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Safety and Efficacy of Second-Generation Everolimus-Eluting Xience V Stents Versus Zotarolimus-Eluting Resolute Stents in Real-World Practice

Patient-Related and Stent-Related Outcomes from the Multicenter Prospective EXCELLENT and RESOLUTE-Korea Registries

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Objectives This study sought to compare the safety and efficacy of the Xience V/Promus everolimus-eluting stent (EES; Abbott Vascular, Temecula, California) with the Endeavor Resolute zotarolimus-eluting stent (ZES-R; Medtronic Cardiovascular, Santa Rosa, California) in "all-comer" cohorts.

Background Only 2 randomized controlled trials have compared these stents.

Methods The EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) and RESOLUTE-Korea registries prospectively enrolled 3,056 patients treated with the EES and 1,998 patients treated with the ZES-R, respectively, without exclusions. Stent-related composite outcomes (target lesion failure [TLF]) and patient-related composite outcomes were compared in crude and propensity score-matched analyses.

Results Of 5,054 patients, 3,830 (75.8%) had off-label indication (2,217 treated with EES and 1,613 treated with ZES-R). The stent-related outcome (82 [2.7%] vs. 58 [2.9%], p = 0.662) and the patient-related outcome (225 [7.4%] vs. 153 [7.7%], p = 0.702) did not differ between EES and ZES-R, respectively, at 1 year, which was corroborated by similar results from the propensity score-matched cohort. The rate of definite or probable stent thrombosis (18 [0.6%] vs. 7 [0.4%], p = 0.306) also was similar. In multivariate analysis, off-label indication was the strongest predictor of TLF (adjusted hazard ratio: 2.882; 95% confidence interval: 1.226 to 6.779; p = 0.015).

Conclusions In this robust real-world registry with unrestricted use of EES and ZES-R, both stents showed comparable safety and efficacy at 1-year follow-up. Overall incidences of TLF and definite stent thrombosis were low, even in the patients with off-label indication, suggesting excellent safety and efficacy of both types of second-generation drug-eluting stents. (J Am Coll Cardiol 2013;xx:xxx) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

CI = confidence interval
CoCr-EES = cobalt-chromium everolimus-eluting stent
DES = drug-eluting stent
EES = everolimus-eluting stent
MI = myocardial infarction
PCI = percutaneous coronary intervention
POCO = patient-oriented composite outcome
RCT = randomized controlled trial
ST = stent thrombosis
TLF = target lesion failure
TLR = target lesion revascularization
ZES-R = Resolute zotarolimus-eluting stent

First-generation drug-eluting stents (DESs) substantially reduced angiographic and clinical measures of restenosis; however, safety issues remained (1). The most widely used second-generation DESs, the Xience V/Promus everolimus-eluting stent (EES) (Abbott Vascular, Temecula, California) and the Endeavor Resolute zotarolimus-eluting stent (ZES-R) (Medtronic Cardiovascular, Santa Rosa, California), both made of cobalt-chromium with biocompatible polymers, were compared in only 2 randomized controlled trials (RCTs) (2–4). Thus, more data about their everyday use are needed. The purpose of this study was to evaluate the safety and efficacy of the EES and ZES-R in everyday real-world use with a wide range of patient and lesion complexity.

Methods

An extended description of the study methods is presented in the Supplementary Appendix.

Study design and patient population. This study evaluated the clinical outcomes of the EES and ZES-R from 2 prospective, multicenter registries—the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) and RESOLUTE-Korea—that enrolled all-comers treated with ≥1 EES or ZES-R (3,056/29 and 1,998/25 patients/participating centers, respectively) without exclusions (Supplementary Fig. 1). The patients enrolled in the EXCELLENT registry were different from those enrolled in the previously reported EXCELLENT RCT, which had strict inclusion and exclusion criteria, the main results of which have been published (5).

Follow-up. After index percutaneous coronary intervention (PCI), follow-ups were performed at 1, 3, 9, and 12 months; angiography was optional at 9 months. For any clinical events, all relevant medical records were reviewed and adjudicated by an external clinical event committee. With the use of the Korean health system's unique identification numbers, the vital status of 100% of patients was crosschecked. The study protocol was approved by the ethics committee at each participating center and conducted according to the principals of the Declaration of Helsinki. All patients provided written informed consent.

Definition and outcome analysis. The primary outcome was target lesion failure (TLF), a composite of cardiac death, myocardial infarction (MI) (not clearly attributed to a nontarget vessel), or a clinically indicated target lesion revascularization (TLR). The key secondary outcome, the patient-oriented composite outcome (POCO), included all-cause mortality, any MI (including nontarget vessel territory), and any revascularization. Other secondary outcomes included individual components of TLF and POCO, and stent thrombosis (ST) defined as definite, probable, or possible, according to the Academic Research Consortium (6).

