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Comparison of Zotarolimus- and Everolimus-Eluting Coronary Stents
Final 5-Year Report of the RESOLUTE All-Comers Trial

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Background—Newer-generation drug-eluting stents that release zotarolimus or everolimus have been shown to be superior to the first-generation drug-eluting stents. However, data comparing long-term safety and efficacy of zotarolimus- (ZES) and everolimus-eluting stents (EES) are limited. RESOLUTE all-comers (Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention) trial compared these 2 stents and has shown that ZES was noninferior to EES at 12-month for the primary end point of target lesion failure. We report the secondary clinical outcomes at the final 5-year follow-up of this trial.

Methods and Results—RESOLUTE all-comer clinical study is a prospective, multicentre, randomized, 2-arm, open-label, noninferiority trial with minimal exclusion criteria. Patients (n=2292) were randomly assigned to treatment with either ZES (n=1140) or EES (n=1152). Patient-oriented composite end point (combination of all-cause mortality, myocardial infarction, and any revascularizations), device-oriented composite end point (combination of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularization), and major adverse cardiac events (combination of all-cause death, all myocardial infarction, emergent coronary bypass surgery, or clinically indicated target lesion revascularization) were analyzed at 5-year follow-up. The 2 groups were well-matched at baseline. Five-year follow-up data were available for 98% patients. There were no differences in patient-oriented composite end point (ZES 35.3% versus EES 32.0%, *P*=0.11), device-oriented composite end point (ZES 17.0% versus EES 16.2%, *P*=0.61), major adverse cardiac events (ZES 21.9% versus EES 21.6%, *P*=0.88), and definite/probable stent thrombosis (ZES 2.8% versus EES 1.8%, *P*=0.12).

Conclusions—At 5-year follow-up, ZES and EES had similar efficacy and safety in a population of patients who had minimal exclusion criteria.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00617084.

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Key Words: drug-eluting stent ■ everolimus ■ percutaneous coronary interventions ■ zotarolimus

Percutaneous coronary intervention has revolutionized the treatment of patients with flow limiting coronary artery disease. Balloon angioplasty without stenting had limited success because of a high incidence of acute vessel closure caused by dissection or elastic recoil, late vascular remodeling, and neointimal proliferation.[1–3] The introduction of bare metal stents improved procedural success and acute outcomes[1]; however, the clinical outcomes remained affected by high risk of in-stent restenosis.[4–6] The drug-eluting stents

(DES) substantially reduced neointimal proliferation,[5–7] but first-generation DES eluting sirolimus or paclitaxel from a durable polymer raised safety concerns about late and very late stent thrombosis possibly because of delayed endothelialization by the antiproliferative drugs and chronic inflammation or delayed hypersensitivity reaction caused by the polymers in these DES.[8–11] The second-generation DES have newer antiproliferative drugs (including zotarolimus and everolimus) and biocompatible or biodegradable polymers

along with improved stent design and thinner struts.[12] These newer stents have shown promising results and improved clinical outcomes compared with first-generation DES[13,14];

however, the long-term data on direct comparison between the newer-generation DES is scarce.

The RESOLUTE all-comers (Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention) trial aimed to compare the Resolute zotarolimus-eluting stent (ZES; Medtronic CardioVascular Ltd) and Xience-V everolimus-eluting stent (EES; Abbott Vascular Ltd).[13] It has been shown that ZES was noninferior to the EES with respect to the primary end point of target lesion failure at 12 months, which occurred in 8.2% and 8.3% of patients, respectively ($P<0.001$ for noninferiority). There were no significant between-group differences in the rate of death from cardiac causes, any myocardial infarction, repeat revascularization, or stent thrombosis at 12 months. We report the clinical outcomes at the final 5-year follow-up of this trial.

Methods

The study complies with the Declaration of Helsinki. Study protocol was approved by the relevant ethics committees and informed consent was obtained from all participants (or their guardians).

