Favorable Vessel Healing After Nobori Biolimus A9-Eluting Stent Implantation

– 6- and 12-Month Follow-up by Optical Coherence Tomography –

Akihide Konishi, MD; Toshiro Shinke, MD; Hiromasa Otake, MD; Tomofumi Takaya, MD; Masayuki Nakagawa, MD; Takumi Inoue, MD; Hirotooshi Hariki, MD; Tsuyoshi Osue, MD; Yu Taniguchi, MD; Masamichi Iwasaki, MD; Ryo Nishio, MD; Noritoshi Hiranuma, MD; Hiroto Kinutani, MD; Masaru Kuroda, MD; Hachidai Takahashi, MD; Daisuke Terashita, MD; Junya Shite, MD; Ken-ichi Hirata, MD

Background: Nobori is a novel biolimus A9-eluting stent (BES) coated with a biodegradable polymer only on the abluminal side, which degrades over 6–9 months post-stent deployment. The course of vessel reaction after deployment at these time points remains unclear.

Methods and Results: We serially evaluated 28 BES implanted in de novo coronary lesions of 23 patients using optical coherence tomography (OCT) at 6 and 12 months post-stenting. Standard OCT variables, the percentage of stent with peri-strut low-intensity area (PLIA, a region around stent struts homogeneously showing lesser intensity than the surrounding tissue, suggesting fibrin deposition or impaired neointima maturation) and that with in-stent thrombi were evaluated. There was a significant, but small increase in neointimal thickness (72 ± 23 to $82 \pm 25 \mu\text{m}$, $P=0.006$) from the 6- to the 12-month follow-up, without a significant decrease in minimum lumen area ($P=0.30$). The incidences of uncovered and malapposed struts were low at 6 months and reduced further at 12 months ($3.96 \pm 3.97\%$ to $1.51 \pm 1.63\%$, $P=0.001$, and $0.50 \pm 1.84\%$ to $0.06 \pm 0.24\%$, $P=0.20$, respectively). The frequency of stent with PLIA decreased during the follow-up (57% to 32%, $P=0.05$) and that with in-stent thrombi also numerically decreased (7% to 0%, $P=0.24$).

Conclusions: Neointimal hyperplasia was persistently suppressed following BES implantation up to 12 months. Simultaneously, favorable vessel healing was achieved at 6 months without a delaying adverse reaction for up to 12 months. (*Circ J* 2014; **78**: 1882–1890)

Key Words: Biolimus A9-eluting stent; Mid-term vessel healing; Optical coherence tomography

The durable polymers used in first-generation drug-eluting stents (DES) are associated with a persistent inflammatory reaction, delayed healing, and incomplete endothelialization that may increase the risk of late stent thrombosis as compared with bare metal stents, which have fewer complications.^{1–4} In contrast to the first-generation DES, the Nobori is a novel biolimus A9-eluting stent (BES) coated only on the abluminal side with a biodegradable polymer that is degraded over 6–9 months after stent implantation.^{5,6} There emerged a concern about adverse vessel reactions to polymer degradation that may evoke inflammatory reactions.

Optical coherence tomography (OCT) provides high-resolution cross-sectional images to evaluate vessel healing in response to stent placement.⁷ Using OCT, a recent study reported the association between late stent thrombosis and the percentage of uncovered struts measured by OCT.⁸ This suggests that findings such as uncovered struts assessed by mid-term OCT could be a potential surrogate for the risk assessment of future stent thrombosis.

Although guidelines recommend at least 12 months of dual antiplatelet therapy (DAPT) after DES implantation, several studies suggest that 6-month DAPT is safe and does not compromise the efficacy of the stent.^{9,10} However, there is a limited notion of vessel healing at this time point and the 6-month OCT

Editorial p 1826

Received December 3, 2013; revised manuscript received April 24, 2014; accepted May 1, 2014; released online June 9, 2014 Time for primary review: 20 days

Division of Cardiovascular and Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

Mailing address: Toshiro Shinke, MD, Department of Cardiology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. E-mail: shinke@med.kobe-u.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-13-1474

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

parameters after BES implantation have yet to be investigated in Japanese patients.

In this study, the primary endpoint was to evaluate the percentage of uncovered struts at 6-month OCT after BES implantation. Also, because of the theoretical concern of adverse vessel reaction induced by polymer degradation, we examined vessel reaction after polymer degradation on 12-month OCT analysis in patients who agreed to serial 6- and 12-month OCT evaluation. Therefore, the present study aimed to clarify the time course of arterial healing after BES implantation using matched, serial OCT at 6 and 12 months in patients with coronary artery disease.

