Circulation
Cardiovascular Interventions
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

# Comparison of Zotarolimus-Eluting Stents With Sirolimus-Eluting and Paclitaxel-Eluting Stents : Intimal Hyperplasia and Vascular Changes Assessed by Volumetric Intravascular Ultrasound Analysis

Soo-Jin Kang, Gary S. Mintz, Duk-Woo Park, Seung-Whan Lee, Young-Hak Kim, Cheol Whan Lee, Ki-Hoon Han, Jae-Joong Kim, Seong-Wook Park and Seung-Jung Park

*Circ Cardiovasc Interv* 2011;4;139-145; originally published online March 1, 2011;
DOI: 10.1161/CIRCINTERVENTIONS.110.957936
Circulation: Cardiovascular Interventions is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1941-7640. Online ISSN: 1941-7632

# Comparison of Zotarolimus-Eluting Stents With Sirolimus-Eluting and Paclitaxel-Eluting Stents

## Intimal Hyperplasia and Vascular Changes Assessed by Volumetric Intravascular Ultrasound Analysis

Soo-Jin Kang, MD; Gary S. Mintz, MD; Duk-Woo Park, MD; Seung-Whan Lee, MD; Young-Hak Kim, MD; Cheol Whan Lee, MD; Ki-Hoon Han, MD; Jae-Joong Kim, MD; Seong-Wook Park, MD; Seung-Jung Park, MD

***Background***—As a substudy of the large, randomized ZEST (Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent with Sirolimus-Eluting and PacliTaxel-Eluting Stent for Coronary Lesions) trial comparing first- and second-generation drug-eluting stents, we evaluated intimal hyperplasia (IH) and vascular changes using volumetric intravascular ultrasound analysis.

***Methods and Results***—Complete angiographic and volumetric intravascular ultrasound data immediately after stenting and at 9-month follow-up were available in 162 patients with 183 lesions: 61 sirolimus-eluting stents (SES), 64 paclitaxel-eluting stents (PES), and 58 zotarolimus-eluting stents (ZES). External elastic membrane, stent, lumen, and peristent plaque volumes (external elastic membrane minus stent) were normalized by stent length. Percent IH volumes were calculated as [IH volume/stent volume]×100, %. Reduction of minimal luminal area) was greater in PES than SES ($-1.4\pm1.5$ mm$^2$ versus $-0.7\pm0.9$ mm$^2$, $P=0.003$), whereas minimal luminal area change in ZES was not significantly different from SES ($-1.2\pm1.0$ mm$^2$ versus $-0.7\pm0.9$ mm$^2$, $P=0.055$). Percent IH volume was less in SES compared with PES ($9.8\pm6.0\%$ versus $17.5\pm11.2\%$, $P=0.002$) or with ZES ($9.8\pm6.0\%$ versus $18.2\pm7.6\%$, $P=0.005$). Comparing ZES versus PES, there were no significant differences in %IH volume ($17.5\pm11.2\%$ versus $18.2\pm7.6\%$, $P=0.779$) or changes in normalized lumen volume ($-1.2\pm1.3$ mm$^2$ versus $-1.1\pm0.8$ mm$^2$, $P=0.452$). Late stent malapposition was identified in 8 (13%) SES and 2 (3%) PES but in no ZES ($P=0.050$). Angiographic restenosis was detected in 6 lesions (3 PES and 3 ZES).

***Conclusions***—The degree of neointimal growth in ZES was similar to that in PES but less than that in SES. ZES had no late stent malappositions.

***Clinical Trial Registration***—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00418067.

**(*Circ Cardiovasc Interv*. 2011;4:139-145.)**

**Key Words:** zotarolimus-eluting stents ■ intimal hyperplasia ■ intravascular ultrasound

The 2 first-generation, polymer-based, drug-eluting stents (DES) approved by the US Food and Drug Administration—sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES)—have reduced the rate of restenosis and the need for repeat revascularization. However, there are concerns about stent thrombosis and late neointimal "catch-up" related to an altered arterial healing or to an inflammatory response to the DES.[1–3] Although the second-generation zotarolimus-eluting stent (ZES) has been developed to enhance safety and offer similar or better efficacy compared with first-generation DES, there are few intravascular ultrasound (IVUS) studies demonstrating these effects.[4,5]

### Clinical Perspective on p 145

The ZEST (Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent with Sirolimus-Eluting and PacliTaxel-Eluting Stent for Coronary Lesions) trial is a multicenter, prospectively randomized, "all comers" study to compare ZES versus SES and PES in 2645 patients undergoing percutaneous coronary intervention. The data showed that the use of ZES resulted in similar rates of major adverse cardiac events compared with SES, and in fewer major adverse cardiac events compared with PES during 1 year of follow-up.

Received January 8, 2010; accepted December 21, 2010.

From the Department of Cardiology (S.-J.K., D.-W.P., S.-W.L., Y.-H.K., C.W.L., K.-H.H., J.-J.K., S.-W.P., S.-J.P.), University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; and the Cardiovascular Research Foundation (G.S.M.), New York, NY.

Correspondence to Seung-Jung Park, MD, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul, South Korea, 138-736. E-mail sjpark@amc.seoul.kr



*Circ Cardiovasc Interv* **is available at http://circinterventions.ahajournals.org** **DOI: 10.1161/CIRCINTERVENTIONS.110.957936**

As a substudy of the ZEST trial, we performed a volumetric IVUS substudy to compare intimal hyperplasia (IH), late stent malapposition (LSM), and vascular remodeling among these 3 stents.