Statistical analysis. First, analysis of primary and secondary clinical outcomes was performed in the crude population. Second, a propensity score-matched population was selected to adjust for uneven distribution of baseline characteristics. Multivariable-adjusted Cox proportional hazard regression and subgroup analysis were performed in propensity score-matched cohorts. Probability values were 2-sided; $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics. The number of patients and lesions were 5,054 of 7,084 for the total cohort, 3,056 of 4,248 for the EES group, and 1,998 of 2,836 for the ZES-R group, respectively. Fifty-five (1.8%) and 32 (1.6%) patients were lost to follow-up in the EES and ZES-R groups respectively; however, all were confirmed alive. The distribution of cardiac risk factors was similar, except for dyslipidemia, lesion complexity, and left main disease (Tables 1 and 2). High-risk patients and lesions were frequent, implying that our registries were an enriched population with PCI, reflecting real-world practice in Korea. The device, lesion, and procedure success rates were excellent and similar for both stents (Table 2).

Clinical outcomes of the crude population. At 1 year, the incidence of TLF and its individual components did not differ between the EES and ZES-R groups (2.7% vs. 2.9%, $p = 0.662$) (Table 3). POCO also was similar (7.4% vs. 7.7%, respectively, $p = 0.702$), as were its individual components. The cumulative incidence of TLF, POCO (Fig. 1), and their individual components (Supplementary Fig. 2) did not differ between the 2 stents.

Stent thrombosis. Definite or probable ST occurred in 25 patients (25/5,054, 0.5%) without between-group difference (Table 4 and Fig. 2). When ST occurred, only 2 patients in the EES group were not taking dual antiplatelet therapy. In the pooled analysis regarding definite or probable ST

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Table 1 Baseline Clinical Characteristics of Patients in Crude Population

	Total (N = 5,054)	EES (Abbott Vascular, Temecula, California) (N = 3,056)	ZES-R (Medtronic Cardiovascular, Santa Rosa, California) (N = 1,998)	p Value
Demographics				
Age, yrs	63.9 ± 10.8 (5,054)	63.9 ± 10.8 (3,056)	63.9 ± 10.9 (1,998)	0.897
Male	3,419/5,054 (67.6%)	2,053/3,056 (67.2%)	1,366/1,998 (68.4%)	0.389
BMI (kg/m^2)	24.9 ± 9.32 (4,892)	25.0 ± 11.8 (2,935)	24.8 ± 3.1 (1,957)	0.333
Coexisting condition				
Diabetes mellitus	1,855/5,029 (36.9%)	1,149/3,031 (37.9%)	706/1,998 (35.3%)	0.068
Hypertension	3,251/5,025 (64.7%)	1,980/3,027 (65.4%)	1,271/1,998 (63.6%)	0.195
Dyslipidemia	3,268/5,017 (65.1%)	1,850/3,019 (61.3%)	1,418/1,998 (71.0%)	<0.001
Peripheral artery disease	80/4,989 (1.6%)	47/2,991 (1.6%)	33/1,998 (1.7%)	0.909
Chronic renal failure	186/5,017 (3.7%)	105/3,019 (3.5%)	81/1,998 (4.1%)	0.321
Cardiac risk factors				
Current smoker	1,506/4,971 (29.8%)	893/2,998 (29.8%)	613/1,973 (31.1%)	0.344
Previous PCI	757/5,035 (15.0%)	440/3,041 (14.5%)	317/1,998 (15.9%)	0.184
Previous CABG	87/5,039 (1.7%)	56/3,041 (1.8%)	31/1,998 (1.6%)	0.507
Previous MI	326/5,034 (6.5%)	212/3,036 (7.0%)	114/1,998 (5.7%)	0.079
Previous CHF	102/4,992 (2.0%)	62/2,994 (2.1%)	40/1,998 (2.0%)	0.919
Previous CVA	395/4,996 (7.9%)	250/2,998 (8.3%)	145/1,998 (7.3%)	0.181
Family history of CAD	263/4,898 (5.4%)	171/2,900 (5.9%)	92/1,998 (4.6%)	0.053
LVEF	58.8 ± 11.4 (4,453)	59.3 ± 11.4 (2,714)	58.0 ± 11.4 (1,739)	<0.001
LV dysfunction (LVEF <30%)	75/4,453 (1.7%)	41/2,714 (1.5%)	34/1,739 (2.0%)	0.283
Clinical Indication of PCI				**<0.001**
Stable angina	1,696/5,036 (33.7%)	1,095/3,038 (36.0%)	601/1,998 (30.1%)	<0.001
Unstable angina	1,856/5,036 (36.9%)	1,117/3,038 (36.8%)	739/1,998 (37.0%)	0.881
AMI	1,330/5,036 (26.4%)	729/3,038 (24.0%)	601/1,998 (30.1%)	<0.001
NSTEMI	624/5,036 (12.4%)	344/3,038 (11.3%)	280/1,998 (14.0%)	0.005
STEMI	706/5,036 (14.0%)	385/3,038 (12.7%)	321/1,998 (16.1%)	0.001
Silent ischemia	154/5,036 (3.1%)	97/3,038 (3.2%)	57/1,998 (2.9%)	0.505
Complexity of CAD				
Angiographic disease extent				<0.001
1 VD	2,207/5,037 (43.8%)	1,424/3,046 (46.7%)	783/1,991 (39.3%)	
2 VD	1,597/5,037 (31.7%)	923/3,046 (30.3%)	674/1,991 (33.9%)	
3 VD	1,233/5,037 (24.5%)	699/3,046 (22.9%)	534/1,991 (26.8%)	
No. of treated lesion/patients	1.49 ± 0.77 (5,024)	1.47 ± 0.74 (3,038)	1.53 ± 0.80 (1,986)	0.009
At least 1 ISR	373/5,054 (7.4%)	231/3,056 (7.6%)	142/1,998 (7.1%)	0.548
At least 1 bifurcation	832/5,054 (16.5%)	388/3,056 (12.7%)	444/1,998 (22.2%)	<0.001
At least 1 thrombotic total	561/5,054 (11.1%)	293/3,056 (9.6%)	268/1,998 (13.4%)	<0.001
At least 1 small vessel*	1,033/5,054 (20.4%)	612/3,056 (20.0%)	421/1,998 (21.1%)	0.368
At least 1 long lesion†	2,215/5,054 (43.8%)	1,240/3,056 (40.6%)	975/1,998 (48.8%)	<0.001
Multivessel PCI	1,569/5,054 (31.0%)	930/3,056 (30.4%)	639/1,998 (32.0%)	0.250
GP IIb/IIIa antagonist use	133/4,759 (2.8%)	61/2,763 (2.2%)	72/1,996 (3.6%)	0.004
At least 1 off-label indication‡	3,830/5,054 (75.8%)	2,217/3,056 (72.5%)	1,613/1,998 (80.7%)	<0.001
Medication at discharge				
Aspirin	4,929/5,018 (98.2%)	2,969/3,030 (98.0%)	1,960/1,988 (98.6%)	0.126
Clopidogrel	4,937/5,017 (98.4%)	2,974/3,027 (98.2%)	1,963/1,990 (98.6%)	0.301
Statin	4,335/4,998 (86.7%)	2,613/3,023 (86.4%)	1,722/1,975 (87.2%)	0.468
ACE inhibitor	1,843/4,966 (37.1%)	1,113/3,011 (37.0%)	730/1,955 (37.3%)	0.810
Angiotensin-II receptor blocker	1,562/4,939 (31.6%)	939/3,016 (31.1%)	623/1,923 (32.4%)	0.363
Beta-blocker	3,159/4,970 (63.6%)	1,853/3,009 (61.6%)	1,306/1,961 (66.6%)	<0.001
Calcium-channel blocker	1,343/4,931 (27.2%)	830/3,016 (27.5%)	513/1,915 (26.8%)	0.577

