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A Randomized Comparison of the Endeavor Zotarolimus-Eluting Stent Versus the TAXUS Paclitaxel-Eluting Stent in De Novo Native Coronary Lesions

12-Month Outcomes From the ENDEAVOR IV Trial

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Objectives The ENDEAVOR IV (Randomized Comparison of Zotarolimus-Eluting and Paclitaxel-Eluting Stents in Patients with Coronary Artery Disease) trial evaluated the safety and efficacy of the zotarolimus-eluting stent (ZES) compared with the paclitaxel-eluting stent (PES).

Background First-generation drug-eluting stents have reduced angiographic and clinical restenosis, but long-term safety remains controversial. A second-generation drug-eluting stent, which delivers zotarolimus, a potent antiproliferative agent, via a biocompatible phosphorylcholine polymer on a cobalt alloy thin-strut stent has shown promising experimental and early clinical results.

Methods This is a prospective, randomized (1:1), single-blind, controlled trial comparing outcomes of patients with single de novo coronary lesions treated with ZES or PES. The primary end point was noninferiority of 9-month target vessel failure defined as cardiac death, myocardial infarction, or target vessel revascularization.

Results Among a total of 1,548 patients assigned to ZES (n = 773) or PES (n = 775), at 9 months, ZES was noninferior to PES with rates of target vessel failure 6.6% versus 7.1%, respectively ($p_{noninferiority} \leq 0.001$). There were fewer periprocedural myocardial infarctions with ZES (0.5% vs. 2.2%; p = 0.007), whereas at 12 months, there were no significant differences between groups in rates of cardiac death, myocardial infarction, target vessel revascularization, or stent thrombosis. Although incidence of 8-month binary angiographic in-segment restenosis was higher in patients treated with ZES versus PES (15.3% vs. 10.4%; p = 0.284), rates of 12-month target lesion revascularization were similar (4.5% vs. 3.2%; p = 0.228), especially in patients without planned angiographic follow-up (3.6% vs. 3.2%; p = 0.756).

Conclusions These findings demonstrate that ZES has similar clinical safety and efficacy compared with PES in simple and medium complexity single de novo coronary lesions. (ENDEAVOR IV Clinical Trial; NCT00217269) (J Am Coll Cardiol 2010;55:543–54) © 2010 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ARC = Academic Research Consortium
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
DS = diameter stenosis
IVUS = intravascular ultrasound
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization
TVF = target vessel failure
TVR = target vessel revascularization
ZES = zotarolimus-eluting stent(s)

Since the introduction of drug-eluting stents (DES) in the U.S. more than 5 years ago, angiographic restenosis and repeat revascularization procedures after percutaneous coronary interventions have been significantly reduced for both simple ("on-label") and complex ("off-label") lesions (1–5). Safety concerns, however, have been raised for both sirolimus-eluting stents (SES) (Cordis Corporation, Warren, New Jersey) and paclitaxel-eluting stents (PES) (Boston Scientific, Natick, Massachusetts), focusing on a small increase in stent thrombosis occurring longer than 1 year after the index procedure (6–8). Consequently, treatment practices have shifted, resulting in a more selective use of DES, extended dual antiplatelet therapy (DAPT) regimens (to 1 year or longer), and concerns about premature cessation of DAPT due to either patient noncompliance or intervening medical problems (9,10).

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The design features of an "optimally safe" DES remain elusive, although most observers agree that impaired early and late healing responses, perhaps associated with certain biostable polymers, may be partially causative (11,12). The zotarolimus-eluting stent (ZES) (Medtronic CardioVascular, Santa Rosa, California) combines a more rapid elution profile of the antiproliferative drug zotarolimus with a thinner, more biocompatible phosphorylcholine polymer placed on a cobalt alloy thin-strut stent. ZES have been clinically tested in a first-human-use study with extended follow-up (13,14), a double-blind randomized trial versus bare-metal stents (15), and a small randomized trial versus SES (16). These studies have indicated that ZES, when compared with bare-metal stents (15), had an advantageous safety profile and reduced target lesion revascularization (TLR) despite a somewhat higher angiographic late loss than observed with SES and PES (1–3,16). The purpose of the current trial was to compare ZES with commonly used PES in a large randomized trial, emphasizing clinical end points, to limit the impact of systematic angiographic follow-up on repeat revascularization decisions.

Methods

Study design and patient population. The ENDEAVOR IV (Randomized Comparison of Zotarolimus-Eluting and Paclitaxel-Eluting Stents in Patients with Coronary Artery Disease) trial was a prospective, multicenter, single-blinded, randomized, controlled clinical trial that compared clinical and angiographic outcomes between patients treated with ZES and patients treated with PES. Consecutive adult patients with clinical evidence of ischemic coronary disease or a positive functional study were enrolled at 80 centers in the U.S.

Key clinical exclusion criteria included recent acute myocardial infarction (MI), another planned percutaneous coronary intervention within the next 30 days or previous percutaneous coronary intervention in the target vessel within the previous 9 months, recent stroke or transient ischemic attack, left ventricular ejection fraction less than 30%, and contraindication to DAPT (aspirin and a thienopyridine).

Angiographic requirements were the presence of a single de novo native coronary lesion with a diameter stenosis (DS) of at least 50% but <100% by visual estimate, reference vessel diameter ≥2.5 and ≤3.5 mm, and lesion length ≤27 mm. A target vessel with evidence of thrombus or excessive tortuosity or a target lesion that was in a left main or an ostial location, or with severe calcification, or at a bifurcation involving a side branch >2.0 mm in diameter were excluded.

The institutional review board at each site approved the protocol, and each eligible patient provided written, informed consent before the index procedure.

