Clinical Significance of the Presence or Absence of Lipid-Rich Plaque Underneath Intact Fibrous Cap Plaque in Acute Coronary Syndrome

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Background—Although most coronary thromboses occur on the surface of lipid-rich plaque (LRP) with plaque rupture (PR), previous pathological and optical coherence tomography studies demonstrated diversity in the morphological characteristics of culprit plaque underlying the thrombus, including lesions with intact fibrous cap (IFC). We investigated the clinical significance of IFC in relation to the presence or absence of LRP observed via optical coherence tomography in culprit lesions of acute coronary syndrome.

Methods and Results—We investigated 510 patients with acute coronary syndrome who underwent optical coherence tomography for the culprit lesion. Optical coherence tomography analysis included the presence or absence of PR, which were categorized into the PR group and the IFC group, respectively. The IFC group was further categorized on the basis of the presence of LRP. Incidence of major adverse cardiac events (MACEs), including cardiac death, myocardial infarction, and clinically driven remote revascularizations, was compared. Culprit lesions were categorized into 328 PRs and 182 IFCs. MACEs occurred in 85 patients (16.7%) during the median follow-up duration of 621 days. LRP was detected in 325 lesions (99%) with PR, whereas 60 (33.0%) of the lesions with IFC did not show LRP. Kaplan-Meier analysis revealed significantly lower MACEs in the IFC group compared with the PR group. Furthermore, the IFC group without LRP showed significantly lower MACEs compared with the IFC group with LRP. Multivariate Cox proportional hazards analysis demonstrated that IFC without LRP was an independent predictor of better prognosis.

Conclusions—Exclusion of LRP underneath IFC culprit lesions in acute coronary syndrome may predict a lower risk of future MACEs. (J Am Heart Assoc. 2019;8:e011820. DOI: 10.1161/JAHA.118.011820.)

Key Words: acute coronary syndrome • intact fibrous cap • optical coherence tomography • percutaneous coronary intervention • plaque rupture

In the past decade, the clinical outcomes of patients with acute coronary syndrome (ACS) have dramatically improved because of the development of pharmacological and interventional therapies. Nevertheless, ACS remains one of the main causes of death globally. Pathological studies have proposed 3 major mechanisms of coronary thrombosis causing ACS, including plaque rupture (PR), plaque erosion, and calcified nodule, of which PR is the most common phenotype.1,2 Although culprit plaques without evident PR (those with erosion or calcified nodules) account for approximately one third of ACS,3,4 their prevalence has been underestimated in clinical practice because of the limited ability of imaging modalities to identify these phenotypes, particularly in vivo. With the use of high-resolution images from optical coherence tomography (OCT), previous studies proposed an OCT definition of plaque erosion that is characterized by thrombosis overlying a plaque with intact fibrous cap (IFC). It has been reported that ACS caused by plaques with PR and IFC showed different morphological characteristics at both the culprit plaque and nonculprit plaques5; these plaques also yielded different clinical courses.6,7 A large lipid component, represented by a necrotic core, is one of the most important factors of vulnerable plaque, which is considered a precursor of coronary
Clinical Perspective

What Is New?

- This optical coherence tomography study reports that lipid-rich plaque (LRP) was detected in almost all lesions with plaque rupture, whereas 33.0% of the lesions with intact fibrous cap did not show LRP features.
- In patients with acute coronary syndrome, the presence of LRP provides prognostic implication for adverse cardiac events, irrespective of the presence or absence of plaque rupture in the culprit lesion.
- Particularly, exclusion of LRP underneath intact fibrous cap culprit lesions in acute coronary syndrome provided better prognostic information after percutaneous coronary intervention.

What Are the Clinical Implications?

- Classification of culprit plaque morphological characteristics by using optical coherence tomography for both the presence or absence of plaque rupture and the presence of LRP underneath intact fibrous cap may be useful to stratify the risk for subsequent adverse events, which might help manage adjunctive therapeutic strategy and improve secondary prevention after percutaneous coronary intervention.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

The institutional database of intravascular OCT examinations performed at Tsuchiura Kyodo General Hospital (Ibaraki, Japan), between November 2008 and May 2017 (n=3192), was retrospectively queried to identify patients of interest who met the following inclusion criteria: patients who underwent primary/urgent PCI for ACS and those with a consent for OCT examination of the culprit lesion during PCI and future data use and follow-up for the analysis. The culprit lesion was identified on the basis of coronary angiogram, ECG, or echocardiogram. Exclusion criteria were as follows: lesions requiring balloon angioplasty before OCT imaging; in-stent thrombosis, restenosis lesions, and bypass graft lesions; poor OCT image quality; patients with delayed presentation of >12 hours after onset; and patients in whom the culprit lesion could not be identified. Thus, the OCT images of 579 culprit lesions in 579 patients with ACS were analyzed in the present study (Figure 1).

