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Local Determinants of Thrombus Formation Following Sirolimus-Eluting Stent Implantation Assessed by Optical Coherence Tomography

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Objectives We conducted this study to assess the prevalence and determinants of subclinical thrombus after sirolimus-eluting stent (SES) implantation.

Background Angioscopic analyses have demonstrated the presence of thrombus is more common than the clinical incidence of SES thrombosis.

Methods Fifty-three patients (53 lesions) underwent 6-month follow-up optical coherence tomography. A stent eccentricity index ([SEI] minimum/maximum stent diameter) was determined in each cross section. To evaluate unevenness of neointimal thickness, a neointimal unevenness score ([NUS] maximum neointimal thickness in the cross section/average neointimal thickness of the same cross section) was calculated for each cross section. Average SEI and NUS were calculated for each stent. Major adverse cardiac events were defined as a composite of death, myocardial infarction, and target vessel revascularization.

Results Fourteen cases of thrombus (26%) were detected by optical coherence tomography (thrombus: $n = 14$ vs. nonthrombus: $n = 39$). The percentage of thrombus was associated with longer stents (36.4 ± 20.2 mm vs. 25.1 ± 9.8 mm; $p = 0.008$), a larger number of uncovered struts (17 ± 16 vs. 8 ± 11; $p = 0.03$), smaller average SEI (0.89 ± 0.04 vs. 0.92 ± 0.03; $p = 0.001$), and greater average NUS (2.22 ± 0.24 vs. 2.00 ± 0.33; $p = 0.03$). A significant relationship existed between average SEI and average NUS ($p < 0.0001$, $R = 0.68$), and between average SEI and the number of uncovered struts ($p < 0.0006$, $R = 0.46$). There was no significant difference in major adverse cardiac events during follow-up (median: 485 days, 7.1% vs. 12.8%; $p > 0.99$).

Conclusions Longer stents and greater asymmetric stent expansion may be important determinants of thrombus formation after SES implantation. In this small cohort, the presence of thrombus did not increase the risk of major adverse cardiac events. (J Am Coll Cardiol Intv 2009;2:459–66)

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Although sirolimus-eluting stents (SES) have reduced the incidence of restenosis, late thrombosis, a life-threatening complication, has emerged as a major concern in the clinical setting (1,2). Recent angioscopic analyses demonstrated that the presence of subclinical thrombus in SES is more common than the clinical incidence of stent thrombosis (3,4). Although several factors are reported as major predictors of clinical stent thrombosis (5), local determinants of thrombus formation and its clinical significance under antiplatelet therapy are still unclear.

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Several studies have shown that asymmetric stent expansion may affect the pattern of neointimal growth presumably through uneven drug delivery (6,7). Because delayed arterial healing characterized by exposed stent struts is considered a possible risk for thrombosis (8), we hypothesized that asymmetric stent expansion could affect thrombus formation after SES implantation. Thus, the purpose of the present study was to assess the determinants of thrombus formation 6 months after SES implantation and its effect on long-term clinical events using optical coherence tomography (OCT).

Abbreviations and Acronyms

IVUS = intravascular ultrasound

MSA = minimum stent area

NUS = neointimal unevenness score

OCT = optical coherence tomography

SEI = stent eccentricity index

SES = sirolimus-eluting stent(s)

Methods

Study population and methods. Between October 2004 and February 2008, 373 patients underwent elective percutaneous coronary intervention with SES (Cypher, Cordis Corp., Miami Lakes, Florida) for de novo native coronary lesions (546 SES). Of the 258 patients (386 SES) who underwent 6-month follow-up coronary angiography, 67 patients were randomly selected to receive 6-month follow-up OCT analysis. The percutaneous coronary intervention procedure for patients involved in this study was performed with intravascular ultrasound (IVUS) guidance using a mechanical ultrasound transducer (Boston Scientific Corporation, Natick, Massachusetts) or a dynamic-aperture ultrasound transducer (Volcano Corporation, Rancho Cordova, California).

