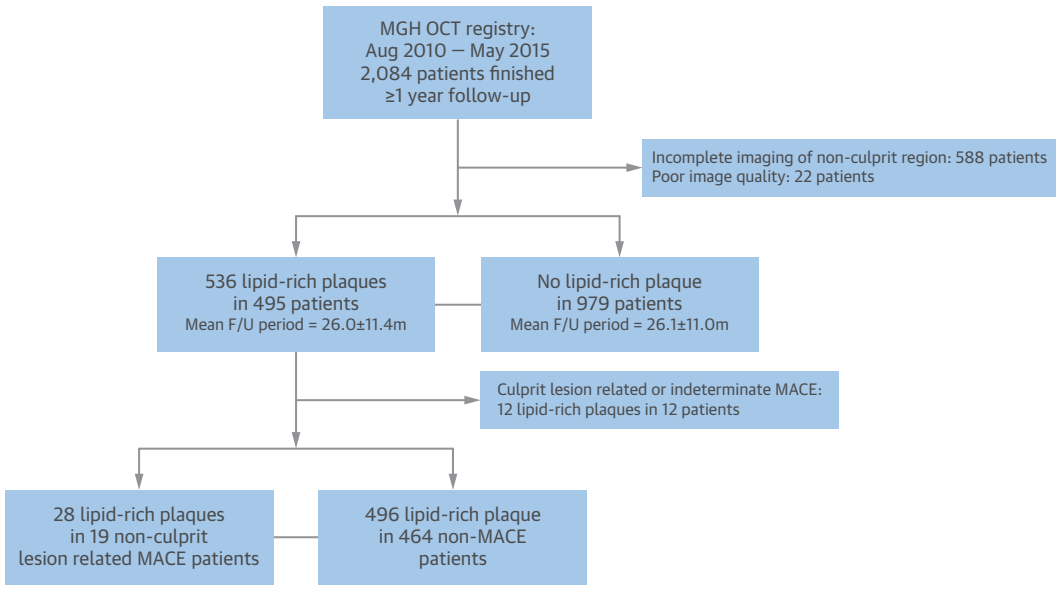
FIGURE 1 Study Group



F/U = follow-up; MACE = major adverse cardiac event; MGH = Massachusetts General Hospital; OCT = optical coherence tomography.

ANGIOGRAPHY AND OCT IMAGE ACQUISITION AND ANALYSIS. Angiography was performed at baseline in patients, followed by post-PCI or stent follow-up OCT. A target vessel was identified on the basis of electrocardiographic changes, left ventricular wall motion abnormalities, nuclear scan, stress test, or angiographic findings. If a patient underwent scheduled follow-up catheterization, the vessel in which a stent had been previously implanted was chosen as the target vessel. The nonculprit lesion was defined as a plaque with stenotic diameter of >30% on angiography and at least 5 mm away from the stent edges.

A frequency-domain OCT system (model C7-XR OCT, Intravascular Imaging System and ILUMIEN OCT Intravascular Imaging Systems, St. Jude Medical, St. Paul, Minnesota) was used in 64.5% of patients, and a time-domain OCT system (model M2/M3, Cardiology Imaging System, LightLab Imaging Inc., Westford, Massachusetts) was used in 35.5% of patients on the basis of available technology at the time of imaging. The technique of intracoronary OCT imaging has been previously described (5,6). All images were digitally stored, deidentified, relabeled, and submitted to the MGH (Boston, Massachusetts) for analysis. Optical coherence tomography images were analyzed by using offline analysis software at the MGH OCT core laboratory. Patients whose angiographic plaque was not imaged by OCT or those who had <50 mm of OCT scanning length were excluded on the basis of incomplete imaging. All OCT images included in the analysis were performed post PCI. Nonculprit plaque should be at least 5 mm from stent edges.

Plaques in the nonculprit regions of the target vessel were analyzed using previously established criteria. Lipid plaque was identified as a low-signal region with a diffuse border. Nonculprit LRP was defined as lipid plaque that was not related to the index event and had lipid arc of >1 quadrant assessed by OCT. Lipid length and lipid arc were measured on the longitudinal reconstructed view and the cross-sectional image, respectively. Fibrous cap thickness was measured 3 times at the thinnest part, and the average value was calculated. Lipid index was defined as the product of mean lipid arc multiplied by lipid length. The reference was defined as the mean of the most normal appearing segments 5 mm proximal and distal to the lesion shoulders by OCT. Percentage of area stenosis was calculated as follows:

$$\text{Percentage area stenosis} = \left(1 - \frac{\text{minimal lumen area}}{\text{mean of proximal and distal reference area}}\right) \times 100\%$$

Other criteria for qualitative OCT analysis are provided in the Online Appendix. All OCT images were analyzed by 2 independent investigators who were blinded to patient information. When there was

discordance between the readers, a consensus reading was obtained from a third independent investigator.

STATISTICAL METHODS. Continuous variables were compared by using Student *t*-test or Mann-Whitney *U* test for comparisons among independent groups, according to the data distribution. Categorical variables were reported as counts (%) and compared by using the Fisher exact test or chi-square test, according to the data distribution. The mean ± SD was reported for normally distributed data. The generalized estimating equations approach was applied to take into account the within-subject correlation due to multiple plaques within a single patient.

The composite cardiac event-free data over the entire 48 months of follow-up were presented as Kaplan-Meier estimates. The OCT-detected LRP and clinical variables at index admission were selected as independent variables for conditional logistic regression analysis. Predictors associated with all MACE and NC-MACE from baseline to the 12-, 24-, 36- and 48-month follow-ups were determined by means of a conditional logistic regression model in order to take into account the site-to-site variation of the event rates and potential within-site aggregation of the cardiac events. Receiver operating curve (ROC) analyses were performed to determine whether the OCT-derived LRP characteristics were predictive of NC-MACE. Statistical significance was defined as a p value of < 0.05. Statistical analyses were performed using SAS version 9.1 software (SAS institute, Cary, North Carolina).