Methods

Study Population

In this prospective observational cohort study, a total of 32 patients treated with BES (Terumo Corporation, Tokyo, Japan) were consecutively enrolled from April 2011 to March 2012. Patients aged over 18 years and eligible for percutaneous coronary intervention (PCI) were included. The index PCI procedure was performed with intravascular ultrasound guidance using a mechanical ultrasound transducer (Boston Scientific Corporation, Natick, MA, USA) or a dynamic-aperture ultrasound transducer (Volcano Corporation, Rancho Cordova, CA, USA). All patients were recommended to take DAPT comprising aspirin 100 mg/day and clopidogrel 75 mg/day for at least 12 months after BES implantation. The exclusion criteria were serious hepatic or renal dysfunction, target lesion in a saphenous vein graft and in-stent restenosis, target lesion revascularization during follow-up, unavailable for repeat coronary angiogram because of renal dysfunction, and discontinuation of DAPT at 6 months. Eventually, 37 BES-treated lesions in

32 patients were enrolled in the study (Figure 1), which was approved by the Ethics Committee of Kobe University, and all enrolled patients gave written informed consent.

Quantitative Coronary Angiography Analysis

Coronary angiograms obtained at baseline and at 6- and 12-month follow-ups were analyzed using a computer-based system using edge-detection techniques (QCA-CMS5.1, Medis Imaging Systems, Leiden, The Netherlands) by investigators masked to the clinical presentation, lesion characteristics, and stent assignment. The quantitative angiographic parameters included: (1) minimal lumen diameter (MLD), (2) reference vessel diameter, (3) percent diameter stenosis, (4) late loss, and (5) delayed late loss. Late loss was defined as the difference between the MLD after the procedure and that at the 6-month follow-up. Delayed late loss was defined as the difference between the MLDs at the 6- and 12-month follow-ups.

OCT Examination

OCT examination was serially performed 6 and 12 months after stenting. Frequency-domain OCT was used as previously reported.¹¹ Briefly, a 0.014-inch standard guide wire was positioned distally in the target vessel, and the frequency-domain OCT catheter (C7 Dragonfly™, St. Jude Medical, St. Paul, MN, USA) was advanced to the distal end of the target lesion. The entire length of the region of interest was scanned using the integrated automated pullback device at 20 mm/s. For image acquisition, blood in the coronary artery was replaced with iodine contrast media continuously flushed using a power injector, in order to create a virtually blood-free environment. The volume and infusion flow rate were decided by the operator and ranged from 8–20 cm³ at 3–7 cm³/s and 400 pounds per square inch.

**A) Peri-strut
low-intensity area**

B) Extra-stent lumen

C) In-stent thrombi

Figure 2. Representative optical coherence tomography images. (A) Peri-strut low-intensity area, (B) extra-stent lumen and (C) in-stent thrombi.

OCT Analysis

Off-line OCT analysis was performed using the dedicated software (LightLab Imaging Inc, Westford, MA, USA). All images were analyzed by independent observers masked to the clinical presentation, lesion characteristics, and stent assignment. For quantitative analysis, cross-sectional OCT images were analyzed at 1-mm intervals. For the image matching, we used the distance from the stent edge and landmarks such as side branches to match the location of the cross-sections in the 6- and 12-month examinations. Struts were classified as uncovered if any part of the strut was visibly exposed to the lumen, or as covered if a layer of tissue was visible over all the reflecting surfaces. Neointimal thickness was measured from the center reflection of the stent strut to the vessel-lumen border (neointimal surface or strut surface if uncovered) for each stent strut. An uncovered strut was defined as a strut with a neointimal thickness equal to $0\mu\text{m}$. The frequency of covered and uncovered struts was calculated as the number of those struts divided by the total number of struts for each stent. To assess for asymmetric stent expansion, a stent eccentricity index was determined by the minimum stent diameter divided by the maximum stent diameter in each cross-section.¹² For assessing the unevenness of neointimal thickness, a neointimal unevenness score (NUS) was calculated for each cross-section as the maximum neointimal thickness in 1 cross-section divided by the average neointimal thickness of the same cross-section.¹³ A malapposed strut was defined as a distance $\geq 140\mu\text{m}$ between the center reflection of the strut to the vessel wall. This criterion was determined by adding the actual strut thickness ($125\mu\text{m}$), Parylene C (which is not an absorbable polymer) thickness ($10\mu\text{m}$) and absorbable polymer thickness ($15\mu\text{m}$ at 0 day, $3\mu\text{m}$ at 6 months (data on file of Terumo corporation), $0\mu\text{m}$ at 12 months) to the OCT resolution limit (6 months: $125+10+3\mu\text{m}=138\mu\text{m}$, 12 months: $125+10+0\mu\text{m}=135\mu\text{m}$).¹⁴ The frequencies of stents with a peri-strut low-intensity area (PLIA) or with an extra-stent lumen (ESL) were calculated. The incidence of stents with PLIA was calculated on a percent basis of any strut with PLIA. PLIA was defined as the region around stent struts that homogeneously had lower intensity than the surrounding tissue on OCT images and did not have significant signal attenuation behind the area, suggestive of fibrin deposition or impaired neointima maturation.¹⁵ If a

cross-section had a lumen outside the stent, the lumen was defined as ESL. Both the lumen of malapposed struts and the excavated lumen without malapposed struts were included as ESL.¹⁶ Stent and lumen area were measured manually, and neointimal area was calculated as stent area plus ESL area minus lumen area.

