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Comparison of Zotarolimus-Eluting and Sirolimus-Eluting Stents in Patients With Native Coronary Artery Disease

A Randomized Controlled Trial

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OBJECTIVES This trial examined the relative clinical efficacy, angiographic outcomes, and safety of zotarolimus-eluting coronary stents (ZES) with a phosphorylcholine polymer versus sirolimus-eluting stents (SES).

BACKGROUND Whether a cobalt-based alloy stent coated with the novel antiproliferative agent, zotarolimus, and a phosphorylcholine polymer may provide similar angiographic and clinical benefit compared with SES is undetermined.

METHODS A prospective, multicenter, 3:1 randomized trial was conducted to evaluate the safety and efficacy of ZES (n = 323) relative to SES (n = 113) in 436 patients undergoing elective percutaneous revascularization of de novo native coronary lesions with reference vessel diameters between 2.5 mm and 3.5 mm and lesion length ≥14 mm and ≤27 mm. The primary end point was 8-month angiographic in-segment late lumen loss.

RESULTS Angiographic in-segment late lumen loss was significantly higher among patients treated with ZES compared with SES (0.34 ± 0.44 mm vs. 0.13 ± 0.32 mm, respectively; $p < 0.001$). In-hospital major adverse cardiac events were significantly lower among patients treated with ZES (0.6% vs. 3.5%, p = 0.04). In-segment binary angiographic restenosis was also higher in the ZES cohort (11.7% vs. 4.3%, p = 0.04). Total (clinically and non-clinically driven) target lesion revascularization rates at 9 months were 9.8% and 3.5% for the ZES and SES groups, respectively (p = 0.04). However, neither clinically driven target lesion revascularization (6.3% zotarolimus vs. 3.5% sirolimus, p = 0.34) nor target vessel failure (12.0% zotarolimus vs. 11.5% sirolimus, p = 1.0) differed significantly.

CONCLUSIONS Compared with SES, treatment with a phosphorylcholine polymer-based ZES is associated with significantly higher late lumen loss and binary restenosis at 8-month angiographic follow-up. (The Endeavor III CR; http://clinicaltrials.gov/ct/show/NCT00265668?order=1?) (J Am Coll Cardiol 2006;48:2440–7) © 2006 by the American College of Cardiology Foundation

Compared with bare metal coronary stents, the beneficial treatment with drug-eluting stents to avoid restenosis and the need for repeat revascularization has been consistently demonstrated in systematic, randomized clinical trials (1–8) and observational studies (9–11) that have included both selected and broad patient populations with varying clinical and angiographic characteristics. Because of their efficacy in limiting neointimal hyperplasia after percutaneous coronary revascularization, drug-eluting stents have become routine therapy in clinical practice, and currently available paclitaxel- eluting stents and sirolimus-eluting stents (SES) have become the comparative standard for evaluation of novel anti-proliferative therapies and stent technologies.

Whether safety, clinical efficacy, and angiographic outcomes are similar between differing drug-eluting stents has only been recently examined (12–18). An important emerging controversy in clinical trials comparing drug-eluting stent therapies has been the relationship of clinical end points such as target lesion revascularization or target vessel failure (generally considered the "gold standards" for assessing safety and efficacy) and surrogate angiographic end points such as late lumen loss, which measure more precisely the biological effects of these novel anti-restenosis therapies on intimal hyperplasia (19,20).

Zotarolimus (ABT-578, Abbott Pharmaceuticals, Abbott Park, Illinois) is a novel pharmacologic therapy with both

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Abbreviations and Acronyms

CK = creatine kinase
IVUS = intravascular ultrasound
MACE = major adverse cardiac events
MLD = minimal lumen diameter
SES = sirolimus-eluting stent
ZES = zotarolimus-eluting stent

anti-proliferative and anti-inflammatory effects. A tetrazole-containing macrocyclic immunosuppressant, zotarolimus shares structural homology and biological activity with the anti-restenotic agent sirolimus. Recently, in a randomized trial comparing coronary revascularization with zotarolimus-eluting (ZES) and bare metal stents, treatment with ZES was associated with significant reductions in angiographic restenosis and repeat target lesion revascularization (8). Despite this marked benefit relative to conventional bare metal stents, the comparative efficacy between ZES and other effective drug-eluting stents, such as SES, is undetermined. We therefore performed a randomized, multicenter trial to examine the relative safety, clinical efficacy, and angiographic outcomes of a phosphorylcholine polymer-based coronary stent eluting zotarolimus versus sirolimus in patients with native coronary lesions.

