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Final 5-Year Outcomes From the Endeavor Zotarolimus-Eluting Stent Clinical Trial Program

Comparison of Safety and Efficacy With First-Generation Drug-Eluting and Bare-Metal Stents

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Objectives The aim of this study was to evaluate late safety and efficacy outcomes among patients enrolled in clinical trials comparing Endeavor zotarolimus-eluting stents (E-ZES) (Medtronic, Inc., Santa Rosa, California) with first-generation drug-eluting stents (DES) and bare-metal stents (BMS).

Background Despite demonstration of higher angiographic luminal loss and restenosis with E-ZES compared with alternative DES, whether differences in these early angiographic measures translate into more disparate late clinical events is uncertain.

Methods Among 3,616 patients undergoing percutaneous coronary revascularization in 5 registration trials, late safety and efficacy events were compared between E-ZES (n = 2,132) versus sirolimus- or paclitaxel-eluting stents (n = 888) or BMS (n = 596).

Results Compared with a parallel cohort of patients treated with first-generation DES and BMS, 5-year rates of cardiac death/myocardial infarction (MI) (5.8% vs. 8.8% DES, p = 0.003; vs. 8.4% BMS, p = 0.02) and major adverse cardiac events (16.1% vs. 20.6% DES, p = 0.009; vs. 24.6% BMS, p < 0.001) were significantly lower with E-ZES. The E-ZES was associated with significantly lower target lesion revascularization (TLR) compared with BMS (7.4% vs. 16.3%, p < 0.001) but similar to comparator DES (7.4% vs. 8.1%, p = 0.63). Despite higher TLR in the first year with E-ZES compared with DES, between 1- and 5-year follow-up, rates of cardiac death/MI, TLR, and definite/probable stent thrombosis were significantly lower with E-ZES.

Conclusions Over 5 years, significant differences in cardiac death/MI and composite endpoints favored treatment with E-ZES over comparator BMS and DES. Rates of clinical restenosis and safety events, including stent thrombosis beyond the first year of revascularization, remain stable with E-ZES, leading to significant differences compared with first-generation DES. (J Am Coll Cardiol Intv 2013;6:504–12) © 2013 by the American College of Cardiology Foundation

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An important focus of early drug-eluting stent (DES) trials involved the comparison of angiographic surrogate indexes related to the anti-proliferative effect of DES (1–3) and its correlation with intermediate-term (e.g., 9- to 12-month) revascularization rates (4–6). Despite variance in angiographic measures between DES, differences in clinical outcomes were less distinct, and the clinical phenotype of DES was considered a "class effect" (7). In comparison with late lumen loss or angiographic restenosis as endpoints, more contemporary trials directed toward patient-oriented clinical outcomes have identified

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emerging differences in late efficacy and safety events between DES that are less closely linked to early measures (8–10).

The ENDEAVOR zotarolimus-eluting stent (E-ZES) clinical trial program constituted 5 registration studies that included patients treated with E-ZES, bare-metal stents (BMS), or first-generation sirolimus- and paclitaxel-eluting stents (3,11–15). Among randomized trials with protocol-mandated angiographic surveillance, E-ZES was associated with significantly higher angiographic late lumen loss and binary restenosis compared with alternative DES yet lower restenosis and repeat revascularization versus BMS. As part of planned 5-year follow-up, an important objective is not only to compare events relative to treatment assignment but also to determine whether the early observation of greater neointimal hyperplasia with E-ZES is associated with progression of adverse events beyond the initial study reports. Therefore we evaluated, as a final report, the combined late-term safety and efficacy outcomes among patients enrolled in the ENDEAVOR trials, comparing E-ZES, BMS, and first-generation DES patient cohorts over the entire 5-year study period.

Methods

Overview of trials and study population. The Endeavor stent clinical trials program constitutes a series of a prospective, international trials enrolling patients with symptomatic ischemic heart disease due to de novo stenotic lesions (>50% angiographic diameter stenosis by visual estimate) in native coronary arteries (3,11–15). Study population sizes/trial were: ENDEAVOR I (n = 100); ENDEAVOR II (n = 1,194); ENDEAVOR II Continued Access Study (n = 296); ENDEAVOR III (n = 436); ENDEAVOR IV (n = 1,548); and ENDEAVOR pharmacokinetic/pharmacodynamic study (n = 42). Further detail with regard to enrollment criteria and study methods has been previously reported. In all trials, patients were excluded if they experienced recent (<72 h) myocardial infarction (MI), 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 pharmacological 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, total occlusions, and Thrombolysis in Myocardial Infarction flow grade <2 in the treatment vessel. The studies (with prespecified follow-up through 5 years) were approved by the institutional review boards or ethics committees at each enrolling site, and consecutive, eligible patients signed written informed consent before the interventional procedure.

