

## CLINICAL RESEARCH

# Examination of the In Vivo Mechanisms of Late Drug-Eluting Stent Thrombosis

CME

## Findings From Optical Coherence Tomography and Intravascular Ultrasound Imaging

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**CME Objective for This Article:** After reading this paper, the reader should be able to discuss the

OCT and IVUS features associated with LST, recognize the independent OCT and IVUS predictors of LST, and describe the inflammatory cell types found in thrombus aspirate of patients with LST.

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## Examination of the In Vivo Mechanisms of Late Drug-Eluting Stent Thrombosis

### Findings From Optical Coherence Tomography and Intravascular Ultrasound Imaging

**Objectives** This study investigated the role of uncovered stent struts on late stent thrombosis (LST) after drug-eluting stent (DES) implantation with optical coherence tomography (OCT).

**Background** Autopsy studies have identified delayed healing and lack of endothelialization of DES struts as the hallmarks of LST. DES strut coverage has not previously been examined in vivo in patients with LST.

**Methods** We studied 54 patients, including 18 with DES LST (median 615 days after implant) undergoing emergent percutaneous coronary interventions and 36 matched DES control subjects undergoing routine repeat OCT and intravascular ultrasound (IVUS) who did not experience LST for  $\geq 3$  years. Thrombus aspiration was performed during emergent percutaneous coronary intervention before OCT and IVUS assessment.

**Results** By OCT, patients with LST—compared with control subjects—had a higher percentage of uncovered (median [interquartile range]) (12.27 [5.50 to 23.33] vs. 4.14 [3.00 to 6.22],  $p < 0.001$ ) and malapposed (4.60 [1.85 to 7.19] vs. 1.81 [0.00 to 2.99],  $p < 0.001$ ) struts. The mean neointimal thickness was similar in the 2 groups ( $0.23 \pm 0.17$  mm vs.  $0.17 \pm 0.09$  mm,  $p = 0.28$ ). By IVUS, stent expansion was comparable in the 2 groups, although positive remodeling was increased in patients with LST (mean vessel cross-section area  $19.4 \pm 5.8$  mm<sup>2</sup> vs.  $15.1 \pm 4.6$  mm<sup>2</sup>,  $p = 0.003$ ). Thrombus aspiration demonstrated neutrophils and eosinophils in most cases. By multivariable analysis, the length of segment with uncovered stent struts by OCT and the remodeling index by IVUS were independent predictors of LST.

**Conclusions** In this in vivo case-controlled study, the presence of uncovered stent struts as assessed by OCT and positive vessel remodeling as imaged by IVUS were associated with LST after DES. (J Am Coll Cardiol Intv 2012;5:12–20) © 2012 by the American College of Cardiology Foundation

Enthusiasm for drug-eluting stents (DES) was initially fueled by the ability of these devices to markedly reduce restenosis (1,2). This initial fervor was tempered by a persistent 0.4% to 0.6% annual incidence of late stent thrombosis (LST) with first-generation DES (3).

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Lack of healing and absence of endothelial cell coverage of the stent struts have been strongly associated with DES LST in human autopsy studies (4). To date, no in vivo evidence has linked persistent lack of strut coverage to LST

in DES, except for single case reports (5,6). Given its greater resolution, optical coherence tomography (OCT) is superior to intravascular ultrasound (IVUS) imaging for assessment of stent strut coverage and thrombus deposition (7). Conversely, due to its greater tissue penetration, IVUS provides complementary information on vessel remodeling not available from OCT, which along with stent malapposition has previously been associated with LST (8). Therefore, we performed an in vivo mechanistic explorative study with OCT and IVUS imaging in patients with and without DES LST to determine the role of strut coverage, malapposition, and vascular remodeling on late adverse events.

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Inc., Arsenal Medical, Biosensors International, GlaxoSmithKline, and Lutonix. Atrium Medical Corporation. Dr. Stone serves on the scientific advisory boards for and has received honoraria from Boston Scientific and Abbott Vascular; he receives research support from Volcano Corporation and InfraRedx; and he is a consultant to Medtronic, Abbott Vascular, Boston Scientific, and Volcano Corporation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## Methods

**Study population and protocol.** We implemented a protocol in which immediate thrombus aspiration followed by OCT and IVUS were performed during emergency percutaneous coronary intervention (PCI) in patients presenting with ST-segment elevation myocardial infarction (STEMI) caused by DES LST. Only patients with definite LST as defined by the Academic Research Consortium criteria (9) in a native coronary artery were included. Patients with occlusion at the coronary ostium or in vessels >4.0 mm in diameter or in presence of excessive vessel tortuosity were excluded, because these factors could interfere with OCT image acquisition (10). Additional exclusion criteria were

