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ORIGINAL ARTICLE
Cardiovascular Intervention

Clinical Impact of Irregular Protrusion Angle After Coronary Stenting at Culprit Lesions With ST-Elevation Myocardial Infarction

— An Intravascular Optical Coherence Tomography Study —

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Background: A recent optical coherence tomography (OCT) registry showed that the presence of irregular protrusion (IP) after coronary stenting was a predictor of worse 1-year cardiovascular events. This study evaluated the clinical impact of OCT-detected IP after coronary stenting at ST-elevation myocardial infarction (STEMI) culprit lesions.

Methods and Results: In all, 139 consecutive STEMI patients with OCT-detected IP after stenting were analyzed retrospectively. The maximum IP angles were measured and patients with IP were divided into 2 groups (large IP, maximum IP angle ≥180°; small IP, 0°<angle<180°). The primary endpoints were cardiac death, target vessel myocardial infarction, target lesion revascularization, and stent thrombosis at 1 year after the index percutaneous coronary intervention (PCI). Of STEMI patients with IP, 51.8% had large IP. The incidence of the primary endpoints higher was higher in the large than small IP group (12.5% vs. 1.5%, respectively; P=0.018). The occurrence of plaque rupture was an independent predictor of large IP (odds ratio 4.58; 95% confidential interval 1.86–11.27; P=0.001).

Conclusions: Maximum IP angle ≥180° was an independent predictor of clinical events in STEMI patients with IP.

Key Words: Irregular protrusion; Optical coherence tomography; ST-elevation myocardial infarction; Stent

Globally, ST-elevation myocardial infarction (STEMI) is one of the most life-threatening cardiac events. The development of primary percutaneous coronary intervention (PCI), coronary stenting, and imaging modalities has improved patient outcomes, and patients treated with drug-eluting stents (DES) have lower rates of repeat revascularization than patients treated with bare-metal stents.[1] However, DES, including newer-generation DES, are still associated with problems such as stent restenosis, stent thrombosis (ST), and adverse clinical events.[1,2]

Recently, an intravascular optical coherence tomography (OCT) study revealed that the presence of irregular protrusion (IP) and a small minimum stent area (MSA) at the deployed coronary stent were predictors of 1-year device-oriented clinical events, including cardiac death, target vessel-related myocardial infarction (MI), target lesion revascularization (TLR), and ST after coronary stenting.[3] However, the clinical impact of IP volume has rarely been studied to predict future culprit lesion-related events after coronary stenting. This study investigated the clinical impact of OCT-detected IP angle after coronary stenting at STEMI culprit lesions.

Methods

Study Population

From January 2013 to November 2016, 217 STEMI patients were treated with OCT-guided PCI at Nara Medical University Hospital. Patients with an onset to recanalization time >48 h and those with poor image quality were excluded from the study. After post-stent OCT analysis, patients without IP were also excluded from the study.

STEMI was defined as continuous chest pain lasting >30 min, arrival at the hospital within 48 h of the onset of chest pain, ST-elevation >0.1 mV in ≥2 contiguous leads or new left bundle branch block on the 12-lead electrocardiogram (ECG), and elevated cardiac markers (creatine kinase [CK]-MB or troponin T/I).

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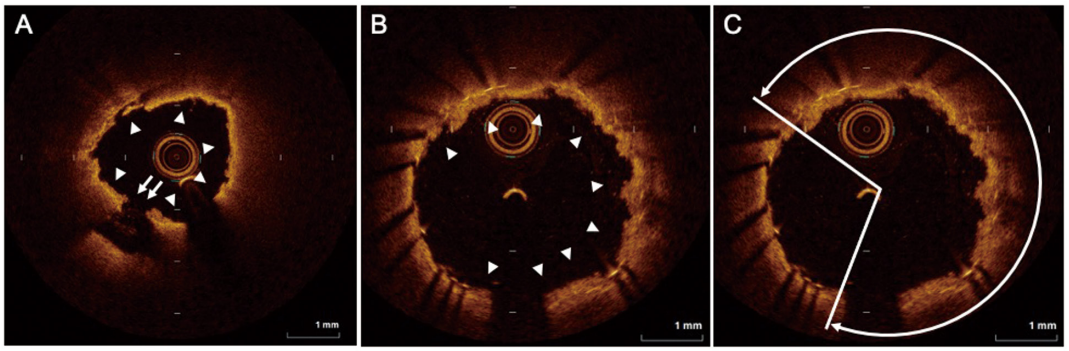

Figure 1. Measurement of maximum irregular protrusion angle. (**A**) Pre-stenting image of the culprit lesion after thrombectomy. Optical coherence tomography (OCT) showed the presence of plaque rupture (arrows) and lipid-rich plaque (arrowheads). (**B**) Post-stent OCT image. An irregular protrusion (IP) was identified in the luminal surface over the stent strut (arrowheads). (**C**) Measurement of the IP angle (arrow). The IP angle was measured using the center of the lumen as the angle point. In this image, the IP angle was 228°, and this was the maximum IP angle for this case.