Institutional exclusion criteria for OCT imaging in patients with ACS were cardiogenic shock, congestive heart failure, significant left main coronary artery disease, and suboptimal results after thrombectomy with TIMI (Thrombolysis in Myocardial Infarction) 0 to 2 flow. ST-segment–elevation myocardial infarction was defined as follows: continuous chest pain that lasted >30 minutes, arrival at the hospital within 12 hours from the onset of symptoms, ST-segment elevation >0.1 mV in >2 contiguous leads or new left bundle-branch block on a 12-lead ECG, and elevated cardiac markers. Non–ST-segment–elevation myocardial infarction was defined as ischemic symptoms in the absence of ST-segment elevation on ECG with elevated cardiac markers. Unstable angina was defined as angina at rest or one episode lasting >20 minutes during the preceding 48 hours and normal levels of cardiac markers. The primary outcome measure was major adverse cardiac events (MACEs), which is defined as a composite of cardiac death, acute myocardial infarction, and ischemia-driven remote revascularization (>3 months from the index PCI). Scheduled revascularization for nonculprit lesions that were identified in index coronary angiograms was not considered as a MACE. Device-oriented composite end point was defined as a composite of cardiac death, target-vessel myocardial infarction, and ischemia-driven target lesion remote revascularization.

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

OCT Image Acquisition and Analysis

OCT images were acquired before PCI procedures for lesions showing TIMI 3 flow without suspected angiographic thrombi and evaluated (Data S1). PR was defined as a plaque showing...
disruption of the fibrous cap with or without cavity formation. IFC was defined as a plaque where the fibrous cap of the culprit lesion was intact. Lipid was characterized as a diffusely bordered, signal-poor region underlying a signal-rich band that corresponded to the fibrous cap. For plaques with lipid, lipid length and arc were measured on the longitudinal reconstructed view or cross-sectional image by an independent investigator (E.U.). LRP was defined as a plaque with lipid having the maximal lipid arc (>90°) and lipid length (>1 mm). In addition, thrombus length, maximal arc of the thrombus, and thrombus volume were measured according to the previous studies. In brief, for the measurements of thrombus, OCT images were analyzed at 0.2-mm intervals. Thrombus area was traced by planimetry in frames with clear visualization of the vessel contours >270°; otherwise, thrombus area was calculated by subtracting residual lumen area from the vessel contour area extrapolated from the nearest visible frames. Thrombus length was calculated by the number of frames with OCT thrombus multiplied by frame interval (0.2 mm). Thrombus arc was measured from the center of the residual lumen, and the maximum value was obtained as the maximum thrombus arc. Lesions with massive thrombus or calcified nodules were excluded from further analysis because plaque morphological characteristics could not be identified in those with massive thrombus, and the pathological nature of calcified nodules is different from that of LRP. Thereafter, culprit lesions were divided into 3 categories, according to the OCT findings: lesions with PR (PR group), IFC with LRP (IFC-LRP group), and IFC without LRP (IFC–non-LRP group) (Figure 2).

**Angiography Analysis**

Baseline coronary angiograms obtained before OCT image acquisition or interventional procedures were analyzed with offline software (QAngio XA 7.3; Medis, Leiden, the Netherlands). Angiographic lesion morphological characteristics were classified according to the American Heart Association/American College of Cardiology lesion classification.

