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Intravascular Ultrasound Findings in Patients With Very Late Stent Thrombosis After Either Drug-Eluting or Bare-Metal Stent Implantation

Cheol Whan Lee, MD,* Su-Jin Kang, MD,* Duk-Woo Park, MD,* Seung-Hwan Lee, MD,* Young-Hak Kim, MD,* Jae-Joong Kim, MD, PHD,* Seong-Wook Park, MD, PHD,* Gary S. Mintz, MD,† Seung-Jung Park, MD, PHD*

Seoul, Korea; and New York, New York

Objectives This study compared intravascular ultrasound (IVUS) findings at drug-eluting stent (DES) and bare-metal stent (BMS) sites in patients with very late stent thrombosis (VLST).

Background VLST is being increasingly identified since the introduction of DES. VLST can also develop after BMS placement, but the underlying mechanisms remain unknown.

Methods A total of 30 consecutive VLST patients with acute myocardial infarction (DES, n = 23; BMS, n = 7) were enrolled. Patients underwent IVUS examination before coronary angioplasty.

Results The baseline characteristics were similar for the 2 groups, with the exception of reference vessel size, lesion length, stent length, minimal lumen diameter, and diameter stenosis after the procedure. Overall, VLST occurred at a mean 50.8 ± 36.2 months after the index procedure, and occurred earlier after DES than BMS (33.2 ± 12.5 months vs. 108.4 ± 26.5 months, $p < 0.001$). IVUS variables were generally similar for the 2 groups. However, plaque burden at the distal reference segment, stent, and neointimal area of the in-stent segment were smaller in the DES group. Stent malapposition was observed in 73.9% of DES patients, but in no BMS patients ($p = 0.001$). Disease progression with neointimal rupture within the stent was observed in 10 DES patients (43.5%) and 7 BMS patients (100%; $p = 0.010$).

Conclusions Stent malapposition was unique to DES-related VLST, whereas disease progression with neointimal rupture was more common in BMS patients. These findings suggest that different biological mechanisms underlie VLST development depending upon the stent type. (J Am Coll Cardiol 2010;55:1936–42) © 2010 by the American College of Cardiology Foundation

Drug-eluting stents (DES) reduce the risk of restenosis compared with bare-metal stents (BMS) (1,2). However, concerns have been raised regarding the long-term safety of DES, especially in terms of very late stent thrombosis (VLST), namely, thrombosis occurring beyond 1 year after deployment (3–5). VLST as a rare, but potentially life-threatening complication has been increasingly recognized since the introduction of DES. Several studies have shown that delayed arterial healing and stent malapposition may be important causes of VLST after DES placement (6–9). Nevertheless, although VLST is typically associated with DES, it has also been reported after BMS placement (10); and little is known about the mechanisms underlying BMS-related VLST. The present study compared intravascular ultrasound (IVUS) findings in DES-treated patients versus BMS-treated patients who presented with VLST.

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Methods

Study population. The Asan Medical Center clinical and IVUS laboratory database included 38 patients who presented with VLST between October 2004 and April 2009. Of those, 30 VLST patients underwent IVUS before coronary intervention and comprised the study population. There were 23 patients with VLST after DES (19 Cypher stents, Cordis–Johnson & Johnson, Bridgewater, New Jersey; and 4 Taxus stents, Boston Scientific, Natick, Massa-

From the *Department of Medicine, Asan Medical Center, University of Ulsan, Seoul, Korea; and the †Cardiovascular Research Foundation, New York, New York. This study was supported by grants from the Korean Society of Cardiology (Grant 2004-0567) and the Korea Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea (A090264). Dr. Mintz has received grant support from Boston Scientific and Volcano Corp., and has a consulting relationship with Volcano Corp.

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chusetts) placement and 7 patients with VLST after BMS placement. No patients received thrombolytic therapy or thrombus aspiration before IVUS examination. VLST was defined as acute myocardial infarction and angiographic confirmation of thrombotic stent occlusion occurring beyond 1 year after stent implantation in accordance with the Academic Research Consortium definition of VLST (11). Acute myocardial infarction was diagnosed as typical rise and fall of cardiac injury markers with sudden onset of resting chest pain lasting >20 min and new ischemic electrocardiogram changes.

