

Quantitative and Qualitative Changes in DES-Related Neointimal Tissue Based on Serial OCT

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OBJECTIVES The study evaluated serial quantitative and qualitative changes in vascular responses to drug-eluting stents (DES) using optical coherence tomography (OCT).

BACKGROUND Serial changes in stent strut coverage and neointima characteristics in DES-treated lesions have not been sufficiently investigated using OCT.

METHODS Serial OCT was performed in 72 patients with 76 DES-treated lesions at 9 months and 2 years after DES implantation (sirolimus-eluting stent, n = 23; paclitaxel-eluting stent, n = 20; zotarolimus-eluting stent, n = 25; everolimus-eluting stent, n = 8). Serial changes in quantitative parameters (neointimal thickness, stent strut coverage, and apposition at each strut) and qualitative characteristics of the neointima were evaluated.

RESULTS Mean neointimal thickness significantly increased from 164 μm to 214 μm between 9 months and 2 years ($p < 0.001$), and the percentage of uncovered stent struts significantly decreased (from 4.4% to 2.3%, $p < 0.001$). Completely covered lesions were more frequently observed at 2 years (44.7% vs. 59.2%, $p = 0.07$). However, the percentage of malapposed struts (0.6% vs. 0.9%, $p = 0.24$) and incidence of intracoronary thrombi (10.5% vs. 9.2%, $p > 0.99$) were similar. On qualitative evaluation of neointimal morphology, lipid-laden neointima (27.6% vs. 14.5%, $p = 0.009$) and thin-cap neoatheroma (13.2% vs. 3.9%, $p = 0.07$) were more frequently detected at 2-year follow-up compared with 9 months. In matched cross-sectional evaluation, the change of neointimal morphology from homogeneous to heterogeneous or lipid-laden pattern was observed in 23 (30.3%) of 76 lesions. There was a significant increase in percent neointimal hyperplasia cross-sectional area in those lesions.

CONCLUSIONS This OCT study suggested that neointimal coverage improved from 9 months to 2 years without significant changes in the incidence of malapposed struts and intracoronary thrombus. Additionally, in-stent neoatherosclerosis including transformation to lipid-laden neointima might progress during extended follow-up periods after DES implantation. (J Am Coll Cardiol Img 2012;5: 1147–55) © 2012 by the American College of Cardiology Foundation

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Drug-eluting stents (DES) remarkably suppress neointimal growth and improve angiographic outcomes compared with bare-metal stents (1,2). However, late stent thrombosis has become a critical long-term safety issue because it can cause serious clinical events, such as sudden death or acute myocardial infarction (3,4). Although multifactorial predictors may be associated with late stent thrombosis, delayed vascular healing after DES implantation is suggested as a strong predictor among several factors (3,5). In addition, recent studies demonstrated that development of neoatherosclerosis within neointimal tissues could be another cause of stent thrombosis due to neointimal rupture (6,7).

Optical coherence tomography (OCT) is a high-resolution intravascular imaging modality to evaluate neointimal tissue adequately in vivo. In a previous OCT study with bare-metal stent-treated lesions, significant differences in neoatherosclerosis were detected within neointimal tissue between <6 months and ≥ 5 years after bare-metal stent implantation (8). However, there have been little quantitative or qualitative in vivo data investigating serial changes in neointimal tissue characteristics of DES-treated lesions using OCT. Therefore, the present study evaluated serial changes in quantitative and qualitative characteristics of neointimal tissue in DES-treated lesions between 9-month and 2-year follow-up.

ABBREVIATIONS AND ACRONYMS

CSA	= cross-sectional area
DES	= drug-eluting stent(s)
EES	= everolimus-eluting stent(s)
NIH	= neointimal hyperplasia
OCT	= optical coherence tomography
PES	= paclitaxel-eluting stent(s)
SES	= sirolimus-eluting stent(s)
TCNA	= thin-cap neoatheroma
ZES	= zotarolimus-eluting stent(s)