Study Design and Population

The study design of the RESOLUTE all-comers trial has previously been described[13] and is outlined in Figure 1. Briefly, the RESOLUTE all-comers trial is a multicentre prospective double-arm randomized controlled noninferiority trial. From April 30, 2008, to October 28,
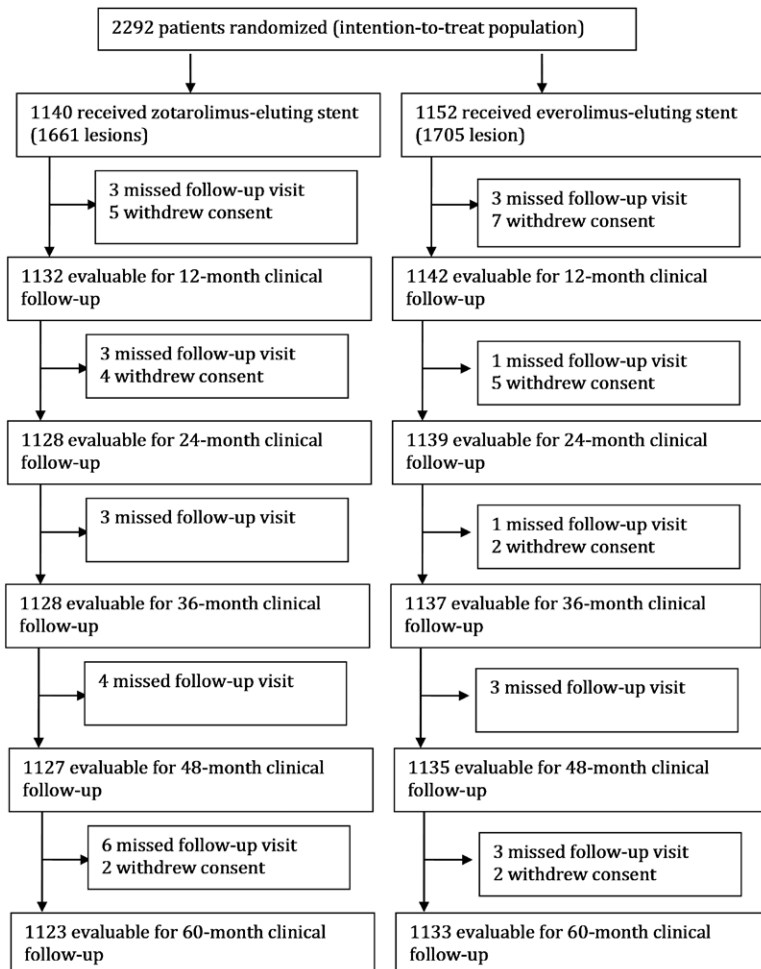

Figure 1. Flow diagram of RESOLUTE all-comers trial. RESOLUTE indicates Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention.

2008, we recruited 2292 adult patients with chronic, stable coronary artery disease or acute coronary syndromes, including myocardial infarction with or without ST-segment–elevation. The trial was powered for noninferiority testing of the primary end point at 12 months on an intention-to-treat basis; the details of power calculation have been described previously.[13] Patients were randomly assigned to undergo percutaneous coronary intervention with either ZES or EES. Patients were eligible if they had at least one coronary lesion with percentage diameter stenosis >50% in a vessel with a reference diameter of 2.25 to 4.0 mm. There were minimal exclusion criteria and no restrictions on total number of treated lesions, treated vessels, lesion length, or number of stents implanted.

Study Procedure

Procedures were performed according to standard techniques with the aim to treat all coronary lesions in one session; however, staged procedures within 6 weeks were permitted. Mixture of different DES types was prohibited unless the operator was unable to insert the study stent. Procedural anticoagulation was achieved with unfractionated heparin at a dose of 5000 IU or 70 to 100 IU per kilogram of body weight to maintain an activated clotting time of >250 seconds; the use of glycoprotein IIb/IIIa inhibitors was at the operators' discretion. All patients received at least 75 mg of acetylsalicylic acid before the procedure. A loading dose of 300 to 600 mg of clopidogrel was administered if the patient had received no clopidogrel during the previous 7 days. All patients were discharged with a prescription of at least 75 mg of acetylsalicylic acid indefinitely and 75 mg of clopidogrel for a minimum of 6 months after the index procedure.