Study device. The Endeavor ZES (Medtronic) consists of a cobalt-based alloy stent with a phosphorylcholine coating that releases the drug zotarolimus. The synthetic phosphorylcholine drug carrier is composed of an outer phospholipid portion that mimics the outer membrane of red blood cells to provide biocompatibility and an inner

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hydrophobic region to confer stability and adhesion to the stent surface (17). A confluent coating of phosphorylcholine on bare-metal stents reduces thrombogenicity in in vitro models (18). Zotarolimus (ABT-578) is a tetrazole ring containing macrocyclic lactone analogue of sirolimus and is the first cytostatic agent developed exclusively for delivery from a DES to prevent restenosis (19). The phosphorylcholine coating thickness is approximately 4 μm and the concentration of zotarolimus is 10 μg/mm stent length. The ZES formulation results in rapid drug elution from the stent surface (~80% in 1 week and ~95% in 2 weeks). In animal studies, ZES were associated with less platelet adhesion, improved early healing responses compared with other first-generation DES, and reduced neointimal area (20,21).

The TAXUS Express PES (Boston Scientific) consists of a 316L surgical grade stainless steel Express stent, a Translute (Boston Scientific) polymer carrier, and paclitaxel loaded in a concentration of 1 μg/mm^2 in a slow release formulation.

Randomization, implantation procedure, adjunct pharmacology, and follow-up. Patients were stratified by diabetic status and clinical site and were randomized (using an Interactive Voice Response System) in a 1:1 manner to receive either ZES or PES. Diabetes was defined as treatment for diabetes mellitus with insulin, oral antidiabetic agents, or a modified diet.

Target lesions were pre-treated using standard balloon angioplasty, followed by stent implantation and post-dilation (as needed) to achieve a final lumen DS of <10%. Patients were treated with 75 mg of aspirin within 24 h before the procedure, which was continued indefinitely. All patients received a loading dose of clopidogrel of at least 300 mg followed by 75 mg/day for at least 6 months. Continuation of clopidogrel beyond 6 months was at the operator's discretion. During the procedure, bivalirudin or unfractionated heparin (to maintain an activated clotting time >250 s) was administered. Platelet glycoprotein IIb/IIIa receptor inhibitors were used at the discretion of the operator.

Following the interventional procedure, patients were assessed at 30 days; 6, 9, and 12 months; and yearly thereafter up to 5 years after the procedure. Patients in the angiographic and intravascular ultrasound (IVUS) subgroups were evaluated at 8 months after the procedure.

Data management and analysis. An independent data management organization (Harvard Clinical Research Institute, Boston, Massachusetts) collected and managed all data analyses. All authors had full access to the database and analysis upon which this manuscript is

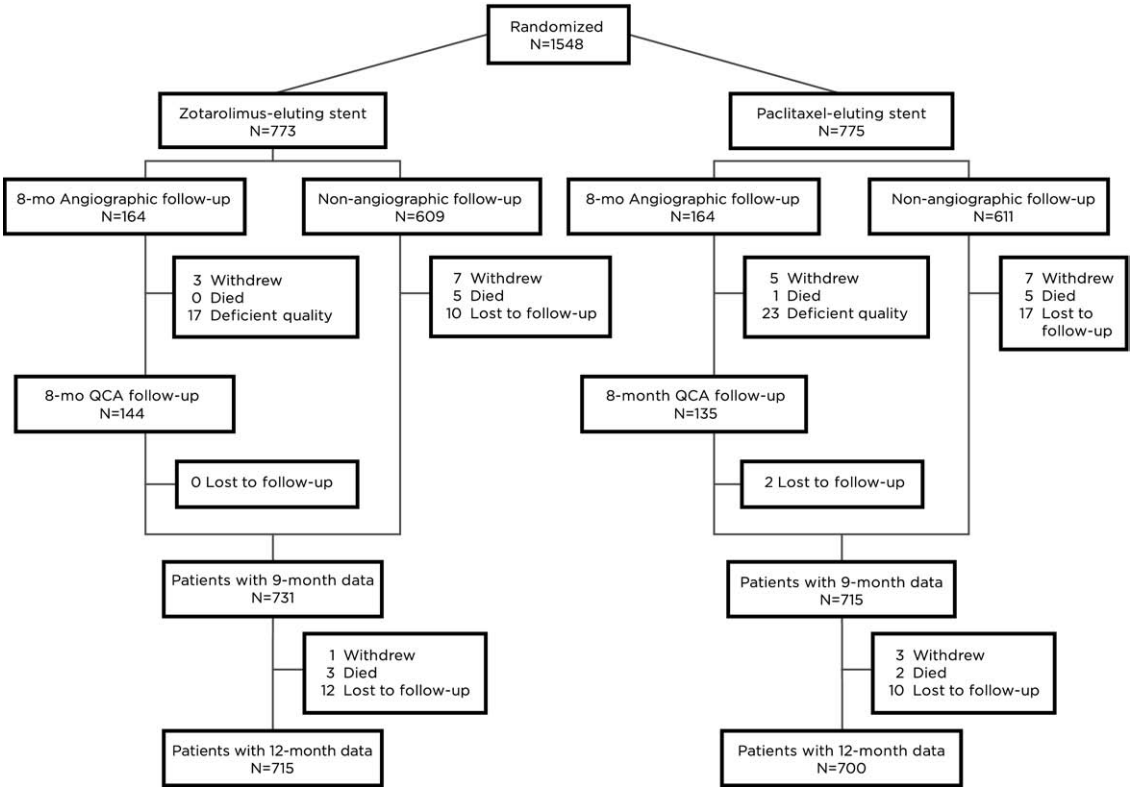

Figure 1 Patient Disposition and Follow-Up

Randomization, angiographic follow-up, and clinical follow-up. mo = month; QCA = quantitative coronary angiography.

based. An independent clinical events committee, blinded to the study stent identity, adjudicated all primary and secondary end point events. An independent data safety monitoring board, composed of 4 independent physicians and 1 biostatistician blinded to study treatment, was responsible for regular review of the clinical safety data and could recommend study discontinuation or modification.

End points and definitions. The primary clinical end point was target vessel failure (TVF), defined as the composite of cardiac death, MI, or clinically driven target vessel revascularization (TVR) at 9 months after the procedure. Secondary clinical end points were acute device, lesion, and procedure success and major adverse cardiac event, defined as death, MI, or clinically driven TLR. Secondary angiographic end points were in-segment and in-stent late lumen loss and binary restenosis. The IVUS end points at follow-up were neointima hyperplasia volume, percent volume obstruction, stent strut apposition to the vessel wall, and positive vessel remodeling.