### Abbreviations and Acronyms

**CSA** = cross-section area

**DES** = drug-eluting stent(s)

**EEM** = external elastic membrane

**IQR** = interquartile range

**ISA** = incomplete stent apposition

**IVUS** = intravascular ultrasound

**LST** = late stent thrombosis

**OCT** = optical coherence tomography

**PCI** = percutaneous coronary intervention

**PES** = paclitaxel-eluting stent(s)

**SES** = sirolimus-eluting stent(s)

**ST** = stent thrombosis

**STEMI** = ST-segment elevation myocardial infarction

**WBC** = white blood cell

patients resuscitated from cardiac arrest or in cardiogenic shock. The study complied with the Declaration of Helsinki with regard to investigation of human subjects. The Ethics Review Committee of Ospedale Riuniti di Bergamo approved the protocol. Written informed consent was obtained from all patients.

**Coronary angiography and blood flow restoration.** After intracoronary injection of 0.1 to 0.2 mg nitroglycerin, coronary angiography was performed to document the presence of the thrombotic stent occlusion. Thereafter, a standard 0.014-inch coronary guidewire was passed through the occluded stent, and multiple sequences of thrombus aspiration were performed with an aspiration catheter (Export Aspiration System, Medtronic, Minneapolis, Minnesota) to restore Thrombolysis In Myocardial Infarction flow grade 2 to 3, followed by OCT and IVUS.

**Histopathologic analysis.** All thrombus aspirates were fixed in 4% Neutral Buffered Formalin and sent to an Independent Core Laboratory (CV Path Institute, Gaithersburg, Maryland) for analysis. Each thrombus aspirate was measured in aggregate and subsequently submitted for paraffin embedding. Sections were cut at 5  $\mu$ m on a rotary microtome, mounted on slides, and stained with hematoxylin and eosin, Movat pentachrome, and Luna stain. The histological sections were examined by light microscopy for platelets, fibrin, red blood cells, plaque constituents, and inflammatory cells, including eosinophils. In addition, 5 high-power fields ( $\times 40$ ) demonstrating the greatest severity of inflammation were selected for quantitative analysis. Data were recorded as total eosinophil number, total

white blood cells (WBCs), and mean eosinophil fraction expressed as total eosinophil/total WBC.

**OCT imaging and analysis.** The OCT was performed with a time domain commercially available System (M2CV OCT Imaging system, LightLab Imaging, Inc., Westford, Massachusetts). The occlusive technique, with low-volume continuous flushing, was adopted to completely remove blood from the artery (10). The OCT images were obtained with motorized pullback at 1.0 mm/s. In case of multiple pullbacks integrated information was obtained by using fiducial points (i.e., stent edges, side branches). Quantitative measurements of OCT images were performed offline throughout the length of the stent, including distal and proximal reference segments at every 1-mm interval, with a dedicated automated contour-detection system (OCT system software B.0.1, LightLab). All cross-sectional images (frames) were screened for quality and excluded from analysis if >25% of the image was out of the screen, if a side-branch was present in the cross-section, or for inadequate image quality due to some artifacts (11). Qualitative imaging assessment was performed in every frame to detect the presence of intraluminal thrombus. Intracoronary thrombus was identified as any abnormal mass protruding beyond the stent struts into the lumen, with a sharp gap with underlying neointima, signal backscattering, and various degrees of attenuation (12). White thrombi were characterized by homogeneous signal rich and low-backscattering attenuation. A ruptured plaque was defined with validated criteria for plaque characterization (13).

Stent and lumen contours were semiautomatically delineated, and tissue hyperplasia thickness, strut coverage, and wall apposition were assessed for the entire circumference of the vessel. Quantitative strut-level analysis was performed on each individual strut along the entire target segment. Struts were graded as covered (>10- $\mu$ m tissue thickness) or uncovered (<10- $\mu$ m thickness), on the basis of the current axial resolution of the available OCT system.