Follow-Up and Clinical End Points

Patients were followed-up by telephone call or hospital visit at 1, 6, and 12 months and yearly thereafter until 5 years. The primary end point of the trial was target lesion failure (TLF) defined as the composite of cardiac death, myocardial infarction (not clearly attributable to a nontarget vessel), and target lesion revascularization (clinically indicated) at 12 months.[13] The current article reports the secondary clinical outcomes of this trial at final 5-year follow-up. These predefined end points include device-oriented composite end point or TLF (combination of cardiac death, myocardial infarction not clearly attributable to a nontarget vessel, and clinically indicated target lesion revascularization), patient-oriented composite end point (combination of all-cause mortality, myocardial infarction, and any revascularizations), target vessel failure (combination of cardiac death, myocardial infarction not clearly attributable to a nontarget vessel, and clinically indicated target vessel revascularization) and major adverse cardiac events (combination of all-cause death, all myocardial infarction, emergent coronary bypass surgery, or clinically indicated target lesion revascularization). We have also presented all the individual end points, as defined previously,[13] and stent thrombosis as defined by the Academic Research Consortium.[15]

Statistical Analysis

Categorical variables are presented as counts and percentages and compared using Chi-square or Fisher exact test. Continuous variables are presented as means±standard deviation and compared using the Student's unpaired t test or 1-way analysis of variance, as appropriate. Survival curves were constructed using Kaplan–Meier estimates and

Table 1.   Comparison of Baseline Characteristics Between the Groups Treated With Zotarolimus- and Everolimus-Eluting Stents

Patient Characteristics	Resolute (ZES) (N=1140 Patients)	Xience-V (EES) (N=1152 Patients)	Difference [95% CI]	P Value
Age, y	64.4±10.9	64.2±10.8	0.2 [−0.7, 1.1]	0.67
BMI, kg/m²	27.8±4.4	27.8±4.3	0.1 [−0.3, 0.4]	0.68
Male	76.6%	77.2%	−0.6% [−4.0, 2.9]	0.77
Prior MI	28.8%	30.4%	−1.7% [−5.4, 2.1]	0.41
Prior PCI	31.8%	32.1%	−0.3% [−4.1, 3.5]	0.89
Current smoker	26.5%	26.5%	0.0% [−3.6, 3.6]	1.00
Hyperlipidemia	64.0%	67.7%	−3.7% [−7.6, 0.2]	0.064
Diabetes mellitus	23.5%	23.4%	0.1% [−3.4, 3.5]	1.00
Hypertension	71.1%	71.3%	−0.1% [−3.8, 3.6]	0.96
Prior CABG	10.0%	9.5%	0.5% [−2.0, 2.9]	0.73
Revascularization for AMI	34.5%	33.7%	0.8% [−3.1, 4.7]	0.69
Serum creatinine, μmol/L	87.2±50.6	85.7±37.2	1.6 [−2.1, 5.2]	0.41
Syntax score	14.8±9.3	14.6±9.2	0.2 [−0.6, 1.0]	0.60
Procedural characteristics				
Prestent balloon dilatation	69.5%	70.2%	−0.7% [−4.5, 3.1]	0.75
Maximum balloon pressure, atm	15.60±3.03	15.87±3.18	−0.27 [−0.53, −0.01]	0.038
Duration of procedure, min	45.01±31.32	43.31±28.34	1.70 [−0.74, 4.15]	0.17
Fluoroscopy time, min	14.76±14.1	14.05±11.0	0.71 [−0.35, 1.76]	0.19
Total contrast, mL	233.2±110.3	230.9±104.0	2.3 [−6.5, 11.1]	0.61
Duration of hospitalization, days	2.74±3.59	2.79±3.66	−0.05 [−0.35, 0.24]	0.72
Number of treated lesions	1.46±0.73	1.48±0.77	−0.02 [−0.08, 0.04]	0.46
Staged PCI	8.2%	9.2%	−1.0% [−3.3, 1.3]	0.42
Total stent length per patient, mm	34.42±24.49	36.98±26.49	−2.56 [−4.65, −0.47]	0.016
Number of stents per patient	1.90±1.21	2.02±1.34	−0.12 [−0.23, −0.02]	0.021

