ISSN 1936-8798/09/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2009.10.006

Evaluation in 3 Months Duration of Neointimal Coverage After Zotarolimus-Eluting Stent Implantation by Optical Coherence Tomography

The ENDEAVOR OCT Trial

Jung-Sun Kim, MD, PhD,* Ik-Kyung Jang, MD, PhD,† Chunyu Fan, MD,*
Tae Hoon Kim, MD,* Jin-Sun Kim, MD,* Sang Min Park, MD,*
Eui-Young Choi, MD, PhD,* Sang Hak Lee, MD, PhD,* Young-Guk Ko, MD,*
Donghoon Choi, MD, PhD,* Myeong-Ki Hong, MD, PhD,* Yangsoo Jang, MD, PhD*

Seoul, Korea; and Boston, Massachusetts

Objectives We performed this study to investigate the vascular response in early period after zotarolimus-eluting stent (ZES) (Endeavor Sprint, Medtronic CardioVascular, Minneapolis, Minnesota) implantation.

Background The ZES has different characteristics, with biocompatible polymer and rapid drug-elution, compared with the first-generation drug-eluting stents (DES).

Methods The ENDEAVOR OCT (Evaluation in 3 Months Duration of Neointimal Coverage after Zotarolimus-Eluting Stent Implantation by Optical Coherence Tomography) trial is a prospective, single-center study evaluating vascular healing patterns with optical coherence tomography (OCT) at 3 months after stent implantation. A total of 31 ZES in 30 patients underwent serial OCT at immediate post-intervention and 3 months. Neointimal growth and malapposition were analyzed at each stent strut of cross-sectional OCT images with 0.5-mm intervals.

Results The incidence of malapposition at post-intervention and 3 months was 6.0% and 0.2%, respectively. However, late acquired malapposition was not detected at 3 months. Of 31 stents, 27 stents (87.1%) were covered completely with neointima, but the remaining 4 stents had 2 (0.8%), 4 (0.9%), 4 (1.2%), and 6 (1.4%) uncovered struts. Overall mean percentage of covered stent struts was 99.9 ± 0.4%. This finding was consistent among groups with acute coronary syndrome and stable angina pectoris (99.9 ± 0.3% vs. 99.9 ± 0.4%, $p = 0.92$). Intracoronary thrombus was documented in 1 stent (3.2%) among 31 stents.

Conclusions Most of the stent struts were covered with neointima, and late acquired malapposition was not found at 3 months after ZES implantation. Therefore, the current study demonstrated that ZES might have a favorable in vivo vascular response at 3 months after stent implantation. (Evaluation of Zotarolimus Eluting Stent at 3 Months Using Optical Coherence Tomography [ENDEAVOR OCT]; NCT00815139) (J Am Coll Cardiol Intv 2009;2:1240–7) © 2009 by the American College of Cardiology Foundation

From the *Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Korea; and the †Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. This study was partly supported by a grant of the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (no. A085012 and A000385), a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (no. A085136), Cardiovascular Research Center, Seoul, Korea.

Manuscript received June 25, 2009; revised manuscript received October 13, 2009, accepted October 15, 2009.

The first-generation drug-eluting stents (DES) remarkably reduced the rate of in-stent restenosis and subsequent target lesion revascularization. However, excessive inhibition of neointimal formation caused delayed vascular healing with incomplete endothelialization, which has been associated with an increased risk of late stent thrombosis (LST) (1,2). Pathology studies also demonstrated that incomplete endothelialization as well as partial neointimal coverage were important risk factors for LST after DES implantation (3,4).

Second-generation DES have been developed to overcome safety concerns and maintain the efficacy similar to first generation DES. Zotarolimus-eluting stents (ZES) have a cobalt chromium-based thin-strut stent with a phosphorylcholine biocompatible polymer and shorter drug-elution time within 2 weeks (5). Recent studies reported that ZES was associated with a higher rate of neointimal coverage at 8 months than sirolimus-eluting stents (SES) on intravascular ultrasound (IVUS) and had as similar pattern of neointimal coverage as that of bare-metal stents (BMS) on angioscopy (6,7). In the randomized clinical trial that compared ZES with SES or paclitaxel-eluting stent, most of the stent struts in ZES were covered by neointima on optical coherence tomography (OCT) at 6 months after implantation (8).

It has been proposed, on the basis of previous findings, that favorable arterial healing with early endothelialization could be achieved in ZES (6). However, there have been no OCT data regarding stent strut coverage and malapposition of ZES in the early period. Therefore, the present study was designed to evaluate the vascular response of neointima formation and malapposition at 3 months after ZES implantation with serial OCT evaluation.

Methods

Study design and patients. The ENDEAVOR OCT (Evaluation in 3 Months Duration of Neointimal Coverage after Zotarolimus-Eluting Stent Implantation by Optical Coherence Tomography) trial was a prospective, single-center study to investigate the vascular healing pattern of the ZES (Endeavor Sprint, Medtronic CardioVascular, Minneapolis, Minnesota) with OCT at 3 months after stent implantation.

