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Safety and Effectiveness of the Endeavor Zotarolimus-Eluting Stent in Real-World Clinical Practice

12-Month Data From the E-Five Registry

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Objectives The E-Five registry was designed to evaluate the safety and effectiveness of the Endeavor zotarolimus-eluting stent (ZES) (Medtronic CardioVascular, Santa Rosa, California) for the treatment of coronary artery stenosis across a wide range of patients treated in real-world clinical practice settings.

Background Early clinical trials with the Endeavor ZES have demonstrated low rates of target lesion revascularization with a favorable safety profile including low late stent thrombosis with up to 4 years of follow-up. A clinical registry was designed to complement controlled trial data by examining a large patient population, including high-risk patient subsets.

Methods The E-Five registry is a prospective, nonrandomized, multicenter global registry conducted at 188 centers worldwide. Adult patients (n = 8,314) with coronary artery disease who underwent single-vessel or multivessel percutaneous coronary intervention were enrolled. The primary end point was the rate of major adverse cardiac events (MACE) at 12 months. A secondary analysis stratified patients by standard versus extended-use clinical and lesion characteristics.

Results Overall 12-month outcome rates were MACE 7.5%; cardiac death 1.7%; myocardial infarction (all) 1.6%; target lesion revascularization 4.5%; and stent thrombosis (Academic Research Consortium definite and probable) 1.1%. The 12-month MACE rates were 4.3% and 8.6% for standard- and extended-use patients, respectively ($p < 0.001$).

Conclusions This large, international multicenter registry provides important information regarding the long-term safety and efficacy of the Endeavor ZES across standard and extended-use patients in the real-world setting. Rates of MACE and measures of safety including cardiac death, myocardial infarction, and stent thrombosis were low and consistent with pooled results of clinical trials.
(E-Five Registry: A World-Wide Registry With The Endeavor Zotarolimus Eluting Coronary Stent [eFive Registry]; NCT00623441) (J Am Coll Cardiol Intv 2009;2:1227–35) © 2009 by the American College of Cardiology Foundation

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Results from multiple randomized trials demonstrate that drug-eluting stents (DES) significantly reduce rates of restenosis and target lesion revascularization (TLR) in patients with symptomatic coronary artery disease when compared with bare-metal stents (BMS) (1–4). Although concerns have been raised about the safety of DES due to

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apparent increases in late stent thrombosis, the clinical benefits seem to outweigh the risks (5). Experience with DES now extends to patients outside of controlled clinical trials, allowing for the inclusion of patients with diverse characteristics and more complex clinical or angiographic presentations, such as diabetes, multivessel disease, acute myocardial infarction (MI), or long lesions, as is often seen in real-world practice settings.

Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
CEC = clinical events committee
CK-MB = creatine kinase-myocardial band
DES = drug-eluting stent(s)
MACE = major adverse cardiac events
MI = myocardial infarction
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization
TVF = target vessel failure
TVR = target vessel revascularization
ZES = zotarolimus-eluting stent(s)

Clinical registries are excellent complements to randomized controlled studies because they provide insight into the performance of DES in broader patient populations as well as special patient subsets. The E-Five registry is a prospective, nonrandomized, multicenter global registry conducted at 188 centers in Europe, Asia/Pacific, and Latin America designed to evaluate the safety and effectiveness of the Endeavor zotarolimus-eluting stent (ZES) (Medtronic CardioVascular, Santa Rosa, California) in routine treatment of patients with coronary artery stenosis, including patients with clinical characteristics or lesion types that are often excluded from randomized controlled trials (6). The registry includes over 8,000 adult patients who underwent single-vessel or multivessel percutaneous coronary intervention (PCI). The primary end point was the rate of major adverse cardiac events (MACE) at 12 months (6).

The Endeavor ZES received Conformité Européenne (CE) marking in August 2005 and U.S. Food and Drug Administration approval in February 2008. The safety and efficacy of the Endeavor ZES has been evaluated in a number of clinical trials, and the results consistently show low rates of angiographic restenosis and repeat revascularization as well as a favorable safety profile, with a low rate of late stent thrombosis beyond 12 months of follow-up (4,7–12).

Preliminary 30-day data for 1,989 patients enrolled in the E-Five registry were published in 2007 (6). The acute procedure success rate was 98.6%, which is comparable with procedure success rates observed in previous Endeavor ZES clinical trials. The 30-day rate of MACE in these patients was 1.7%, which is also comparable with 30-day rates of MACE observed in previous Endeavor clinical trials.