METHODS

Trial overview and study population. The ENDEAVOR III (A Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions) trial was a prospective, randomized, single-blinded multicenter trial comparing ZES and SES in elective percutaneous coronary revascularization at 29 hospitals in the U.S. Individuals eligible for enrollment were consecutive patients age 18 years or older with symptomatic ischemic heart disease due to de novo stenotic lesions (>50% angiographic diameter stenosis by visual estimate) in native coronary arteries. Angiographic inclusion criteria were a reference vessel diameter between 2.5 mm and 3.5 mm and lesion length ≥14 mm and ≤27 mm. Patients were excluded if they experienced recent (<72 h) myocardial infarction, underwent prior stent placement within the target vessel or any other vessel within 30 days of the index procedure, or had any general contraindication to the revascularization procedure and routine pharmacologic therapies. Principal angiographic exclusion criteria were a left ventricular ejection fraction <30%, stenosis >40% elsewhere in the target vessel (other than the target lesion), involvement of a sidebranch ≥2.0 mm in diameter, unprotected left main coronary disease, chronic total occlusions, and Thrombolysis In Myocardial Infarction flow grade <2 in the treatment vessel. The study was approved by the institutional review board at each enrolling site, and consecutive, eligible patients signed written informed consent before the interventional procedure.

Device description. The Endeavor drug-eluting coronary stent (Medtronic Vascular, Inc., Santa Rosa, California) is a cobalt-based alloy stent with a phosphorylcholine polymer (21) and zotarolimus dose concentration of 10 μg/mm stent length. In a porcine coronary model, stents coated with a phosphorylcholine polymer and zotarolimus were associated with significant reductions in neointimal area and percent area stenosis (22). In a similar preclinical study, approximately 95% of zotarolimus is eluted from the stent within 15 days of implantation, although drug concentrations within surrounding vascular tissue may be detected as late as 30 days after stent deployment (23). Zotarolimus-eluting stents were available in diameters ranging from 2.5 mm to 3.5 mm and in lengths from 9 mm to 30 mm. The control SES stent (Cypher, Cordis Corporation, Miami Lakes, Florida) was available in diameters ranging from 2.5 mm to 3.5 mm and in lengths from 8 mm to 33 mm.

Randomization, interventional procedure, and adjunctive drug therapies. Patients were blinded to treatment assignment and randomized to the ZES or SES in a 3:1 fashion. Revascularization was to be performed with no more than 1 study stent except in instances of insufficient lesion coverage or as a "bailout" procedure for dissection or thrombus. All lesions were pre-dilated with balloon angioplasty, and the protocol specified that stent length should be 3 to 5 mm longer than the lesion for adequate coverage. Both the ZES and SES were expanded to achieve <10% residual stenosis by visual estimate in the treated segment, with a combination of the stent deployment balloon and, at the operator's discretion, subsequent post-dilatation balloons. After stent implantation was optimized by angiographic criteria, routine intravascular ultrasound (IVUS) of the target lesion was performed.

Before revascularization, all patients received treatment with aspirin (325 mg/day) and clopidogrel (75 mg/day) for at least 48 h, followed by dual antiplatelet therapy for a minimum of 3 months after the procedure and indefinite aspirin therapy. In those patients not receiving at least 48 h of dual anti-platelet therapy before the procedure, a loading dose of clopidogrel (300 to 600 mg) was given immediately before or during the procedure. Unfractionated heparin was administered to achieve an activated clotting time ≥250 s or 200 to 250 s if an intravenous glycoprotein IIb/IIIa inhibitor was used. Treatment with additional device therapies (e.g., atherectomy) was not permitted.

Clinical events were assessed during hospital stay and at clinic visits at 30 days and at 9 months after the index procedure. All patients were scheduled to undergo follow-up angiography and IVUS at 8 months or sooner if the patient developed angina or objective evidence of target vessel ischemia.

