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Clinical and Angiographic Outcomes in Diabetics From the ENDEAVOR IV Trial

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

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Objectives The aim of this study was to examine outcomes related to the use of the Endeavor zotarolimus-eluting stent (ZES) (Medtronic CardioVascular, Santa Rosa, California) compared with the TAXUS paclitaxel-eluting stent (PES) (Boston Scientific Corp., Natick, Massachusetts) in the 477 patients with diabetes mellitus (DM) enrolled in the randomized ENDEAVOR IV (Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients with Coronary Artery Disease) trial.

Background Percutaneous coronary intervention (PCI) in diabetic patients is associated with increased rates of restenosis-related end points compared with PCI in nondiabetic patients. Although ZES has been associated with similar clinical efficacy compared with PES in the overall trial population of the ENDEAVOR IV trial, whether these results are maintained in the higher-risk restenosis subgroup of patients with DM has not been determined.

Methods Clinical and angiographic outcomes were compared according to randomized treatment assignment to either ZES or PES.

Results Baseline characteristics were similar among ZES (n = 241) and PES (n = 236) diabetic patients, with slightly longer lesion lengths in PES-treated patients (12.9 mm vs. 14.0 mm, p = 0.041). Among the 86 DM patients assigned to routine angiographic follow-up (18% of the overall DM cohort), in-stent percent diameter stenosis at 8 months was greater among ZES-treated patients (32.9 vs. 21.1, p = 0.023), with a trend toward higher in-stent late loss. One-year clinical outcomes were similar among DM patients treated with either ZES or PES (target vessel failure: 8.6% vs. 10.8%, p = 0.53; target lesion revascularization: 6.9% vs. 5.8%, p = 0.70; target vessel revascularization: 8.6% vs. 9.4%, p = 0.87). There were no significant interactions between DM status and stent type with respect to the outcomes measured, and the relative efficacy/safety of ZES and PES were similar among insulin- and noninsulin-requiring subgroups.

Conclusions One-year clinical outcomes were similar among DM patients treated with ZES and PES in the ENDEAVOR IV trial. These findings parallel the overall trial results, which demonstrated similar efficacy and safety of ZES and PES for single de novo coronary lesions. (J Am Coll Cardiol Intv 2009;2:967–76) © 2009 by the American College of Cardiology Foundation

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Although bare-metal stents (BMS) have been demonstrated to improve acute outcomes and reduce rates of restenosis compared with balloon angioplasty alone, a significant proportion of patients treated with BMS experience both angiographic and clinical restenosis, leading to repeat revascularization procedures. Patients with diabetes mellitus (DM) are at a particularly greater risk for restenosis and repeat revascularization procedures (1) and are also at greater risk for other adverse clinical outcomes, including stent thrombosis (2), myocardial infarction (MI), and death (1,3).

Drug-eluting stents (DES) have been shown to significantly reduce the rates of clinical restenosis compared with BMS, with similar effects observed in patients with and without DM (4–11). A newer DES recently approved in the U.S., the Endeavor zotarolimus-eluting stent (ZES) (Medtronic CardioVascular, Santa Rosa, California), has been demonstrated in a blinded randomized trial to reduce angiographic and clinical restenosis compared with the same control BMS (12). Despite higher in-stent late loss, the ZES has been associated with similar clinical outcomes compared with the TAXUS paclitaxel-eluting stent (PES) (Boston Scientific Corporation, Natick, Massachusetts) in the randomized ENDEAVOR IV (Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients with Coronary Artery Disease) trial (13). Because restenosis can be more aggressive in patients with DM, it is important to characterize whether these results are maintained in this higher-risk subgroup of patients undergoing percutaneous coronary intervention (PCI) with ZES. We therefore sought to examine outcomes in the ENDEAVOR IV trial related to the randomized use of ZES compared with PES and stratified by diabetic status.

Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent
DM = diabetes mellitus
IDDM = insulin-dependent diabetes mellitus
MACE = major adverse cardiac events
MLD = minimum lumen diameter
NIDDM = noninsulin-dependent diabetes mellitus
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent
QCA = quantitative coronary angiography
TLR = target lesion revascularization
TVR = target vessel revascularization
TVF = target vessel failure
ZES = zotarolimus-eluting stent

Methods

Study population. The ENDEAVOR IV trial was a prospective, multicenter, single-blind, randomized, controlled clinical trial that compared clinical and angiographic outcomes between patients randomized to either ZES or 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 MI, another planned PCI within the next 30 days or previous PCI in the target vessel within the previous 9 months, recent stroke or transient ischemic attack, left ventricular ejection fraction <30%, and contraindication to dual anti-platelet therapy (aspirin and a thienopyridine).

Angiographic requirements were the presence of a single de novo native coronary lesion with a diameter stenosis (DS) at least 50% but <100% by visual estimate, reference vessel diameter ≥2.5 mm 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 an ostial location or with severe calcification or at a bifurcation involving a side branch >2.0 mm diameter were excluded. Patients with unprotected left main coronary disease were also excluded.

After confirmation of eligibility criteria, patients were stratified by diabetic status and clinical site and were subsequently randomized to receive either the ZES or the PES. Diabetes was defined as treatment for DM with insulin, oral antidiabetic agents, or a modified diet.