The study protocol of the current report was approved by the Institutional Review Board of Yonsei University College of Medicine, and written consent was obtained from all patients before inclusion.

From February 2008 to August 2008, 30 patients (15 acute coronary syndrome [ACS] and 15 stable angina pectoris [SAP]) suitable for an OCT procedure and who consented to the study protocol were enrolled in this study. Patients were eligible for the study if they had: 1) a de novo lesion with ≥50% diameter stenosis related to myocardial ischemia with objective study or ≥70% diameter stenosis; and 2) a native coronary artery with a reference vessel diameter (RVD) between 2.5 and 3.5 mm that could be covered by a single stent. The exclusion criteria were: 1) significant left main disease; 2) bifurcation lesion requiring 2 stents; 3) apparent congestive heart failure or ejection fraction ≤30%; 4) an allergy to antiplatelet agents or contrast dye; 5) known renal failure with baseline creatinine ≥2.0 mg/dl; 6) life expectancy <1 year; 7) lesions unsuitable for OCT (proximal vessel size >3.5 mm or proximal lesions <15 mm from the ostium of each artery); 8) overlapping stent; and 9) treatment with other DES at same or other vessels.

Study procedure. After enrollment, all patients were treated with a ZES, and target lesions were evaluated with IVUS and OCT immediately after and 3 months after stent implantation. Before intervention, all patients with ACS were pretreated with 300 mg or 600 mg loading dose of clopidogrel in case of myocardial infarction (MI) requiring percutaneous coronary intervention (PCI) within 6 h, and patients with SAP received clopidogrel 75 mg for at least 5 days before PCI. After the intervention, all patients received dual antiplatelet therapy (DAT) (aspirin 100 mg and clopidogrel 75 mg daily) for at least 3 months.

Abbreviations and Acronyms

ACS = acute coronary syndrome
DAT = dual antiplatelet therapy
DES = drug-eluting stent(s)
IVUS = intravascular ultrasound
LST = late stent thrombosis
MI = myocardial infarction
NIH = neointimal hyperplasia
OCT = optical coherence tomography
PCI = percutaneous coronary intervention
RVD = reference vessel diameter
SAP = stable angina pectoris
SES = sirolimus-eluting stents(s)
ZES = zotarolimus-eluting stent(s)

Coronary angiography. Quantitative coronary angiography was performed with a computerized edge-detection quantitative coronary angiographic system (CASS system, Pie Medical Instruments, Maastricht, the Netherlands) by a single individual blinded to the patient's information. The minimal lumen diameter and RVD of treated coronary segments on baseline angiogram were determined in the view that demonstrated lesions to be the most severe and not foreshortened. Post-procedure and follow-up angiograms were evaluated in the same projection.

IVUS image protocol and analysis. The IVUS assessments were performed with a commercially available system (Boston Scientific, Natick, Massachusetts) after intracoronary administration of 200 μg of nitroglycerin. Motorized transducer pullback permitted cross-sectional area measurements at 0.5-mm axial increments from 5-mm distal to proximal reference segments including the length of the stent. The IVUS images were independently analyzed with an offline

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 2, NO. 12, 2009
DECEMBER 2009:1240–7

analysis index system (Echoplaque 2, INDEC Systems, Inc., Mountain View, California) by an independent single individual. The reference segment was the most visibly normal cross section (largest lumen with least plaque burden) within 5 mm proximal or distal to the lesion. External elastic membrane cross-sectional area, lumen cross-sectional area at reference segment, and minimal lumen area at stent segment were determined both after intervention and 3 months later.

Neointimal volume (NV) was calculated as stent volume (SV) minus lumen volume (LV), and NV index was the value of NV divided by stent length. The percent neointimal obstruction was calculated as: NV divided by SV × 100. The percent neointimal coverage was defined as the measurement of circumferential stent length covered with neointima divided by stent perimeter at every 0.5-mm cross-sectional image throughout the stented segment (6).