This analysis included all patients enrolled in these trials who were treated with the E-ZES, a cobalt-based alloy stent with a phosphorylcholine polymer and zotarolimus dose concentration of 10 μg/mm stent length; a cobalt alloy bare-metal stent (Driver, Medtronic, Santa Rosa, California); a sirolimus-eluting stent (Cypher, Cordis Corporation, Bridgewater, New Jersey); or a paclitaxel-eluting stent (Taxus, Boston Scientific Corporation, Natick, Massachusetts). The E-ZES were available, depending upon the trial, in diameters ranging from a minimum of 2.25 mm to a maximum 3.5 mm and in lengths from 9 to 30 mm. Before revascularization, all patients received treatment with aspirin and clopidogrel per protocol, and all patients were treated with a minimum of 3 months of dual antiplatelet therapy (DAPT), except for those in the ENDEAVOR IV trial, in which patients received a minimum of 6 months of DAPT to maintain blinding of DES assignment with the comparator paclitaxel-eluting stent. Aspirin therapy was recommended for an indefinite time period.

Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
E-ZES = ENDEAVOR zotarolimus-eluting stent(s)
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
ST = stent thrombosis
TLR = target lesion revascularization
ZES = zotarolimus-eluting stent(s)

Study endpoints and definitions. The primary objective of this pooled analysis was to evaluate late-term safety and outcomes among patients treated with E-ZES and to compare these events with a parallel cohort of patients treated with either BMS or alternative DES. Clinical safety outcomes included all-cause and cardiac death, MI, stroke, and stent thrombosis (ST) (per Academic Research Consortium criteria [16]) annually through 5-year follow-up. Cardiac death was considered as any fatal event not attrib-

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utable to a noncardiac cause. Myocardial infarction was defined as a creatine kinase elevation ≥2× above the upper limit of normal with any associated elevation in the creatine kinase myocardial band or the development of new pathological Q waves in at least 2 contiguous electrocardiographic leads. An independent clinical events committee adjudicated all clinical endpoints, and except for the single-arm ENDEAVOR I trial and ENDEAVOR II continued access registry, reviewers were blinded to the treatment assignment of the patient.

Statistical methods. From the individual trials, patients were analyzed for all safety and efficacy endpoints 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's exact test or the Cochran-Mantel-Haenszel test, and continuous variables were compared by 2-sample *t* test or analysis of variance. 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, SAS Institute Inc., Cary, North Carolina).

Results

As part of 5 registration trials involving patients undergoing percutaneous revascularization with E-ZES (n = 2,132), alternative DES (n = 888; 775 paclitaxel-eluting stent [PES], 113 sirolimus-eluting stent [SES]), and BMS (n = 596), clinical follow-up through 5 years was complete for 95.1% of patients (95.4%, 93.1%, and 97.2% of the E-ZES, first-generation DES, and BMS cohorts, respectively). Overall, 39% of patients underwent protocol-mandated angiographic surveillance before 1 year. Baseline clinical and angiographic characteristics were generally similar across treatment groups, although modest but statistically significant differences were observed (Table 1). Overall, the average age of the study population was 63 years, and the prevalence of diabetes was 26%, prior MI was 23%, and prior coronary revascularization was 46%. Treatment involving the left anterior descending artery as the target vessel was most common, and 70% of lesions were characterized as type B2/C. The presence of diabetes was greatest in the first-generation DES cohort, intermediate in the E-ZES group, and least common in the BMS group. In the E-ZES cohort, the mean ± SD reference vessel diameter and lesion length were 2.73 ± 0.47 mm and 14.17 ± 6.10 mm, respectively, and did not statistically differ from first-generation DES or BMS comparator groups.

Although similar at 30 days, late-term adherence to DAPT varied considerably across treatment groups and was highest among those receiving first-generation DES and lowest among patients treated with BMS at 1 and 5 years (Fig. 1). Compared with first-generation DES, treatment with DAPT among E-ZES patients was significantly lower at 1 year and approximately one-half that of first-generation DES annually thereafter.