The frequency of stents with atherogenic neointima (AN) or with in-stent thrombi was calculated. AN was defined as neointima containing a diffuse border and poor-signal region with invisible struts underneath because of marked signal attenuation. Layered morphology such as high abluminal and low adluminal layers with visible strut was not defined as AN.^{17,18} In-stent thrombi were defined as a mass protruding beyond the stent strut into the lumen with significant attenuation behind the mass.¹³ The presence of stent with PLIA, ESL, AN, and in-stent thrombi required the agreement of 2 independent experienced observers. Representative images of cases of PLIA, ESL, and in-stent thrombi are shown in **Figure 2**.

Clinical Events

Clinical outcome data (>12 months) were obtained from outpatient record reviews or telephone interviews of 30 patients. Cardiac death, myocardial infarction (MI: defined according to the World Health Organization definition using creatine kinase and creatine kinase-MB increases),¹⁹ target lesion revascularization [(TLR) and target vessel revascularization (TVR) both defined as the need for a repeat PCI], stent thrombosis according to ARC definition,²⁰ and the composite endpoint of major adverse cardiac events (cardiac death, MI, stent thrombosis, TLR) were evaluated. Although OCT images were not always available because of quality in patients with adverse cardiac events, they were evaluated for the entire study population (**Figure 1**).

Statistical Analysis

Statistical analysis was conducted using a commercially available SPSS software version 16.0 (SPSS Inc, Chicago, IL, USA). Qualitative data are presented with frequencies, and quantitative data are shown as mean $\pm$ SD. For continuous variables, comparisons between 2 groups were performed using a 2-tailed, paired t-test, or Wilcoxon test. Discrete variables are presented as percentages, and comparisons were performed using the

Table 1. Baseline Patient and Lesion Characteristics in a Study of Nobori Biolimus A9-Eluting Stent Implantation

Variable	Entire population (n=30)	OCT cohort (n=23)	P value
Age (years)	70.5±9.0	68.0±8.1	0.29
Male (%)	81.2	82.6	0.89
BMI (kg/m²)	24.3±3.9	24.8±4.0	0.60
Risk factors (%)			
Diabetes mellitus	59.3	65.2	0.66
Hypertension	84.3	78.2	0.56
Dyslipidemia	68.7	65.2	0.78
Current smoker	31.2	30.4	0.65
Prior MI	15.6	17.3	0.86
Prior PCI	40.6	43.4	0.83
Prior CABG	0.0	0.0	
Ejection fraction (%)	56.4±9.9	58.8±9.5	0.38
Angina status (%)			
Stable	84.3	91.3	0.62
Unstable	9.3	4.3	
Acute MI	6.2	4.3	
Lesion characteristics			
Vessel treated (LAD/LCX/RCA) (%)	46/16/38	50/11/39	0.41
ACC-AHA class (A-B1/B2-C) (%)	30/70	36/64	0.61
De novo/in-stent restenosis (%)	100/0	100/0	
Total no. of stents (n)	41	30	
Average stent length (mm)	22.6	21.7	0.66
Average stent diameter (mm)	3.09	3.12	0.79
Antiplatelet therapy at 6-month follow-up (%)			
Aspirin		100	
Clopidogrel		100	
Antiplatelet therapy at 12-month follow-up (%)			
Aspirin		100	
Clopidogrel		78.2	

Values are mean ± SD or percent.

ACC-AHA, American College of Cardiology-American Heart Association; BMI, body mass index; CABG, coronary artery bypass graft; LAD, left anterior descending; LCX, left circumflex; MI, myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; RCA, right coronary artery.

Table 2. Quantitative Angiographic Analysis in a Study of Nobori Biolimus A9-Eluting Stent Implantation at 6- and 12-Month Follow-up

Variable	Pre-intervention	Post-intervention	6 months	12 months	P value
Reference vessel diameter (mm)	2.41±0.51	3.00±0.43	3.01±0.53	3.04±0.45	0.57
Minimal luminal diameter (mm)	0.76±0.37	2.75±0.38	2.62±0.52	2.59±0.46	0.60
Percent diameter stenosis (%)	68.2±14.3	10.4±4.83	12.9±6.84	14.5±7.27	0.18
Late loss (mm)			0.08±0.36		
Delayed late loss (mm)				0.02±0.31	

Values are mean ± SD. Abbreviation as in Table 1.

chi-square analysis or Fisher's exact test. A probability value (P) less than 0.05 was considered significant.

Results

Baseline Patient and Lesion Characteristics

There were 2 patients lost to follow-up, and 7 patients were excluded for various reasons (Figure 1), so a total number of 23 patients with 28 lesions prospectively underwent serial OCT at 6 and 12 months.

Baseline patient and lesion characteristics were well matched

between the OCT cohort and the entire study population (Table 1). In the OCT cohort, the mean duration from BES implantation to the 6- and the 12-month follow-ups were 6.5±0.5 months and 12.4±0.4 months, respectively. The 26 BES were implanted in patients with stable angina (91%), acute coronary syndrome (1 patient, 4.3%), and acute MI (1 patient, 4.3%). The 23 patients (100%) continued DAPT with aspirin 100mg/day and clopidogrel 75 mg/day up to the 6-month follow-up, and 18 (78.2%) continued it to the 12-month follow-up; 5 patients ceased DAPT at 6 months by clinic physicians' discretion with the patients' consent.

