Long-Term Follow-up of Neointimal Coverage of Sirolimus-Eluting Stents

— Evaluation With Optical Coherence Tomography —

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Background: Late stent thrombosis related to delayed neointimal growth is a major concern after drug-eluting stent (DES) implantation. The time course of neointimal growth and risk factors of uncovered stent struts after sirolimus-eluting stent (SES) was studied using optical coherence tomography (OCT).

Methods and Results: The 60 patients were enrolled and classified into G1 (follow-up period <9 months, n=27), G2 (9–24 months, n=18), and G3 (>25 months, n=15). The time elapsed since SES implantation was associated with a significant increase in mean neointimal area and neointimal thickness, and also with a significant decrease in the number of uncovered stent struts (G1: 14.8%, G2: 11.7%, and G3: 4.1%, $P<0.001$). However, only 17.6% of implanted SES was completely covered by neointima, even in the G3 period. Small-diameter SES, complex coronary lesions with lipid and calcium content adjacent to stent struts, and diabetes predicted delayed neointimal coverage of SES struts in G1.

Conclusions: Neointima inside SES progressively increases after the routine follow-up period, but only a few SES were completely covered at 3 years after implantation. OCT is a useful modality for assessing neointimal formation after SES implantation, and may give important information about the strategy of antiplatelet therapy after DES implantation. (Circ J 2009; 73: 2300–2307)

Key Words: Antiplatelet therapy; Drug-eluting stents; Optical coherence tomography; Thrombosis

Recent clinical trials have proved that drug-eluting stents (DES) inhibit neointimal proliferation and reduce the risk of in-stent restenosis.^{1,2} However, there have been major concerns regarding the potential development of late stent thrombosis related to delayed neointimal formation over the struts of the DES and the discontinuation of dual antiplatelet therapy.³ Although the incidence of DES thrombosis is reported to be less than 1%,^{4–8} the incidence of death or myocardial infarction associated with this thrombosis is greater than 60%,⁹ and related mortality rates range from 20% to 45%.^{6,10} In 2008, the AHA/ACC/SCAI recommended that dual antiplatelet drug therapy should continue for at least 12 months after DES implantation if patients are not at high risk of bleeding,¹¹ longer than had previously been suggested. In order to establish guidelines for the safe cessation of antiplatelet therapy after DES implantation, a large randomized clinical trial should be performed. Furthermore, it seems important to know whether adequate neointimal coverage of DES has been achieved before stopping dual antiplatelet therapy, especially the thienopyridines. With this clinical perspective, several intravascular ultrasound (IVUS) studies have

sought to evaluate the neointimal coverage of sirolimus-eluting stent (SES), but they have revealed that IVUS is unable to detect the neointimal layers covering the struts of most DES, even at long-term follow-up, because of its relatively low spatial resolution.¹²

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Intravascular optical coherence tomography (OCT) is a newly developed intravascular imaging modality with a maximal spatial resolution of 10 μm ,^{13–15} which is approximately 10-fold higher than that of IVUS. The aim of the present study was to use intravascular OCT to analyze the time course of neointimal coverage of SES in the chronic phase, and to identify the predictive factors influencing delayed neointimal coverage of stent struts.

Methods

Study Population

From September 2006 to January 2009, we enrolled 60 patients (50 men, 10 women)¹² with coronary artery disease

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Figure 1. OCT images of strut apposition and neointimal coverage of a sirolimus-eluting stent. (A) Strut apposing the vessel wall and covered by neointimal tissue. (B) Strut apposing the vessel wall, but not covered by neointimal tissue. (C) Strut not apposing the vessel wall (arrows). Bidirectional arrow indicates the distance between the center reflection of the strut and the internal margin of the vessel wall just behind the strut. Arrows indicate the struts.

who had previously received SES in native coronary arteries. At the time of SES implantation, the endpoint of deployment was determined by angiography. All patients enrolled in this study underwent routine angiographic follow-up within 8 months after SES implantation, and 27 patients also underwent OCT study at that time. The remaining 33 patients voluntarily underwent an OCT study and concomitant second coronary angiography from several months to 43 months after the completion of the first follow-up angiography by accepting the purpose of the present study. None of the patients underwent OCT study more than twice. Patients were excluded from the study if they had left main or ostial coronary lesions, congestive heart failure, or renal insufficiency with baseline serum creatinine >2.0 mg/dL.