This report describes 12-month safety and clinical data from the E-Five registry for all patients in the registry and further examines the outcomes among patients with clinical and lesion characteristics similar to those enrolled in randomized clinical trials (standard-use group) compared with patients with more complex clinical (e.g., acute MI) and lesion (e.g., bifurcation, left main) characteristics (extended-use group) (Fig. 1).

Methods

Study design and objectives. The E-Five registry is a prospective, nonrandomized, multicenter registry conducted at 188 centers in Europe, Asia/Pacific, and Latin America. The registry includes 8,314 adult patients who underwent single-vessel or multivessel PCI. The primary objective of the E-Five registry was to evaluate the safety and overall clinical performance of the Endeavor ZES (Medtronic CardioVascular) in real-world patients who required stent implantation. The secondary objective was to assess the event rate in patient subgroups known to have a higher risk of MACE, such as those with diabetes mellitus, small vessels, and long lesions.

Study population and protocol. All patients with coronary artery lesions suitable for stenting were eligible for recruitment in the registry. Consecutive patients for whom implantation with an Endeavor ZES was intended were enrolled at the time of stent introduction into the guiding catheter. The registry population included a large number of patients with clinical and lesion characteristics that did not fit the standard-use criteria of previous clinical trials and thus are included in an extended-use group. The extended-use group was defined as patients with a baseline acute MI (within 72 h), left main stenting, saphenous vein grafts, in-stent restenosis, bifurcated or ostial lesions, severe tortuosity, multivessel stenting, moderate/severe calcification, reference vessel diameter <2.5 mm or >3.5 mm, lesion length >27 mm, or moderate or severe renal impairment. All other patients were classified as standard use.

Patients were permitted to have 1 or more Endeavor ZES implanted, and implantation of BMS or other DES was allowed if the investigators deemed it beneficial.

Before stent implantation, all patients received daily aspirin per their physician's usual practice and either clopidogrel 75 mg/day for 3 days before the procedure or a preprocedural loading dose of clopidogrel (at least 300 mg). The recommended maintenance regimen was clopidogrel

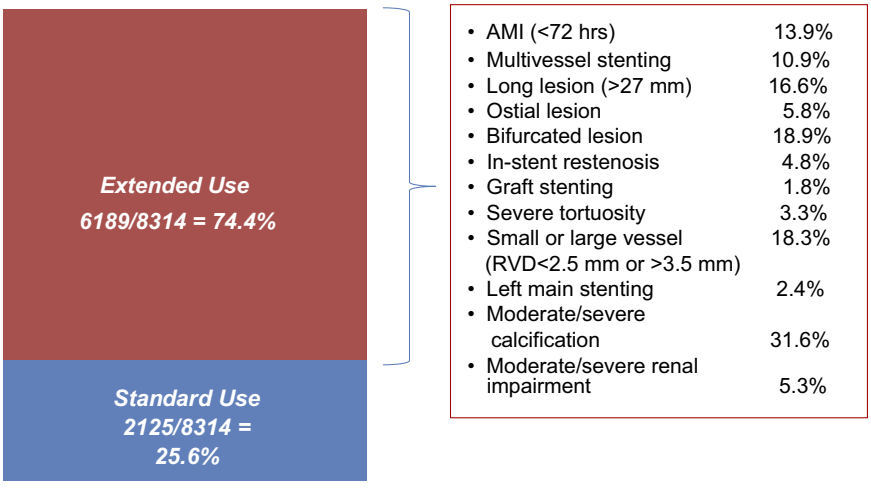

Figure 1. Patient and Lesion Characteristics of Extended-Use Group Patients

Distribution and specific characteristics defining the extended-use group are shown **(right)**. All other patients made up the standard-use group. AMI = acute myocardial infarction; RVD = reference vessel diameter.

75 mg/day for at least 12 weeks and at least 75 mg/day of aspirin indefinitely. Glycoprotein IIb/IIIa inhibitors were allowed at physician discretion.

Clinical follow-up was scheduled at 30 days, 6 months, and 12 months and consisted of telephone or in-office assessments. Patients were followed for 12 months to determine the mid-term clinical outcome of the index procedure.

