JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 14, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.05.043

CELL THERAPY

Prevalence and Clinical Impact of Tissue Protrusion After Stent Implantation

An ADAPT-DES Intravascular Ultrasound Substudy

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the prevalence and long-term clinical impact of tissue protrusion (TP) after stent implantation.

BACKGROUND Stent implantation may be associated with tissue (plaque or thrombus) protrusion, especially in unstable lesions, but its clinical impact is unknown.

METHODS ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) was a prospective multicenter study of 8,663 patients undergoing percutaneous coronary intervention (PCI) using drug-eluting stents. In a pre-specified intravascular ultrasound (IVUS) substudy, 2,072 patients with 2,446 culprit lesions underwent post-PCI IVUS (among whom some also underwent pre-PCI IVUS) and were classified according to the presence or absence of post-stent TP.

RESULTS After PCI, 34.3% of lesions displayed TP on IVUS. Median maximum TP was 0.7 mm^2 (interquartile range: 0.5 to 1.2 mm^2) in area and 3.0 mm (interquartile range: 1.4 to 6.7 mm) in length. Patients with TP more often presented with ST-segment elevation myocardial infarction or non–ST-segment elevation myocardial infarction but less often with unstable angina or stable ischemic heart disease. In 893 culprit lesions that were also examined pre-PCI, TP was associated with larger reference luminal area, greater plaque burden, and more plaque ruptures, attenuated plaque, and virtual histology thin-cap fibroatheromas. Because a larger stent or post-dilation balloon was used, post-PCI luminal area was significantly larger in lesions with versus without TP. At 2-year follow-up, there was less clinically driven target lesion revascularization in lesions with TP and no significant difference in major adverse cardiac events (defined as cardiac death, myocardial infarction, or stent thrombosis) in patients with versus without TP.

CONCLUSIONS IVUS-detected TP after drug-eluting stent implantation was not associated with worse long-term clinical outcomes, in part because of greater stent expansion in lesions with TP. (J Am Coll Cardiol Intv 2016;9:1499–507) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CK = creatine kinase

DES = drug-eluting stent(s)

EEM = external elastic membrane

IQR = interquartile range

IVUS = intravascular ultrasound

MACE = major adverse cardiac event(s)

MI = myocardial infarction

MLA = minimal luminal area

NSTEMI = non-ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

RCA = right coronary artery

STEMI = ST-segment elevation myocardial infarction

TCFA = thin-cap fibroatheroma

TLR = target lesion revascularization

TP = tissue protrusion

ULN = upper limit of normal

VH = virtual histology

Before the introduction of intravascular ultrasound (IVUS), the incidence of intrastent tissue protrusion (TP) after percutaneous coronary intervention (PCI) was underestimated (1) because of the limitations of coronary angiography. Conversely, TP is frequently detected by IVUS (2–8), although previous IVUS studies examining the clinical impact of TP were inconsistent (3–6,9,10) and were usually conducted in relatively small patient cohorts or selected patient populations.

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ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) was a large-scale, prospective, multicenter study designed to assess the relationship between platelet reactivity and other clinical and procedural variables with subsequent stent thrombosis and adverse clinical events in patients treated with drug-eluting stents (DES) (11). In a pre-specified substudy, culprit lesions were prospectively evaluated using grayscale and virtual histology (VH) IVUS before and after IVUS-guided DES implantation (12). The aims of the current ADAPT-DES IVUS substudy were to assess the frequency, predictors, and prognostic impact of TP after DES implantation.

METHODS

PATIENT SELECTION AND IMAGING. The design, major inclusion and exclusion criteria, endpoints, and definitions of the ADAPT-DES study have been previously described in detail (11,12). In brief, ADAPT-DES was a prospective, multicenter, observational study of 8,663 patients who were treated successfully with 1 or more U.S. Food and Drug Administration– or CE mark–approved DES regardless of patient or lesion complexity. Procedural IVUS use was per operator discretion; however, the operator was required to report the timing of IVUS imaging and how the IVUS information influenced the procedure. Among 2,179 patients enrolled in a pre-specified IVUS substudy, 2,072 patients with analyzable post-PCI IVUS were included in the present report; 780 of them also had analyzable pre-PCI IVUS. Clinical follow-up was done until 2 years. The study was approved by the Institutional Review Board at each participating center, and all eligible patients provided written informed consent.

Periprocedural myocardial infarction (MI) in the present study was defined as total creatine kinase (CK) >2 times the upper limit of normal (ULN) with positive CK-MB or troponin I or T. If the total CK level was not available, CK-MB >3 times ULN was considered evidence of periprocedural MI. If neither CK nor CK-MB was available, troponin elevation >5 times the 99th percentile of the upper reference limit or ULN for the specific institution was considered evidence of periprocedural MI (12).