End points and definitions. Study end points were assessed prospectively and were adjudicated by an independent clinical events committee. The primary end point of the current analysis was the rate of target vessel failure (TVF) (a composite of cardiac death, MI, or clinically-driven target vessel revascularization [TVR] of the treated vessel), the same end point as for the overall ENDEAVOR IV trial (assessed at 12 months for this analysis). Secondary end points included target lesion revascularization (TLR) and TVR. Additional end points were assessed to evaluate stent safety, including death (all cause, cardiac, noncardiac), MI (all, Q-wave, non–Q-wave), composite death or MI, major adverse cardiac events (MACE; a composite of death, Q-wave MI, non–Q-wave MI, and target site revascularization), and stent thrombosis as assessed by the Academic Research Consortium (ARC) definitions (14). Additionally, protocol-mandated quantitative coronary angiography (QCA) was performed at 8 months in a consecutive series of study patients and analyzed by an independent angiographic core laboratory (Brigham and Women's Hospital, Boston, Massachusetts).

Statistical analysis. Of the original study population of 1,548 patients (ZES = 773; PES = 775), 477 (30.8%) had diabetes (ZES = 241; PES = 236). Overall, 18% of patients in the trial underwent protocol-mandated angiographic follow-up (86 diabetic patients, 193 nondiabetic patients). The primary comparison in the present analysis was between the randomized treatment arms (ZES and PES) among diabetic and nondiabetic patients. Further analyses were conducted to assess differences between stent types among the subgroups of patients with insulin-dependent diabetes mellitus (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM).

Categorical variables were compared with the chi-square or Fisher exact test, as appropriate. Continuous variables are presented as means with SD and were compared with unpaired *t* tests. Time-to-event data are reported and displayed as Kaplan-Meier estimates, with comparisons between groups by the log-rank test. All analyses are by intention-to-treat, with all patients randomized to each study stent included. First-order tests of interaction terms for primary end points were conducted according to diabetic status (vs. nondiabetic status). Data collection, clinical event adjudication, and analysis were performed at the Harvard Clinical Research Institute (Boston, Massachusetts).

Results

Baseline and angiographic characteristics. Compared with patients without DM, patients with DM were more likely to be women and more frequently had coexisting cardiovascular risk factors including a history of smoking, hypertension, and hyperlipidemia. The baseline demographic and clinical characteristics of the randomized ZES- and PES-treated groups were well-matched in patients with and without DM (Table 1), consistent with the study stratification by diabetic status, although there was a slightly higher prevalence of hyperlipidemia in diabetic persons randomized to PES. Periprocedural glycoprotein IIb/IIIa inhibitors were used in a similar proportion of ZES- and PES-treated patients (23.7% vs. 25.4%, p = 0.653).

Patients with DM had smaller reference vessel diameters compared with patients without DM (2.67 mm vs. 2.74 mm, p = 0.007). Baseline lesion characteristics were similar between ZES and PES among both DM and non-DM patients (Tables 2 and 3), except for slightly longer treated lesions among PES-treated patients with DM (14.0 mm vs. 12.9 mm, p = 0.041), resulting in more discrete lesions treated in ZES patients with DM, although total stent length was similar in patients with DM (20.5 mm for ZES vs. 21.2 mm for PES, p = 0.28). Other baseline lesion characteristics, including lesion location, presence of thrombus, and Thrombolysis In Myocardial Infarction flow, were similar among DM and non-DM patients treated with ZES and PES. Post-procedural QCA of lesions treated with ZES and PES was also similar in the DM and non-DM patient groups (Table 3).

8-month angiography. A total of 86 patients with DM underwent mandatory angiographic follow-up at 8 months (Table 4). Compared with patients without DM, patients with DM had smaller reference vessel diameters, smaller minimum lumen diameters (MLD), and greater

Table 1. Baseline Demographic Data and Clinical Characteristics

	DM			No DM		
	ZES (n = 241)	PES (n = 236)	p Value	ZES (n = 532)	PES (n = 539)	p Value
Age (yrs), mean ± SD (n)	64.24 ± 11.08 (241)	63.84 ± 9.87 (236)	0.679	63.17 ± 11.10 (532)	63.43 ± 11.45 (539)	0.711
Male	59.8% (144/241)	61.0% (144/236)	0.780	70.1% (373/532)	71.8% (387/539)	0.546
History of smoking	54.4% (129/237)	53.8% (126/234)	0.926	66.3% (350/528)	63.3% (336/531)	0.335
Prior percutaneous coronary revascularization	32.8% (79/241)	32.6% (77/236)	1.000	26.1% (139/532)	28.2% (152/539)	0.451
Hyperlipidemia requiring treatment	83.8% (202/241)	90.3% (213/236)	0.041	80.3% (427/532)	82.4% (444/539)	0.389
Hypertension requiring treatment	90.5% (218/241)	90.7% (214/236)	1.000	74.4% (396/532)	79.0% (426/539)	0.083
Medications						
Beta-blockers	66.8% (161/241)	77.1% (182/236)	0.014	70.5% (375/532)	69.0% (372/539)	0.642
ACE inhibitors	77.2% (186/241)	77.5% (183/236)	1.000	52.3% (278/532)	54.5% (294/539)	0.463
Medications for diabetes	88.4% (213/241)	90.3% (213/236)	0.555	9.0% (48/532)	12.4% (67/539)	0.076
Statins	83.0% (200/241)	85.2% (201/236)	0.534	83.5% (444/532)	82.6% (445/539)	0.745
Prior MI	23.0% (54/235)	24.0% (56/233)	0.828	20.2% (107/529)	22.8% (120/526)	0.330
Prior CABG	15.8% (38/241)	11.4% (27/236)	0.183	7.1% (38/532)	7.1% (38/539)	1.000
Clinical presentation						
Stable	43.9% (79/180)	51.1% (91/178)	0.345	46.3% (202/436)	46.6% (201/431)	0.878
Unstable	53.3% (96/180)	47.2% (84/178)		50.9% (222/436)	51.0% (220/431)	
MI	2.8% (5/180)	1.7% (3/178)		2.8% (12/436)	2.3% (10/431)	
Number of diseased vessels						
Single	48.5% (117/241)	51.3% (121/236)	0.814	57.8% (307/531)	59.9% (322/538)	0.528
Double	32.8% (79/241)	28.0% (66/236)		26.7% (142/531)	25.3% (136/538)	
Triple	18.7% (45/241)	20.8% (49/236)		15.4% (82/531)	14.9% (80/538)	
Ejection fraction, mean ± SD (n)	57.21 ± 10.40 (239)	56.93 ± 10.34 (231)	0.768	57.34 ± 9.70 (521)	57.70 ± 10.29 (522)	0.553