All patients were taking aspirin 100 mg/day. Ticlopidine 200 mg/day or clopidogrel 75 mg/day were additionally given for at least 3 months after SES implantation. Clopidogrel was not used until May 2006 because it had not been approved for clinical use in Japan before then. This study was approved by the ethical committee of Kobe University, and all enrolled study patients gave their written informed consent.

Quantitative coronary angiographic evaluation. Quantitative angiographic parameters were calculated for the target lesion before and after the procedure and at the time of angiographic follow-up using dedicated software (QCA-CMS 5.1, Medis Imaging Systems, Leiden, the Netherlands). In-stent restenosis was defined as diameter stenosis >50% within the stented segment. In-stent late luminal loss was defined as the difference between the minimal luminal diameter immediately after the procedure and the minimal luminal diameter at 6 months.

OCT examination. An OCT examination was performed as previously reported (9). Briefly, a 0.016-inch OCT catheter (ImageWire, LightLab Imaging, Westford, Massachusetts) was advanced to the distal end of the stented lesion through an occlusion balloon catheter (Helios, LightLab Imaging). To clear the blood from the field of view, the occlusion balloon was inflated to 0.6 atm at the proximal site of the culprit lesion, and lactated Ringer's solution was infused into the coronary artery from the distal tip of the occlusion balloon catheter at 0.5 ml/s. The entire length of the stent was automatically imaged at 1 mm/s.

OCT analysis. All images were analyzed by an independent observer who was blinded to the clinical presentations and lesion characteristics. Cross-sectional OCT images were analyzed at 1-mm intervals (every 15 frames). Bifurcation lesions with major side branches were excluded from this analysis.

Neointimal thickness inside each SES strut was measured. Stent area and maximum and minimum stent diameters were measured manually. Any SES struts with measured neointimal thickness equal to 0 μm were defined as uncovered struts. Maximum distance >170 μm between the center reflection of the strut and adjacent vessel surface was defined as incomplete strut apposition (9). The frequency of uncovered struts and incomplete strut apposition was calculated as the number of those struts divided by total struts for each stent. To assess for stent asymmetric expansion, a stent eccentricity index (SEI) was determined by the minimum stent diameter divided by the maximum stent diameter in each cross section. For the assessment of the unevenness of neointimal thickness, a neointimal unevenness score (NUS) was calculated for each cross section as maximum neointimal thickness in one cross section divided by the average neointimal thickness of the same cross section (Fig. 1). Then, the average SEI and NUS were calculated for each stent. Intracoronary thrombus was defined as a protruding mass beyond the stent strut into the lumen with significant attenuation behind the mass (Fig. 2) (10,11). To differentiate thrombus from plaque protrusion or neointimal hyperplasia, we excluded protruding masses without significant signal attenuation and surface irregularity. All stents involved in this study were divided into 2 groups (thrombus and nonthrombus) according to the presence of thrombus detected by OCT. In addition,