Quantitative coronary angiographic analysis. Coronary angiograms were independently analyzed by experienced angiographers unaware of the study goal. Percent diameter stenosis, minimal lumen diameter, and reference diameter using an on-line quantitative angiographic analysis system (CASS 2.0, Pie Medical Imaging, Eindhoven, the Netherlands) were measured before pre-dilation and after the stenting procedure. Angiographic measurements were made during diastole after intracoronary nitroglycerin administration using a guiding catheter to calibrate magnification.

Image acquisition and analysis. The IVUS imaging was performed after intracoronary administration of 0.2 mg nitroglycerin using a motorized transducer pullback system (0.5 mm/s) and a commercial scanner (SCIMED/Boston Scientific, Natick, Massachusetts) that consisted of a rotating 40 mHz transducer within a 3.2- or 2.6-F imaging sheath. The IVUS images were recorded on s-VHS videotape or computer disk and analyzed by personnel unaware of the type of stent implanted.

Using computerized planimetry, the external elastic membrane, lumen, and stent cross-sectional area (CSA [mm^2]) were measured every 1 mm in the stented and reference segments; and volumes were calculated using Simpson's rule and normalized for analysis length to yield mean values of external elastic membrane, stent, and lumen CSA. The proximal and distal reference segments selected for analysis were the most normal-looking cross-sections within 5 mm proximal or distal to the lesion but before any side branch. Stent malapposition was defined as separation of at least 1 stent strut from the intimal surface of the arterial wall that was not overlapping a side branch with evidence of blood flow (speckling) behind the strut. Neointimal area was calculated as the stent minus lumen CSA, and the neointima volume index as the neointima volume divided by stent volume.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CSA = cross-sectional area
DES = drug-eluting stent(s)
IVUS = intravascular ultrasound
VLST = very late stent thrombosis

Statistical analysis. Data are expressed as mean ± SD for continuous variables and frequencies for categorical variables. Continuous variables were compared using Mann-Whitney *U* tests, and categorical variables using the chi-square test or Fisher exact test. Statistical significance was defined as a 2-sided p value <0.05.

Results

Clinical characteristics. Baseline characteristics were generally similar for the 2 groups (Table 1). Overall, VLST occurred at a mean of 50.8 ± 36.2 months after the index procedure, and occurred earlier in the DES group (33.2 ± 12.5 months, range 14.0 to 60.4 months) than in the BMS group (108.4 ± 26.5 months, range 81.4 to 163.1 months; $p < 0.001$). Clinical presentations at the time of VLST was

Table 1 Clinical Characteristics

Variables	DES (n = 23)	BMS (n = 7)	p Value
Age, yrs	53.2 ± 11.9	61.7 ± 6.3	0.077
Sex, male/female	17/6	7/0	0.290
Risk factors			
Current smoker	14 (60.9)	5 (71.4)	1.000
Diabetes mellitus	6 (26.1)	2 (28.6)	1.000
Hypertension	13 (56.5)	4 (57.1)	1.000
Hypercholesterolemia, >200 mg/dl	6 (26.1)	3 (42.9)	0.661
Diagnosis at the index procedure			0.390
Stable angina	13 (56.5)	2 (28.6)	
Acute coronary syndrome	10 (43.5)	5 (71.4)	
Left ventricular ejection fraction, %	57.9 ± 10.4	58.2 ± 9.4	0.914
Months after the index procedure	33.2 ± 12.5	108.4 ± 26.5	<0.001
Clinical presentation at time of VLST			1.000
STEMI	18 (78.3)	6 (85.7)	
NSTEMI	5 (21.7)	1 (14.3)	
Antiplatelet therapy at time of VLST			0.625
Aspirin plus clopidogrel	2 (8.7)	0 (0)	
Aspirin	16 (69.6)	4 (57.1)	
None	5 (21.7)	3 (42.9)	

Values are mean ± SD, n, or n (%).

BMS = bare-metal stent(s); DES = drug-eluting stent(s); NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; VLST = very late stent thrombosis.