By 5 years, all-cause mortality (7.4% vs. 9.6%, p = 0.057) (Table 2) and definite/probable stent thrombosis (0.9% vs. 1.8%, p = 0.178) (Fig. 2A) tended to be lower among patients treated with E-ZES compared with first-generation DES. However, the cumulative incidence of MI (3.3% vs. 5.8%, p = 0.002) and combined cardiac death/MI were significantly lower with E-ZES, also resulting in significant differences between groups with regard to composite endpoints of major adverse cardiac events (MACE) and target vessel failure. Overall target lesion revascularization (TLR) was similar between cohorts (7.4% E-ZES vs. 8.1% alternative DES, p = 0.63).

In comparison with BMS, overall 5-year survival and occurrence of definite/probable stent thrombosis were similar for E-ZES patients (Fig. 2A, Table 2). A trend toward lower MI with E-ZES was observed (3.3% vs. 4.8%, p = 0.07), and combined with a more than 50% reduction in TLR (7.4% vs. 16.3%, p < 0.001), this variance contributed to significant differences in composite safety and efficacy endpoints favoring E-ZES.

When late-term events were examined for patients with event-free survival beyond the first year of index revascularization and through 5 years, comparisons between E-ZES and first-generation DES followed a pattern similar to overall 5-year outcomes, except for repeat revascularization (Fig. 3, Table 2). Specifically, the occurrences of late MI (1.1% vs. 3.2%, p < 0.001) and combined cardiac death/MI were significantly lower with E-ZES (Fig. 4). Late stent thrombosis was also significantly less common with E-ZES, compared with first-generation DES (0.31% vs. 1.73%, p = 0.001) (Fig. 2B). In contrast to overall 5-year TLR, in a landmark analysis, subsequent revascularization between 1 and 5 years was significantly less common with E-ZES, compared with PES and SES (2.7% vs. 5.3%, p < 0.001) (Fig. 3); in addition to differences in safety events, this disparity contributed to overall significant differences in late MACE and target vessel failure. In comparisons of BMS and E-ZES, no statistically significant differences in late safety or efficacy outcomes were identified.

Discussion

In the final 5-year report of registration studies representing 3,616 patients treated in the E-ZES clinical trials program, significant differences in the cumulative incidence of cardiac death/MI, stent thrombosis, and composite safety and efficacy endpoints favored treatment with E-ZES over first-generation comparator DES. Despite consistently higher angiographic late lumen loss with E-ZES compared