In the present analysis, major adverse cardiac events (MACE) included cardiac death, MI, and stent thrombosis, as defined previously and as adjudicated by an independent clinical events committee (11–13). Clinically driven target lesion revascularization (TLR) was site reported but not centrally adjudicated.

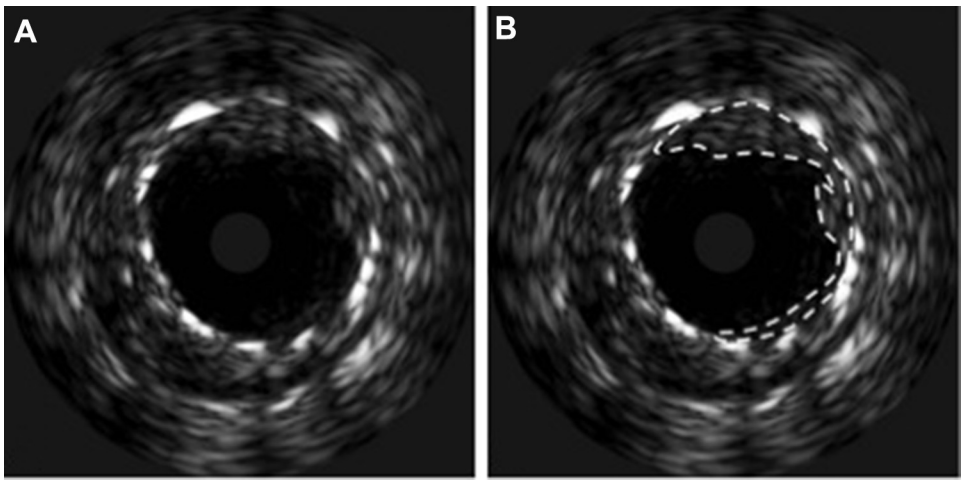
ANGIOGRAPHIC ANALYSIS. Angiograms were evaluated visually by operators at the time of the procedure. Thrombus was defined as a discrete intraluminal filling defect with defined borders, largely separated from the adjacent wall and with or without contrast staining. Calcium was defined as readily visible densities noted within the apparent vascular wall at the site of the stenosis. A bifurcation lesion had a branch >1.5 mm in size originating within the stenosis that was completely surrounded by stenotic portions of the lesion to be treated.

GRAYSCALE IVUS AND IVUS-VH IMAGE ACQUISITION. Pre- and post-stenting grayscale IVUS and IVUS-VH were performed using a synthetic aperture array, 20-MHz, 3.2-F catheter (Eagle Eye, Volcano, Rancho Cordova, California) after intracoronary nitroglycerin administration. The IVUS catheter was advanced distal to the lesion and pulled backed to the aorto-ostial junction using an R-100 motorized catheter pull-back system (0.5 mm/s). During pull-back, grayscale IVUS was recorded, raw radiofrequency data were captured at the top of the R-wave, and reconstruction of the color-coded map by an IVUS-VH data recorder (s5, Volcano) was performed. IVUS studies

Dr. Kirtane has received institutional research grants to Columbia University from Boston Scientific, Medtronic, Abbott Vascular, Abiomed, St. Jude Medical, Vascular Dynamics, and Eli Lilly. Dr. Maehara has received grant support from Boston Scientific; is a consultant for Boston Scientific and ACIST; and has received speaking fees from St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 1, 2016; accepted May 5, 2016.

FIGURE 1 Representative Intravascular Ultrasound Image of Tissue Protrusion



Intravascular ultrasonographic images **(A and B)** show tissue intrusion through the stent struts into the lumen as tissue protrusion **(dotted line in B)**.

were archived onto DVDs. Using computerized planimetry software (echoPlaque; INDEC Systems, Mountain View, California), contouring, and data output, offline grayscale IVUS and IVUS-VH analyses of all imaged segments were performed prospectively at an independent IVUS core laboratory (Cardiovascular Research Foundation, New York, New York) that was blinded to the clinical events.

GRAYSCALE IVUS AND IVUS-VH ANALYSIS. The culprit lesion was defined as the lesion that was stented. Proximal and distal 5-mm-long segments from each culprit lesion edge (pre-PCI) or stent edge (post-PCI), but before a significant (>1.5 mm in diameter) side branch, were defined as the reference segments.