Angiographic Analysis

Coronary angiograms performed before intervention and at the end of the procedure were analyzed. Antegrade coronary flow was evaluated according to the standard Thrombolysis in Myocardial Infarction (TIMI) criteria.[4]

OCT Image Acquisition and Analysis

OCT imaging was performed with an OPTIS Integrated system (Abbott Laboratories, Abbott Park, IL, USA). The OCT imaging catheter (Dragonfly OPTIS; Abbott Laboratories) was advanced distal to the target lesion. Pullback was performed during continuous injection of the contrast medium through the guide catheter. OCT images were acquired automatically at a pullback rate of 36 mm/s (180 frames/s) or 40 mm/s (160 frames/s) in the OPTIS Integrated system. OCT recording was performed 5 mm proximal and 5 mm distal to the implanted coronary stents. All OCT images were analyzed by 2 experienced investigators (A.K. and T.S.) who were blinded to the patients' information. In the case of a disagreement between the readers, a consensus reading was obtained from a third independent investigator (M.W.).

OCT analysis included baseline and post-procedural evaluations. For qualitative analysis, all cross-sectional images within the entire stent length and 5-mm peri-stent segments were analyzed. All post-stent OCT findings needed to be visible in at least 2 consecutive cross-sectional images. The morphology of the STEMI culprit lesion was evaluated immediately after successful recanalization and classified as plaque rupture, plaque erosion, or calcified nodules. Plaque rupture was defined as the presence of fibrous cap discontinuity on the lipid core or cavity formation within the plaque.[5] Plaque erosion was identified by the presence of an attached thrombus overlying an intact and visualized plaque, luminal surface irregularity at the culprit lesion in the absence of a thrombus, or attenuation of the underlying plaque by a thrombus without superficial lipids or calcification immediately proximal or distal to the site of the thrombus.[5,6] The calcified nodule was defined by fibrous cap disruption detected over a calcified plaque characterized by protruding calcification, superficial calcium, or the presence of substantive calcium proximal and/or distal to the lesion.[5]

The presence of IP, thrombus, stent edge dissection (SED), incomplete stent apposition (ISA), and MSA were evaluated after the procedure.

IP was defined as the protrusion of tissue with an irregular surface into the lumen between stent struts. Because struts are sometimes buried within the intima, we included only in-stent protrusions with a maximum height ≥100 μm for analysis.[3] If IP was identified, the IP angle was measured using the center of the mass of the lumen as the angle point instead of the center of the OCT catheter according to a previous consensus document[7] (**Figure 1**). Patients with IP were divided into 2 groups according to the maximum IP angle: large IP (maximum IP angle ≥180°) and small IP (0°<maximum IP angle≤180°). Total IP length and maximum IP height were also documented.

A thrombus was defined as a mass with a diameter ≥250 μm attached to the luminal surface, stent strut, or floating within the lumen. When a thrombus could not be completely differentiated from IP, we categorized it as IP. SED was defined as disruption of the vessel luminal surface with a visible flap at 5.0-mm proximal and distal reference segments. When SED was observed, the maximum flap length was measured. In segments without a side branch, ISA was defined as separation of the inner surface of a stent strut from the inner vessel wall by a distance greater than or equal to the axial resolution of OCT plus the width of the stent strut of each stent type, including the polymer coating. For quantitative parameters of ISA, maximum strut-to-vessel wall distance was measured as maximum ISA distance.

Cross-sectional OCT images were analyzed at 1.0-mm intervals for the following parameters: minimum lumen diameter, lesion length, mean reference diameter, and MSA. According to a previous study,[3] we defined small MSA as a lesion with an MSA <5.0 mm^2 for DES and <5.6 mm^2 for bare-metal stents.

Clinical Outcomes at the 1-Year Follow-up

All patients were scheduled for a follow-up hospital visit around 8–12 months after coronary stenting. The primary clinical endpoints were defined as device-oriented clinical endpoints (DoCE) according to pervious research 3 and

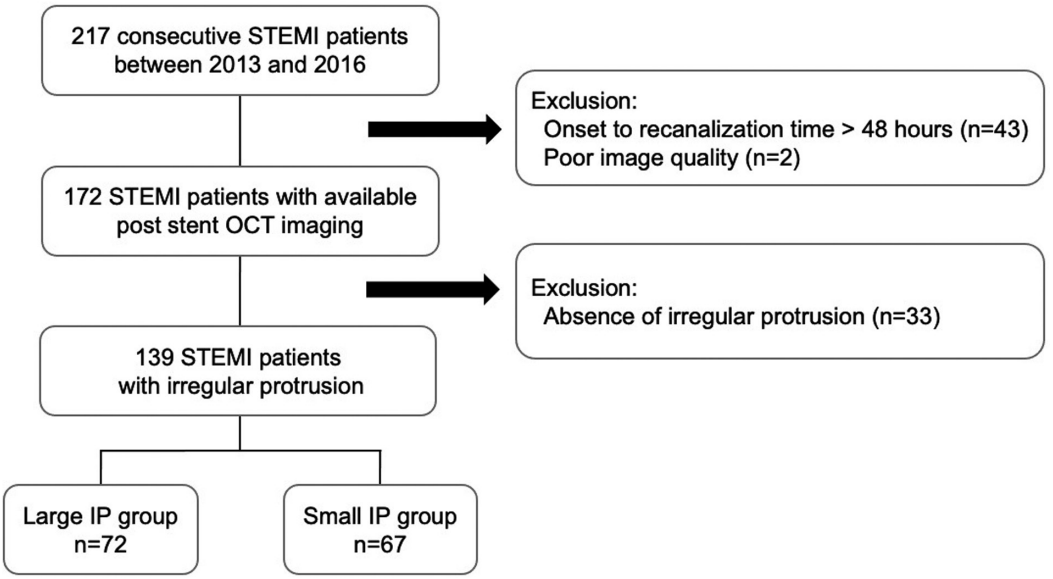

Figure 2. Study flowchart. IP, irregular protrusion; OCT, optical coherence tomography; STEMI, ST-elevation myocardial infarction.