Data management and core laboratories. All data were submitted to a central data coordinating facility (Cardiovascular Data Analysis Center, Harvard Clinical Research

Institute, Harvard Medical School, Boston, Massachusetts). Coronary angiograms performed at baseline and at follow-up were reviewed by an independent angiographic core laboratory (Brigham and Women's Angiographic Core Laboratory, Boston, Massachusetts). Standard image acquisition was performed with 2 or more angiographic projections of the stenosis before and after stent placement. Compulsory angiography was planned 240 ± 30 days after the procedure with identical angiographic projections. Qualitative analysis was performed with the modified American College of Cardiology (ACC)/American Heart Association (AHA) classification (24). Quantitative angiographic analysis was performed with a validated automated edge detection algorithm (Medis CMS, Leiden, the Netherlands) (25). Frames were selected for analysis in the 2 "sharpest and tightest" views that minimized foreshortening and vessel overlap. The contrast-filled injection catheter was used as the calibration source. A 5- to 10-mm segment of reference diameter proximal and distal to the stenosis was used to calculate the average reference vessel diameter at baseline, after stent implantation, and at follow-up. Similarly, IVUS images were examined by an independent core laboratory (Cardiovascular Core Analysis Laboratory, Stanford University, Stanford, California) (26,27). Reviewers from each core laboratory were unaware of the type of stent implanted. For both coronary angiograms and IVUS images, quantitative analysis was performed to evaluate the in-stent region (bordered by the stent margins) as well as the in-segment region (in-stent region plus 5-mm margins proximal and distal to the stent).

Study end points and definitions. The primary end point of in-segment late lumen loss was examined by quantitative coronary angiography at 8-month angiographic follow-up. Late lumen loss was defined as the difference between the in-segment minimal lumen diameter (MLD) at the completion of the stenting procedure and the in-segment MLD measured at angiographic follow-up.

Secondary clinical safety and efficacy end points included major adverse cardiac events (MACE: all-cause death, myocardial infarction, and clinically driven target lesion revascularization); the individual components of the composite end point in-hospital, at 30 days, and at 9 months; stent thrombosis (acute, <1 day; subacute, 1 to 30 days; and late, >30 days); clinically driven target vessel revascularization at 9 months; and target vessel failure (cardiovascular death, myocardial infarction, and clinically driven target vessel revascularization) at 9 months. Device success was defined as a <50% diameter stenosis of the target lesion (determined by the core angiographic laboratory) with the assigned study stent, and procedure success was defined as device success and no in-hospital MACEs. Myocardial infarction was defined as a creatine kinase (CK) elevation ≥2 times above the upper limit of normal with any associated elevation in the CK myocardial band or the development of new pathologic Q waves in 2 contiguous electrocardiographic leads. Clinically driven revascularization was identified as any repeat revascularization of the target lesion or target vessel associated with either: 1) ischemic symptoms and/or an abnormal functional study and a ≥50% coronary stenosis by quantitative angiography; or 2) any revascularization of a ≥70% diameter stenosis. All primary and secondary clinical end points were adjudicated by an independent clinical events committee blinded to the patient's treatment assignment.

Secondary angiographic and IVUS efficacy end points included in-stent late lumen loss at 8 months, angiographic binary restenosis (both in-stent and in-segment) at 8 months, and percent volume obstruction assessed by IVUS at 8 months. Development of acquired incomplete late stent apposition at IVUS follow-up was identified according to previously described methods (28). Angiographic binary restenosis was defined as a stenosis ≥50% of the lumen diameter of the target lesion (determined by the core angiographic laboratory). Percent diameter stenosis was defined as $(1 - [\text{MLD}/\text{reference vessel diameter}]) \times 100$, and acute gain was defined as the MLD immediately after the procedure minus the MLD before the procedure. Restenosis patterns were characterized according to established criteria (29).

Statistical methods. This randomized study was designed to determine the equivalence (non-inferiority) of 8-month in-segment late lumen loss with an equivalence definition (delta) such that the ZES would have a mean in-segment late lumen loss ≤0.2 mm plus the control SES in-segment late lumen loss. With a 3:1 (ZES/SES) randomization and assuming a common SD of 0.55 mm, a sample size of 436 patients (323 ZES, 113 SES) with at least 80% angiographic follow-up was required for the trial to have 90% statistical power to detect a significant difference at an alpha level of 0.05. Patients were analyzed for all primary and secondary efficacy and safety end points on the basis of the intent-to-treat principle. Baseline characteristics of study patients were summarized in terms of frequencies and percentages for categorical variables and by means with SDs for continuous variables. Categorical variables were compared by Fisher exact test. Continuous variables were compared by the 2-sample t test. Cumulative event-free survival was summarized as Kaplan-Meier estimates. A p value of 0.05 was established as the level of statistical significance for all tests. All analyses were performed with SAS software (version 8.2 or higher, SAS Institute, Cary, North Carolina).