RESULTS

STUDY POPULATION. Among 1,474 patients, 536 LRPs were detected in 495 patients (33.6%) in nonculprit regions of the target vessel (Figure 1). Patients were divided into 2 groups: those with LRP in nonculprit regions (LRP group) and those without (non-LRP group). Baseline demographic, clinical, and laboratory findings are shown in Table 1. The mean follow-up periods were similar between the 2 groups. Male patients, diabetes mellitus, and current smoking were more frequent in the LRP group. Lipid-rich plaque patients had higher levels of low-density lipoprotein and high-sensitivity C-reactive protein.

OCT FINDINGS AT INDEX. There were no differences in vessels imaged. In the LRP group, there were 49.1% in the left anterior descending artery (LAD), 13.5% in the left circumflex artery (LCX), and 37.4% in the right coronary artery (RCA) compared with the non-LRP group, in which there were 52.4% in the LAD, 15.9% in the LCX, and 31.7% in the RCA ($p = 0.067$) or the length of the segment imaged by OCT (76.5 ± 24.6 mm vs. 77.2 ± 25.1 mm, respectively; $p = 0.615$) between the LRP and non-LRP groups at index. Of the LRPs found, 47.6% were in the LAD, 12.7% in the LCX, and 39.7% in the RCA. The distribution in location of the vessels was 34.0% in the proximal segment, 30.0% in the middle segment, and 36.0% in the distal segment (Online Table 1).

TABLE 1 Baseline Characteristics

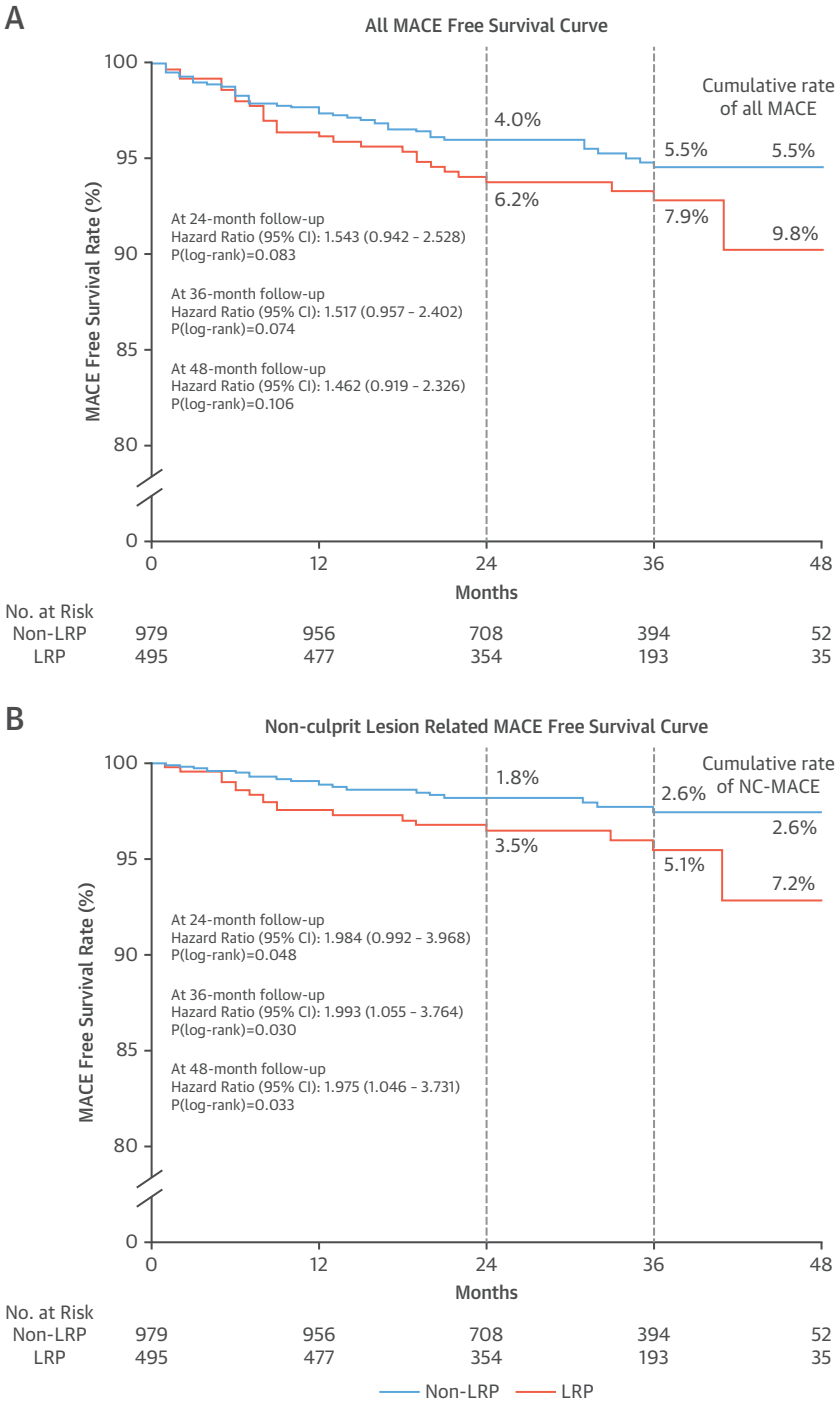
	LRP Group (n = 495)	Non-LRP Group (n = 979)	Standardized Mean Difference	p Value
Follow-up period, months	26.0 ± 11.4	26.1 ± 11.0	0.002	0.817
Age, yrs	61.6 ± 11.1	61.3 ± 11.4	0.028	0.611
Male	395 (79.8)	735 (75.1)	0.112	0.043
Body mass index, kg/m^2	26.0 ± 5.4	25.6 ± 4.2	0.097	0.143
Hypertension	317 (64.0)	636 (65.0)	0.019	0.726
Dyslipidemia	363 (73.3)	718 (73.3)	0.000	0.998
Diabetes mellitus	263 (53.1)	464 (47.4)	0.115	0.037
Current smoker	284 (57.4)	501 (51.2)	0.124	0.024
Family history of CAD	52 (10.5)	90 (9.2)	0.047	0.420
Prior myocardial infarction	140 (28.3)	255 (26.0)	0.050	0.360
Prior stent	263 (53.1)	505 (51.6)	0.031	0.574
Prior CABG	10 (2.0)	12 (1.2)	0.072	0.235
Chronic kidney disease	24 (4.8)	52 (5.3)	0.021	0.704
Index clinical presentation				
Acute coronary syndrome	188 (38.0)	396 (40.4)	0.051	0.360
STEMI	37 (19.7)	67 (16.9)		
NSTEMI	35 (18.6)	40 (10.1)		
Unstable angina	116 (61.7)	286 (73.0)		
Laboratory data				
Total cholesterol, mg/dl	168.2 ± 45.2	165.0 ± 44.4	0.072	0.217
Low-density lipoprotein, mg/dl	97.5 ± 38.9	93.2 ± 36.1	0.116	0.046
High-density lipoprotein, mg/dl	44.0 ± 15.1	45.5 ± 15.5	0.098	0.087
Triglyceride, mg/dl	145.8 ± 98.1	149.1 ± 111.7	0.031	0.596
hs-CRP, mg/l	1.0 (0.7-3.0)	1.0 (0.2-3.0)	0.106	0.033
Medication at discharge				
Aspirin	488 (98.6)	970 (99.1)	0.047	0.387
Dual antiplatelet therapy	437 (88.3)	866 (88.5)	0.005	0.921
Statin	467 (94.3)	934 (95.4)	0.050	0.376
Beta-blocker	337 (68.1)	637 (65.1)	0.063	0.248
ACEI/ARB	264 (53.3)	485 (49.5)	0.076	0.169