1-year culprit lesion-related events, and included cardiac death, target-vessel-related MI, TLR, and ST.[3] Cardiac death was defined as death related to immediate cardiac causes or procedure-related complications. Target vessel-related MI was defined as acute MI (AMI) related with the stented vessel. TLR was defined as any revascularization procedure of the target lesion in the presence of angiographic restenosis and signs or symptoms of ischemia. ST was defined according to the Academic Research Consortium criteria.[8] The parameters for DoCE were recorded as secondary endpoints. AMI was defined as cardiac biomarker elevation, with at least 1 value above the 99th percentile of the upper reference limit, and with evidence of myocardial ischemia according to any one of the following criteria: (1) symptoms of ischemia; (2) ECG changes indicative of new ischemia (ST and T wave changes or new left bundle branch block); (3) development of pathological Q waves on the ECG; or (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Quantitative analysis of IP in post-procedure OCT imaging was evaluated to identify the OCT predictors for the primary endpoints.

The incidence of individual clinical endpoints was recorded in a non-hierarchical manner, whereas the composite endpoint was analyzed in a hierarchical manner. Finally, 1-year follow-up data were obtained for all patients. The median follow-up duration was 288.8 days (interquartile range [IQR] 349.5–255.3 days).

Statistical Analysis

Categorical variables are presented as counts and percentages. The distribution of continuous variables was evaluated with the Kolmogorov-Smirnov test. Normally distributed data are reported as the mean±SD, whereas non-normally distributed data are reported as the median and IQR. Fisher's exact test or the Chi-squared test was used for categorical variables, and Student's t-test or the Mann-Whitney U test was used to compare continuous variables. Multivariable logistic regression analyses were performed to determine the independent predictors of a large IP. Receiver operating characteristic (ROC) curve analyses were performed to determine the best cut-off values (using the Youden Index) for maximum IP angle and the primary endpoint. Two-sided $P<0.05$ was considered statistically significant. All statistical analyses were performed using JMP version 14.3.0 (SAS Institute, Cary, NC, USA).

This study was approved by the Institutional Review Board (IRB) at Nara Medical University (IRB no. 1759-2) and complied with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Informed consent was obtained from all patients.

Results

Baseline Characteristics

In all, 139 patients with IP after PCI were included in this study. Patients were divided into 2 groups: those with large IP (n=72; 51.8%) and those with small IP (n=67; 48.2%). The study flowchart is shown in **Figure 2**. The baseline characteristics of patients in the large and small IP groups are presented in **Table 1**. There was no significant difference between the 2 groups.

Angiographic and Procedural Findings in Patients With IP

Stent diameter was significantly larger in the large IP than small IP group (3.18±0.45 mm vs. 3.03±0.38 mm; P=0.041). Thrombectomy was performed in most patients. The incidence of distal protection was significantly higher in the large IP than small IP group (20.8% vs. 6.0%; P=0.013). The onset to recanalization time was significantly shorter in the large IP group than small IP group (240.5±141.3 min vs. 304.3±180.5 min; P=0.021; **Table 1**).

OCT Findings

The large IP group had a significantly higher incidence of plaque rupture (87.5% vs. 61.2%; P<0.001), but a significantly lower incidence of plaque erosion (8.3% vs. 28.4%; P=0.004) than the small IP group.

The large IP group had a significantly greater maximum IP angle (260.8±68.1° vs. 124.5±34.2°; P<0.001), longer total IP length (13.0±6.7 mm vs. 9.1±5.9 mm; P<0.001), and greater maximum IP height (0.32±0.11 mm vs. 0.23±0.08 mm; P<0.001) than the small IP group. However, the incidence of SED was lower in the large IP than small IP group (20.8% vs. 38.8%; P=0.026; **Table 2**).

Intra- and interobserver reliability was assessed using the kappa statistic in OCT analysis. The intra- and interobserver variabilities of the IP angle using the intraclass correlation coefficient were 0.960 and 0.886, respectively.

Clinical Events at the 1-Year Follow-up

Primary endpoints occurred in 12.5% of patients in the large IP group, compared with 1.5% of patients in the small IP group (P=0.016; **Figure 3**). Patients in the large IP group tended to have a higher incidence of cardiac death, target vessel-related MI, TLR, and ST compared with patients in in the small IP group; however, the differences did not reach statistical significance (**Table 3**). Representative OCT images of 2 stent thromboses are shown in **Supplementary Figure 1**. Target vessel-related MI was observed in only 1 case in the large IP group during the follow-up period.

Differences in primary endpoints among patients with large IP, small IP, and without IP are presented in **Supplementary Table 1**.

Medications at the 1-year follow-up are listed in **Supplementary Table 2**. There was no significant difference between the 2 groups (Large IP vs. Small IP).