OCT image protocol and analysis. The IVUS was conducted before OCT in all cases to evaluate each lesion for the positioning of balloon occlusion and vessel size. A time domain M2 OCT system (M2 Cardiology Imaging System, LightLab Imaging, Inc., Westford, Massachusetts) combined with a 0.014-inch wire-tip imaging catheter (ImageWire, LightLab Imaging, Inc.) was used in this study. During image acquisition, the occlusion balloon (Helios, Avantec Vascular Corp., Sunnyvale, California) was inflated to 0.4 to 0.6 atm, and Ringer's lactate was infused at 0.5 to 1.0 ml/s. The imaging wire was automatically pulled back from distal to proximal at 1 mm/s. The OCT analysis was independently performed by 2 physicians blinded to the patient's information with the same method as previous reports (9,10). Cross-sectional OCT images were analyzed at 0.5-mm intervals (every 7 or 8 frames). Among 1,368 cross sectional images, 133 images (9.8%) at post-intervention and 27 images (2.0%) at the 3-month follow-up OCT could not be measured due to the poor image quality. Strut malapposition was defined as detachment from the vessel wall ≥110 μm for ZES (11). When there was no definite neointima (<10 μm of neointima thickness due to axial resolution of current OCT technology) over the stent strut, it was defined as an uncovered strut. A completely covered stent was defined as a stent with all analyzable struts covered with neointima. Stent struts at the level of bifurcation were included in this analysis for neointimal coverage but excluded in the analysis for malapposition. Thrombus was defined as an irregular mass protruding into the lumen discontinuing or beyond stent struts with a signal-free shadowing in the OCT image (12).

Clinical follow-up. All patients received DAT (aspirin and clopidogrel) for at least 3 months. Death, nonfatal MI, target vessel revascularization, and stent thrombosis were considered major cardiac adverse events.

Study end points. The primary end point of this trial was to evaluate the neointimal coverage of ZES with OCT at 3 months after stent implantation. Secondary end points were: 1) malapposition rate at immediate post-intervention and 3 months after stent implantation with serial OCT; 2) comparison of the stent strut coverage and malapposition rate with OCT between ACS and SAP; and 3) comparison of stent strut coverage and malapposition rate between OCT and IVUS.

Statistical analysis. Results are expressed as a mean ± SD (median) or number (percent). Comparisons of categorical variables were made with the chi-square test and the Fisher exact test when the expected frequency was <5. Student *t* test or paired *t* test was used to compare continuous variables, and the Mann-Whitney *U* test was applied if the distributions were skewed. For OCT analysis in this study, interobserver and intraobserver variabilities in measured distance and area were assessed by evaluation of 20 random cross-sectional images by 2 independent readers and by the same reader at 2 separate time points, respectively. The variations between measurements were calculated with the linear mixed model (1- and 2-way mixed models). The intraobserver correlation coefficient of neointimal hyperplasia (NIH) thickness or distance and area between the variabilities of the single observer was 0.99 (95% confidence interval [CI]: 0.99 to 1.00) and 0.99 (95% CI: 0.99 to 0.99) with the 1-way mixed model, respectively, where patient effects are random. The inter-observer correlation coefficient of NIH thickness or distance and area between variabilities of 2 observers with the 2-way mixed model, where patient effects are random and observers effects are fixed, was 0.99 (95% CI: 0.99 to 1.00) and 0.99 (95% CI: 0.99 to 1.00), respectively. All analyses were performed with the Statistical Analysis System software (version 9.1.3., SAS Institute, Cary, North Carolina). A p value <0.05 was considered statistically significant.

Results

Patient characteristics. Baseline characteristics in the study population are presented in Table 1. The prevalence of diabetes was 26.7% in all patients, with no difference between patients with ACS and SAP. Among patients with ACS, ST-segment elevation MI was present in 3 (20.0%), non–ST-segment elevation MI was present in 5 (33.3%), and unstable angina was present in 9 (46.7%). Mean stent diameter was 3.0 ± 0.4 (median 3.0) mm in all patients. Maximum balloon inflation pressure was 16.2 ± 1.9 (median 16.0) atm.

Angiographic results. Angiographic findings are summarized in Table 2. Overall mean RVD was 2.8 ± 0.3 (median 2.7) mm and was similar between groups with ACS and SAP. Late loss at the 3-month follow-up was 0.4 ± 0.3 (median 0.4) mm without any difference between 2 groups.

IVUS findings. Table 3 summarizes the IVUS data. Minimal lumen diameter immediately after stenting was 5.4 ± 1.5

Table 1. Baseline Characteristics

	Total	ACS	SAP	p Value
Patients characteristics	(n = 30)	(n = 15)	(n = 15)	
Age, yrs	62.1 ± 9.1 (62.7)	61.3 ± 8.1 (60.4)	63.1 ± 10.2 (67.4)	0.59
Male	18 (60%)	9 (60.0%)	9 (60.0%)	1.00
Hypertension	15 (50.0%)	8 (53.3%)	7 (46.7%)	0.72
Diabetes mellitus	9 (26.7%)	3 (20.0%)	6 (40.0%)	0.43
Hyperlipidemia	18 (60.0%)	9 (60.0%)	9 (60.0%)	1.00
Current smoking	6 (20.0%)	3 (20.0%)	3 (20.0%)	1.00
Previous MI	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00
Chronic total occlusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00
Lesions characteristics	(n = 31)	(n = 16)	(n = 15)	
Target vessel				0.04
LAD	12 (38.7%)	4 (25.0%)	8 (53.3%)	
LCX	8 (25.8%)	3 (18.8%)	5 (33.3%)	
RCA	11 (35.5%)	9 (56.3%)	2 (13.3%)	
Lesion type				0.75
A or B_1	13 (41.9%)	7 (43.8%)	6 (40.0%)	
B_2 or C	18 (58.1%)	9 (56.2%)	9 (60.0%)	
Stent diameter (mm)	3.0 ± 0.4 (3.0)	3.1 ± 0.3 (3.0)	3.0 ± 0.4 (2.8)	0.10
Stent length (mm)	22.0 ± 5.3 (20.0)	22.1 ± 4.9 (22.0)	21.9 ± 5.8 (18.0)	0.77
Maximal pressure (atm)	16.2 ± 1.9 (16.0)	16.3 ± 1.8 (16.0)	16.1 ± 2.1 (16.0)	0.71