Quantitative measurements pre- and post-PCI were performed every 1 mm of the external elastic membrane (EEM), lumen, and stent areas (post-PCI), and plaque and media (EEM minus lumen) and plaque burden (plaque and media divided by EEM) were calculated. The slice with the minimal luminal area (MLA) and minimal stent area within each culprit lesion and the slice with largest luminal cross-sectional area with the smallest plaque burden (most normal site) within each reference segment were identified and assessed. Volumes were calculated using Simpson's rule and reported as total and normalized volumes (volume divided by analysis length).

Pre-PCI qualitative grayscale IVUS morphologic analysis included plaque rupture (intraplaque cavity that communicated with the lumen with an overlying residual fibrous cap fragment) and attenuated plaque (ultrasound attenuation of deeper arterial structures despite the absence of bright calcium) (14). Post-PCI qualitative analysis included: 1) intrastent TP (plaque and/or thrombus intrusion through the stent struts into the lumen) (Figure 1); 2) stent malapposition (blood speckle behind stent struts not overlaying a side branch); and 3) edge dissection (intimal, medial, intramural hematoma, or outside the EEM) (6,14).

IVUS-VH plaque components were color-coded as dense calcium (white), necrotic core (red), fibrofatty (light green), or fibrous tissue (dark green) and reported as normalized volumes (15). A fibroatheroma had >10% confluent necrotic core (spotty red color was not considered confluent necrotic core). If there was >30° of necrotic core abutting the lumen in 3 consecutive slices, the fibroatheroma was classified as VH thin-cap fibroatheroma (TCFA) (15).

STATISTICAL ANALYSIS. Baseline patient clinical characteristics were analyzed on a patient level, angiographic and procedural characteristics were analyzed on both patient and lesion levels, and IVUS characteristics were analyzed on a lesion level. Categorical variables were compared using chi-square or Fisher exact test as appropriate. Continuous variables were compared using the Wilcoxon rank sum test and are expressed as median (interquartile range [IQR]). Predictors of TP were identified by screening clinical, angiographic, procedural, and IVUS variables in univariate analyses. The multivariate model was developed by including candidate variables in a stepwise model procedure (entry and stay criterion, $p = 0.10$)

TABLE 1 Baseline Clinical Characteristics

	Tissue Protrusion (n = 797)	No Tissue Protrusion (n = 1,275)	p Value
Age, yrs	64.0 (55.0–71.0)	64.0 (56.0–71.0)	0.86
Male	76.0% (606)	75.0% (956)	0.59
Current smoking	30.9% (246)	29.5% (376)	0.51
Diabetes mellitus	25.3% (202)	31.1% (396)	0.005
Insulin-treated	9.2% (73)	11.0% (140)	0.18
Hypertension	74.9% (597)	78.7% (1,004)	0.04
Hyperlipidemia	57.2% (456)	66.0% (842)	<0.0001
Renal insufficiency*	10.3% (82)	8.9% (114)	0.31
Body mass index, kg/m^2	28.1 (25.3–31.7)	27.6 (24.9–31.1)	0.02
Previous MI	21.7% (173)	27.4% (349)	0.004
Previous PCI	32.2% (257)	43.1% (550)	<0.0001
Previous CABG	10.0% (80)	12.2% (155)	0.14
Presenting clinical syndrome			
ST-segment elevation MI	25.2% (201)	13.3% (169)	<0.0001
Non-ST-segment elevation MI	21.6% (172)	15.8% (201)	0.0008
Unstable angina	20.2% (161)	24.2% (309)	0.03
Stable ischemic heart disease	33.0% (263)	46.7% (596)	<0.0001
Left ventricular ejection fraction,† %	60.0 (50.0–68.0)	60.0 (50.0–70.0)	0.07
Medications (pre-admission)			
Aspirin	75.0% (598)	78.7% (1,004)	0.05
Thienopyridine	43.0% (343)	43.1% (549)	0.99
Statin	46.0% (367)	59.3% (756)	<0.0001

Values are median (interquartile range) or % (n). *Creatinine clearance <60 ml/min calculated using the Cockcroft-Gault formula. †Available in only 746 patients in the tissue protrusion group and 1,191 patients in the no-tissue-protrusion group.

CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention.

and summarizing the selected variables using Poisson regression. Time-to-event data were summarized as Kaplan-Meier estimates by TP status and were compared using the log-rank test. TP violated the assumption of proportional hazard; therefore, Poisson regression also modeled TLR at 2 years with the inclusion of an offset for follow-up time. This model included TP along with clinically relevant variables. All lesion-level analyses were modeled with a generalized estimating equation approach to correct for multiple lesions from the same patient. A p value of <0.05 was considered to indicate statistical significance. Statistical analyses were performed using SAS versions 9.2 and 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CLINICAL CHARACTERISTICS. Among 2,072 patients with 2,446 lesions, the overall prevalence of TP was 38.5% per patient and 34.3% per lesion. On a patient level, there was a decreasing gradient in TP prevalence from 54.3% in ST-segment elevation myocardial infarction (STEMI) to 46.1% in non-ST-segment elevation myocardial infarction (NSTEMI) to 34.3% in unstable angina to 30.6% in stable ischemic heart disease.