Values are n (%) or mean ± SD. *Small vessel denotes lesion with reference diameter ≤2.75 mm. †Long lesion denotes lesion with length ≥28 mm. ‡Off-label indication: The indication of PCI was considered "off label" if any of the following features were present: serum creatinine concentration ≥140 μmol/l (1.6 mg/dl); LVEF <30%; an acute MI within the previous 72 h; >1 lesion per vessel; ≥2 vessels treated with a stent; a lesion length ≥28 mm; or a bifurcated lesion, bypass graft, in-stent restenosis, unprotected left main coronary artery, presence of thrombus, or total occlusion.

ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; CVA = cerebrovascular accident; EES = everolimus-eluting stent; GP = glycoprotein; ISR = in-stent restenosis; LV = left ventricle; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; VD = vessel disease; ZES-R = Resolute zotarolimus-eluting stent.

Table 2 Baseline Angiographic Characteristics of Lesions in Crude Population

	Total (N = 7,084)	EES (N = 4,248)	ZES-R (N = 2,836)	p Value
Target vessel location				0.001
Left main artery	258/7,084 (3.6%)	178/4,248 (4.2%)	80/2,836 (2.8%)	0.003
LAD	3,179/7,084 (44.9%)	1,907/4,248 (44.9%)	1,272/2,836 (44.9%)	0.981
LCX	1,567/7,084 (22.1%)	976/4,248 (23.0%)	591/2,836 (20.8%)	0.035
RCA	2,071/7,084 (29.2%)	1,182/4,248 (27.8%)	889/2,836 (31.3%)	0.002
Bypass graft	9/7,084 (0.1%)	5/4,248 (0.1%)	4/2,836 (0.1%)	>0.999
ACC/AHA lesion class				<0.001
A	564/7,084 (8.0%)	247/4,248 (5.8%)	317/2,836 (11.2%)	
B1	1,705/7,084 (24.1%)	1,064/4,248 (25.0%)	641/2,836 (22.6%)	
B2	1,650/7,084 (23.3%)	987/4,248 (23.2%)	663/2,836 (23.4%)	
C	2,285/7,084 (32.3%)	1,358/4,248 (32.0%)	927/2,836 (32.7%)	
Type B2 or C lesions*	3,935/7,084 (55.5%)	2,345/4,248 (55.2%)	1,590/2,836 (56.1%)	0.479
In-stent restenosis	424/7,084 (6.0%)	257/4,248 (6.0%)	167/2,836 (5.9%)	0.798
Severe calcification	623/7,084 (8.8%)	388/4,248 (9.1%)	235/2,836 (8.3%)	0.231
Bifurcation†	919/7,084 (13.0%)	419/4,248 (9.9%)	500/2,836 (17.6%)	<0.001
Bifurcation treatment	394/7,084 (5.6%)	194/4,248 (4.6%)	200/2,836 (7.1%)	<0.001
Thrombus present	633/7,084 (8.9%)	336/4,248 (7.9%)	297/2,836 (10.5%)	<0.001
Small vessel‡	1,200/7,084 (16.9%)	704/4,248 (16.6%)	496/2,836 (17.5%)	0.316
Long lesion§	2,671/7,084 (37.7%)	1,504/4,248 (35.4%)	1,167/2,836 (41.1%)	<0.001
Maximum pressure deployment, atm	13.56 ± 4.63 (6,487)	13.45 ± 4.79 (3,790)	13.72 ± 4.40 (2,697)	0.024
Mean stent diameter/lesion, mm	3.13 ± 3.39 (7,084)	3.16 ± 4.31 (4,248)	3.09 ± 0.85 (2,836)	0.363
Total stent length, mm				
Per patient	38.97 ± 26.01 (5,054)	37.41 ± 25.50 (3,056)	41.35 ± 26.58 (1,998)	<0.001
Per lesion	27.97 ± 14.34 (7,084)	26.90 ± 14.06 (4,248)	29.61 ± 14.61 (2,836)	<0.001
No. of stents				
Per patient	1.67 ± 0.97 (5,054)	1.65 ± 0.97 (3,056)	1.70 ± 0.98 (1,998)	0.091
Per lesion	1.19 ± 0.49 (7,084)	1.19 ± 0.48 (4,248)	1.19 ± .51 (2,836)	0.467
IVUS-guided stenting	2,695/7,084 (38.0%)	1,601/4,248 (37.7%)	1,094/2,836 (38.6%)	0.454
Device success	6,908/7,084 (97.5%)	4,147/4,248 (98.2%)	2,761/2,836 (98.5%)	0.484
Lesion success	6,903/7,084 (97.4%)	4,145/4,248 (98.1%)	2,758/2,836 (98.5%)	0.399
Procedure success	6,912/7,084 (97.6%)	4,140/4,248 (98.1%)	2,772/2,836 (98.5%)	0.479