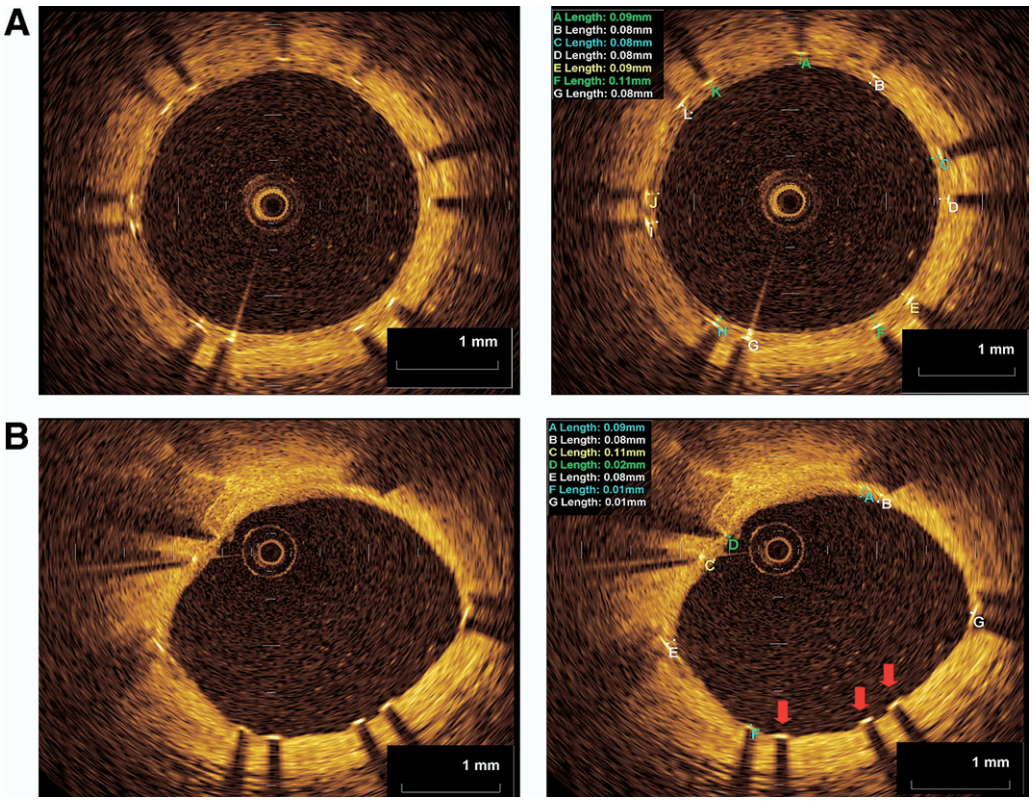

Figure 1. OCT Measurements in Length and Area

(A) A representative image of symmetric stent expansion. Average neointimal thickness: 0.09 mm. Maximum neointimal thickness: 0.11 mm. Neointimal unevenness score (NUS): 0.11/0.09 = 1.22. Stent area: 8.03 mm^2. Stent eccentricity index (SEI): 3.15/3.19 = 0.99. Number of uncovered struts: 0. **(B)** A representative image of asymmetric stent expansion. Average neointimal thickness: 0.04 mm. Maximum neointimal thickness: 0.11 mm. NUS: 0.11/0.04 = 2.75. Stent area: 6.59 mm^2. SEI: 2.55/3.21 = 0.79. Number of uncovered struts **(red arrows)** = 3. OCT = optical coherence tomography.

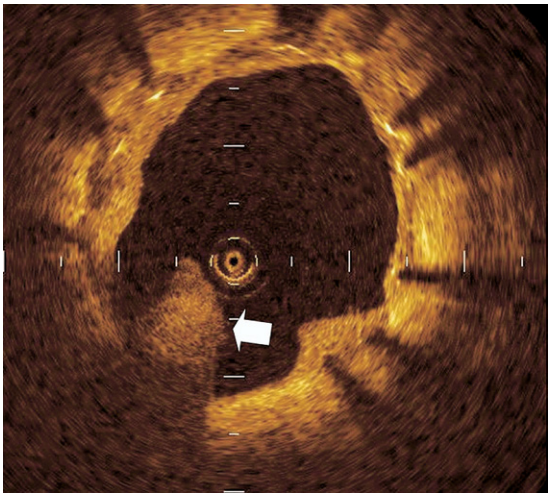

Figure 2. A Representative Image of Intracoronary Thrombus

The **white arrow** points to an intracoronary thrombus.

because a minimum stent area (MSA) of <5.0 mm^2 was observed in 80% of SES thrombosis cases according to a previous study (12), we performed a subgroup analysis for the subset of stents with MSA >5.0 mm^2 to assess the determinants of thrombus formation in the absence of stent underexpansion.