## Methods

Data were derived from the ZEST trial that was a prospective, randomized, single-blind, controlled study conducted in 19 centers between October 2006 and January 2008. The study was an "all-comers" design involving consecutive enrollment of patients with stable angina or acute coronary syndromes who had at least 1 coronary lesion (defined as a stenosis of >50%) suitable for stent implantation. Exclusion criteria were ST-elevation myocardial infarction necessitating primary percutaneous coronary intervention; severely compromised ventricular dysfunction (ejection fraction <25%) or cardiogenic shock; drug allergy; left main coronary artery disease (defined as a stenosis of >50%); in-stent restenosis of previously implanted DES; terminal illness; and participation in another coronary device study. Eligible patients were randomly assigned on a 1:1:1 basis to treatment with ZES (Endeavor; Medtronic Vascular), SES (Cypher select; Cordis, Johnson & Johnson, Miami Lakes, FL), or PES (TAXUS Liberte, Boston Scientific Corp, Natick, MA). All patients signed written informed consent. The sponsor of this study contributed to study design but had no role in data collection, monitoring, analysis, interpretation, or writing of the manuscript.

The current follow-up angiographic and IVUS analysis, which was a single-center substudy of the ZEST trial, included all patients evaluated and treated at the Asan Medical Center, Seoul, Korea, who underwent poststenting and 9-month IVUS and quantitative angiography.

All procedures were performed by standard techniques. Heparin was administered during the procedure to maintain an activated clotting time of 250 seconds or longer. The use of glycoprotein IIb/IIIa inhibitors was at the discretion of the operators. Before the procedure, all patients received at least 100 mg of aspirin and a 300 to 600 mg loading dose of clopidogrel; this was followed by aspirin (100 to 200 mg/d) indefinitely and clopidogrel (75 mg/d) for at least 12 months.

### Angiographic Analysis

All eligible patients were requested to return for angiographic follow-up between 8 to 10 months after the procedure. Quantitative angiographic measurements were done by standard techniques with automated edge-detection algorithms (CASS-5, Pie-Medical, Maastricht, the Netherlands) in the angiographic analysis center of the CardioVascular Research Foundation, Seoul, Korea.[6,7] Angiographic image acquisition was performed at target sites using 2 or more angiographic projections of the stenosis at baseline, after stenting, and at 9 months. Angiographic restenosis was defined as a diameter stenosis >50% at follow-up angiography.

### IVUS Imaging and Analysis

IVUS imaging was performed after intracoronary administration of 0.2 mg nitroglycerin, using a motorized transducer pullback (0.5 mm/s) and a commercial scanner (Boston Scientific/SCIMED, Minneapolis, MN) consisting of a rotating 40-MHz transducer within a 3.2F imaging sheath. The decision to perform IVUS and the decision to use IVUS information to guide the percutaneous coronary intervention procedure was at the operator's discretion.

All IVUS data were assessed off-line by experienced accessors unaware of the allocated stent type or clinical information in a core laboratory at the Asan Medical Center. Quantitative volumetric IVUS analysis was performed as previously described.[8,9] Using computerized plannimetry (EchoPlaque 2.7, Indec Systems, Mountain View, CA), stent and reference segments were assessed every 1 mm. Reference segment external elastic membrane (EEM), lumen, and plaque+media (EEM minus lumen) areas were measured over a 5-mm length adjacent to each stent edge and averaged. In-stent measurements were also obtained every 1 mm and included EEM, stent, intrastent lumen, peristent plaque+media (EEM minus stent), and IH (stent minus intrastent lumen) areas and volumes. Percent IH was defined as IH divided by stent. All volumes were calculated using the Simpson rule and then normalized by stent length (normalized volume).