Table 1. Baseline Clinical and Angiographic Characteristics

	E-ZES	1st-Gen DES	p Value*	BMS	p Value†
Patient characteristics					
Age, yrs	62.5 ± 10.7 (2,132)	63.3 ± 11.1 (888)	0.052	61.9 ± 10.5 (596)	0.226
Male	71.5% (1,524/2,132)	70.2% (623/888)	0.481	75.3% (449/596)	0.070
Diabetes mellitus	26.1% (555/2,129)	30.2% (268/888)	0.022	22.2% (132/595)	0.055
Hypertension	73.0% (1,551/2,126)	81.5% (724/888)	<0.001	68.2% (403/591)	0.026
Hyperlipidemia	81.2% (1,720/2,118)	85.0% (755/888)	0.012	76.9% (455/592)	0.023
History of smoking	49.2% (1,035/2,105)	62.3% (547/878)	<0.001	35.2% (207/588)	<0.001
Prior MI	28.5% (604/2,117)	22.9% (199/870)	0.001	41.5% (247/595)	<0.001
Prior PCI	26.0% (554/2,130)	27.9% (248/888)	0.278	18.0% (107/594)	<0.001
Prior coronary bypass surgery	6.7% (143/2,132)	8.3% (74/888)	0.122	4.9% (29/596)	0.106
Clinical presentation			0.504		0.514
Stable angina	40.8% (752/1,843)	50.8% (359/707)		33.3% (181/543)	
Unstable angina	49.3% (909/1,843)	46.8% (331/707)		50.8% (276/543)	
MI	9.9% (182/1,843)	2.4% (17/707)		15.8% (86/543)	
CCS class III/IV	43.0% (869/2,022)	39.0% (344/882)	0.050	48.9% (262/536)	0.016
Angiographic characteristics					
Target vessel			0.364		0.173
Left anterior descending	43.8% (931/2,124)	41.3% (366/887)		47.6% (281/591)	
Left circumflex	24.4% (518/2,124)	26.4% (234/887)		21.2% (125/591)	
Right coronary	31.8% (675/2,124)	32.4% (287/887)		31.3% (185/591)	
Type B2/C lesion	71.4% (1,516/2,124)	69.1% (613/887)	0.219	79.0% (467/591)	<0.001
Number of diseased vessels (>50% stenosis)			0.369		0.030
Single	58.8% (1,253/2,131)	57.4% (509/887)		62.9% (375/596)	
Double	26.7% (569/2,131)	26.6% (236/887)		26.3% (157/596)	
Triple	14.5% (309/2,131)	16.0% (142/887)		10.7% (64/596)	
Left ventricular ejection fraction, %	58.9 ± 10.9 (1,841)	57.3 ± 10.2 (863)	<0.001	60.8 ± 11.9 (453)	0.002
Reference vessel diameter, mm	2.7 ± 0.5 (2,124)	2.7 ± 0.5 (887)	0.350	2.8 ± 0.5 (591)	0.127
Lesion length, mm	14.2 ± 6.1 (2,110)	13.9 ± 6.3 (885)	0.359	14.4 ± 5.7 (588)	0.456
Minimum lumen diameter, mm	0.9 ± 0.4 (2,124)	0.9 ± 0.4 (887)	0.015	0.8 ± 0.4 (591)	0.004
Diameter stenosis, %	67.5 ± 12.4 (2,124)	66.0 ± 13.0 (887)	0.003	69.6 ± 11.0 (591)	<0.001

Values are mean ± SD (N) or % (n/N). *Comparison Endeavor zotarolimus-eluting stents (E-ZES) versus drug-eluting stents (DES); †comparison E-ZES versus bare-metal stents (BMS).
CCS = Canadian Cardiovascular Society; MI = myocardial infarction; PCI = percutaneous coronary intervention.

with SES and PES (3,15), rates of clinical restenosis and thrombotic events beyond the initial year of index revascularization remained relatively stable with E-ZES, also leading to significant differences in safety and efficacy outcomes. In contrast, E-ZES was associated with a more than halving in repeat revascularization, a trend toward lower MI, and no difference in stent thrombosis over 5 years versus a comparable patient group treated with BMS.

Since initial reports associating late stent thrombosis and restenosis with delayed hypersensitivity and neoatherosclerosis among first-generation DES (17–21), development of newer DES that effectively suppress neointimal hyperplasia yet enhance biocompatibility, promote vessel healing, and restore vasomotor function after percutaneous coronary intervention has become an increasing focus. In particular, long after dissipation of anti-proliferative drug, the persistence of selected durable polymer coatings has been associated with incomplete endothelialization, expansive vessel remodeling, neoatherosclerosis, and delayed arterial healing associated with chronic inflammation (20–24). The E-ZES is constructed from a thin-strut cobalt alloy platform and biomimetic phosphorylcholine polymer that might permit more rapid and complete endothelial coverage and recovery of vasomotor reactivity similar to that observed with BMS and distinct from alternative DES (25–29). Unlike other polymer-based DES, however, the more rapid elution kinetics of the rapamycin derivative zotarolimus (>95% within 14 days of implantation) also permit greater angiographic late lumen loss compared with other DES yet less than conventional BMS (3,12,15).

Although assessment of late safety events after DES revascularization has become commonplace in clinical trials, only recently have temporal patterns in progression of luminal loss and TLR been examined. Among patients treated with SES, for example, progression of angiographic in-stent late lumen loss and TLR beyond intermediate follow-up has been described as a "late catch-up" (30–32) and might be distinct from E-ZES (32,33). In

