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Intravascular Ultrasound Results From the ENDEAVOR IV Trial

Randomized Comparison Between Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease

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Objectives The aim of this study was to compare the vessel response between zotarolimus-eluting stents (ZES) and paclitaxel-eluting stents (PES) using intravascular ultrasound.

Background The ENDEAVOR IV (Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease) trial was a randomized controlled study of zotarolimus-eluting, phosphorylcholine-coated, cobalt-alloy stents for the treatment of *de novo* coronary lesions compared with using PES for the same treatment.

Methods Data were obtained from patients with serial (baseline and 8-months follow-up) intravascular ultrasound analysis available (n = 198). Volumetric analysis was performed for vessel, lumen, plaque, stent, and neointima. Cross-sectional narrowing (given as percentage) was defined as neointimal area divided by stent area. Neointima-free frame ratio was calculated as the number of frames without intravascular ultrasound-detectable neointima divided by the total number of frames within the stent. Subsegment analysis was performed at every matched 1-mm subsegment throughout the stent.

Results At follow-up, the ZES group showed significantly greater percentage of neointimal obstruction (16.6 ± 12.0% vs. 9.9 ± 8.9%, $p < 0.01$) and maximum cross-sectional narrowing (31.8 ± 16.1% vs. 25.2 ± 14.9%, $p < 0.01$) with smaller minimum lumen area than the PES group did. However, the incidence of maximum cross-sectional narrowing >50% was similar in the 2 groups. Neointima-free frame ratio was significantly lower in the ZES group. In overall analysis, whereas the PES group showed positive remodeling during follow-up (13.7 ± 4.2 mm^3/mm to 14.3 ± 4.3 mm^3/mm), the ZES group showed no significant difference (12.7 ± 3.6 mm^3/mm to 12.9 ± 3.5 mm^3/mm). In subsegment analysis, significant focal positive vessel remodeling was observed in 5% of ZES and 25% of PES cases ($p < 0.05$).

Conclusions There were different global and focal vessel responses for ZES and PES. Both drug-eluting stents showed a similar incidence of lesions with severe narrowing despite ZES having a moderate increase in neointimal hyperplasia compared with neointimal hyperplasia in PES. There was a relatively lower neointima-free frame ratio in ZES, suggesting a greater extent of neointimal coverage. (The ENDEAVOR IV Clinical Trial: A Trial of a Coronary Stent System in Coronary Artery Lesions; NCT00217269) (J Am Coll Cardiol Intv 2009;2:779–84) © 2009 by the American College of Cardiology Foundation

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Recently approved by the U.S. Food and Drug Administration, the Endeavor zotarolimus-eluting stent (ZES) (Medtronic CardioVascular Inc., Santa Rosa, California) is a drug-eluting stent (DES) that uses the Driver cobalt-based alloy platform to deliver 10 μg/mm zotarolimus (Abbott Pharmaceuticals, Abbott Park, Illinois) via the phosphorylcholine polymer (1). The ENDEAVOR IV (Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease) trial was a multicenter study assessing the equivalence of efficacy and safety between ZES and paclitaxel-eluting stent (PES) for the treatment of *de novo* coronary artery lesions. The purpose of this intravascular ultrasound (IVUS) subanalysis was to fully describe the vascular responses following ZES implantation compared with those following PES using serial IVUS analysis.

Methods

Abbreviations and Acronyms

CSN = cross-sectional narrowing
DES = drug-eluting stent(s)
ISA = incomplete stent apposition
IVUS = intravascular ultrasound
PES = paclitaxel-eluting stent(s)
VI = volume index
ZES = zotarolimus-eluting stent(s)

Patients. Data were derived from the ENDEAVOR IV trial, a multicenter, single-blind, randomized 2-arm, control study comparing the efficacy and safety between ZES and PES for the treatment of *de novo* coronary artery lesions. Patients were stratified by center and diabetic status and randomized to either ZES or PES in a 1:1 manner. The study protocol was approved by the institutional review board at each participating site, and consecutive, eligible patients signed written informed consent prior to the interventional procedure.

IVUS procedure and analysis. The IVUS interrogation was planned for all patients at pre-specified enrollment sites following the procedure and at 8 months after stent implantation. The IVUS procedure was performed in a standard fashion using automated motorized pullback (0.5 mm/s) with commercially available imaging systems (40-MHz IVUS catheter [Boston Scientific Corp., Natick, Massachusetts] or 20-MHz IVUS catheter [Volcano Corp., Rancho Cordova, California]). The IVUS analysis was performed at an independent core laboratory at Stanford University (Cardiovascular Core Analysis Laboratory, Stanford, California) by clinicians blinded to the treatment arm.