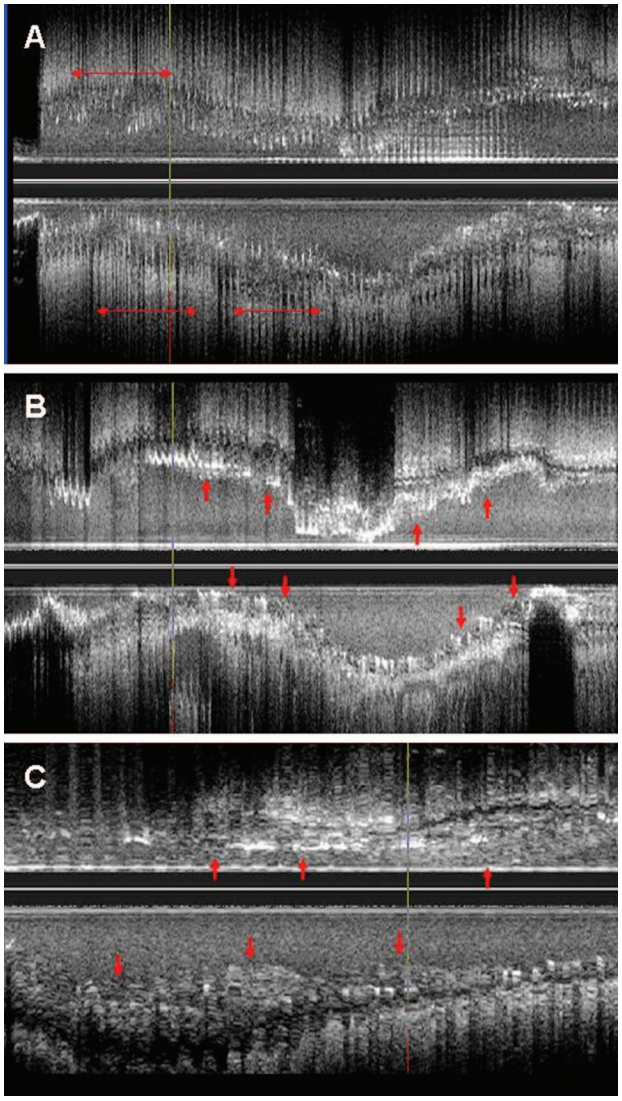


**Figure.** Longitudinal IVUS images of in-stent lesion. **A,** Nine-month follow-up of sirolimus-eluting stents. Huge LSM is shown. Red arrows indicate longitudinal extent of malapposition; **B,** 9-month follow-up of zotarolimus-eluting stents (diffuse in-stent segment is covered with small amount of neointima [arrows] without any evidence of malapposition); **C,** 9-month follow-up of paclitaxel-eluting stents (greater intimal hyperplasia is diffusely involved inside the stent [arrows]).

Using segmental analysis with head-to-head comparison between poststenting and follow-up images, vascular remodeling was assessed by the serial changes in %EEM area ([follow-up EEM area−poststenting EEM area]/poststenting EEM area)×100. Focal expansive remodeling was defined as a >10% increase in EEM area over at least 3 consecutive 1-mm segments, and focal constrictive remodeling was defined as a >10% decrease in EEM area over at least 3 consecutive 1-mm segments. Diffuse expansive or constrictive remodeling was defined as >10% increase or decrease in normalized vessel volume of the entire in-stent region compared with poststenting normalized vessel volume. Lesions were excluded if they showed nonuniform rotational distortion, a difference in total

**Table 1. Baseline Clinical Characteristics in the Overall Cohort of 162 Patients in the IVUS Substudy**

| Variable | Cypher | Taxus | Endeavor | *P* Value* |
|---|---|---|---|---|
| No. of patients | 54 | 56 | 52 | |
| Age, y | 57.0±8.8 | 60.0±9.0 | 60.8±7.2 | 0.058 |
| Male, n (%) | 41 (76%) | 38 (68%) | 33 (64%) | 0.37 |
| Hypertension, n (%) | 26 (48%) | 28 (50%) | 33 (64%) | 0.23 |
| Hypercholesterolemia, n (%) | 30 (56%) | 35 (63%) | 27 (52%) | 0.53 |
| Diabetes mellitus, n (%) | 11 (20%) | 11 (20%) | 15 (29%) | 0.46 |
| Smoking, n (%) | 14 (26%) | 12 (21%) | 8 (15%) | 0.41 |
| Family history of CAD, n (%) | 5 (9%) | 3 (5%) | 4 (8%) | 0.73 |
| Body mass index | 24.5±2.8 | 25.6±3.0 | 24.7±2.0 | 0.074 |
| Left ventricular ejection fraction (%) | 60.4±5.1 | 59.8±4.8 | 60.9±4.8 | 0.51 |
| Previous percutaneous intervention, n (%) | 7 (13%) | 5 (9%) | 2 (4%) | 0.25 |
| Previous myocardial infarction, n (%) | 4 (7%) | 2 (4%) | 0 (0%) | 0.13 |
| Clinical presentation, n (%) | | | | 0.40 |
| Silent ischemia | 3 (6%) | 2 (3%) | 4 (8%) | |
| NSTEMI | 5 (9%) | 5 (9%) | 6 (11%) | |
| Chronic stable angina | 26 (48%) | 20 (36%) | 14 (27%) | |
| Unstable angina | 20 (37%) | 29 (52%) | 28 (54%) | |
| Multivessel disease, n (%) | 25 (46%) | 23 (41%) | 24 (46%) | 0.82 |

CAD indicates coronary artery disease; NSTEMI, non–ST-elevation myocardial infarction.

**P* value by 1-way ANOVA.

stent length >2 mm between poststenting and follow-up, or mismatched segments.

LSM was defined as separation of at least 1 stent strut away from the intimal surface of the arterial wall that was not overlapping a side branch, was not present immediately after stent implantation, and had evidence of blood speckling behind the strut.[10] Within LSM sections, LSM and plaque+media [EEM minus stent minus LSM] volumes (and normalized volumes) were calculated with the Simpson rule. Longitudinal IVUS images of in-stent lesion of each DES were shown in the Figure.

## Statistical Analysis

All statistical analyses were performed using SAS release 9.1 (SAS Institute Inc, Cary, NC) or SPSS (version 10.0, SPSS Inc, Chicago, IL). Data were analyzed on a per-patient and per-lesion basis for the corresponding calculations. All values are expressed as mean±standard deviation (continuous variables) or as counts and percentages (categorical variables). For the per-patient data, continuous variables were compared by use of 1-way ANOVA or nonparametric Kruskal-Wallis test; categorical variables were compared with the $\chi^2$ statistics or Fisher exact test. For the per-lesion data, linear mixed models that accounted for the clustering between lesions in same subject were created. All probability values were 2-sided, and probability values <0.05 were considered to indicate statistical significance.

In post hoc analysis, all IVUS parameters were compared among the 3 DES types; Bonferroni corrections were made for multiple comparisons of continuous variables. All probability values were 2-sided, and probability values after Bonferroni correction <0.05 were considered to indicate statistical significance.