Values are n (%) or mean ± SD. *Type B2 or C lesions according to ACC/AHA classification. †Bifurcation means bifurcated lesion that have been treated solely by DES. ‡Small vessel denotes lesion with reference diameter ≤2.75 mm. §Long lesion denotes lesion with length ≥28 mm.

ACC = American College of Cardiology; AHA = American Heart Association; atm = atmosphere(s); EES = everolimus-eluting stent; IVUS = intravascular ultrasound; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; ZES-R = Resolute zotarolimus-eluting stent.

with the RESOLUTE All Comers trial and the TWENTE trial (3,4), the incidence of definite or probable ST was 0.76% (37/4,876 patients) in the EES group and 0.89% (34/3,814 patients) in the ZES-R group, and did not differ between the 2 groups (odds ratio [OR]: 1.00; 95% confidence interval [CI]: 0.46 to 2.19; p = 0.99) (Supplementary Fig. 3).

Propensity score-matched group analysis. Matching by propensity score yielded 1,014 pairs with more balanced baseline characteristics (Supplementary Table 1 and Supplementary Fig. 4). The cumulative incidence of TLF and POCO were comparable between the 2 groups (log-rank p = 0.675 and 0.708, respectively) (Fig. 1), as were the individual components and definite or probable ST (0.6% vs. 0.2%, p = 0.288) (Supplementary Tables 2 and 3).

Independent predictors of TLF. In multivariate analysis, off-label indication was the strongest predictor of TLF (adjusted HR: 2.882; 95% CI: 1.226 to 6.779; p = 0.015); other significant predictors of TLF included chronic renal failure, diabetes mellitus, and age (Table 5 and Supplementary Table 4).

Subgroup analysis of propensity score-matched population. Significant interaction was observed between stent type and multivessel PCI ($p_{interaction}$ = 0.032) and long lesion ($p_{interaction}$ = 0.016) (Fig. 3). The other subgroups did not interact significantly with stent type and had comparable rates of TLF.

Discussion

To date, this is the largest observational study comparing EES with ZES-R. In both crude and propensity score-matched analyses, 1-year rates of TLF and POCO were comparable for these stents. Clinical events occurred more often after off-label use, the strongest predictor of TLF. Finally, the rates of ST were low in both stents considering the complexity of the lesions treated. In contrast to previous RCTs, the rates of definite and probable ST were comparable between EES and ZES-R. Although well-designed