Table 1. Clinical and Procedural Characteristics of Patients With Irregular Protrusion (IP) at the Index Percutaneous Coronary Intervention (PCI)

	Large IP (n=72)	Small IP (n=67)	P value
IP at index PCI			
Age (years)	64.3±10.4	67.1±12.6	0.157
Male sex	60 (82.7)	55 (82.1)	1.000
Hypertension	45 (62.5)	45 (69.2)	0.374
BMI (kg/m^2)	24.8±2.9	24.1±3.3	0.256
Obesity	31 (43.1)	29 (43.3)	1.000
Current smoker	28 (43.3)	29 (43.3)	0.745
Dyslipidemia	67 (93.1)	59 (88.0)	0.388
Diabetes	21 (29.2)	25 (37.3)	0.368
Insulin user	4 (5.6)	4 (6.0)	1.000
Family history of CAD	15 (20.8)	14 (20.9)	1.000
Prior MI	2 (2.8)	2 (3.0)	1.000
Prior PCI	4 (5.6)	3 (4.5)	1.000
CKD	16 (22.2)	18 (26.8)	0.558
Dialysis	0 (0)	3 (4.5)	0.109
Atrial fibrillation	3 (4.2)	2 (3.0)	1.000
Laboratory data on admission			
Total cholesterol (mg/dL)	191.4±42.7	182.0±42.4	0.198
LDL-C (mg/dL)	125.0±44.9	112.0±35.9	0.066
HDL-C (mg/dL)	45.7±11.3	46.9±12.4	0.564
HbA1c (%)	6.4±1.1	6.3±1.0	0.583
Peak CK (IU/L)	3,607±3,193	3,109±2,521	0.313
Peak CK-MB (IU/L)	325±274	303±285	0.639
SCr (mg/dL)	0.87±0.30	1.18±1.40	0.075
eGFR (mL/min/1.73 m^2)	76.8±25.2	70.1±24.0	0.116
LVEF (%)	59.2±9.4	57.4±9.9	0.269
Medication on admission			
Aspirin	10 (13.9)	9 (13.4)	1.000
Clopidogrel	1 (1.4)	0 (0)	1.000
Prasugrel	0 (0)	0 (0)	NA
DAPT	0 (0)	0 (0)	NA
Oral anticoagulation	0 (0)	0 (0)	NA
RAS blocker	19 (26.4)	25 (37.3)	0.203
β-blocker	4 (5.6)	3 (4.5)	1.000
Calcium channel antagonist	19 (26.4)	23 (34.3)	0.358
Statin	16 (22.2)	11 (16.4)	0.402

(**Table 1** continued the next page.)

	Large IP (n=72)	Small IP (n=67)	P value
Patients with IP			
Angiographic characteristics			
Baseline TIMI flow Grade 0–2	60 (83.3)	58 (86.6)	0.642
Final TIMI flow Grade 3	57 (79.2)	51 (76.1)	0.689
ACC/AHA lesion Class B2/C	60 (83.3)	60 (89.6)	0.330
Culprit vessel			0.173
Left anterior descending artery	31 (43.1)	39 (58.2)	
Left circumflex artery	4 (5.6)	4 (6.0)	
Right coronary artery	37 (52.4)	24 (35.8)	
Procedural characteristics			
No. stents			0.996
1	61 (84.7)	55 (82.1)	
2	10 (13.9)	11 (16.4)	
3	1 (1.4)	1 (1.5)	
Multiple stents	11 (15.3)	10 (14.9)	0.996
Stent type			0.546
Bare-metal stent	3 (4.2)	3 (4.5)	
Sirolimus-eluting stent	6 (7.1)	4 (5.0)	
Everolimus-eluting stent	56 (66.7)	55 (68.8)	
Zotarolimus-eluting stent	14 (16.7)	10 (12.5)	
Biolimus-eluting stent	5 (6.0)	8 (10.0)	
Stent diameter (mm)	3.18±0.45	3.03±0.38	0.041*
Total stent length (mm)	26.0±10.8	26.1±13.2	0.474
Thrombectomy	67 (93.1)	58 (86.6)	0.263
Distal protection	15 (20.8)	4 (6.0)	0.013*
Post dilatation	61 (84.7)	55 (82.0)	0.746
Onset to recanalization time (min)	240.5±141.3	304.3±180.5	0.021*

*Indicate significant difference. Categorical variables are shown as the number (percentage) and continuous variables are shown as the mean±SD. ACC, American College of Cardiology; AHA, American Heart Association; BMI, body mass index; CAD, coronary artery disease; CK, creatine kinase; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; RAS, renin-angiotensin system; SCr, serum creatinine.

Predictors of Primary Endpoints

Univariate analysis demonstrated that large IP (P=0.009), peak CK (P=0.009), statin use at follow-up (P=0.014), left ventricular ejection fraction (P=0.042), and stent diameter (P=0.035) were correlated with the primary endpoints (**Table 4**).

Predictors of Large IP

The univariate model showed that large IP was positively correlated with stent diameter (P=0.040) and plaque rupture (P<0.001). Higher low-density lipoprotein cholesterol (LDL-C) levels tended to be correlated with large IP (P=0.062). However, the multivariate model revealed plaque rupture was an independent predictor for large IP (odds ratio 4.58, 95% confidence interval 1.86–11.27, P=0.001; **Table 5**).

Cut-Off Value for IP Angle to Predict Primary Endpoints

ROC curve analysis showed that the best cut-off value to predict primary endpoints was a maximum IP angle ≥180.0° (area under the curve=0.74; **Supplementary Figure 2**).