Stent thrombosis as defined by the clinical protocol required 1 of the following: 1) coronary symptoms and target vessel angiographic confirmation of thrombus or occlusion; 2) pathologic confirmation of acute thrombosis in the target vessel; 3) unexplained death within 30 days; or 4) target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesions within 30 days. Patients with intervening TLR events were excluded and protocol-defined stent thrombosis was assessed within 24 h (acute), at 1 to 30 days (subacute), and after 30 days following stent placement (late). Stent thrombosis (both early and late) was also adjudicated by a subcommittee of the clinical events committee blinded to study stent identity and according to the definitions proposed by the Academic Research Consortium (ARC) (22).

Angiography and IVUS core laboratories. Coronary angiograms were obtained at baseline in all patients, and at 8 months after the procedure in the first 328 consecutive patients enrolled and assigned to routine angiographic follow-up and in any patient who received multiple stents. All angiograms were evaluated by reviewers blinded to the study stent, by an independent core laboratory (Brigham and Women's Angiographic Core Laboratory, Boston, Massachusetts).

All patients in the angiographic subgroup underwent IVUS imaging at 8 months, which was evaluated by reviewers blinded to the study stent at an independent IVUS

Table 1 Baseline Clinical and Angiographic Characteristics of the Study Population

	ZES	PES	p Value
Patient demographics			
Age, yrs	63.5 ± 11.1 (773)	63.6 ± 11.0 (775)	0.930
Men	66.9% (517/773)	68.5% (531/775)	0.514
Diabetes	31.2% (241/773)	30.5% (236/775)	0.783
Hypertension	79.4% (614/773)	82.6% (640/775)	0.120
Hyperlipidemia	81.4% (629/773)	84.8% (657/775)	0.078
History of smoking	62.6% (479/765)	60.4% (462/765)	0.401
Prior myocardial infarction	21.1% (161/764)	23.2% (176/759)	0.324
Prior percutaneous coronary intervention	28.2% (218/773)	29.5% (229/775)	0.575
Prior coronary bypass surgery	9.8% (76/773)	8.4% (65/775)	0.332
Angina			0.367
Stable	45.6% (281/616)	47.9% (292/609)	
Unstable	51.6% (318/616)	49.9% (304/609)	
Myocardial infarction	2.8% (17/616)	2.1% (13/609)	
CCS class III or IV	50.3% (309/614)	47.9% (292/610)	0.392
Angiographic characteristics			
Target vessel			0.791
Left anterior descending	42.2% (326/772)	41.5% (321/774)	
Left circumflex	26.9% (208/772)	26.1% (202/774)	
Right coronary	30.8% (238/772)	32.4% (251/774)	
Type B2/C lesion	69.6% (537/772)	70.9% (549/774)	0.358
Number of diseased, native, major epicardial coronary vessels (>50% stenosed)			0.485
Single	54.9% (424/772)	57.2% (443/774)	
Double	28.6% (221/772)	26.1% (202/774)	
Triple	16.5% (127/772)	16.7% (129/774)	
Left ventricular ejection fraction, %	57.3 ± 9.9 (760)	57.5 ± 10.3 (753)	0.745
Reference vessel diameter, mm	2.73 ± 0.47 (772)	2.70 ± 0.46 (774)	0.197
Lesion length, mm	13.41 ± 5.67 (771)	13.80 ± 6.09 (773)	0.199
Minimal lumen diameter, mm	0.96 ± 0.40 (772)	0.93 ± 0.40 (774)	0.149
Diameter stenosis, %	64.83 ± 13.29 (772)	65.68 ± 13.10 (774)	0.204

Values are presented as % (n/total) or mean ± SD (n).
CCS = Canadian Cardiovascular Society angina class; PES = paclitaxel-eluting stent(s); ZES = zotarolimus-eluting stent(s).

core laboratory (Cardiovascular Core Analysis Laboratory, Stanford University, Palo Alto, California).

Statistical methods. This randomized study was designed to determine if the primary end point (TVF at 9 months) of ZES was noninferior to PES. The sample size estimation was based on a noninferiority test using the Farrington-Manning approach at alpha = 0.05 (1-sided) significance level with 84% statistical power to reject the null hypothesis of inferiority (23). Assuming an expected TVF rate for ZES and PES to be 7.6%, a noninferiority margin of 3.8% with at least 90% clinical follow-up and 1:1 randomization, a total sample size of 1,548 enrolled patients was required.

In-segment late lumen loss at 8 months comparing ZES and PES was a secondary powered noninferiority angiographic end point. The estimated sample size for the angiographic subset was based on a 2-sample *t* test at alpha = 0.05 (1-sided) significance level with 90% statistical power to reject the null hypothesis of inferiority. Assuming a true equivalence of the means between the 2 groups, a noninferiority margin of 0.2 mm, with a common SD of 0.55 mm, 80% angiographic follow-up rate, and 1:1 randomization, a total sample size of 328 patients was required for the angiographic substudy.

For other secondary clinical and angiographic outcomes, the 2-sample *t* test (2-sided) was used to compare continuous variables, and Fisher exact test was used to compare binary variables. Kaplan-Meier cumulative incidence estimates were used to analyze outcome events, which were compared between treatment groups using the log-rank test.

To identify the predictors of TLR and TVF at 12 months, a stepwise multivariable logistic regression analysis was performed for overall patients and for ZES and PES patient groups separately. The level of significance to enter and stay in the model was set at 0.05. Appropriate candidate variables were entered into the model, including assignment to angiographic follow-up and ZES versus PES for the overall patients.

To explore whether the treatment effects of TVF and TLR were consistent across important subgroups, logistic regression analysis was performed to test the interaction among the treatment assignment and the subsets.

All analyses were performed with SAS software (version 8.2 or higher, SAS Institute, Cary, North Carolina).

Results

Patient enrollment and baseline characteristics. Between April 11, 2005, and June 27, 2006, a total of 1,548 patients were enrolled at 80 clinical sites in the U.S. (ZES: n = 773, PES: n = 775) (Fig. 1). Clinical follow-up at 30 days was obtained in 770 ZES and 773 PES patients (99.6% and 99.7%, respectively). Clinical follow-up for ZES patients was 98.3% at 9 months and 97.5% at 12 months, and for PES patients was 97.5% at 9 months and 96.9% at 12 months. Angiographic follow-up at 8 months was obtained in 144 ZES patients (87.8% of eligible) and in 135 PES patients (82.3% of eligible).