Values are mean ± SD, n (%), or median (interquartile range).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass graft; CAD = coronary artery disease; hs-CRP = high-sensitivity C-reactive protein; LRP = lipid-rich plaque; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

PROGNOSTIC SIGNIFICANCE OF LRP. Kaplan-Meier analysis showed that there were no significant differences between the cumulative rate of all MACE in the LRP group and that in the non-LRP group at 48 months of follow-up (hazard ratio [HR]: 1.462; 95% confidence interval [CI]: 0.919 to 2.326; $p = 0.106$) (Figure 2A). However, the cumulative rate of NC-MACE was significantly higher in the LRP group than in the non-LRP group at 48 months

FIGURE 2 All MACE and NC-MACE Free Curves



All MACE **(A)** and NC-MACE **(B)** free curves on the basis of the presence or absence of LRP in nonculprit regions in target vessel are shown. There were no differences in cumulative rates of all MACE at 24-, 36-, or 48-month follow-up between the groups. The cumulative rates of NC-MACE were higher in the LRP group than in the non-LRP group at the 24-month ($p = 0.048$), 36-month ($p = 0.030$), and 48-month ($p = 0.033$) follow-up examinations. CI = confidence interval; LRP = lipid-rich plaque; NC-MACE = nonculprit lesion-related major adverse cardiac event; other abbreviations as in Figure 1.

TABLE 2 Kaplan-Meier Estimates for Cumulative Number (Rate) of MACE

	All Events	Culprit Lesion-Related	Nonculprit Lesion-Related	Undetermined	LRP Group (n = 495)	Non-LRP Group (n = 979)	p Value (Log-Rank) (LRP Vs. Non-LRP)
Cardiac death	5 (0.4)	1 (0.1)	0 (0.0)	4 (0.3)	1 (0.3)	4 (0.4)	0.532
Acute myocardial infarction	21 (1.8)	11 (1.0)	9 (0.7)	1 (0.1)	8 (2.1)	13 (1.6)	0.653
STEMI	7 (0.6)	4 (0.4)	2 (0.2)	1 (0.1)	1 (0.3)	6 (0.7)	
NSTEMI	14 (1.2)	7 (0.6)	7 (0.6)	0 (0.0)	7 (1.9)	7 (0.9)	
Ischemia-driven revascularization	66 (6.5)	28 (2.4)	38 (4.3)	0 (0.0)	30 (9.3)	36 (4.7)	0.046
Composite cardiac events	74 (7.1)	31 (2.6)*	38 (4.3)	5 (0.3)	31 (9.8)	43 (5.5)	0.106

Values are n (%). *Of the 31 culprit lesion-related MACE, 24 were in-stent restenosis, which was treated with repeat revascularizations. The other 7 were stent thrombosis cases: 4 were treated with repeat stent implantation and 3 by aspiration thrombectomy and balloon dilation.

MACE = major adverse cardiac event(s); other abbreviations as in Table 1.