Values are presented as mean ± SD (median) or n (%).
ACS = acute coronary syndrome; LAD = left anterior descending artery; LCX = left circumflex artery; MI = myocardial infarction; RCA = right coronary artery; SAP = stable angina pectoris.

(median 5.0) mm^2. On qualitative IVUS analysis, a malapposition was detected in 3 stents (9.7%) at post-intervention and in 2 stents (6.5%) at 3 months. Late acquired malapposition was not detected in ZES at 3 months after stent implantation. Approximately 26% of all stent surfaces were covered with neointima in IVUS analysis without difference according to the clinical presentation (Fig. 1). No thrombus was detected during serial IVUS examination.

OCT findings. All stents were serially evaluated by OCT without any serious complication during the procedure. Mean neointima thickness at 3 months was 154 μm, which resulted in approximately 19% of a neointimal volume obstruction. However, one-third of neointima over stent strut was <100 μm in NIH thickness. General OCT findings are summarized in Table 4. The mean lumen area was 7.5 ± 1.7 (median 6.9) mm^2 at post-intervention and 6.6 ± 1.8 (median 6.2) mm^2 at 3 months. The incidence of malapposed struts was 6.0 ± 6.2% (4.5%) at post-intervention and significantly decreased to 0.2 ± 1.1 (0%) without any late acquired malapposed struts at 3 months ($p < 0.001$). Stent edge dissection was detected in 14 lesions (45.2%) at the post-intervention but completely disappeared

Table 2. QCA Findings

	Total (n = 31)	ACS (n = 16)	SAP (n = 15)	p Value
Pre-PCI				
Mean RVD (mm)	2.8 ± 0.3 (2.7)	2.8 ± 0.3 (2.9)	2.7 ± 0.3 (2.7)	0.21
MLD (mm)	0.8 ± 0.5 (0.9)	0.7 ± 0.5 (0.7)	0.9 ± 0.5 (0.9)	0.23
Post-PCI				
Mean RVD (mm)	2.9 ± 0.3 (3.0)	3.0 ± 0.3 (3.0)	2.8 ± 0.3 (2.9)	0.07
MLD (mm)	2.7 ± 0.4 (2.6)	2.7 ± 0.4 (2.7)	2.6 ± 0.3 (2.5)	0.50
Acute gain (mm)	1.9 ± 0.5 (1.8)	2.0 ± 0.5 (2.0)	1.7 ± 0.6 (1.5)	0.09
Follow-up QCA data at 3 months				
Mean RVD (mm)	2.8 ± 0.4 (2.8)	2.8 ± 0.3 (2.8)	2.7 ± 0.4 (2.7)	0.44
MLD (mm)	2.2 ± 0.4 (2.2)	2.3 ± 0.3 (2.3)	2.1 ± 0.4 (2.1)	0.11
Late loss (mm)	0.4 ± 0.3 (0.4)	0.4 ± 0.3 (0.3)	0.5 ± 0.3 (0.5)	0.29

Values are presented as n (%) or mean ± SD (median).
DS = diameter stenosis; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; RVD = reference vessel diameter; other abbreviations as in Table 1.