**Statistical Analysis**

Categorical values are presented as counts and proportions, and comparisons between groups were performed using the $\chi^2$ test or Fisher’s exact test, depending on the data. Continuous values, showing a normal distribution, are
expressed as mean±SD; and Student t test was performed to compare the values among groups. Nonnormally distributed, continuous values are expressed as median (25th–75th percentile), and the Mann-Whitney U test was used to compare between the groups. The Kruskal-Wallis test was performed to compare continuous variables among the 3 groups; post hoc comparisons were performed using pairwise comparisons between groups. Intraobserver and interobserver variabilities for categorical OCT variables were estimated using the $\kappa$ coefficient. Survival curves using the Kaplan-Meier methods were produced for the presence of PR, LRP, or massive thrombus as the culprit lesion; and they were compared using the log-rank test. The predictors of MACEs were determined using the Cox proportional hazards regression model. The covariates used in multivariate analysis were selected using the criterion of $P<0.20$ in the univariate analysis. The proportional hazards assumption was checked using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals. A collinearity index was used for checking linear combinations among covariates, and the Akaike information criterion was used for avoiding overfitting. All statistical analyses were performed with SPSS 18.0 (SPSS Inc, Chicago, IL) and R, version 3.0.2 (The R Foundation for Statistical Computing, Vienna, Austria). $P<0.05$ was considered statistically significant.

Results

Patient Characteristics and Angiographic and Procedural Findings

Of 579 culprit lesions of ACS analyzed in the present study, underlying plaque morphological characteristics could not be categorized via OCT in 69 lesions because of massive thrombus (n=45), calcified nodule (n=21), or spontaneous coronary dissection (n=3). After excluding these lesions, 510 culprit lesions of ACS were included in the final analysis. In the subsequent OCT analysis, 328 lesions (64.3%) were categorized into the PR group, 122 lesions (23.9%) were categorized into the IFC-LRP group, and 60 lesions (11.8%) were categorized into the IFC-non-LRP group (Figure 1).

OCT Findings

OCT findings were compared among the 3 groups (Table 3). Compared with IFC-LRP, lesions with PR had significantly thinner fibrous caps, more frequent thin-cap fibroatheroma, longer lipid length, and greater maximum lipid arc at the culprit lesion. Culprit lesions with PR had significantly greater volume of OCT-defined thrombus than those with IFC-LRP or IFC–non-LRP. The intraobserver and interobserver $\kappa$ values for the qualitative assessments of PR were 0.89 and 0.87, respectively; for LRP assessment, they were 0.88 and 0.85, respectively.

Follow-Up Data

During a median follow-up duration of 621 days (range, 415–1589 days), 85 patients (16.7%) experienced MACEs. The numbers of adverse events are summarized in Table 4, and the comparison of patient characteristics between those with and without MACEs is summarized in Table S1. Second-generation, drug-eluting stents were used less frequently in
Table 1. Patient Characteristics

| Characteristics               | PR Group (n=328) | IFC-LRP Group (n=122) | IFC–Non-LRP Group (n=60) | P Value |
|-------------------------------|-----------------|-----------------------|--------------------------|---------|
| Age, y                        | 67.0 (58.0–74.0) | 68.0 (58.3–73.0)      | 67.0 (55.0–74.0)         | 0.728   |
| Men                           | 264 (80.5)      | 97 (79.5)             | 42 (70.0)                | 0.184   |
| Hypertension                  | 213 (64.9)      | 83 (68.0)             | 40 (66.7)                | 0.820   |
| Dyslipidemia                  | 160 (48.8)      | 63 (51.6)             | 30 (50.0)                | 0.863   |
| Diabetes mellitus             | 105 (32.0)      | 43 (35.2)             | 20 (33.3)                | 0.808   |
| Current smoker                | 133 (40.5)      | 55 (45.1)             | 31 (51.7)                | 0.240   |
| Clinical presentation         |                 |                       |                          |         |
| STEMI                         | 171 (52.1)      | 29 (23.8)             | 19 (31.7)                | <0.001* |
| NSTEMI                        | 131 (39.9)      | 63 (51.6)             | 36 (60.0)                |         |
| Unstable angina               | 26 (7.9)        | 30 (24.5)             | 5 (8.3)                  |         |
| Prior PCI                     | 32 (9.8)        | 9 (7.4)               | 4 (6.7)                  | 0.709   |
| Prior MI                      | 24 (7.3)        | 5 (4.1)               | 4 (6.7)                  | 0.503   |
| LDL cholesterol, mg/dL        | 122.0 (99.0–144.0) | 124.0 (99.0–144.0)  | 111.0 (94.8–134.8)       | 0.326   |
| HDL cholesterol, mg/dL        | 44.0 (38.0–51.0) | 45.0 (39.0–53.0)      | 48.0 (40.5–57.0)         | 0.073   |
| eGFR, mL/min per 1.73 m²      | 72.6 (58.0–84.2) | 73.8 (64.5–87.0)      | 69.1 (52.0–85.7)         | 0.068   |
| CRP, mg/dL                    | 0.15 (0.05–0.50) | 0.16 (0.04–0.52)      | 0.12 (0.06–0.44)         | 0.973   |
| Medication                    |                 |                       |                          |         |
| Prior aspirin use             | 60 (18.3)       | 25 (20.5)             | 12 (20.0)                | 0.851   |
| Prior statin use              | 70 (21.3)       | 25 (20.5)             | 16 (26.7)                | 0.607   |