**Table 2. Angiographic Data and Procedural Characteristics of 183 Treated Lesions in the IVUS Substudy**

| Variable | Cypher | Taxus | Endeavor | *P* Value* |
|---|---|---|---|---|
| No. of lesions | 61 | 64 | 58 | |
| Angiographic findings | | | | |
| Chronic total occlusion, n (%) | 4 (7%) | 3 (5%) | 5 (9%) | 0.79 |
| In-stent restenosis, n (%) | 0 (0%) | 1 (2%) | 0 (0%) | 0.40 |
| TIMI grade 0, n (%) | 4 (7%) | 2 (3%) | 4 (7%) | 0.81 |
| Thrombus, n (%) | 0 (0%) | 0 (0%) | 2 (3%) | 0.21 |
| Severe calcification, n (%) | 3 (5%) | 1 (2%) | 32 (3%) | 0.16 |
| Lesion site, n (%) | | | | 0.81 |
| Left anterior descending artery | 37 (61%) | 36 (56%) | 39 (67%) | |
| Left circumflex artery | 8 (13%) | 8 (13%) | 8 (14%) | |
| Right coronary artery | 16 (26%) | 19 (29%) | 9 (16%) | |
| Diagonal | 9 (%) | 1 (2%) | 2 (3%) | |
| Procedural findings | | | | |
| Direct stenting, n (%) | 6 (10%) | 8 (13%) | 5 (9%) | 0.98 |
| Stent in the side branch, n (%) | 8 (13%) | 8 (13%) | 6 (10%) | 0.99 |
| Maximal balloon pressure, atm | 16.3±4.2 | 16.3±4.1 | 16.2±4.2 | 0.96 |
| No. of DES per lesion | 1.2±0.4 | 1.1±0.4 | 1.2±0.5 | 0.53 |
| Stent length, mm | 30.5±11.6 | 25.7±10.1 | 29.1±11.6 | 0.12 |
| Proximal reference diameter, mm | 3.5±0.4 | 3.7±0.6 | 3.4±0.5 | 0.077 |
| Distal reference diameter, mm | 2.7±0.4 | 2.8±0.6 | 2.6±0.5 | 0.045§ |
| Minimal lumen diameter, mm | | | | |
| Preintervention | 0.9±0.5 | 1.0±0.6 | 1.0±0.5 | 0.48 |
| Postintervention | 2.5±0.5 | 2.6±0.5 | 2.4±0.5 | 0.20 |
| 9-Month follow-up | 2.3±0.4 | 2.2±0.5 | 2.0±0.5 | 0.007‡ |
| Late luminal loss, mm | 0.17±0.29 | 0.38±0.47 | 0.39±0.41 | 0.005†‡ |
| Restenosis at 9 months, n % | 0 (0%) | 3 (5%) | 3 (6%) | 0.25 |

TIMI indicates Thrombolysis In Myocardial Infarction.

**P* value by linear mixed model, post hoc multiple comparisons with Bonferroni correction; †*P*<0.05, Cypher versus Taxus; ‡*P*<0.05, Cypher versus Endeavor; §*P*<0.05, Taxus versus Endeavor.

## Results

Complete angiographic and volumetric IVUS data immediately after stenting and at 9-month follow-up were available in 162 patients with 183 lesions: 61 SES, 64 PES, and 58 ZES. Twenty-one patients had 2 lesions. Baseline clinical and angiographic characteristics were similar among the groups (Table 1). Follow-up angiography showed that late luminal loss at 9 months in SES was less than in PES or ZES, but late luminal loss at 9 months in ZES was not significantly

**Table 3. Volumetric IVUS Measurements After Stenting and at 9-Month Follow-Up**

| | After Stenting | | | | Follow-Up | | | |
|---|---|---|---|---|---|---|---|---|
| | Cypher | Taxus | Endeavor | *P* Value* | Cypher | Taxus | Endeavor | *P* Value* |
| No. of lesions | 61 | 64 | 58 | | 61 | 64 | 58 | |
| Proximal reference | | | | | | | | |
| Mean EEM area, $mm^2$ | 16.2±4.2 | 16.5±4.3 | 14.8±4.0 | 0.25 | 15.4±4.0 | 16.1±4.3 | 14.8±4.1 | 0.29 |
| MLA, $mm^2$ | 8.6±2.5 | 9.8±2.9 | 7.8±2.0 | 0.002 | 7.7±2.2 | 8.8±2.9 | 7.3±2.5 | 0.14 |
| Mean P+M area, $mm^2$ | 7.6±3.1 | 6.8±2.4 | 7.2±2.4 | 0.47 | 7.7±3.1 | 7.4±2.7 | 7.6±2.1 | 0.89 |
| Stented segment | | | | | | | | |
| MLA, $mm^2$ | 6.0±1.9 | 6.8±2.0 | 5.7±1.7 | 0.013 | 5.3±1.7 | 5.4±2.3 | 4.5±1.7 | 0.056 |
| Stent volume, $mm^3$ | 230.2±93.2 | 216.6±104.1 | 206.4±86.7 | 0.38 | 236.2±89.6 | 222.1±103.5 | 211.8±90.0 | 0.37 |
| Lumen volume, $mm^3$ | 230.2±93.2 | 216.6±104.1 | 206.4±86.7 | 0.38 | 213.1±84.2 | 183.3±88.1 | 173.2±74.7 | 0.041 |
| IH volume, $mm^3$ | | | | | 23.1±15.8 | 38.8±32.8 | 38.6±23.3 | 0.003 |
| IH volume, % | | | | | 9.8±6.0 | 17.5±11.1 | 18.2±7.6 | <0.001 |
| EEM volume, $mm^3$ | 457.3±183.7 | 419.1±200.5 | 408.0±167.7 | 0.26 | 474.1±189.3 | 434.6±212.9 | 417.6±177.1 | 0.24 |
| P+M volume, $mm^3$ | 227.1±99.1 | 202.5±104.7 | 201.6±87.3 | 0.18 | 236.5±189.3 | 211.9±112.7 | 205.8±93.6 | 0.18 |
| Normalized stent volume, $mm^2$ | 7.7±2.0 | 8.5±2.3 | 7.2±1.8 | 0.008 | 8.0±2.0 | 8.7±2.2 | 7.4±1.8 | 0.002 |
| Normalized lumen volume, $mm^2$ | 7.7±2.0 | 8.5±2.3 | 7.2±1.8 | 0.008 | 7.2±1.8 | 7.3±2.4 | 6.1±1.8 | 0.009 |
| Normalized IH volume, $mm^2$ | | | | | 0.8±0.5 | 1.5±1.0 | 1.3±0.6 | <0.001 |
| Normalized EEM volume, $mm^2$ | 15.3±4.3 | 16.4±4.3 | 14.4±4.0 | 0.050 | 15.9±4.3 | 17.0±4.4 | 14.6±4.1 | 0.030 |
| Normalized P+M volume, $mm^2$ | 7.7±2.7 | 7.9±2.6 | 7.1±2.4 | 0.24 | 7.9±2.6 | 8.2±2.5 | 7.2±2.5 | 0.14 |
| Distal reference | | | | | | | | |
| Mean EEM area, $mm^2$ | 11.3±4.9 | 12.1±4.7 | 9.9±4.3 | 0.076 | 11.0±4.4 | 12.5±5.3 | 10.1±3.9 | 0.046 |
| MLA, $mm^2$ | 7.0±2.5 | 7.6±2.6 | 6.3±1.9 | 0.027 | 6.9±2.4 | 7.5±3.3 | 6.1±2.0 | 0.035 |
| Mean P+M area, $mm^2$ | 4.4±2.8 | 4.7±3.4 | 3.7±2.9 | 0.23 | 4.1±2.4 | 5.0±3.0 | 4.0±2.5 | 0.12 |