METHODS

Study patients and design. We identified 250 patients from the OCT registry database of our institute who underwent follow-up OCT examination at 9 months (± 3 months) after DES implantation between November 2007 and August 2009. Among these patients, a second follow-up OCT examination at 2 years (± 3 months) after stent implantation was performed in 72 patients. A total of 76 stented lesions were evaluated serially: 23 sirolimus-eluting stents (SES) (Cypher, Cordis, Miami, Florida), 20 paclitaxel-eluting stents (PES) (Taxus, Boston Scientific, Natick, Massachusetts), 25 zotarolimus-eluting stents (ZES) (Endeavor sprint, Medtronic, Santa Rosa, California), and 8 everolimus-eluting stents (EES) (Xience, Abbott Vascular, Santa Clara, California). The reasons for 2-year follow-up angiogram were: 1) evidence of

myocardial ischemia by stress test or clinical presentation of coronary artery disease ($n = 24$ lesions); or 2) planned follow-up angiography for other stented segments ($n = 52$ lesions). The selection of DES at the time of coronary intervention was at the physician's discretion. Inclusion and exclusion criteria of follow-up OCT procedures have been previously reported (9). Specifically, the patients with in-stent restenotic lesions treated by repeated target lesion revascularization before 2-year follow-up were excluded from this study. The study protocol was approved by the institutional review board of our institutes, and written informed consent was obtained from all patients before the procedure. DES implantation was performed using conventional techniques and most patients received dual (aspirin and clopidogrel) antiplatelet therapy for at least 12 months. Quantitative coronary angiography analysis was previously described (9). Angiographic late loss was defined as the difference between follow-up and post-procedure minimal lumen diameter.

OCT image protocol and analysis. OCT examination using a conventional OCT system (Model M2 Cardiology Imaging System, LightLab Imaging, Westford, Massachusetts) with a motorized pull-back system at 1.0 mm/s was previously described (10). OCT analysis was performed by an independent investigator blinded to patient and procedural information. For serial comparison, total stent length was measured at the 9-month and 2-year follow-up, and unchanged stent length was confirmed in all lesions. Cross-sectional OCT images at 9 months and 2 years were meticulously matched using distance from the stent edge and landmarks such as side branches and calcified plaques. Inadequate images including noncircumferential cross sections, poor quality or mismatched images, and cross sections with major side branches (diameter ≥ 2.0 mm) were excluded from this analysis. A total of 1,947 matched cross-sectional images at both 9 months and 2 years had analyzable image quality. Cross-sectional OCT images were analyzed at 1-mm intervals (every 15 frames). Stent and luminal cross-sectional areas (CSA) were measured at 1-mm intervals, and neointimal hyperplasia (NIH) CSA was calculated as the stent CSA minus the luminal CSA. Percent NIH CSA was calculated as $\text{NIH CSA} \times 100/\text{stent CSA}$. Mean values are reported in this study. The thickness of NIH was measured as the distance between the endoluminal surface of the neointima and the strut (11). An uncovered strut was defined as having an NIH