Table 3. Intravascular Ultrasound Findings

	Total (n = 31)	ACS (n = 16)	SAP (n = 15)	p Value
Post-PCI				
Reference EEM CSA (mm^2)	11.2 ± 2.7 (11.0)	11.6 ± 3.0 (11.7)	10.6 ± 2.4 (10.4)	0.29
Reference lumen CSA (mm^2)	6.9 ± 1.9 (6.4)	7.3 ± 2.1 (7.1)	6.4 ± 1.4 (6.2)	0.22
MLA at stent segment (mm^2)	5.4 ± 1.5 (5.0)	5.5 ± 1.3 (5.2)	5.3 ± 1.8 (4.9)	0.38
Malapposition at post-PCI	3/31 (9.7%)	1/16 (6.3%)	2/15 (13.3%)	0.60
Follow-up at 3 months				
Reference EEM CSA (mm^2)	11.6 ± 3.3 (11.1)	12.2 ± 3.4 (11.9)	10.9 ± 3.1 (10.1)	0.34
Reference lumen CSA (mm^2)	7.1 ± 2.1 (6.3)	7.4 ± 2.3 (6.4)	6.8 ± 1.8 (6.3)	0.77
MLA at stent segment (mm^2)	5.1 ± 1.5 (4.8)	5.1 ± 1.3 (4.8)	5.0 ± 1.7 (4.9)	0.60
NVI (mm^3/mm)	0.5 ± 0.5 (0.3)	0.5 ± 0.5 (0.2)	0.5 ± 0.5 (0.4)	0.52
NV obstruction (%)	6.8 ± 6.9 (4.4)	6.8 ± 7.9 (3.5)	6.7 ± 5.8 (6.4)	0.63
Persistent malapposition	2/31 (6.5%)	1/16 (6.3%)	1/15 (6.7%)	1.00
Late-acquired malapposition	0/31 (0.0%)	0/16 (0.0%)	0/15 (0.0%)	1.00

Values are presented as mean ± SD (median) or n (%). Index values were defined as each parameter divided by stent length.
CSA = cross-sectional area; EEM = external elastic membrane; MLA = minimal lumen area; NVI = neointimal volume index; other abbreviations as in Tables 1 and 2.

on OCT examination after 3 months. Thrombus was detected in 1 stent (3.2%) at 3 months, although it was visible in 11 stents (35.5%) at post-intervention.

Representative cases of neointimal coverage over well-apposed and malapposed struts and struts at the side branch are shown in Figure 2. Most of the stent struts were covered with neointima (99.9 ± 0.4% [100%]) (Fig. 1), and this finding was comparable between groups with ACS and SAP. Of the 31 stents evaluated, 27 (87.1%) were completely covered with neointima. The remaining 4 partially covered stents had only 2 (0.8%), 4 (0.9%), 4 (1.2%), and 6 (1.4%) uncovered struts.

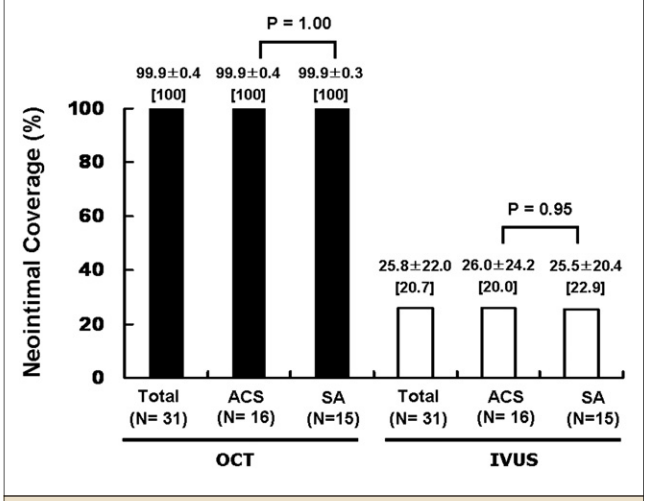

Figure 1. Rate of Neointimal Coverage in Zotarolimus-Eluting Stents at 3-Month Follow-Up

The rate of neointimal coverage was nearly 100% in optical coherence tomography (OCT) but only 25% in intravascular ultrasound (IVUS). The percent neointimal coverage was defined as the measurement of circumferential stent length covered with NIH divided by stent perimeter at every 0.5-mm cross-sectional image throughout the stented segment in IVUS (6). The rate of neointimal coverage is expressed as a mean ± SD (median). ACS = acute coronary syndrome; SA = stable angina.

Clinical outcome. At 3 months, target vessel revascularization occurred in 2 patients, but there were no deaths, nonfatal MI, or stent thrombosis during the 3-month follow-up period.

Discussion

This is the first study to evaluate the in vivo vascular response at 3 months after ZES implantation with serial OCT examination. This study demonstrated that most of stent struts were covered with neointima and were well-apposed in ZES at 3 months.

Evaluation of neointimal coverage with intravascular imaging modalities. Neointimal coverage after stent implantation has been known to prevent LST as found by autopsy study and could be a key parameter to guide the optimal duration of DAT (3). Also, residual thrombi have been reported as another parameter responsible for subacute and late ST (13–15). Therefore, the detection of neointima of stents and thrombi might give important clinical information to be able to estimate the risk of LST. However, identifying thin neointima and thrombus has numerous limitations in the clinical setting. Intravascular ultrasound has been widely used to detect neointima after stent implantation, but its resolution is a critical limitation, because it can only detect neointima thicker than 100 μm (9,16). Angioscopy is a useful tool to evaluate neointima by providing direct visualization; however, it is not able to generate quantitative information (17). Recently, OCT was introduced as a high-resolution image modality with 10 to 20 μm of axial resolution with an infrared light source (18,19). This new intravascular imaging tool is able to clearly detect thin neointima and provide quantitative information about neo-