EEM indicates external elastic membrane; MLA, minimal lumen; IH, intimal hyperplasia.
**P* value by linear mixed model.

different from PES (Table 2). Angiographic restenosis was detected in 6 lesions (3 PES and 3 ZES). Clinical characteristics and angiographic findings in the IVUS substudy patients were similar to the overall ZEST study cohort (data not shown).

## IVUS Analysis

At baseline, ZES had a smaller poststenting minimal lumen area (MLA) and a smaller poststenting normalized lumen volume compared with PES. Volumetric IVUS measurements after stenting and at 9-month follow-up are summarized in Table 3. The 9-month reduction in IVUS MLA was more remarkable in PES than SES (−1.4±1.5 $mm^2$ versus −0.7±0.9 $mm^2$, $P=0.003$), whereas the 9-month reduction in MLA in ZES was not significantly different from SES (−1.2±1.0 $mm^2$ versus −0.7±0.9 $mm^2$, $P=0.055$, Table 4). The changes in MLA were similar between ZES and PES (−1.2±1.0 $mm^2$ versus 1.4±1.5 $mm^2$, $P=0.24$).

The %IH volume at 9 months was less in SES compared with PES (9.8±6.0% versus 17.5±11.2%, $P=0.002$) or with ZES (9.8±6.0% versus 18.2±7.6%, $P=0.005$). Moreover, the reduction of normalized luminal volume in SES was less than in ZES (−0.5±0.7 $mm^2$ versus −1.1±0.8 $mm^2$, $P=0.007$) or PES (−0.5±0.7 $mm^2$ versus −1.2±1.3 $mm^2$ $P<0.001$). However, comparing PES to ZES, there was no significant difference in %IH volumes at 9 months (17.5±11.2% versus 18.2±7.6%, $P=0.78$) or changes in normalized lumen volume (−1.2±1.3 $mm^2$ versus −1.1±0.8 $mm^2$, $P=0.45$).

## Vascular Remodeling and LSM

There was no significant difference among the 3 DES groups with regard to changes in normalized vessel, stent, or peristent plaque volumes. Diffuse expansive remodeling was detected in 14 (23%) SES-treated, 13 (20%) PES-treated, and 9 (16%) ZES-treated lesions ($P=0.58$). Diffuse constrictive remodeling was seen in 3 (5%) SES-treated, 4 (6%) PES-treated, and 2 (3%) ZES-treated lesions ($P=0.77$). Additionally, focal expansive remodeling was identified in 33 (54%) SES-treated, 32 (50%) PES-treated, and 23 (40%) ZES-treated lesions ($P=0.27$), whereas 12 (20%) SES-treated, 9 (14%) PES-treated, and 14 (24%) ZES-treated lesions included segments with focal constrictive remodeling ($P=0.37$). Severe focal expansive remodeling (>20% increase in EEM area) was observed in 22 (40%) SES-treated, 18 (30%) PES-treated, and 13 (25%) ZES lesions ($P=0.08$). Overall, 10 (5.5%) lesions revealed both expansive and constrictive remodeling in the same in-stent segment.

LSM was identified in 8 (13%) SES-treated and 2 (3%) PES-treated but in no ZES-treated lesions ($P=0.050$, which was calculated by logistic regression with generalized estimation equation).