The number and percentage of completely apposed versus unapposed and covered versus uncovered struts were determined. The proportion of frames with >30% uncovered struts was calculated. The maximum uncovered segment length was defined as the number of consecutive frames at 1-mm intervals with uncovered struts. Strut malapposition was defined as separation of the stent strut surface from the inner vessel wall by a distance greater than the width of the stent strut plus the polymer coating, according to the different manufacture specifications (14). The maximum malapposition length was defined as the number of consecutive frames at 1-mm intervals with malapposed struts.

**IVUS imaging and analysis.** The IVUS was performed after intracoronary administration of 0.1 to 0.2 mg of nitroglycerin, with a commercially available iLab system with Atlantis SR Pro 40-MHz catheters (Boston Scientific, Fremont, California). Imaging was acquired with a motorized pull-

back at 0.5 mm/s to include the stent and at least 5-mm segments proximal and distal to the stent. Quantitative analysis was performed with standard methods and definitions (15), via validated planimetry software (CAAS-QIVA 4.0, PieMedical Imaging, Maastricht, the Netherlands). External elastic membrane (EEM), stent, lumen, and malapposition cross-sectional areas (CSA) were measured at 1-mm axial increments throughout the length of the stent and 5-mm segments proximally and distally to the stent. Incomplete stent apposition (ISA) was defined as lack of contact with the underlying vessel wall of at least 1 stent strut, not overlying a side branch, and with evidence of blood speckle behind the strut. In the segment with ISA, the lumen contours were delineated within and outside the stent strut boundaries. The ISA CSA was defined as the fraction of the lumen area outside the stent. The minimum stent CSA divided by the average of proximal and distal reference lumen CSA ratio was calculated as a parameter of stent expansion. Remodeling index was calculated, dividing the maximum in-stent EEM CSA by the reference segment EEM CSA. Marked positive remodeling was defined as a remodeling index >1.1 (15).

**Case-control analysis.** Control cases were identified from a large sample of DES patients who underwent routine OCT and IVUS follow-up at >6 months in whom, with late follow-up to ≥3 years, ST never developed. The following criteria were used for matching (all criteria had to be concomitantly met to qualify as control subject): 1) same stent type; 2) comparable IVUS reference vessel EEM CSA (within ±2 mm<sup>2</sup>); 3) comparable IVUS reference lumen CSA (within ±2 mm<sup>2</sup>); and 4) comparable IVUS stent diameter. Two control subjects were identified for each LST case.

**Statistical analysis.** Categorical variables are presented as numbers and frequencies and were compared by the chi-square test or Fisher exact tests. Continuous variables are expressed as mean ± SD or median (first to third quartile) for nonparametric data (p < 0.05 at Shapiro–Wilk test) and were compared by the Wilcoxon rank-sum test, given the small sample and potential presence of outliers. An exploratory multivariable logistic regression analysis picking only the 2 strongest univariate predictors was performed, given the small number of cases. All analyses were performed with SAS statistical software (version 9.1 or higher, SAS Institute, Inc., Cary, North Carolina) and based throughout on nonpaired methods, given our preference for a more robust bivariate analysis, even if at the price of reduced statistical power.

## Results

**Patients.** From June 2006 to April 2009, 547 primary PCIs in STEMI patients were performed at our hospital. Definite stent thrombosis (ST) occurred in 41 of 547 patients. Among them, 23 patients were excluded from the study due to ST: in bare-metal stent (n = 6), acute/subacute (n = 4),

**Table 1. Clinical and Procedural Characteristics at the Time of Drug-Eluting Stent Implantation**

	ST (n = 18)	Control (n = 36)	p Value
Age, yrs	61 (51–72)	67 (56–76)	0.28
Male	29 (80.6)	11 (61.1)	0.12
Hypertension	11 (61.1)	20 (55.6)	0.69
Hyperlipidemia	12 (66.7)	20 (55.6)	0.43
Diabetes	2 (11.1)	13 (36.1)	0.06
Prior myocardial infarction	6 (33.3)	9 (25.0)	0.51
Prior PCI	13 (72.2)	9 (25.0)	0.001
Prior CABG	0 (0)	1 (2.8)	0.67
Multivessel disease	11 (61.1)	20 (55.6)	0.69
Original stent implanted during an acute coronary syndrome	14 (77.8)	15 (41.7)	0.01
Stents implanted/patient	1.83 ± 0.78	2.31 ± 0.52	0.03
Total stent length, mm	33 (24–48)	37 (32–44)	0.09
Stent diameter, mm	2.88 ± 0.22	2.96 ± 0.28	0.40
Stent overlap	13 (76.5)	34 (94.4)	0.06
Stent type			
SES	6 (33.3)	12 (33.3)	1.00
PES	10 (55.5)	20 (55.6)	1.00
EES	1 (5.6)	2 (5.6)	1.00
ZES	1 (5.6)	2 (5.6)	1.00