Data are presented as number (percentage) or median (quartile 1–quartile 3). CRP indicates C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IFC, intact fibrous cap; LDL, low-density lipoprotein; LRP, lipid-rich plaque; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; PCI, percutaneous coronary intervention; PR, plaque rupture; STEMI, ST-segment–elevation MI.

*P<0.05 for PR vs IFC-LRP, †P<0.05 for PR vs IFC–non-LRP, ‡P<0.05 for IFC-LRP vs IFC–non-LRP by post hoc test.

Discussion

To the best of our knowledge, this is the first study demonstrating the prognostic significance of LRP in culprit lesions with IFC defined via OCT. Major findings of the present study were as follows: (1) the vast majority of culprit lesions with PR exhibited LRP using OCT, whereas approximately one third of the lesions with IFC did not show LRP; (2) MACE-free survival rate was significantly worse in patients with PR than in those with IFC; (3) MACE-free survival rate was significantly worse in patients with LRP in culprit lesions compared with
those without LRP; and (4) MACE-free survival was significantly preferable in patients with IFC showing no LRP than in those with IFC with LRP.

**Differing Clinical Courses Based on Different Morphological Plaque Characteristics**

Previous OCT studies demonstrated that the patients with ACS exhibiting IFC in the culprit lesions showed preferable clinical outcomes after PCI compared with those with PR.6,7 Niccoli et al investigated 139 patients with ACS, in whom the culprit lesions were categorized into PR (n=82) and IFC (n=57).6 The researchers reported that MACE was significantly more frequent in patients with PR, which is consistent with the present study. In our previous OCT study comprising 318 patients with ACS (141 patients with PR and 131 patients with IFC), we showed a lower rate of clinical cardiac events in patients with IFC than in those with PR.7 In both previous studies,6,7 each adverse event besides target vessel revascularization showed a nonsignificant trend toward a higher incidence in patients with PR, which potentially indicates greater atheromatous burden not only in the culprit vessels, but also in nonculprit vessels of patients with PR compared with those with IFC. In fact, previous OCT and computed tomography studies showed that patients with ACS with concurrent PR in the culprit lesion exhibited vulnerable plaque morphological characteristics in nonculprit lesions or nonculprit vessels.14–16 In the present study, macrophage infiltration was significantly less in the IFC group without lipid than in the other 2 groups. Macrophage degradation of fibrous cap is an important contributor to atherosclerotic plaque instability. Previous reports showed a significantly higher macrophage density at the rupture site and LRP site.17 Moreover, macrophage was associated with arterial wall lipid deposition contributing to inflammatory processes.18 Previous reports also showed more macrophage volume suggested the extent of initial coronary plaque inflammation and had a possible role for the recurrence of angina after PCI.19,20 Therefore, our finding that macrophage infiltration was significantly less in the IFC–non-LRP group.