Discussion

To the best of our knowledge, this is the first report of the relationship between IP volume and clinical events in patients with STEMI. The main findings of this study were that: (1) IP was frequently seen at the STEMI culprit lesion; (2) a maximum IP angle ≥180° was found in almost half the STEMI culprit lesions; (3) the incidence of primary endpoints at the 1-year follow-up was significantly higher in the large IP than small IP group; (4) large IP and statin use at follow-up were strong predictors for clinical events at 1 year after the procedure; and (5) large IP was associated with high serum LDL-C levels, larger stent diameter, and an increased incidence of plaque rupture at the STEMI culprit lesion.

Incidence of IP

IP was found in 80% of STEMI culprit lesions after coronary stenting. This incidence is consistent with that in a previous study, which found that plaque rupture occurred in 67% of STEMI culprit lesions [6] In addition, the incidence of large IP was 51.8% in the present study. Plaque rupture site have high incidence of large lipid core,[6] and this is one of the predictors of IP;[9] therefore, it is not surprising that approximately half the STEMI culprit lesions with IP had a large IP after coronary stenting.

It is important to investigate ways in which IP volume can be reduced. There is no promising device to reduce IP

Table 2. OCT Findings in Patients With IP

	Large IP (n=72)	Small IP (n=67)	P value
Baseline OCT findings			
Lesion measurement			
Mean reference diameter (mm)	3.04±0.57	2.96±0.66	0.456
Minimal lumen diameter (mm)	1.09±0.40	1.09±0.31	0.989
Lesion length (mm)	21.6±10.9	20.9±10.4	0.674
Culprit morphology			
Plaque rupture	63 (87.5)	41 (61.2)	<0.001*
Plaque erosion	6 (8.3)	19 (28.4)	0.004*
Calcified nodule	2 (2.8)	7 (10.5)	0.088
Post-stent OCT findings			
IP			
Maximum IP angle (°)	260.8±68.1	124.5±34.2	<0.001*
Total IP length (mm)	13.0±6.7	9.1±5.9	<0.001*
Maximum IP height (mm)	0.32±0.11	0.23±0.08	<0.001*
Thrombus	65 (90.3)	59 (88.1)	0.787
SED	15 (20.8)	26 (38.8)	0.026*
SED length (mm)	1.00±0.55	0.91±0.60	0.330
ISA	52 (72.2)	50 (74.6)	0.848
Maximum ISA distance (mm)	0.33±0.13	0.36±0.16	0.263
MSA (mm^2)	6.68±2.61	5.96±2.47	0.096
Small MSA	19 (26.4)	28 (41.8)	0.073

*Indicate significant difference. Categorical variables are shown as the number (percentage) and continuous variables are shown as the mean±SD. IP, irregular protrusion; ISA, incomplete stent apposition; MSA, minimal stent area; SED, stent edge dissection; OCT, optical coherence tomography.

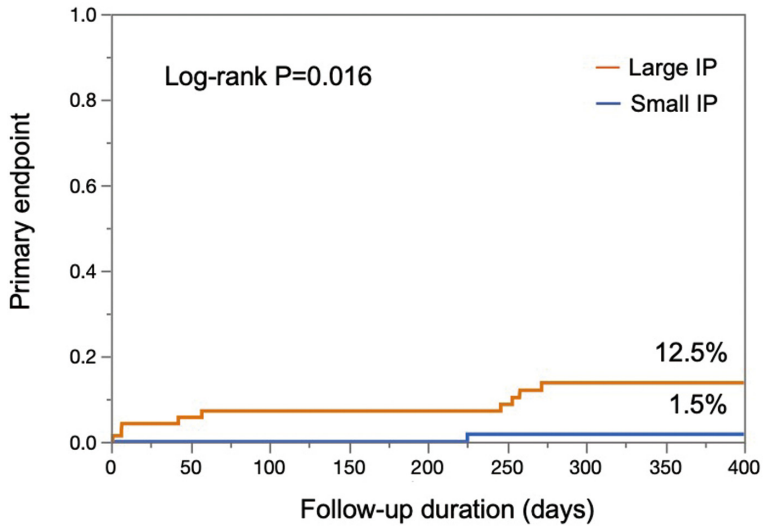

Figure 3. Kaplan-Meier survival curve for the primary endpoint in patients with large and small irregular protrusions (IPs). ST, stent thrombosis; TLR, target lesion revascularization.

volume. However, excimer laser coronary atherectomy or directional coronary atherectomy may reduce IP volume by reducing the lipid core volume. It is also unknown whether reducing IP volume can prevent future cardiac events. Because the IP is generated by a following penetration of lipid plaques with a large lipid core by stent struts, aggressive medical intervention may be one way to reduce lipid volume, large IP, and the rate of clinical events.

