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CVN Interview

Late-Term Clinical Outcomes With Zotarolimus- and Sirolimus-Eluting Stents

5-Year Follow-Up of 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)

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Objectives This study sought to compare late safety and efficacy outcomes following percutaneous coronary revascularization with zotarolimus-eluting stents (ZES) and sirolimus-eluting stents (SES).

Background Despite higher late lumen loss and binary restenosis with ZES compared with SES, it is uncertain whether differences in early angiographic measures translate into more disparate late clinical events.

Methods Clinical outcomes were prospectively evaluated through 5 years in 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) that randomized 436 patients of relatively low anatomic and clinical risk to treatment with ZES (n = 323) or SES (n = 113) and evaluated a primary endpoint of 8-month angiographic late lumen loss.

Results At 5 years (completeness of follow-up: 95.2%), pre-specified endpoints of all-cause mortality (5.2% vs. 13.0%, p = 0.02), myocardial infarction (1.0% vs. 4.6%, p = 0.03), and the composite event rates of cardiac death/myocardial infarction (1.3% vs. 6.5%, p = 0.009) and major adverse cardiac events (14.0% vs. 22.2%, p = 0.05) were significantly lower among patients treated with ZES. Rates of target lesion (8.1% ZES vs. 6.5% SES, p = 0.68) and target vessel revascularization were similar between treatment groups. Stent thrombosis was infrequent and similar in both groups (0.7% ZES vs. 0.9% SES, p = 1.0). Between 9 months and 5 years, progression of major adverse cardiac events was significantly more common with SES than with ZES (16.7% vs. 7.8%, p = 0.015).

Conclusions Despite initially higher angiographic late lumen loss, rates of clinical restenosis beyond the protocol-specified angiographic follow-up period remain stable with ZES compared with the rates for SES, resulting in similar late-term efficacy. Over 5 years, significant differences in death, myocardial infarction, and composite endpoints favored treatment with ZES. (The Medtronic Endeavor III Drug Eluting Coronary Stent System Clinical Trial [ENDEAVOR III]; NCT00217256) (J Am Coll Cardiol Intv 2011;4:543–50) © 2011 by the American College of Cardiology Foundation

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A common theme of early drug-eluting stent (DES) trials involved the comparison of angiographic surrogate indexes related to the antiproliferative effect of DES and reduction in neointimal hyperplasia (1–3). Correlating angiographic results with intermediate-term (e.g., 9- to 12-month) revascularization rates, predictive models were designed to estimate the likelihood of revascularization, extrapolating the relationship between biological and clinical efficacy for any particular DES (4–6). In comparison with late lumen loss or angiographic restenosis as endpoints, more contemporary trials directed toward patient-oriented clinical outcomes have identified emerging differences in late efficacy and safety events between DES that are less closely linked to early measures (7–10).

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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) was a randomized evaluation of angiographic late lumen loss as a primary endpoint among patients undergoing percutaneous coronary revascularization with zotarolimus-eluting stents (ZES) (Endeavor, Medtronic Cardiovascular, Santa Rosa, California) and sirolimus-eluting stents (SES) (Cypher, Cordis Corporation, Bridgewater, New Jersey) (3). In this study, angiographic measures of late lumen loss and restenosis were significantly higher with ZES and were also associated a small relative difference in target lesion revascularization (TLR) that was not statistically significant, with no difference in death or myocardial infarction (MI) at 9 months. As part of the planned 5-year follow-up, an important focus of the investigation is not only to compare events relative to DES assignment, but also to try to determine whether the early observation of greater neointimal hyperplasia with ZES is associated with progression of adverse events beyond the initial study report. Therefore, we evaluated safety and efficacy outcomes among patients enrolled in the ENDEAVOR III trial, comparing ZES and SES patient cohorts over the entire 5-year study period in addition to the interval from 9 months to latest follow-up.