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

CABG = coronary artery bypass grafting; EES = everolimus-eluting stent(s); PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); ST = stent thrombosis; ZES = zotarolimus-eluting stent(s).

in cardiogenic shock or resuscitated patients (n = 4), in grafts (n = 4), with unsuitable anatomy to OCT assessment (n = 5). Eighteen consecutive patients (with 35 DES) who presented with STEMI due to definite LST with suitability for OCT were included into the study. Six patients had LST due to sirolimus-eluting stent (SES), 10 due to paclitaxel-eluting stent (PES), 1 due to everolimus-eluting stent, and 1 due to zotarolimus-eluting stent. One PES patient had LST simultaneously in 2 different vessels. The median time from DES implantation to LST was 615 (interquartile range [IQR]: 394 to 1,186) days (range 172 to 1,836 days). Fifteen patients (83%) had very late ST (beyond 1 year after DES implantation). Stent thrombosis occurred within 90 days of clopidogrel discontinuation in 4 cases (23%). A significant creatine kinase increase (>2× the upper value of the normal range) was confirmed in all patients. All patients included into the study had IVUS and OCT imaging performed after thrombus aspiration. No major complications occurred because of the imaging assessments, and all patients included into the study were discharged alive from the hospital.

Baseline clinical, lesion, and stent features at the time of implant in the patients with LST compared with the control group are reported in Table 1. The patients with LST had a higher incidence of prior PCI, slightly fewer stents

implanted, and were more likely to have the original stents implanted during an acute coronary syndrome.

**Histopathology of thrombus.** A total of 16 thrombus specimens were submitted for histopathology analysis; in 2 patients there was insufficient thrombus material for analysis. The mean thrombus volume was  $25.9 \pm 35.2 \text{ mm}^3$ . All analyzed thrombi demonstrated platelet- and fibrin-rich areas (white thrombus) with varying numbers of red blood cells associated with the platelet aggregates. No pure red thrombi were present in our series; only 2 were mixed in composition. Most aspirates showed inflammatory cell infiltrates (median 264 [IQR: 167 to 400] WBCs/high power field) consisting predominantly of neutrophils admixed with chronic inflammatory cells. Eosinophils identified by Luna staining were present in most thrombi (ranging from 1% to 49% of WBCs) and were more commonly observed in SES compared with PES (eosinophil fraction 12.87 [IQR: 5.36 to 17.80] vs. 1.19 [IQR: 0.85 to 2.72], respectively,  $p = 0.027$ ). No significant correlation was found between histopathology components of thrombus, including high eosinophil fraction (>20%), and all OCT findings.

**OCT analysis.** A complete visualization of all stents involved with LST, including proximal and distal reference segment, was achieved in all patients. However, in 4 patients a second pullback was needed to obtain the complete stent visualization. A total of 484 cross-sections with 4,407 struts in 35 stents of the LST group and 1,088 cross-sections with 9,064 struts in 83 stents of the control group were analyzed. Of all recorded frames, 27% in the LST group and 25% in the control group were excluded from the analysis due to out-of-the-screen, sidebranch present, or presence of artifacts ( $p = 0.13$ ). Very few frames ( $3.6 \pm 2.2\%$ ) were excluded due to attenuation induced by residual red thrombus. As shown in Table 2, the proportion of uncovered struts/patient was significantly higher in the LST group compared with the control group (12.27 [IQR: 5.50 to 23.33] vs. 4.14 [IQR: 3.00 to 6.22],  $p < 0.001$ ). Most patients with LST had sections with >30% uncovered struts (13 of 18, 72%). In addition, patients with LST also had longer stent segments with uncovered struts. Similarly, the rate of malapposed struts/patient and the length of segments with malapposed struts were higher in the LST group. Three patients with LST (16.7%), however, did not have uncovered or malapposed struts but instead demonstrated severe in-stent tissue hyperplasia (1 patient with zotarolimus-eluting stent) or a ruptured plaque within or immediately adjacent to the DES (PES) (in 2 of these patients), as the likely mechanism of LST.