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; DM = diabetes mellitus; MI = myocardial infarction; PES = paclitaxel-eluting stent(s); ZES = zotarolimus-eluting stent(s).

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Table 2. Baseline Lesion Characteristics

	DM			No DM		
	ZES (n = 241)	PES (n = 236)	p Value	ZES (n = 532)	PES (n = 539)	p Value
Vessel location						
LAD	40.0% (96/240)	39.0% (92/236)	0.759	43.2% (230/532)	42.6% (229/538)	0.945
LCX	30.0% (72/240)	28.0% (66/236)		25.6% (136/532)	25.3% (136/538)	
RCA	30.0% (72/240)	33.1% (78/236)		31.2% (166/532)	32.2% (173/538)	
Lesion description						
Discrete (<10 mm)	34.7% (83/239)	28.4% (67/236)	0.022	29.7% (158/532)	30.9% (166/537)	0.991
Tubular (10–19.9 mm)	56.1% (134/239)	54.7% (129/236)		57.3% (305/532)	54.6% (293/537)	
Diffuse (≥20 mm)	9.2% (22/239)	16.9% (40/236)		13.0% (69/532)	14.5% (78/537)	
Thrombus	1.3% (3/240)	0.8% (2/236)	1.000	1.7% (9/532)	1.3% (7/538)	0.625
TIMI flow grade						
1	0.4% (1/240)	0.8% (2/236)	0.780	0.4% (2/531)	0.6% (3/538)	0.962
2	3.3% (8/240)	3.4% (8/236)		6.0% (32/531)	5.8% (31/538)	
3	96.3% (231/240)	95.8% (226/236)		93.6% (497/531)	93.7% (504/538)	
Modified ACC/AHA						
A	8.3% (20/240)	9.3% (22/236)	0.244	6.0% (32/532)	5.4% (29/538)	0.757
B1	21.7% (52/240)	21.6% (51/236)		24.6% (131/532)	22.9% (123/538)	
B2	49.6% (119/240)	39.0% (92/236)		41.2% (219/532)	44.6% (240/538)	
C	20.4% (49/240)	30.1% (71/236)		28.2% (150/532)	27.1% (146/538)	

ACC/AHA = American College of Cardiology/American Heart Association; LAD = left anterior descending coronary artery; LCX = left circumflex artery; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

mean late loss at 8 months when pooling both the ZES and PES stent arms.

At follow-up, compared with DM patients treated with a PES, DM patients receiving a ZES had smaller in-stent MLD (1.70 mm vs. 2.01 mm, p = 0.037) and greater in-stent percent diameter stenosis (32.9 mm vs. 21.1 mm, p = 0.023), with a trend toward higher in-stent late loss (0.81 mm vs. 0.56 mm, p = 0.073). The rate of in-stent and -segment binary angiographic restenosis was correspondingly higher among ZES-treated patients, although this did not achieve statistical significance (in-stent: 25.0% vs. 16.7%, p = 0.43; in-segment: 27.3% vs. 23.8%, p = 0.81).