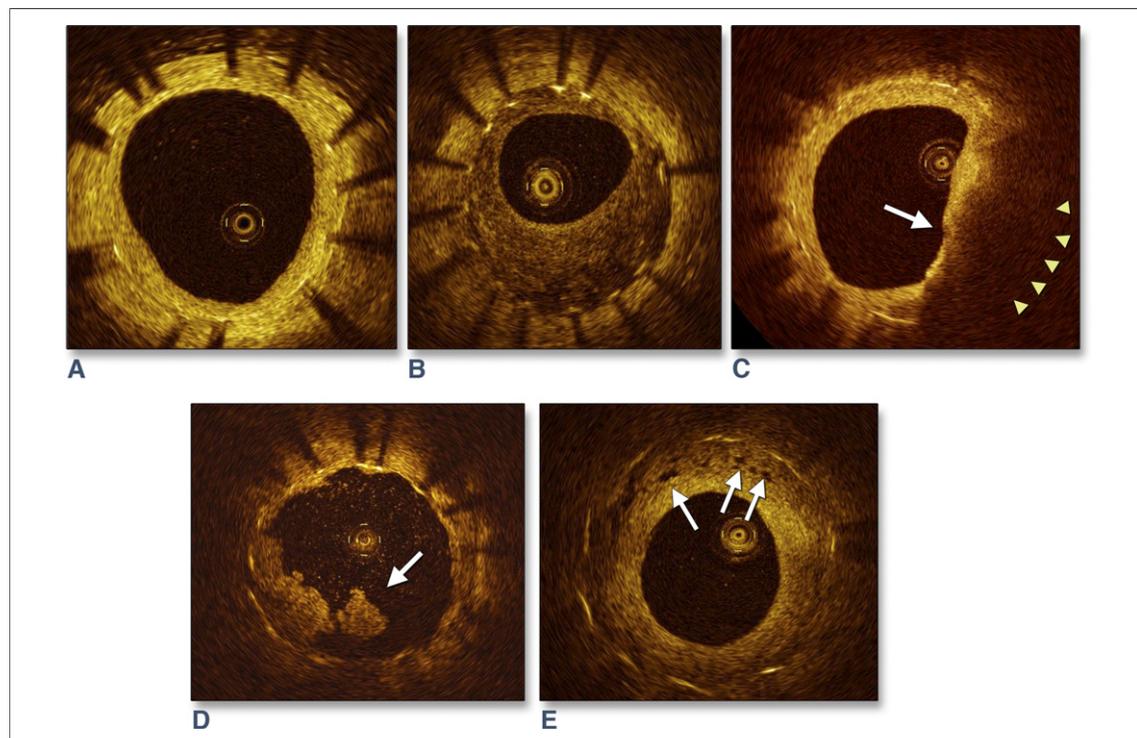


Figure 1. Representative Optical Coherence Tomographic Images of Neointimal Tissue

Images shown are (A) homogeneous neointima, (B) heterogeneous neointima, (C) thin-cap neoatheroma (arrows) and lipid-laden neointima (arrowheads), (D) intracoronary thrombi (arrow), and (E) neovascularization (arrows).

thickness of $0 \mu\text{m}$ (11). A completely covered lesion was defined as a stented lesion with $>99\%$ of struts covered with neointima. A malapposed strut was defined as a strut that had detached from the vessel wall (SES $\geq 160 \mu\text{m}$, PES $\geq 130 \mu\text{m}$, ZES $\geq 110 \mu\text{m}$, EES $\geq 100 \mu\text{m}$) (10–13). The percentage of malapposed or uncovered struts in each stented lesion were calculated as the (number of malapposed or uncovered struts/total number of struts in all cross sections of the lesion) $\times 100$, respectively. Qualitative evaluation was performed in stent level and in matched cross section level at 1-mm intervals between 9 months and 2 years. Neointimal tissue was classified as follows (Fig. 1): 1) homogeneous neointima, a uniform signal rich band without focal variation or attenuation; 2) heterogeneous neointima, focally changing optical properties and various backscattering patterns; and 3) lipid-laden neointima, a diffuse border, signal-poor region with marked attenuation (8,14). A thin-cap neoatheroma (TCNA) was defined as fibrous cap thickness at the thinnest part $\leq 65 \mu\text{m}$ and an angle of lipid-laden neointima $\geq 180^\circ$ (15). The morphology of thrombi was signal-rich, low-backscattering protrusions or high-backscattering protrusions inside the lumen of the artery with

signal-free shadowing on OCT images (dimension $\geq 250 \mu\text{m}$) (9). Visible microvessels were defined as well-delineated low backscattering structures $<200 \mu\text{m}$ in diameter and showing a trajectory within the vessel (Fig. 1) (14). The extrastent lumen was defined when external lumen of the stent was shown in a cross section (16).

Statistical analysis. Statistical analysis was performed using SAS software, version 9.1.3 (SAS Institute, Cary, North Carolina). Data are expressed as mean \pm SD or n (%). Comparisons were made using McNemar test for the categorical data, and paired *t* test for the continuous variables. Comparisons between 52 lesions without ischemia

Table 1. Baseline Clinical Characteristics (N = 72)

Age, yrs	60.4 \pm 8.8
Male	51 (70.8)
Acute coronary syndrome	45 (62.5)
Hypertension	37 (51.4)
Diabetes mellitus	23 (31.9)
Dyslipidemia	31 (43.1)
Current smoking	18 (25.0)
Previous myocardial infarction	3 (4.2)
Values are mean \pm SD or n (%).	

and 24 lesions with ischemia at 2-year follow-up OCT examination were made using Student *t* test, chi-square statistics, or Fisher exact test. If the distributions were skewed, a nonparametric test was used. A *p* value <0.05 was considered statistically significant.