Baseline clinical characteristics for ZES and PES cohorts were well-balanced (Table 1). For the overall study population, mean age was 63.5 years, 67.7% were male, and 30.8% were diabetic. Approximately one-half of the patients had stable angina, unstable angina, or Canadian Cardiovascular Society class III/IV angina.

Table 2 Procedural Characteristics and Angiographic Results

	ZES	PES	p Value
Procedural characteristics			
Number of stents	1.07 ± 0.32 (763)	1.12 ± 0.38 (762)	0.007
Stent length, mm	21.12 ± 7.94 (763)	21.30 ± 8.15 (761)	0.666
Maximum stent diameter, mm	3.04 ± 0.38 (763)	3.04 ± 0.38 (761)	0.804
Maximum inflation pressure, atm	13.28 ± 2.61 (762)	13.96 ± 2.79 (765)	<0.001
Glycoprotein IIb/IIIa inhibitors used	26.8% (207/773)	26.7% (207/775)	1.000
Procedural angiographic results			
Minimum lumen diameter, mm			
In-stent	2.62 ± 0.43 (763)	2.61 ± 0.44 (763)	0.703
In-segment	2.22 ± 0.47 (770)	2.19 ± 0.50 (772)	0.196
Diameter stenosis, %			
In-stent	5.50 ± 9.61 (763)	5.01 ± 10.49 (763)	0.348
In-segment	20.47 ± 9.54 (770)	20.97 ± 11.12 (772)	0.344
Acute gain, mm			
In-stent	1.66 ± 0.48 (763)	1.68 ± 0.47 (763)	0.425
In-segment	1.26 ± 0.50 (770)	1.26 ± 0.51 (772)	0.937
Device success	97.3% (751/772)	97.9% (757/773)	0.412
Lesion success	99.6% (767/770)	99.2% (766/772)	0.507
Procedure success	98.7% (760/770)	96.8% (747/772)	0.015

Values are presented as mean ± SD (n) or % (n/total).
Abbreviations as in Table 1.

Table 3 Angiographic Outcomes at 8 Months

	ZES	PES	p Value
No. of lesions	144	135	
Reference vessel diameter, mm	2.65 ± 0.47 (144)	2.68 ± 0.45 (135)	0.635
Minimum lumen diameter, mm			
In-stent	1.95 ± 0.61 (143)	2.25 ± 0.61 (135)	<0.001
In-segment	1.80 ± 0.55 (144)	1.98 ± 0.56 (135)	0.008
Diameter stenosis, %			
In-stent	26.41 ± 19.74 (143)	16.09 ± 17.99 (135)	<0.001
In-segment	32.28 ± 17.02 (144)	26.61 ± 15.52 (135)	0.004
Late loss, mm			
In-stent	0.67 ± 0.49 (142)	0.42 ± 0.50 (135)	<0.001
In-segment	0.36 ± 0.47 (143)	0.23 ± 0.45 (135)	0.023
Binary restenosis			
In-stent	13.3% (19/143)	6.7% (9/135)	0.075
In-segment	15.3% (22/144)	10.4% (14/135)	0.284

Values are presented as mean ± SD (n) or % (n/total).
Abbreviations as in Table 1.

Target vessel location was in the left anterior descending coronary in 41.8% of patients and 56.1% had single-vessel disease (Table 1). Mean reference vessel diameter for all patients was 2.72 mm, mean lesion length was 13.60 mm, and pre-procedure percent DS was 65.3%.

Procedural results and angiographic outcomes. Although stent length and stent diameter were similar between ZES and PES patients, the numbers of stents per lesion and maximum inflation pressures were lower in ZES patients (Table 2). Post-procedural minimal lumen diameter, percent DS, and acute gain were similar among ZES and PES treatment arms (Table 2). Procedure success was significantly higher for ZES when compared with PES (98.7% vs. 96.8%, p = 0.015).

In those patients assigned to angiographic follow up at 8 months, there were statistically significant differences in minimal lumen diameter, percent DS, and late lumen loss (both in-stent and in-segment) favoring PES (Table 3). The powered secondary end point, in-segment late lumen loss, was 0.36 mm for ZES and 0.23 mm for PES ($p_{noninferiority}$ = 0.089). Binary angiographic in-stent restenosis was 13.3% for ZES and 6.7% for PES (p = 0.075), and in-segment restenosis was 15.3% for ZES and 10.4% for PES (p = 0.284) (Table 3).

IVUS results. Quantitative IVUS imaging was performed at 8 months follow-up in 164 ZES patients and 164 PES patients. Neointimal volume was 24.14 mm^3 for ZES and 14.88 mm^3 for PES (p = 0.002) and percent volume obstruction was 15.72 for ZES and 9.88 for PES (p < 0.001). Incomplete stent strut apposition immediately after the procedure was similar in both groups and late acquired incomplete apposition was present in 1 ZES patient (0.9%) and 3 PES patients (3.2%; p = 0.346) (Table 4).

30-day clinical outcomes. At 30 days, there were fewer non–Q-wave MIs in patients receiving ZES versus patients receiving PES (0.5% vs. 2.2%, p = 0.007) (Table 5). Similarly, ZES patients had reduced rates of cardiac death or MI, TVF, and major adverse cardiac events (p = 0.042, p = 0.010, and p = 0.019, respectively). There were no significant differences between treatment arms for death, cardiac death, and stent thrombosis (protocol definition and ARC definition) (Table 5).

9- and 12-month clinical outcomes. The primary end point, TVF at 9 months, was similar when comparing ZES and PES patients (6.6% for ZES and 7.1% for PES, $p_{noninferiority}$ < 0.001) (Table 6, Fig. 2A). At 9 and 12 months, there were trends showing fewer non–Q-wave MIs with ZES compared with PES (p = 0.118 and p = 0.095, respectively) (Table 6). There were no significant differences at 9 or 12 months between treatment arms for death, cardiac death, any MI, and major adverse cardiac events (Table 6, Fig. 2B).