Abbreviations and Acronyms

DES = drug-eluting stent(s)
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization
ZES = zotarolimus-eluting stent(s)

Methods

Study overview. The ENDEAVOR III trial was a prospective, multicenter trial designed to enroll 436 patients with symptomatic ischemic heart disease undergoing single-vessel percutaneous coronary intervention of a target lesion with diameter between 2.5 and 3.5 mm and lesion length ≥14 and ≤27 mm. The primary endpoint evaluated in this study was in-segment late lumen loss assessed by quantitative coronary angiography at 8 months. Further detail regarding enrollment criteria and study methods has been previously reported (3). Patients were blinded to treatment assignment and were randomized to ZES or SES in a 3:1 fashion. Following revascularization, patients were recommended per protocol to receive indefinite aspirin therapy and a minimum of 3 months of thienopyridine treatment. Angiographic follow-up at 8 months was indicated per protocol for all patients and performed in 371 patients (85.1%). The study protocol (with pre-specified follow-up through 5 years) was approved by the institutional ethics committees at each enrolling site, and consecutive, eligible patients signed written informed consent before the interventional procedure.

Data management and study endpoints. Clinical events were assessed annually through patient contact with source document verification and independent adjudication. Clinical and angiographic results were submitted to a central data coordinating facility (Harvard Clinical Research Institute, Boston, Massachusetts). Coronary angiograms performed at baseline and any time during follow-up were reviewed by an independent core laboratory (Beth Israel Deaconess Medical Center, Boston, Massachusetts).

The primary objective of this patient-level analysis was to compare 5-year clinical outcomes between patients treated with ZES and SES against the background result of statistically significant differences in angiographic measures at 8 months. Clinical safety and efficacy endpoints included: major adverse cardiac events (MACE) (the composite of all-cause death, MI, emergency coronary artery bypass surgery, and clinically driven TLR) and the individual

from Abbott Vascular, Medtronic Cardiovascular, and Cordis Corporation. Dr. Mauri has served as a consultant to Cordis Corporation; and has received institutional research grant support from Medtronic Cardiovascular, Abbott Vascular, Boston Scientific, Cordis Corporation, Eli Lilly, Daiichi Sankyo, Bristol-Myers Squibb, and sanofi-aventis. Dr. Popma has received research grants from Abbott Vascular, Biosensors, Boston Scientific, Cordis Corporation, ev3, and Medtronic; and he has served as a consultant for Abbott Vascular, Boston Scientific, Cordis Corporation, Lilly, and Medtronic, and as a speaker for Boston Scientific, Bristol-Myers Squibb, Cordis Corporation, Eli Lilly, The Medicines Company, Medtronic, Pfizer, and sanofi-aventis. Dr. Turco has served as an adviser and speaker for and received research support from Medtronic, Boston Scientific, and Abbott Vascular. Dr. Gurbel has received research grants from AstraZeneca, Novartis/Portola, Pozen, Medtronic, and sanofi-aventis; and he has received consulting fees from AstraZeneca, Portola, Pozen, sanofi-aventis, Bayer, Eli Lilly, Daiichi Sankyo, National Institutes of Health, and Schering-Plough/Merck. Dr. Fitzgerald has served as a consultant for Abbott, Boston Scientific, Cordis Corporation, EndoTex, St. Jude Medical, Biosensor, ev3, Medtronic Cardiovascular, GlaxoSmithKline, ATI, Volcano Corporation, Novadaq, AorTx, CardioMind, Cytograft Tissue Engineering, FlowCardia, Cardio Optics, Optics, CardioMind, RTI Medical, SurModics, Hospira, and CatherosMed. Dr. Leon has served as a consultant to Abbott Vascular, Boston Scientific, Cordis Corporation, Medinol, Medtronic Cardiovascular, and Volcano Corporation.

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Table 1. Selected Patient Clinical, Angiographic, and Procedural Characteristics

	ZES (n = 323)	SES (n = 113)	p Value
Clinical characteristics			
Age, yrs	61.42 ± 10.58 (323)	61.73 ± 11.59 (113)	0.80
Male	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 and procedural characteristics			
Target vessel			0.53
Left anterior descending artery	41.2 (133/323)	39.8 (45/113)	
Left circumflex artery	23.2 (75/323)	28.3 (32/113)	
Right coronary artery	35.6 (115/323)	31.9 (36/113)	
Type B2/C lesions	67.2 (217/323)	56.6 (64/113)	0.05
Reference vessel diameter, mm	2.75 ± 0.46 (323)	2.79 ± 0.46 (113)	0.49
Lesion length, mm	14.96 ± 6.20 (322)	14.95 ± 7.28 (112)	0.96
Number of stents	1.14 ± 0.40 (323)	1.19 ± 0.45 (113)	0.28
Stent length, mm	22.31 ± 6.18 (323)	23.02 ± 7.69 (112)	0.33
Stent diameter, mm	3.07 ± 0.38 (317)	3.12 ± 0.35 (111)	0.21
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	55.7 ± 9.1 (307)	56.3 ± 9.3 (110)	0.54

Values are mean ± SD (n) or % (n/N). Angina severity classified according to Canadian Cardiovascular Society classification.
SES = sirolimus-eluting stent (s); ZES = zotarolimus-eluting stent(s).