RESULTS

Patient characteristics. Among 436 patients undergoing elective percutaneous coronary revascularization, 323 patients were randomized to treatment with ZES and 113 patients were treated with SES. No significant differences were present in the baseline clinical or demographic characteristics between patients randomized to receive ZES versus the control SES, except that fewer patients assigned

Table 1. Baseline Patient Clinical and Angiographic Characteristics

	Zotarolimus-Stent Group (n = 323)	Sirolimus-Stent Group (n = 113)	p Value
Clinical characteristics			
Age (yrs)	61.42 ± 10.58 (323)	61.73 ± 11.59 (113)	0.80
Male gender (%)	65.3 (211/323)	81.4 (92/113)	0.001
Diabetes mellitus (%)	29.7 (96/323)	28.3 (32/113)	0.81
Hypertension (%)	70.7 (227/321)	74.3 (84/113)	0.54
History of smoking (%)	66.5 (212/319)	75.2 (85/113)	0.10
Hyperlipidemia (%)	83.5 (268/321)	86.7 (98/113)	0.46
Prior myocardial infarction (%)	19.9 (64/321)	20.7 (23/111)	0.89
Angina class III/IV (%)	59.3 (156/263)	55.9 (52/93)	0.62
Prior percutaneous revascularization (%)	22.6 (73/323)	16.8 (19/113)	0.23
Prior coronary bypass surgery (%)	5.3 (17/323)	8.0 (9/113)	0.35
Angiographic characteristics			
Target vessel (%)			0.55
Left anterior descending artery	41.3 (133/322)	39.8 (45/113)	
Left circumflex artery	23.3 (75/322)	28.3 (32/113)	
Right coronary artery	35.4 (114/322)	31.9 (36/113)	
Type B2/C lesions (%)	67.4 (217/322)	56.6 (64/113)	0.05
Reference vessel diameter (mm)	2.75 ± 0.46 (322)	2.79 ± 0.46 (113)	0.49
Lesion length (mm)	14.98 ± 6.20 (321)	14.95 ± 7.28 (112)	0.96
Number of diseased vessels (%)			0.40
1	62.2 (201/323)	58.4 (66/113)	
2	29.1 (94/323)	30.1 (34/113)	
3	8.7 (28/323)	11.5 (13/113)	
Left ventricular ejection fraction (%)	55.66 ± 9.11 (307)	56.28 ± 9.28 (110)	0.54

Values expressed as number (%) or mean (± SD). Angina severity according to Canadian Cardiovascular Society classification.

to ZES were male (65.3% vs. 81.4%, p = 0.001) (Table 1). Overall, the mean age was 61.5 years, 21.1% underwent prior percutaneous coronary intervention, 68.8% had a history of smoking, and 29.4% had diabetes mellitus. Most patients (61.2%) had single-vessel coronary disease, and 20.1% of patients had a history of prior myocardial infarction.

Baseline angiographic characteristics were also similar (Table 1), except for a higher frequency of moderate complexity lesions characterized as type B2 or C according to the modified ACC/AHA classification (24) in the ZES group (67.4% vs. 56.6%, p = 0.047). Overall, the mean lesion length was 14.97 mm, the average reference vessel diameter was 2.76 mm, and most lesions (40.9%) were located in the left anterior descending artery.

Procedural and in-hospital outcomes. The number, length, and diameter of stents implanted were similar in patients assigned to each treatment group (Table 2). The average number of stents/target lesion was 1.15, with overlapping stents in 23.6% of patients. Importantly, device success was significantly higher among patients treated with ZES (98.8% vs. 94.7%, p = 0.02). By intention to treat analysis, the reason for device failure in SES cases was an inability to deliver the assigned study stent to the target lesion, except for 1 instance of an inadvertent protocol exclusion, in which a patient was treated with a non-study stent.