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Table 2 Angiographic Characteristics

Variables	DES (n = 23)	BMS (n = 7)	p Value
Target artery			0.248
Left main	0 (0)	1 (14.3)	
Left anterior descending coronary	16 (69.6)	2 (28.6)	
Left circumflex coronary	2 (8.7)	0 (0)	
Right coronary	5 (21.7)	4 (57.1)	
DES types			
Cypher stent	19 (82.6)		
Taxus stent	4 (17.4)		
Stent size, mm	3.1 ± 0.3	3.6 ± 0.5	0.062
Number of stents per lesion	1.4 ± 0.8	1.3 ± 0.5	0.980
QCA at the index procedure			
Lesion length, mm	25.5 ± 10.8	15.4 ± 4.0	0.006
Total stented length, mm	36.3 ± 17.3	23.7 ± 9.9	0.001
Reference vessel diameter, mm	2.97 ± 0.40	3.66 ± 0.70	0.010
Pre-intervention			
Minimal lumen diameter, mm	0.81 ± 0.53	1.09 ± 0.84	0.384
Diameter stenosis, %	72.5 ± 16.9	73.2 ± 18.1	0.896
Post-intervention			
Minimal lumen diameter, mm	2.70 ± 0.43	4.08 ± 1.01	<0.001
Diameter stenosis, %	9.2 ± 8.5	−5.9 ± 9.9	0.003

Values are n (%) or mean ± SD.
QCA = quantitative coronary angiography; other abbreviations as in Table 1.

acute ST-segment elevation myocardial infarction in 80.0% of patients and non–ST-segment elevation myocardial infarction in 20.0% of patients.

Angiographic characteristics. The 2 groups differed in terms of angiographic characteristics with respect to reference vessel size, lesion length, stent length, minimal lumen

Table 3 Intravascular Ultrasound Measurements

Variables	DES (n = 23)	BMS (n = 7)	p Value
Proximal reference segment, mm^2			
Mean EEM CSA	18.30 ± 6.30	18.60 ± 5.87	0.856
Mean lumen CSA	7.81 ± 3.71	9.17 ± 4.68	0.689
Mean plaque and media CSA	10.50 ± 5.01	9.42 ± 3.52	0.799
Distal reference segment, mm^2			
Mean EEM CSA	9.31 ± 4.15	13.96 ± 5.66	0.078
Mean lumen CSA	3.51 ± 1.78	4.22 ± 1.84	0.438
Mean plaque and media CSA	5.79 ± 3.61	9.75 ± 4.26	0.028
Stent segment			
Total stented length, mm	32.9 ± 13.0	18.6 ± 4.2	0.001
Mean EEM CSA, mm^2	19.55 ± 6.07	18.31 ± 4.17	0.774
Mean stent CSA, mm^2	7.25 ± 1.79	9.75 ± 2.89	0.037
Mean lumen CSA, mm^2	4.20 ± 1.40	4.73 ± 1.64	0.564
Minimal stent CSA, mm^2	6.15 ± 1.58	7.42 ± 3.77	0.413
Mean neointimal area, mm^2	3.07 ± 1.15	5.03 ± 1.78	0.014
Neointima volume index	0.42 ± 0.12	0.51 ± 0.09	0.069
ISA	17 (73.9)	0 (0)	0.001
Length, mm	7.40 ± 5.49		
CSA, mm^2	4.58 ± 1.94		
Volume, mm^3	17.83 ± 4.99		
Arc of ISA, °	158.1 ± 50.8		
Location			
Proximal stent segment	6 (35.3)		
Stent body	7 (41.2)		
Distal stent segment	4 (23.5)		

Values are mean ± SD or n (%).
CSA = cross-sectional area; EEM = external elastic membrane; ISA = incomplete stent apposition; other abbreviations as in Table 1.

diameter, and diameter stenosis after the procedure (Table 2). At the time of VLST, thrombotic stent occlusion was complete in 87.0% of patients and partial in 16.7% of patients. No reflow developed in 10.0% of patients after the procedure. Two patients (6.7%) died of left ventricular failure after the procedure, and the remaining 28 patients were discharged alive.

IVUS findings. Quantitative IVUS data are summarized in Table 3, and a representative case example is shown in Figures 1A and 1B. Plaque rupture was observed in 2 DES patients in the proximal reference segment and in 6 patients (DES, n = 4; BMS, n = 2) at the distal reference segment. Although minimal stent CSA did not differ significantly between the 2 groups, mean stent CSA and mean neointimal CSA were smaller in the DES group than in the BMS group; and the neointima volume index tended to be smaller in the DES group as compared with the BMS group (0.42 ± 0.12 vs. 0.51 ± 0.09, respectively; p = 0.069).