Patients were classified into 3 subgroups according to time since SES implantation: G1 (<9 months, 27 patients), G2 (9–24 months, 18 patients) and G3 (25–43 months, 15 patients). All patients were taking aspirin (100 mg/day) and ticlopidine (200 mg/day) for at least 8 months after SES implantation, after which all patients were taking aspirin 100 mg/day, except 1 patient in the G3 group who was taking only ticlopidine.

For the purpose of assessing coronary risk factors, hypertension was considered to be present if a patient's blood pressure was $>140/90$ mmHg, or antihypertensive medication was being taken. Diabetes mellitus was considered present if the patient was taking glucose-lowering medications or insulin, or the fasting plasma glucose concentration was >126 mg/dL. Dyslipidemia was considered to be present if a patient's low-density lipoprotein level was >120 mg/dL or the patient was taking statins.

This study was approved by the Ethical Committee of Nara Medical University (2006–2020), and written informed consent was given by each patient.

Angiographic and OCT Image Acquisition

The OCT system used in the present study has been described previously.¹⁶ After routine coronary angiography, an intravascular OCT catheter (ImageWire, LightLab Imaging, Westford, MA, USA) was inserted through a 6 or 7Fr guiding catheter into the target coronary arteries beyond the implanted SES. After complete vasodilatation of the coronary artery by nitroglycerin (0.5 mg), OCT images were recorded during continuous infusion of Lactated Ringer's solution at 0.5 mL/s through the occlusion catheter (OBC,

LightLab Imaging) in order to remove blood from the field of view and allow clear visualization of the vessel wall. The coronary occlusion time for each OCT imaging was less than 40 s. Serial OCT images were obtained using an automatic pullback device at a rate of 1.0 mm/s. The images were processed and analyzed using proprietary software from LightLab Imaging.

OCT Data Analysis

OCT images were analyzed by 2 independent observers who did not know the patients' clinical background or angiographic lesion characteristics. For the assessment of neointimal coverage of stent struts, cross-sectional OCT images were obtained at 1-mm intervals (every 15 frames) from the distal to proximal ends of each implanted SES. For each cross-sectional OCT image, the surface of every strut was examined and then classified into 1 of 3 categories: (1) strut apposing vessel wall and covered by neointimal tissue, (2) strut apposing vessel wall, but not covered by neointimal tissue, or (3) strut not apposing vessel wall (malapposition). Because the thickness of the SES struts is $140\text{ }\mu\text{m}$, and the maximal spatial resolution of OCT ranges from 10 to $30\text{ }\mu\text{m}$, malapposition of the stent strut to the vessel wall was defined as the presence of more than $170\text{ }\mu\text{m}$ between the center reflection of the strut and the internal margin of the vessel wall just behind the strut. We excluded segments that overlapped or were located in side branches, and also images with poor quality. Representative OCT images are shown in **Figures 1A–C**.

For each implanted SES, planimetric measurement of neointimal thickness (NIT) and area (NIA) within the SES was performed. NIT and NIA were measured every 1 mm from the distal to the proximal ends of each SES. Stent area and lumen area in every image were measured by manual tracing.

We also evaluated the tissue characteristics of the vascular wall attached to the SES strut every 1 mm from the distal to the proximal ends of each SES. Because the image just behind strut was impossible to determine because of the shadow artifact of the strut, tissue characteristics adjacent to the edge of the shadow artifact were analyzed and classified into 1 of 3 categories: (1) intimal layer consisting of simple fibrous tissue, (2) intimal layer containing lipid and fibrous tissue, and (3) intimal layer containing calcification and fibrous tissue. Discernment of specific tissues with OCT was accomplished using the definitions of Kume