Table 3. Optical Coherence Tomographic Analysis of Patients With Nobori Stent Between 6 and 12 Months After Implantation

Variable	6 months	12 months	P value
No. of struts per stent (n)	210±70	206±68	0.44
Mean neointimal thickness (μm)	72±23	82±25	0.006
Frequency of uncovered struts (%)	3.96±3.97	1.51±1.63	0.001
Frequency of malapposed struts (%)	0.50±1.84	0.06±0.24	0.20
Mean lumen area (mm ²)	6.67±2.04	6.47±2.04	0.12
Mean minimal lumen area (mm ²)	5.11±2.24	4.95±2.06	0.30
Mean stent area (mm ²)	6.84±1.95	6.88±2.02	0.55
Mean neointimal area (mm ²)	0.42±0.29	0.48±0.28	0.06
Neointimal unevenness score	1.99±0.21	1.89±0.21	0.01
Frequency of stent with PLIA (n, %)	16 (57)	9 (32)	0.05
Frequency of stent with 100% covered struts (n, %)	3 (10)	8 (28)	0.09
Frequency of stent with ESL (n, %)	15 (53)	13 (46)	0.37
Frequency of stent with in-stent thrombi (n, %)	2 (7)	0 (0)	0.24
Frequency of stent with AN (n, %)	0 (0)	0 (0)	

Data are presented as mean±SD or percentage of patients.

AN, atherogenic neointima; ESL, extra-stent lumen; PLIA, peri-strut low-intensity area.

Angiographic Analysis

Angiographic results of the OCT cohort at the pre-intervention, post-intervention, 6- and 12-month follow-ups are shown in [Table 2](#). In-stent MLD showed no significant change from 2.62±0.52 mm at the 6-month follow-up to 2.59±0.46 mm at the 12-month follow-up (P=0.60). In-stent late loss was 0.08±0.36 mm, and in-stent delayed late loss was 0.02±0.31 mm.

OCT Analysis

A total of 600 matched cross-sections were analyzed ([Table 3](#)). The average neointimal thickness was 72±23 μm at the 6-month follow-up and 82±25 μm at the 12-month follow-up. There was a significant, but small increase in neointimal thickness (P=0.006) from the 6- to the 12-month follow-up. The average lumen area (6.67±2.04 mm² to 6.47±2.04 mm², P=0.12) and the average minimum lumen area (5.11±2.24 mm² to 4.95±2.06 mm², P=0.30) did not significantly change from the 6-month to the 12-month follow-up. Average NUS significantly changed from the 6- to the 12-month follow-up (1.99±0.21 to 1.89±0.21, P=0.01) ([Table 3](#)).

The incidences of uncovered and malapposed struts were low at the 6-month follow-up, and further reduced at the 12-month follow-up (3.96±3.97% to 1.51±1.63%, P=0.001 and 0.50±1.84% to 0.06±0.24%, P=0.20, respectively). Contrarily, although the incidence of stents with completely covered struts was only 10% at the 6-month follow-up, it had increased to 28% at the 12-month follow-up (P=0.09).

The percentage of stents with PLIA and that with in-stent thrombi decreased from the 6- to the 12-month follow-up ([Table 3](#)). Only 2 stents had attached thrombi at the 6-month follow-up, and these were completely resolved by the 12-month follow-up. The frequency of stents with ESL decreased from the 6- to the 12-month follow-up (53% to 46%, P=0.37). AN was not observed in either phase. Representative OCT images of the 6- and the 12-month follow-ups are shown in [Figure 3](#).

In this study, 5 patients did not take clopidogrel after the 6-month OCT examination, so we analyzed the 12-month OCT findings between the 6- and 12-month DAPT. There was no significant difference in strut coverage at 12-month OCT between the 6- and 12-month DAPT (mean neointimal thickness: 6-month DAPT 80±23 μm vs. 12-month DAPT 82±26 μm,

P=0.86) (frequency of uncovered struts: 6-month DAPT 1.22±1.37% vs. 12-month DAPT 1.57±1.70%, P=0.67) (frequency of malapposed struts: 6-month DAPT 0.00±0.00% vs. 12-month DAPT 0.08±0.23%, P=0.51) (frequency of stent with 100% covered struts: 6-month DAPT 40% vs. 12-month DAPT 26%, P=0.55) ([Table 4](#)).

Clinical Events

Clinical outcome data for >12 months were available for 30 patients ([Table 5](#)); 2 patients required TLR and TVR (6.7%) 6.3±0.3 months after BES deployment. There were no cardiac-related deaths, MI, or stent thrombosis after BES implantation. Thus, the incidence of major adverse cardiac events was 6.7% during the 12-month follow-up.