Table 2. Coronary Angiographic and Optical Coherence Tomographic Findings

Total (n = 76)	9 Months	2 Years	p Value
Quantitative coronary angiography			
Target vessel			
Left anterior descending artery	34 (44.7)	—	
Left circumflex artery	17 (22.4)	—	
Right coronary artery	25 (32.9)	—	
Type B ₂ or C lesion	55 (72.4)	—	
Stent diameter, mm	3.0 ± 0.3	—	
Stent length, mm	26.5 ± 6.5	—	
Maximal inflation pressure, atm	16.0 ± 2.2	—	
Pre-intervention			
Reference vessel diameter, mm	2.7 ± 0.4	—	
Minimal lumen diameter, mm	0.7 ± 0.5	—	
Post-intervention			
Reference vessel diameter, mm	2.8 ± 0.4	—	
Minimal lumen diameter, mm	2.7 ± 0.3	—	
Follow-up			
Reference vessel diameter, mm	2.7 ± 0.4	2.8 ± 0.3	0.23
Minimal lumen diameter, mm	2.3 ± 0.4	2.0 ± 0.4	<0.001
Late loss, mm	0.39 ± 0.38	0.66 ± 0.43	<0.001
OCT			
Time interval to OCT, days	276 ± 56	735 ± 79	
Quantitative analysis			
Cross-sectional level analysis			
Mean stent CSA, mm ²	7.0 ± 1.6	7.0 ± 1.6	0.92
Mean lumen CSA, mm ²	5.7 ± 1.4	5.4 ± 1.6	0.01
Mean NIH area, mm ²	1.3 ± 0.9	1.7 ± 1.1	0.001
Percent NIH CSA, %	18.7 ± 11.3	23.4 ± 14.5	<0.001
Cross sections with any uncovered strut, %	21.2 ± 22.1	12.2 ± 16.9	<0.001
Cross sections with uncovered strut ratio >0.3, %	7.7 ± 14.5	4.3 ± 11.9	<0.001
Cross sections with any malapposed strut, %	2.4 ± 5.7	3.1 ± 9.0	0.36
Strut level analysis			
Mean NIH thickness, μm	164 ± 95	214 ± 132	<0.001
Percentage of uncovered struts, %	4.4 ± 6.1	2.3 ± 4.0	<0.001
Percentage of malapposed strut, %	0.6 ± 1.9	0.9 ± 3.5	0.24
Percentage of uncovered and malapposed struts, %	0.3 ± 1.3	0.3 ± 1.9	0.89
Qualitative analysis			
Intracoronary thrombus	8 (10.5)	7 (9.2)	>0.99
Lipid-laden neointima	11 (14.5)	21 (27.6)	0.009
Thin-cap neoatheroma	3 (3.9)	10 (13.2)	0.07
Heterogeneous pattern	49 (64.5)	47 (61.8)	>0.99
Neovascularization	34 (44.7)	56 (73.7)	<0.001
Extrastent lumen	15 (19.7)	21 (27.6)	0.04

Values are n (%) or mean ± SD.
CSA = cross-sectional area; NIH = neointimal hyperplasia; OCT = optical coherence tomography.

RESULTS

Baseline characteristics. Baseline characteristics of the study population are presented in Table 1. The time intervals from stent implantation to the first and second OCT examinations were 276 ± 55 and 735 ± 78 days, respectively. Quantitative angiographic findings are shown in Table 2. A total of 76 stented lesions were serially evaluated by OCT without any serious complications.

Serial changes of OCT findings. Table 2 summarizes the serial OCT data. Representative cases of the change in neointimal coverage, malapposition, and neointimal tissues are shown in Figure 2. Mean NIH thickness and percent NIH CSA increased from 164 μm and 18.7% at 9 months to 214 μm and 23.4% at 2 years (*p* < 0.001 for both). The percentage of uncovered struts significantly decreased from 4.4% at 9 months to 2.3% at 2 years (*p* < 0.001). Completely covered lesions were more frequently observed at 2 years (44.7% vs. 59.2%, *p* = 0.07), but approximately one-half of the stented lesions were still not completely covered during extended follow-up. In addition, malapposed struts and intracoronary thrombi were similarly detected during follow-up (0.6% vs. 0.9% and 10.5% vs. 9.2%, respectively). About one-half of thrombi were detected over the uncovered strut (62.5% at 9 months and 42.9% at 2 years) and part of them was observed over the malapposed strut (12.5% at 9 months and 14.3% at 2 years). Lipid-laden neointima (14.5% vs. 27.6%, *p* = 0.009) and TCNA (3.9% vs. 13.2%, *p* = 0.07) were more frequently detected at 2 years compared with 9-month follow-up. The incidence of neovascularization also significantly increased from 44.7% at 9 months to 73.7% at 2 years (*p* < 0.001).