### Table 2. Angiographic and Procedural Data

| Variable                              | PR Group (n=328) | IFC-LRP Group (n=122) | IFC-Non-LRP Group (n=60) | P Value |
|---------------------------------------|------------------|-----------------------|--------------------------|---------|
| **Lesion location**                   |                  |                       |                          |         |
| RCA                                  | 132              | 33                    | 12                       | 0.005†  |
| LAD                                  | 135              | 63                    | 37                       |         |
| LCX                                  | 61               | 26                    | 11                       |         |
| **Quantitative coronary angiography data** |                  |                       |                          |         |
| Reference diameter, mm               | 2.78 (2.40–3.22) | 2.70 (2.34–3.00)      | 2.91 (2.38–3.24)         | 0.263   |
| Minimum lumen diameter, mm           | 0.53 (0.00–0.79) | 0.64 (0.46–0.80)      | 0.65 (0.14–0.98)         | 0.009*  |
| Diameter stenosis, %                 | 80.5 (71.2–100.0) | 76.8 (68.9–83.1)      | 76.0 (61.9–93.0)         | 0.003*  |
| Lesion length, mm                    | 13.3 (10.0–16.6) | 12.1 (9.9–16.9)       | 9.9 (8.3–12.8)           | <0.001†:‡|
| ACC/AHA classification B2/C          | 170 (51.8)       | 41 (33.6)             | 22 (36.7)                | <0.001†:‡|
| **TIMI flow grade**                  |                  |                       |                          |         |
| Pre-PCI TIMI 0–2                     | 196 (64.9)       | 51 (43.2)             | 32 (55.2)                | <0.001* |
| Post-PCI TIMI 0–2                    | 40 (13.2)        | 4 (3.4)               | 6 (10.9)                 | 0.048   |
| Multivessel disease                  | 121 (36.9)       | 45 (36.9)             | 13 (21.7)                | 0.068   |
| **Stent**                             |                  |                       |                          |         |
| Stent size, mm                       | 3.5 (3.0–3.5)    | 3.38 (3.0–3.5)        | 3.5 (3.0–3.5)            | 0.023*  |
| Stent length, mm                     | 24.0 (19.0–33.0) | 24.0 (19.0–33.0)      | 20.0 (16.0–28.0)         | 0.011‡:‡|
| DES                                  | 200              | 87                    | 36                       | <0.001‡:‡|
| BMS                                  | 123              | 31                    | 10                       |         |
| POBA/aspiration                      | 4                | 3                     | 13                       |         |
| Second-generation DES                | 175 (53.4)       | 68 (55.7)             | 35 (58.3)                | 0.739   |

Data are presented as number (percentage) or median (quartile 1–quartile 3). ACC indicates American College of Cardiology; AHA, American Heart Association; BMS, bare-metal stent; DES, drug-eluting stent; IFC, intact fibrous cap; LAD, left anterogradend artery; LCX, left circumflex; LRP, lipid-rich plaque; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; PR, plaque rupture; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction.

*P<0.05 for plaque rupture vs IFC with LRP, †P<0.05 for plaque rupture vs IFC without LRP, ‡P<0.05 for IFC with LRP vs IFC without LRP.
than in the other 2 groups in patients with ACS might be linked with better prognosis after PCI.

Clinical Implications of LRP

Vulnerable plaque, which is generally defined as a plaque prone to rupture, is associated with a large necrotic core and thin fibrous cap, modified by inflammatory activities within the plaque.\(^1\)\(^,\)\(^2\)\(^,\)\(^1\)\(^1\) Therefore, plaque with a large lipid component is considered a precursor of cardiac events, which was elucidated in recent studies using intracoronary imaging modalities.\(^8\)\(^,\)\(^9\)\(^,\)\(^2\)\(^2\)\(^,\)\(^2\)\(^3\) The PROSPECT (PROviding Regional Observations to Study Predictors of Events in the Coronary Tree) study,\(^2\)\(^2\) in which patients presenting with ACS underwent 3-vessel virtual histological intravascular ultrasound after successful PCI, demonstrated that thin-cap fibroatheroma in nonculprit lesions, indicated via virtual histological intravascular ultrasound, was associated with future cardiac events. On the other hand, a subgroup analysis from the PROSPECT study showed that lesions without fibroatheroma were clinically stable and were rarely associated with clinical events during 3 years of follow-up.\(^2\)\(^4\) Conversely, Xing et al showed that in patients with LRP, identified via OCT at the nonculprit region of the coronary artery, LRP was associated with a higher MACE rate in comparison to those without LRP.\(^8\) In the present study, patients exhibiting LRP using OCT in the culprit lesion showed worse clinical outcomes compared with those without LRP (Figure 3B), which might be plausible considering the impact of LRP on future coronary events and the association between culprit lesion morphological characteristics and nonculprit lesion morphological