Discussion

We evaluated the time course of arterial healing after BES implantation using matched, serial OCT at 6 and 12 months in patients with coronary artery disease. The major findings of the present study are as follows. (1) The OCT findings at 6 months revealed that BES had a low percentage of uncovered and malapposed struts, and from the 6- to the 12-month follow-up there was further strut coverage. (2) There was a small increase in neointimal thickness from 6 to 12 months, and this neointimal growth did not compromise the lumen area within the stent. (3) AN was not detected by OCT imaging.

Qualitative and Quantitative OCT Assessment After BES Implantation

Recent reports have concluded that delayed arterial healing because of uncovered struts, malapposed struts, in-stent thrombi, and PLIA is associated with in-stent restenosis.^{21,22} Furthermore, a greater percentage of uncovered struts is associated with the incidence of stent thrombosis.²³ In a previous study, the 6-month OCT findings after paclitaxel-eluting stent (PES) implantation revealed that the frequency of uncovered struts, malapposed struts, and that of stent with in-stent thrombi was 5.2%, 1.9%, and 47%, respectively.²⁴

In contrast, our study results showed that for BES the frequency of uncovered struts, malapposed struts and that of stent

A) Representative cases of favorable vessel healing

6-month follow-up

12-month follow-up

B) Uncovered-to-covered strut

6-month follow-up

12-month follow-up

C) Disappearance of the extra-stent lumen

6-month follow-up

12-month follow-up

D) Disappearance of the peri-strut low-intensity area

6-month follow-up

12-month follow-up

Figure 3. Temporal changes in representative cases of (A) satisfactory vessel healing, (B) uncovered-to-covered strut, (C) disappearance of extra-stent lumen and (D) disappearance of peri-strut low-intensity area.

Table 4. Optical Coherence Tomographic Analysis of Patients With Nobori Stent at 12 Months Between 6- and 12-Month DAPT

Variable	6-month DAPT (n=5)	12-month DAPT (n=23)	P value
Mean neointimal thickness (μm)	80 $\pm$ 23	82 $\pm$ 26	0.86
Frequency of uncovered struts (%)	1.22 $\pm$ 1.37	1.57 $\pm$ 1.70	0.67
Frequency of malapposed struts (%)	0.00 $\pm$ 0.00	0.08 $\pm$ 0.23	0.51
Mean lumen area (mm^2)	7.53 $\pm$ 2.72	6.10 $\pm$ 1.90	0.16
Mean stent area (mm^2)	7.92 $\pm$ 2.73	6.65 $\pm$ 1.83	0.20
Neointimal unevenness score	1.80 $\pm$ 0.23	1.91 $\pm$ 0.20	0.31
Frequency of stent with 100% covered struts (n, %)	2 (40)	6 (26)	0.55
Frequency of stent with in-stent thrombi (n, %)	0 (0)	0 (0)	

Data are presented as mean $\pm$ SD or percentage of patients. DAPT, dual antiplatelet therapy.

Table 5. Clinical Events in Patients With Nobori Stent

Variable	Entire population (n=30)
Death (n, %)	0 (0)
MI (n, %)	0 (0)
Stent thrombosis (n, %)	0 (0)
TLR (n, %)	2 (6.7)
TVR (n, %)	2 (6.7)
MACE (n, %)	2 (6.7)

Values are percentage of patients.

MACE, major adverse cardiac events; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

with in-stent thrombi was 3.96%, 0.5% and 7.0%, respectively. BES had stabilized in the 6-month OCT findings. Progressive vessel healing was observed in lesions from 6 to 12 months after BES implantation. Therefore, we consider BES is safer than first-generation DES at the 1-year follow-up.

Furthermore, the percentage of stent with PLIA decreased from the 6- to the 12-month follow-up. PLIA is suggestive of fibrin deposition or premature neointima with inflammatory cell infiltration, which is often observed in the healing process. In most cases, fibrin deposition is replaced by smooth muscle cell following disappearance of inflammation around the stent struts. As a result, when OCT-based morphology was serially assessed, PLIA was replaced by highly homogeneous neointima from the 6- to the 12-month imaging. Additionally, in other DES neointimal hyperplasia is observed during this healing process; whereas, despite the decrease of PLIA, BES showed minimal neointimal growth from 6 to 12 months, suggesting benign polymer degradation and slow-release kinetics of biolimus A9.

Possibility for Shortening the Duration of DAPT

An emerging challenge in DES treatment is the shortened DAPT duration. Second-generation DES such as everolimus-eluting stent (EES) have a more favorable healing profile,²⁵ which has been associated with a lower incidence of late stent thrombosis compared with first-generation DES.²⁶ Recently, Puricel et al reported that at 2 years the frequency of stent thrombosis after BES implantation is equal to that after EES implantation.²⁷ According to the Japanese Circulation Society guidelines, DAPT should be taken for at least 1 year.²⁸ However, recent data have revealed that the incidence of stent thrombosis at 24 months was not different between 6-month and 24-month DAPT groups after second-generation DES implantation.^{10,29}

Using OCT, a recent study reported an association between the percentage of uncovered struts measured by mid-term OCT and subsequent occurrence of late and very late stent thrombosis.⁸ Given the association between late stent thrombosis and the percentage of uncovered struts measured by OCT, it is rational to measure these parameters when physicians are considering cessation of DAPT. The few reports of 6-month OCT examination with EES have revealed that the frequency of uncovered struts and malapposed struts is 2.3% and 2.1%, respectively,²⁴ which is as good as that with BES in the present study. The frequency of stents with in-stent thrombi with EES was 19%,²⁴ which is higher than that with BES. However, from the clinical evidence as of now, the duration of DAPT should not be decided only from imaging results. Further study is warranted to prospectively assess the effect of the OCT findings on clinical outcome after cessation of DAPT.