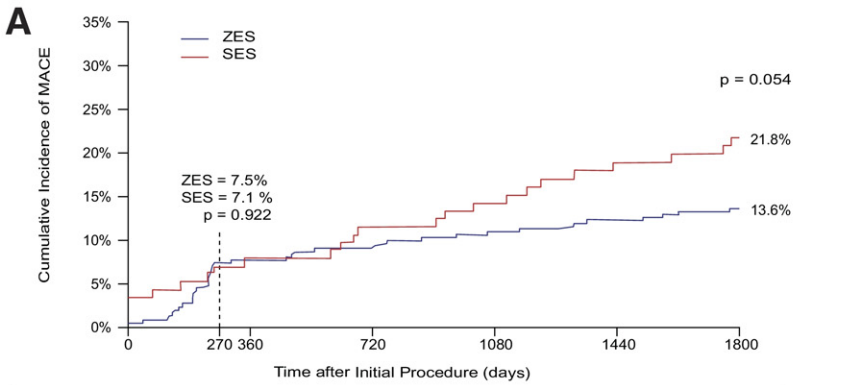
components of the composite endpoint; stent thrombosis (per Academic Research Consortium definition criteria (11) and reported as early: ≤30 days, late: 31 days to 1 year, very late: >1 year); clinically driven target vessel revascularization; and target vessel failure (cardiac death, MI, and clinically driven target vessel revascularization). Clinically driven repeat revascularization was defined as revascularization in the target vessel associated with a positive functional ischemia study or ischemic symptoms and an angiographic minimal lumen diameter stenosis ≥50% by quantitative coronary angiography or as revascularization of a target vessel with diameter stenosis ≥70% by quantitative coronary angiography without either ischemic symptoms or positive functional study.

Statistical methods. All primary analyses were performed according to the intention-to-treat principle. Categorical variables were compared using Fisher exact test, and continuous variables were compared using a nonparametric test (Wilcoxon score). As an exploratory evaluation of late-term events beyond the initial study period, event rates were compared between 9 months and 5 years. To maintain balanced patient characteristics by randomization, patients with events before 9 months were not excluded. The Kaplan-Meier method was used to calculate the time to clinical endpoints, and the log-rank test was used to compare between-group differences. All statistical calculations were programmed using SAS (version 9.0 or above, SAS Institute, Cary, North Carolina).

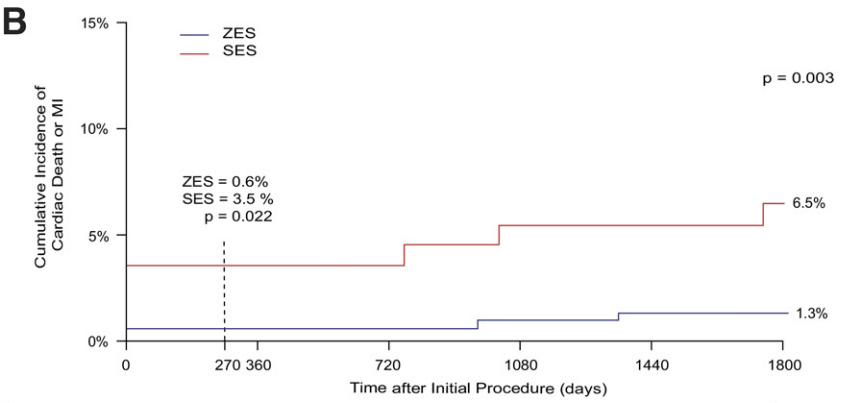
Results

Patient characteristics. The demographics of the study population and lesion characteristics are detailed in Table 1. No significant differences were observed between treatment cohorts other than a lower prevalence of men assigned to treatment with ZES (65.3% vs. 81.4%, p = 0.001). Among the 436 patients treated, overall clinical characteristics included: age: 61.5 ± 10.8 years; diabetes: 29.4%; angina class III/IV: 58.4%; and multivessel disease: 38.8%. The average lesion length was 14.96 ± 6.49 mm, and the mean reference vessel diameter was 2.76 ± 0.46 mm.