BMI indicates body mass index; CABG, coronary artery bypass grafting; CI, confidence interval; EES, everolimus-eluting stents; MI, myocardial infarction; PCI, percutaneous coronary intervention; RESOLUTE, Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention; and ZES, zotarolimus-eluting stents.
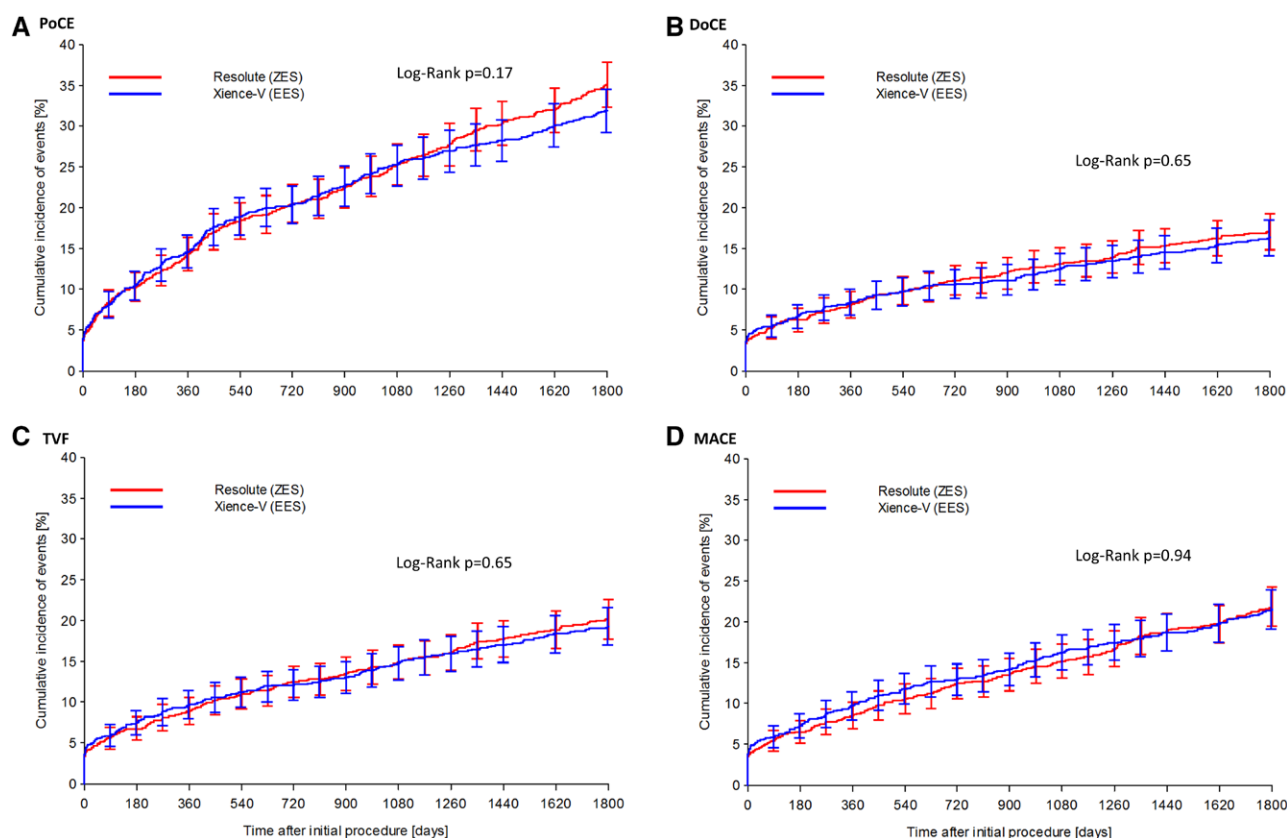
Figure 2. Kaplan–Meier curves comparing zotarolimus- and everolimus-eluting stents for clinical end points. Zotarolimus- and everlomius-eluting stents had similar patient-oriented composite end point (PoCE; combination of all-cause mortality, myocardial infarction, and any revascularization; **A**), device-oriented composite end point (DoCE; combination of cardiac death, myocardial infarction not clearly attributable to a nontarget vessel, and clinically indicated target lesion revascularization; **B**), target vessel failure (TVF; combination of cardiac death, myocardial infarction not clearly attributable to a nontarget vessel, and clinically indicated target vessel revascularization; **C**), and major adverse cardiac events (MACE; combination of all-cause death, all myocardial infarction, emergent coronary bypass surgery, or clinically indicated target lesion revascularization; **D**). Error bars indicate a point-wise 2-sided 95% confidence interval (1.96 SD). Standard error based on the Greenwood Formula.

compared using log-rank test. A 2-tailed *P* value of <0.05 was considered to indicate statistical significance. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc, Cary).