Table 3 Clinical Outcomes in Crude Population at 1 Year

	Total (N = 5,054)	EES (N = 3,056)	ZES-R (N = 1,998)	RR (95% CI)	p Value
All-cause death	108 (2.1%)	62 (2.0%)	46 (2.3%)	1.13 (0.78–1.65)	0.551
Cardiac death	65 (1.3%)	37 (1.2%)	28 (1.4%)	1.16 (0.71–1.89)	0.610
Any MI	25 (0.5%)	17 (0.6%)	8 (0.4%)	0.72 (0.31–1.66)	0.541
Target vessel	19 (0.4%)	14 (0.5%)	5 (0.3%)	0.55 (0.20–1.51)	0.254
Nontarget vessel	6 (0.1%)	3 (0.1%)	3 (0.2%)	2.29 (0.38–13.72)	0.686
MI due to ST	10 (0.2%)	7 (0.2%)	3 (0.2%)	0.66 (0.17–2.53)	0.749
Any revascularization	267 (5.3%)	161 (5.3%)	106 (5.3%)	1.00 (0.79–1.28)	0.954
Clinically driven revascularization	193 (3.8%)	120 (3.9%)	73 (3.7%)	0.93 (0.70–1.24)	0.653
TLR	68 (1.3%)	40 (1.3%)	28 (1.4%)	1.07 (0.66–1.73)	0.803
Target vessel revascularization	109 (2.2%)	60 (2.0%)	49 (2.5%)	1.25 (0.86–1.81)	0.276
Cerebrovascular accident	30 (0.6%)	18 (0.6%)	12 (0.6%)	1.02 (0.49–2.11)	0.958
TLF*	140 (2.8%)	82 (2.7%)	58 (2.9%)	1.08 (0.78–1.51)	0.662
Target vessel failure†	182 (3.6%)	102 (3.3%)	80 (4.0%)	1.20 (0.90–1.60)	0.217
POCO‡	378 (7.5%)	225 (7.4%)	153 (7.7%)	1.04 (0.85–1.27)	0.702

Values are n (%), unless otherwise indicated. *TLF defined as a composite of cardiac death, MI (not clearly attributed to a nontarget vessel), or clinically indicated TLR by percutaneous or surgical methods at 1 year. †Target vessel failure defined as a composite of cardiac death, MI (not clearly attributed to a nontarget vessel), or clinically indicated target vessel revascularization by percutaneous or surgical methods at 1 year. ‡The POCOs included all-cause mortality, any MI (includes nontarget vessel territory), and any revascularization (includes all target and nontarget vessel, regardless of percutaneous or surgical methods).

CI = confidence interval; EES = everolimus-eluting stent; MACE = major adverse cardiovascular events; MI = myocardial infarction; POCO = patient-oriented composite outcome; RR = relative risk; ST = stent thrombosis; TLF = target lesion failure; TLR = target lesion revascularization; ZES-R = Resolute zotarolimus-eluting stent.

large RCTs usually have high internal validity, their subjects and protocols often are not generalizable to routine practice (7). Conversely, prospective registries have the strengths of a broader patient population and reflection of routine clinical practices.

Although the patients in the EES or ZES-R group showed several significant differences in baseline clinical and angiographic characteristics, which is an inherent limitation of nonrandomized studies, these differences were balanced with propensity score matching, and the clinical outcome (both primary and all secondary) showed comparable results between 2 stent groups.

The RCTs that previously compared these DESs reported 1-year TLF rates (EES/ZES-R) of 8.3%/8.2% ($p = 0.94$) and 6.8%/7.9%, respectively ($p = 0.42$) (2,4). In the present study, the TLF rate was lower (2.7% vs. 2.9%, $p = 0.662$) despite a more enriched population with PCI in whom the rate of off-label DES use was relatively higher (72.5% and 80.7%, respectively) than in the RESOLUTE All Comers trial (65.6% and 67.0%, respectively). Although 77.4% of enrolled patients had off-label indication in the TWENTE trial, the study excluded patients with ST-segment MI. Likewise, the incidence of definite or probable ST also was low and comparable (0.6% vs. 0.4%, for EES vs. ZES-R, respectively). Of note, ST occurred only after off-label use. Several trials with all-comers design and unrestricted use of DES reported rates of definite ST, before 18 months, ranging from 0% to 0.8% in EES (2,4,8–11) and 0.1% to 1.2% in ZES-R (2,4,12,13). A recent meta-analysis found significantly lower rates of definite ST in cobalt-chromium everolimus-eluting stents (CoCr-EES) compared with ZES-R at 1 year, but the rates of definite or probable ST did not differ significantly (14). Because most of the pooled CoCr-EES data were extracted from the studies that did not compare CoCr-EES directly with ZES-R, these findings should be interpreted carefully. More direct comparisons between EES versus ZES-R regarding ST are needed to clarify this issue.

In multivariate analysis, off-label DES use was the strongest predictor of TLF, concordant with previous literature (15). Despite the extremely low TLF rates with second-generation DESs in this and other studies, the risk still increases significantly, approximately 3-fold, with off-label DES use. However, even in off-label use, the performance of both EES and ZES-R was excellent and comparable. Other independent predictors of TLF were chronic renal failure, diabetes mellitus, and increasing age, established risk factors after PCI (16–20).

Subgroup analysis suggested that in 2 subgroups, multivessel PCI and lesions ≥28 mm, EES might have worse outcomes than ZES-R. However, caution is warranted in interpreting these results because EES >28 mm were not available during the study period, TLF rates for ZES-R unexpectedly decreased with increased lesion complexity, and exploratory subgroup analysis is limited statistically by multiple testing and small sample size.