Table 4 IVUS Findings at 8 Months

	ZES (n = 164)	PES (n = 164)	p Value
Neointimal volume, mm^3	24.14 ± 19.38 (74)	14.88 ± 16.62 (77)	0.002
Volume obstruction, %	15.72 ± 10.40 (74)	9.88 ± 9.24 (77)	<0.001
Incomplete apposition			
Post-procedure	12.5% (17/136)	11.8% (15/127)	1.000
Persistent	8.5% (9/106)	10.5% (10/95)	0.638
Resolved	3.8% (4/106)	2.1% (2/95)	0.686
Late acquired	0.9% (1/106)	3.2% (3/95)	0.346

Values are presented as mean ± SD (n) or % (n/total).
IVUS = intravascular ultrasound; other abbreviations as in Table 1.

Table 5 Clinical Outcomes at 30 Days

	ZES	PES	p Value
Death (all)	0.3% (2/770)	0.0% (0/773)	0.249
Cardiac	0.1% (1/770)	0.0% (0/773)	0.499
Noncardiac	0.1% (1/770)	0.0% (0/773)	0.499
Myocardial infarction (all)	0.8% (6/770)	2.3% (18/773)	0.022
Q-wave	0.3% (2/770)	0.1% (1/773)	0.624
Non–Q-wave	0.5% (4/770)	2.2% (17/773)	0.007
Death or myocardial infarction	1.0% (8/770)	2.3% (18/773)	0.073
Cardiac death or myocardial infarction	0.9% (7/770)	2.3% (18/773)	0.042
Stent thrombosis			
Protocol definition			
Acute (≤1 day)	0.0% (0/770)	0.0% (0/773)	
Subacute (>1–≤30 days)	0.4% (3/770)	0.1% (1/773)	0.374
Acute and subacute	0.4% (3/770)	0.1% (1/773)	0.374
ARC definition (early)			
Definite	0.3% (2/770)	0.1% (1/773)	0.624
Probable	0.1% (1/770)	0.0% (0/773)	0.499
Definite and probable	0.4% (3/770)	0.1% (1/773)	0.374
Target lesion revascularization	0.4% (3/770)	0.8% (6/773)	0.507
Target vessel revascularization	0.4% (3/770)	0.9% (7/773)	0.342
Nontarget lesion, target vessel revascularization	0.0% (0/770)	0.3% (2/773)	0.500
Target vessel failure	1.0% (8/770)	3.0% (23/773)	0.010
Major adverse cardiac events	1.2% (9/770)	3.0% (23/773)	0.019

Values are presented as % (n/total).
ARC = Academic Research Consortium; other abbreviations as in Table 1.

Table 6 Clinical Outcomes at 9 and 12 Months

	9-Month Outcomes			12-Month Outcomes		
	ZES (n = 773)	PES (n = 775)	p Value	ZES (n = 773)	PES (n = 775)	p Value
Death (all)	0.7% (5/760)	0.8% (6/756)	0.773	1.1% (8/754)	1.1% (8/751)	1.000
Cardiac	0.4% (3/760)	0.3% (2/756)	1.000	0.5% (4/754)	0.5% (4/751)	1.000
Noncardiac	0.3% (2/760)	0.5% (4/756)	0.451	0.5% (4/754)	0.5% (4/751)	1.000
Myocardial infarction (all)	1.4% (11/760)	2.4% (18/756)	0.195	1.6% (12/754)	2.7% (20/751)	0.158
Q-wave	0.3% (2/760)	0.1% (1/756)	1.000	0.3% (2/754)	0.1% (1/751)	1.000
Non–Q-wave	1.2% (9/760)	2.2% (17/756)	0.118	1.3% (10/754)	2.5% (19/751)	0.095
Death or myocardial infarction	2.1% (16/760)	3.2% (24/756)	0.204	2.7% (20/754)	3.7% (28/751)	0.244
Cardiac death or myocardial infarction	1.8% (14/760)	2.6% (20/756)	0.304	2.1% (16/754)	3.2% (24/751)	0.204
Stent thrombosis						
Protocol definition						
Acute (≤1 day)	0.0% (0/760)	0.0% (0/756)	1.000	0.0% (0/754)	0.0% (0/751)	1.000
Subacute (>1–≤30 days)	0.4% (3/760)	0.1% (1/756)	0.625	0.4% (3/754)	0.1% (1/751)	0.625
Late (>30 days to ≤1 year)	0.4% (3/760)	0.0% (0/756)	0.250	0.4% (3/754)	0.0% (0/751)	0.250
Any	0.8% (6/760)	0.1% (1/756)	0.124	0.8% (6/754)	0.1% (1/751)	0.124
ARC definition (early and late)						
Definite	0.7% (5/760)	0.1% (1/756)	0.218	0.7% (5/754)	0.1% (1/751)	0.218
Probable	0.3% (2/760)	0.0% (0/756)	0.500	0.3% (2/754)	0.0% (0/751)	0.500
Possible	0.3% (2/760)	0.3% (2/756)	1.000	0.4% (3/754)	0.4% (3/751)	1.000
Definite and probable	0.9% (7/760)	0.1% (1/756)	0.070	0.9% (7/754)	0.1% (1/751)	0.070
Any	1.2% (9/760)	0.4% (3/756)	0.144	1.3% (10/754)	0.5% (4/751)	0.178
Target lesion revascularization	4.1% (31/760)	2.6% (20/756)	0.154	4.5% (34/754)	3.2% (24/751)	0.228
Target vessel revascularization	5.4% (41/760)	4.9% (37/756)	0.728	6.2% (47/754)	6.8% (51/751)	0.677
Nontarget lesion, target vessel revascularization	2.0% (15/760)	2.8% (21/756)	0.317	2.5% (19/754)	4.3% (32/751)	0.065
Target vessel failure	6.6% (50/760)	7.1% (54/756)	0.685	7.7% (58/754)	9.6% (72/751)	0.200
Major adverse cardiac events	5.5% (42/760)	5.6% (42/756)	1.000	6.5% (49/754)	6.7% (50/751)	0.918

Values are presented as % (n/total).
Abbreviations as in Tables 1 and 5.