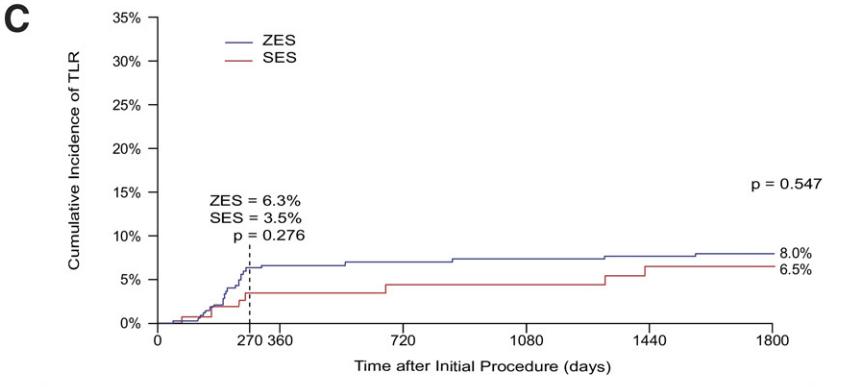
Dual antiplatelet therapy (aspirin and thienopyridine) adherence at 1 year was 17.5% and 16.5% (p = 0.88) for ZES



MACE	0	270	360	720	1080	1440	1800
ZES, N	323	321	298	293	284	275	268
Events, n (%)	2 (0.6)	22 (7.5)	1 (7.8)	4 (9.0)	6 (11.0)	4 (12.3)	4 (13.6)
SES, N	113	109	105	103	98	94	88
Events, n (%)	4 (3.5)	4 (7.1)	1 (8.0)	4 (11.5)	3 (14.3)	5 (18.9)	3 (21.8)



CD/MI	0	270	360	720	1080	1440	1800
ZES, N	323	321	318	314	306	298	290
Events, n (%)	2 (0.6)	0 (0.6)	0 (0.6)	0 (0.6)	1 (1.0)	1 (1.3)	0 (1.3)
SES, N	113	109	109	107	103	98	94
Events, n (%)	4 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)	2 (5.5)	0 (5.5)	1 (6.5)



MACE	0	270	360	720	1080	1440	1800
ZES, N	323	323	289	280	272	263	257
Events, n (%)	0 (0)	20 (6.3)	1 (6.6)	1 (6.9)	1 (7.3)	1 (7.7)	1 (8.0)
SES, N	113	113	109	107	101	97	91
Events, n (%)	0 (0)	4 (3.5)	0 (3.5)	1 (4.5)	0 (4.5)	2 (6.5)	0 (6.5)

Figure 1. 5-Year Cumulative Incidence of MACE, Cardiac Death/MI, and Clinically Driven TLR

Five-year cumulative incidence of major adverse cardiac event(s) (MACE) **(A);** cardiac death (CD)/myocardial infarction (MI) **(B);** and clinically driven target lesion revascularization (TLR) **(C)** are shown. Cumulative event curves, produced by Kaplan-Meier methods, compare zotarolimus-eluting stents (ZES) to sirolimus-eluting stent (SES) through 5-year follow-up. The p values at 270 and 1,800 days are log ranked.

Table 2. 5-Year Clinical Outcomes in the ENDEAVOR III Trial

	ZES (n = 307)	SES (n = 108)	p Value
Death	5.2 (16)	13.0 (14)	0.02
Cardiac death	0.3 (1)	2.8 (3)	0.06
Myocardial infarction	1.0 (3)	4.6 (5)	0.03
Q-wave	0.3 (1)	0.9 (1)	0.45
Non–Q-wave	0.7 (2)	3.7 (4)	0.04
Cardiac death/myocardial infarction	1.3 (4)	6.5 (7)	0.009
Definite/probable stent thrombosis	0.7 (2)	0.9 (1)	1.00
0–360 days	0.3 (1)	0 (0)	1.00
361–1,800 days	0.3 (1)	0.9 (1)	0.45
Target lesion revascularization	8.1 (25)	6.5 (7)	0.68
Target vessel revascularization	16.9 (52)	13.0 (14)	0.36
Major adverse cardiac events	14.0 (43)	22.2 (24)	0.05
Target vessel failure	17.9 (55)	18.5 (20)	0.89

Values are % (n).
Abbreviations as in Table 1.

and SES groups, respectively, and 7.0% and 6.4% (p = 1.00) at 5 years.