Long-term clinical follow-up. Long-term (i.e., beyond 6 months) clinical follow-up data were obtained from outpatient record reviews or telephone interviews. Major adverse cardiac events were defined as a composite of death, myocardial infarction, and target vessel revascularization. Target vessel revascularization was defined as any reintervention (surgical or percutaneous) to treat a luminal stenosis occurring in the same coronary vessel treated at the index procedure, within and beyond the target lesion limits. All patients were followed up for a minimum of 6 months (median: 485 days) after the index procedure.

Statistical analysis. Statistical analysis was conducted with a commercially available software package (StatView 5.0, SAS Institute Inc., Cary, North Carolina). Continuous variables are presented as mean ± SD. Differences in

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Table 1. Patient Characteristics

	Thrombus (n = 14)	Nonthrombus (n = 39)	p Value
Age, yrs	69 ± 9	68 ± 9	0.71
Male	10 (72)	28 (71)	>0.99
Hypertension	11 (75)	30 (67)	>0.99
Diabetes	6 (43)	21 (54)	0.54
Smoking	3 (21)	13 (33)	0.51
Hyperlipidemia	9 (64)	27 (69)	0.75
Anginal status			0.36
Stable	11 (79)	35 (90)	
Unstable	3 (21)	4 (10)	
Chronic total occlusion	3 (21)	5 (13)	0.42
Follow-up, days	197 ± 18	185 ± 34	0.29
Dual antiplatelet therapy	8 (57)	17 (44)	0.53

Values are presented as mean ± SD or n (%).

continuous parameters between the 2 groups were calculated using an unpaired Student *t* test. Categorical variables were presented using frequency counts, and intergroup comparisons were analyzed by Fisher exact test. Because every multiple stenting was performed with overlapping, statistical analysis was performed on a patient (lesion) basis. Factors with a probability value <0.10 in univariate analysis were included in multivariate logistic regression analyses. Results are reported with odds ratio (OR), 95% confidence interval (CI), and probability value. Simple correlations between the average SEI, average NUS, average neointimal thickness, and the percentage and number of uncovered struts were examined by Spearman correlation. A p value of <0.05 or less was considered to be statistically significant.

Results

Of the 67 patients who received 6-month follow-up OCT analysis after SES implantation, we excluded 11 patients with incomplete image acquisition, 2 patients with left main stenting, and 1 patient with SES fracture. Thus, 53 patients (53 lesions treated with 66 SES) were included in this study. The average interval of follow-up OCT study was 190 days. Thrombus was identified in 14 patients (14 SES) by OCT. Therefore, the incidence of cases with thrombus was 26% in our study (thrombus: n = 14 vs. nonthrombus: n = 39). Baseline characteristics for these cases are shown in Table 1. Aspirin was continued until follow-up for all SES and the percentage of dual antiplatelet therapy was similar. There were no significant differences in patient characteristics between the 2 groups (Table 1).

Lesion and procedural characteristics. Total stent length in the thrombus group was significantly longer than that in the nonthrombus group. Otherwise, no significant differences were noted between the 2 groups with regard to angiographic and procedural characteristics (Table 2).

OCT findings. In 1,271 cross-sectional images, 10,062 struts were identified. Mean stent area and MSA were similar between the 2 groups. There was no significant difference in average neointimal thickness. The thrombus group, however, had a larger number of uncovered struts, smaller average SEI, and greater average NUS (Table 3).

The relationship among the average SEI, average NUS, and number and frequency of uncovered struts are shown in Figure 3. For all of the 53 patients, a significant relationship was found to exist between average SEI and average NUS. In addition, average SEI was associated with the number and frequency of uncovered struts. There was no significant correlation between average SEI and average neointimal thickness (Fig. 3).

Although this study is not powered to determine independent predictors for subclinical thrombus, multivariate logistic models showed that SEI (OR: 0.3; 95% CI: 0.10 to 0.87; p = 0.03) and stent length (OR: 1.07; 95% CI: 1.01 to 1.13; p = 0.04) were associated with the presence of thrombus in these patients. Variables tested included age, sex, SEI, total stent length, and NUS.