(HR: 1.975; 95% CI: 1.046 to 3.731; p = 0.033) (Figure 2B). Estimations of the cumulative number and rate of individual MACE were done by Kaplan-Meier analysis (Table 2). The composite event rate was 7.1% for the whole group (culprit lesion-related MACE rate of 2.6%; NC-MACE rate of 4.3%; and undetermined rate of 0.3%). Of 74 instances of MACE, 66 (89.2%) were related to ischemia-driven revascularization compared with 5 (6.8%) cardiac deaths and 21 (28.4%) AMIs. Among 21 AMIs, 18 patients underwent revascularization, but were counted as 1 composite cardiac event for analysis. The LRP group had higher cumulative rates of ischemia-driven revascularization compared with the non-LRP group in individual MACE (p = 0.046).

The conditional logistic regression analyses revealed that family history of coronary artery disease and interruption of statin therapy ≥1 year were independently associated with all MACE in every follow-up period in the patients (all $p < 0.05$). Acute coronary syndrome (ACS) at index presentation was independently associated with all MACE only in the 12- and 24-month follow-up periods (both $p < 0.05$). Acute coronary syndrome at index presentation, interruption of statin use ≥1 year, and LRP on index imaging in nonculprit regions of the target vessel were independently associated with NC-MACE (all $p < 0.05$) (Table 3). There was no statistical significance for other variables in conditional logistic regression analyses in all MACE or in NC-MACE, which is shown in Online Tables 2 and 3.

COMPARISON BETWEEN NC-MACE AND NON-MACE GROUPS. During the follow-up period, 19 of 483

TABLE 3 Conditional Logistic Regression Analyses of All MACE and NC-MACE

		All MACE			NC-MACE		
	Follow-Up Periods	RR	95% CI	p Value	RR	95% CI	p Value
Family history of CAD	12 months	2.485	1.173–5.265	0.018			
	24 months	2.551	1.341–4.854	0.004			
	36 months	2.419	1.311–4.465	0.005			
	48 months	2.400	1.301–4.426	0.005			
ACS at index presentation	12 months	2.541	1.333–4.843	0.005	5.304	2.010–13.996	0.001
	24 months	1.475	1.066–2.514	0.035	2.528	1.181–5.410	0.017
	36 months	1.537	0.965–2.554	0.058	2.447	1.192–5.024	0.015
	48 months	1.579	0.953–2.616	0.076	2.538	1.246–5.173	0.010
Interruption of statin therapy ≥1 yr	12 months	3.002	1.224–7.363	0.016	3.450	1.054–11.293	0.041
	24 months	3.013	1.410–6.439	0.004	3.466	1.304–9.215	0.013
	36 months	3.566	1.779–7.150	<0.001	4.744	2.014–11.179	<0.001
	48 months	3.459	1.728–6.924	0.001	4.517	1.923–10.610	0.001
LRP at index imaging	12 months				2.250	1.064–5.308	0.034
	24 months				2.021	1.003–4.155	0.046
	36 months				2.182	1.005–4.737	0.049
	48 months				2.061	1.050–4.044	0.036

ACS = acute coronary syndrome; CI = confidence interval; NC-MACE = nonculprit lesion-related major adverse cardiac events; RR = risk ratio; other abbreviations as in Tables 1 and 2.

TABLE 4 Comparison of Baseline Characteristics Between NC-MACE and Non-MACE Groups

	NC-MACE Group (n = 19)	Non-MACE Group (n = 464)	Standardized Mean Difference	p Value
Age, yrs	61.0 ± 16.1	61.7 ± 10.9	0.058	0.871
Male	15 (78.9)	370 (79.7)	0.020	>0.999
Body mass index, kg/m^2	27.8 ± 6.6	26.0 ± 5.3	0.351	0.147
Hypertension	13 (68.4)	295 (63.6)	0.100	0.809
Dyslipidemia	17 (73.7)	339 (73.1)	0.014	>0.999
Diabetes mellitus	10 (52.6)	245 (52.8)	0.003	>0.999
Current smoker	11 (57.9)	267 (57.5)	0.007	>0.999
Family history of CAD	3 (15.8)	47 (10.1)	0.194	0.433
Prior myocardial infarction	6 (31.6)	132 (28.4)	0.069	0.797
Prior stent	9 (47.4)	246 (53.0)	0.113	0.647
Prior CABG	0 (0.0)	9 (1.9)	0.167	>0.999
Chronic kidney disease	3 (15.8)	21 (4.1)	0.505	0.062
Index clinical presentation				
Acute coronary syndrome	12 (63.2)	171 (36.9)	0.547	0.028
STEMI	1 (8.3)	35 (20.5)		
NSTEMI	5 (41.7)	29 (16.9)		
Unstable angina	6 (50.0)	107 (62.6)		
Laboratory data				
Total cholesterol, mg/dl	159.7 ± 48.5	168.8 ± 45.1	0.201	0.657
Low-density lipoprotein, mg/dl	91.8 ± 45.3	97.9 ± 38.6	0.157	0.562
High-density lipoprotein, mg/dl	40.4 ± 10.5	44.1 ± 15.2	0.246	0.535
Triglycerides, mg/dl	149.5 ± 82.3	146.4 ± 99.4	0.032	0.500
Medication at discharge				
Aspirin	18 (94.7)	458 (98.7)	0.317	0.246
Dual antiplatelet therapy	16 (84.2)	410 (88.4)	0.128	0.481
Statin	15 (78.9)	444 (95.7)	0.784	0.011
Beta-blocker	14 (73.7)	312 (67.2)	0.137	0.621
ACEI/ARB	10 (52.6)	247 (53.2)	0.012	>0.999

Values are mean ± SD or n (%).
Abbreviations as in Tables 1 to 3.