This study was conducted according to the Declaration of Helsinki. The medical ethics committees approved the study protocol at sites at which such approval was required. In other cases, the medical ethics committees were notified of the study or investigators signed a statement before patient enrollment confirming that neither approval by nor notification of their ethics committees was necessary and that this approach was in accordance with local regulations. Written informed consent was obtained from all patients.

Device description. There are 3 main components of the Endeavor ZES: 1) the cobalt alloy stent; 2) zotarolimus (10 μg/mm stent length), an antiproliferative drug that is a synthetic analog of sirolimus and has a similar mechanism of action; and 3) a proprietary biomimetic phosphorylcholine polymer coating. The Endeavor ZES is available in diameters of 2.25 to 4.0 mm and in lengths of 8 to 30 mm.

Data collection and management. Data were recorded on web-based electronic case report forms. For quality control purposes, clinical sites were randomly monitored, and 10% of the data was monitored.

The following data were collected at baseline: eligibility criteria, demographic data, cardiac risk factors, current cardiac status, lesion characteristics, and results from preprocedure angiography. Visual estimation of lesion characteristics in relation to the index procedure was performed by the operator and recorded. Cardiac enzymes were measured after the procedure according to local hospital practice, including measurement of creatine kinase (CK), creatine kinase-myocardial band (CK-MB), and troponin.

Data on the index procedure, including the number of lesions treated, devices used, and the implantation technique, were recorded as well as the angiographic outcome (visual), antiplatelet medications used, MACE, and electrocardiography results. During discharge and after 30 days, 6 months, and 12 months, current cardiac status, antiplatelet medications, and MACE events were recorded. If a non–Q-wave or Q-wave myocardial infarction (MI) occurred after PCI, peak CK and CK-MB values were collected for adjudication by the clinical events committee (CEC). After all ischemic or MACE events, angiographic results and electrocardiograms were collected.

There was no mandatory angiographic follow-up in the protocol; however, if a patient had angiography for revascularization, the angiogram was reviewed by a central CEC (Cardialysis, Rotterdam, the Netherlands). The CEC, consisting of independent cardiologists who were not investigators in the registry, was responsible for adjudicating all reported MACE and stent thrombosis events and classifying the events according to the protocol definitions and, for stent thrombosis, the Academic Research Consortium (ARC) definitions (13).

Study end points. The primary end point of the E-Five registry was the rate of MACE at 12 months. For this study, we defined MACE as the composite end point of death, MI (Q-wave and non–Q-wave), emergent cardiac bypass surgery, or TLR (repeat percutaneous transluminal coronary

angioplasty or coronary artery bypass graft). Non–Q-wave MI was defined as elevated CK ≥2× the upper limit of normal with the presence of elevated CK-MB in the absence of new pathologic Q waves.

Secondary end points were the rates of MACE at 30 days and 6 months; the per protocol stent thrombosis rate (early defined as 0 to 30 days; late defined as 31 to 360 days); the procedural success rate; device success rate; and lesion success rate. Per-protocol stent thrombosis was defined as documented ischemia with angiographic thrombus within the stented vessel at any time or any death attributed to a cardiac cause within the first 30 days in the absence of angiographic confirmation. The ARC-defined definite and probable stent thrombosis rates (early and late) were also analyzed.

Statistical analyses. With an estimated event rate for MACE at 12 months of approximately 11% and with an assumed loss to follow-up rate of 10%, a sample size of 8,000 patients was needed so that the 95% confidence interval of MACE at 12 months would not exceed 11.7%.

The primary analytical population consisted of all enrolled patients in whom an Endeavor stent was attempted and/or implanted. A secondary analysis compared outcomes in the extended-use and standard patient subgroups.

The baseline demographic and lesion characteristics, procedural characteristics, and the clinical outcomes were estimated and reported for overall population and then for the 2 subgroups. Categorical variables were reported with percentages and counts, and continuous variables were reported with the means and standard deviations. The time to MACE event, stent thrombosis, and TLR were summarized and displayed with cumulative incidence curves by Kaplan-Meier methods.

Extended- and standard-use subgroups were compared for baseline characteristics and clinical outcomes. The p values were calculated with a 2-sample *t* test for continuous variables or Fisher exact test for categorical variables.

Results

Patient demographic data and characteristics. In total, 8,314 patients were recruited to the E-Five registry at 188 sites worldwide. Twelve-month data were available for 7,832 (94.2%) of the 8,314 patients enrolled. The mean age was 63.3 ± 11.1 years, and 76.7% of patients were men (Table 1). The incidence of diabetes was 32.7%, acute coronary syndrome occurred in 47.8% of patients, and moderate-to-severe renal impairment was reported in 6.5% of patients (Table 1). The population included patients with clinical risk factors and lesion characteristics not typically studied in randomized clinical trials (Table 2). The extended-use group comprised 6,189 (74.4%) patients (Fig. 1).