**IVUS analysis.** As shown in Table 3, the 2 groups were well-matched for mean reference vessel size and lumen CSA as well as stent expansion. However, the EEM at the stent segment was markedly larger in patients with LST; positive remodeling was present in 14 of 18 patients (77.8%) with LST, compared with 11 of 36 (30.6%) of control subjects

( $p = 0.001$ ). Among the LST patients with >30% uncovered struts/section by OCT, 12 had positive remodeling by IVUS (92%). The ISA CSA at the maximal malapposition site was also significantly greater in the LST group than the control group ( $4.1 \pm 2.3 \text{ mm}^2$  vs.  $1.2 \pm 1.5 \text{ mm}^2$ ,  $p = 0.001$ ).

**Exploratory multivariable analysis.** Multivariable logistic regression analysis, picking only the 2 strongest univariate predictors of LST (namely maximum length of segments with uncovered struts at OCT, and remodeling index at IVUS), showed that both were concomitantly and independently associated with LST (Table 4).

## Discussion

The present study represents the first attempt for the in vivo investigation of the role of uncovered struts in patients with definite LST after DES. The main findings of this study are: 1) LST after DES was associated with OCT evidence of an increased frequency and length of uncovered and malapposed struts; 2) positive vessel remodeling was more frequently observed in patients with compared with those without LST and tend to be associated with sections with >30% uncovered struts; and 3) LST after DES is not always related to lack of stent coverage or vessel remodeling—other mechanisms might on occasion be implicated, including in-stent or peri-stent plaque rupture and occlusive restenosis.

Histopathology obtained from human autopsy cases have demonstrated delayed healing and incomplete endothelial cell coverage as strong correlates of LST after DES implantation (16). This pathological phenomenon has not been reported in patients with bare-metal stent (14). Furthermore, the presence of >30% uncovered struts/cross-section was identified to be highly predictive of ST after DES implantation (17). Before the present report, however, these observations had never been confirmed in vivo.

In the current study, 14 of the 18 patients (78%) with definite LST exhibited uncovered struts (Fig. 1), and 13 patients (72%) had >30% uncovered struts/section. The frequency of cross-sections with >30% uncovered struts was 26.7% in patients with LST, compared with 4.1% in the matched control subjects from the present study and 2% at 2 years in asymptomatic patients after SES implantation from a prior study (18). Katoh et al. (19) reported that, in patients without ST, the rate of uncovered SES struts decreases by 12 months, but complete coverage is the exception. The current study confirms that uncovered DES struts might persist for several years and might be a frequent finding for LST.

Long stents and multiple overlapping stents have been previously identified as predictors of LST after DES (20). In the present study, despite similar stent length and neointimal thickness in patients with and without LST, those with LST had a significantly higher rate and longer segments of uncovered and malapposed struts. Of note, the frequency of uncovered struts reported at 6- to 12-month

**Table 2. Optical Coherence Tomography Imaging Measurements**

	ST (n = 18 Lesions; 4,407 Struts)	Control Subjects (n = 36 Lesions; 9,064 Struts)	p Value
<b>Cross-section level analysis</b>			
Analyzed cross-sections/patient, n	27 ± 12	30 ± 13	0.47
Struts analyzed/cross-section, n	6.78 ± 1.22	6.74 ± 1.41	0.93
Frequency of cross-sections with uncovered struts, %	33.30 (11.82–53.00)	0.00 (0.00–7.80)	0.003
Frequency of cross-sections with >30% uncovered struts, %	21.59 (0.00–43.70)	0.00 (0.00–6.09)	0.002
Maximum length of segments with uncovered struts, mm	3.30 (1.35–4.13)	0.90 (0.00–1.55)	<0.001
Maximum length of segments with malapposed struts, mm	1.40 (0.68–1.93)	0.00 (0.00–0.00)	0.001
Maximum malapposition distance, mm	0.35 (0.00–0.75)	0.00 (0.00–0.62)	0.002
Area of malapposition, mm <sup>2</sup>	1.02 (0.00–1.92)	0.00 (0.00–0.32)	0.002
Minimum stent area, mm <sup>2</sup>	5.04 ± 1.23	5.50 ± 1.27	0.26
Mean stent area, mm <sup>2</sup>	7.24 ± 0.97	7.69 ± 1.61	0.20
Mean neointimal area, mm <sup>2</sup>	1.57 ± 0.68	1.68 ± 0.71	0.41
<b>Strut-level analysis</b>			
Number of struts analyzed/patient	244 ± 131	251 ± 86	0.81
Number of uncovered struts/patient	25.00 (8.25–52.25)	9.00 (4.25–14.00)	0.006
Frequency of uncovered struts/patient, %	12.27 (5.50–23.33)	4.14 (3.00–6.22)	0.001
Number of malapposed struts/patient	10.00 (2.25–21.75)	4.00 (0.00–7.00)	0.02
Frequency of malapposed struts/patient, %	4.60 (1.85–7.19)	1.81 (0.00–2.99)	0.001
Neointimal thickness of covered struts, mm	0.23 ± 0.15	0.17 ± 0.09	0.28