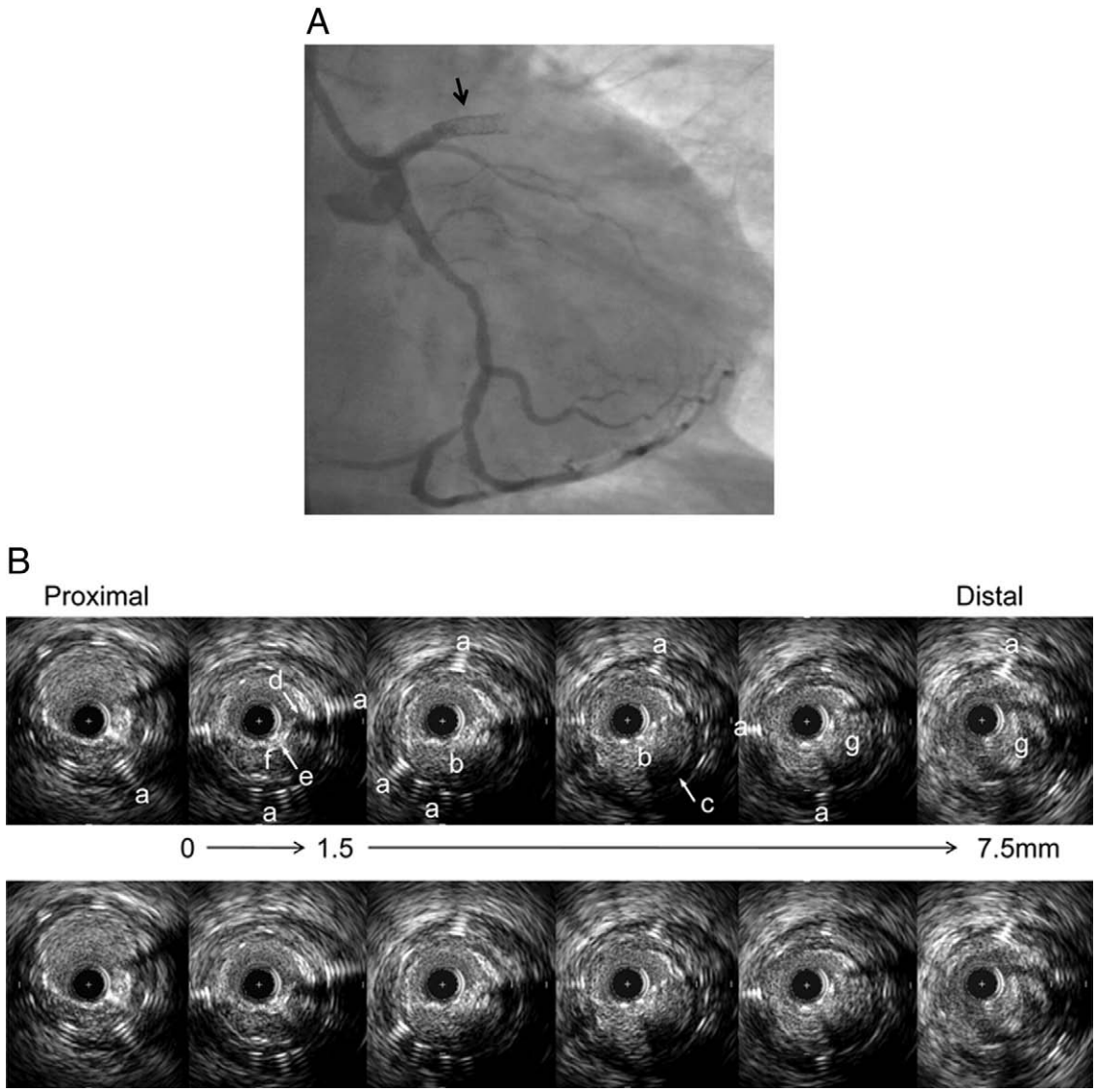

Figure 1 IVUS Images in a Patient With VLST

(A) A Cordis stent (4.0 mm × 15 mm) was implanted at the ostial left anterior descending coronary artery in a 42-year-old male patient. Thirteen and a half years later, he presented with very late stent thrombosis (VLST). Coronary angiogram showed total occlusion at previous bare-metal stent site **(arrow)**. **(B)** Intravascular ultrasound (IVUS) images from the patient demonstrating very eccentric intra-stent plaque, fibrous cap rupture, evacuated intrastent plaque cavity, and thrombus formation. The sequence of 6 image slices representing a 7.5-mm segment of the thrombosed stent is duplicated to allow annotation. **a** = typical Cordis stent struts (note: not all stent struts are annotated); **b** = highly eccentric intrastent plaque; **c** = echolucent zone separating the inner highly eccentric intrastent plaque from a thinner concentric rim of tissue just within the stent struts; **d** = site of plaque rupture at the shoulder of the fibrous cap; **e** = residual fibrous cap remnant; **f** = evacuated plaque cavity (note: the evacuated plaque cavity may extend distally as part of the intrastent plaque "b"); **g** = intraluminal thrombus. These features are virtually indistinguishable from a ruptured plaque in a nonstented arterial segment.