Long-term clinical follow-up. Long-term clinical follow-up data (median: 485 days) after the index procedure were obtained for all patients involved in this study. No death or myocardial infarction was observed, but 1 patient in the thrombus group and 5 patients in the nonthrombus group required target vessel revascularization. All target vessel revascularization events were related to in-stent or edge restenosis of SES. There was no significant difference in major adverse cardiac events during the follow-up period (thrombus: 7.1%, nonthrombus: 12.8%; p > 0.99).

Substudy: comparison within the stents with MSA of >5.0 mm². We detected 9 thrombus in 9 patients (9 SES) in the subset of 34 patients (42 SES) who had SES with an MSA of >5.0 mm^2. There were no significant differences in demographics (age, sex, and coronary risk factors), procedural, and lesion characteristics between the 2 groups. In this subset, the thrombus group (n = 9) showed greater SEI than the nonthrombus group. Furthermore, a significant relationship still existed between average SEI and average NUS (p < 0.0001, R = 0.66), as well as between average SEI and the frequency (p = 0.01, R = 0.42) and numbers (p = 0.05, R = 0.34) of uncovered struts (Fig. 4).

Discussion

The present study demonstrated the following. 1) Thrombus was detected in 14 out of 53 patients (26%) by OCT. 2) The presence of thrombus following SES implantation was associated with longer stent length, more frequent OCT evidence of uncovered stent struts, asymmetric stent expansion, and uneven neointimal thickness. A significant relationship existed between the average SEI and average NUS, as well as between the average SEI and the number and

Table 2. Angiographic and Procedural Characteristics

	Thrombus (n = 14)	Nonthrombus (n = 39)	p Value
Vessel treated			0.48
LAD/RCA/LCX, %	29/42/29	46/36/18	
Lesion location			0.75
Proximal	6 (43%)	14 (36%)	
Mid/distal	8 (57%)	25 (64%)	
AHA/ACC lesion classification			
A/B1/B2/C, %	14/21/43/22	13/39/31/17	0.69
Procedural characteristics			
Total number of stents	1.4 ± 0.5	1.2 ± 0.4	0.18
Total stent length, mm	36.4 ± 20.2	25.1 ± 9.8	0.008
Stent diameter, mm	3.00 ± 0.20	2.89 ± 0.39	0.29
Maximum inflation pressure, atm	16	17	0.28
Final balloon size, mm	3.04 ± 0.24	3.01 ± 0.41	0.84
Post dilation	6 (43%)	21 (54%)	0.54
Multiple stenting, %	5 (36%)	7 (18%)	0.26
Debulking	2 (14%)	7 (18%)	>0.99
Quantitative coronary angiography			
Lesion length, mm	19.9 ± 9.3	17.7 ± 8.5	0.49
Reference diameter, mm	2.72 ± 0.40	2.75 ± 0.50	0.81
Minimum lumen diameter, mm			
Before	0.50 ± 0.44	0.75 ± 0.52	0.12
After	2.12 ± 0.36	2.33 ± 0.54	0.19
Follow-up	1.98 ± 0.47	2.08 ± 0.50	0.51
% Diameter stenosis			
Before	81.3 ± 15.8	74.1 ± 15.5	0.15
After	19.8 ± 6.9	14.8 ± 10.8	0.12
Follow-up	25.1 ± 7.5	23.5 ± 11.7	0.63
Acute gain, mm	1.62 ± 0.56	1.50 ± 0.70	0.57
Late loss, mm	0.14 ± 0.44	0.24 ± 0.36	0.41

Values are presented as mean ± SD or n (%).