Lesion and procedural characteristics. Lesion and procedural characteristics are reported in Table 2. The average lesion length was 18.5 ± 10.6 mm. On average, the number of stents implanted/patient was 1.47. In total, 28.6% of lesions were treated with small stents (≤2.5 mm in diameter). The average stent length was 23.5 ± 12.2 mm, and the stent-to-lesion ratio

Table 1. Patient Characteristics and Demographic Data

	Overall (n = 8,314)	Standard-Use* (n = 2,125)	Extended-Use† (n = 6,189)	p Value (Standard- vs. Extended-Use)
Age, yrs	63.3 ± 11.1	61.3 ± 10.6	64.0 ± 11.1	<0.001
Female	23.3 (1,940)	24.8 (527)	22.8 (1,413)	0.065
Prior MI	32.2 (2,673)	29.9 (636)	32.9 (2,037)	0.011
Prior PCI	25.3 (2,106)	22.7 (482)	26.2 (1,624)	0.001
Prior CABG	7.5 (627)	4.9 (104)	8.5 (523)	<0.001
Hypertension	68.6 (5,704)	67.1 (1,426)	69.1 (4,278)	0.088
Hypercholesterolemia	63.1 (5,243)	62.2 (1,321)	63.4 (3,922)	0.322
Current smoker	22.6 (1,882)	22.7 (483)	22.6 (1,399)	0.904
Diabetes	32.7 (2,721)	31.1 (661)	33.3 (2,060)	0.068
Insulin-dependent	8.2 (682)	7.0 (149)	8.6 (533)	0.022
Noninsulin-dependent	24.5 (2,039)	24.1 (512)	24.7 (1,527)	0.599
Acute coronary syndrome	47.8 (3,973)	N/A	50.0 (3,093)	—
Acute MI (<72 h)	13.9 (1,153)	N/A	18.6 (1,153)	—
Unstable angina	33.9 (2,820)	41.4 (880)	31.3 (1,940)	<0.001
Moderate renal impairment (serum creatinine 140–220 mol/l)	4.7 (317/6,720)	N/A	6.3% (317/5,094)	—
Severe renal impairment (serum creatinine >220 mol/l)	1.8 (120/6,720)	N/A	2.4% (120/5,094)	—

Values are mean ± SD or % (n). *Standard-use excludes patients with baseline acute myocardial infarction (MI) (within 72 h), left main, saphenous vein graft, in-stent restenosis, bifurcation, ostial, severe tortuosity, multivessel stenting, moderate/severe calcification, reference vessel diameter <2.5 mm, reference vessel diameter >3.5 mm, lesion length >27 mm, moderate or severe renal impairment. †Extended-use includes all other patients.

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

was 1.4 ± 0.7 mm. The Endeavor ZES was the only stent implanted in 94.9% of lesions. Other patients received a BMS (2.1%) or another DES (2.7%) or both (0.3%) in addition to the Endeavor ZES. The overall lesion success rate was 99.7%, and the overall procedure success rate was 98.6%.

Antiplatelet therapy. At baseline, periprocedure, 90.4% of patients were taking aspirin plus clopidogrel or ticlopidine, 1.9% were taking clopidogrel or ticlopidine alone, 6.1% were taking aspirin alone, and 1.6% of patients were not taking any antiplatelet therapy. The percentage of patients taking dual antiplatelet therapy was 97.9% at 30 days, 85.0% at 6 months, and 61.0% at 12 months.

Clinical outcomes. OVERALL RESULTS. The 12-month rate of MACE for all patients in the registry was 7.5% (95% confidence interval: 6.9% to 8.1%) (Table 3). Of note, there were no cases of emergent cardiac bypass surgery. Among patients receiving the Endeavor ZES plus a BMS or another DES, the MACE rates were 12.7% and 10.7%, respectively. The 12-month overall incidence of all ARC-defined stent thrombosis was 1.8%. At 12 months, the ARC definite and probable stent thrombosis rate was 1.1%, and the per protocol stent thrombosis rate was 1.0%. The ARC definite and probable late stent thrombosis rate was 0.4%, and the per protocol late stent thrombosis rate was 0.3%. Stent thrombosis rates were 1.4% for patients receiving ZES and BMS and 1.8% for those receiving ZES with another DES. At 12 months, the rate of TLR was 4.5%, nontarget lesion target vessel revascularization (TVR) was 0.7%, TVR was 4.9%, and target vessel failure (TVF) was 7.2%.