Results

A total of 2292 patients were enrolled and randomly assigned to treatment with ZES (n=1140) or EES (n=1152). The 2 groups were well-matched for the baseline demographical, clinical, and angiographic characteristics, except for difference in number of stents used, total length of stents used, and the maximum balloon pressure (Table 1), as previously reported.[13] The mean age was 64±11 years, with 77% males and 23% diabetics in both groups. There were ≈34% patients in both study arms who underwent revascularization for acute myocardial infarction. The mean SYNTAX score was also similar in both groups (ZES 14.8±9.3 versus EES 14.6±9.2, *P*=0.63).

Follow-up data at 5 years were available for 98% patients. There was no difference in usage of dual antiplatelet therapy between the 2 groups at 30 day (ZES 93.9% versus EES 94.3%, *P*=0.72), 1 year (ZES 84.2% versus 83.3%, *P*=0.61), 2 year (ZES 17.8% versus 18.2%, *P*=0.82), and 5 year (ZES 11.0% versus EES 10.9%, *P*=0.94).

At 5-year follow-up, there were no differences in the incidence of patient-oriented (ZES 35.3% versus EES 32.0%, *P*=0.11) or device-oriented (ZES 17.0% versus EES 16.2%, *P*=0.61) end points between the 2 groups (Figure 2). Furthermore, we noted no differences between the 2 stent groups for major adverse cardiac events (ZES 21.9% versus EES 21.6%, *P*=0.88) and target vessel failure (ZES 20.0% versus EES 19.1%, *P*=0.60) at the final follow-up (Figure 2). The 2 groups also had no difference in other clinical end points, including death, cardiac death, myocardial infarction, revascularization, and stent thrombosis (Table 2). The detailed incidence of stent thrombosis in the 2 groups during 5-year follow-up period is provided in Table in the Data Supplement.

Stratified analysis of the primary end point (device-oriented composite end point/TLF) at 5 years across different patient subgroups (including diabetics and acute coronary syndromes) and anatomic complexity of coronary artery disease revealed no difference in outcomes between ZES- and EES-treated patients (Figure 3).

Discussion

The RESOLUTE all-comers trial directly compared the performance of 2 newer-generation stents in an all-comers population over a long follow-up period. The main finding of the present study is that at 5-year follow-up, ZES and EES were similar in clinical efficacy and safety with no difference