Table 3. Pre-PCI OCT Findings

| Findings        | PR Group (n=328) | IFC-LRP Group (n=122) | IFC-Non-LRP Group (n=60) | P Value |
|-----------------|------------------|------------------------|--------------------------|---------|
| Thrombus        | 274 (83.5)       | 74 (60.7)              | 29 (48.3)                | <0.001* |
| TCFA            | 211 (64.5)       | 43 (35.2)              | ...                     | <0.001  |
| LRP             | 325 (99.1)       | 122 (100)              | ...                     | ...     |
| Calcified plaque| 124 (37.8)       | 47 (38.5)              | 25 (41.7)                | 0.848   |
| Macrophage      | 236 (72.0)       | 79 (64.8)              | 22 (36.7)                | <0.001* |
| Fibrous cap thickness, µm | 63 (57–80)     | 83 (60–120)            | ...                     | <0.001  |
| Max lipid arc, °| 246.8 (205.4–294.6) | 229.5 (192.7–273.9) | ...                     | 0.020   |
| Lipid length, mm| 8.1 (5.3–11.9)  | 5.6 (3.7–8.1)          | ...                     | <0.001  |
| Thrombus volume, mm\(^3\) | 0.76 (0.06–2.45) | 0.11 (0.0–0.45) | 0.0 (0.0–0.59) | <0.001* |
| Thrombus length, mm | 2.9 (0.8–5.3) | 1.1 (0.0–2.6) | 0.0 (0.0–2.1) | <0.001* |
| Maximum thrombus arc, ° | 108.1 (45.3–158.5) | 53.8 (0.0–120.3) | 0.0 (0.0–99.3) | <0.001* |

Data are presented as number (percentage) or median (quartile 1–quartile 3). IFC indicates intact fibrous cap; LRP, lipid-rich plaque; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PR, plaque rupture; TCFA, thin-cap fibroatheroma.

\(^*\)P<0.05 for plaque rupture vs IFC with LRP, \(^†\)P<0.05 for plaque rupture vs IFC without LRP, \(^‡\)P<0.05 for IFC with LRP vs IFC without LRP.

Table 4. Clinical Events During the Follow-Up Period

| Clinical Event            | PR Group (n=328) | IFC-LRP Group (n=122) | IFC-Non-LRP Group (n=60) | P Value |
|---------------------------|------------------|------------------------|--------------------------|---------|
| MACE                      | 65 (19.8)        | 18 (14.8)              | 2 (3.3)                  | 0.002   |
| Cardiac death             | 10               | 1                      | 0                        | 0.288   |
| Nonfatal myocardial infarction | 4               | 0                      | 0                        | 0.745   |
| TVR                       | 31               | 11                     | 1                        | 0.106   |
| Non-TVR                   | 20               | 6                      | 1                        | 0.420   |
| DOCE                      | 45 (13.7)        | 12 (9.8)               | 1 (0.02)                 | 0.011   |
| Cardiac death             | 8                | 1                      | 0                        | 0.452   |
| Nonfatal myocardial infarction | 5               | 0                      | 0                        | 0.491   |
| TVR                       | 32               | 11                     | 1                        | 0.101   |

Data are presented as number (percentage). DOCE indicates device-oriented composite end point; IFC, intact fibrous cap; LRP, lipid-rich plaque; MACE, major adverse cardiac event; PR, plaque rupture; TVR, target vessel revascularization.
Moreover, in the present study, even if we selected the patients with plaques with IFC in the culprit lesions, the presence of LRP in the culprit lesion was associated with worse clinical outcomes in terms of composite adverse events (Figure 4A), which is primarily driven by revascularization for recurrent ischemia (Figure 4B).

Figure 3. Kaplan-Meier curves showing major adverse cardiac event (MACE)–free survival, according to the culprit plaque morphological characteristics. A, The incidence of MACEs was significantly higher in patients with plaque rupture (PR) than in those with intact fibrous cap (IFC). Compared with patients with PR, the adjusted hazard ratio (HR) of those with IFC was generated from multivariate Cox proportional hazards model, including estimated glomerular filtration rate (eGFR), prior myocardial infarction (MI), second-generation drug-eluting stent (DES), and American Heart Association/American College of Cardiology (AHA/ACC) classification B2/C. B, The incidence of MACEs was significantly higher in patients with lipid-rich plaque (LRP) than in those without LRP. Compared with patients with LRP, the adjusted HR of those without LRP was generated from multivariate Cox proportional hazards model, including eGFR, prior MI, second-generation DES, and AHA/ACC classification B2/C.