RESULTS FOR PATIENTS WITH STANDARD- VERSUS EXTENDED-USE LESIONS AND CHARACTERISTICS. Clinical outcomes at 12 months were compared between patients in the standard group and patients in the extended-use group (Figs. 2 to 4, Table 3). The 12-month rate of MACE was 4.3% for patients in the standard group compared with a rate of 8.6% ($p < 0.001$) for patients treated in the extended-use group. There were 24 of 191 (1.2%) deaths in the standard group, of which 19 were attributed by the CEC to cardiac causes, and 167 of 6,189 (2.9%) deaths in the extended-use group, of which 116 were deemed cardiac death by the CEC. The 12-month incidence of ARC definite and probable stent thrombosis was 0.4% in the standard group and 1.4% in the extended-use group ($p < 0.001$) (Fig. 3). Compared with the standard group, the rates of TLR for the extended-use group were significantly higher (2.8% vs. 5.0%, $p < 0.001$). Similar

Table 2. Lesion and Procedure Characteristics

	Overall n = 8,314 Patients n = 10,339 Lesions	Standard-Use n = 2,125 Patients n = 2,258 Lesions	Extended-Use n = 6,189 Patients n = 8,081 Lesions	p Value (Standard- vs. Extended-Use)
Total stent length (mm)	23.48 ± 12.21	20.08 ± 7.55	24.43 ± 13.06	<0.001
Vessel location				
LAD	46.6 (4,817)	49.9 (1,127)	45.7 (3,690)	<0.001
LCX	22 (2,274)	23.3 (525)	21.6 (1,749)	0.108
RCA	27.8 (2,877)	26.8 (606)	28.1 (2,271)	0.243
Left main	1.9 (196)	N/A	2.4 (196)	—
SVG	1.7 (175)	N/A	2.2 (175)	—
Lesion class				
A	9 (928)	15.5 (351)	7.1 (577)	<0.001
B1	30.8 (3,182)	41.5 (938)	27.8 (2,244)	<0.001
B2	35 (3,623)	30.2 (681)	36.4 (2,942)	<0.001
C	25.2 (2,606)	12.8 (288)	28.7 (2,318)	<0.001
Reference vessel diameter, mm				
<2.5	9.7 (999)	N/A	12.4 (999)	—
2.5–3.0	63.7 (6,584)	75.6 (1,707)	60.4 (4,877)	<0.001
>3.0	26.7 (2,756)	24.4 (551)	27.3 (2,205)	0.006
Lesions treated	1.24 ± 0.52	1.06 ± 0.26	1.31 ± 0.58	<0.001
Stents implanted/patient	1.47 ± 0.80	1.13 ± 0.39	1.59 ± 0.87	<0.001
Lesion length, mm	18.5 ± 10.6	15.32 ± 5.54	19.40 ± 11.48	<0.001
Long lesions (>20 mm)	30.4 (3,139)	18.7 (422)	33.6 (2,717)	<0.001
Ratio stent/lesion length	1.36 ± 0.69	1.37 ± 0.51	1.36 ± 0.74	0.869
Minimum stent diameters implanted, mm				
≤2.5	28.6 (2,951)	21.2 (479)	30.6 (2,472)	<0.001
>2.5	71.4 (7,388)	78.8 (1,779)	69.4 (5,609)	<0.001

Values are reported as mean ± SD or % (n).
LAD = left anterior descending coronary artery; LCX = left circumflex artery; RCA = right coronary artery; SVG = saphenous vein graft.