Matched cross-sectional evaluation. Mean NIH thickness increased in 74.4% of cross sections, which was different according to types of DES (SES, 81.3%; PES, 60.0%; ZES, 73.8%; EES, 88.9%; *p* < 0.001). The serial change of neointimal tissue pattern is also shown in Figure 3. The change of neointimal morphology from homogeneous to heterogeneous or lipid-laden pattern was observed in 23 (30.3%) of 76 lesions. There was a significant increase in percent NIH CSA in those lesions (Fig. 4).

OCT findings according to presence of ischemia at 2-year follow-up. Compared to 52 lesions without ischemia, the incidence of thrombi was significantly higher in 24 lesions with ischemia in

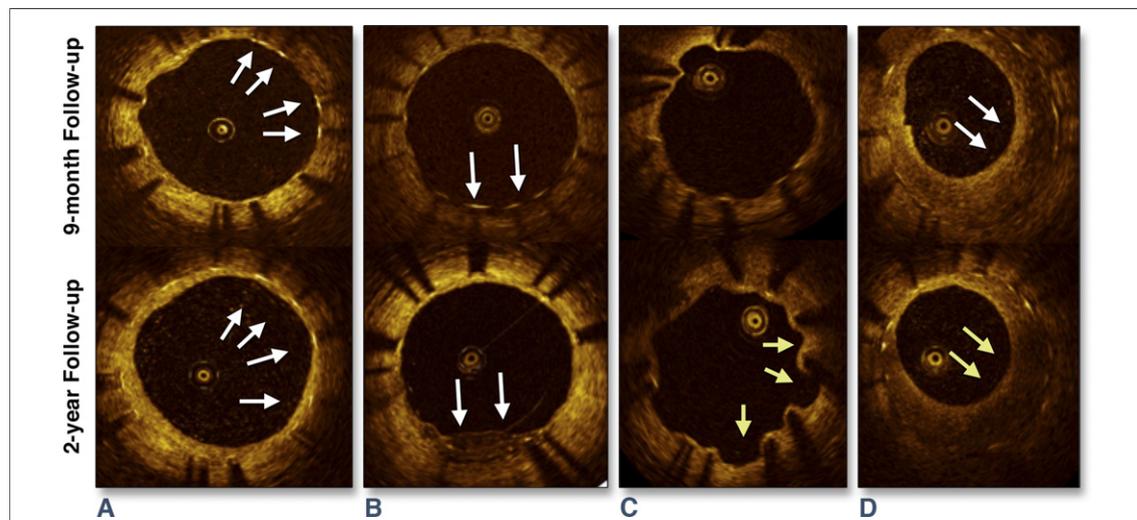


Figure 2. Representative Cases of Changes in Neointimal Coverage, Malapposition, and Neointimal Tissues

(A) Uncovered struts at 9 months were covered with neointima on follow-up at 2 years (white arrows). (B) A low-density abnormal tissue structure appeared over uncovered struts during serial follow-up (white arrows). (C) Extrastent lumen not present at 9 months was noted at 2-year follow-up (yellow arrows). (D) Increase in the low-density signal within heterogeneous neointima was observed between 9 months (white arrows) and 2 years (yellow arrows).

2-year follow-up OCT examination (Fig. 5A). The serial changes of neointimal tissue pattern between the 2 groups are also shown in Figure 5B.

DISCUSSION

This serial OCT study showed changes in both quantitative and qualitative characteristics of the neointima between 9 months and 2 years after DES

implantation. There were significant increases in mean NIH thickness, percent NIH CSA, percentage of uncovered struts, lipid-laden neointima, and TCNA, but similar incidences of malapposed struts and intracoronary thrombi.

A higher incidence of late stent thrombosis has been reported in patients following DES implantation compared to bare-metal stents (3,17). Adequate vascular healing including sufficient endothe-