Comparisons of baseline clinical characteristics between patients with versus without TP are summarized in Table 1. Patients with TP had a lower prevalence of coronary risk factors such as diabetes mellitus, hypertension, and hyperlipidemia. Also, patients with TP less frequently had histories of MI and PCI. Patients with TP were more likely to have higher body mass index (BMI) and presented more often with STEMI or NSTEMI but less often with unstable angina or stable ischemic heart disease. Patients with TP were less likely to receive aspirin and statins pre-admission compared with those without TP; however, at discharge and follow-up, both groups were similarly medicated (data not shown).

ANGIOGRAPHIC AND PROCEDURAL FINDINGS. Angiographic and procedural findings are shown in Table 2. The group with TP was associated with more thrombus, worse baseline TIMI (Thrombolysis In Myocardial Infarction) flow, and less calcium. In the TP group, lesions were more likely to be treated with larger sized devices (DES and/or post-dilating balloons), higher maximal inflation pressures, and longer stents. In addition, second-generation stents tended to be used less often in the TP group versus the no-TP group.

IVUS FINDINGS. As shown in Table 3, in 893 culprit lesions examined by pre-PCI IVUS, lesions with TP more frequently had plaque ruptures, attenuated plaques, and VH TCFA compared with lesions without TP. Quantitative analysis revealed that TP was associated with larger reference size, longer lesions, larger lesion EEM areas, greater lesion plaque burden, and more positive remodeling compared with those without TP.

Post-PCI, median TP length was 3.0 mm (IQR: 1.4 to 6.7 mm), and median TP area was 0.7 mm^2 (IQR: 0.5 to 1.2 mm^2); TP occupied a median 8.8% (IQR: 5.8% to 13.6%) of the stent area at the maximum TP site. Final MLA <5 mm^2 was observed in 26.3% of the 840 lesions with TP. Among lesions with TP and MLA <5 mm^2, median TP area was 0.5 mm^2 (IQR: 0.3 to 0.8 mm^2), and TP occupied a median 9.0% (IQR: 5.8% to 13.9%) of the stent area at the maximum TP site.

As shown in Table 4, lesions with TP were located more frequently in the right coronary artery (RCA), whereas lesions without TP were located more often in the left anterior descending coronary artery. Stent edge dissection was more prevalent in lesions with TP versus those without TP. In the TP group, stent length was significantly longer than in the no-TP group (31.8 mm vs. 26.2 mm, $p < 0.0001$). Furthermore, stent expansion (as a percentage of reference luminal area) was significantly greater (74.8% vs. 72.8%;

p = 0.01) in lesions with TP, leading to larger post-PCI luminal areas (MLA 6.7 mm^2 vs. 6.0 mm^2; p < 0.0001) compared with lesions without TP.

PREDICTORS OF TP. Variables included in the multivariate model selection analysis were age, sex, BMI, diabetes mellitus, previous MI, hypertension, acute coronary syndrome, left ventricular ejection fraction, statin treatment before admission, RCA location, angiographic presence of calcium, pre-PCI TIMI flow grade 0 or 1, second-generation DES, total stent length, maximal device (i.e., stent or balloon) diameter, maximal balloon pressure, and stent expansion (Table 5). The positive predictors of TP were age, BMI, STEMI or NSTEMI presentation, RCA location, pre-PCI TIMI flow grade 0 or 1, total stent length, maximal device diameter, and stent expansion, whereas the negative predictors included statin treatment before admission and angiographic presence of calcium.

CLINICAL OUTCOMES. In subgroups of patients with normal enzyme values pre-PCI, the incidence of post-PCI peak CK greater than ULN (33.4% vs. 17.4%; p < 0.0001), peak CK-MB greater than ULN (39.8% vs. 23.3%; p < 0.0001), and peak troponin (I or T) greater than ULN (68.8% vs. 38.5%; p < 0.0001) was significantly higher in the TP group than in the no-TP group.