ACC = American College of Cardiology; AHA = American Heart Association; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

Table 3. Optical Coherence Tomography Measurements

	Thrombus (n = 14)	Nonthrombus (n = 39)	p Value
Average number of struts	232 ± 131	174 ± 103	0.10
Average number of incompletely apposed struts	9 ± 10	5 ± 7	0.11
Frequency of incompletely apposed struts, %	3.6 ± 3.9	3.4 ± 6.1	0.94
Average number of uncovered stent struts	17 ± 16	8 ± 11	0.03
Frequency of uncovered stent struts, %	8.0 ± 5.1	6.1 ± 8.3	0.43
Average stent area, mm^2	7.34 ± 1.41	7.56 ± 2.04	0.72
Minimum stent area, mm^2	5.67 ± 1.63	6.04 ± 2.06	0.54
Average neointimal thickness, μm	74 ± 44	70 ± 49	0.82
Average SEI	0.89 ± 0.04	0.92 ± 0.03	0.001
Average NUS	2.22 ± 0.24	2.00 ± 0.33	0.03

Values are presented as mean ± SD or n (%).

NUS = neointimal unevenness score; SEI = stent eccentricity index.

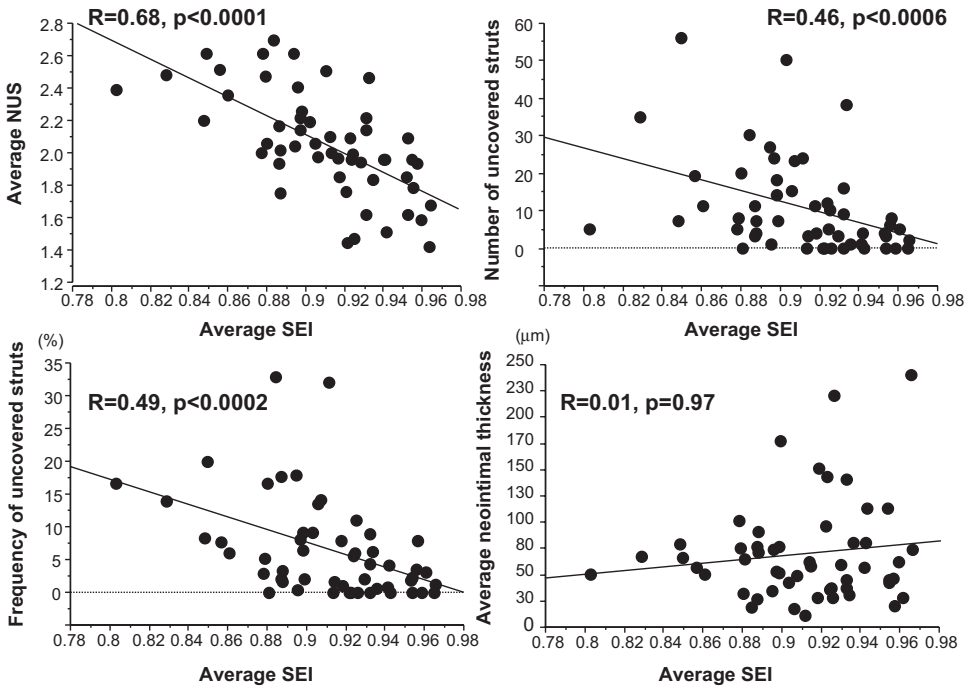

Figure 3. Relationships Among OCT Parameters in Overall Patients

The graphs show the relationships among OCT parameters to the overall patient population. Abbreviations as in Figure 1.