Values are mean ± SD or mean (range).  
 ST = stent thrombosis.

follow-up in asymptomatic patients treated with first-generation DES has varied from 0% to 8.4% (7,18,21), significantly less than that we observed in patients with LST in the present study. Lüscher et al. (22) have demonstrated that DES implantation in lesions with abundant necrotic core might result in delayed or absent healing and endothelialization. This observation is consistent with the findings of our study, where an acute coronary syndrome during the

original stent implant was more frequently present in patients with compared with those without LST.

The role of stent malapposition and vascular remodeling in the pathogenesis of LST remains controversial. Cook et al. (8) previously reported an increased incidence of stent malapposition and positive vessel remodeling as assessed by IVUS in patients with compared with those without very late ST after DES. In the present study, ISA was observed in 78% of patients with LST (Fig. 2), and the maximal ISA CSA and degree of positive remodeling were significantly greater in patients with versus without LST. Localized strut hypersensitivity with resultant positive remodeling after SES has been associated with LST (23), whereas medial necrosis with arterial dilation and excessive fibrin deposition was the underlying cause after PES (24). We also found, consistent with the findings of Cook et al. (24), eosinophilic-rich inflammatory

**Table 3. Intravascular Ultrasound Imaging Measurements**

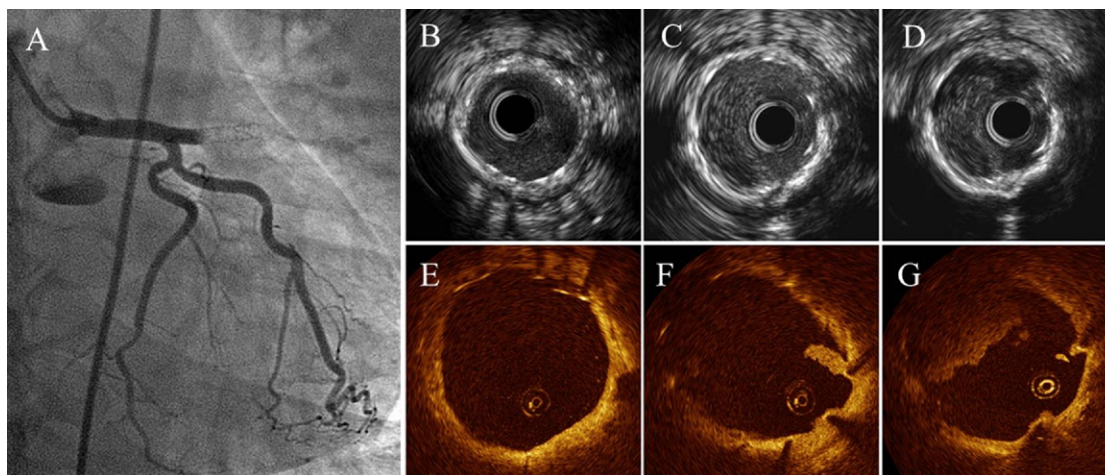
	ST (n = 18)	Control Subjects (n = 36)	p Value
<b>Reference segment</b>			
Mean EEM CSA, mm <sup>2</sup>	13.6 ± 3.9	13.7 ± 3.5	0.50
Mean lumen CSA, mm <sup>2</sup>	6.9 ± 1.7	6.9 ± 1.8	0.96
<b>Stent segment</b>			
Mean EEM, mm <sup>2</sup>	19.4 ± 5.8	15.1 ± 4.6	0.003
Remodeling index	1.24 (1.06–1.43)	0.99 (0.90–1.11)	<0.001
Mean stent CSA, mm <sup>2</sup>	7.8 ± 1.6	7.6 ± 1.4	0.42
Minimal stent CSA, mm <sup>2</sup>	5.7 ± 1.4	5.9 ± 1.4	0.99
Minimal stent CSA < 4 mm <sup>2</sup>	3 (16.7)	3 (8.3)	0.38
Stent expansion index	0.87 ± 0.3	0.91 ± 0.3	0.69
ISA	14 (77.8)	15 (41.7)	0.01
Maximal ISA CSA, mm <sup>2</sup>	4.11 ± 2.3	1.16 ± 1.5	0.001

Values are mean ± SD, mean (range), or n (%).  
 CSA = cross sectional area; EEM = external elastic membrane; ISA = incomplete stent apposition; ST = stent thrombosis.