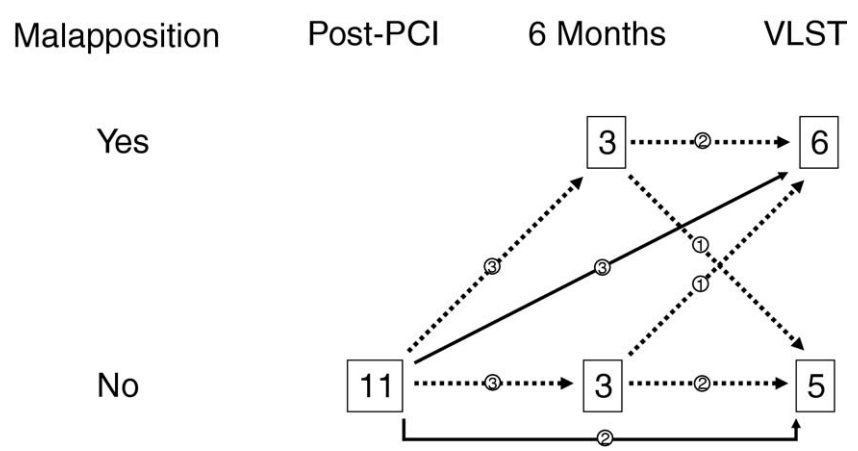

Figure 2 Serial Changes in Stent Malapposition

Serial changes in stent malapposition after percutaneous coronary intervention (post-PCI), at 6-month follow-up, and at the time of very late stent thrombosis (VLST).

There were 17 stent malappositions in the DES group with VLST, but none in the BMS group (73.9% vs. 0%, respectively; p = 0.001). Of the 17 DES-treated patients with VLST, 11 had post-intervention IVUS; none had evidence of acute stent malapposition, 6 had stent–vessel wall malapposition at the time of VLST, and 5 had VLST in the absence of stent–vessel wall malapposition. In addition, 6 of 11 of these patients with post-procedure IVUS had 6-month follow-up IVUS showing stent malapposition (Fig. 2). One patient with late stent malapposition at 6 months showed disappearance of stent malapposition at the time of VLST, whereas another patient without stent malapposition at 6 months had late stent malapposition at the time of VLST. External elastic membrane CSA was greatest at the site of stent malapposition and measured 25.20 ± 6.28 mm^2. This was located at the proximal stent segment in 35.3% of patients, at the stent body in 41.2%, and at the distal stent segment in 23.5% of patients.

Neointimal rupture within the stents was observed in 10 DES patients (43.5%) and 7 BMS patients (100%, p = 0.010). Thus, in-stent neointimal rupture or reference segment plaque rupture was seen in 65.2% of DES VLST versus 100% of BMS VLST (p = 0.143); and either late stent malapposition or neointimal/plaque rupture accounted for all but 2 cases in the overall cohort of BMS VLST and DES VLST. The DES VLST with plaque rupture was associated with larger minimum stent areas (6.7 ± 1.4 mm^2 vs. 5.1 ± 1.4 mm^2, p = 0.019) and more neointima (volume index = 0.46 ± 0.11 vs. 0.35 ± 0.11, p = 0.028) than DES VLST without plaque rupture. Finally, 2 BMS patients with VLST (28.6%) had superficial neointimal calcification within the BMS.

Discussion

This study showed that stent malapposition was unique to DES-related VLST; it was not seen in BMS-related VLST. Conversely, there was more in-stent neointimal tissue with neointimal rupture in BMS-related VLST sites compared with DES-related VLST sites. Although VLST occurs with both BMS and DES, our findings suggest that different biological mechanisms underlie BMS-related and DES-related VLST.