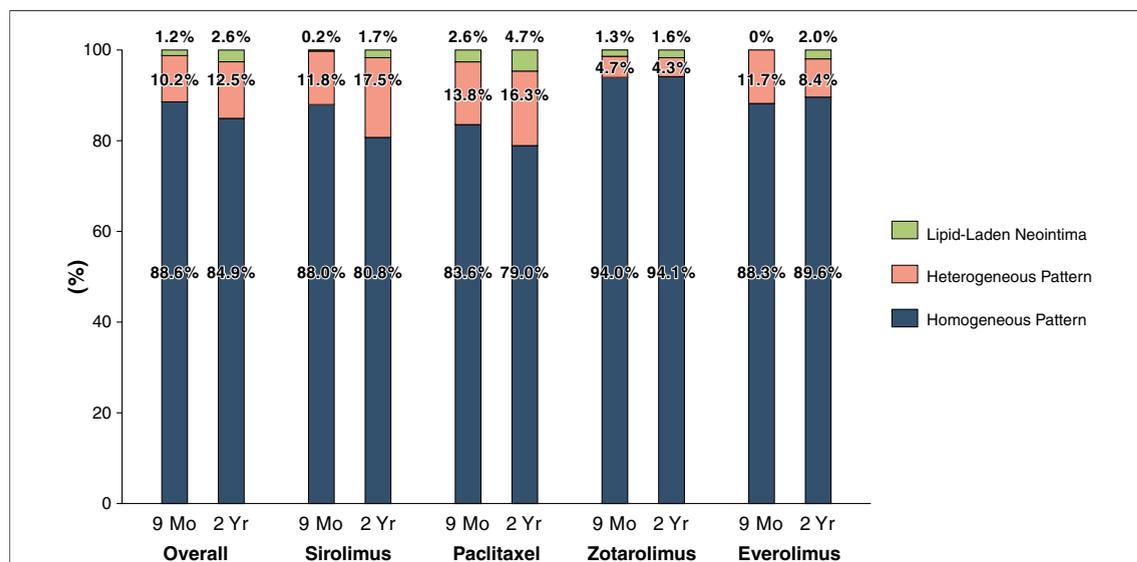


Figure 3. Serial Change of Neointimal Tissue Pattern

The serial change of neointimal tissue pattern was different in each drug-eluting stent by matched cross-sectional evaluation.