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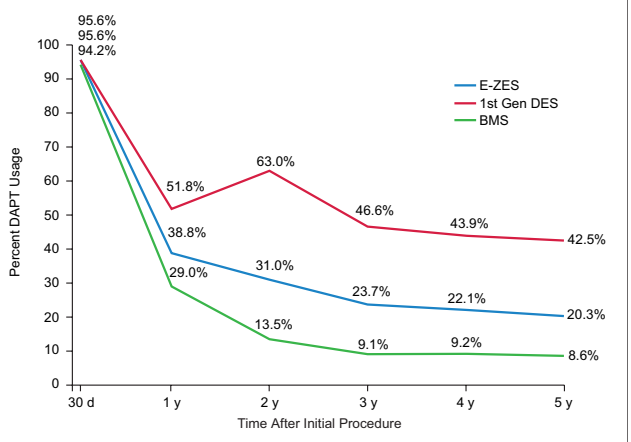


Figure 1. DAPT Adherence Through 5 Years

Dual antiplatelet therapy (DAPT) use for Endeavor zotarolimus-eluting stents (E-ZES), first-generation (1st Gen) drug-eluting stents (DES), and bare-metal stents (BMS) at 30 days (p = NS) and annually through 5 years post stent implantation (p < 0.001 for E-ZES vs. 1st Gen DES and E-ZES vs. BMS for each year).

the ISAR TEST 2 (Intracoronary Stenting and Angiographic Results: Test Efficacy of Three Limus-Eluting Stents) trial that included serial angiographic follow-up (32), accrual of binary angiographic restenosis between 1 and 2 years was more common for SES compared with E-ZES, corresponding to higher incident TLR between 1 and 2 years for SES. Similarly, erosion of angiographic luminal dimensions and progression of late TLR have also been described with paclitaxel- and everolimus-eluting stents (30,34). In the ENDEAVOR III and IV trials, despite numerically higher TLR at time of the primary endpoint with E-ZES, accrual of late TLR was numerically but not significantly more common with SES and PES compared with E-ZES beyond the initial period of angiographic surveillance (33,35). In comparisons of these outcomes observed with PES and SES with a broader E-ZES population in the present study, the difference in late TLR achieved statistical significance but notably not in comparison with BMS.

Altogether, these results support the effectiveness of E-ZES over long-term follow-up and are particularly suggestive of their relative effectiveness compared with first-generation DES, especially beyond the period of angiographic surveillance and despite initial angiographic late loss that is nearly 2 to 3 times higher than comparator DES. The stability in TLR beyond 1 year was consistently observed across individual studies; proportionately, in all ENDEAVOR trials, TLR beyond the first year represented less than one-half of cumulative 5-year repeat revascularization versus more than one-half with SES and PES (in ENDEAVOR III and IV). As such, late outcomes are likely more representative of spontaneous, clinically driven events than a result of protocol-mandated angiographic surveillance. In this regard, early angiographic measures might be less predictive of late-term efficacy, and a clinical threshold might exist for angiographic measures below which the risk of repeat revascularization is similar for DES, unless driven by scheduled angiography (36,37). As an example, in the ENDEAVOR III and IV trials, qualifying angiographic binary restenosis (i.e., ≥50% stenosis) was higher with ZES compared with SES and PES, respectively, yet a similar proportion of patients were identified with an in-segment percentage diameter stenosis of 70% or greater (26.5% ZES vs. 25.0% SES, p = 1.00; 37.8% ZES vs. 39.6% PES, p = 0.47). Furthermore, restenosis risk was dissociated from clinical endpoints of death and MI that instead favored treatment with E-ZES, contesting the notion that less favorable early angiographic surrogates of efficacy accurately predict important clinical events.

Safety-related outcomes in the present study for E-ZES are also consistent within the individual trials in addition to external investigation. Cumulative event-free survival from all-cause death and stent thrombosis tended to be lower with E-ZES compared with first-generation DES, and overall cardiac death/MI and very late stent thrombosis were significantly less common. These results, particularly those related to very late stent thrombosis, are especially remarkable against the background of less frequent adherence to DAPT among E-ZES patients after the first year. Whether biocompatibility of the phosphorylcholine polymer or more permissive neointimal hyperplasia with E-ZES allow less intensive antiplatelet therapy is speculative, although adherence to aspirin and thienopyridine treatment for durations <12 months after E-ZES revascularization has been associated with favorable long-term outcomes (38). Through 5-year follow-up in the ENDEAVOR IV trial, a significant difference in cardiac death and MI in addition to very late stent thrombosis emerged favoring treatment with E-ZES versus PES (35). Over 5-year follow-up in the ENDEAVOR III trial, differences in mortality and MI also developed favoring E-ZES compared with SES with no statistically significant difference in TLR (33). Among less selected patient populations as studied in the SORT OUT III (Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care) trial (n = 2,332), modest but statistically significant differences in all-cause mortality, TLR, and MI instead favored treatment with SES at 18-month follow-up (39); however, at 3 years, these differences no longer were significant, and the occurrence of very late definite stent thrombosis was in fact significantly lower with E-ZES (40). In another inclusive randomized trial comparing ZES, PES, and SES, 1-year MACE outcomes did not