Table 3. 12-Month Clinical Outcomes for Overall Population and Patients With Standard Versus Extended-Use Clinical and Lesion Characteristics

	Overall (n = 7,832)	Standard-Use (n = 2,125)	Extended-Use (n = 6,189)	p Value (Standard- vs. Extended-Use)
Death (all)	2.4 (191)	1.2 (24)	2.9 (167)	<0.001
Cardiac	1.7 (135)	0.9 (19)	2.0 (116)	<0.001
MI (all)	1.6 (128)	0.7 (15)	1.9 (113)	<0.001
Q-wave	0.4 (31)	0.2 (4)	0.5 (27)	0.147
Non–Q-wave	1.3 (98)	0.5 (11)	1.5 (87)	0.001
Death (cardiac) + MI (all)	3.0 (238)	1.5 (30)	1.6 (208)	0.001
ARC definite stent thrombosis	0.6 (49)	0.1 (3)	0.8 (46)	<0.001
0–30 days	0.4 (28)	0.1 (2)	0.4 (26)	0.028
31–365 days	0.3 (23)	0.0 (1)	0.4 (22)	0.015
ARC definite + probable stent thrombosis	1.1 (88)	0.4 (9)	1.4 (79)	<0.001
0–30 days	0.8 (59)	0.4 (8)	0.9 (51)	0.035
31–365 days	0.4 (31)	0.0 (1)	0.5 (30)	0.002
All ARC stent thrombosis	1.8 (144)	0.8 (16)	2.2 (128)	<0.001
0–30 days	0.8 (59)	0.4 (8)	0.9 (51)	0.035
31–365 days	1.1 (89)	0.4 (9)	1.4 (80)	<0.001
Per protocol stent thrombosis	1.0 (82)	0.4 (9)	1.3 (73)	0.001
0–30 days	0.8 (62)	0.4 (8)	0.9 (54)	0.019
31–365 days	0.3 (21)	0.0 (1)	0.3 (20)	0.024
TLR	4.5 (349)	2.8 (56)	5.0 (293)	<0.001
TVR	4.9 (387)	3.0 (61)	5.6 (326)	<0.001
TVR (nontarget lesion)	0.7 (52)	0.3 (6)	0.8 (46)	0.017
TVF	7.2 (565)	4.3 (87)	8.2 (478)	<0.001
MACE	7.5 (587)	4.3 (87)	8.6 (500)	<0.001

Values are % (n).

ARC = Academic Research Consortium; MACE = major adverse cardiac events; MI = myocardial infarction; TLR = target lesion revascularization; TVF = target vessel failure; TVR = target vessel revascularization.

differences exist for the 12-month rates of TVR (3.0% vs. 5.6%, $p < 0.001$) and TVF (4.3% vs. 8.2%, $p < 0.001$).

SUBGROUP OUTCOMES. The rates of MACE, TLR, and ARC definite and probable stent thrombosis at 12 months are reported for key subgroups in Table 4.

Discussion

This report describes 12-month data from the first large prospective registry of the Endeavor ZES. These results,

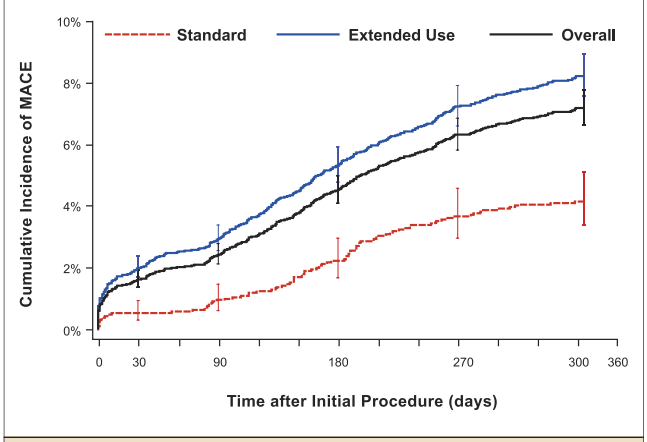

Figure 2. Cumulative Incidence of MACE at 12 Months

Cumulative incidence curves of major adverse cardiac events (MACE) for all patients and patients in the standard- and extended-use groups at 12 months.

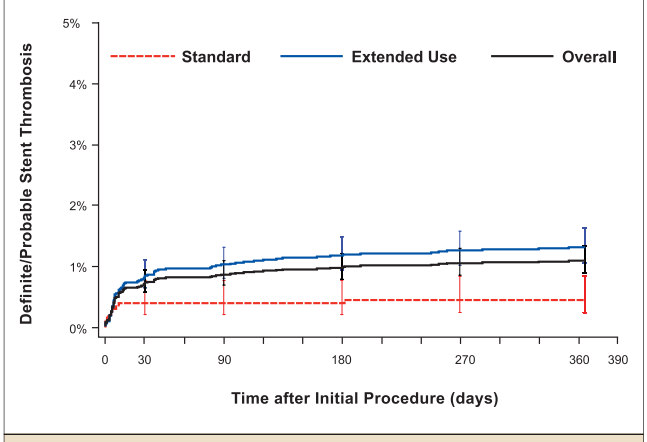

Figure 3. Cumulative Incidence of ARC Definite And Probable Stent Thrombosis at 12 Months

Cumulative incidence curves of Academic Research Consortium (ARC) definite and probable stent thrombosis for all patients and patients in the standard- and extended-use groups at 12 months.