Table 3. Baseline Pre- and Post-Procedural QCA

	DM			No DM		
	ZES (n = 241)	PES (n = 236)	p Value	ZES (n = 532)	PES (n = 539)	p Value
Pre-procedure						
Lesion length (mm)	12.88 ± 5.58 (239)	14.00 ± 6.38 (236)	0.041	13.65 ± 5.69 (532)	13.71 ± 5.96 (537)	0.880
Reference vessel diameter (mm)	2.68 ± 0.48 (240)	2.66 ± 0.47 (236)	0.670	2.76 ± 0.47 (532)	2.72 ± 0.46 (538)	0.195
MLD (mm)	0.95 ± 0.40 (240)	0.94 ± 0.43 (236)	0.735	0.96 ± 0.41 (532)	0.93 ± 0.39 (538)	0.129
% stenosis	64.69 ± 12.90 (240)	65.15 ± 13.47 (236)	0.700	64.89 ± 13.48 (532)	65.91 ± 12.93 (538)	0.207
Post-procedure						
Reference vessel diameter (mm)	2.72 ± 0.49 (240)	2.71 ± 0.48 (235)	0.711	2.82 ± 0.46 (530)	2.79 ± 0.46 (537)	0.222
In-segment MLD (mm)	2.17 ± 0.48 (240)	2.14 ± 0.51 (235)	0.467	2.25 ± 0.46 (530)	2.21 ± 0.49 (537)	0.271
In-segment % stenosis	20.47 ± 9.64 (240)	21.33 ± 12.79 (235)	0.408	20.46 ± 9.50 (530)	20.81 ± 10.31 (537)	0.575
In-stent MLD (mm)	2.55 ± 0.42 (238)	2.58 ± 0.48 (232)	0.558	2.65 ± 0.43 (525)	2.63 ± 0.43 (531)	0.364
In-stent % stenosis	5.58 ± 10.17 (238)	4.47 ± 12.20 (232)	0.283	5.46 ± 9.35 (525)	5.25 ± 9.65 (531)	0.725
Proximal edge MLD (mm)	2.66 ± 0.55 (230)	2.68 ± 0.56 (224)	0.676	2.76 ± 0.58 (500)	2.76 ± 0.56 (504)	0.881
Proximal edge % stenosis	2.61 ± 11.15 (230)	1.47 ± 11.21 (224)	0.280	2.36 ± 12.11 (500)	0.90 ± 11.89 (504)	0.054
Distal edge MLD (mm)	2.31 ± 0.54 (238)	2.32 ± 0.52 (231)	0.858	2.39 ± 0.53 (520)	2.36 ± 0.54 (527)	0.330
Distal edge % stenosis	15.22 ± 11.59 (238)	14.36 ± 11.58 (231)	0.423	15.43 ± 11.61 (520)	15.93 ± 11.35 (527)	0.486

All data are presented as mean ± SD and include the number of patients with available data.
MLD = minimum lumen diameter; QCA = quantitative coronary angiography; other abbreviations as in Table 1.

Table 4. Angiographic Follow-Up at 8 Months

	DM			No DM		
	ZES (n = 44)	PES (n = 42)	p Value	ZES (n = 100)	PES (n = 93)	p Value
Reference vessel diameter (mm)	2.55 ± 0.46 (44)	2.54 ± 0.42 (42)	0.953	2.70 ± 0.47 (100)	2.74 ± 0.45 (93)	0.530
In-segment MLD (mm)	1.60 ± 0.55 (44)	1.73 ± 0.67 (42)	0.298	1.89 ± 0.54 (100)	2.09 ± 0.47 (93)	0.006
In-segment % stenosis	36.91 ± 19.86 (44)	32.75 ± 21.23 (42)	0.351	30.25 ± 15.29 (100)	23.83 ± 11.18 (93)	0.001
In-stent MLD (mm)	1.70 ± 0.62 (44)	2.01 ± 0.73 (42)	0.037	2.06 ± 0.58 (99)	2.36 ± 0.52 (93)	<.001
In-stent % stenosis	32.88 ± 22.43 (44)	21.13 ± 24.62 (42)	0.023	23.53 ± 17.80 (99)	13.82 ± 13.58 (93)	<.001
Proximal edge MLD (mm)	2.36 ± 0.55 (42)	2.27 ± 0.80 (42)	0.542	2.48 ± 0.61 (97)	2.61 ± 0.62 (91)	0.181
Proximal edge % stenosis	6.48 ± 15.54 (42)	11.83 ± 24.66 (42)	0.239	7.99 ± 16.41 (97)	4.93 ± 15.15 (91)	0.186
Distal edge MLD (mm)	2.03 ± 0.56 (44)	2.11 ± 0.54 (42)	0.501	2.24 ± 0.46 (99)	2.30 ± 0.51 (93)	0.413
Distal edge % stenosis	20.09 ± 16.70 (44)	17.38 ± 15.04 (42)	0.431	16.81 ± 10.19 (99)	16.58 ± 10.65 (93)	0.879
Binary restenosis						
In-segment	27.3% (12/44)	23.8% (10/42)	0.807	10.0% (10/100)	4.3% (4/93)	0.168
In-stent	25.0% (11/44)	16.7% (7/42)	0.430	8.1% (8/99)	2.2% (2/93)	0.102
Proximal edge	4.8% (2/42)	9.5% (4/42)	0.676	3.1% (3/97)	1.1% (1/91)	0.622
Distal edge	2.3% (1/44)	2.4% (1/42)	1.000	0% (0/99)	0% (0/93)	
In-segment late loss (mm)	0.46 ± 0.55 (44)	0.38 ± 0.58 (42)	0.526	0.31 ± 0.42 (99)	0.16 ± 0.35 (93)	0.009
In-stent late loss (mm)	0.81 ± 0.58 (44)	0.56 ± 0.66 (42)	0.073	0.61 ± 0.44 (98)	0.35 ± 0.39 (93)	<.001

All data are presented as mean ± SD and include the number of patients with available data.
Abbreviations as in Tables 1 and 3.

In patients without DM, ZES-treated patients had smaller in-stent MLD, greater in-stent percent diameter stenosis, and higher in-stent late loss at follow-up compared with PES-treated patients (0.61 mm vs. 0.35 mm, $p < 0.001$), similar to the findings in patients with DM. The rate of in-stent and in-segment binary angiographic restenosis in patients without DM was numerically higher among ZES-treated patients but did not achieve statistical significance (in-stent: 8.1% vs. 2.2%, $p = 0.10$; in-segment: 10.0% vs. 4.3%, $p = 0.17$).