Two-year MACE after stent implantation are summarized in Table 6. The incidence of cardiac death, MI, or stent thrombosis was similar between patients with TP versus those without TP. In terms of stent thrombosis, there was no difference in the frequency of early (<30 days), late (30 days to 1 year), or very late (>1 year) thrombosis between the 2 groups. Multivariate analysis for the predictors of 2-year MACE was performed. Variables included in this model were diabetes mellitus, previous PCI, visual vessel diameter, total stent length, post-procedural MLA, post-procedural plaque burden at MLA site, presence of TP, and presence of stent edge dissection. The results showed that diabetes mellitus and total stent length were the significant predictors, whereas TP was not a predictor of MACEs (data not shown). The incidence of clinically driven TLR at 2-year follow-up was significantly lower in lesions with TP versus without TP (1.9% vs. 4.0%; p = 0.008). Figure 2 shows the corresponding Kaplan-Meier curves. Adjusted results also showed that TP was associated with a reduced risk for clinically driven TLR (adjusted relative risk: 0.48; 95% confidence interval: 0.27 to 0.88; p = 0.02) even after controlling for diabetes mellitus, previous PCI, visual angiographic vessel diameter, total stent length, post-procedural MLA, post-procedural plaque burden at the MLA site, and presence of stent edge dissection.

TABLE 2 Angiographic and Procedural Findings

	Tissue Protrusion	No Tissue Protrusion	p Value
Patient level	n = 797	n = 1,275	
3-vessel disease	1.0% (8)	1.0% (13)	0.97
Lesion level	n = 836	n = 1594	
Thrombus	34.1% (285)	17.9% (285)	<0.0001
Calcium	29.9% (250)	35.6% (567)	0.046
Bifurcation lesion	13.8% (115)	15.7% (250)	0.41
Lesion length, mm	26.5 (25.4–27.7)	22.0 (21.2–22.7)	<0.0001
Pre-maximal diameter stenosis, %	89.7 (89.0–90.5)	84.5 (83.9–85.2)	<0.0001
Post-maximal diameter stenosis, %	0.7 (0.5–0.9)	0.7 (0.5–0.8)	0.69
Pre-TIMI flow grade 0/1	21.1% (176)	10.3% (164)	<0.0001
Final TIMI flow grade 3	99.6% (833)	99.8% (1,591)	0.43
Second-generation drug-eluting stent*	76.0% (635)	78.5% (1,251)	0.06
Total stent length, mm	31.8 (30.6–33.1)	26.3 (25.5–27.1)	<0.0001
Maximal device diameter, mm†	3.6 (3.5–3.6)	3.3 (3.3–3.3)	<0.0001
Maximal balloon pressure, atm	16.5 (16.2–16.7)	16.1 (15.9–16.3)	0.01

Values are % (n) or median (interquartile range). *Everolimus-eluting or zotarolimus-eluting stent. †Device is defined as stent or post-dilating balloon.
TIMI = Thrombolysis In Myocardial Infarction.

Angiographic visual vessel diameter was also a negative predictor of clinically driven TLR, whereas positive predictors were previous PCI, total stent length, post-procedural plaque burden at the MLA site, and presence of stent edge dissection (Table 7). In lesions with TP, the rate of clinically driven TLR was not significantly different among different tertiles of TP

TABLE 3 Pre-Procedural Intravascular Ultrasound Findings

	Tissue Protrusion (n = 335 Lesions)	No Tissue Protrusion (n = 558 Lesions)	p Value
Qualitative analysis			
Plaque rupture	49.0% (164)	24.2% (135)	<0.0001
Attenuated plaque	77.9% (261)	71.3% (398)	0.02
Calcified nodule	4.5% (15)	6.5% (36)	0.22
VH TCFA	62.1% (208)	45.9% (256)	<0.0001
Quantitative analysis			
Lesion length, mm	32.3 (30.5–34.1)	26.0 (24.6–27.3)	<0.0001
Proximal reference luminal area, mm^2	11.3 (10.7–11.9)	10.0 (9.5–10.4)	0.0002
Distal reference luminal area, mm^2	8.0 (7.5–8.5)	7.2 (6.9–7.4)	0.006
Minimal lumen site			
EEM area, mm^2	15.1 (14.4–15.8)	12.7 (12.2–13.1)	<0.0001
Luminal area, mm^2	2.7 (2.6–2.8)	2.9 (2.8–3.0)	0.002
Plaque burden, %	78.9 (77.8–80.0)	73.8 (72.9–74.8)	<0.0001
Remodeling index*	1.05 (1.00–1.10)	0.99 (0.96–1.02)	0.05
Volumetric analysis			
Mean EEM area, mm^3/mm	15.4 (14.8–16.0)	13.3 (12.9–13.7)	<0.0001
Mean luminal area, mm^3/mm	6.0 (5.8–6.2)	5.7 (5.5–5.9)	0.04
Percentage plaque volume, %	60.3 (55.0–66.4)	56.3 (50.1–61.9)	<0.0001
Percentage necrotic core volume, %	23.1 (22.3–24.0)	22.4 (21.7–23.0)	0.15
Percentage dense calcium volume, %	9.6 (9.0–10.2)	11.1 (10.4–11.8)	0.0006

Values are % (n) or median (interquartile range). *EEM area at the minimal lumen site divided by the average of the proximal and distal reference EEM areas.
EEM = external elastic membrane; TCFA = thin-cap fibroatheroma; VH = virtual histology.