Table 4. Optical Coherence Tomographic Findings

	Total (n = 31)	ACS (n = 16)	SAP (n = 15)	p Value
Post-PCI				
Lumen area (mm^2)	7.5 ± 1.7 (6.9)	7.6 ± 1.4 (7.3)	7.4 ± 2.0 (6.5)	0.26
Plaque prolapse	29 (93.5%)	16 (100%)	13 (86.7%)	0.86
Malapposition at post-PCI	6.0 ± 6.2 (4.5)	6.9 ± 8.3 (4.1)	5.0 ± 2.6 (4.8)	0.41
Stent edge dissection	14 (45.2%)	7 (43.8%)	7 (46.2%)	0.87
Presence of thrombi	11 (35.5%)	7 (43.8%)	4 (26.7%)	0.32
Follow-up at 3 months				
Lumen area (mm^2)	6.6 ± 1.8 (6.2)	6.6 ± 1.9 (6.1)	6.5 ± 1.7 (6.5)	0.91
Neointimal thickness (μm)	154 ± 77 (137)	157 ± 94 (136)	151 ± 56 (142)	0.82
NIH area (%)	18.6 ± 7.9 (16.0)	19.0 ± 9.5 (16.4)	18.2 ± 6.1 (16.0)	0.78
Persistent malapposition	0.2 ± 1.1 (0)	0.4 ± 1.6 (0)	0.02 ± 0.1 (0)	0.77
Late-acquired malapposition	0	0	0	1.00
Both of malapposed and uncovered strut (%)	0.03 ± 0.1 (0)	0.03 ± 0.1 (0)	0.02 ± 0.09 (0)	1.00
Stent edge dissection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00
Presence of thrombi	1 (3.2%)	1 (6.3%)	0 (0.0%)	1.00

Values are presented as mean ± SD (median) or n (%). Stent malapposition was defined as struts with detachment from the vessel wall ≥110 μm for zotarolimus-eluting stent.
NIH = neointimal hyperplasia; other abbreviations as in Tables 1 and 2.

intima. The data from this study showed a large discrepancy in the rate of neointimal coverage between IVUS and OCT (25.8 ± 22.0% [20.7%] in IVUS vs. 99.9 ± 0.4% [100%] in OCT), although the method of measurement was somewhat different. The distribution of NIH thickness evaluated with OCT might provide an explanation for this finding (proportion of NIH thickness <100 μm: 35.4%).

Findings at immediate post-intervention and 3-month follow-up after ZES implantation. This study demonstrated that IVUS and OCT showed a considerable numbers of stents were malapposed immediately after ZES implantation, which was similar to that previously observed (6). Interestingly, any stent edge dissection was not detected in IVUS, but was shown in 14 cases (45.2%) on OCT. No further procedures were performed in these cases, because they were not associated with flow limitation. Subsequently, there were no stent edge dissections detected at 3-month follow-up OCT.

The first generation of DES yielded significantly lower percent neointimal obstruction than BMS (3% to 5% in SES vs. 8% to 13% in paclitaxel-eluting stent vs. 29% to 35% in BMS) (6,20,21). However, excessive suppression of neointima increased the concern of ST, because of incomplete endothelization during the vascular healing process after stent implantation (22). Attention has recently shifted from late loss or percent neointimal obstruction to endo-

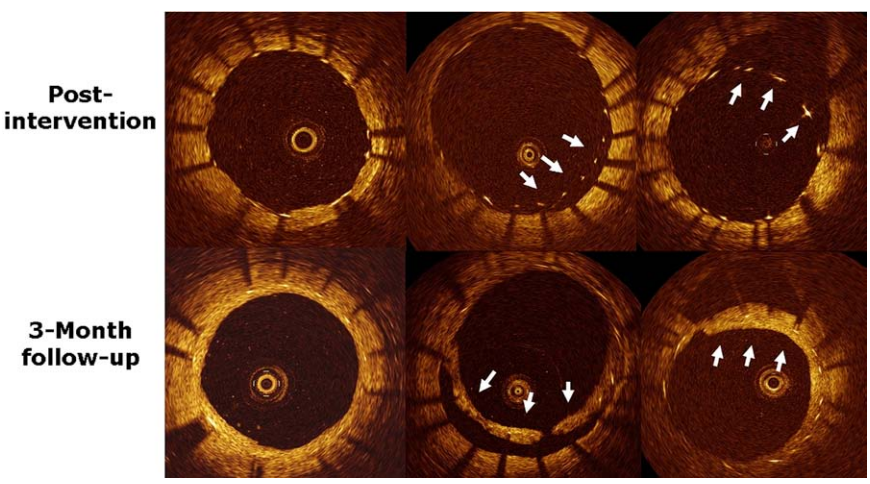

Figure 2. Representative Serial Optical Coherence Tomography Images

Neointima were covered at well-apposed struts **(left)**, malapposed struts **(middle)**, and struts at bifurcation **(right)**.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 2, NO. 12, 2009
DECEMBER 2009:1240–7

thelial coverage over the stent strut. To this point, the presence of a moderate amount of neointimal growth with endothelialization is likely a valid solution to avoid in-stent restenosis and to minimize the risk of ST.