Table 1. Patients' Baseline Characteristics

	G1 (5–8 months)	G2 (9–24 months)	G3 (25–43 months)	P value
Clinical background				
No. of patients	27	18	15	
Time to OCT procedure (months)	7.1±0.8	13.8±3.6	32.6±5.6	
Age, years	65.0±10.4	63.4±9.6	65.1±10.3	0.52
Men (%)	21 (77.8%)	15 (83.3%)	14 (93.3%)	0.43
ACS (%)	4 (14.8%)	3 (16.7%)	3 (20.0%)	0.91
Risk factors				
Dyslipidemia, n (%)	16 (59.3%)	12 (66.7%)	9 (60.0%)	0.87
Hypertension,* n (%)	16 (59.3%)	12 (66.7%)	9 (60.0%)	0.87
Diabetes mellitus,† n (%)	13 (48.1%)	9 (50.0%)	8 (53.3%)	0.94
Smoking, n (%)	16 (59.3%)	12 (66.7%)	8 (53.3%)	0.73
HDL-cholesterol (mg/dl)	54±16	52±16	49±15	0.60
LDL-cholesterol (mg/dl)	121±29	108±25	110±30	0.26
Triglyceride (mg/dl)	117±45	112±52	98±36	0.49
Procedural background				
No. of stents	28	21	17	
LAD/LCX/RCA, (n)	15/10/3	12/4/5	6/4/7	0.15
AHA type of lesion				
A/B1, (n)	1/8	0/5	0/7	
B2/C, (n)	12/7	10/6	6/4	
Stent diameter (mm)	2.75±0.29	2.97±0.34	2.85±0.36	0.10
Stent length (mm)	20.4±5.32	22.9±5.28	20.5±5.10	0.21
Max. inflation pressure (atm)	18.4±3.73	16.8±4.20	18.1±3.90	0.59

*Defined as systolic and diastolic pressure >140mmHg and/or >90mmHg, respectively, or subject taking antihypertensive medication.

†Based on use of glucose-lowering medications and/or insulin or if fasting plasma glucose ≥126mg/dl.

OCT, optical coherence tomography; ACS, acute coronary syndrome; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; AHA, American Heart Association.

Table 2. Quantitative Analysis of OCT Images

	G1 (5–8 months)	G2 (9–24 months)	G3 (25–43 months)
No. of patients	27	18	15
No. of stents	28	21	17
MLD (mm)	2.85±0.37	3.01±0.41	2.97±0.43
LA (mm ²)	6.23±1.12	6.84±1.48	6.43±1.56
SA (mm ²)	6.86±1.36	7.71±1.62	7.58±2.02
NIA (mm ²)	0.63±0.17	0.87±0.44†	1.15±0.54*
NIT (μm)	53.4±23.9	70.1±40.6	98.6±40.2*
No. of stent struts counted	3,531	2,735	2,209
Malapposition, n (%)	49 (1.4%)	15 (0.5%)	7 (0.3%)*
Uncovered strut, n (%)	523 (14.8%)	320 (11.7%)	91 (4.1%)*,‡
Fully covered stent, n (%)	2/28 (7.1%)	1/21 (4.8%)	3/17 (17.6%)
Thrombus, n (%)	2 (7.1%)	0	1 (5.9%)

*P<0.001, G1 vs G3; †P<0.05, G1 vs G2; ‡P=0.01, G2 vs G3.

MLD, minimum lumen diameter; LA, lumen area; SA, stent area; NIA, neointimal area; NIT, neointimal thickness. Other abbreviation see in Table 1.

et al.¹⁷ In order to validate the assessment of tissue characteristics adjacent to the stent strut, 2 observers compared the first or last cross-sectional image showing both ends of the stent and the cross-sectional image just one frame distal or proximal to the target image.

Statistical Analysis

Continuous data are expressed as means±SD. Baseline characteristics and measurements were analyzed using the Pearson chi-square test or 1-way ANOVA, as appropriate. Univariate and multivariate regression analysis was conducted to determine the independent variables for a higher rate of uncovered stent struts (more than the median value of each group). For the assessment of interobserver variability of plaque diagnosis, we calculated Cohen's kappa coefficient. Statistical analysis was performed with StatView 5.0 software (SAS Institute, Cary, NC, USA). A P value

≤0.05 was specified as the confidence level for statistical significance.

Results

Baseline Characteristics

Clinical and procedural background data for the patients classified by follow-up period are listed in **Table 1**.