In the present study, 5 patients with BES did not take clopidogrel after the 6-month OCT examination. We compared the 12-month OCT findings between 6- and 12-months of DAPT. There was no significant difference in strut coverage at 12-month OCT between the 6- and 12-month DAPT groups. Further randomized clinical trials comparing vessel healing between 6-month and prolonged DAPT are warranted.

Vascular Reactions and Vessel Healing After BES Implantation

BES are coated on the abluminal side only with a biodegradable polymer that degrades over the 6–9 months after stent deployment. Although biodegradability, in part, may reduce the long-term adverse reactions of durable polymers, there is a theoretical risk of polymer degradation-induced adverse vessel reaction. In fact, Willen et al reported that in a porcine model an array of biodegradable polymers can induce marked inflammatory reactions within coronary arteries and subsequent neointimal thickening.³⁰ However, serial in-vivo assessment of vascular responses during polymer degradation period has not been performed. In the present study, the average neointimal thickness was 72 μm at 6 months. Additionally, there was a small increase in neointimal thickness from the 6- to the 12-month follow-up.

The kinetics of drug release may affect the mid-term strut coverage. A recent study revealed that in a 9-month OCT analysis of BES and SES, the average tissue thickness was 67 μm in vessels implanted with BES and 57 μm in those implanted with SES ($P=0.19$).³¹ Therefore, mid-term neointimal suppression after BES implantation was as good as that after SES implantation. The elution period for BES is 6–9 months, which is longer than for EES or SES.³² In a recent study, the neointimal thickness was 80 μm in EES at 6 months²⁴ which is as good

as that in BES. However, in another study, the average neointimal thickness with EES at 12 months was $97\mu\text{m}$,³³ which is thicker than that with BES. Moreover, another study revealed that the mean thickness of coverage was $142\mu\text{m}$ at 13 months after EES implantation.³² Furthermore, we reported that the average neointimal thickness with EES was $72\mu\text{m}$ at 6 months and $126\mu\text{m}$ at 12 months.³⁴ Neointimal growth from 6 to 12 months after implantation with EES was greater than that with BES. The slow-release kinetics of biolimus A9 after BES implantation minimized neointimal growth from the 6- to the 12-month follow-up. We speculate that the antiinflammatory and highly lipophilic properties of biolimus A9 may inhibit polymer degradation-induced inflammatory reactions.

We should also consider adverse vessel reactions at the long-term follow-up after complete drug release and polymer degradation. Robert reported that the 2-year repeat angiographic data indicated that neointimal suppression with polymer-free DES is greater than that with permanent-polymer DES.³⁵ Persistent inflammatory effect and failure of stent endothelialization with permanent-polymer DES generates a nidus for platelet activation and fibrin deposition that, in turn, initiates the chemokine cascade leading to neointimal hyperplasia. Therefore, we speculate that neointimal suppression may be greater in a lesion treated with BES than in one treated with permanent-polymer DES such as SES, even at long-term follow-up.

Atherosclerotic Changes in the Neointima After BES Implantation

Neoatherosclerosis is frequently observed after implantation of first-generation DES and has been reported to occur earlier with first-generation stents (1.5 ± 0.4 years) than with bare metal stents (6.1 ± 1.5 years).³⁶ A recent study revealed that the earliest duration of implantation showing neoatherosclerosis with SES and PES was 120 days and 70 days, respectively.³⁷ Instant neoatherosclerosis, which can be assessed using OCT, may be an important mechanism for DES failure.¹⁷ In the present study, AN was not observed at either follow-up.

Hamilos et al reported that, unlike that in SES, endothelium-dependent vasomotion at the adjacent stent segment is preserved after BES implantation.³⁸ Similarly, Pendyala et al revealed a significantly lowered inflammatory response in the stented segments and rapid recovery of endothelial function in persistent segments in the BES group compared with the Cypher group.³⁹ We speculate that a lower inflammatory response and rapid recovery of endothelial function after BES implantation might protect against atherogenic change. Larger and longer follow-up studies are warranted to validate our hypothesis.

Study Limitations

This was a single-center, observational study with a small sample. Additionally, we only examined BES and did not compare its effect with other DES. Moreover, we enrolled only event-free patients, which may lead to selection bias. Furthermore, neoatherosclerosis occurs in lesions much later after DES implantation. This study shows only mid-term follow-up data. Therefore, a larger sample population and a longer follow-up period are warranted.