In-hospital major adverse events were higher among patients randomized to SES, principally owing to a significantly higher incidence of non–Q-wave myocardial infarction (0.6% with ZES vs. 3.5% with SES for both non–Q-wave myocardial infarction and in-hospital MACE; p = 0.04) (Table 2). Among patients with myocardial infarction, a CK-MB elevation >3 times the upper normal limit occurred in all patients except 1 ZES patient, and a CK elevation >3 times the upper normal limit occurred in only 1 patient, who was treated with SES. Administration of intravenous glycoprotein IIb/IIIa inhibitors did not differ between groups (44.0% with ZES vs. 44.6% with SES, p = 0.91). Among patients with myocardial infarction, 2 of the 4 events in the SES group and none in the ZES group were related to sidebranch occlusion. There were no differences in the frequency of myocardial infarction between patients receiving multiple and/or overlapping stents in either treatment group. Procedure success was significantly higher with ZES than with SES (98.1% vs. 91.2%, p = 0.002).

Angiographic and IVUS outcomes. Eight-month follow-up angiography was performed in 282 (87.3%) of patients in the ZES group and 94 (83.2%) patients in the SES group. There were no differences in baseline characteristics and clinical outcomes in patients who did and those who did not undergo follow-up angiography. Both in-stent late lumen loss and in-stent binary restenosis were significantly higher after ZES versus SES therapy (Table 3). The primary end point, in-segment late lumen loss, was also significantly higher among patients treated with ZES versus SES (0.34 ± 0.44 mm vs. 0.13 ± 0.32 mm, p < 0.001; p = 0.65 for non-inferiority), corresponding to a higher frequency of in-segment binary restenosis (11.7% vs. 4.3%, p = 0.04) (Table 3). Although the pattern of in-stent

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Table 2. Procedural Angiographic Results and In-Hospital Clinical Events

	Zotarolimus-Stent Group (n = 323)	Sirolimus-Stent Group (n = 113)	p Value
Procedural characteristics			
Number of stents	1.14 ± 0.41 (317)	1.19 ± 0.46 (111)	0.28
Stent length (mm)	22.33 ± 6.18 (322)	23.02 ± 7.69 (112)	0.40
Stent diameter (mm)	3.07 ± 0.39 (316)	3.11 ± 0.35 (107)	0.31
Inflation pressure (atm)	13.54 ± 2.51 (318)	14.52 ± 2.89 (110)	<0.01
>1 stent implanted (%)	12.0 (38/317)	16.2 (18/111)	0.26
Minimal luminal diameter (mm)			
Before procedure			
In-lesion	0.92 ± 0.41 (322)	0.90 ± 0.39 (113)	0.60
After procedure			
In-stent	2.67 ± 0.42 (322)	2.67 ± 0.40 (112)	1.00
In-segment	2.26 ± 0.45 (322)	2.28 ± 0.47 (113)	0.82
Diameter stenosis (%)			
Before procedure			
In-lesion	66.79 ± 12.41 (322)	67.91 ± 12.42 (113)	0.41
After procedure			
In-stent	4.35 ± 9.77 (322)	5.92 ± 9.07 (112)	0.14
In-segment	19.43 ± 9.23 (322)	20.17 ± 11.74 (113)	0.55
Device success (%)	98.8 (318/322)	94.7 (107/113)	0.02
Procedural success (%)	98.1 (316/322)	91.2 (103/113)	0.002
In-hospital outcomes			
Death (%)	0 (0/323)	0 (0/113)	—
Myocardial infarction (%)	0.6 (2/323)	3.5 (4/113)	0.04
Q-wave (%)	0 (0/323)	0 (0/113)	—
Non–Q-wave (%)	0.6 (2/323)	3.5 (4/113)	0.04
Stent thrombosis (%)	0 (0/323)	0 (0/113)	—
Target lesion revascularization (%)	0 (0/323)	0 (0/113)	—
Target vessel revascularization (%)	0 (0/323)	0 (0/113)	—
Major adverse cardiac events (%)	0.6 (2/323)	3.5 (4/113)	0.04

Values expressed as number (%) or mean (± SD).

restenosis was most frequently focal in both ZES- and SES-treated patients, the restenosis lesion length was significantly greater in patients treated with ZES (12.94 mm with ZES vs. 6.46 mm with SES, $p < 0.001$). There were no differences in restenosis within the proximal or distal margins of the stents comparing ZES versus SES patients.