Study limitations. This study has limitations inherent to nonrandomized comparisons, such as allocation bias and uneven distribution of risk factors. The stent groups differed significantly in baseline clinical and angiographic characteristics. These differences were balanced with propensity score matching (Supplementary Tables 5 to 7); however, unmeasured variables were not controlled. Second, because data were from observational registries, detection of events and patient follow-up were less

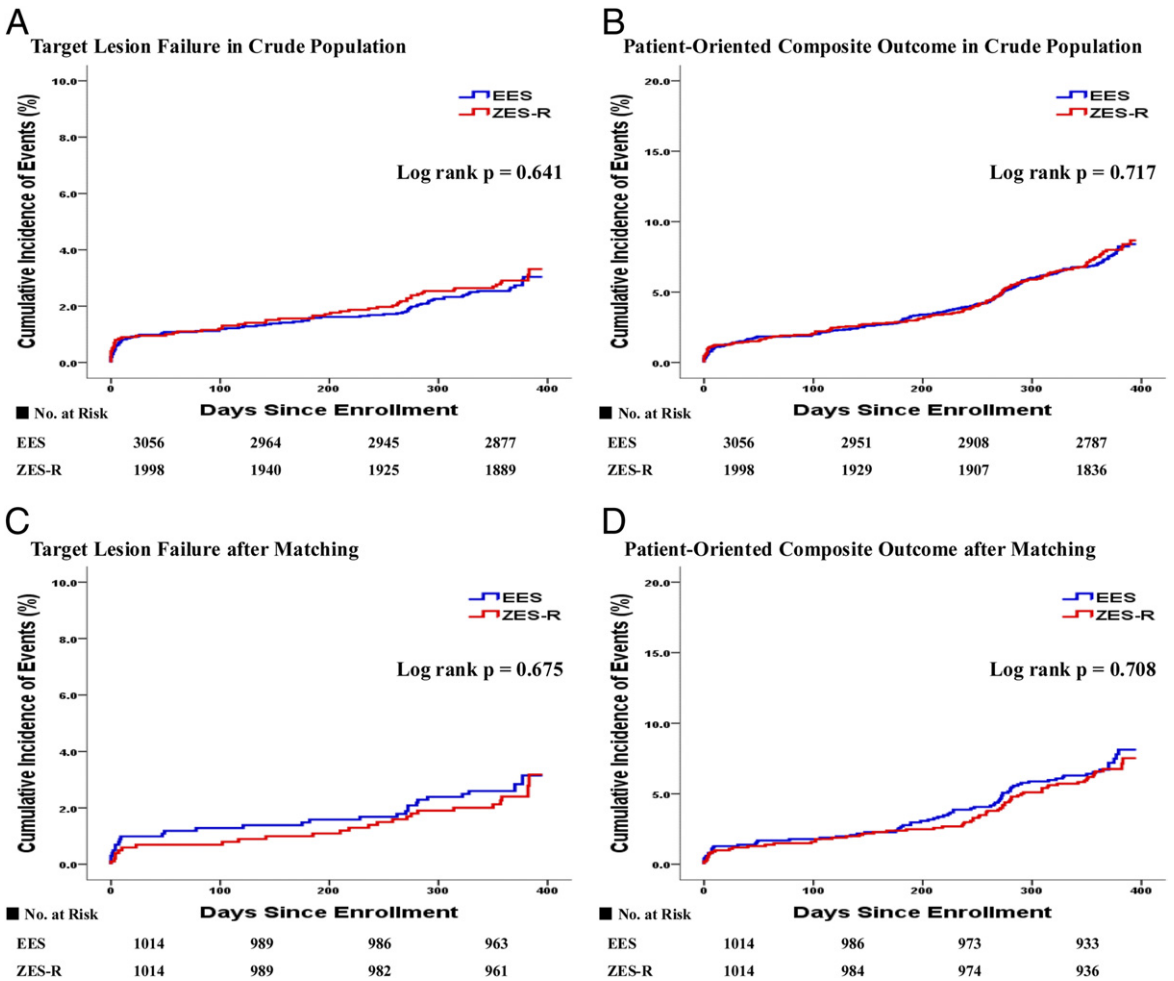

Figure 1 **Survival Analysis: Primary and Major Secondary Outcomes**

Kaplan-Meier curves are shown for each outcome and cohort combination **(A–D)**. EES = everolimus-eluting stent (Abbott Vascular, Temecula, California); ZES-R = Resolute zotarolimus-eluting stent (Medtronic Cardiovascular, Santa Rosa, California).

Table 4 **Stent Thrombosis in Crude Population at 1 Year**

	Total (N = 5,054)	EES (N = 3,056)	ZES-R (N = 1,998)	p Value
Definite	9 (0.2%)	6 (0.2%)	3 (0.2%)	0.751
Acute (0–1 day)	4 (0.1%)	3 (0.1%)	1 (0.1%)	0.657
Subacute (2–30 days)	3 (0.1%)	2 (0.1%)	1 (0.1%)	1.000
Late (31–360 days)	2 (<0.1%)	1 (<0.1%)	1 (0.1%)	1.000
Probable	17 (0.3%)	12 (0.4%)	5 (0.3%)	0.464
Acute (0–1 day)	4 (0.1%)	1 (<0.1%)	3 (0.2%)	0.307
Subacute (2–30 days)	12 (0.2%)	10 (0.3%)	2 (0.1%)	0.142
Late (31–360 days)	1 (<0.1%)	1 (<0.1%)	0 (0%)	1.000
ST				
Definite or probable	25 (0.5%)	18 (0.6%)	7 (0.4%)	0.306
Duration of dual antiplatelet agent				
6 months	4,271/4,412 (96.8%)	2,599/2,684 (96.8%)	1,672/1,728 (96.8%)	0.930
1 yr	3,740/4,412 (84.8%)	2,277/2,684 (84.8%)	1,463/1,728 (84.7%)	0.898
Mean duration of DAT	351.09 ± 62.62 (4,412)	351.19 ± 62.94 (2,684)	350.94 ± 62.15 (1,728)	0.896

Values are n (%), unless otherwise indicated.
DAT = dual antiplatelet agent therapy; EES = everolimus-eluting stent; ST = stent thrombosis; ZES-R = Resolute zotarolimus-eluting stent.