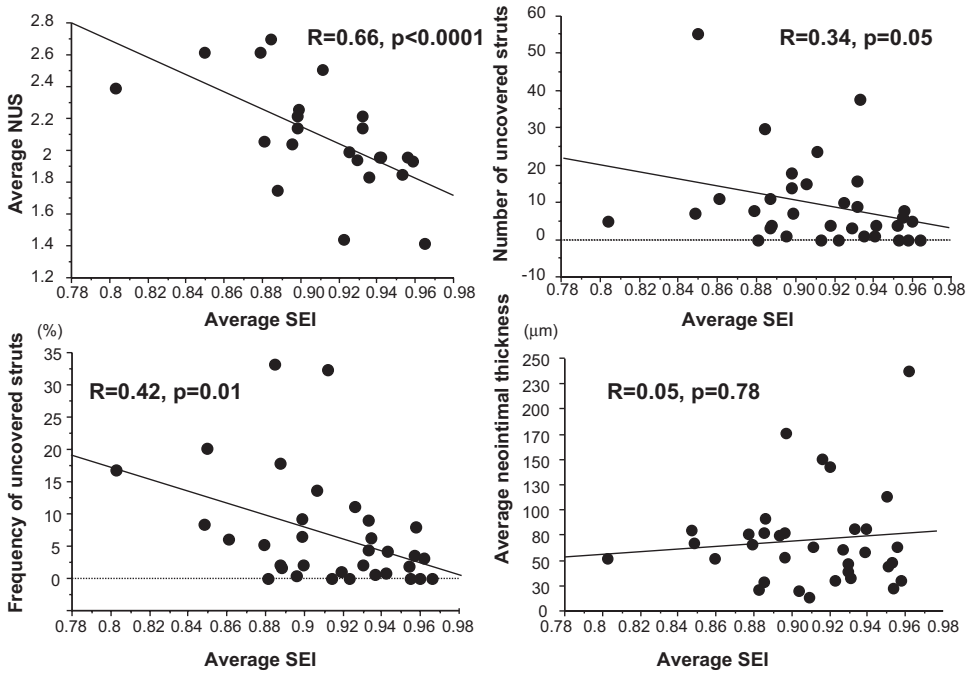

Figure 4. Relationships Among OCT Parameters in Patients With MSA >5 mm^2

The graphs show the relationships among OCT parameters in patients with minimum stent area (MSA) >5 mm^2. Abbreviations as in Figure 1.

frequency of uncovered stent struts. 3) There was no significant increase in major adverse cardiac events in patients with thrombus after SES implantation.

Incidence of the thrombus after SES implantation. In this study, thrombus was detected in 14 out of 53 patients (66 SES). A 26% incidence rate of cases with thrombus at 6 months may seem relatively higher than expected from the clinical incidence of SES thrombosis reported in the major randomized trials (13–15). However, the results from our study are comparable to previous angioscopic findings. Awata et al. (4) reported the incidence of thrombus formation as 30% (3 patients with thrombus of 10 patients) at 4, 10, and 21 months, and Takano et al. (16) reported it as 40% of patients at 6 months and 30% of patients at 2 years. In our study, the incidence of subclinical thrombus was similar between patients who are taking only aspirin and those who are under dual antiplatelet therapy. Even under dual antiplatelet therapy, a 30% to 40% rate of incidence of thrombus formation has been reported and several cases with newly formed thrombus were also observed (4,16). Therefore, although dual antiplatelet therapy is an important factor to reduce the risk of clinical thrombosis, it may not be effective enough to completely suppress thrombus formation after SES implantation.

Despite the relatively high incidence of thrombus formation after SES implantation, none of these patients experienced thrombotic clinical events during the follow-up period in our study or in previous studies. Additional factors such as antiplatelet resistance, intrinsic thrombogenicity, or coronary flow dynamics might trigger clinical stent thrombosis. Large-scale controlled studies are required to address whether the presence of thrombus in SES could be a factor for future clinical thrombosis or negative cardiac events.

Local determinants on the presence of thrombus. Although it is an infrequent complication, stent thrombosis is a catastrophic event when it occurs. An angioscopic study by Kotani et al. (3) demonstrated that thrombus formation was associated with incomplete neointimal coverage that tended to be more common in SES than in bare-metal stents. The results of our study and of the previous study are in agreement, showing that the presence of thrombus following SES implantation was associated with more frequent OCT evidence of uncovered stent struts. In addition, our results showed that asymmetric stent expansion could be an important factor in thrombus formation by increasing the number of uncovered struts and the heterogeneity of neointimal thickness, adding a new insight to previously published studies. Within the same SES, some struts showed healing as neointimal coverage but others remain uncovered. These uncovered struts may serve as a nidus for mural thrombus formation. A recent human autopsy study (8) has shown that the existence of uncovered struts without endothelialization is a common finding of late stent thrombosis. Therefore, we speculate that asymmetric stent expansion affects thrombus formation in part due to uneven stent coverage and healing.