Table 3. Angiographic and IVUS Outcomes at Eight Months

	Zotarolimus-Stent Group (n = 323)	Sirolimus-Stent Group (n = 113)	p Value
Quantitative angiography			
Late lumen loss (mm)			
In-stent	0.60 ± 0.48 (281)	0.15 ± 0.34 (94)	<0.001
In-segment	0.34 ± 0.44 (281)	0.13 ± 0.32 (94)	<0.001
Minimal luminal diameter (mm)			
In-stent	2.08 ± 0.57 (282)	2.52 ± 0.56 (94)	<0.001
In-segment	1.92 ± 0.52 (282)	2.16 ± 0.50 (94)	<0.001
Diameter stenosis (%)			
In-stent	24.31 ± 17.08 (282)	10.98 ± 15.88 (94)	<0.001
In-segment	29.88 ± 15.27 (282)	23.86 ± 13.87 (94)	<0.001
Binary restenosis (%)			
In-stent	9.2 (26/282)	2.1 (2/94)	0.02
In-segment	11.7 (33/282)	4.3 (4/94)	0.04
Proximal margin	1.5 (4/270)	1.1 (1/87)	1.0
Distal margin	1.4 (4/281)	1.1 (1/92)	1.0
IVUS outcomes			
Volume obstruction (%)	16.1 ± 10.8 (185)	2.7 ± 3.1 (61)	<0.001
Incomplete stent apposition (%)			
Baseline	12.6 (31/247)	17.9 (17/95)	0.22
Persistent	6.8 (13/190)	11.8 (8/68)	0.21
Resolved	5.8 (11/190)	7.4 (5/68)	0.77
Acquired	0.5 (1/190)	5.9 (4/68)	0.02

IVUS = intravascular ultrasound.

Table 4. Clinical Events at Nine Months

	Zotarolimus-Stent Group (n = 323)	Sirolimus-Stent Group (n = 113)	p Value	Relative Risk [95% Confidence Interval]
Death (%)	0.6 (2/316)	0 (0/113)	1.0	—
Myocardial infarction (%)	0.6 (2/316)	3.5 (4/113)	0.04	0.18 [0.03, 0.96]
Q-wave (%)	0 (0/316)	0 (0/113)	—	—
Non–Q-wave (%)	0.6 (2/316)	3.5 (4/113)	0.04	0.18 [0.03, 0.96]
Stent thrombosis (%)	0 (0/316)	0 (0/113)	—	—
Target lesion revascularization (%)	6.3 (20/316)	3.5 (4/113)	0.34	1.79 [0.62, 5.12]
Percutaneous	5.4 (17/316)	3.5 (4/113)	0.61	1.52 [0.52, 4.42]
Surgical	0.9 (3/316)	0 (0/113)	0.57	—
Target vessel revascularization—not involving target lesion (%)	6.0 (19/316)	5.3 (6/113)	1.0	1.13 [0.46, 2.76]
Percutaneous	5.7 (18/316)	5.3 (6/113)	1.0	1.07 [0.44, 2.63]
Surgical	0.3 (1/316)	0 (0/113)	1.0	—
Major adverse cardiac events (%)	7.6 (24/316)	7.1 (8/113)	1.0	1.07 [0.50, 2.32]
Target vessel failure (%)	12.0 (38/316)	11.5 (13/113)	1.0	1.05 [0.58, 1.89]

Immediate post-procedural IVUS measurements did not differ significantly among the 2 study groups. Follow-up IVUS at 8 months (with images suitable for analysis) was performed in 187 (59.2%) patients in the ZES group and 61 (54.0%) patients in the SES group. At 8 months, percent volume obstruction (16.1 ± 11% vs. 2.7 ± 3%, $p < 0.001$) was significantly greater with ZES compared with SES (Table 3). Importantly, newly observed incomplete late stent apposition with abnormal remodeling and vessel expansion occurred in 4 patients (5.9%) treated with SES and in only 1 (0.5%) patient receiving ZES ($p = 0.02$) (Table 3).