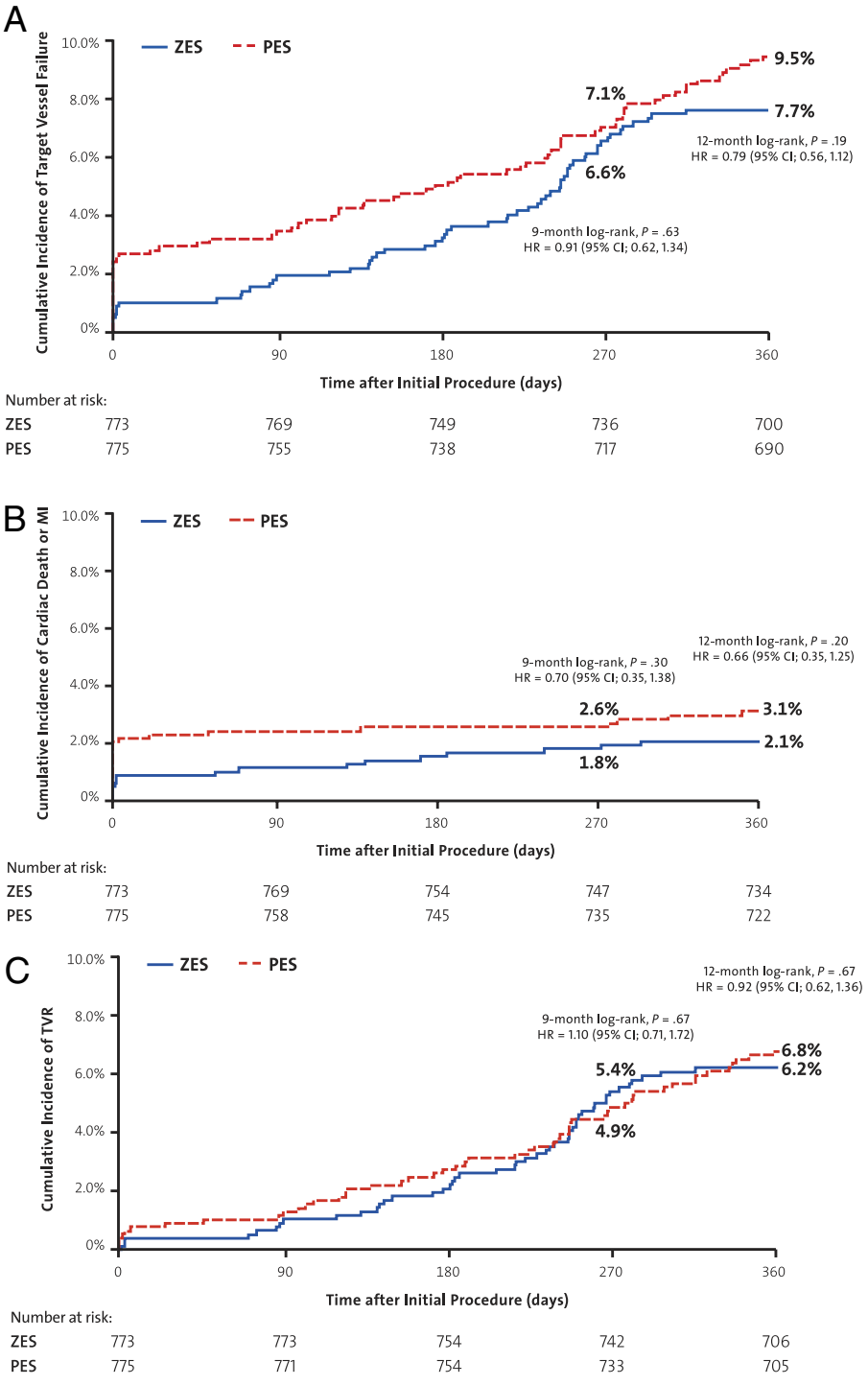

Figure 2 **Cumulative Incidence of Target Vessel Failure, Cardiac Death and Myocardial Infarction, and TVR at 360 Days (ZES vs. PES)**

Time-to-event curves through 1 year for target vessel failure **(A)**, cardiac death or myocardial infarction (MI) **(B)**, and target vessel revascularization (TVR) **(C)** in patients treated with zotarolimus-eluting stent (ZES) versus paclitaxel-eluting stent (PES). Event rates represent Kaplan-Meier estimates. The p values are based on the log-rank test. CI = confidence interval; HR = hazard ratio.

Although there were no significant differences in stent thrombosis among the treatment cohorts, there was a trend toward more frequent protocol definition and ARC definition (definite or probable) stent thrombosis with ZES compared with PES at 9- and 12-month follow-up (Table 6). Of the 7 ZES patients with ARC stent thrombosis (definite or probable), 3 occurred before 30 days (2 definite and 1 probable) and 4 occurred between

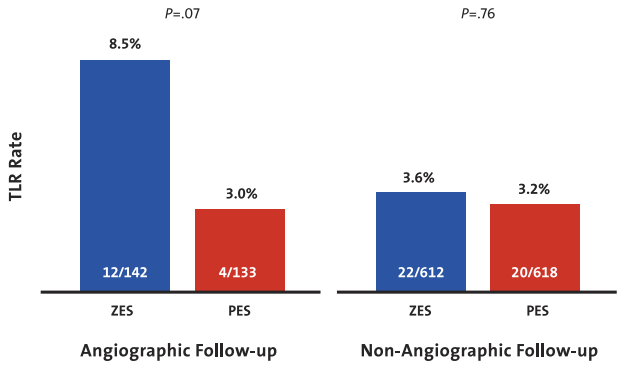

Figure 3 TLR at 12 Months for Angiographic and Nonangiographic Follow-Up Subgroups

Rates of target lesion revascularization (TLR) at 12 months in patients with and without angiographic follow-up treated with ZES versus PES. Abbreviations as in Figure 2.