The mechanisms by which SES induce nonuniform incomplete healing are not fully understood. Various factors such as lesion characteristics (17), drug distribution, and strut apposition (7) are considered to be involved. One possible mechanism is uneven drug delivery to the vessel wall due to asymmetric stent expansion. It has already been shown that local drug concentrations and concentration gradients are inextricably linked to the biological effect of a drug (7). Hwang et al. (7) have shown that inhomogeneous strut placement dramatically affects local drug concentrations without changing mean concentrations. Therefore, drug concentration gradients resulting from nonuniform strut distribution may lead to nonuniform healing. This hypothesis may be supported by a study of Finn et al. (18), in which a delayed healing process was exhibited by overlapping stent segments when compared with proximal and distal nonoverlapping segments in animals.

Performance of OCT. In a previous study where IVUS was used, asymmetric stent expansion did not seem to affect the average neointimal hyperplasia area after SES implantation (19), similar to the findings in our study (Fig. 3). However, OCT provided more detailed analysis on the condition of neointimal growth as shown in this study.

Although IVUS is a robust tool for the quantification of neointima, the resolution of IVUS (100 to 150 μm) may not be sufficient for detecting a suppressed, small degree of neointimal hyperplasia (19). As previously reported (9), the median thickness of neointimal hyperplasia after SES implantation is less than IVUS resolution. Because OCT is an imaging modality with high axial resolution (10 to 20 μm), it is a tool most suitable for the visualization of lumen/stent surfaces, especially for measuring suppressed neointima after SES (9). Optical coherence tomography is also a powerful modality for evaluation of thrombus in vivo. Histology-controlled studies have shown that the resolution of OCT can detect the microstructure of atherosclerotic plaque including thrombus (11,20). In a recent study comparing the ability of OCT, IVUS, and angioscopy to assess coronary plaque, OCT was able to visualize intracoronary thrombus as clearly as coronary angioscopy (21).

Clinical implications. The observations from this study have several potentially important clinical implications. Stent underexpansion was reported to be associated with SES thrombosis (12). On the other hand, our results suggest that asymmetric stent expansion may contribute to thrombus formation even in stents with an MSA >5.0 mm^2. Although bigger-is-better strategy is not critically important in SES implantation compared with bare-metal stenting (22), stent symmetry could be important for the reduction of thrombus formation regardless of MSA. Intravascular imaging technologies such as IVUS and OCT can still play an

important role to optimize stenting in the era of drug-eluting stents.

Study limitations. Several limitations should be noted in this study. First, this study was based on a relatively small sample size, raising the possibility of selection bias. Although we performed multivariate analysis, this study is not sufficiently powered to detect independent predictors for subclinical thrombus. Second, angioscopy, considered the gold standard for thrombus detection, and serial OCT analysis were not performed in this study. Therefore, there is a question of whether the protruding masses were in fact thrombus. An angioscopy-controlled study or serial OCT analysis will be required to further confirm our results. Third, this study only examined SES without any comparison with bare-metal stents and other drug-eluting stents. Finally, the study design was observational; therefore, it is still unclear whether additional interventions to acquire optimal stent expansion could further reduce the incidence of thrombus formation in patients receiving SES.

Conclusions

In this OCT study, longer stent length and greater asymmetric stent expansion were found to be determinants of thrombus formation following SES implantation. Asymmetric stent expansion may interfere with even neointimal coverage of the stent surface after SES deployment; uneven neointimal coverage is perhaps a key mechanism for thrombus formation. The implications of this study suggest the clinical utility of additional imaging modalities to ensure that intracoronary stents are properly and fully deployed so patients are not subjected to the risk of future thrombus formation.

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