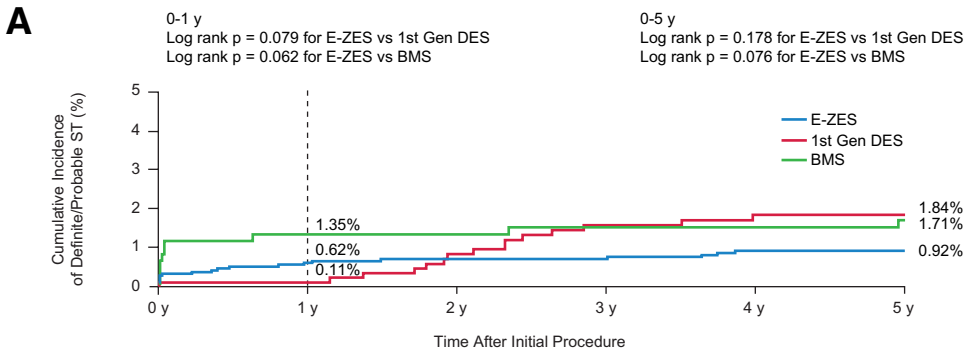
Table 2. Clinical Outcomes

	E-ZES	1st-Gen DES	p Value*	BMS	p Value†
Through 5 years	(n = 2,033)	(n = 826)		(n = 582)	
Death (all)	7.4% (151)	9.6% (79)	0.057	7.6% (44)	0.057
Cardiac death	2.8% (57)	3.6% (30)	0.235	3.6% (21)	0.235
MI (all)	3.3% (67)	5.8% (48)	0.003	4.8% (28)	0.072
Q-wave	0.5% (10)	0.7% (6)	0.455	1.2% (7)	0.065
Non–Q-wave	2.9% (58)	5.1% (42)	0.005	3.6% (21)	0.310
Cardiac death or MI	5.8% (117)	8.8% (73)	0.003	8.4% (49)	0.017
Target lesion revascularization	7.4% (151)	8.1% (67)	0.625	16.3% (95)	<0.001
Target vessel revascularization	13.1% (266)	14.8% (122)	0.297	20.1% (117)	<0.001
Nontarget lesion, target vessel revascularization	7.1% (144)	9.3% (77)	0.044	6.2% (36)	0.491
Target vessel failure	17.1% (348)	20.9% (173)	0.026	24.4% (142)	<0.001
Major adverse cardiac events	16.1% (328)	20.6% (170)	0.009	24.6% (143)	<0.001
Stent thrombosis (ARC)					
Definite	0.7% (15)	1.2% (10)	0.389	1.5% (9)	0.063
Probable	0.2% (4)	0.6% (5)	0.248	0.2% (1)	0.918
Possible	1.8% (37)	2.7% (22)	0.388	2.2% (13)	0.207
Definite or probable	0.9% (19)	1.8% (15)	0.178	1.7% (10)	0.076
Any	2.8% (56)	4.5% (37)	0.099	4.0% (23)	0.048
1–5 years	(n = 1,961)	(n = 789)		(n = 570)	
Death (all)	6.6% (129)	8.7% (69)	0.051	7.0% (40)	0.654
Cardiac death	2.2% (43)	3.2% (25)	0.136	3.0% (17)	0.258
MI (all)	1.1% (21)	3.2% (25)	<0.001	0.9% (5)	0.714
Q-wave	0.3% (5)	0.6% (5)	0.151	0.4% (2)	0.689
Non–Q-wave	0.9% (17)	2.5% (20)	0.001	0.5% (3)	0.441
Cardiac death or MI	3.1% (60)	6.0% (47)	<0.001	3.9% (22)	0.320
Target lesion revascularization	2.7% (52)	5.3% (42)	<0.001	3.7% (21)	0.166
Target vessel revascularization	6.1% (120)	9.8% (77)	<0.001	7.2% (41)	0.293
Nontarget lesion, target vessel revascularization	4.0% (79)	6.2% (49)	0.014	4.0% (23)	0.927
Target vessel failure	8.6% (169)	14.2% (112)	<0.001	9.8% (56)	0.313
Major adverse cardiac events	9.6% (188)	15.6% (123)	<0.001	11.1% (63)	0.252
Stent thrombosis (ARC)					
Definite	0.2% (4)	1.1% (9)	0.008	0.2% (1)	0.815
Probable	0.1% (2)	0.6% (5)	0.069	0.2% (1)	1.000
Possible	1.5% (29)	2.2% (17)	0.511	1.8% (10)	0.215
Definite or probable	0.3% (6)	1.8% (14)	0.002	0.4% (2)	0.652
Any	1.8% (35)	3.9% (31)	0.009	2.1% (12)	0.223