**Table 4. Exploratory Multivariable Logistic Regression Analysis of Late Stent Thrombosis**

Variable	OR (95% CI)	p Value
Maximum length of segments with uncovered struts at OCT, mm	2.45 (1.27–4.73)	0.007
Remodeling index at IVUS*	1.05 (1.01–1.11)	0.019

Only the 2 covariates with strongest association at univariate analysis were included in the model, given the limited number of cases. \*Per 0.01-increase.  
 CI = confidence interval; IVUS = intravascular ultrasound; OCT = optical coherence tomography; OR = odds ratio.



**Figure 1. OCT Evidence of Uncovered Struts in DES Late Stent Thrombosis**

Representative angiographic (A), intravascular ultrasound (IVUS) (B to D), and optical coherence tomography (OCT) (E to G) cross-sectional images from a patient with very late stent thrombosis at 1,836 days in a single sirolimus-eluting stent implanted in proximal left anterior descending artery. After thrombus aspiration, uncovered struts are detected by OCT, with remaining intraluminal thrombus adherent to some strut. Positive remodeling was not observed by IVUS. DES = drug-eluting stent(s).

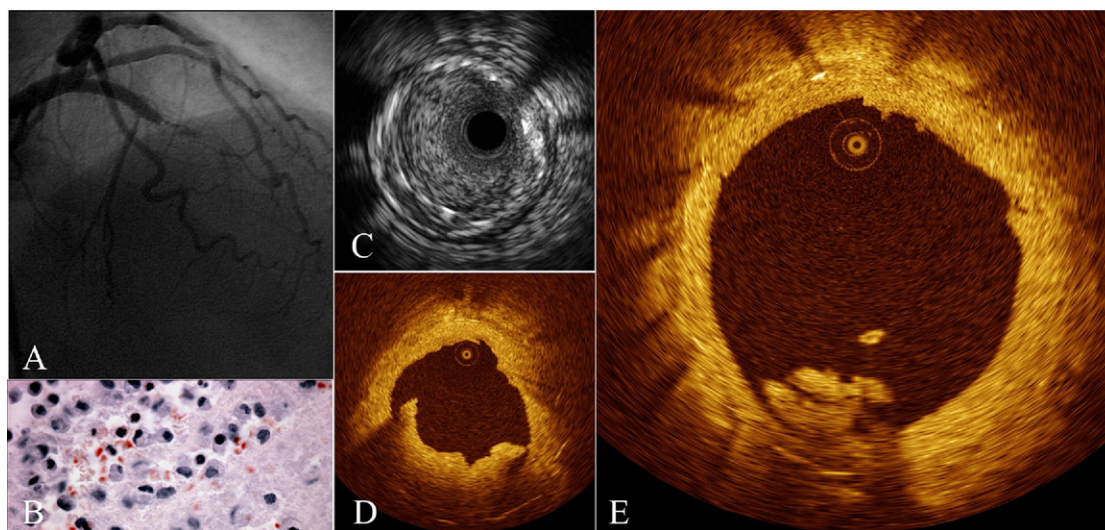
infiltrates in several cases of LST (Fig. 2). These data are consistent with the contention that late-acquired stent malapposition and extensive vessel remodeling, rather than causing LST, might only be a marker of underlying vascular toxicity and inflammation, the likely proximate cause of ST.

Other mechanisms in addition to delayed healing and vascular toxicity might occasionally be etiological in LST. With intracoronary angioscopy, Higo et al. (25) found a 35% increase in yellow neointima 10 months after DES implantation and hypothesized that the development of neoatherosclerosis within the stented segment might serve as a possible

substrate for LST. Pathological studies have also suggested accelerated atherosclerosis and plaque progression after DES placement (26). In the present study, 2 patients had OCT evidence of a disrupted plaque with thrombus within or immediately adjacent to a DES as the likely cause of LST, without evidence of positive remodeling, stent malapposition, or uncovered struts (Fig. 3). Finally, although usually considered a benign process, severe in-stent restenosis can present as an acute coronary syndrome or myocardial infarction (27,28) and was the likely cause of LST in at least 1 of our patients. Thrombus has also been associated with severe SES restenosis,