Large IP and Clinical Events at 1 Year

To the best of our knowledge, no previous OCT study has evaluated the correlation between the size of the IP and clinical events. One qualitative OCT study demonstrated a correlation between IP and DoCE and proposed that IP may be an indicator of deep vessel injury.[3] That study reported that the incidence of DoCE and TLR at 1 year was 6.5% and 5.8%, respectively.[3] In contrast, in the present study, patients with large IP had a much higher inci-

Table 3. Clinical Events at the 1-Year Follow-up in Patients With IP

	Large IP (n=72)	Small IP (n=67)	P value
Primary endpoints	9 (12.5)	1 (1.5)	0.018*
Secondary endpoints			
Cardiac death	4 (5.6)	1 (1.5)	0.367
Target vessel-related MI	1 (1.4)	0 (0)	1.000
TLR	4 (5.6)	1 (1.5)	0.367
Stent thrombosis	2 (2.8)	0 (0)	0.497

*Indicate significant difference. Categorical variables are shown as the number (percentage). IP, irregular protrusion; MI, myocardial infarction; TLR, target lesion revascularization.

Table 4. Univariate Analysis for Primary Endpoints in Patients With IP

	OR	95% CI	P value
Male sex	1.16	0.24–5.62	0.849
Age (per 5 years)	0.83	0.66–1.04	0.118
BMI (per 5 kg/m^2)	1.09	0.90–1.32	0.245
Dyslipidemia	1.90	0.37–9.68	0.464
CKD	1.87	0.39–8.90	0.402
LVEF (per 5%)	0.75	0.57–0.99	0.042*
Hemoglobin	1.35	0.91–2.00	0.105
LDL-C (per 10 mg/dL)	1.14	0.99–1.30	0.062
Peak CK (per 100 IU)	1.02	1.01–1.04	0.009*
Distal protection	3.29	0.600–10.13	0.238
Stent diameter (per 0.5 mm)	2.03	1.04–3.99	0.035*
Plaque rupture	1.13	0.29–4.38	0.853
Large IP	5.86	1.25–27.52	0.009*
IP length (per 5 mm)	1.22	0.83–1.79	0.586
SED	0.69	0.18–2.67	0.704
Incomplete stent apposition	2.11	0.45–10.0	0.311
Small MSA	0.55	0.15–2.14	0.376
Lesion length (per 5 mm)	0.98	0.74–1.29	0.872
Final TIMI flow Grade 0–2	2.40	0.73–7.96	0.165
Statin at follow-up	0.15	0.04–0.61	0.014*

*Indicate significant difference. CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1,2.

Table 5. Predictors for Large IP

	OR	95% CI	P value
Univariate analysis			
Age per (5 years)	0.89	0.77–1.04	0.152
Male sex	1.09	0.45–2.63	0.846
BMI per (5 kg/m^2)	1.37	0.78–2.35	0.248
Dyslipidemia	1.82	0.56–5.86	0.311
LDL-C (per 10 mg/dL)	1.08	0.99–1.18	0.062
Statin at admission	1.45	0.63–3.41	0.386
Stent diameter (per 0.5 mm)	1.52	1.01–2.28	0.040*
Total stent length (per 5 mm)	0.92	0.87–1.14	0.947
Plaque rupture	4.43	1.89–10.43	<0.001*
Multivariate analysis			
Plaque rupture	4.58	1.86–11.27	0.001*
Stent diameter (per 0.5 mm)	1.52	0.99–2.36	0.052
LDL-C (per 10 mg/dL)	1.07	0.98–1.17	0.144

*Indicate significant difference. Abbreviations as in Tables 1,4.

dence of DoCE (12.5%) at the 1-year follow-up. The presence of large IP may indicate the presence of deep vessel injury after coronary stenting. Cardiac death and TLR were the most common clinical events seen at the 1-year follow-up. Because the presence of IP was correlated with the presence of lipid-rich plaque before stenting,[8] a large IP may be caused by a large lipid core. In addition, our study showed that plaque rupture, precursors of which are lipid-rich plaques or thin-capped fibroatheromas (TCFA), was correlated with large IP. In previous OCT studies that included only patients with acute coronary syndrome (ACS), patients with OCT-detected plaque rupture generated from lipid-rich plaque and TCFA in culprit lesions had worse prognoses or clinical events that those with erosion or an intact fibrous cap after PCI.[10,11] This may be due to lipid core penetration by stent struts, which induces accelerated arterial inflammatory changes and neointimal growth.[12,13] Lesions with large IP potentially result in thicker neointimal growth than those with small IP. The correlation between pre-stenting lipid-rich plaques in culprit lesions and TLR remains unclear. A study using near-infrared spectroscopy showed no correlation between baseline lipid size and clinical events after PCI.[14] The reason for this may be that the study failed to show lipid injury after PCI.

The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study, which used virtual histology intravascular ultrasound (IVUS), evaluated the incidence of clinical events in ACS patients who underwent coronary intervention.[15] Culprit lesion-related clinical events were observed in only 12.9% of ACS patients during the 3-year follow-up period. Compared with the PROSPECT study, STEMI patients with a large IP showed a much higher incidence of culprit lesion-related events (12.5%) at the 1-year follow-up in the present study, although 30% of patients included in the PROSPECT study had STEMI. Therefore, the presence of a large IP may be a good surrogate marker to predict future culprit lesion-related events.

There were 2 cases (2.8%) of ST in patients with large IP in the present study; no cases of ST were seen in patients with small IP. Although there was no significant difference in the incidence of ST between the 2 groups, the incidence of ST in the present study was higher than that reported in a previous study.[16] In another study, lesions with ST had a higher incidence of IP angles >180° in post-stent OCT findings at the index PCI compared with the control group, which included patients without ACS for at least 5 years from the index PCI.[17] The presence of large IP may also be a predictive marker of ST during the 1-year follow-up.