Table 4. MACE and ARC Definite and Probable Stent Thrombosis Rates for Key Subgroups at 12 Months

	Diabetes (n = 2,563)	Lesions >20 mm (n = 2,668)	Lesions <3.0 mm (n = 3,408)	Multivessel* (n = 854)
MACE	9.7 (248)	9.8 (261)	8.6 (277)	9.8 (84)
TLR	5.3 (136)	5.5 (148)	5.4 (173)	6.2 (53)
ARC definite/probable	1.5 (39)	1.5 (41)	1.5 (49)	1.9 (19)
0–30 days	1.1 (29)	1.1 (29)	1.1 (35)	1.4 (12)
31–365 days	0.4 (11)	0.4 (12)	0.5 (16)	0.5 (4)

Values are % (n). *At least 2 lesions in different vessels.
Abbreviations as in Table 3.

obtained from 188 treatment centers, provide compelling evidence for the safe and effective use of the Endeavor ZES in routine clinical practice. The results are similar to those reported in randomized clinical trials, despite the high proportion of patients with high-risk characteristics and complex lesions that are usually excluded from randomized trials.

Outcome data were available for 7,832 of 8,314 patients, which represents a 94.2% 1-year follow-up rate. The low number of patients lost to follow-up compares favorably with other published registries (88% to 95%) (14–16) and further strengthens the validity of the data reported. Additionally, all events related to end points were adjudicated by an independent CEC, and although there was no mandatory angiographic follow-up, if a patient underwent angiography-related revascularization, the angiogram was available for adjudication of the event by the committee. All reported events were adjudicated—unique to registry studies—supporting the high quality of the registry. Additionally, the database was queried for possible events not reported to assure accuracy of the data. Random monitoring of 10% of patients was performed to detect and correct any inaccuracies in the registry data and to check for underreporting of events.

The overall 12-month MACE rate was 7.5%. The rate was 4.3% in the standard group, which was more representative of those enrolled in randomized trials (4,7–11), and 8.6% in the extended-use group. It is important to note that in the E-Five registry the MACE definition included emergent cardiac bypass surgery, which was not included in definitions used by other DES registries (e-Cypher, STENT [Strategic Transcatheter Evaluation of New Therapies] REWARDS [Cypher Registry Experience at the Washington Hospital Center With Drug-Eluting Stents], ARRIVE [The TAXUS Peri-Approval Registry: A Multicenter Safety Surveillance]) (14–17). Overall outcomes reported for the sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) in recent registry reports suggest that the Endeavor ZES performs similarly to other DES (14–17). The overall rate of MACE at 12 months was reported to be 5.8% for the SES in the e-Cypher registry (13) and at 9 months was 8.0% and 7.5% for the SES and PES groups, respectively, in the STENT registry report (15). The REWARDS registry, which compared outcomes with everolimus-eluting stent and PES placement in over 2,700 consecutive patients treated at a single site, reported no difference in the rate of MACE at 12 months (hazard ratio: 1.06, 95% confidence interval: 0.85 to 1.33), although actual rates were not reported (16).

Stent thrombosis. Events were adjudicated, unlike other stent registries, to confirm the per protocol and ARC-defined stent thrombosis outcomes. The incidence of ARC definite and probable stent thrombosis was 1.1% overall, with 0.8% occurring early (0 to 30 days) and 0.4% occurring late (31 to 365 days) (Table 3). This value is consistent with the pooled analysis from 6 clinical trials of Endeavor DES (n = 2,132), which revealed an ARC definite and probable stent thrombosis rate of 0.7% among patients without complex indications (18). The per protocol stent thrombosis rates for the Endeavor ZES were 1.0% overall, 0.8% early, and 0.3% late, which are similar to the cumulative 12-month data from the e-Cypher registry, which reported a 0.87% incidence of per protocol stent thrombosis overall with a rate of late stent thrombosis of 0.19% (14). However,