Clinical end points. Overall rates of TVF at 1 year were similar among DM and non-DM patients when pooled across ZES and PES stent types (Table 5). Compared with patients without DM, patients with DM had higher rates of TLR (6.4% vs. 2.8%, $p = 0.002$) and TVR (9.0% vs. 5.4%, $p = 0.012$) but slightly lower rates of MI at 1 year (0.9% vs. 2.6%, $p = 0.030$).

There were no significant differences in the rates of TVF for ZES- and PES-treated patients, either in patients with DM (8.6% vs. 10.8%, $p = 0.53$) or without DM (7.4% vs. 8.9%, $p = 0.43$) (Table 5, Fig. 1). Similarly, at 1 year, there were no differences between DES types in the rates of TLR or TVR in either DM or non-DM patients (Table 5, Fig. 2). Overall MACE was similar among ZES- and PES-treated patients in DM patients (6.9% vs. 7.2%, $p > 0.99$) and non-DM patients (6.4% vs. 6.4%, $p = 1.0$), and there were no differences in any of the individual MACE components when compared by DES type in either the DM or non-DM cohorts. The rate of ARC-defined stent thrombosis was low in patients with and without DM, with no significant differences between ZES and PES-treated patients in either cohort. There were no significant interactions for the effect of ZES versus PES on the end points of TVF, TLR, TVR, and MACE by DM status.

Outcomes in IDDM and NIDDM patients. The baseline demographic, lesion, and procedural characteristics of patients randomized to ZES and PES implantation were largely similar among patients with either IDDM (n = 144) or NIDDM (n = 333). There was a greater prevalence of a family history of coronary artery disease in IDDM patients treated with ZES and a lesser prevalence of hyperlipidemia in NIDDM patients treated with ZES. Baseline QCA demonstrated similar pre- and post-procedural lesion characteristics for patients treated with ZES and PES in both IDDM and NIDDM patient groups (all p values >0.05, data not shown).

Patients with IDDM and NIDDM had angiographic follow-up and outcomes consistent with the broader DM cohort, with no evidence of a differential effect of insulin-requiring status. Of the 27 patients with IDDM undergoing mandatory 8-month angiography, ZES-treated patients trended toward smaller in-stent MLD (1.84 mm vs. 2.19 mm, $p = 0.19$), greater in-stent percent diameter stenosis (30.7% vs. 13.7%, $p = 0.05$), and higher in-stent late loss (0.77 mm vs. 0.41 mm, $p = 0.21$). Of the 59 NIDDM patients, ZES-treated patients trended toward smaller in-stent MLD (1.63 mm vs. 1.94 mm, $p = 0.09$), greater in-stent percent diameter stenosis (34.0% vs. 24.1%, $p = 0.13$), and higher in-stent late loss (0.83 vs. 0.63 mm, $p = 0.19$).

The type of diabetes, defined by insulin use, did not impact clinical end points for ZES or PES differently

Table 5. Outcomes and Major Adverse Events at 1 Year

	DM			No DM		
	ZES (n = 241)	PES (n = 236)	p Value	ZES (n = 532)	PES (n = 539)	p Value
MACE (death, MI, emergent CABG, TLR)	6.9% (16/233)	7.2% (16/223)	1.000	6.4% (33/516)	6.4% (33/518)	1.000
Death	0.0% (0/233)	0.9% (2/223)	0.239	1.6% (8/516)	1.2% (6/518)	0.604
Cardiac death	0.0% (0/233)	0.9% (2/223)	0.239	0.8% (4/516)	0.4% (2/518)	0.451
MI (Q-wave or non–Q-wave)	0.9% (2/233)	0.9% (2/223)	1.000	1.9% (10/516)	3.3% (17/518)	0.242
Q-wave MI	0.0% (0/233)	0.0% (0/223)		0.4% (2/516)	0.2% (1/518)	0.624
Non–Q-wave MI	0.9% (2/233)	0.9% (2/223)	1.000	1.6% (8/516)	3.1% (16/518)	0.147
Emergent CABG	0.0% (0/233)	0.4% (1/223)	0.489	0% (0/516)	0.2% (1/518)	1.000
TLR	6.9% (16/233)	5.8% (13/223)	0.704	3.5% (18/516)	2.1% (11/518)	0.193
TL-CABG	0.4% (1/233)	1.8% (4/223)	0.207	0.6% (3/516)	0.4% (2/518)	0.686
TL-PTCA	6.4% (15/233)	4.0% (9/223)	0.297	3.1% (16/516)	1.7% (9/518)	0.163
TVR not involving the target lesion	2.6% (6/233)	4.5% (10/223)	0.315	2.5% (13/516)	4.1% (21/518)	0.222
TVR/non–TL-CABG	0.0% (0/233)	1.3% (3/223)	0.116	0.6% (3/516)	0.8% (4/518)	1.000
TVR/non–TL-PTCA	2.6% (6/233)	3.6% (8/223)	0.595	2.1% (11/516)	3.3% (17/518)	0.338
TVR	8.6% (20/233)	9.4% (21/223)	0.870	5.2% (27/516)	5.6% (29/518)	0.891
Target vessel failure	8.6% (20/233)	10.8% (24/223)	0.526	7.4% (38/516)	8.9% (46/518)	0.426
Stent thrombosis (ARC)						
Definite	0.9% (2/233)	0.4% (1/223)	1.000	0.6% (3/516)	0% (0/518)	0.124
Probable	0.4% (1/233)	0% (0/223)	1.000	0.2% (1/516)	0% (0/518)	0.499
Definite/probable	1.3% (3/233)	0.4% (1/223)	0.624	0.8% (4/516)	0% (0/518)	0.062