TABLE 4 Post-Procedural Intravascular Ultrasound Findings

	Tissue Protrusion (n = 840 Lesions)	No Tissue Protrusion (n = 1,606 Lesions)	p Value
Lesion location			
Left main	2.0% (17)	2.7% (43)	0.32
Left anterior descending	33.7% (283)	45.5% (730)	<0.0001
Left circumflex	19.4% (163)	22.2% (356)	0.11
Right coronary artery	41.1% (345)	26.8% (431)	<0.0001
Graft	3.8% (32)	2.9% (46)	0.21
Qualitative analysis			
Stent malapposition	13.0% (109)	12.4% (199)	0.68
Stent edge dissection	8.6% (72)	5.6% (89)	0.004
Quantitative analysis			
Total stent length, mm	31.8 (30.5–33.0)	26.2 (25.5–27.0)	<0.0001
In-stent MLA, mm^2	6.7 (6.5–6.8)	6.0 (5.8–6.1)	<0.0001
MSA, mm^2	6.8 (6.6–7.0)	6.0 (5.8–6.1)	<0.0001
In-stent mean luminal area, mm^3/mm	8.3 (8.2–8.5)	7.4 (7.2–7.5)	<0.0001
Mean stent area, mm^3/mm	8.4 (8.3–8.6)	7.3 (7.2–7.5)	<0.0001
Stent expansion,* %	74.8 (73.5–76.1)	72.8 (72.0–73.7)	0.01

Values are % (n) or median (interquartile range). *MSA divided by the average of the proximal and distal reference luminal areas.
MLA = minimal luminal area; MSA = minimal stent area.

area or percentage of TP (defined as TP area divided by stent area) at the maximum TP site, indicating that there was no correlation between the amount of TP and clinically driven TLR (data not shown).

As a sensitivity analysis, all multivariate models were analyzed by adjusting for U.S. versus non-U.S. sites and selecting 1 observation per patient (data not shown). These results were consistent with the results presented.

DISCUSSION

The major findings of the present study were the following. First, the overall prevalence of TP detected by IVUS was 34.3% per lesion, with a decreasing gradient in prevalence from STEMI to NSTEMI to unstable angina to stable ischemic heart disease. Second, patient age, BMI, STEMI or NSTEMI presentation, RCA location, pre-PCI TIMI flow grade 0 or 1, total stent length, maximal device diameter, and stent expansion were the positive predictors of TP, whereas statin treatment before admission and angiographic presence of lesion calcium were the negative predictors of TP. Third, there was more periprocedural enzyme elevation in the setting of TP. Last, at 2-year follow-up, there was less clinically driven TLR in lesions with TP and no significant difference in incidence of cardiac death, MI, or stent thrombosis between patients with and those without TP.

TABLE 5 Multivariate Predictors of Tissue Protrusion

	Relative Risk	95% Confidence Interval	p Value
Age, per 10 yrs	1.08	1.02–1.14	0.007
Body mass index	1.01	1.00–1.02	0.008
Acute coronary syndrome presentation	1.31	1.15–1.49	<0.0001
Statin treatment before admission	0.81	0.72–0.90	0.003
Right coronary artery location	1.25	1.11–1.40	0.0001
Angiographic presence of calcium	0.82	0.73–0.93	0.002
Pre-TIMI flow grade 0/1	1.24	1.09–1.41	0.001
Total stent length (per 10 mm)	1.06	1.03–1.09	<0.0001
Maximal device diameter	1.41	1.29–1.54	<0.0001
Stent expansion (per 10%)	1.05	1.02–1.08	0.001

TIMI = Thrombolysis In Myocardial Infarction.