Diagnostic examination was performed 5–43 months after SES implantation. The average time between stent implantation and OCT imaging follow-up was 7.1±0.8 months in the routine follow-up group (G1: 5–8 months), 13.8±3.6 months in the mid-term follow-up group (G2: 9–24 months), and 32.6±5.6 months in the long-term follow-up group (G3: 25–43 months).

No significant differences in demographic or baseline characteristics, including coronary risk factors, were found

Figure 2. Thrombus formation in a sirolimus-eluting stent. (A) Thrombus on a stent strut not covered by neointimal tissue. (B) Thrombus on a stent strut covered with neointimal tissue. Arrows indicate thrombus.

Table 3. Clinical and Procedural Background and Percentage of Uncovered Stent Struts in G1

Clinical background	Rate of uncovered struts (%)	P value
Diabetes, +/-	18.7/12.0	0.018
Hypertension, +/-	15.4/14.2	0.69
Dyslipidemia, +/-	14.8/15.1	0.92
Smoking, +/-	13.9/16.6	0.39
Stent diameter, 2.5 mm/3 or 3.5 mm	18.9/11.3	0.009
Stent length, ≤18 mm/>18 mm	17.1/12.6	0.13
Stented coronary artery LAD/LCX/RCA	13.9/16.2/15.3	0.78
AHA lesion type, A/B1/B2/C	11.3/11.6/16.6/17.7	0.39

Abbreviations see in Table 1.

between groups. The treated vessel segments were distributed as follows: 30 left anterior descending lesions treated with 33 stents, 18 left circumflex lesions treated with 18 stents, and 15 right coronary artery lesions treated with 15 stents. The 3 follow-up groups did not differ significantly in terms of implanted stent diameter or length. In the present study, none of the SES exhibited angiographic restenosis as defined by more than 50% luminal loss. None of the patients in this study developed coronary events related to stent thrombosis.

Changes in Neointimal Coverage After SES Implantation

OCT findings for each follow-up period are summarized in **Table 2**. OCT images of 66 SES were obtained from 60 patients, and the total number of evaluated stent struts was 8,475 (3,531 struts in G1, 2,735 in G2, and 2,209 in G3). There were no significant differences in minimal lumen diameter, lumen area or stent area among the 3 groups. Both mean NIA and NIT increased significantly with the length of follow-up period (NIA: G1 $0.63 \pm 0.17 \text{ mm}^2$, G2 $0.87 \pm 0.44 \text{ mm}^2$, G3 $1.15 \pm 0.54 \text{ mm}^2$, $P=0.001$; NIT: G1 $53.4 \pm 23.9 \mu\text{m}$, G2 $70.1 \pm 40.6 \mu\text{m}$, G3 $98.6 \pm 40.2 \mu\text{m}$, $P<0.01$). A longer follow-up was associated with a significant decrease in the percentage of incompletely apposed stent struts (G1 1.4%, G2 0.5%, G3 0.3%, $P<0.01$) and uncovered stent struts (G1 14.8%, G2 11.7%, G3 4.1%, $P<0.01$). However, even in the G3 group, only 17.6% of SES were completely covered by neointimal tissue. We observed thrombus formation on 3 stents (4.5%), even with antiplatelet therapy,

2 thrombi attached to uncovered stent struts (**Figure 2A**), and another thrombus located on the neointimal tissue over the stent strut (**Figure 2B**).

Clinical Factors Influencing Neointimal Coverage

Table 3 shows the relationship between coronary risk factors and the percentage of uncovered SES struts in the G1 patient-group. Patients with diabetes had a significantly higher percentage of uncovered stent struts than those without diabetes (19.7% vs 11.4%, $P<0.01$), but this percentage was not influenced by smoking, dyslipidemia, or hypertension. In both the G2 and G3 groups, clinical parameters did not correlate with the percentage of uncovered rate of SES strut (data not shown).

The relationship between procedural indices of percutaneous coronary intervention (PCI) and the percentage of uncovered stent struts in the G1 group was also examined. Small diameter stents (2.5 mm) were associated with a significantly higher percentage of uncovered struts than larger diameter stents (3.0 and 3.5 mm; 19.7% vs 10.8%, $P<0.001$). Complex coronary lesions (AHA type B2/C) had a higher percentage of uncovered stent struts than simple coronary lesions (AHA type A/B1), but this difference did not reach statistical significance. In the G2 group, smaller diameter stents also showed a significantly higher rate of uncovered struts compared with larger stents (15.4% vs 10.5%, $P<0.05$), but no procedural parameters correlated with the uncovered rate in the G3 group (**Table 3**).