Figure 4. Kaplan-Meier curves showing major adverse cardiac event (MACE)–free survival according to the presence or absence of lipid-rich plaque (LRP) in patients with intact fibrous cap (IFC). Compared with patients with IFC–non-LRP, patients with IFC-LRP had the higher incidence of MACEs (A) and device-oriented composite end point (DOCE; B). Compared with patients with IFC-LRP, adjusted hazard ratio (HR) of those with IFC–non-LRP was generated from multivariate Cox proportional hazards models, including hyperlipidemia and second-generation drug-eluting stents.
Study Limitations
First, this study was a retrospective, observational study at a single center; therefore, selection bias may have influenced the results and the results may not be generalizable. Second, because of the wide range of the study period, adherence to optimal medical therapy was not excellent in the early period of the study. Third, the final decision to perform OCT examination was at the operator’s discretion. Furthermore, as shown in the

Table 5. Univariate and Multivariate Cox Proportional Hazards Analysis for MACEs

| Variable                     | Univariate Analysis | Multivariate Analysis |
|------------------------------|---------------------|-----------------------|
|                              | HR                  | 95% CI                | P Value | HR                  | 95% CI                | P Value |
| OCT-LRP                      | 5.86 (1.44–23.83)   | 0.014                 |         | ...                 | ...                   | ...     |
| OCT-TCFA                     | 1.92 (1.21–3.03)    | 0.005                 |         | ...                 | ...                   | ...     |
| OCT-PR                       | 2.06 (1.23–3.43)    | 0.006                 |         | ...                 | ...                   | ...     |
| eGFR                         | 0.99 (0.98–1.00)    | 0.046                 |         | 0.99 (0.98–1.00)    | 0.032                 |         |
| Prior MI                     | 1.74 (0.87–3.49)    | 0.116                 |         | 1.74 (0.86–3.53)    | 0.123                 |         |
| Multivessel disease          | 1.37 (0.89–2.11)    | 0.155                 |         | ...                 | ...                   | ...     |
| Second-generation DES        | 0.58 (0.37–0.92)    | 0.021                 |         | 0.61 (0.38–0.97)    | 0.038                 |         |
| Stent length                 | 1.01 (1.00–1.03)    | 0.146                 |         | ...                 | ...                   | ...     |
| AHA/ACC classification B2/C  | 1.85 (1.19–2.87)    | 0.006                 |         | 1.70 (1.09–2.67)    | 0.021                 |         |
| Statin at discharge          | 0.64 (0.37–1.10)    | 0.108                 |         | ...                 | ...                   | ...     |
| Culprit lesion morphological characteristics on OCT | | | | | | |
| Reference                    | ...                 | ...                   | Reference | ... | ...                   | ...     |
| IFC-LRP                      | 0.67 (0.39–1.12)    | 0.127                 | 0.81     | 0.47–1.37           | 0.426                 |         |
| IFC-non-LRP                  | 0.16 (0.04–0.67)    | 0.012                 | 0.17     | 0.04–0.70           | 0.014                 |         |

ACC indicates American College of Cardiology; AHA, American Heart Association; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IFC, intact fibrous cap; LRP, lipid-rich plaque; MACE, major adverse cardiac event; MI, myocardial infarction; OCT, optical coherence tomography; PR, plaque rupture; TCFA, thin-cap fibroatheroma.
Methods section, OCT was not performed in patients with cardiogenic shock, congestive heart failure, significant left main disease, and TIMI 0 to 2 flow after thrombectomy because of safety concerns, which may have led to selection bias. Fourth, ACS with calcified nodules was excluded from the analysis to avoid confusion about the definition of IFC. Fifth, the presence of thrombus overlying the culprit lesion might have reduced the accuracy to assess the underlying plaque characteristics by OCT. Finally, because the identification of small PR in the thrombotic event is often difficult, PR might have been misdiagnosed as IFC in certain cases. This is an important limitation of OCT-derived plaque categorization.

Conclusions

In patients with culprit lesions with IFC, the presence of LRP via OCT was significantly associated with an increased risk for future MACES compared with those with IFC without LRP, which is primarily driven by revascularization for recurrent ischemia. Classification of culprit plaque morphological characteristics via OCT was significant for both the presence or absence of PR and the underlying presence of LRP underneath IFC may be useful to stratify the risk for subsequent adverse events.

Disclosures

None.