TABLE 6 2-Year Kaplan-Meier Event Rates

	Tissue Protrusion	No Tissue Protrusion	p Value
Patient level	n = 797	n = 1,275	
Major adverse cardiac events*	4.2% (33)	4.8% (59)	0.61
Cardiac death	1.2% (9)	1.7% (20)	0.41
Myocardial infarction	3.2% (25)	3.3% (40)	0.99
Periprocedural	1.8% (14)	0.9% (12)	0.10
Nonperiprocedural	1.4% (11)	2.3% (28)	0.18
Stent thrombosis (definite/probable)	0.60% (5)	0.38% (6)	0.44
Lesion level	n = 836	n = 1,594	
Clinically driven target lesion revascularization	1.9% (16)	4.0% (62)	0.008

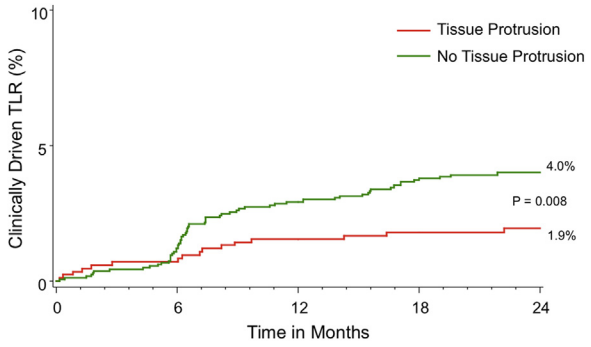
Values are % (n). *Cardiac death, myocardial infarction, or stent thrombosis.

PREVALENCE OF TP. Brack et al. (16) first reported TP detected by angiography and characterized it as persistent residual in-stent haziness despite several full balloon inflations; however, because of the limitations of angiography, small TP was probably missed, and TP was considered a rare phenomenon detected by angiography alone (1). IVUS detected TP more commonly than angiography, and TP appeared as plaque and/or thrombus intrusion through the stent struts into the lumen after stent implantation. Maehara et al. (2) showed plaque and/or thrombus protrusion through stent struts in 69% of lesions in patients with STEMI presentation. Hong et al. (7) reported that TP was detected in 33% of patients with STEMI and 24% of those with NSTEMI. Wu et al. (8) reported TP in 30.5% of patients. Futamatsu et al. (4) revealed that in patients with diabetes with coronary artery disease, 16.6% of lesions had TP after stent implantation. In the present study involving a large number of unselected patients, TP was detected in 38.5% overall and 54.3% of those with STEMI, 46.1% of those with NSTEMI, 34.3% of those with unstable angina, and 30.6% of those with stable ischemic heart disease, similar to previous studies.

PREDICTORS OF TP. A previous IVUS study demonstrated that factors such as plaque rupture, positive remodeling, and stent length were independent predictors of TP (5). Using optical coherence tomography, Sugiyama et al. (17) showed that RCA lesion location, lesion length, and TCFA were significantly related to larger TP volume. Moreover, using IVUS, Hong et al. (18) detected TP after stent implantation into saphenous vein graft disease and suggested that "soft plaque," plaque burden, stent length, and stent expansion were independent predictors of TP. In general, the present study supports and extends these findings. For example, the greater the risk for vulnerable plaque (VH TCFA) or thrombus (suggested by unstable clinical presentation), the more frequently TP was detected by IVUS. Conversely, solid calcium may not easily protrude into the lumen through the stent struts. Statins have a stabilizing effect on lesion morphology by reducing the atheroma burden and lipid content, necrotic core, plaque rupture, and attenuated plaque (19-21). These are the findings that are most closely associated with TP. In addition, statins may reduce periprocedural myocardial injury (22), which might be associated with TP. In the present study, patients without TP were more often taking statins pre-PCI and had a reduced prevalence of plaque rupture, attenuated plaque, and VH TCFA. More aggressive treatment strategies using larger devices (stents or balloons), higher inflation pressures, or longer stents that resulted in greater stent expansion also resulted in a higher prevalence of TP. Shen et al. (23) demonstrated that stent type was an independent predictor of TP. However, many other studies showed no significant difference in TP prevalence among lesions treated by different types of stents (5,6,8). In the present study, the type of metal or design of the stent did not appear to be as important as the underlying lesion morphology or the aggressiveness of the implantation technique.

OUTCOMES RELATED TO TP. Hong et al. (5,6) demonstrated greater post-PCI elevation of CK-MB or troponin I in patients with acute MI with TP compared with those with acute MI with no TP, and TP was among the independent predictors of post-stenting CK-MB elevation. However, Jin et al. (24) showed that there was no difference in CK-MB elevation among groups with different severities of TP. In the present study, elevations of CK, CK-MB, and troponin I or T were more common in patients with TP than those without TP; however, the prevalence of no-reflow or enzyme elevations that met the threshold for periprocedural MI was similar between the TP and no-TP groups.

FIGURE 2 Kaplan-Meier Curves for Clinically Driven Target Lesion Revascularization



Kaplan-Meier curves for clinically driven target lesion revascularization (TLR). The incidence of clinically driven TLR on the lesion level was significantly lower for lesions with tissue protrusion compared with those without tissue protrusion at 2-year follow-up.