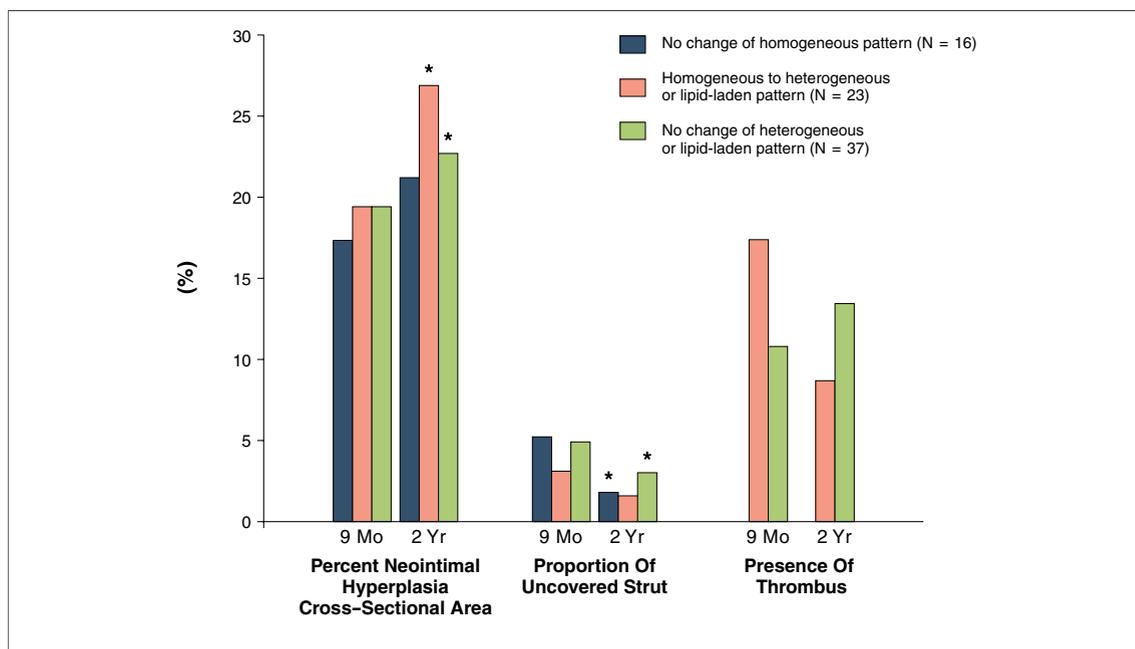


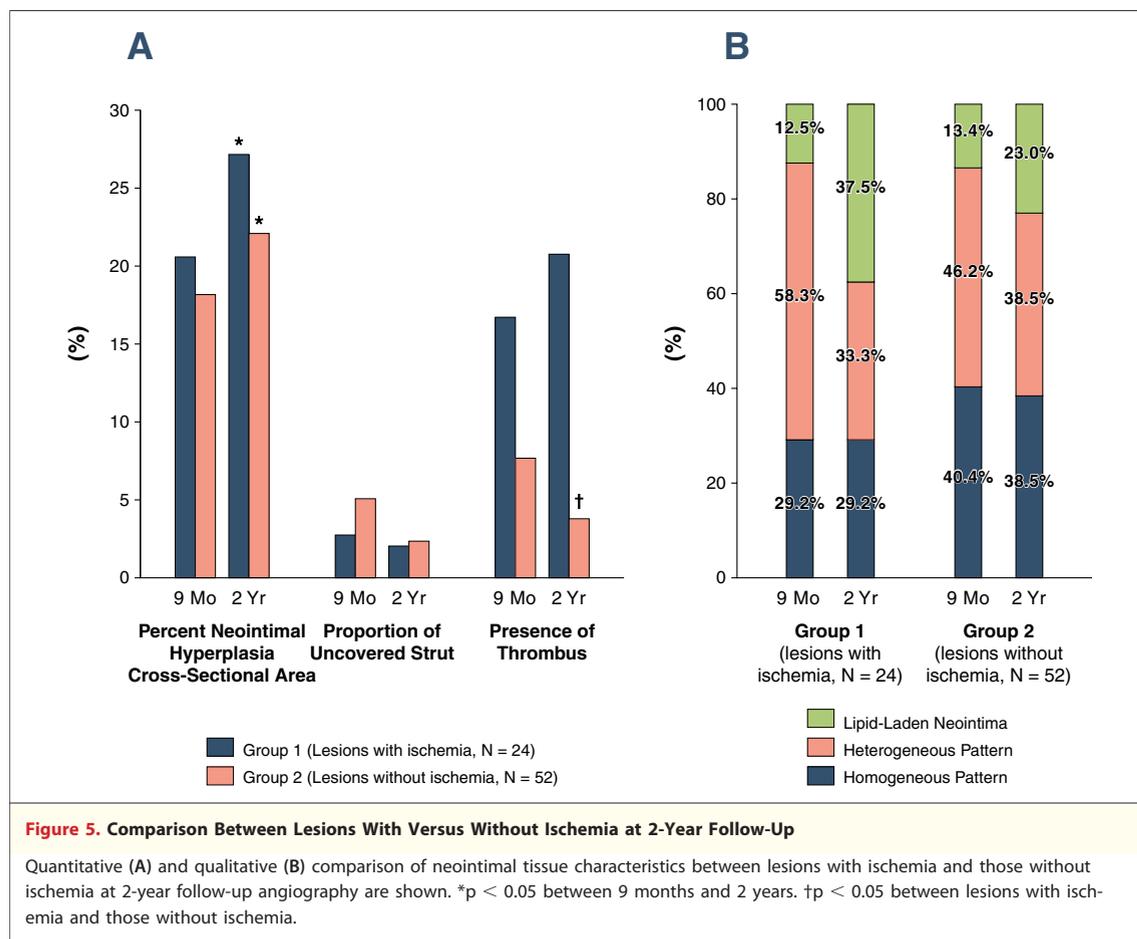
Figure 4. Relationship Between Quantitative Parameters and Serial Change of Neointimal Tissue Morphology

The change of neointimal morphology from homogeneous to heterogeneous or lipid-laden pattern was observed in 30.3% of 76 lesions. There was a significant increase in percent neointimal hyperplasia cross-sectional area in those lesions. * $p < 0.05$ between 9 months and 2 years.

lial coverage after stent implantation could play a protective role against late stent thrombosis and might be an important parameter in determining the optimal duration of dual antiplatelet therapy (5,18). However, detection of thin-layer neointimal tissue in vivo has been a challenging problem. Recently, high-resolution intravascular OCT was introduced in clinical practice and can evaluate the vascular healing pattern including stent strut coverage and proper apposition. Previous OCT studies reported that the percentage of uncovered struts was 15% at 3 months (19), 8.9% to 13.3% at 6 months (20–22), and 12.2% at 9 to 12 months after SES implantation (23). These figures were 2.7% to 7.1% at 6 months (21,22) and 4.9% at 9 to 12 months after PES implantation (24); and 0.01% at 3 months (10), 0.02% at 6 months (21), and 0.01% at 9 to 12 months after ZES implantation (23). As the time interval from stent implantation to follow-up OCT was longer, there was a trend toward decreased rate of uncovered struts in general. However, because the previous OCT studies were not performed serially, the findings of decreased tendency in the rate of uncovered struts with time could not be adequately validated. In addition, until now, serial or long-term (≥ 2 years) follow-up OCT studies after DES implantation were very rare and the number of study patients in those studies was