Overall 5-year and interval clinical outcomes. Through 5 years, ascertainment of clinical events was complete for 95.0% (307 of 323) of ZES patients and 95.6% (108 of 113) of SES patients. Compared with the SES group, events including all-cause mortality (5.2% vs. 13.0%, p = 0.02), MI (1.0% vs. 4.6%, p = 0.03), and the composite event rates of cardiac death/MI (1.3% vs. 6.5%, p = 0.009) and MACE (14.0% vs. 22.2%, p = 0.05) were significantly less common among patients treated with ZES (Fig. 1, Table 2). Rates of target lesion (8.1% ZES vs. 6.5% SES, p = 0.68) (Fig. 1) and target vessel revascularization were similar between treatment groups. Definite or probable stent thrombosis was infrequent and similar in both groups (0.7% ZES vs. 0.9% SES, p = 1.0).

At 9 months, the MACE rate was similar between treatment arms, but after 9 months, MACE was significantly more frequent in the SES arm than in the ZES arm (16.7% vs. 7.8%, p = 0.015). This was principally driven by higher rates of all-cause death (4.6% vs. 13.0%, p = 0.006) and cardiac death (0.3% vs. 2.8%, p = 0.056) in the SES cohort (Fig. 1, Table 3).

Discussion

In the ENDEAVOR III trial, although higher angiographic restenosis was observed in ZES in the primary results reported for the 9-month follow-up, cumulative outcomes through 5 years demonstrated that the composite endpoint of MACE and the important components of death, as well as cardiac death and MI, favored treatment with ZES compared with SES. After 9 months, composite events were more common in the SES cohort and were principally driven by mortality (all-cause and cardiovascular). Conversely, despite early differences in angiographic outcome, rates of clinical restenosis beyond the period of protocol-specified angiographic follow-up remain stable with ZES compared with SES, resulting in similar late-term efficacy as measured by the need for repeat procedures.

Considering the clinical need for DES to effectively inhibit restenosis more than bare-metal stents, yet exhibit a similar safety profile, an opportunity exists to develop newer generation DES that may enhance biocompatibility, promote vessel healing and vasomotor function following PCI, and permit a clinical safety profile similar to bare-metal stents. Compared with alternative DES, the Endeavor ZES consists of a thin-strut cobalt alloy platform and phosphorylcholine polymer that enable more rapid and complete endothelial coverage and recovery of vasomotor reactivity (12–16). Unlike most DES, however, the more rapid elution kinetics of zotarolimus (>95% within 14 days of implantation [3]) also permit greater angiographic late lumen loss compared with other DES yet less than conventional bare-metal stents (3,17,18).

Whereas DES polymers have been implicated in delayed healing and late safety events, only recently has late efficacy been evaluated. Among SES-treated patients undergoing 5-year angiographic follow-up in the SIRTAX LATE (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization-Late) trial (19), for example, in-stent late lumen loss increased approximately 2-fold compared with 8-month angiographic results (0.12 ± 36 mm vs. 0.25 ± 49 mm, p < 0.001) that paralleled similar increases in TLR. In the ISAR TEST-2 (Intracoronary Stenting and Angiographic Results–Test Efficacy of 3 Limus-Eluting Stents) trial that included serial angiographic follow-up (20), angiographic restenosis at 1 year and TLR were highest with ZES. However, accrual of binary angiographic restenosis between 1 and 2 years was more common for SES compared with ZES or a polymer-free DES, corresponding to higher incident TLR between 1 and 2 years for SES versus comparator groups ($\Delta_{1\text{-}2\ \text{Years}}$: SES: 3.5%, ZES: 0.7%, polymer-free DES: 0.9%). Progression of angiographic late loss has been similarly observed with both paclitaxel- and everolimus-eluting stents (19,22).