ARC = Academic Research Consortium; MACE = major adverse cardiac event; PTCA = percutaneous transluminal coronary angioplasty; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

from the overall study population (Table 6). The rate of TVF was no different among ZES- and PES-treated patients with either IDDM (3.8% vs. 8.5%, p = 0.29) or NIDDM (11.0% vs. 11.6%, p = 1.0). Similarly, the rates of TLR and TVR were comparable with both stents in both the IDDM and NIDDM cohorts. The overall MACE rate was similar with ZES and PES in the IDDM (3.8% vs. 5.1%, p = 1.0) and NIDDM (8.4% vs. 7.9%, p = 1.0) cohorts. There were no differences in individual MACE components or ARC-defined stent thrombosis by stent type in patients with either IDDM or NIDDM.

Discussion

In the ENDEAVOR IV trial, treatment of single de novo coronary lesions with either ZES or PES was associated with comparable clinical outcomes at 1 year (13). In this

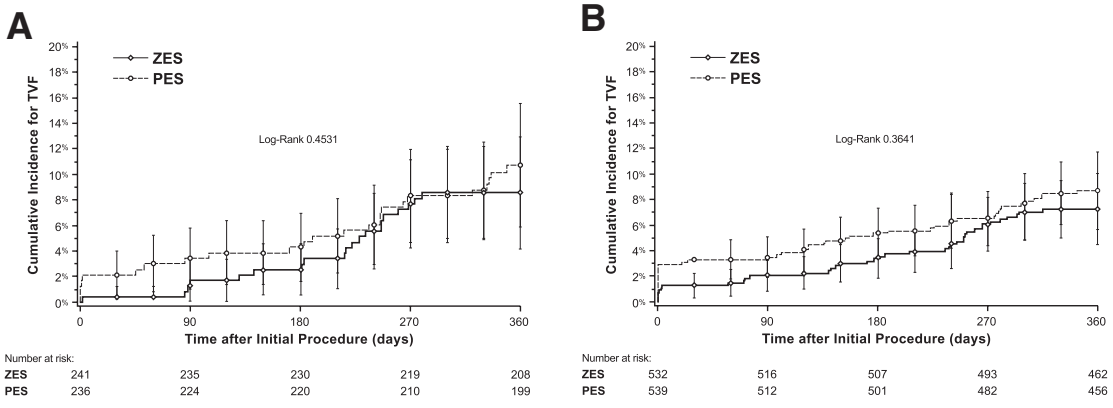

Figure 1. TVF

Kaplan-Meier estimates representing the 1-year incidence of the primary study end point, target vessel failure (TVF) for zotarolimus-eluting stent (ZES)- and paclitaxel-eluting stent (PES)-treated patients with diabetes mellitus **(A)** and without diabetes mellitus **(B)**. **Error bars** represent 95% confidence intervals.

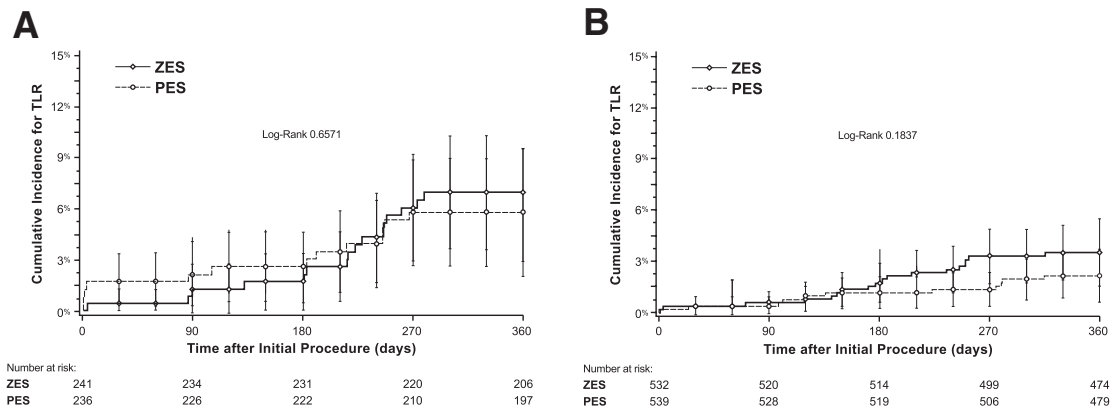

Figure 2. TLR

Kaplan-Meier estimates representing the 1-year incidence of target lesion revascularization (TLR) for ZES- and PES-treated patients with diabetes mellitus **(A)** and without diabetes mellitus **(B)**. **Error bars** represent 95% confidence intervals. Abbreviations as in Figure 1.

subset analysis of the ENDEAVOR IV trial, we sought to further characterize trial outcomes in the high-restenosis-risk subgroup of patients with DM, representing 30.8% of the overall study population. The principal findings of this subgroup analysis are: 1) despite a relative increase in rates of QCA-based restenosis end points in the cohort of patients undergoing protocol-mandated follow-up angiography, ZES and PES had virtually identical rates of clinical restenosis end points in patients both with and without DM, with both stents demonstrating similar rates of TVF, TLR, and TVR at 1 year; 2) the angiographic and clinical outcomes in patients both with and without DM mirrored the overall ENDEAVOR IV population, without evidence of effect modification with respect to the assessed end points; 3) the incidences of other safety end points, including death, MI, and stent thrombosis, were comparable to ZES and PES throughout the follow-up period in