In the current study, several intravascular imaging modalities were used to evaluate neotintimal coverage. As mentioned previously regarding the resolution according to the different methods of intravascular imaging, frequencies of detectable neointima were quite different. In the IVUS examination, Miyazawa et al. (6) reported that more than one-half of the ZES struts were covered with detectable neointima with even distribution, whereas only 10% of SES struts were covered with small but focal accumulation at 8 months. This study showed that with IVUS, 25% of stent struts were covered with neointima at 3 months after ZES implantation. The low rate of neointimal coverage might be related to inherent limitation in IVUS resolution (100 to 150 μm), because the mean NIH thickness was 150 μm at 3 months compared with 250 μm at 9 months in previous OCT study (11). A recent angioscopy study of ZES demonstrated that all stent struts were covered with grade 2 or 3 of endothelization without detectable thrombus at 8 months after stent implantation. Several OCT studies reported a similar finding in ZES. The ODESSA (Optical coherence tomography in Drug Eluting Stent Safety) trial and a previous study we reported (OCT evaluation at 9 months in ZES) have shown that ZES had nearly complete neointimal coverage of stent struts at 6 months and 9 months after stent implantation, respectively (8,10).

The ZES has different properties compared with other DES, which includes rapid drug-elution and a biocompatible polymer. Hence, the vascular response might be different even in the early period after ZES implantation. The follow-up OCT data at 3 months revealed that approximately 15% of stent struts were uncovered with neointima in SES, whereas most of the stent struts were covered with neointima in BMS (17). However, there were no data on ZES in the early period before 6 months. In the current study, most of the stent struts were covered with neointima even at 3 months, irrespective of clinical presentations. Therefore, this study provides new information on the time required for complete neointimal coverage to occur, with 3 months being sufficient for a ZES. The question remains as to whether the neointima coverage of stent struts is preventive for LST, and large randomized trial or registry data might be warranted to determine the optimal duration of DAP in ZES.

Although the relationship between late malapposition as seen by IVUS and LST is not well-known, it could be a concern for future clinical events after DES implantation. Previous studies have shown a late acquired malapposition rate of 3% to 13% with SES and 2% to 8% with paclitaxel-eluting stent (23–25). However, the ENDEAVOR III IVUS study reported only 1 case (0.5%) of late acquired malapposition with the ZES and this study also showed no late acquired malapposition for either IVUS or OCT. On OCT evaluation, the total late malapposition rate, including persistent and late acquired malapposition, was similar to BMS and low-incidence compared with SES at 3-month follow-up when compared with previous studies (1.1% in BMS, and 15.0% in SES vs. 0.2% in ZES in this study) (17). Therefore, this finding suggests that the ZES has favorable vascular responses in term of stent apposition as well as neointimal coverage over stent.

Study limitations. First, because pre-interventional OCT evaluation was not performed in this study, we cannot assess the effect of underlying plaque characteristics on the vascular response after ZES implantation. However, because most of the stent struts were covered with neointima and well-apposed at 3 months irrespective of clinical presentation, we believe that there was little effect of underlying plaque characteristics on vascular healing and stent apposition after ZES implantation. Second, this study was a single-center study with a relatively small population and might have a risk of selection bias. However, over 12,000 stent struts were evaluated for neointimal coverage or malapposition. Also, we analyzed quantitative coronary angiography, IVUS, and OCT independently. Third, quality evaluation of NIH might be important to investigate the risk of future thrombus formation, but the present study did not clarify the quality of NIH because the current OCT technology might have some limitations to separate fibrin or microthrombi from healthy neointima. Fourth, the clinical relevance of neointimal coverage detected by OCT or IVUS remains unknown. Finally, OCT analysis was not performed in an independent core laboratory, although inter-observer and intra-observer variabilities were assessed to prove the consistence and accuracy of measurement.

Conclusions

This is the first study to evaluate the vascular healing response with neointimal coverage and malapposition of ZES at 3 months after stent implantation with serial OCT examination. This study demonstrated that neointimal coverage was nearly complete and no late acquired malapposition was detected at 3 months after ZES implantation. Therefore, this study implies that the ZES has a favorable vascular healing process in the early period after stent implantation.

Acknowledgments

The authors thank Dr. Nam Wook Hur at the Medical Research Support Section of Yonsei University for statistical support; Dr. Kenichi Fujii of Hyogo University; and Dr. Hiram G. Bezerra at University Hospital, Case Medical Center for careful review for our manuscript.