Predictors of Large IP

The first OCT-detected IP study conducted showed that IP was more frequently observed in AMI patients.[3] After this initial study, several studies revealed other predictors of IP. For example, Bryniarski et al reported obesity, AMI presentation, high serum LDL-C concentrations, percentage atheroma volume, and stent length as predictors of IP.[9] Sanuki et al showed that TCFA, lipid-rich plaque, positive remodeling, and thrombus were predictors of IP.[18] Considering that most patients in these studies had stable coronary artery disease, the strongest predictors of IP were ACS-related factors, such as AMI presentation, the presence of TCFA, and the presence of a thrombus. Because all patients in the present study were STEMI, we could dem- onstrate the worst prognostic type of IP and predictors of large IP. The predictors of large IP found in this study were plaque rupture, mean stent diameter, and serum LDL-C concentration. Plaque rupture was usually caused by TCFA, including lipid-rich plaque and a large plaque burden.[19] Other etiologies of STEMI, such as plaque erosion and calcified nodules, rarely presented with TCFA or large lipid plaques in the culprit lesion; therefore, it was considered that lipid penetration by stent struts generated large IP. Mean stent diameter was significantly larger in the large IP group. This may be due to vessel diameter, because the lesions with large IP had a larger vessel diameter and larger plaque atheroma volume, allowing the larger stent to easily penetrate the lipid core. The OPINION (OPtical frequency domain imaging versus INtravascular ultrasound in percutaneous coronary interventiON) study compared post-stent OCT findings between IVUS- and OCT-guided PCI and showed a larger stent area and higher incidence of IP in IVUS-guided PCI, although the reference vessel areas were similar between the 2 groups.[20,21] Therefore, optimal stent sizing with imaging modalities is important to avoid the occurrence of large IP.

This study also demonstrated that a high serum LDL-C concentration was a discriminator for large IP. High serum LDL-C concentrations are associated with the presence of TCFA and lipid-rich plaque,[22] whereas a decrease in serum LDL-C concentration was shown to increase the thickness of the fibrous cap on the lipid core and stabilize intimal inflammation.[23–25] Hence, large IP may be prevented by early introduction of lipid-lowering agents. Nishiguchi et al reported that the early introduction of statins in ACS patients resulted in a rapid increase in fibrous cap thickness in non-culprit lesions compared with patients in whom statins were introduced later.[26]

Study Limitations

This study has several limitations. First, this study was retrospective in nature and was conducted at a single center that enrolled a limited number of patients. Second, the treatment strategy and the OCT procedure were performed at the discretion of each interventionist. Therefore, potential selection bias could not be avoided. Third, our classification of IP in this study is novel, and we have not investigated the correlation between OCT-detected IP and histopathological findings. Recently, combined OCT and angioscopic analysis for tissue protrusion revealed that yellow plaque was observed at a significantly higher rate in OCT-detected IP.[27] Fourth, it is often challenging to discriminate thrombus from protruding tissue, including IP, that is generated from a necrotic core using OCT. Previous research suggested a close association between thrombus and IP.[9] In addition, in the first report of IP, when a thrombus could not be completely differentiated from IP the authors categorized it as IP,[3] and we used the same criteria in the present study. Therefore, IP and thrombus were not completely discriminated. Fifth, we reported an association between large IP and worse clinical prognosis; however, the methods to reduce IP volume remain unknown. While stenting with a small-diameter stent may reduce the incidence of large IP, a minimum stent area $<5.0\,mm^2$ in DES is also a predictor of DoCE.

Conclusions

In conclusion, IP was frequently observed in post-stent

OCT imaging during primary PCI to manage STEMI culprit lesions. The maximum IP angle was an independent predictor of culprit lesion-related clinical events. The clinical impact of maximum IP angle in STEMI patients requires further investigation.

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Disclosures

The authors have no conflicts of interest to declare for this study.

IRB Information

This study was approved by the Ethics Committee of Nara Medical University (Approval no. 1759-2).

Data Availability

The deidentified participant data will not be shared.