Table 6. Outcomes and Major Adverse Events at 1 Year by IDDM Status

	IDDM			NIDDM		
	ZES (n = 80)	PES (n = 64)	p Value	ZES (n = 161)	PES (n = 172)	p Value
MACE (death, MI, emergent CABG, TLR)	3.8% (3/78)	5.1% (3/59)	1.000	8.4% (13/155)	7.9% (13/164)	1.000
Death	0.0% (0/78)	0.0% (0/59)		0.0% (0/155)	1.2% (2/164)	0.499
Cardiac death	0.0% (0/78)	0.0% (0/59)		0.0% (0/155)	1.2% (2/164)	0.499
MI (Q-wave or non–Q-wave)	1.3% (1/78)	0.0% (0/59)	1.000	0.6% (1/155)	1.2% (2/164)	1.000
Q-wave MI	0.0% (0/78)	0.0% (0/59)		0.0% (0/155)	0.0% (0/164)	N/A
Non–Q-wave MI	1.3% (1/78)	0.0% (0/59)	1.000	0.6% (1/155)	1.2% (2/164)	1.000
Emergent CABG	0.0% (0/78)	1.7% (1/59)	0.431	0.0% (0/155)	0.0% (0/164)	N/A
TLR	3.8% (3/78)	5.1% (3/59)	1.000	8.4% (13/155)	6.1% (10/164)	0.518
TL-CABG	0.0% (0/78)	3.4% (2/59)	0.184	0.6% (1/155)	1.2% (2/164)	1.000
TL-PTCA	3.8% (3/78)	1.7% (1/59)	0.634	7.7% (12/155)	4.9% (8/164)	0.358
TVR not involving the target lesion	1.3% (1/78)	3.4% (2/59)	0.577	3.2% (5/155)	4.9% (8/164)	0.575
TV/non–TL-CABG	0.0% (0/78)	0.0% (0/59)		0.0% (0/155)	1.8% (3/164)	0.248
TV/non–TL-PTCA	1.3% (1/78)	3.4% (2/59)	0.577	3.2% (5/155)	3.7% (6/164)	1.000
TVR	3.8% (3/78)	8.5% (5/59)	0.290	11.0% (17/155)	9.8% (16/164)	0.854
Target vessel failure	3.8% (3/78)	8.5% (5/59)	0.290	11.0% (17/155)	11.6% (19/164)	1.000
Stent thrombosis (ARC)						
Definite	0% (0/78)	0% (0/59)		1.3% (2/155)	0.6% (1/164)	0.613
Probable	1.3% (1/78)	0% (0/59)	1.000	0.0% (0/155)	0.0% (0/164)	
Definite/probable	1.3% (1/78)	0% (0/59)	1.000	1.3% (2/155)	0.6% (1/164)	0.613

IDDM = insulin-dependent diabetes mellitus; NIDDM = noninsulin-dependent diabetes mellitus; other abbreviations as in Tables 1 and 5.

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patients with and without DM; and 4) the relative safety, efficacy, and angiographic outcomes of ZES compared with PES in patients with DM did not seem to be significantly impacted by insulin-requiring status.

The Endeavor ZES is a DES that employs a phosphorylcholine polymer on a cobalt alloy stent to locally deliver the antiproliferative agent zotarolimus to the arterial wall during PCI. This stent has been associated with improvements in both angiographic and clinical restenosis end points in a randomized comparison with the Driver cobalt alloy stent (12). Two subsequent trials have demonstrated that the ZES is associated with greater angiographic late loss compared with other DES (13,15). Nonetheless, despite the greater angiographic late loss observed in these trials, clinical follow-up from these trials has demonstrated comparable rates of clinically driven TLR and TVR with ZES.

Some have hypothesized that the higher angiographic late loss associated with the ZES has not translated into a greater frequency of clinical restenosis events due to the relatively low-risk patient characteristics of the enrolled patients in these randomized trials. Alternatively, it is possible that, in a given population of PCI patients, the range of "tolerated late loss" might be wider than initially proposed and, moreover, is dependent not only on the mean value of late loss but also on the relative homogeneity of the late loss distribution. One way to test these assumptions is to assess the performance of the ZES in higher-risk patient cohorts, such as patients with DM, as was performed in this analysis.

Patients with DM represent a considerable proportion of patients with coronary artery disease undergoing PCI, and the risk of adverse outcomes—related both to restenosis of the treated target lesion as well as to areas remote from the target lesion—is typically higher in patients with DM compared with nondiabetic patients (1–3). In the present analysis from the ENDEAVOR IV trial, angiographic parameters such as in-stent late loss and percent diameter stenosis were greater for both stents (ZES and PES) among patients with DM compared with those without DM. This finding is consistent with prior observations that have found DM to be associated with more aggressive neointimal hyperplastic response to stenting and confirms the greater restenotic risk of patients with DM, irrespective of stent type.

There are limited data regarding the comparative efficacy of various DES in patients with DM. For example, the overall pooled experiences from pivotal randomized trials comparing 2 approved DES with their base BMS in patients with DM have consisted of 428 patients (from trials of the CYPHER sirolimus-eluting stent [Cordis Corporation, Warren, New Jersey] vs. BMS) (5) and 827 patients (from trials of the PES vs. BMS) (16), respectively. The current DM subgroup analysis of the ENDEAVOR IV randomized trial represents the largest direct comparison of 2 commercially available DES.