In the proximal and distal reference segments, there were no significant changes in EEM, lumen, or P&M areas

**Table 4. Changes in IVUS Parameters Over 9 Months**

| | Cypher | Taxus | Endeavor | *P* Value* |
|---|---|---|---|---|
| No. of lesions | 61 | 64 | 58 | |
| Proximal reference | | | | |
| ΔMean EEM area, $mm^2$ | −0.8±2.5 | −0.5±2.0 | −0.03±1.9 | 0.57 |
| ΔMLA, $mm^2$ | −1.0±1.9 | −1.0±1.8 | −0.6±1.4 | 0.55 |
| ΔMean plaque area, $mm^2$ | 0.1±1.6 | 0.6±1.5 | 0.3±1.6 | 0.46 |
| Stented segment | | | | |
| ΔMLA, $mm^2$ | −0.7±0.9 | −1.4±1.5 | −1.2±1.0 | 0.010† |
| ΔStent volume, $mm^3$ | 6.1±15.7 | 5.5±19.3 | 5.5±16.3 | 0.99 |
| ΔLumen volume, $mm^3$ | −17.1±23.0 | −33.3±35.9 | −33.1±26.7 | 0.011†‡ |
| ΔIH volume, $mm^3$ | 23.1±15.8 | 38.8±32.9 | 38.6±23.3 | 0.003†‡ |
| ΔIH volume, % | 9.8±6.0 | 17.5±11.2 | 18.2±7.6 | <0.001†‡ |
| ΔEEM volume, $mm^3$ | 16.8±52.4 | 15.5±36.6 | 9.6±34.2 | 0.75 |
| ΔP+M volume, $mm^3$ | 9.4±44.4 | 9.4±25.3 | 4.2±26.7 | 0.77 |
| ΔNormalized stent volume, $mm^2$ | 0.3±0.5 | 0.2±0.8 | 0.2±0.6 | 0.86 |
| ΔNormalized lumen volume, $mm^2$ | −0.5±0.7 | −1.2±1.3 | −1.1±0.8 | 0.002†‡ |
| ΔNormalized EEM volume, $mm^2$ | 0.5±1.7 | 0.6±1.4 | 0.3±1.1 | 0.68 |
| ΔNormalized P+M volume, $mm^2$ | 0.2±1.4 | 0.3±0.9 | 0.1±0.9 | 0.76 |
| Distal reference | | | | |
| ΔMean EEM area, $mm^2$ | −0.4±1.7 | 0.4±2.1 | 0.1±1.4 | 0.11 |
| ΔMLA, $mm^2$ | −0.1±1.3 | −0.1±1.8 | −0.2±1.3 | 0.92 |
| ΔMean P+M area, $mm^2$ | −0.3±1.0 | 0.2±2.1 | 0.3±1.1 | 0.15 |

EEM indicates external elastic membrane; MLA, minimal lumen; IH, intimal hyperplasia.

*$P$ value by linear mixed model, post hoc multiple comparisons with Bonferroni correction; †$P<0.05$, Cypher versus Taxus; ‡$P<0.05$, Cypher versus Endeavor; §$P<0.05$, Taxus versus Endeavor.

in the 3 DES groups between stent implantation and 9 months.

## Discussion

The mean %IH volume of 18.2% in ZES in the current study was in accordance with previous randomized, controlled trials (17.4% in ENDEAVOR II and 16.1% in the IVUS cohort of ENDEAVOR III).[11–14] Despite much greater %IH volume in ZES compared with SES in these and in the current study, the loss of MLA in ZES was not significantly different from that in SES. Because of the longitudinal pattern of neointimal distribution over the stented length, focal neointimal accumulation will result in a smaller %IH volume than diffuse neointimal distribution. Most neointimal proliferation seen in SES has been reported to be focal, whereas a previous study reported that ZES evenly inhibited neointimal growth resulting in more diffuse neointimal hyperplasia.[4] The current findings are more notable because, unlike ENDEAVOR II or ENDEAVOR III, our study was an attempt to reflect routine clinical practice and had an "all-comers" design involving the consecutive enrollment of eligible patients with either stable angina or acute coronary syndrome who had at least 1 coronary lesion with no limitation on the number of lesions or vessels or on the lengths of the lesions.

In the present study, %IH volumes and the reduction in normalized lumen volume in ZES are similar to PES. Because %IH volume presumably represents the overall inhibitory effect of each device on neointimal growth, these findings indicate that the efficacy of ZES is comparable to PES. In most patients treated with PES, neointimal accumulation is below the threshold of physiological significance.[15] However, the permissible range of neointimal growth still remains unclear.

A recent report demonstrates that the lack of intimal hyperplasia is related to late DES thrombosis as the result of impaired reendothelialization and delayed arterial healing.[16] ENDEAVOR II and III demonstrate an improved safety profile in ZES that was attributed to the relatively complete and uniform neointima that, nevertheless, is associated with a clinically acceptable late lumen loss.[4,5] Although excessive neointimal growth results in target lesion revascularization, the coverage of stent struts with a small amount of neointima as seen in ZES may provide a potential advantage for device safety.[11,12]

### Late Stent Malapposition

Concerns have been raised about late acquired stent malapposition and long-term clinical events such as late stent thrombosis.[17,18] The incidence of late acquired stent malapposition has been reported from 3% to 13% in SES and from 2% to 8% in PES[19,20–22]; our data showed a similar incidence. No LSM was detected in ZES-treated lesions, also consistent with previous data; there was no late-acquired incomplete stent appositions in patients treated with ZES in ENDEAVOR II and only 1 such case in ENDEAVOR III.[11,12]

Recent studies have suggested that LSM may result from pathological positive vessel remodeling at the site there the strut becomes separated from the vessel.[23,24] Previous studies

showed no unfavorable vascular responses with ZES compared with the control bare metal stent,[4] and no significant serial changes in mean vessel area were found in ZES-treated lesions.[11,12] Similarly, our data revealed no significant differences in changes in normalized EEM volumes or in the incidence of diffuse expansive remodeling among the three DES groups. However, there was a trend toward a lower incidence of severe focal expansive remodeling in ZES compared with SES (25% versus 40%, $P=0.080$). We need further studies to confirm if these IVUS findings including a lower incidence of LSM, greater neointimal coverage of stent struts, and smaller and less frequent expansive remodeling may enhance the safety of ZES compared with SES and PES.