Nine-month clinical outcomes. Clinical follow-up was completed in 316 patients (97.8%) in the ZES group and in 113 patients (100%) in the SES group (Table 4). There were no episodes of acute, subacute, or late stent thrombosis in either treatment group. There were 2 (0.6%) deaths in the ZES group and none in the SES group. The deaths in the ZES group were due to stroke in 1 patient and pancreatic cancer in the other patient. There were no out-of-hospital myocardial infarctions in either group, such that the early lower frequency of myocardial infarctions with ZES persisted during the follow-up period. The occurrence of clinically driven target lesion revascularization did not significantly vary between the ZES and SES groups (6.3% ZES vs. 3.5% SES, $p = 0.34$) (Table 4). Target vessel revascularization unrelated to the target lesion was also similar between ZES and SES groups (6.0% with ZES vs. 5.3% with SES, $p = 1.0$). Target lesion revascularization adjudicated as non-clinically driven (i.e., occurring without an abnormal functional study or ≥70% stenosis) occurred in an additional 11 (3.5%) patients treated with ZES; therefore, the total (clinically and non-clinically driven) target lesion revascularization rates were 9.8% and 3.5% for the ZES and SES groups, respectively ($p = 0.04$). There were no significant differences between ZES and SES in the occurrence of MACEs (7.6% vs. 7.1%, $p = 1.0$) and target vessel failure (12.0% vs. 11.5%, $p = 1.0$). Actuarial event-free survival at 9 months for clinically driven target lesion revascularization, MACEs, and target vessel failure did not significantly differ among ZES and SES patients (Fig. 1).

DISCUSSION

In this prospective, randomized trial comparing the clinical efficacy, safety, and angiographic outcomes among patients treated with ZES and SES, treatment with ZES was associated with increased neointimal hyperplasia resulting in greater angiographic late lumen loss.

The reasons for higher late lumen loss observed with ZES in this trial compared with SES (the primary end point) and other studies are incompletely understood. Among patients treated with ZES in the first-in-man ENDEAVOR I (100-patient) and large (1,200-patient), randomized ENDEAVOR II trials (8,30), for example, angiographic measurement of in-stent late lumen loss was 0.61 mm in both studies, compared with 0.60 mm in the current study. Increased neointimal hyperplasia with ZES might be due to differences in biological activity of zotarolimus compared with sirolimus, although in vitro cell culture experiments and animal studies would suggest equivalent nanomolar potencies in suppressing smooth muscle cell proliferation (23).

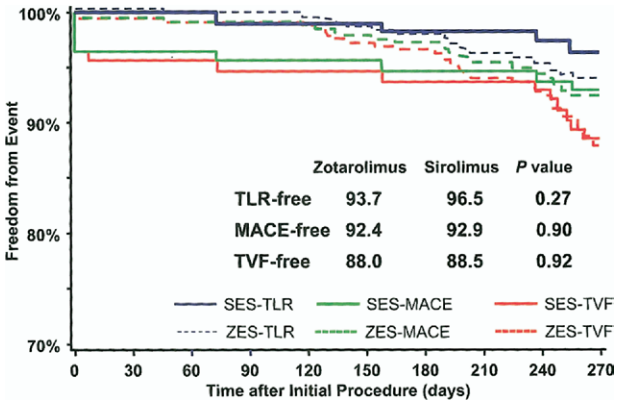

Figure 1. Kaplan-Meier event-free survival to 9 months for patients treated with zotarolimus- (ZES) and sirolimus-eluting (SES) stents. MACE = major adverse cardiac events; TLR = target lesion revascularization; TVF = target vessel failure.

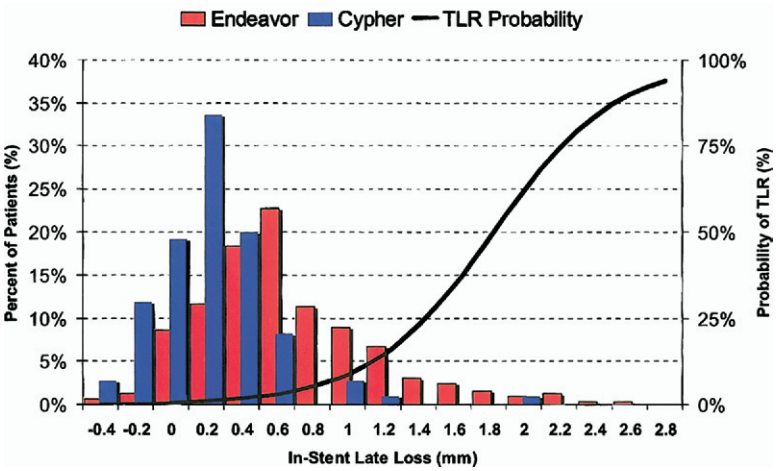

Figure 2. Logistic regression relationship between late lumen loss and target lesion revascularization (TLR) for patients treated with zotarolimus-eluting stents.