TABLE 5 Quantitative and Qualitative OCT Findings (Lesion-Level Analysis)

	NC-MACE Group (n = 28)	Non-MACE Group (n = 496)	Standardized Mean Difference	p Value
Quantitative				
Fibrous cap thickness, μm	100 ± 64	101 ± 52	0.007	0.977
Lipid length, mm	9.9 ± 3.6	7.9 ± 4.6	0.421	<0.001
Mean lipid arc, °	176.7 ± 61.2	166.9 ± 55.7	0.176	0.461
Maximal lipid arc, °	240.9 ± 78.4	205.1 ± 69.3	0.510	0.023
Lipid index*	1723 ± 880	1411 ± 1139	0.277	0.081
Minimal lumen area, mm^2	3.71 ± 2.18	5.22 ± 2.87	0.531	0.003
Percent area stenosis	56.7 ± 15.1	47.4 ± 15.4	0.604	0.007
Reference lumen area, mm^2	8.85 ± 4.58	9.75 ± 3.92	0.227	0.333
Qualitative				
Thin cap fibroatheroma	9 (32.1)	165 (33.3)	0.024	0.897
Macrophage	14 (50.0)	245 (49.4)	0.012	0.960
Calcification	13 (46.4)	171 (34.5)	0.250	0.199
Microchannel	10 (37.5)	141 (28.4)	0.161	0.481
Cholesterol crystals	5 (17.9)	84 (16.9)	0.025	0.891
Thrombus	2 (7.1)	36 (7.3)	0.004	0.979
Rupture	4 (14.3)	35 (7.1)	0.275	0.148

Values are mean ± SD or n (%). *Lipid index = lipid length multiplied with mean lipid arc.
OCT = optical coherence tomography; other abbreviations as in Tables 2 and 3.

patients with LRP had NC-MACE. In these patients, baseline characteristics and OCT findings were compared between 19 patients (28 LRPs) with NC-MACE and 464 patients (496 LRPs) with non-MACE (Figure 1). Compared with the non-MACE group, those with NC-MACE had a higher incidence of ACS (63.2% vs. 36.9%, respectively; p = 0.028) and lower statin use (78.9% vs. 95.7%, respectively; p = 0.011) at presentation (Table 4). The NC-MACE group also had a longer lipid length (9.9 ± 3.6 mm vs. 7.9 ± 4.6 mm, respectively; p < 0.001), a wider maximal lipid arc (240.9 ± 78.4° vs. 205.1 ± 69.3°, respectively; p = 0.023), and smaller minimal lumen area (3.71 ± 2.18 mm^2 vs. 5.22 ± 2.87 mm^2, respectively; p = 0.003) with higher percentage of area stenosis (%AS) rate (56.7 ± 15.1% vs. 47.4 ± 15.4%, respectively; p = 0.007) (Table 5). The prevalence of thin-cap fibroatheroma, macrophage, or calcium deposition was not significantly different between the 2 groups.

OCT PREDICTORS FOR NC-MACE. Receiver operating curve analysis was performed to identify parameters of OCT to predict NC-MACE in 483 patients with LRP. The best cutoff values to predict NC-MACE were lipid length, >5.9 mm (area under curve [AUC]: 0.656; p = 0.005); maximal lipid arc of >192.8° (AUC: 0.640; p = 0.012); and %AS of >68.5% (AUC: 0.656; p = 0.005) (Figure 3). Minimal lumen area was not included in this analysis because of an AUC of <0.5. The best cutoff values of lipid length, >5.9 mm; maximal lipid arc of >192.8°; and %AS of >68.5%, which came from the ROC curve analysis, were used for further NC-MACE cumulative rate Kaplan-Meier estimates analysis (Figure 4). When lipid length of >5.9 mm was combined with %AS of >68.5%, the NC-MACE cumulative rate rose to 25.7%, compared with the rate of 3.9% when both were absent (p < 0.001). When maximal lipid arc of >192.8° was combined with %AS of >68.5%, the NC-MACE cumulative rate rose to 30.4%, compared with the rate of 4.2% when both were absent (p < 0.001). The NC-MACE cumulative rate rose to 35.0% when larger lipid arc, longer lipid length, and larger %AS were all combined.

DISCUSSION

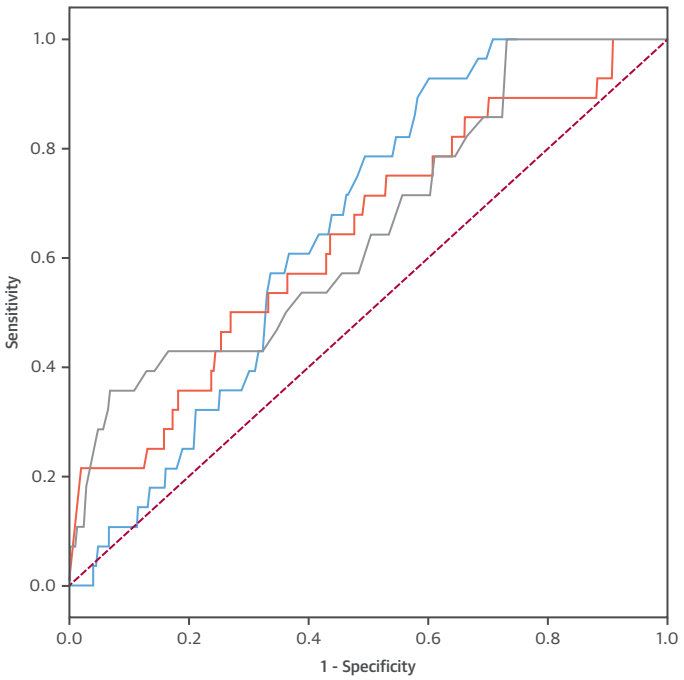
To the best of our knowledge, this is the first report investigating the prognostic significance of LRP detected by OCT in patients undergoing PCI. The main findings are: 1) LRP was present in the nonculprit region of the target vessel in one-third of patients; 2) patients with LRP in nonculprit regions had a higher incidence of future cardiac events than those without LRP (Central Illustration); 3) the presence of LRP, ACS at index presentation, and interruption of

statin use were independently associated with increased risk of NC-MACE (**Central Illustration**); and 4) LRPs in NC-MACE patients showed longer lipid length, wider lipid arc, and smaller luminal size. Our study suggests that OCT imaging of the target vessel may help to stratify the risk of patients undergoing PCI for future cardiac events.