Volumetric measurements were performed using echoPlaque software (Indec Systems Inc., Santa Clara, California) as previously described (2). Neointimal volume was calculated as stent volume minus lumen volume, and percentage of neointimal obstruction was defined as neointimal volume divided by stent volume. Each volume was divided by measurement stent length to adjust for different stent length (volume index [VI]). Cross-sectional narrowing ([CSN] given as a percentage) was defined as neointima area divided by stent area and the cases with maximum CSN >50% were considered as having severe narrowing (3). Neointima-free frame ratio (given as a percentage) was calculated as the number of frames without IVUS-detectable neointima divided by the total number of frames within the stent. Peristent plaque volume was calculated as vessel volume minus stent volume. Focal vessel area changes were analyzed at every matched 1-mm subsegment throughout the stent. Significant focal positive remodeling was defined as >20% vessel area increase during follow-up in at least 3 consecutive subsegments.

Tissue prolapse, stent edge dissection, and incomplete stent apposition (ISA) were assessed by qualitative IVUS analysis. We identified ISA as 1 or more struts clearly separated from the vessel wall with evidence of blood speckles behind the strut. Then, ISA was classified as "persistent," "resolved," or "late acquired" (4). All images were reviewed by 2 independent observers and adjudication of opinion was based on the consensus of these observers.

Statistical analysis. Statistical analysis was performed using Statview 5.0 (SAS Institute, Cary, North Carolina). Continuous variables are expressed as mean ± SD or median (interquartile range). For continuous variables with normal distributions, comparisons between ZES and PES were performed with a 2-tailed, unpaired *t* test, and comparisons between baseline and follow-up were done by 2-tailed, paired *t* test. The Mann-Whitney *U* statistic test was used when normality tests of these variables failed. Categorical variables were compared using chi-square test. Correlations between vessel volume change and neointimal volume were analyzed using the Spearman correlation analysis. A p value <0.05 was considered statistically significant.

Results

Study population and patient characteristics. Data were derived from the ENDEAVOR IV clinical trial in which serial (baseline and 8-months follow-up) IVUS analysis was possible in 198 cases (ZES: 100, PES: 98). After excluding cases with inconsistent pullback, follow-up volumetric analysis was available in 165 cases (ZES: 79, PES: 86), and serial volumetric analysis was available in 105 cases (ZES: 53, PES: 52). Patient and lesion characteristics are summarized in Table 1. There was no significant difference between the entire ENDEAVOR IV trial group and the IVUS subgroup, except for lesion location. Patient and lesion characteristics among the IVUS subgroup were similar between the ZES and PES groups.

Quantitative IVUS analysis. The ZES group demonstrated a significantly greater magnitude of percentage of neointimal obstruction than the PES group did (16.6 ± 12.0% vs. 9.9 ± 8.9%, $p < 0.01$) (Table 2, Fig. 1). Maximum CSN was

Table 1. Baseline Patient and Lesion Characteristics

	ZES (n = 100)	PES (n = 98)	p Value
Age, yrs	62.2 ± 11.7	62.8 ± 11.2	NS
Male sex, %	65.0	62.2	NS
Hypertension, %	82.0	74.5	NS
Hyperlipidemia, %	84.0	74.5	NS
Diabetes mellitus, %	32.0	30.6	NS
History of smoking, %	59.2	57.1	NS
Unstable angina, %	53.6	62.3	NS
Target vessel, %, LAD/LCX/RCA	53/21/26	51/20/29	NS
Lesion type (>B2/C), %	72.0	65.3	NS
Reference vessel diameter by QCA, mm	2.7 ± 0.5	2.7 ± 0.4	NS
Lesion length by QCA, mm	14.2 ± 5.9	14.1 ± 7.0	NS

LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; NS = not significant; PES = paclitaxel-eluting stent(s); QCA = quantitative coronary angiography; RCA = right coronary artery; ZES = zotarolimus-eluting stent(s).

significantly higher in the ZES group (31.8 ± 16.1% vs. 25.2 ± 14.9%, $p < 0.01$); however, the incidence of stents with severe narrowing (maximum CSN more than 50%) was similar between the 2 groups (ZES: 16.5%, PES: 10.5%, p = NS). The ZES group showed significantly lower neointima-free frame ratio than the PES group did (11.8 ± 17.4% vs. 30.9 ± 28.2%, $p < 0.01$).