30 days and 6 months (3 definite and 1 probable). In the 3 ZES patients with ARC definite or probable stent thrombosis before 30 days, 2 were associated with edge dissection and incomplete stent expansion and 1 had an unplanned surgical procedure. In the 4 ZES patients with ARC definite or probable stent thrombosis between 30 days and 6 months, 3 patients were no longer taking DAPT (time of DAPT cessation to stent thrombosis was 2 days, 20 days, and 2 months), 1 of which also had an unplanned surgical procedure.

There were no differences in overall clinically driven TLR or TVR comparing ZES with PES at either 9- or 12-month follow-up (Table 6, Fig. 2C). In those patients with angiographic follow-up (18% of the total study population), TLR at 12 months was 8.5% for ZES and 3.0% for PES ($p = 0.071$) (Fig. 3). In those patients without angiographic follow-up (82% of the study population), TLR was 3.6% for ZES and 3.2% for PES ($p = 0.756$) (Fig. 3).

Subgroup analysis and predictors of TLR. Analyses of clinical subgroups emphasizing high restenosis-risk patients revealed no significant differences (nonsignificant interaction p values) between ZES and PES at 1-year clinical follow-up for either TVF or TVR (Figs. 4A and 4B).

Multivariate predictors of TLR at 12 months for all patients were history of diabetes, left anterior descending target vessel and the presence of multiple stents (Table 7). A history of diabetes, multiple stents, and age were significant predictors of TLR for the PES group. The only significant predictor of TLR for patients in the ZES group was assignment to angiographic follow-up.

Discussion

The main findings from the randomized ENDEAVOR IV study comparing ZES versus PES in patients with simple and medium complexity single de novo coronary lesions are:

1. The primary clinical end point, 9-month TVF, was similar in ZES and PES patients.
2. The powered secondary end point was not met in this study with in-segment late lumen loss being significantly higher in ZES versus PES patients.
3. Despite the less robust reduction in intimal hyperplasia seen on angiography with ZES versus PES, the clinical expression of restenosis (TLR and TVR) were similar among the 2 study cohorts after 9- and 12-month follow-up.

The primary clinical end point, 9-month TVF, which includes both safety and efficacy measures, was very close in ZES and PES patients (6.6% and 7.1%, respectively, $p_{noninferiority} < 0.001$). Individual safety end points such as cardiac death and MI were also similar in the 2 groups, though non–Q-wave MIs were still more frequent in PES patients (19 vs. 10 events; $p = 0.095$), undoubtedly a reflection of the earlier increase in periprocedural non–Q-wave MIs after PES treatment. Similar reduction in periprocedural non–Q-wave MIs was observed when ZES was compared with SES in a smaller randomized trial (from 3.5% with SES to 0.6% with ZES, $p = 0.042$) (16). Importantly, in ENDEAVOR IV, of the 17 periprocedural non–Q-wave MIs after PES, 8 (47%) were large MIs with >10× upper limit of normal creatine kinase-myocardial band rises. Other studies have indicated a higher than expected frequency of periprocedural MIs associated with PES implantation with a reported incidence of 3.5% to 5.4% (2,3) and post hoc angiographic analyses have suggested that disproportionate changes in PES covered side branches (both occlusion and/or reduced flow) may be partially responsible for these early clinical events (3,24).

During the 12-month follow-up, there was an increase in both protocol-defined and ARC-defined stent thrombosis after ZES therapy, which although not significant, requires further comment. Early stent thrombosis (within 30 days of the procedure) for both bare-metal stents and DES is usually influenced by anatomic, procedural, and clinical factors (25). Of the 7 ARC definite or probable ZES thrombosis events, 3 occurred within 30 days and all were associated procedural mishaps (edge dissection or incomplete stent expansion) or clinical comorbid situations (unplanned surgery). The remaining 4 ZES thrombosis events occurred between 1 and 6 months, and in 3 patients, clopidogrel therapy was discontinued before the event, and 1 of these patients also had unplanned surgery immediately before the event. Study-to-study variations in stent thrombosis within the first year of follow-up are commonly observed among DES trials and the frequency of stent thrombosis for ZES in this trial was greater than reported in previous studies (13,15,16,26,27), whereas the stent thrombosis rates for PES in this trial were lower than previously reported (2,3,28). Such variations in the incidence of stent thrombosis during the first year of follow-up are exemplified in the reports from 2 recent

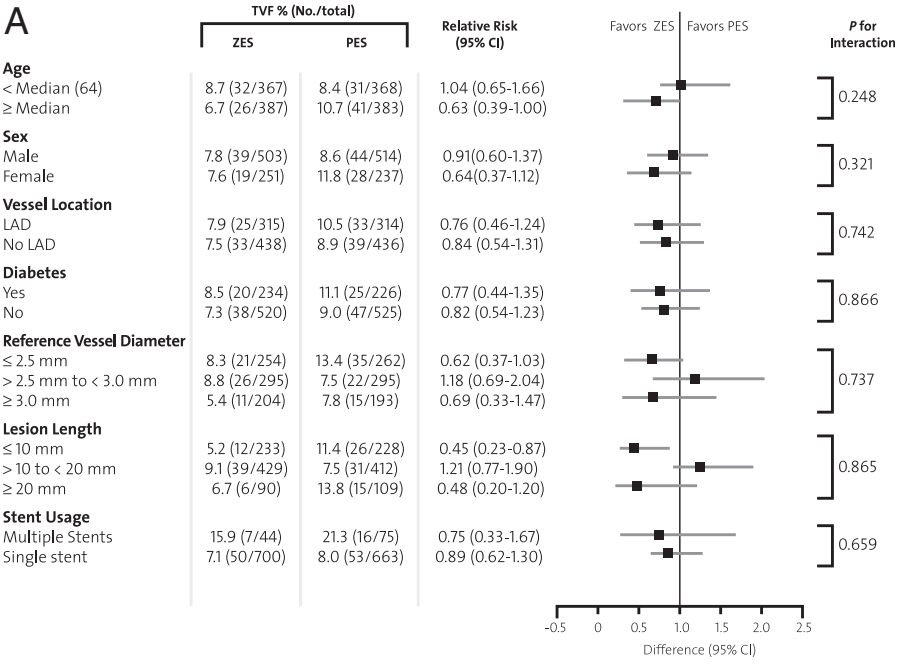

Figure 4 **Subgroup Analyses of the 1-Year Rates of TVF and TVR (ZES vs. PES)**

Subgroup analyses of the 1-year target vessel failure (TVF) **(A)** and TVR **(B)** among the patients randomized to receive a ZES versus PES. Probability for interaction represents the likelihood for interaction between the variable and the relative treatment effect. LAD = left anterior descending artery; other abbreviations as in Figure 2.