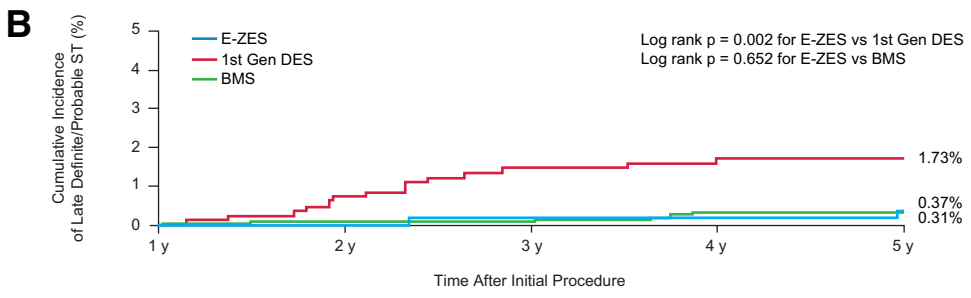
Values are % (n). *Comparison E-ZES versus DES; †comparison E-ZES versus BMS.
ARC = Academic Research Consortium; other abbreviations as in Table 1.

differ significantly between SES and ZES groups (41), although the 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 5-year follow-up of the ENDEAVOR IV trial (35).

Study limitations. Nonetheless, despite similarity of enrollment criteria and consistency of ZES outcomes in this larger pooled analysis, the sample size estimates for individual trials were intended to evaluate angiographic or composite clinical endpoints, and the overall low event rates described in this investigation still limit the statistical power for comparison of component endpoints, such as stent thrombosis and mortality. Therefore, these results with regard to such endpoints should be considered exploratory rather than definitive and serve as a foundation for ongoing comparative investigation. Even in such studies, there are some consistencies with the present results; in the PROTECT (Patient Related Outcomes with Endeavor versus Cypher Stenting Trial), for example, although overall 3-year definite or probable stent thrombosis was similar between E-ZES and SES, very late (>1 year) stent thrombosis was significantly lower with E-ZES (0.3% vs. 1.1%, $p < 0.001$) (42). Although this patient level overview of trials with homogenous inclusion and exclusion requirements, comparisons across stent types nevertheless represent a composite of randomized and indirect evaluation and



E-ZES, N	2132	2131	2049	2001	1952	1879
Events, n (%)	1 (0.05%)	12 (0.62%)	2 (0.71%)	0 (0.71%)	4 (0.92%)	0 (0.92%)
1st Gen DES, N	888	887	844	812	775	740
Events, n (%)	0	1 (0.11%)	6 (0.84%)	6 (1.58%)	2 (1.84%)	0 (1.84%)
BMS, N	596	595	570	559	543	538
Events, n (%)	1 (0.17%)	7 (1.35%)	0 (1.35%)	1 (1.52%)	0 (1.52%)	1 (1.71%)



E-ZES, N	2059	2059	2010	1961	1888
Events, n (%)	0	2 (0.10%)	0 (0.10%)	4 (0.31%)	0 (0.31%)
1st Gen DES, N	845	845	813	776	741
Events, n (%)	0	6 (0.72%)	6 (1.47%)	2 (1.73%)	0 (1.73%)
BMS, N	578	578	567	551	545
Events, n (%)	0	0	1 (0.18%)	0 (0.18%)	1 (0.37%)