Conclusions

Neointimal hyperplasia was persistently suppressed up to 12 months following BES implantation. Simultaneously, favorable vessel healing was achieved at 6 months without a delaying adverse reaction for up to 12 months.

Acknowledgments

The authors thank all the patients who agreed to participate in this study.

Disclosures

Conflict of Interest: none declared.

References

- Kotani J, Awata M, Nanto S, Uematsu M, Oshima F, Minamiguchi H, et al. Incomplete neointimal coverage of sirolimus-eluting stents: Angioscopic findings. *J Am Coll Cardiol* 2006; **47**: 2108–2111.
- Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, et al. Pathological correlates of late drug-eluting stent thrombosis: Strut coverage as a marker of endothelialization. *Circulation* 2007; **115**: 2435–2441.
- Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: Data from a large two-institutional cohort study. *Lancet* 2007; **369**: 667–678.
- Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004; **350**: 221–231.
- Chevalier B, Silber S, Park SJ, Garcia E, Schuler G, Suryapranata H, et al. Randomized comparison of the Nobori Biolimus A9-eluting coronary stent with the Taxus Liberté paclitaxel-eluting coronary stent in patients with stenosis in native coronary arteries: The NOBORI I trial – Phase 2. *Circ Cardiovasc Interv* 2009; **2**: 188–195.
- Kadota K, Muramatsu T, Iwabuchi M, Saito S, Hayashi Y, Ikari Y, et al. Randomized comparison of the Nobori biolimus A9-eluting stent with the sirolimus-eluting stent in patients with stenosis in native coronary arteries. *Catheter Cardiovasc Interv* 2012; **80**: 789–796.
- Matsumoto D, Shite J, Shinke T, Otake H, Tanino Y, Ogasawara D, et al. Neointimal coverage of sirolimus-eluting stents at 6-month follow-up: Evaluated by optical coherence tomography. *Eur Heart J* 2007; **28**: 961–967.
- Won H, Shin DH, Kim BK, Mintz GS, Kim JS, Ko YG, et al. Optical coherence tomography derived cut-off value of uncovered stent struts to predict adverse clinical outcomes after drug-eluting stent implantation. *Int J Cardiovasc Imaging* 2013; **29**: 1255–1263.
- Schulz S, Schuster T, Mehilli J, Byrne RA, Ellert J, Massberg S, et al. Stent thrombosis after drug-eluting stent implantation: Incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period. *Eur Heart J* 2009; **30**: 2714–2721.
- Valgimigli M, Borghesi M, Tebaldi M, Vranckx P, Parrinello G, Ferrari R, et al. Should duration of dual antiplatelet therapy depend on the type and/or potency of implanted stent? A pre-specified analysis from the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia study (PRODIGY). *Eur Heart J* 2013; **34**: 909–919.
- Gonzalo N, Tearney GJ, Serruys PW, van Soest G, Okamura T, Garcia-Garcia HM, et al. Second-generation optical coherence tomography in clinical practice: High-speed data acquisition is highly reproducible in patients undergoing percutaneous coronary intervention. *Rev Esp Cardiol* 2010; **63**: 893–903.
- Otake H, Shite J, Shinke T, Miyoshi N, Kozuki A, Kawamori H, et al. Impact of stent platform of paclitaxel-eluting stents: Assessment of neointimal distribution on optical coherence tomography. *Circ J* 2012; **76**: 1880–1888.
- Otake H, Shite J, Ako J, Shinke T, Tanino Y, Ogasawara D, et al. Local determinants of thrombus formation following sirolimus-eluting stent implantation assessed by optical coherence tomography. *JACC Cardiovasc Interv* 2009; **2**: 459–466.
- Otsuka Y, Saito S, Nakamura M, Shuto H, Mitsudo K. Comparison of pharmacokinetics of the limus-eluting stents in Japanese patients. *Catheter Cardiovasc Interv* 2011; **78**: 1078–1085.
- Teramoto T, Ikeno F, Otake H, Lyons JK, van Beusekom HM, Fearon WF, et al. Intriguing peri-strut low-intensity area detected by optical coherence tomography after coronary stent deployment. *Circ J* 2010; **74**: 1257–1259.
- Takano M, Yamamoto M, Mizuno M, Murakami D, Inami T, Kimata N, et al. Late vascular responses from 2 to 4 years after implantation of sirolimus-eluting stents: Serial observations by intracoronary optical coherence tomography. *Circ Cardiovasc Interv* 2010; **3**: 476–483.
- Kang SJ, Mintz GS, Akasaka T, Park DW, Lee JY, Kim WJ, et al. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. *Circulation* 2011; **123**: 2954–2963.
- Takano M, Yamamoto M, Inami S, Murakami D, Ohba T, Seino Y,