PREVALENCE OF LRP. Cheruvu et al. (7) reported that the prevalence of thin-cap fibroatheroma was 1.1/heart in patients dying of cardiovascular causes. Previous 3-vessel OCT studies have also shown a similar prevalence, with an average of 1.3 LRPs/patient (8,9). In our study, only the culprit vessel was imaged. Therefore, LRP in 33.6% of the patients is consistent with the rate in previous studies. In our study, LRP was more frequently detected in men, those with diabetes mellitus, and current smokers. The previous pathological study also showed male predominance (7) and that coronary plaques in nonculprit lesions in patients with diabetes had larger plaque burdens with larger necrotic cores (10). It has also been reported that the prevalence of lipid plaques was significantly higher in smokers (68.0%) than in former smokers (45.9%) and nonsmokers (52.6%) (11).

LRP AND CARDIOVASCULAR EVENTS. Lipid-rich and soft plaques are more unstable, prone to rupture, and highly thrombogenic when disrupted (12). A previous autopsy study in patients with fatal myocardial infarction demonstrated LRP with superimposed thrombus at most of the culprit sites (13). Studies of LRP at culprit sites detected by OCT and other intravascular imaging modalities in ACS patients documented a close association between LRP and cardiovascular events (14,15). Recently, Madder et al. (16) reported the association between large LRPs, detected by intracoronary near-infrared spectroscopy, at nonstented sites in a target vessel and subsequent events. The aim of the present study was to evaluate the association of OCT findings with subsequent cardiovascular events up to 4 years. The cumulative rate of NC-MACE was significantly higher in patients with nonculprit LRP than in those without LRP (**Figure 2**). These findings indicate that detection of LRP by OCT in the nonculprit regions of the target vessel can predict increased risk for future NC-MACE. The curve also shows that one-half of all MACE comes from nonculprit lesions, which is consistent with the findings of the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study (17). The presence of LRP in the target vessel doubles the risk for all MACE and triples the risk of NC-MACE at 4 years. It is important to note that the LRP found in the target vessel does not necessarily lead to MACE in the future, but it is an indicator of higher risk for future cardiac events. Because LRP appears to be evenly distributed among the 3 coronary arteries, treating LRP in the target vessel may prevent only one-third of future MACE, underscoring the importance of systemic therapy. It should be mentioned that the MACE rate in this study was lower than that in the PROSPECT study (a comparison of our study with the PROSPECT study showed: 0.4% vs. 1.9% in cardiac death, 1.8% vs. 3.3% in AMI, and 6.5% vs. 17.1% in revascularization, respectively). However, it is important to note that occurrence of MACE in the present study and in the PROSPECT study was largely driven by

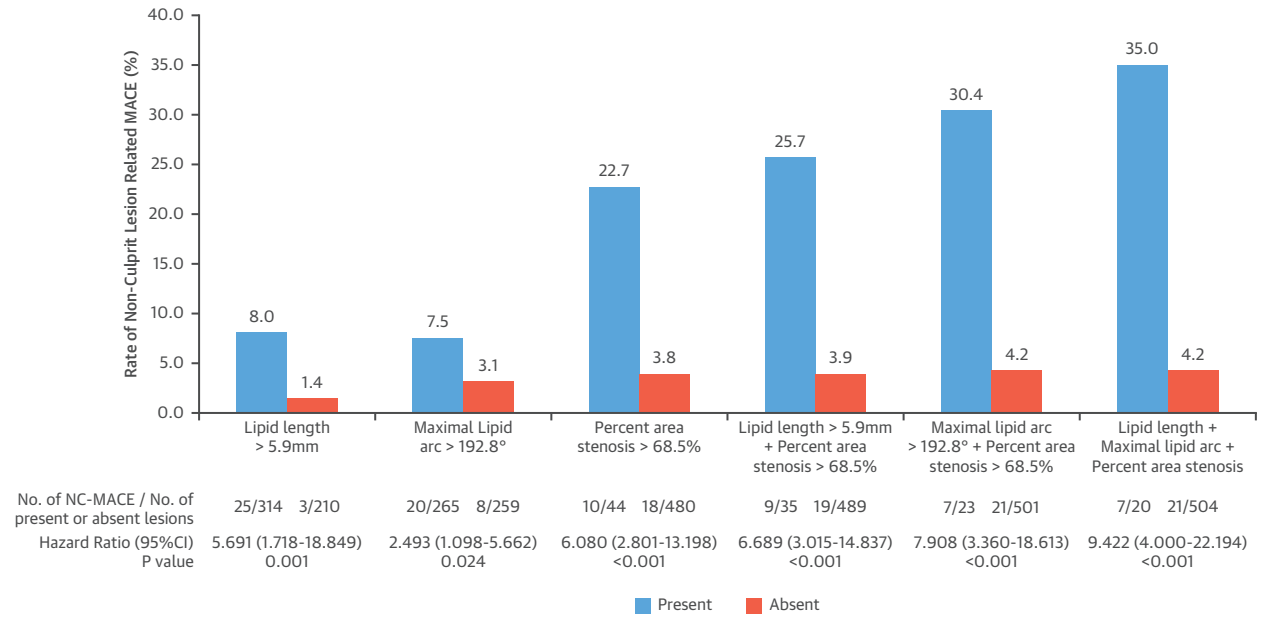
FIGURE 3 ROC Curve Analysis to Predict NC-MACE