Reprint requests and correspondence: Dr. Yangsoo Jang, Division of Cardiology, Yonsei Cardiovascular Center, Yonsei University College of Medicine, 250 Seongsanno, Seodaemun-gu, 120-752 Seoul, South Korea. E-mail: jangys1212@yuhs.ac.

REFERENCES

1. Babapulle MN, Joseph L, Belisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. Lancet 2004;364:583–91.
2. Jeremias A, Sylvia B, Bridges J, et al. Stent thrombosis after successful sirolimus-eluting stent implantation. Circulation 2004;109:1930–2.
3. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435–41.
4. Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. Circulation 2003; 108:1701–6.
5. Kandzari DE, Leon MB, Popma JJ, et al. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. J Am Coll Cardiol 2006;48:2440–7.
6. Miyazawa A, Ako J, Hongo Y, et al. Comparison of vascular response to zotarolimus-eluting stent versus sirolimus-eluting stent: intravascular ultrasound results from ENDEAVOR III. Am Heart J 2008;155: 108–13.
7. Awata M, Nanto S, Uematsu M, et al. Angioscopic comparison of neointimal coverage between zotarolimus- and sirolimus-eluting stents. J Am Coll Cardiol 2008;52:789–90.
8. Guagliumi G, Musumeci G, Sirbu V, et al. A prospective, randomized, controlled study using optical coherence tomography to evaluate strut coverage of sirolimus-, paclitaxel-, and zotarolimus-eluting coronary stents in long lesions requiring overlapping. Paper presented at: Late Breaking Trials, Transcatheter Cardiovascular Therapeutics Annual Meeting; October 14, 2008; Washington, DC.
9. Takano M, Inami S, Jang IK, et al. Evaluation by optical coherence tomography of neointimal coverage of sirolimus-eluting stent three months after implantation. Am J Cardiol 2007;99:1033–8.
10. Kim JS, Jang IK, Kim JS, et al. Optical coherence tomography evaluation of zotarolimus-eluting stents at 9 month follow up: comparison with sirolimus-eluting stents. Heart 2009;95:1907–12.
11. Tanigawa J, Barlis P, Di Mario C. Intravascular optical coherence tomography: optimisation of image acquisition and quantitative assessment of stent strut apposition. EuroInterv 2007;3:127–36.
12. Kume T, Akasaka T, Kawamoto T, et al. Assessment of coronary arterial thrombus by optical coherence tomography. Am J Cardiol 2006;97:1713–7.
13. Cheneau E, Leborgne L, Mintz GS, et al. Predictors of subacute stent thrombosis: results of a systematic intravascular ultrasound study. Circulation 2003;108:43–7.
14. Sianos G, Papafaklis MI, Daemen J, et al. Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. J Am Coll Cardiol 2007;50:573–83.
15. Wenaweser P, Daemen J, Zwahlen M, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. J Am Coll Cardiol 2008;52:1134–40.
16. Matsumoto D, Shite J, Shinke T, et al. Neointimal coverage of sirolimus-eluting stents at 6-month follow-up: evaluated by optical coherence tomography. Eur Heart J 2007;28:961–7.
17. Xie Y, Takano M, Murakami D, et al. Comparison of neointimal coverage by optical coherence tomography of a sirolimus-eluting stent versus a bare-metal stent three months after implantation. Am J Cardiol 2008;102:27–31.
18. Jang IK, Bouma BE, Kang DH, et al. Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: comparison with intravascular ultrasound. J Am Coll Cardiol 2002;39: 604–9.
19. Kume T, Akasaka T, Kawamoto T, et al. Measurement of the thickness of the fibrous cap by optical coherence tomography. Am Heart J 2006;152:755.e1–4.
20. Weissman NJ, Koglin J, Cox DA, et al. Polymer-based paclitaxel-eluting stents reduce in-stent neointimal tissue proliferation: a serial volumetric intravascular ultrasound analysis from the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1201–5.
21. Sousa JE, Costa MA, Sousa AG, et al. Two-year angiographic and intravascular ultrasound follow-up after implantation of sirolimus-eluting stents in human coronary arteries. Circulation 2003;107:381–3.
22. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008;52:333–42.
23. Ako J, Morino Y, Honda Y, et al. Late incomplete stent apposition after sirolimus-eluting stent implantation: a serial intravascular ultrasound analysis. J Am Coll Cardiol 2005;46:1002–5.
24. Hong MK, Mintz GS, Lee CW, et al. Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. Circulation 2006;113:414–9.
25. Tanabe K, Serruys PW, Degertekin M, et al. Incomplete stent apposition after implantation of paclitaxel-eluting stents or bare metal stents: insights from the randomized TAXUS II trial. Circulation 2005;111:900–5.

Key Words: drug-eluting stent ■ optical coherence ■ tomography ■ zotarolimus.