### Limitations

We did not evaluate neointimal coverage over the stent surface. The endothelial layer is below the axial resolution of IVUS. Furthermore, to validate the clinical utility of the ZES and to find the relationship between the neointimal coverage and clinical outcomes, additional long-term follow-up investigations in larger patient numbers are needed. The current substudy was single-center based and could not include all patients enrolled in ZEST trial because of early restenosis, repeat revascularization, patient refusal for IVUS examination, or technical difficulty in the test. Because the substudy cohort could not completely reflect the characteristics of overall population in the real world, these pitfalls and potential for selection bias may limit the external validity of the findings and should be thoroughly considered before extending these observations to the general cohort of patients undergoing routine DES implantation.

### Conclusions

Although ZES is less effective in inhibiting intimal hyperplasia than SES, ZES showed efficacy comparable to PES. The implication of lack of LSM on the safety of ZES needs further study with long-term follow-up.

## Sources of Funding

This study was supported by funds from the CardioVascular Research Foundation, Seoul, Korea, and Medtronic Vascular, Santa Rosa, CA.

## Disclosures

Dr Park received consulting fees from Cordis, lecture fees from Cordis, Medtronic, and Boston Scientific, and research grant support from Cordis and Medtronic; Dr Kim received lecture fees from Cordis; Dr Lee received lectures fees from Medtronic; and Dr Park received research grant support from Medtronic.

## References

1. Liistro F, Stankovic G, Di Mario C, Takagi T, Chieffo A, Moshiri S, Montorfano M, Carlino M, Briguori C, Pagnotta P, Albiero R, Corvaja N, Colombo A. First clinical experience with a paclitaxel derivate-eluting polymer stent system implantation for in-stent restenosis: immediate and long-term clinical and angiographic outcome. *Circulation*. 2002;105:1883–1886.
2. Finn AV, Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, Virmani R. Vascular responses to drug eluting stents: importance of delayed healing. *Arterioscler Thromb Vasc Biol*. 2007;27:1500–1510.
3. Park DW, Hong MK, Mintz GS, Lee CW, Song JM, Han KH, Kang DH, Cheong SS, Song JK, Kim JJ, Weissman NJ, Park SW, Park SJ. Two-year follow-up of the quantitative angiographic and volumetric intravascular ultrasound analysis after nonpolymeric paclitaxel-eluting stent implantation: late "catch-up" phenomenon from ASPECT Study. *J Am Coll Cardiol*. 2006;48:2432–2439.
4. Fajadet J, Wijns W, Laarman GJ, Kuck KH, Ormiston J, Munzel T, Popma JJ, Fitzgerald PJ, Bonan R, Kuntz RE. Randomized, doubleblind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation*. 2006;114:798–806.
5. Kandzari DE, Leon MB, Popma JJ, Fitzgerald PJ, O'Shaughnessy C, Ball MW, Turco M, Applegate RJ, Gurbel PA, Midei MG. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. *J Am Coll Cardiol*. 2006;48:2440–2447.
6. Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB III, Loop FD, Peterson KL, Reeves TJ, Williams DO, Winters WL. Guidelines for percutaneous transluminal coronary angioplasty: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). *Circulation*. 1988;78:486–502.
7. Popma JJ, Leon MB, Moses JW, Holmes DR Jr, Cox N, Fitzpatrick M, Douglas J, Lambert C, Mooney M, Yakubov S, Kuntz RE, SIRIUS Investigators. Quantitative assessment of angiographic restenosis after sirolimus-eluting stent implantation in native coronary arteries. *Circulation*. 2004;110:3773–3780.
8. Park SJ, Shim WH, Ho DS, Raizner AE, Park SW, Hong MK, Lee CW, Choi D, Jang Y, Lam R, Weissman NJ, Mintz GS. A paclitaxel-eluting stent for the prevention of coronary restenosis. *N Engl J Med*. 2003;348:1537–1545.
9. Mintz GS, Weissman NJ, Teirstein PS, Ellis SG, Waksman R, Russo RJ, Moussa I, Tripuraneni P, Jani S, Kobayashi Y, Giorgianni JA, Pappas C, Kuntz RA, Moses J, Leon MB. Effect of intracoronary gamma-radiation therapy on in-stent restenosis: an intravascular ultrasound analysis from the gamma-1 study. *Circulation*. 2000;102:2915–2918.
10. Shah VM, Mintz GS, Apple S, Weissman NJ. Background incidence of late malapposition after bare-metal stent implantation. *Circulation*. 2002;106:1753–1755.
11. Sakurai R, Hongo Y, Yamasaki M, Honda Y, Bonneau HN, Yock PG, Cutlip D, Popma JJ, Zimetbaum P, Fajadet J, Kuntz RE, Wijns W, Fitzgerald PJ. ENDEAVOR II Trial Investigators. Detailed intravascular ultrasound analysis of Zotarolimus-eluting phosphorylcholine-coated cobalt-chromium alloy stent in de novo coronary lesions (results from the ENDEAVOR II trial). *Am J Cardiol*. 2007;100:818–823.
12. Miyazawa A, Ako J, Hongo Y, Hur SH, Tsujino I, Courtney BK, Hassan AH, Kandzari DE, Honda Y, Fitzgerald PJ, ENDEAVOR III Investigators. Comparison of vascular response to zotarolimus-eluting stent versus sirolimus-eluting stent: intravascular ultrasound results from ENDEAVOR III. *Am Heart J*. 2008;155:108–113.
13. Sakurai R, Bonneau HN, Honda Y, Fitzgerald PJ. Intravascular ultrasound findings in ENDEAVOR II and ENDEAVOR III. *Am J Cardiol*. 2007;100:71M–76M.
14. Gershlick A, Kandzari DE, Leon MB, Wijns W, Meredith IT, Fajadet J, Popma JJ, Fitzgerald PJ, Kuntz RE, ENDEAVOR Investigators. Zotarolimus-eluting stents in patients with native coronary artery disease: clinical and angiographic outcomes in 1,317 patients. *Am J Cardiol*. 2007;100:45M–55M.
15. Weissman NJ, Koglin J, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Kutcher M, Wong SC, Strickland W, Mooney M, Russell ME, Ellis SG, Stone GW. 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;45:1201–1205.
16. Joner M, Finn A, Kolodgie F, Burke A, Ladich E, Gold H, Virmani R. Lack of neointimal growth is a predictor of late stent thrombosis [abstract]. *Circulation*. 2006;114:453.
17. Hassan AK, Bergheanu SC, Stijnen T, van der Hoeven BL, Snoep JD, Plevier JW, Schalij MJ, Jukema JW. Late stent malapposition risk is higher after drug-eluting stent compared with bare-metal stent implantation and associates with late stent thrombosis. *Eur Heart J*. 2010;31:1172–1180.
18. Cook S, Ladich E, Nakazawa G, Eshtehardi P, Neidhart M, Vogel R, Togni M, Wenaweser P, Billinger M, Seiler C, Gay S, Meier B, Pichler WJ, Jüni P, Virmani R, Windecker S. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation*. 2009;120:391–399.