Variables	Best Cut-off	AUC	Youden's index	Sensitivity	Specificity	P value
Lipid length	5.9mm	0.656	0.328	92.9%	39.9%	0.005
Maximal lipid arc	192.8°	0.640	0.220	71.4%	50.6%	0.012
Percent area stenosis	68.5%	0.656	0.289	35.7%	93.1%	0.005

The best cutoff value for lipid length, maximal lipid arc, and percentage of area stenosis of lipid-rich plaque in nonculprit regions of target vessel to predict nonculprit lesion related major adverse cardiac event are shown in the figure. AUC = area under the curve; NC-MACE = nonculprit lesion-related major adverse cardiac event; ROC = receiver operating characteristic.

FIGURE 4 Rate of NC-MACE



Specific OCT parameters alone or in combination and rate of NC-MACE are shown. The best cutoff values of lipid length >5.9 mm, maximal lipid arc >192.8°, and %AS >68.5% from the ROC curve analysis were used for further NC-MACE cumulative rate Kaplan-Meier estimate analyses. Lesions in patients with culprit lesion-related and indeterminate events were excluded. %AS = percentage of area stenosis; other abbreviations as in Figures 1 to 3.

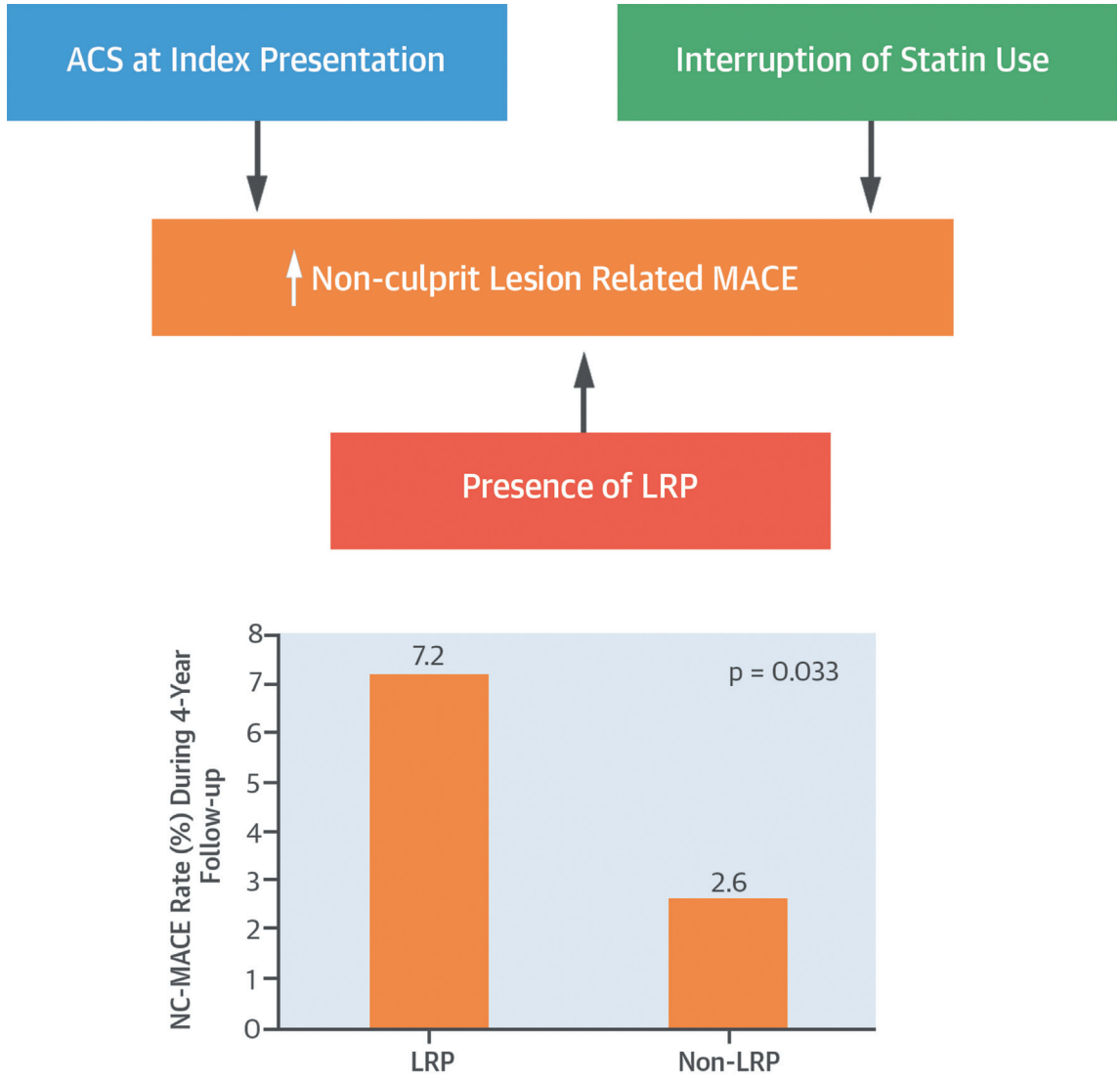
revascularization and not by hard endpoints, such as cardiac death or AMI. In our study, of 66 of 74 MACE (89.2%) were due to ischemia-driven revascularization, and only 26 (35.1%) were due to cardiac death or AMI. Among 21 AMI cases, 18 were included also in ischemia-driven revascularization. This may also explain the lack of difference in fibrous cap thickness between the NC-MACE group and the non-MACE group.