Serial IVUS measurements at in-stent segments are summarized in Table 3. In the overall analyses, baseline IVUS measurements within the stent were not significantly different between the ZES and PES groups except for minimum lumen area. Although there was a significant increase in vessel volume of the PES group with significant increase in peristent plaque, there was no significant difference in the ZES group. Delta vessel VI was significantly lower in the ZES group than in the PES group (delta vessel VI: 0.3 ± 1.0 mm^3/mm vs. 0.8 ± 1.0 mm^3/mm, $p < 0.05$; delta peristent plaque VI: 0.2 ± 0.8 mm^3/mm vs. 0.7 ± 0.8 mm^3/mm, $p < 0.05$). In subsegment analyses, delta vessel area changes were significantly lower in the ZES group than in the PES group (1.6 ± 0.8 mm^2 vs. 2.2 ± 1.4 mm^2, $p < 0.05$) at maximum remodeling site, although there was a significant increase in vessel area during the follow-up period in both stent groups. Per patient analysis, the incidence of significant focal positive vessel remodeling (>20% vessel area increase) was significantly lower in the ZES group than in the PES group (5% vs. 25%, $p < 0.05$). Change in peristent dimensions did not correlate with neointimal volume in either stent type (ZES: r = 0.03, p = 0.85; PES: r = 0.004, p = 0.98).

Regarding reference segments, baseline IVUS measurements were not significantly different between the ZES and PES groups. In proximal reference segments, there was a significant decrease in lumen volume of PES with negative remodeling during the follow-up period. Regarding distal reference segments, ZES lumen volume showed a significant decrease with an increase in plaque volume. Delta volume changes (VI at follow-up minus VI at baseline) were not significantly different between the 2 stent groups (Table 4).

Qualitative IVUS analysis. Table 5 summarizes the results of the qualitative analysis. The incidence of tissue prolapse was significantly higher in the PES group than in the ZES group. Late ISA was observed in both the ZES (1 case) and PES (3 cases) groups; however, there was no significant difference between the 2 stent groups.

Discussion

The main findings of this IVUS analysis are as follows: 1) patients treated with ZES had a greater amount of neointima than did those treated with PES; 2) the ZES group showed lower neointima-free frame ratio than did the PES group; 3) the ZES group had no significant change in

Table 2. Neointimal Characteristics

	ZES (n = 79)	PES (n = 86)	p Value
Neointima obstruction, %	16.6 ± 12.0	9.9 ± 8.9	<0.01
Median (IQR)	13.8 (7.0–22.8)	7.7 (2.7–13.0)	
Maximum CSN, %	31.8 ± 16.1	25.2 ± 14.9	<0.01
Stent with maximum CSN >50%, n (%)	13 (16.5%)	9 (10.5%)	NS
Neointima-free frame ratio, %	11.8 ± 17.4	30.9 ± 28.2	<0.01

CSN = cross-sectional narrowing; IQR = interquartile ranges; other abbreviations as in Table 1.

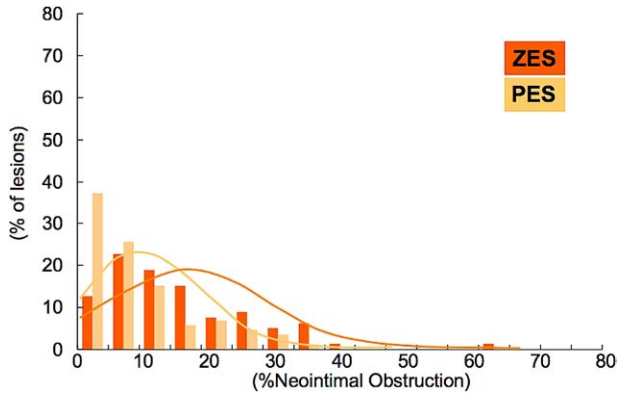

Figure 1. Statistical Distribution of Percentage of Neointimal Obstruction for ZES and PES

The distribution of percentage of neointimal obstruction of zotarolimus-eluting stent (ZES) was shifted to the right and average percentage of neointimal obstruction was significantly higher when compared with obstruction of paclitaxel-eluting stent (PES) ($p < 0.01$).

peristent vessel structure, whereas the PES group showed positive vessel remodeling during follow-up in the overall analysis; 4) the ZES group, when compared with the PES group, showed a low incidence of focal vessel remodeling; and 5) incidence of late ISA was not significantly different between the 2 stent groups.

Neointimal hyperplasia formation. The percentage of neointimal obstruction may represent the overall magnitude of neointimal suppression of a DES (5). Previous reports have demonstrated that the percentage of neointimal obstruction was 29% to 33% in bare-metal stents (6,7), 8% to 13% in polymer-based PES (8,9), and 16% to 17% in ZES (5,7). The percentage of neointimal obstruction from our analysis, 9.9% in PES and 16.6% in ZES, was consistent with that of previously published data describing the same stent technology.