Multiple linear regression analysis revealed that a smaller

Table 4. Univariate and Multivariate Analyses for Predicting Higher Rate of Uncovered Struts

	G1		G2	G3
	Univariate	Multivariate	Univariate	Univariate
Diabetes	0.02	0.85	0.90	0.43
Hypertension	0.67	–	0.87	0.69
Dyslipidemia	0.30	–	0.21	0.43
Smoking	0.15	–	0.18	0.55
Stent diameter	0.0012	0.028	0.01	0.69
Stent length	0.06	–	0.63	0.25
AHA lesion type	0.29	–	0.40	0.38

Abbreviation see in Table 1.

Figure 3. Representative optical coherence tomography images of vascular wall attachment to a sirolimus-eluting stent. (A) Fibrous tissue marked by a thickened intimal layer with a homogeneous, signal-rich texture. (B) Lipid-rich tissue with homogenous, diffusely bordered, signal-poor regions with overlying signal-rich bands at 5–7 o'clock (curved line indicates the region of lipid accumulation). (C) Calcified tissue with sharply delineated, signal-poor or signal-rich regions. Arrowheads indicate the border between fibrous tissue and calcium deposits. Arrows indicate the stent struts in each panel.**Table 5. Coronary Arterial Lesion Characteristics and Rate of Uncovered Stent Struts**

	Fibrous	Lipid	Calcium
G1			
No. of stent struts	3,446	39	46
No. of uncovered struts	494	11	18
Rate of uncovered struts (%)	14.3	28.2*	39.1†
G2			
No. of stent struts	2,678	22	35
No. of uncovered struts	302	6	12
Rate of uncovered struts (%)	11.3	27.2*	34.2†
G3			
No. of stent struts	2,141	23	45
No. of uncovered struts	85	2	4
Rate of uncovered struts (%)	4.0	8.7	8.9

*P<0.05 vs Fibrous, †P<0.01 vs Fibrous.

diameter stent was an independent predictor for a higher rate of uncovered struts in the G1 group ($F=5.5$, $P<0.001$) (Table 4).

OCT-Based Tissue Characteristics of the Vascular Wall and Uncovered Stent Struts

Figure 3 shows representative OCT images of various tissue characteristics of the arterial wall adjacent to stent struts: a stent strut located on simple fibrous intimal layer, lipid-rich plaque or atheromatous plaque with calcium accumulation. Two observers assessed the tissue characteristics adjacent to the strut artifact and in successive images. The agreement in diagnosis of strut-containing images and successive OCT images without struts was 100% for both

observers. Interobserver agreement on tissue diagnosis was 99.3% (Cohen's K value, 0.87).

Table 5 shows the relationship between the OCT-based characteristics of plaques adjacent to each stent strut and the percentage of uncovered SES. In the G1 and G2 groups this percentage was significantly higher for stent struts located on either lipid- or calcium-containing plaques than those positioned over simple fibrous plaques (G1 14.3%, 28.2%, 39.1%, respectively, $P<0.01$; G2 11.3%, 27.2%, 34.2%, respectively, $P<0.01$). By contrast, in the G3 group, the rate of uncovered stent struts tended to be higher for plaque containing lipid and calcium, but this difference did not reach statistical significance.

Discussion

We used the newly developed intravascular OCT system with an excellent spatial resolution of $10\mu\text{m}$ to visualize the very thin neointimal tissue covering SES struts, a task that was not possible with IVUS. The salient findings of the present study are that 14.8% of SES struts were not covered by neointimal tissue at 8 months after SES implantation, and that the percentage of uncovered stent struts continued to decrease by 4.1% in patients with the longest follow-up period, secondary to late neointimal growth. However, complete coverage of stent struts was achieved only in 17.6% of all implanted SES, even 32 months after implantation. Furthermore, a smaller diameter SES, the presence of underlying coronary lesions with lipid and calcium content, and diabetes correlated with delayed local neointimal coverage of the stent struts.