In the present study, despite an 8-month angiographic late loss nearly 3× higher than with SES (0.36 ± 0.46 mm vs. 0.13 ± 0.33 mm, p < 0.001), there was instead less progression of clinical restenosis observed in the ZES cohort beyond the initial 9 months, demonstrating a stable and low rate of late TLR that is consistent among ZES trials through the most recent follow-up (Table 4). Similarly, results for SES in this analysis are in accord with longitudinal data for SES represented in the SIRTAX LATE (19) and SIRIUS (Sirolimus-Eluting Stent in Coronary Lesions) (23) trials, demonstrating that progression of TLR beyond the first year accounts for approximately one-half of total TLR. In comparison, more than 80% of

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Table 3. Clinical Outcomes From 9 Months to 5 Years for ZES and SES in the ENDEAVOR III Trial

	ZES (n = 307)	SES (n = 108)	p Value
Death	4.6 (14)	13.0 (14)	0.006
Cardiac death	0.3 (1)	2.8 (3)	0.06
Myocardial infarction	0.3 (1)	0.9 (1)	0.45
Q-wave	0.3 (1)	0.9 (1)	0.45
Non–Q-wave	0 (0)	0 (0)	—
Cardiac death/myocardial infarction	0.7 (1)	3.7 (4)	0.04
Target lesion revascularization	2.9 (9)	3.7 (4)	0.75
Target vessel revascularization	7.5 (23)	7.4 (8)	1.00
Target vessel failure	8.1 (25)	10.2 (11)	0.55
ARC definite/probable ST	0.7 (2)	0.9 (1)	1.00
ARC ST all	1.0 (3)	3.7 (4)	0.08
MACE	7.8 (24)	16.7(18)	0.02

Values are % (n).
ARC = Academic Research Consortium; MACE = major adverse cardiac event(s); ST = stent thrombosis; other abbreviations as in Tables 1 and 2.

total TLR for ZES in the ENDEAVOR III trial was observed within 1 year of index revascularization. This finding is consistent with the pooled analysis of 2,132 ZES-treated patients (42% angiographic follow-up) in which a nearly identical proportion of overall TLR through latest duration of follow-up occurs within the first year (21) (Table 4).

Safety- and efficacy-related outcomes in the present study for ZES parallel more recent comparative trial results with other DES. Through 3-year follow-up in the ENDEAVOR IV trial comparing ZES and paclitaxel-eluting stents (PES), a significant difference in cardiac death and MI emerged favoring treatment with ZES (7). In both the ENDEAVOR III and ENDEAVOR IV trials, differences in MI emerged early, possibly in part due to side branch closure related to stent design (24). Also similar to the ENDEAVOR III trial, despite higher angiographic restenosis and late lumen loss compared with PES, overall TLR did not statistically vary, and differences in TLR between 1 and 3 years were less disparate for ZES versus PES (4.5% ZES vs. 3.3% PES at 1 year; 6.5% ZES vs. 6.0% PES at 3 years, p = NS for all comparisons).

Altogether, these results support the effectiveness of ZES over long-term follow-up and are particularly suggestive of their relative effectiveness compared with alternative DES, particularly beyond the period of angiographic surveillance. Considering the influence of angiographic surveillance on assessment of clinical restenosis (25,26), examination of events following the initial 9 months are insightful as they are more likely related to clinical presentation than to scheduled angiography. In this regard, several potential reasons exist why intermediate-term angiographic late lumen loss may not correlate with late efficacy. Although late loss may be closely associated with TLR when measured over a similar time interval, early angiographic measures may be less predictive of late-term efficacy, particularly if progression of neointimal hyperplasia occurs. Moreover, a clinical threshold may exist for angiographic measures below which the risk of repeat revascularization is similar for DES, unless driven by angiographic surveillance (25,26). As an example, in the ENDEAVOR III trial, qualifying angiographic binary restenosis (i.e., ≥50% stenosis) was significantly more common with ZES, yet a similar proportion of patients were identified with an in-segment percent diameter stenosis of 70% or greater (26.5% ZES vs. 25.0% SES, p = 1.00).

In addition, over 5 years of follow-up, differences in mortality and MI developed favoring ZES compared with SES aside from no difference in late efficacy. Nonetheless, despite consistency of ZES outcomes in larger trials, the sample size estimate for the ENDEAVOR III trial was intended to evaluate a primary angiographic endpoint, and the overall low event rates described for both groups limit the statistical power for comparison of clinical events. Therefore, these results should be considered hypothesis-generating rather than definitive. Despite significantly lower MI than in the SES cohort, it is uncertain how treatment with ZES is associated with lower mortality; although a trend toward lower cardiovascular-related mortality was observed in the ZES cohort, differences in survival were principally related to noncardiac causes.