**Figure 2. Vascular Toxicity as a Hallmark of DES Late Stent Thrombosis**

Corresponding angiographic (A), IVUS long-view reconstruction (B), thrombus aspirate histopathology (C), and OCT cross-sectional images (D, E) from a patient with very late stent thrombosis at 1,103 days at the site of multiple overlapping sirolimus-eluting stents in the mid left anterior descending artery. Expansive vessel remodeling was seen by IVUS at the site of uncovered struts with adherent thrombi visualized by OCT. Large numbers of eosinophils were present in the thrombus aspirate (C). Abbreviations as in Figure 1.



**Figure 3. Neointimal hyperplasia with plaque rupture in DES late stent thrombosis**

Correspondent angiographic (A), thrombus aspirate histology (B), IVUS (C), and OCT (D, E) cross-sectional images of very late stent thrombosis (365 days) in multiple paclitaxel-eluting stents implanted in the mid left anterior descending artery in a patient with stable angina. A ruptured plaque with associated intraluminal thrombus is visualized by OCT (D, E), with rare eosinophils from the thrombus aspirate (B). Positive vessel remodeling was not present by IVUS (C). Abbreviations as in Figure 1.

suggesting that neointimal hyperplasia developing after SES might lack antithrombotic properties (29).

**Study limitations.** Although the 18 cases of LST in the present report represent the largest such cohort acutely examined with OCT and IVUS, the number of LST cases is still modest. There was no comparative bare-metal stent arm, so the findings of the present study apply only to LST after DES. At the time of the study, PES and SES were the most frequently used stents in our institution; whether the vascular responses and mechanisms of LST fundamentally differ with next-generation DES, such as everolimus-eluting and zotarolimus-eluting stents, cannot be answered from this study. Furthermore, we compared OCT and IVUS data in the LST group at a median of 615 days to imaging data acquired at 180 to 270 days in the control group, the longest available for appropriate matching. Ideally, the OCT control group would have been performed at a time-point more closely matching the occurrence of LST. Longer-term follow-up in the control cohort might have demonstrated greater strut coverage and/or more positive remodeling. Although both OCT and IVUS were used in these patients, correlation between IVUS and OCT findings was not attempted, due to the limited number of cases and methodological differences in analyses. The lack of OCT/IVUS imaging at index procedure is an important limitation with regard to remodeling and late acquired stent malapposition, especially in cases with stent originally implanted in acute coronary syndrome patients, where positive remodeling could be already present at baseline. Whenever thrombus is present, a reliable assessment of strut

coverage is difficult. All analyzed aspirated thrombi were platelet-rich, with low drops in OCT signal intensity. However, some shadowing was still present in OCT images with residual thrombus, thus proportion and extent of uncovered struts in the LST group is likely underestimated. Current OCT cannot differentiate between neointimal and other tissue types. Endothelial cell dimensions are below the resolution of even OCT, and it is possible that some struts appearing bare were covered by endothelium and thus misclassified. We cannot exclude that thrombus aspiration might have partially removed the material covering the struts. Our study failed to identify underexpansion as related to LST, most likely due to the use of expansion feature in the matching process. Clinical variables that might contribute to LST were not taken into account, because increasing the number of matching factors beyond 4 would have made matching altogether unfeasible. Finally, extensive multivariable analyses were not possible, given the small sample, and only a model combining the 2 strongest univariate predictors was analyzed with an exploratory scope.

## Conclusions

The present in vivo study offers important insights into the mechanisms underlying LST. Late stent thrombosis after DES is associated with OCT evidence of uncovered struts and IVUS evidence of positive remodeling consistent with underlying vascular toxicity. Compared with asymptomatic DES control subjects, those with LST had similar stent CSA and expansion. Collectively these results support prior



human autopsy studies identifying delayed healing, lack of endothelial cell coverage, and vascular toxicity as the hallmarks of DES LST. Furthermore, the underlying mechanisms of LST after DES are multifactorial, with etiologies other than abnormal healing occasionally identified, including neoatherosclerosis with new plaque rupture and thrombosis and occlusive in-stent restenosis

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**Key Words:** acute myocardial infarction ■ drug-eluting stent(s) ■ late stent thrombosis ■ optical coherence tomography ■ percutaneous coronary intervention.

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