In addition to the overall suppression of neointimal volume, focal accumulation of neointima is another important factor that should be incorporated into the analysis. The IVUS parameters describing focal neointimal characteristics, such as stents with severe narrowing, and late area loss may be important as well as overall neointimal volume. We have previously reported that patients treated with ZES showed more evenly distributed neointimal formation than those treated with sirolimus-eluting stents did (5). In this IVUS analysis, the ZES group showed significantly greater neointimal hyperplasia than the PES group did. However, stents with severe narrowing and late area loss, both of which are relevant to focal neointimal characteristics, were not statistically different between the 2 groups. These results suggest a greater extent of neointimal coverage is present throughout the ZES group than in the PES group. Therefore, the relatively greater neointimal coverage seen in the ZES group may have contributed to minimizing adverse clinical outcomes, despite the greater amount of neointimal hyperplasia seen in the ZES group.

Neointimal coverage. Neointimal coverage over stent struts has been reported using IVUS data. An IVUS analysis from the TAXUS trial showed that 48.8% of total stent length was neointima-free in the PES arm and 13.4% of stent length was neointima-free in the bare-metal stent arm (10). In this IVUS subanalysis, the neointima-free frame ratio was 11.8% and 30.9% for ZES and PES, respectively. In this study, the neointimal-free frame ratio of the ZES group was similar to that of the bare-metal stent arm in TAXUS IV and confirming a significantly higher value for the PES

Table 3. In-Stent Segment Quantitative IVUS Analysis

	ZES (n = 53)			PES (n = 52)		
Entire Stent Segment Analysis	**Baseline**	**Follow-Up**	**p Value**	**Baseline**	**Follow-Up**	**p Value**
Vessel VI	12.7 ± 3.6	12.9 ± 3.5	NS	13.6 ± 4.1	14.3 ± 4.3	<0.01
Delta vessel VI		0.3 ± 1.0			0.8 ± 1.0*	
Lumen VI	6.6 ± 1.8	5.6 ± 1.7	<0.01	7.2 ± 2.0	6.6 ± 2.0*	<0.01
Delta lumen VI		−0.9 ± 0.9			−0.6 ± 0.9	
Peristent plaque VI	6.1 ± 2.3	6.2 ± 2.1	NS	6.4 ± 2.6	7.1 ± 2.7	<0.01
Delta peristent plaque VI		0.2 ± 0.8			0.7 ± 0.8*	
Minimum lumen area, mm^2	5.5 ± 1.5†	4.4 ± 1.6	<0.01	6.2 ± 1.9	5.3 ± 1.9*	<0.01
Late area loss, mm^2		1.1 ± 1.0			0.9 ± 1.1	
Subsegment Analysis						**p Value‡**
Focal vessel remodeling, %		5.0			25.0	<0.05
% vessel VI change at maximum remodeling site		13.7 ± 6.8			18.2 ± 9.2	<0.05
% plaque VI change at maximum remodeling site		28.3 ± 20.3			47.2 ± 29.8	<0.01

*$p < 0.05$ for ZES follow-up vs. PES follow-up, †$p < 0.05$ for ZES baseline vs. PES baseline, ‡p value for ZES vs. PES.
IVUS = intravascular ultrasound; VI = volume index (mm^3/mm); other abbreviations as in Table 1.

Table 4. Reference Segment Quantitative IVUS Analysis

	ZES			PES		
	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value
Proximal						
Vessel VI	13.5 ± 4.0	13.4 ± 4.1	NS	14.4 ± 4.5	14.1 ± 4.3	<0.05
Delta vessel VI		−0.1 ± 1.4			−0.3 ± 1.0	
Lumen VI	7.5 ± 2.8	7.1 ± 2.7	<0.05	7.7 ± 2.6	7.2 ± 2.7	<0.05
Delta lumen VI		−0.4 ± 1.0			−0.5 ± 1.2	
Plaque VI	6.3 ± 2.4	6.5 ± 2.4	NS	6.5 ± 2.9	6.7 ± 2.4	NS
Delta plaque VI		0.2 ± 1.0			0.2 ± 1.5	
Distal						
Vessel VI	10.0 ± 3.5	9.8 ± 3.4	NS	11.0 ± 4.2	10.9 ± 4.2	NS
Delta vessel VI		−0.2 ± 1.2			0.0 ± 1.4	
Lumen VI	6.1 ± 2.0	5.7 ± 1.8	<0.01	6.6 ± 2.4	6.2 ± 2.3	NS
Delta lumen VI		−0.5 ± 1.1			−0.3 ± 1.5	
Plaque VI	3.8 ± 2.0	4.0 ± 2.1	<0.05	4.2 ± 2.7	4.7 ± 2.8	<0.05
Delta plaque VI		0.2 ± 0.6			0.4 ± 1.1	

p = NS for ZES baseline vs. PES baseline.
Abbreviations as in Tables 1 and 3.