Late Neointimal Growth After SES Implantation

Because DESs are associated with a striking reduction in restenosis after PCI, they are routinely and widely used around the world.^{18,19} However, in 2004, McFadden et al reported 4 cases of late thrombosis of a DES after discontinuation of antiplatelet therapy because of surgery or invasive endoscopic examination.²⁰ Their report raised general concerns about the safety of routine use of DES, because late thrombosis often results in myocardial infarction or death. Subsequently, physicians have aimed to prolong the duration of dual antiplatelet therapy,²¹ because the likelihood of late stent thrombosis rises considerably with inadequate or discontinued antiplatelet therapy and delayed reendothelialization of the DES.^{22,23}

Recently, Matsumoto et al used OCT to study neointimal growth over stent struts after SES implantation.²⁴ Although their findings were limited to observations at 6 months after implantation, they showed that the average percentage of neointima-covered struts in an individual SES was 89%, and that only 16% of implanted SES had struts fully covered by neointimal tissue. We also observed that a relatively low percentage of implanted SES was fully covered by neointima at 8 months after implantation. In the present study, we found that neointimal growth over stent struts continued for as long as 32 months after implantation, and this late neointimal growth was accompanied by a higher rate of covered SES struts and lower rate of malapposed stent struts. Such progressive decrease in the rate of uncovered SES struts seems necessary for preventing stent thrombosis, and our observations support the recent principle that longer therapy with dual antiplatelet drugs is safer. Furthermore, our observation is partly consistent with previous reports by Takano et al in which they demonstrated that 5% of SES struts were uncovered in patients for up to 24 months after SES implantation.^{25,26} We were not able to confirm the plateau stage of neointimal growth after SES implantation, so we need know whether all implanted SES are completely covered at 3 years after implantation, as well as whether late neointimal growth results in angiographic restenosis at time points long after SES implantation.

Clinical Predictors for Delayed Neointimal Coverage of SES

Based on the findings of previous large DES-related clinical trials, science advisory committees of the ACC/AHA/SCAI/ACS/ADA summarized the factors relating to late stent thrombosis:²⁷ stenting in small vessels, multiple lesions, long stents, overlapping stents, ostial or bifurcated lesions, prior brachytherapy, suboptimal stenting result, low ejection fraction, advanced age, diabetes, renal failure, acute coronary syndrome, and premature discontinuation of antiplatelet therapy. In the present study, we found that small diameter (2.5 mm) stents, the tissue characteristics of the stented coronary segment, and diabetes were important predictors for a higher rate of uncovered struts.

The mechanisms whereby these factors suppress neointimal growth over SES struts are not clear, but tissue distribution of eluted sirolimus might play an important role. The dose of sirolimus loaded on the struts for a given length of SES is fixed, irrespective of stent diameter,²⁸ so the tissue concentration of sirolimus per unit area may be higher with smaller rather than larger diameter stents. Accordingly, the higher rate of uncovered struts in smaller diameter SES may be because of more significant suppression of vascular cell proliferation as compared with larger diameter SES,

and this might mediate the delayed neointimal coverage of smaller SES.

Several previous studies have demonstrated the feasibility of intravascular OCT for evaluating the vascular tissue characteristics of coronary atherosclerotic plaques.^{29,30} Our OCT observations revealed that neointimal growth is impaired when SES struts are deployed in coronary segments with atheromatous plaques containing either lipid or calcium, as compared with normal coronary segments or plaque consisting of simple fibrous tissue. Supporting this finding, preprocedural angiographic findings showed that complex coronary lesions (type B2/C) tended to be accompanied by a higher rate of uncovered SES in the chronic phase. These findings indicate the importance of the histopathological characteristics of coronary lesion on the healing process after SES implantation, especially with regard to neointimal formation. We assume the reason for this finding is that sirolimus inhibited smooth muscle cell proliferation more strongly in calcified or lipid plaque than in the simple fibrous plaque lesion. One explanation is the increased stiffness of the coronary artery because of complex coronary plaque, especially with calcium deposition. In the case of SES implantation in hard coronary segments, inhomogeneous distribution of the stent struts occurs because of incomplete expansion, and this may lead to an increased focal drug concentration that induces focal over-suppression of neointimal formation. Secondly, it is possible that there is a relatively small volume of viable fibrous tissue at the focal site of a complex coronary atheroma. In such complex lesions, the nonviable calcium and/or lipid content is separated by relatively thin fibrous tissue. Vascular smooth muscle cells and fibroblasts included in thin fibrous tissue are known to be the origin of proliferation and production of extracellular matrix.³¹ Accordingly, the constant dose of sirolimus for a smaller volume of fibrous tissue in complex lesions might be responsible for the over-suppression of neointimal coverage of the stent struts.