randomized Danish trials with similar study designs comparing the safety and efficacy of SES versus PES (SORT OUT II [Comparison of Paclitaxel- and Sirolimus-Eluting Stents in Everyday Clinical Practice] trial) (29) or ZES (SORT OUT III [Comparison of Zotarolimus-Eluting Stents and Sirolimus-Eluting Stents in Patients with Coronary Artery Disease] trial) (30) in a real-world study population. The rates of definite stent thrombosis at 9 months in patients randomized to SES were unusually low in SORT OUT III (0.2%) and considerably higher in SORT OUT II (1.7%), despite similar methodology and patient populations. Importantly, DES safety has usually been associated with increased stent thrombosis events occurring longer than 1 year after the index procedure. Therefore, long-term patient follow-up from the ENDEAVOR IV trial is

Table 7 Multivariate Predictors of TLR and TVF at 12 Months

	Odds Ratio (95% CI)	p Value
TLR predictors		
All patients		
History of diabetes	2.63 (1.50–4.64)	<0.001
LAD (vs. all others)	2.03 (1.15–3.57)	0.014
Multiple vs. single stents	3.31 (1.59–6.89)	0.001
ZES patients		
Angiographic follow-up vs. clinical follow-up	2.88 (1.36–6.09)	0.006
PES patients		
Age (yrs)	1.06 (1.02–1.11)	0.010
History of diabetes	3.73 (1.50–9.26)	0.005
Multiple vs. single stents	4.33 (1.57–11.96)	0.005
TVF predictors		
All patients		
History of hyperlipidemia	0.53 (0.29–0.98)	0.044
Multiple vs. single stents	1.82 (1.24–2.66)	0.002
ZES patients		
Multiple vs. single stents	2.38 (1.00–5.67)	0.049
Pre-diameter stenosis, %	1.03 (1.01–1.05)	0.016
PES patients		
Age (yrs)	1.03 (1.00–1.05)	0.036
History of prior MI	0.52 (0.30–0.89)	0.018
Multiple vs. single stents	3.11 (1.63–5.92)	<0.001

CI = confidence interval; LAD = left anterior descending; MI = myocardial infarction; TLR = target lesion revascularization; TVF = target vessel failure; other abbreviations as in Table 1.

required to determine if the frequency of very late stent thrombosis is impacted by ZES therapy. Moreover, the ongoing PROTECT (Patient Related OuTcomes with Endeavor versus Cypher stenting Trial), the largest randomized trial focusing on the comparative safety of DES (n = 8,800) will assess rates of stent thrombosis in patients assigned to SES versus ZES after 3 years of clinical follow-up (31).

Angiographic follow-up, performed at 8 months after the index procedure in 18% of the patients indicated significantly lower in-segment minimum lumen diameter, a higher in-segment percent diameter stenosis, and a higher in-segment late loss with ZES compared with PES. The angiographic follow-up findings after ZES in this study were comparable to multiple other ZES clinical trials, which have shown a consistent in-stent late loss of approximately 0.60 mm (13,15,16,26). Although in-segment binary restenosis was higher with ZES than with PES (15.3% vs. 10.4%), the difference was not statistically significant (p = 0.284). The rates of in-segment restenosis in the PES arm in this study are somewhat higher than in the PES arm in the pivotal TAXUS IV trial (8.6%) and lower than in PES arm in the TAXUS V trial (18.9%), which likely corresponds to the different complexity of treated lesions (2,3).

Despite the less robust reduction in intimal hyperplasia seen on angiography with ZES versus PES, the clinical expression of restenosis (TLR and TVR) were similar among the 2 study cohorts after 9- and 12-month follow-up both in the entire trial population and in high restenosis subgroups (including diabetics, longer lesions, smaller vessels, and multiple stent cases). The most likely explanation for the disparity between ZES versus PES differences in rates of angiographic and clinical restenosis is the remarkable influence of routine angiographic follow-up examinations on the frequency repeat revascularization events known as "oculo-stenotic reflex" (32). In this study, there was more than a 2-fold higher frequency of TLR after ZES in those patients with versus those without systematic angiographic follow-up. The higher late loss after ZES, eliciting many situations in which the visual estimate of follow-up angiographic diameter stenosis approaches or exceeds 50%, likely heightens this tendency. Further confirmation is derived from the multivariable analysis, wherein unlike PES, the only multivariable predictor of TLR after ZES was assignment to routine angiographic follow-up.

Study limitations. As with most pivotal early stage randomized clinical trials used for Food and Drug Administration approval of a DES in the U.S. (1,2,4,17), the lesion and patient inclusion criteria for ENDEAVOR IV are somewhat restrictive. Thus, the reported findings can only be applied to the simple-to-medium complexity lesions and stable patients that were treated. This study was designed to test the noninferiority of ZES versus PES for TVF and in-segment late loss; the p values for all the other end points should be viewed with caution. Definitive conclusions regarding ZES safety, especially very late stent thrombosis, will necessitate prolonged clinical follow-up for several additional years. In addition, the trial was not specifically powered to evaluate the differences in rates of individual clinical end points including MI and TLR, and therefore these results should be viewed as hypothesis-generating rather than definitive.

Conclusions

The ENDEAVOR IV trial should be viewed as a component of the larger comprehensive assessment of the new Endeavor ZES. Compared with the well-characterized PES, findings from this randomized trial indicate that in single de novo coronary lesions, the Endeavor ZES has improved periprocedural safety, similar 12-month clinical safety and efficacy outcomes, and despite more frequent angiographic restenosis, similar clinical repeat revascularization events.

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Key Words: drug-eluting stents ■ target lesion revascularization ■ zotarolimus-eluting stent.

APPENDIX

For a list of principal investigators and participating institutions for ENDEAVOR IV, please see the online version of this article.