group. Previous studies have shown that impaired or delayed neointimal coverage may be associated with stent thrombosis (11,12). Although direct assessment of endothelialization by IVUS is difficult due to limited IVUS resolution, neointimal coverage based on IVUS may serve as a surrogate for assessment of the degree of endothelialization.

It is still an open question whether there is an association between neointima-free frame ratio and clinical outcomes. It could theoretically minimize the risk of stent thrombosis if DES allowed an adequate amount of endothelialization or neointimal coverage without significantly compromising the lumen (13). Strut coverage throughout the stent may be protective and possibly lessen obligatory dependence on strict long-term antiplatelet therapy. The ideal neointimal coverage for efficacy and safety, however, is yet to be determined.

Table 5. Qualitative IVUS Analysis

	ZES (n = 100)	PES (n = 98)	p Value
Tissue prolapse, n	10	25	<0.01
Stent edge dissection, n			
Proximal edge/distal edge	0/0	1/0	NS
ISA			
ISA at baseline, n	12	14	NS
Resolved ISA	8	7	NS
Persistent ISA	4	7	NS
Late ISA, n	1	3	NS

ISA = incomplete stent apposition; other abbreviations as in Table 1.

Vessel remodeling. Previous trials evaluating PES (8,14) showed significantly increased vessel and plaque volume during the follow-up period, whereas those evaluating ZES (5,7) did not show significant changes in vessel volume in the stented segment. Our IVUS analysis supports these previous results regarding the peristent vascular response. In addition to the global vessel volume change, we performed detailed IVUS analysis on focal vessel remodeling. Even though the ZES group showed no significant change in vessel and plaque volume for the entire stented segment, subsegment analysis demonstrated that focal vessel remodeling (patient with >20% vessel area increase) was observed in 5% of ZES cases. Compared with the PES group, however, the magnitude and incidence of focal vessel remodeling were significantly lower in the ZES group.

A previous pathologic report examined the vessel response to different DES. In a rabbit experimental model, the extent of inflammation and fibrin deposit was significantly higher with PES than with ZES. In addition, bare-metal stents did not show any inflammation and fibrin deposit after stent implantation (15). Although the mechanism underlying positive vessel remodeling after DES is poorly understood, inflammation is thought to be involved in this process (16,17). The impact of vessel remodeling on clinical outcome is still unclear, however, careful follow-up may be required to elucidate the consequence of these IVUS findings.

Late ISA. The occurrence of late ISA have been reported in 3% to 13% of sirolimus-eluting stents (4,18,19), 2% to 16% of PES (18,20,21), and 0% to 1% of ZES (5,7). In this IVUS analysis, late ISA was observed in 1 ZES case, which was only the second case of late ISA throughout the entire

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ENDEAVOR trial series (ENDEAVOR I, II, III, IV, and II Continued Access). The incidence of late ISA in this study showed no significant difference between the 2 stents.

Study limitations. First, this analysis is based on a cohort of patients who completed serial IVUS examinations, and the limited sample size may pose a risk for selection bias. Second, follow-up IVUS analysis was limited to a mid-term period of 8 months. Further studies with longer-term follow-up may be necessary to more adequately assess efficacy and safety. Third, due to limited IVUS resolution (>80 μm axially and 200 μm laterally), the degree of endothelialization on stent surface(s) may not be fully visualized. Fourth, clinical implications of new IVUS parameters, such as neointima-free frame ratio and focal vessel response, are still an open question. Further investigations may be required to clarify the significance of these IVUS results.

Conclusions

The IVUS analysis from the ENDEAVOR IV trial demonstrated that the ZES and PES groups had different global and focal peristent and in-stent vessel responses. Both DES groups showed a similar incidence of lesions with severe narrowing, despite the ZES group having a moderate increase in neointimal hyperplasia as compared with neointimal hyperplasia in the PES group. There was a relatively lower neointima-free frame ratio in the ZES group, suggesting a greater extent of neointimal coverage.

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Key Words: ultrasound ■ zotarolimus-eluting stent ■ coronary artery disease.