Figure 2. Cumulative Incidence of Definite and Probable ST

Cumulative incidence curves of **(A)** Academic Research Consortium-defined definite and probable stent thrombosis (ST) from 0 to 5 years and **(B)** very late Academic Research Consortium-defined definite and probable ST from 1 to 5 years for E-ZES, 1st Gen DES, and BMS. Abbreviations as in Figure 1.

might introduce confounding not resolved by randomization alone. Furthermore, these findings were observed among patients undergoing elective percutaneous revascularization with relatively simple to moderate lesion complexity, and thus the results cannot be extended to high clinical risk and complex lesion patient populations. Whether unblinding to DES type after endpoint ascertainment also introduced treatment bias that could influence outcomes is uncertain. However, less frequent prescription of DAPT in the E-ZES cohort might pose higher risk for late thrombotic events, and awareness of treatment with a higher late lumen loss stent might lower the threshold for repeat angiography and intervention, yet in fact the opposite direction in clinical events was observed. Finally, given the frequent performance of surveillance angiography in the ENDEAVOR trials, it is plausible that temporal differences in late TLR between DES are the result of a frame-shift of E-ZES–related TLR to earlier time points. Most TLR events, however, were clinically rather than angiographically driven, and in the comparative trials with first-generation DES, equal proportions of patients in each treatment group underwent follow-up angiography.

Conclusions

In the context of comparison with first-generation DES and BMS, these results support the early- and late-term safety and efficacy after percutaneous revascularization with E-ZES. In the final 5-year report of patients enrolled in the E-ZES clinical trials program, treatment with E-ZES was associated with statistically significant reductions in cardiac death and MI and very late stent thrombosis compared with

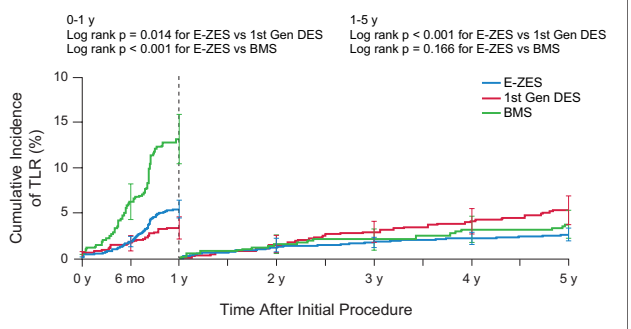


Figure 3. Landmark Analysis of TLR From 0 to 1 and 1 to 5 Years

Landmark analysis of target lesion revascularization (TLR) showing cumulative incidence of TLR from 0 to 1 year and from 1 to 5 years for E-ZES, 1st Gen DES, and BMS. Abbreviations as in Figure 1.

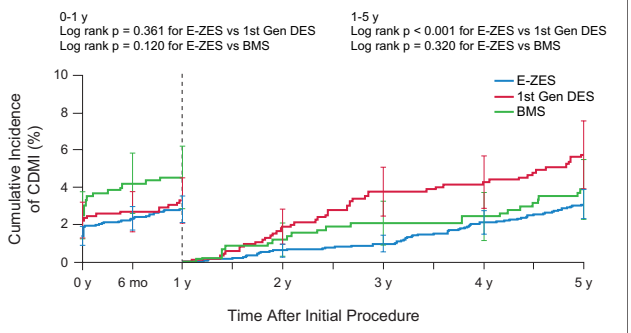


Figure 4. Landmark Analysis of CDMI From 0 to 1 and 1 to 5 Years

Landmark analysis of cardiac death and myocardial infarction (CDMI) showing cumulative incidence of CDMI from 0 to 1 year and from 1 to 5 years for E-ZES, first-generation DES, and BMS. Abbreviations as in Figure 1.

a pooled cohort of patients receiving first-generation SES and PES. Despite higher angiographic restenosis with E-ZES, the cumulative need for repeat revascularization was similar between DES types. Over late-term follow-up, important differences emerged favoring E-ZES with regard to very late stent thrombosis and TLR. In comparison with BMS, treatment with E-ZES demonstrated durable and significant reductions in repeat revascularization with no safety differences observed. Overall, these findings are consistent with those from additional recent studies identifying differential temporal progression of angiographic measures and clinical events among DES and challenge earlier models relating early angiographic measures to long-term outcomes.

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Key Words: drug-eluting stent ■ percutaneous coronary intervention ■ stent thrombosis ■ zotarolimus.