Diabetes is an established risk factor for in-stent restenosis, but why diabetes correlated with a higher rate of uncovered struts in this study is unknown. Previous experimental studies have shown that hyperglycemia promotes endothelial cell apoptosis and inhibits endothelial cell proliferation.^{32,33} We further speculate that the increased stiffness of the coronary arteries in diabetic patients because of the presence of complex coronary plaque, such as calcium deposition or diffuse and long atheroma distribution, is related to such divergent coronary lesions. In the complex coronary lesions of diabetes, heterogeneous tissue concentration of sirolimus would occur because of the uneven strut distribution, and might induce focal over- or under-suppression of neointimal formation over the stent struts.^{28,31} The result of multivariable analysis that a small diameter stent was an independent predictor supports the concept that diabetic patients have a higher rate of uncovered strut because they often have diffuse and longer narrowing of the coronary stenosis with complex lesion characteristics.

Together with the longer follow-up period, the effects of both clinical and procedural parameters on the rate of uncovered SES struts decreased, which we assume is partly the reason for the significantly lower rate of uncovered struts in the G2 and G3 groups than in G1. This finding suggests that, irrespective of the patient's background, slow but steady growth of neointima over the struts continues in all implanted SES in the chronic phase.

Late Stent Thrombosis and Uncovered Struts of SES

None of the patients in this study experienced ischemic events after SES implantation, but 3 small thrombi inside the SES were incidentally observed, even with continued antiplatelet therapy; 2 were found on uncovered stent struts, supporting the theory that uncovered or malapposed stent struts are the primary cause of late stent thrombosis. On the other hand, 1 thrombus was located on neointimal tissue covering the stent struts, which suggests that neointimal tissue may be related to the endothelium in 2 ways: first, its margin may be lined by dysfunctional endothelial cells, and second, it may not be accompanied by an endothelial cell layer.^{34,35} It is difficult to investigate these points using OCT, so further studies examining the function of neointimal tissue covering the SES struts need to be performed. On the other hand, the actual incidence of late stent thrombosis was much lower than the incidence we would expect based on the high percentage of uncovered SES struts,^{36,37} and that suggests factors other than delayed endothelialization, such as the patient's hemostatic status, focal hemodynamic alterations in the implanted SES, and so on, also play an important role in the development of late stent thrombosis.³⁸

Study Limitations

First, our findings were based on observations in a relatively small number of patients, and we did not use a prospective or randomized study protocol. Second, OCT is unable to image the stent struts and vascular wall in the presence of blood. Insufficient blood removal limits the application of OCT for certain coronary lesions, especially ostial and very tortuous lesions, and we were not able to assess SES that were deployed in such coronary segments. A third limitation is the resolution of OCT. Although the spatial resolution of OCT is the highest of all available intravascular imaging modalities, we might have incorrectly judged some monolayers of regenerated endothelial cells covering the stent struts as uncovered struts. Fourth, none of the enrolled patients developed cardiac events related to stent thrombosis during the observation period. Moreover, we were not able to identify factors predicting delayed neointima coverage of the SES at 24 months after implantation. Because it is reported that stent thrombosis steadily develops, even in the very late phase of SES implantation, further study with more patients should be performed in the future to clarify the relationship between the patients' background and delayed neointimal growth, as well as the development of stent thrombosis.

Conclusions

OCT imaging enabled us to visualize the thin neointimal tissue covering SES struts. Neointimal growth inside the SES progressively increased after the 8-month routine follow-up period, but complete coverage of the stent struts was established in only 17.6% of SES, even 32 months after implantation. In determining when dual antiplatelet therapy should be discontinued, the clinician should consider the patient's clinical background, especially a history of diabetes, whether or not a small diameter SES is implanted, and the tissue characteristics of the stented coronary segment.

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