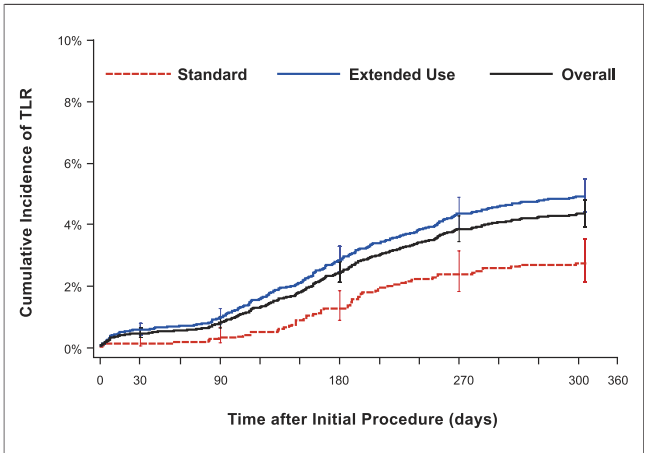

Figure 4. Cumulative Incidence of TLR at 12 Months

Cumulative incidence curves of target lesion revascularization (TLR) for all patients and patients in the standard- and extended-use groups at 12 months.

the e-Cypher registry used a more restrictive definition of stent thrombosis, requiring angiography or autopsy for definite stent thrombosis and target vessel-related MI or cardiac death for likely stent thrombosis occurring within 30 days of the index procedure. The proportion of patients with SES-related thrombosis who were being treated with dual antiplatelet therapy was 84.1% in eCypher, and 71.5% of patients in ARRIVE with PES thrombosis were receiving dual antiplatelet therapy at 12 months (16,17). Patients receiving the Endeavor ZES experienced a low rate of stent thrombosis, despite a comparatively low 12-month rate (61.0%) of dual antiplatelet therapy.

As expected, the rates of ARC definite and probable stent thrombosis are greater among patients in the extended-use group compared with the standard group (1.4% vs. 0.4%, adjusted $p < 0.001$). These rates are lower than those reported for PES in the ARRIVE registry, although the patient groups are defined in the same way (1.8% and 0.9% for extended-use and standard-use groups, respectively). Identified factors that might impact the incidence of stent thrombosis include the duration of antiplatelet therapy, the presence of diabetes or acute coronary syndrome, renal failure, low ejection fraction, and bifurcation lesions (19,20), and the ability to compare outcomes across nonrandomized studies is limited by selection bias.

Study limitations. An important limitation of this study is the potential for underreporting of adverse events. Several measures, including ongoing random monitoring of 10% of patients enrolled and adjudication of events by review of electrocardiogram and laboratory values for MI and angiography for stent thrombosis and revascularization, were employed to minimize this occurrence in E-Five, but the inherent possibility exists for inaccuracy of reported outcomes.

Another limitation of this study is the subjective nature of the lesion length data, which were reported by visual estimation or by local quantitative angiographic methods, but were not collected in a core laboratory.

The importance of adequate antiplatelet therapy during and after stent placement has been highlighted in a number of recent publications and is an element that can be highly variable in real-world patient populations. Premature discontinuation of antiplatelet agents has been shown to increase the incidence of stent thrombosis (21,22). In this registry, 85.0% of patients at 6 months and 61.0% at 12 months were taking dual antiplatelet therapy. It is unclear how long dual antiplatelet therapy should be continued, because late stent thrombosis is reported well beyond 12 months (2,16,19,23,24). Longer follow-up of patients receiving the Endeavor ZES will be necessary to confirm the extended long-term safety of this DES and is being undertaken in a subset of approximately 2,000 patients from this study cohort.

Conclusions

Mid-term results from the E-Five registry suggest that real-world outcomes among over 8,000 consecutive patients with both simple and extended-use characteristics and lesions are comparable to those of the pooled Endeavor clinical trials. The 12-month rate of MACE was comparable to rates reported across other registry trials, and safety outcomes as measured by rates of cardiac death, MI, and stent thrombosis were low, despite the high proportion of patients in the extended-use population. These 12-month results clearly provide evidence for safety and effectiveness of the Endeavor ZES in real-world patients and are consistent with those reported in the ENDEAVOR trials.

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Key Words: coronary artery lesion ■ drug-eluting stent ■ multicenter registry ■ restenosis ■ stent thrombosis.

APPENDIX

For a complete list of the E-Five Investigators and institutions, please see the online version of this article.