ACS AND STATIN WITHDRAWAL. Previous studies detailed nonculprit plaque characteristics in patients with ACS and found that patients with ACS are at higher risk for recurrent ischemic events caused by a lesion that is anatomically unrelated to the initial event compared with those with stable angina (18,19). Sano et al. (20) demonstrated that the plaques leading to ACS had higher percentage of lipid area than stable plaques. Kato et al. (8) also showed a higher prevalence of LRP, as well as other features of vulnerability in nonculprit lesions in ACS patients than in non-ACS patients. In line with the previous studies, ACS as an index presentation was associated with future NC-MACE in our study.

Fibrous cap thickness is considered one of the most critical determinants of plaque rupture (21,22). Previous clinical trials demonstrated that lipid-lowering therapy using a statin significantly reduced MACE (23,24). Prospective OCT and intravascular ultrasonography studies investigated the effect of aggressive statin therapy on fibrous cap thickness and other plaque components (25,26). All these studies consistently showed that aggressive cholesterol-lowering therapy stabilizes LRP. In contrast, population-based studies demonstrated that discontinuation of statin was associated with poor adverse outcomes (27,28), which may be related to a drastic decrease in endothelial function to lower than pretreatment levels (29), as well as destabilization of fibrous cap. Consistent with these studies, our study demonstrated that interruption of statin therapy is a predictor of all MACE and NC-MACE.

CHARACTERISTICS OF LRP IN PATIENTS WITH NC-MACE. Although both the PROSPECT study and our analysis attempted to study the natural history of nonculprit plaques and to identify predictors for future MACE, there were differences between the 2 studies. In the PROSPECT study, all 3 coronary arteries were imaged, whereas in our study, only the culprit vessel was visualized. Therefore, nonculprit lesions in the PROSPECT study included plaques in all 3 coronary arteries, whereas the nonculprit lesions in our study were limited to plaques in the culprit vessels. The PROSPECT study demonstrated that a small luminal

CENTRAL ILLUSTRATION **Predictors of Nonculprit Lesion–Related Major Adverse Cardiac Events**



Xing, L. et al. J Am Coll Cardiol. 2017;69(20):2502–13.

In addition to ACS at presentation and interruption of statin use, the presence of LRP in the nonculprit region of the target vessel predicts future cardiac events. Cumulative rate of NC-MACE was almost 3-fold higher in patients with nonculprit LRP than in those without LRP (7.2% vs. 2.6%, respectively; p = 0.033). ACS = acute coronary syndrome; LRP = lipid-rich plaque; MACE = major adverse cardiac events; NC-MACE = nonculprit lesion-related major adverse cardiac events.

area and a large plaque burden were predictors of future events (17). Our study also demonstrated that LRP in the NC-MACE group had greater percentage area stenosis, in addition to longer lipid length and wider lipid arc. These results were consistent with the PROSPECT study. When these features were present, the cumulative NC-MACE rate rose to 25.7% to 35.0% compared with the range of 3.9% to 4.2% when they were absent. When these 3 features were present, the risk of NC-MACE increased to 35.0% at the 4-year follow-up.

STUDY LIMITATIONS. First, this study was a retrospective analysis. However, all patients were followed prospectively. Although all patients undergoing the OCT procedure at participating sites were eligible for inclusion in the registry, the potential for selection bias in the utilization of OCT cannot be excluded

(Online Tables 4 and 5). Second, there were some recent reports questioning OCT assessment of lipid. However, among currently available diagnostic modalities, OCT is one of the superior technologies. When assessed by trained investigators, interobserver and intraobserver reliabilities were acceptable (Online Table 6). Third, although the relationship between the presence of LRP and MACE was demonstrated, it should be emphasized that the MACE rate in the study population was low, and MACE was driven primarily by revascularization. Fourth, only the target vessel was imaged; however, in real-world practice, imaging 3 vessels is impractical and involves unnecessarily high risk. Finally, the median follow-up duration of 2 years was short. Survival curves with a small number of patients were evaluated at the 4-year follow-up (Online Table 7).

CONCLUSIONS

LRP was present in nonculprit regions of the target vessel in 33.6% of patients undergoing PCI. The presence of LRP in the nonculprit regions of the target vessel by OCT predicts increased risk for future NC-MACE, which is primarily driven by revascularization for recurrent ischemia, but not AMI or cardiac death. Patients presenting with LRP of longer lipid length, wider lipid arc, and higher degree of luminal narrowing are at particularly high risk for future cardiac events.

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ADDRESS FOR CORRESPONDENCE: Dr. Ik-Kyung Jang, Cardiology Division, Massachusetts General Hospital, Harvard Medical School, GRB 800, 55 Fruit Street, Boston, Massachusetts 02114. E-mail: ijang@mgh.harvard.edu. OR Dr. Bo Yu, Department of Cardiology, Second Affiliated Hospital of Harbin Medical University, The Key Laboratory of Myocardial Ischemia, Chinese Ministry of Education, 246 Xuefu Road, Harbin 150086, China. E-mail: yubodr@163.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients undergoing PCI, detection by OCT of lipid-rich plaque in other regions of the target vessel is associated with a high risk of future adverse cardiovascular events.

TRANSLATIONAL OUTLOOK: Future studies should address how detection of lipid-rich plaque in patients undergoing PCI should influence secondary prevention therapy.

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KEY WORDS atherosclerotic plaque, coronary artery disease, major adverse cardiac events, nonculprit plaque

APPENDIX For an expanded Methods section as well as a supplemental figure and tables, please see the online version of this article.