Stent thrombosis is acute thrombotic occlusion of the stented segment that most often occurs within 30 days after stent placement. Stent thrombosis can be classified according to the timing of occurrence: acute (<24 h after implantation), subacute (1 to 30 days after implantation), late (1 month to 1 year after implantation), and very late (>1 year after implantation) (11). VLST was rare in the BMS era, but is being increasingly reported in the DES era. The cumulative incidence of DES-related stent thrombosis at 1 year ranges from 0.5% to 1.5%, similar to that for BMS (12,13); but the risk of VLST is greater for DES than for BMS, with an ongoing hazard as high as 0.6% per year (14). Mechanisms underlying VLST may differ from those of early stent thrombosis (6,7,15). Delayed arterial healing with incomplete endothelialization and persistent fibrin or stent–vessel wall malapposition have been suggested as possible mechanisms underlying VLST. Late stent malapposition may develop because of vessel wall remodeling and/or thrombus resorption.

The vessel wall appears to pull away from the stent struts because of vessel remodeling or thrombus resorption, leading to late stent malapposition. Whether this is related to the drug or the polymer remains unknown and may vary among DES types. In the present study, late stent malapposition was observed in 73.9% of patients with DES-related VLST, comparable to that (77%) of previous reports (8). Furthermore, of the 11 patients with serial IVUS imaging and VLST, malapposition was late and acquired rather than acute and persistent.

Late stent malapposition occurs far more frequently with DES than with BMS (9). Although the relationship between stent malapposition and stent thrombosis remains unclear

(8,9,16–18), stent malapposition may serve as a local nidus for VLST by allowing fibrin and platelet deposition (6,19,20). In the current study, no BMS-treated patient who presented with VLST had stent–vessel wall malapposition.

Previously, we failed to identify late stent malapposition that was routinely detected at 6 months as a predictor of subsequent DES thrombosis (16). That failure may have been due to the small number of patients with late stent malapposition (n = 82), to the infrequent occurrence of VLST even among patients with late stent malapposition, and to the dynamic nature of stent malapposition even beyond 6 months, as was seen in some of the patients in the current cohort. In addition, our data suggest that the differences in reference diameter, lesion length, and stent length may contribute to the development of VLST in patients treated with DES.

Although VLST is usually associated with DES, it is also an issue after BMS implantation, as seen in the current report. However, little attention has been paid to VLST after BMS implantation. A large retrospective study reported that the cumulative incidence of stent thrombosis after BMS implantation was 0.5% at 30 days, 0.8% at 1 year, 1.3% at 5 years, and 2.0% at 10 years (10). In the present study, plaque rupture within the stents was identified in 100% of BMS-related VLST, and plaque rupture in reference artery segments was identified in 28.6% of BMS-related VLST. Atherosclerosis is a progressive disease, and neointima within the stents can be a nidus for new disease in both BMS and DES, but especially in DES, where it seems to occur earlier probably because of inflammatory response to the polymer (21,22). The longer interval from implantation to VLST in BMS than in DES was consistent with the longer time needed to develop intrastent neoatherosclerotic plaque and plaque rupture.

We speculate that neoatherosclerotic lesions within the BMS may progress to tight stenosis and/or plaque rupture (21). Plaque rupture can expose the stent struts, in addition to the lipid core, to trigger thrombus formation. Interestingly, neointimal rupture within DES was also observed in our study, supporting the pathologic finding that neoatherosclerosis develops more rapidly within DES than within BMS (21,23). In addition, our study showed that disease progression with plaque rupture occurs in adjacent reference segments during long-term follow-up, potentially contributing to thrombosis of the vessel.

The present study had several potential limitations. First, IVUS examination at the end of the index procedure was not available for one-half of the patients (52.2%); therefore, whether stent malapposition was persistent or was acquired during follow-up procedure could not be determined in all patients. Second, the number of patients with BMS-related VLST was small. Third, the time to VLST may be biased by the sequential advent of the 2 stent types coupled with the more recent interest in VLST and the time from stenting to the data collection era. Further follow-up study may be needed to clarify this issue. Finally, IVUS has inherent image quality limitations that may prevent distinguishing thrombi from plaques.

Conclusions

Our results suggest that different mechanisms underlie VLST depending upon the stent type. Stent malapposition plays a key role in DES-related VLST whereas neoatherosclerosis with plaque rupture plays a key role in BMS-related VLST.

Reprint requests and correspondence: Dr. Seung-Jung Park, Division of Cardiology, Asan Medical Center, University of Ulsan, 388-1 Pungnap-dong, Songpa-gu, Seoul 138-736, Korea. E-mail: sjpark@amc.seoul.kr.

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