References

1. Bønaa KH, Mannsverk J, Wiseth R, Aaberge L, Myreng Y, Nygård O, et al. Drug-eluting or bare-metal stents for coronary artery disease. *N Engl J Med* 2016; **375:** 1242–1252.
2. Stefanini GG, Holmes DR. Drug-eluting coronary-artery stents. *N Engl J Med* 2013; **368:** 254–265.
3. Soeda T, Uemura S, Park SJ, Jang Y, Lee S, Cho JM, et al. Incidence and clinical significance of poststent optical coherence tomography findings. *Circulation* 2015; **132:** 1020–1029.
4. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. *N Engl J Med* 1985; **312:** 932–936.
5. Jia H, Abtahian F, Aguirre AD, Lee S, Chia S, Lowe H, et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J Am Coll Cardiol* 2013; **62:** 1748–1758.
6. Higuma T, Soeda T, Abe N, Yamada M, Yokoyama H, Shibutani S, et al. A combined optical coherence tomography and intravascular ultrasound study on plaque rupture, plaque erosion, and calcified nodule in patients with ST-segment elevation myocardial infarction: Incidence, morphologic characteristics, and outcomes after percutaneous coronary intervention. *JACC Cardiovasc Interv* 2015; **8:** 1166–1176.
7. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: A report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol* 2012; **59:** 1058–1072.
8. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, Es G Van, et al. Clinical end points in coronary stent trials: A case for standardized definitions. *Circulation* 2007; **115:** 2344–2351.
9. Bryniarski KL, Tahk SJ, Choi SY, Soeda T, Higuma T, Yamamoto E, et al. Clinical, angiographic, IVUS, and OCT predictors for irregular protrusion after coronary stenting. *EuroIntervention* 2017; **12:** e2204–e2211.
10. Yonetsu T, Lee T, Murai T, Suzuki M, Matsumura A, Hashimoto Y, et al. Plaque morphologies and the clinical prognosis of acute coronary syndrome caused by lesions with intact fibrous cap diagnosed by optical coherence tomography. *Int J Cardiol* 2016; **203:** 766–774.
11. Niccoli G, Montone RA, Di Vito L, Gramegna M, Refaat H, Scalone G, et al. Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend different outcomes in patients with acute coronary syndrome. *Eur Heart J* 2015; **36:** 1377–1384.
12. Farb A, Sangiorgi G, Carter AJ, Walley VM, Edwards WD, Schwartz RS, et al. Pathology of acute and chronic coronary stenting in humans. *Circulation* 1999; **99:** 44–52.
13. SSchwartz RS, Huber KC, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE, et al. Restenosis and the proportional neointimal response to coronary artery injury: Results in a porcine model. *J Am Coll Cardiol* 1992; **19:** 267–274.
14. Yamamoto MH, Maehara A, Stone GW, Kini AS, Brilakis ES, Rizik DG, et al. 2-year outcomes after stenting of lipid-rich and nonrich coronary plaques. *J Am Coll Cardiol* 2020; **75:** 1371–1382.
15. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011; **364:** 226–235.
16. Windecker S, Meier B. Late coronary stent thrombosis. *Circulation* 2007; **116:** 1952–1965.
17. Kyodo A, Watanabe M, Okamura A, Iwai S, Sakagami A, Nogi K, et al. Post-stent optical coherence tomography findings at index percutaneous coronary intervention: Characteristics related to subsequent stent thrombosis. *Circ J* 2021; **85:** 857–866.
18. Sanuki Y, Sonoda S, Muraoka Y, Shimizu A, Kitagawa M, Takami H, et al. Contribution of poststent irregular protrusion to subsequent in-stent neoatherosclerosis after the second-generation drug-eluting stent implantation. *Int Heart J* 2018; **59:** 307–314.
19. Tian J, Dauerman H, Toma C, Samady H, Itoh T, Kuramitsu S, et al. Prevalence and characteristics of TCFA and degree of coronary artery stenosis: An OCT, IVUS, and angiographic study. *J Am Coll Cardiol* 2014; **64:** 672–680.
20. Kubo T, Shinke T, Okamura T, Hibi K, Nakazawa G, Morino Y, et al. Optical frequency domain imaging vs. intravascular ultrasound in percutaneous coronary intervention (OPINION trial): One-year angiographic and clinical results. *Eur Heart J* 2017; **38:** 3139–3147.
21. Otake H, Kubo T, Takahashi H, Shinke T, Okamura T, Hibi K, et al. Optical frequency domain imaging versus intravascular ultrasound in percutaneous coronary intervention (OPINION Trial): Results from the OPINION imaging study. *JACC Cardiovasc Imaging* 2018; **11:** 111–123.
22. Yonetsu T, Hoshino M, Lee T, Kanaji Y, Yamaguchi M, Hada M, et al. Plaque morphology assessed by optical coherence tomography in the culprit lesions of the first episode of acute myocardial infarction in patients with low low-density lipoprotein cholesterol level. *J Cardiol* 2020; **75:** 485–493.
23. Komukai K, Kubo T, Kitabata H, Matsuo Y, Ozaki Y, Takarada S, et al. Effect of atorvastatin therapy on fibrous cap thickness in coronary atherosclerotic plaque as assessed by optical coherence tomography: The EASY-FIT study. *J Am Coll Cardiol* 2014; **64:** 2207–2217.
24. Tawakol A, Fayad ZA, Mogg R, Alon A, Klimas MT, Dansky H, et al. Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: Results of a multicenter fluorodeoxyglucose-positron emission tomography/computed tomography feasibility study. *J Am Coll Cardiol* 2013; **62:** 909–917.
25. Hou J, Xing L, Jia H, Vergallo R, Soeda T, Minami Y, et al. Comparison of intensive versus moderate lipid-lowering therapy on fibrous cap and atheroma volume of coronary lipid-rich plaque using serial optical coherence tomography and intravascular ultrasound imaging. *Am J Cardiol* 2016; **117:** 800–806.
26. Nishiguchi T, Kubo T, Tanimoto T, Ino Y, Matsuo Y, Yamano T, et al. Effect of early pitavastatin therapy on coronary fibrous-cap thickness assessed by optical coherence tomography in patients with acute coronary syndrome: The ESCORT Study. *JACC Cardiovasc Imaging* 2018; **11:** 829–838.
27. Sakai S, Sato A, Hoshi T, Hiraya D, Watabe H, Ieda M. In vivo evaluation of tissue protrusion by using optical coherence tomography and coronary angioscopy immediately after stent implantation. *Circ J* 2020; **84:** 2235–2243.

Supplementary Files

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