19. Ako J, Morino Y, Honda Y, Hassan A, Sonoda S, Yock PG, Leon MB, Moses JW, Bonneau HN, Fitzgerald PJ. Late incomplete stent apposition after sirolimus-eluting stent implantation: a serial intravascular ultrasound analysis. *J Am Coll Cardiol*. 2005;46:1002–1005.
20. Degertekin M, Serruys PW, Tanabe K, Lee CH, Sousa JE, Colombo A, Morice MC, Ligthart JM, de Feyter PJ. Long-term follow-up of incomplete stent apposition in patients who received sirolimus-eluting stent for de novo coronary lesions: an intravascular ultrasound analysis. *Circulation*. 2003;108:2747–2750.
21. Hong MK, Mintz GS, Lee CW, Park DW, Park KM, Lee BK, Kim YH, Song JM, Han KH, Kang DH, Cheong SS, Song JK, Kim JJ, Park SW, Park SJ. Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. *Circulation*. 2006;113:414–419.
22. Tanabe K, Serruys PW, Degertekin M, Grube E, Guagliumi G, Urbaszek W, Bonnier J, Lablanche JM, Siminiak T, Nordrehaug J, Figulla H, Drzewiecki J, Banning A, Hauptmann K, Dudek D, Bruining N, Hamers R, Hoye A, Ligthart JM, Disco C, Koglin J, Russell ME, Colombo A. TAXUS II Study Group. Incomplete stent apposition after implantation of paclitaxel-eluting stents or bare metal stents. Insights from the randomized TAXUS II Trial. *Circulation*. 2005;111:900–905.
23. Feres F, Costa JR Jr, Abizaid A. Very late thrombosis after drug eluting stents. *Catheter Cardiovasc Interv*. 2006;68:83–88.
24. Cook S, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, Vogel R, Hess O, Meier B, Windecker S. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation*. 2007;115:2426–2434.

## CLINICAL PERSPECTIVE

As a substudy of the ZEST trial (Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent with Sirolimus-Eluting and PacliTaxel-Eluting Stent for Coronary Lesions) that compared first- and second-generation drug-eluting stents, we evaluated intimal hyperplasia (IH) and certain vascular changes using intravascular ultrasound (IVUS) at poststenting and at 9-month follow-up in 183 stented lesions: 61 sirolimus-eluting stents (SES), 64 paclitaxel-eluting stents (PES), and 58 zotarolimus-eluting stents (ZES). Reduction of minimal luminal area was greater in PES than SES ($-1.4\pm1.5$ mm$^2$ versus $-0.7\pm0.9$ mm$^2$, $P=0.003$), whereas minimal luminal area change in ZES was not significantly different from SES ($-1.2\pm1.0$ mm$^2$ versus $-0.7\pm0.9$ mm$^2$, $P=0.055$). Percent IH volume was less in SES compared with PES ($9.8\pm6.0\%$ versus $17.5\pm11.2\%$, $P=0.002$) and with ZES ($9.8\pm6.0\%$ versus $18.2\pm7.6\%$, $P=0.005$). Comparing ZES versus PES, there were no significant differences in %IH volume ($17.5\pm11.2\%$ versus $18.2\pm7.6\%$, $P=0.779$). Late stent malapposition was identified in 8 (13%) SES and 2 (3%) PES but in no ZES ($P=0.050$). Although ZES is less effective in inhibiting intimal hyperplasia than SES, ZES showed efficacy comparable to PES. Further study with long-term follow-up will be required to determine the impact of differences in late stent malapposition.