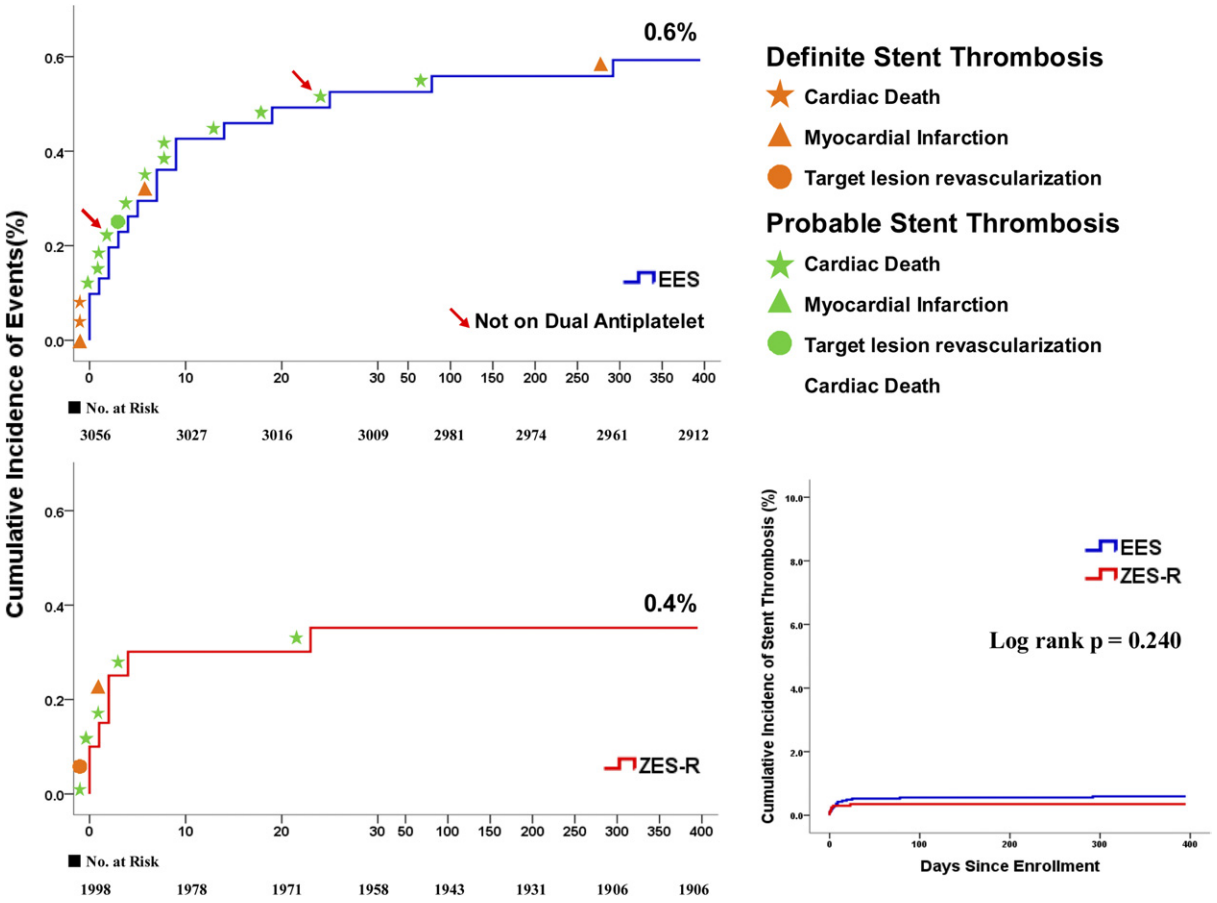

Figure 2 Survival Analysis: Definite or Probable ST

Arrow indicates the patients not taking dual-antiplatelet therapy at time of ST. EES = everolimus-eluting stent; ZES-R = Resolute zotarolimus-eluting stent.

rigorous than in RCTs, perhaps explaining the low event rates. Even though data were collected by dedicated study nurses, ≥98% patients were followed, insurance records were reviewed, and survival status was thoroughly investigated, nonfatal events (e.g., MI or TLR) may have been underreported. Third, follow-up was only reported through 1 year, too short to draw conclusions regarding ST and safety issues. Last, systemic follow-up angiography was not performed, and thus mechanistic insights regarding clinical results could not be suggested from this study.