Although mean late loss and percent diameter stenosis were greater with ZES compared with PES in the current analysis, there were no differences between the 2 stents in clinical restenosis end points, including TLR, TVR, TVF, and MACE in the overall population of DM. This might be due in part to limited sample size but is also likely due to the relative infrequency of mandatory angiographic follow-up that occurred in the ENDEAVOR IV trial. Mandatory angiographic follow-up has been estimated to increase relative risk of TLR (largely occurring from the concomitant "oculostenotic reflex" that occurs after a protocol-mandated angiogram) by up to 40% in patients treated with DES (17). The low overall rates of mandatory angiographic follow-up within the ENDEAVOR IV trial might have resulted in an increase of the clinical margin of "tolerated late loss," therefore providing a more clinically relevant estimate of the relative efficacy of ZES versus PES within the patient population enrolled in the trial.

The use of ZES and PES in patients with and without DM was associated with a similar incidence of clinical safety end points as well, including death, MI, stent thrombosis, and overall MACE. Although the ENDEAVOR IV study was not powered to assess these end points, and therefore a subgroup analysis is limited even further in this regard, it is reassuring that the overall safety profile of both stents was similar. Follow-up is currently ongoing with up to 5 years of follow-up and should allow further monitoring of long-term safety data, a critical issue with the use of DES (10,18,19).

In addition, insulin requirement did not seem to have a significant impact on the rate of efficacy or safety end points; nor did it impact the relative efficacy and safety of ZES compared with PES. These findings parallel those from a recent meta-analysis of 5 double-blind, randomized trials of PES versus BMS, in which IDDM and NIDDM patients had similar rates of TLR and TVR, and insulin requirement did not independently impact death, cardiac death, or MI at 4 years for either stent type (6).

Study limitations. As with any subgroup analysis, this analysis should be viewed as hypothesis-generating and is subject to limited sample size and thereby limited statistical power. Nonetheless, it does represent data in an important and commonly studied subgroup of patients, and the 477 patients with DM in this analysis represent a large sample of patients from a single pivotal randomized controlled trial. Perhaps more compelling than the individual analyses stratified by DM status is the absence of any significant interaction between stent type and DM status with respect to the primary study outcomes.

Although the ENDEAVOR IV trial was critical to establishing the efficacy and safety of ZES and served as a

pivotal trial for commercial approval of ZES, its clinical generalizability is limited to the subset of patients with relatively noncomplex de novo lesions. Because patients with DM frequently have complex coronary lesions and multivessel disease, further data from more complex patient populations are needed before either the efficacy or safety data of the ZES can be translated into these patient populations. Data from the ongoing E-FIVE (Endeavor Zotarolimus Eluting Coronary Stent) registry (8,000 "all comer" patients treated with ZES) and PROTECT (Patient Related OuTcomes With Endeavor Versus Cypher Stenting) trial (8,800 "all comer" patients randomized to either ZES or the CYPHER sirolimus-eluting stent) should help to evaluate the performance of ZES in this regard. Finally, DM is associated with an ongoing risk of adverse cardiovascular outcomes, and thus further follow-up data (beyond 1 year) are needed to adequately characterize the risk of adverse efficacy and safety end points. In one real-world registry of DES use in patients with DM, "late catch-up" has been observed with PES over a follow-up period to 3 years (20).

Conclusions

In patients with DM in the ENDEAVOR IV trial, despite greater angiographic late loss with ZES compared with PES, the clinical efficacy and safety of ZES and PES were similar at 1 year, paralleling the outcomes in patients without DM (and in the overall trial). Longer-term follow-up in this trial and larger randomized trials including more complex patients are underway to better define the role of ZES in these patient and lesion subsets.

Author Disclosures

Dr. Kirtane has served as a consultant, is on the advisory board, and has received lecture fees from Medtronic CardioVascular, and serves as a consultant and has received lecture fees from Abbott Vascular. Dr. O'Shaughnessy has received research grants from Medtronic, Inc. Dr. Mauri has served as a consultant to Abbott, Boston Scientific, Cordis, and Medtronic, Inc. Dr. Fitzgerald has served as a consultant for Abbott, Boston Scientific, J&J/Cordis, EndoTex, St. Jude Medical, Biosensors, Ev3, Medtronic, Inc., GlaxoSmith-Kline, Xtent, ATI, Volcano Tx, Novadaq, AorTx, Cardiomind, Cytograft Tissue Engineering, Flowcardia, CardioOptics, Optics, Cardiomind, RTI Medical, Surmodics, Hospira, and CatherosMed. Dr. Popma has received research grants from Cordis, Boston Scientific, Medtronic, Abbott Vascular, Biosensors, and ev3; has served as a consultant for Medtronic, Boston Scientific, Cordis, Abbott Vascular and Lilly; and has been a speaker for Pfizer, Bristol-Myers Squibb, Sanofi, Lilly, Boston Scientific, Medtronic, Cordis, and Medicines Company. Dr. Kandzari has received research/grant support from Medtronic, and has served as a consultant for Cordis. Dr. Leon has served as consultant for Volcano Corporation and is an advisory board member for Abbott Vascular, Boston Scientific, Cordis, and Medtronic, Inc.

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Key Words: diabetes mellitus ■ drug-eluting stent ■ Endeavor IV ■ zotarolimus.