Another potential reason for the observed differences is that the more rapid elution kinetics of zotarolimus from the phosphorylcholine polymer—95% eluted in approximately 2 weeks (23)—compared with the slower release of sirolimus from the polyethylene-co-vinyl acetate/poly n-butyl methacrylate co-polymer—95% eluted in approximately 6 weeks—might significantly influence biological efficacy. Optimal suppression of procedural-induced injury responses resulting in inflammation and subsequent intimal hyperplasia might require more prolonged tissue exposure to the therapeutic agent. Lastly, there might be differences in biological responses to either the stent or the phosphorylcholine polymer itself.

Regarding secondary end points, the results from this trial are the first among comparative drug-eluting stent trials to demonstrate a statistically significant difference in both procedural device success and in-hospital clinical outcome. First, device success was significantly higher with ZES, owing to enhanced stent deliverability likely associated with a more flexible, low profile thin-strut cobalt alloy stent. Second, although infrequent in both groups, the occurrence of in-hospital non–Q-wave myocardial infarctions was significantly lower with ZES compared with SES. This observation is more difficult to reconcile, given that most procedural, demographic, and baseline angiographic characteristics did not differ between the 2 groups.

Although the angiographic and IVUS follow-up analyses favored SES compared with ZES, differences in clinical outcome were less consistent. Most clinical end points did not statistically differ between these 2 drug-eluting stents (Table 4), including clinically driven target lesion revascularization (6.3% for ZES vs. 3.5% for SES, p = 0.34). However, overall target lesion revascularization (clinically and non-clinically driven) was significantly more common in the ZES group. The modest but statistically significant benefit associated with lower peri-procedural myocardial infarction rates with ZES was offset by the slightly higher follow-up target lesion revascularization frequencies, such that the composite target vessel failure and MACE values for ZES and SES were similar. As with previous studies using paclitaxel-eluting stents (3,6,7), a discordance might exist between angiographic and clinical outcomes in this ZES trial, suggesting that there might be an angiographic late lumen loss threshold or "window" below which the occurrence of repeat clinically driven revascularization events is unlikely (Fig. 2). In low- or medium-complexity lesions, an in-stent late loss of 0.60 mm and an in-segment late loss of 0.34 mm were in most instances well tolerated and not sufficient to induce important changes in clinically driven target lesion revascularization compared with SES. Of course, in higher complexity lesions (such as diffuse disease, in-stent restenosis, or small vessels), where there is the potential for an upward drift in late lumen loss, greater differences between ZES and SES might become apparent. At present, an international "open" registry with ZES is ongoing to provide insights regarding the clinical efficacy of ZES in a broad, unselected patient population with greater lesion complexity and in varied clinical settings.

Study limitations. There are several limitations of this study. Because the primary objective of the study was to compare an angiographic surrogate end point—follow-up in-segment late lumen loss—between 2 drug-eluting stents, the sample size did not enable adequate statistical power to rigorously examine differences among pertinent clinical end points. Moreover, the unbalanced randomization resulted in a very small SES comparison group, such that results for SES were subject to potential over-interpretation due to broad confidence intervals. It is also noteworthy that the differences between ZES and SES were somewhat exaggerated in this clinical trial, owing to an unexpectedly low SES in-segment late lumen loss compared with other recent SES clinical trials (1,2,17). Unlike previous double-blinded drug-eluting stent versus bare metal stent clinical trials, this study was single-blinded, and the identity of the treatment stent was known to the interventional operator, which could introduce bias in procedural outcomes and the performance

of repeat revascularization. As stated, the results from this trial are specific to the patient population studied and cannot be generalized to the much broader population of patients with more complex lesion morphologies.

Conclusions. As demonstrated in this ZES versus SES clinical trial, ZES was shown to have significantly higher angiographic late lumen loss. Although most other angiographic outcomes favored SES, differences in secondary clinical end points were not consistent between the 2 stent groups. Clinical interventional operators will have to consider the overall attributes of ZES versus SES in making decisions concerning preferential device use under specific clinical circumstances.

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APPENDIX

For a list of the ENDEAVOR III trial study sites and principal investigators, please see the online version of this article.