- et al. Appearance of lipid-laden intima and neovascularization after implantation of bare-metal stents extended late-phase observation by intracoronary optical coherence tomography. *J Am Coll Cardiol* 2009; **55**: 26–32.
19. Nomenclature and criteria for diagnosis of ischemic heart disease: Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. *Circulation* 1979; **59**: 607–609.
 20. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: A case for standardized definitions. *Circulation* 2007; **115**: 2344–2351.
 21. Habara M, Terashima M, Nasu K, Kaneda H, Yokota D, Ito T, et al. Morphological differences of tissue characteristics between early, late, and very late restenosis lesions after first generation drug-eluting stent implantation: An optical coherence tomography study. *Eur Heart J Cardiovasc Imaging* 2013; **14**: 276–284.
 22. Nishio R, Shinke T, Otake H, Sawada T, Haraguchi Y, Shinohara M, et al. Effect of cytochrome P450 2C19 polymorphism on target lesion outcome after drug-eluting stent implantation in Japanese patients receiving clopidogrel. *Circ J* 2012; **76**: 2348–2355.
 23. Won H, Shin DH, Kim BK, Mintz GS, Kim JS, Ko YG, et al. Optical coherence tomography derived cut-off value of uncovered stent struts to predict adverse clinical outcomes after drug-eluting stent implantation. *Int J Cardiovasc Imaging* 2013; **29**: 1255–1263.
 24. Takano M, Murakami D, Yamamoto M, Kurihara O, Murai K, Inami T, et al. Six-month follow-up evaluation for everolimus-eluting stents by intracoronary optical coherence tomography: Comparison with paclitaxel-eluting stents. *Int J Cardiol* 2013; **166**: 181–186.
 25. Joner M, Nakazawa G, Finn AV, Quee SC, Coleman L, Acampado E, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. *J Am Coll Cardiol* 2008; **52**: 333–342.
 26. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med* 2010; **362**: 1663–1674.
 27. Puricel S, Oberhansli M, Guntern P, Lehmann S, Goy JJ, Arroyo D, et al. Long-term comparison of everolimus-eluting and biolimus-eluting stents. *EuroIntervention* 2013; **9**: 336–344.
 28. Kimura T, Isshiki T, Hayashi Y, Oshima S, Namura M, Nakashima H, et al. Incidence and outcome of surgical procedures after sirolimus-eluting stent implantation: A report from the j-Cypher registry. *Cardiovasc Interv Ther* 2010; **25**: 29–39.
 29. Kedhi E, Stone GW, Kereiakes DJ, Serruys PW, Parise H, Fahy M, et al. Stent thrombosis: Insights on outcomes, predictors and impact of dual antiplatelet therapy interruption from the SPIRIT II, SPIRIT III, SPIRIT IV and COMPARE trials. *EuroIntervention* 2012; **8**: 599–606.
 30. van der Giessen WJ, Lincoff AM, Schwartz RS, van Beusekom HM, Serruys PW, Holmes DR Jr, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation* 1996; **94**: 1690–1697.
 31. Barlis P, Regar E, Serruys PW, Dimopoulos K, van der Giessen WJ, van Geuns RJ, et al. An optical coherence tomography study of a biodegradable vs. durable polymer-coated limus-eluting stent: A LEADERS trial sub-study. *Eur Heart J* 2010; **31**: 165–176.
 32. Gutierrez-Chico JL, van Geuns RJ, Regar E, van der Giessen WJ, Kelback H, Saunamaki K, et al. Tissue coverage of a hydrophilic polymer-coated zotarolimus-eluting stent vs. a fluoropolymer-coated everolimus-eluting stent at 13-month follow-up: An optical coherence tomography substudy from the RESOLUTE All Comers trial. *Eur Heart J* 2011; **32**: 2454–2463.
 33. Kim SJ, Lee H, Cho JM, Park CB, Kim W, Kato K, et al. Comparison of zotarolimus-eluting stent and everolimus-eluting stent for vascular healing response: Serial 3-month and 12-month optical coherence tomography study. *Coron Artery Dis* 2013; **24**: 431–439.
 34. Otake H, Shinke T, Nakagawa M, Hariki H, Inoue T, Taniguchi Y, et al. Temporal course of vessel healing after everolimus-eluting stent implantation. *J Am Coll Cardiol* 2013; **61**(Suppl): E1877, doi:10.1016/S0735-1097(13)61877-X.
 35. Byrne RA, Iijima R, Mehilli J, Pinieck S, Bruskina O, Schomig A, et al. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. *JACC Cardiovasc Interv* 2009; **2**: 291–299.
 36. Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol* 2011; **57**: 1314–1322.
 37. Otsuka F, Vorpahl M, Nakano M, Foerster JR, Newell JB, Sakakura K, et al. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. *Circulation* 2014; **129**: 211–223.
 38. Hamilos MI, Ostojic M, Beleslin B, Sagic D, Mangovski L, Stojkovic S, et al. Differential effects of drug-eluting stents on local endothelium-dependent coronary vasomotion. *J Am Coll Cardiol* 2008; **51**: 2123–2129.
 39. Pendyala LK, Matsumoto D, Shinke T, Iwasaki T, Sugimoto R, Hou D, et al. Nobori stent shows less vascular inflammation and early recovery of endothelial function compared with Cypher stent. *JACC Cardiovasc Interv* 2012; **5**: 436–444.