Hong et al. (3) suggested that minor TP was not related to in-stent restenosis at 6-month follow-up. Conversely, Hong et al. (6) showed that TP was related to poor short-term outcomes, such as more acute and subacute thrombosis and no-reflow, but was not associated with worse 1-year outcomes, including cardiac death, MI, and late stent thrombosis and target vessel revascularization in patients with acute MI. Choi et al. (25) reported that significant TP that led to a small lumen was more prevalent in patients with early stent thrombosis after primary PCI. Kawamori et al. (26) reported that TP was not associated with TLR at 8-month follow-up. Jin et al. (24) reported that TP was not associated with clinical events during the hospitalization period and 1-year follow-up. Recently, an optical coherence tomographic study characterized TP into 3 types: smooth protrusion, disrupted fibrous TP, and irregular

TABLE 7 Multivariate Predictors of Clinically Driven Target Lesion Revascularization at 2-Year Follow-Up

	Relative Risk	95% Confidence Interval	p Value
Previous percutaneous coronary intervention	2.24	1.38-3.64	0.001
Visual vessel diameter	0.64	0.51-0.80	0.0001
Total stent length, per 10 mm	1.26	1.14-1.39	<0.0001
Post-procedural plaque burden at minimal luminal area site	1.03	1.01-1.06	0.004
Presence of tissue protrusion	0.48	0.27-0.88	0.02
Presence of stent edge dissection	2.49	1.19-5.18	0.02

Other variables in the model that were not significantly associated with target lesion revascularization at 2 years were diabetes mellitus and post-procedural minimal luminal area.

protrusion; irregular protrusion (indicating lipid core penetration or thrombus) was an independent positive predictor of 1-year device-oriented clinical endpoints (27).

The present study showed that at 2-year follow-up, cardiac death and MI did not differ between patients with versus without TP. Furthermore, the incidence of stent thrombosis was similar between the TP and no-TP groups, although the overall incidence of thrombosis was relatively low in both groups. These findings were consistent with those of previous studies. However, and unlike previous studies, TP in the present study was paradoxically and surprisingly associated with TLR of 1.9% versus 4.0% in lesions without TP. This was true even after controlling for clinical, angiographic, IVUS, and procedural variables. In the present study, device size was larger and stent expansion was greater in the TP group than in the no-TP group, leading to a larger luminal area after stenting. This was especially notable because stent expansion had to compensate for TP to result in a larger final luminal area in the TP group. Furthermore, previous studies have shown that most TP can resolve during follow-up, leaving an even larger lumen than immediately post-PCI (2,26). These findings may help explain why TP acted as a negative predictor of clinically driven TLR at 2-year follow-up in the present study, as supported by the Kaplan-Meier curves shown in **Figure 2** that do not begin to diverge until 6 months post-PCI.

STUDY LIMITATIONS. First, this was a cross-sectional analysis: IVUS was not performed at follow-up. Second, the resolution of the IVUS catheter used was relatively low, especially in comparison with optical coherence tomography or even high-definition IVUS; the present study may have missed some TP. Third, pre-PCI IVUS was performed only in some of the patients; therefore, some plaque characteristics, such as attenuated plaque, plaque rupture, and VH TCFA, could not be included in the univariate and multivariate logistic regression analyses as candidates of independent predictors of TP. Fourth, TLR was site reported and not adjudicated by an independent clinical events committee. Fifth, clinical and angiographic confounders could not be eliminated completely. Sixth, the 2-year event rate in both groups was relatively low.

CONCLUSIONS

The present large-scale IVUS data showed that IVUS-detected TP was a common finding after DES implantation, especially in patients with acute coronary syndromes. However, it was not associated with worse long-term clinical outcomes, in part because of greater stent expansion in lesions with TP.

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PERSPECTIVES

WHAT IS KNOWN? Stent implantation may be associated with IVUS-detected tissue (plaque or thrombus) protrusion, especially in unstable lesions, and it tends to resolve during follow-up.

WHAT IS NEW? Our study demonstrated that IVUS-detected TP after DES implantation was not associated with worse long-term clinical outcomes, in part because of greater stent expansion in lesions with TP, presumably because greater stent expansion was among the causes of TP and because greater stent expansion counterbalanced the impact of TP to maintain a good acute result (luminal dimensions).

WHAT IS NEXT? Larger scale prospective studies using serial intravascular imaging modalities (IVUS, optical coherence tomography, near-infrared spectroscopy, and so on) with longer follow-up are needed.

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KEY WORDS coronary artery disease, intravascular ultrasound, tissue protrusion