smaller (16,25). One serial OCT study with 21 SES-treated lesions reported that the percentage of uncovered struts decreased from 3.2% at 2-year follow-up to 0.9% at 4 years (16). Another 2-year follow-up OCT study showed that the percentage of uncovered struts was 6.5% in 20 SES-treated lesions and 3.7% in 12 PES-treated lesions (25). In this serial OCT study with 76 DES-treated lesions, improvement of neointimal coverage was directly observed: mean neointimal thickness, 164 μm to 214 μm ($p < 0.001$); percentage of uncovered stent struts, 4.4% to 2.3% ($p < 0.001$).

Despite augmentation of endothelial coverage in this study, there was no significant change in the incidence of malapposition and intracoronary thrombi between 9 months and 2 years after DES implantation. These results were similar to those in the previous serial OCT study with SES (16). The previous study reported a significant increase in the percentage of malapposed struts from 2.2% at 2 years to 3.0% at 4 years ($p = 0.044$) without significant change in the incidence of intracoronary thrombi (24% vs. 29%, respectively; $p = 1.0$) (16). These findings suggest that DES may be still biologically active and vascular responses of DES-treated lesions may not have completely stabilized up to 2 years after stent implantation. The discrepancy between improvement of neointimal cover-



age and lack of decrease (or increase) in the incidence of malapposed struts or intracoronary thrombi might be partly explained by pathological findings in previous autopsy studies: fibrin accumulation persists around the struts lacking endothelium and the mean percent endothelialization of DES is no more than 60%, regardless of implant duration (5,16,26). Therefore, there is the possibility that OCT might overestimate the extent of neointimal coverage over the stent strut because OCT cannot differentiate fibrin around struts from healthy neointima.

Although incomplete endothelialization and strut coverage after DES implantation could be a critical cause of late stent thrombosis, a recent autopsy study suggested that neoatherosclerosis might be another possible cause (6). A previous OCT study with bare-metal stent-treated lesions showed that the incidence of lipid-laden neointima and neovascularization within neointimal tissue was significantly higher during the late phase (≥ 5 years after stent implantation) compared to early phase (≤ 6 months after stent implantation) (8). Neoath-

erosclerosis tends to develop earlier in DES-treated lesions compared with bare-metal stent-treated lesions. Although atherosclerotic changes do not appear until 2 years after bare-metal stent implantation and remain a rare finding at 4 years, atherosclerotic changes, including foamy macrophage infiltration and early necrotic core formation, were observed in >40% of patients 9 months after SES implantation (27). A more recent autopsy study also reported that the incidence of neointimal atherosclerotic change was significantly greater in DES-treated lesions (31%) compared to bare-metal stent-treated lesions (16%) (6). Compared with DES <20 months after implantation, DES ≥ 20 months after implantation had a higher incidence of TCNA (69% vs. 33%, $p = 0.012$) in a recent OCT study (28). The incidence of neoatherosclerosis in this autopsy study is similar to the presence of lipid-laden neointima (27.6%) in the current study at 2 years follow-up OCT examination. A discrepancy in the incidence of neoatherosclerosis between OCT and histology examination might result from different follow-up duration following stent im-

plantation, the various characteristics of study population and the type of DES (6). However, there have been little data to evaluate the serial changes in neointimal characteristics in DES-treated lesions. This is the first OCT study to perform serial evaluation of qualitative characteristics of the neointima. Lipid-laden neointima, TCNA, and neovascularization were increased, which is suggestive of progression of neoatherosclerosis within neointimal tissue between 9 months and 2 years after DES implantation.

Study limitations. The study population was relatively small and there may be some selection bias. Because this study was composed of small numbers of different types of DES, comparisons among different DES were not possible. OCT evaluation immediately after stent implantation was also not available in this study. The current OCT technology might have some limitations in separating fibrin from healthy neointima and detecting the foamy

macrophage. Additionally, there has been no validation study of neointimal histological tissues in the human stented coronary arteries (29). Finally, the clinical relevance of OCT-based neointimal coverage and morphology could not be investigated in the current study.

CONCLUSIONS

This serial OCT study showed improvement of neointimal coverage and progression of neoatherosclerosis between 9 months and 2 years after DES implantation.

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