Table 5 Independent Predictors of Target Lesion Failure in Propensity Score-Matched Group*

	HR	95% CI	p Value
Off-label indication	2.882	1.226–6.779	0.015
Chronic renal failure	2.774	1.166–6.603	0.021
Diabetes mellitus	1.957	1.128–3.396	0.043
Age	1.051	1.022–1.081	0.001

*Identification of independent predictors was done with stratified Cox proportional hazard regression model, and the variables were presented with multivariable adjusted HRs, 95% CIs, and p values. Variables included in the final model are shown in Supplementary Table 7. The individual components of off-label indication (i.e., STEMI, NSTEMI, in-stent restenosis, bifurcation, thrombotic total occlusion, long lesion, multivessel PCI, severe left ventricular dysfunction [left ventricular ejection fraction <30%], and left main procedure) were not included individually in the final model because of significant correlation with off-label indication itself (i.e., collinearity between these covariates).

CI = confidence interval; HR = hazard ratio.

Conclusions

Both stents had comparable outcomes after 1 year, with low event rates, suggesting their excellent safety and efficacy in real-world practice.

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	EES N = 3056	ZES-R N = 1998	HR (95% C.I.)	Interaction P value
All patients	**2.8 (28/1014)**	**2.5 (25/1014)**	**0.813 (0.466-1.825)**	
Off label indication	3.5 (25/716)	3.0 (22/729)	0.745 (0.409-1.357)	0.798
On label indication	1.0 (3/298)	1.1 (3/285)	1.437 (0.255-8.090)	
Diabetes	4.7 (18/379)	3.2 (12/380)	0.553 (0.253-1.212)	0.224
No diabetes	1.6 (10/635)	2.1 (13/634)	1.178 (0.488-2.844)	
Dyslipidemia	2.7 (18/658)	1.8 (12/653)	0.727 (0.343-1.539)	0.241
No Dyslipidemia	2.8 (10/356)	3.6 (13/361)	0.748 (0.299-1.875)	
Multivessel PCI	5.0 (16/317)	2.2 (7/313)	0.492 (0.191-1.272)	0.032
Single vessel PCI	1.7 (12/697)	2.6 (18/701)	1.314 (0.605-2.851)	
Lesion length ≥28mm	4.1 (16/388)	1.5 (6/390)	0.327(0.116-0.921)	0.016
Lesion length <28mm	1.9 (12/626)	3.0 (19/624)	1.488 (0.701-3.160)	
Vessel diameter < 2.75mm	5.3 (11/209)	3.3 (7/212)	0.654 (0.221-1.931)	0.374
Vessel diameter ≥2.75mm	2.1 (17/805)	2.2 (18/802)	0.991 (0.489-2.005)	
Bifurcation	12.2 (6/49)	6.9 (4/58)	1.000 (0.246-4.072)	0.420
No Bifurcation	2.3 (22/965)	2.2 (21/956)	0.941 (0.510-1.747)	
STEMI	3.1 (4/130)	5.5 (7/127)	2.491 (0.417-14.87)	0.210
Other indication	2.7 (24/884)	2.0 (18/887)	0.710 (0.375-1.345)	
AMI (<72 h)	4.9 (12/246)	4.8 (11/231)	0.538 (0.194-1.492)	0.805
No AMI (72 h)	2.1 (16/768)	1.8 (14/783)	0.880 (0.413-1.873)	
LM	5.7 (3/53)	3.6 (2/55)	0.621 (0.104-3.725)	0.706
No LM	2.6 (25/961)	2.4 (23/959)	0.921 (0.523-1.623)	
Overlapping Stent	6.6 (13/197)	3.4 (7/207)	0.303 (0.103-0.887)	0.127
No Overlapping stent	1.8 (15/817)	2.2 (18/807)	1.168 (0.576-2.368)	

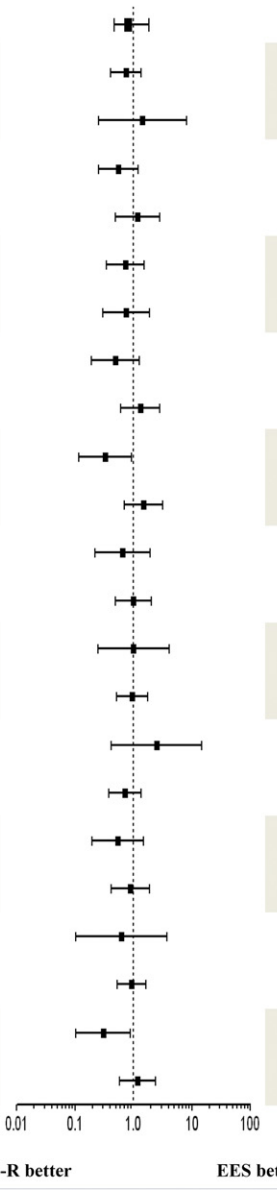

Figure 3 **Subgroup Analysis for TLF in Propensity Score-Matched Group**

Subgroups showed mostly similar results to the total cohort except for two groups. Significant interactions were observed between stent type and multivessel PCI, and stent type and long lesion. AMI = acute myocardial infarction; CI = confidence interval; EES = everolimus-eluting stent; HR = hazard ratio; LM = left main vessel; PCI = percutaneous coronary intervention; STEMI = ST-segment myocardial infarction elevation; ZES-R = Resolute zotarolimus-eluting stent.

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Key Words: clinical outcome ■ everolimus-eluting stent ■ patient-oriented composite outcome ■ Resolute zotarolimus-eluting stent ■ stent thrombosis ■ target lesion failure.

APPENDIX

For supplementary material on the study protocol, please see the online version of this article.