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Supplemental Methods

OCT Image Acquisition and Analysis

Thrombectomy was performed with an aspiration catheter (Eliminate; Terumo, Tokyo, Japan or Export Advance; Medtronic, Minneapolis, MN, USA) to obtain TIMI 3 flow before optical coherence tomography (OCT) imaging. Either the time-domain (M2/M3 Cardiology Imaging System; LightLab Imaging, Inc., Westford, MA, USA) or the frequency-domain (C8-XRTM OCT Intravascular Imaging System; St. Jude Medical, St. Paul, MN, USA or LUNAWAVETM OFDI System; Terumo, Tokyo, Japan) OCT system was used in the present study. The intracoronary OCT imaging technique is described elsewhere 1-3. OCT images were analyzed by two independent investigators (M.H. and T.Y.) who were blinded to clinical information, and consensus reading was performed if there was disagreement in the interpretations. OCT analysis included either the presence or absence of intraluminal thrombus, plaque rupture (PR), thin cap fibroatheroma (TCFA), calcification, and macrophage infiltration according to consensus documents 1, 4, 5. Massive thrombus was defined as a thrombus precluding visualization of underlying plaque morphology that was >90 degrees in circumference and >1 mm in length. Calcified nodule was characterized when fibrous cap disruption was detected over a calcified
plaque by protruding calcification, superficial calcium, and the presence of substantive calcium proximal and/or distal to the lesion \(^6\).
| Characteristic                  | MACE (n=85) | Without MACE (n=425) | P value |
|--------------------------------|-------------|----------------------|---------|
| Age, y                         | 64.0 (57.0-70.0) | 67.0 (58.0-74.0)     | 0.129   |
| Male                           | 69 (81.2)    | 334 (78.6)           | 0.697   |
| Hypertension                   | 63 (74.1)    | 273 (64.2)           | 0.103   |
| Dyslipidemia                   | 39 (45.9)    | 214 (50.4)           | 0.526   |
| Diabetes mellitus              | 31 (36.5)    | 137 (32.2)           | 0.527   |
| Current smoker                 | 42 (49.4)    | 177 (41.6)           | 0.230   |
| Prior PCI                      | 11 (12.9)    | 34 (8.0)             | 0.209   |
| Prior MI                       | 9 (10.6)     | 24 (5.6)             | 0.147   |
| Ejection fraction, %           | 61.0 (55.0-64.0) | 60.0 (52.0-65.0)     | 0.536   |
| eGFR, mL/min/1.73m2            | 69.4 (56.3-83.7) | 73.1 (60.7-85.5)     | 0.239   |
| Medication                     |             |                      |         |
| ACE/ARB                        | 76 (89.4)    | 360 (84.9)           | 0.362   |
| B blocker                      | 53 (62.4)    | 286 (67.3)           | 0.450   |
|                          | Group A (n | Group B (n | p-value |
|--------------------------|------------|------------|---------|
| Statin                   | 68 (80.0)  | 376 (88.5) | 0.052   |
| Quantitative coronary angiography |            |            |         |
| Reference vessel diameter| 2.76 (2.55-3.10) | 2.76 (2.32-3.21) | 0.480 |
| Minimum lumen diameter   | 0.61 (0.19-0.79) | 0.56 (0.14-0.81) | 0.877 |
| Diameter stenosis        | 79.1 (69.4-93.0) | 79.1 (69.9-92.6) | 0.767 |
| Lesion length            | 14.1 (10.5-17.2) | 12.3 (9.7-15.6) | 0.081 |
| Procedural and angiographic |          |            |         |
| 2nd generation DES       | 28 (32.9)  | 250 (58.8) | <0.001 |
| Multi-vessel disease     | 38 (44.7)  | 141 (33.2) | 0.047  |
| AHA/ACC type B2/C        | 52 (61.2)  | 181 (42.6) | 0.003  |
| OCT finding              |            |            |         |
| LRP                      | 83 (97.6)  | 364 (85.6) | <0.001 |
| TCFA                     | 57 (67.1)  | 197 (46.5) | <0.001 |
| Thrombus volume          | 0.4 (0.0-2.7) | 0.3 (0.0-1.5) | 0.397 |
| Culprit lesion morphology on OCT |          |            |         |
| PR                       | 65 (76.5)  | 263 (61.9) | 0.002  |
| Group          | IFC-LRP | IFC-non-LRP |
|---------------|---------|------------|
| n (%)         | 18 (21.2) | 2 (2.4)    |
| Mean (SD)     | 104 (24.5) | 58 (13.6)  |

Data are presented as n (%), mean SD, or median (interquartile range).

IFC indicates intact fibrous cap; PR, plaque rupture; LRP, lipid-rich plaque; ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin II Receptor Blocker; MACE, major adverse cardiac events; DES indicates drug-eluting stent; PCI, percutaneous coronary intervention; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; TCFA, thin-cap fibroatheroma; OCT, optical coherence tomography; MI; myocardial infarction; AHA, American Heart Association; ACC, American College of Cardiology.
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