In addition, these findings were observed among patients undergoing elective percutaneous revascularization with rel-

Table 4. In-Stent Late Lumen Loss and Interval TLR Rates for DES in ENDEAVOR Clinical Trials

Stent/Trial (Ref. #)	N	In-Stent Late Loss at 8 Months (n)	TLR at 1 Year	TLR, Latest Follow-Up	ΔTLR, 1 Year to Latest Follow-Up
Cypher SES/ENDEAVOR III (3)	113	0.15 ± 0.34 (94)	3.6 (4/112)	6.5 (7/108) at 5 yrs	2.8 (3/108)
Taxus PES/ENDEAVOR IV (17)	775	0.42 ± 0.50 (135)	3.3 (25/757)	6.0 (44/734) at 3 yrs	2.6 (19/734)
Endeavor ZES/ENDEAVOR II (18)	598	0.62 ± 0.46 (264)	5.9 (35/590)	7.5 (43/577) at 5 yrs	1.4 (8/577)
Endeavor ZES/ENDEAVOR III (3)	323	0.62 ± 0.49 (277)	6.5 (21/321)	8.1 (25/307) at 5 yrs	1.3 (4/307)
Endeavor ZES/ENDEAVOR IV (17)	773	0.67 ± 0.49 (142)	4.5 (34/756)	6.5 (48/734) at 3 yrs	1.9 (14/734)
Endeavor ZES/pooled ENDEAVOR program (21)	2,132	0.62 ± 0.49 (898)	5.4 (113/2,102)	6.7 (139/2,063) at 3 yrs	1.3 (26/2,063)

Values are mean ± SD (n) or % (n/N).
DES = drug-eluting stent(s); PES = paclitaxel-eluting stent(s); TLR = target lesions revascularization; other abbreviations as in Tables 1 and 2.

atively simple to moderate lesion complexity, and thus the results cannot be extended to high clinical risk and complex lesion patient populations. In broader patient populations as studied in the SORT OUT III (Comparison of Zotarolimus-Eluting Stents and Sirolimus-Eluting Stents in Patients With Coronary Artery Disease) trial (n = 2,332) (10), for example, significant differences in all-cause mortality, TLR, and MI instead favored treatment with SES at 18-months follow-up. Although that study was also underpowered for differences in individual endpoints, the absolute differences observed at 18 months were smaller in magnitude compared with those observed in the present study at 5 years (e.g., SORT OUT III vs. present study: MI: 1% vs. 2%, p = 0.03; death: 3% vs. 4%, p = 0.04). In another inclusive randomized trial comparing ZES, PES, and SES, 12-month MACE outcomes did not differ significantly between SES and ZES groups (27). Although significantly lower MACE with ZES compared with PES in that study is generally consistent with the lower incidence of target vessel failure observed in the 3-year follow-up of the ENDEAVOR IV trial (7), the absence of differences in MACE between ZES and SES represented numerically (but nonsignificantly) lower death or MI with ZES and significantly lower TLR with SES. Most important, emergence of differences in safety endpoints or differential trends in repeat revascularization were more commonly identified in the ENDEAVOR trials over a much later term than were reported in the SORT OUT and ZEST (Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent With Sirolimus-Eluting and Paclitaxel-Eluting Stent for Coronary Lesions) trials (27). Aside from quite dissimilar timing of event reporting and incomparable study populations, further differences in trial methods and endpoint ascertainment (e.g., absence of in-hospital MI reporting, angiographic surveillance, or direct patient contact in follow-up in SORT OUT III) preclude more direct comparison of results between these trials.

Conclusions

Despite significantly higher 8-month angiographic late lumen loss, rates of clinical restenosis during later follow-up remain stable with ZES compared with SES, resulting in relatively small (1.5% absolute) overall differences in clinical restenosis rates at 5 years. These findings are consistent with additional recent studies identifying differential temporal progression of angiographic measures and clinical events among DES, and challenge earlier models relating early angiographic measures to longer-term requirement for repeat procedures. Furthermore, restenosis risk was dissociated from clinical endpoints of death and MI that favored treatment with ZES, contesting the notion that less favorable early angiographic surrogates of efficacy accurately predict important clinical events.

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Key Words: drug-eluting stent(s) ■ percutaneous coronary intervention ■ zotarolimus.