Table 2.   All Clinical End Points at 5-Year Follow-Up

End Point	Resolute (ZES) (N=1140 Patients)	Xience-V (EES) (N=1152 Patients)	Difference [95% CI]	P Value
PoCE	35.3% (396/1123)	32.0% (363/1133)	3.2% [−0.7%, 7.1%]	0.11
DoCE/TLF	17.0% (191/1123)	16.2% (183/1133)	0.9% [−2.2%, 3.9%]	0.61
TVF	20.0% (225/1123)	19.1% (216/1133)	1.0% [−2.3%, 4.2%]	0.60
MACE	21.9% (246/1123)	21.6% (245/1133)	0.3% [−3.1%, 3.7%]	0.88
Death	11.0% (123/1123)	10.8% (122/1133)	0.2% [−2.4%, 2.8%]	0.89
Cardiac death	6.5% (73/1123)	5.7% (65/1133)	0.8% [−1.2%, 2.7%]	0.48
Vascular death	0.8% (9/1123)	1.0% (11/1133)	−0.2% [−0.9%, 0.6%]	0.82
Noncardiovascular death	3.7% (41/1123)	4.1% (46/1133)	−0.4% [−2.0%, 1.2%]	0.66
All MI (extended historical definition)	7.1% (80/1123)	6.8% (77/1133)	0.3% [−1.8%, 2.4%]	0.80
Q wave	1.9% (21/1123)	1.1% (13/1133)	0.7% [−0.3%, 1.7%]	0.17
Non-Q wave	5.6% (63/1123)	5.6% (64/1133)	−0.0% [−1.9%, 1.9%]	1.00
TV MI in target vessel (extended historical definition)	5.7% (64/1123)	5.7% (65/1133)	−0.0% [−2.0%, 1.9%]	1.00
Q wave	1.3% (15/1123)	0.8% (9/1133)	0.5% [−0.3%, 1.4%]	0.23
Non-Q wave	4.6% (52/1123)	4.9% (56/1133)	−0.3% [−2.1%, 1.4%]	0.77
All MI (ARC defined)	18.0% (202/1123)	16.5% (187/1133)	1.5% [−1.6%, 4.6%]	0.37
Q wave	1.9% (21/1123)	1.1% (12/1133)	0.8% [−0.2%, 1.8%]	0.12
Non-Q wave	16.7% (188/1123)	15.5% (176/1133)	1.2% [−1.8%, 4.2%]	0.46
MI in target vessel (ARC defined)	16.0% (180/1123)	15.0% (170/1133)	1.0% [−2.0%, 4.0%]	0.52
Q wave	1.3% (15/1123)	0.7% (8/1133)	0.6% [−0.2%, 1.5%]	0.15
Non-Q wave	15.0% (169/1123)	14.3% (162/1133)	0.8% [−2.2%, 3.7%]	0.63
All revascularizations	24.0% (270/1123)	20.7% (234/1133)	3.4% [−0.0%, 6.8%]	0.055
CABG	3.6% (40/1123)	2.9% (33/1133)	0.6% [−0.8%, 2.1%]	0.41
RePCI	21.6% (243/1123)	18.4% (209/1133)	3.2% [−0.1%, 6.5%]	0.059
TLR	10.2% (114/1123)	8.9% (101/1133)	1.2% [−1.2%, 3.7%]	0.35
CABG	1.9% (21/1123)	1.6% (18/1133)	0.3% [−0.8%, 1.4%]	0.63
RePCI	8.8% (99/1123)	7.6% (86/1133)	1.2% [−1.0%, 3.5%]	0.32
Clinically driven TLR	7.8% (88/1123)	7.1% (81/1133)	0.7% [−1.5%, 2.9%]	0.58
CABG	1.4% (16/1123)	1.4% (16/1133)	0.0% [−1.0%, 1.0%]	1.00
RePCI	6.9% (77/1123)	6.0% (68/1133)	0.9% [−1.2%, 2.9%]	0.44
TVR	14.9% (167/1123)	13.4% (152/1133)	1.5% [−1.4%, 4.3%]	0.33
CABG	2.5% (28/1123)	2.3% (26/1133)	0.2% [−1.1%, 1.5%]	0.78
RePCI	13.1% (147/1123)	11.7% (132/1133)	1.4% [−1.3%, 4.2%]	0.31
Clinically driven TVR	11.4% (128/1123)	10.9% (123/1133)	0.5% [−2.1%, 3.1%]	0.69
CABG	1.9% (21/1123)	1.9% (22/1133)	−0.1% [−1.2%, 1.1%]	1.00
RePCI	10.1% (113/1123)	9.4% (106/1133)	0.7% [−1.7%, 3.2%]	0.62
Target lesion–related stent thrombosis				
Definite	1.6% (18/1123)	0.8% (9/1133)	0.8% [−0.1%, 1.7%]	0.084
Definite+probable	2.4% (27/1123)	1.7% (19/1133)	0.7% [−0.4%, 1.9%]	0.24
Definite+probable+possible	6.8% (76/1123)	5.4% (61/1133)	1.4% [−0.6%, 3.4%]	0.19

All events were adjudicated by the independent clinical event committee. Extended historical definition of MI is used for all the composite end points.

PoCE included combination of all-cause mortality, myocardial infarction, and any revascularization; DoCE or TLF included combination of cardiac death, myocardial infarction not clearly attributable to a nontarget vessel, and clinically indicated target lesion revascularization; TVF included combination of cardiac death, myocardial infarction not clearly attributable to a nontarget vessel, and clinically indicated target vessel revascularization; MACE included combination of all-cause death, all myocardial infarction, emergent coronary bypass surgery, or clinically indicated target lesion revascularization.

ARC indicates academic research consortium; CABG, coronary artery bypass grafting; CI, confidence interval; DoCE, device-oriented composite end point; EES, everolimus-eluting stents; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PoCE, patient-oriented composite end point; RESOLUTE, Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention; TLF, target lesion failure; TLR, target lesion revascularization; TVF, target vessel failure; TVR, target vessel revascularization; and ZES, zotarolimus-eluting stents.
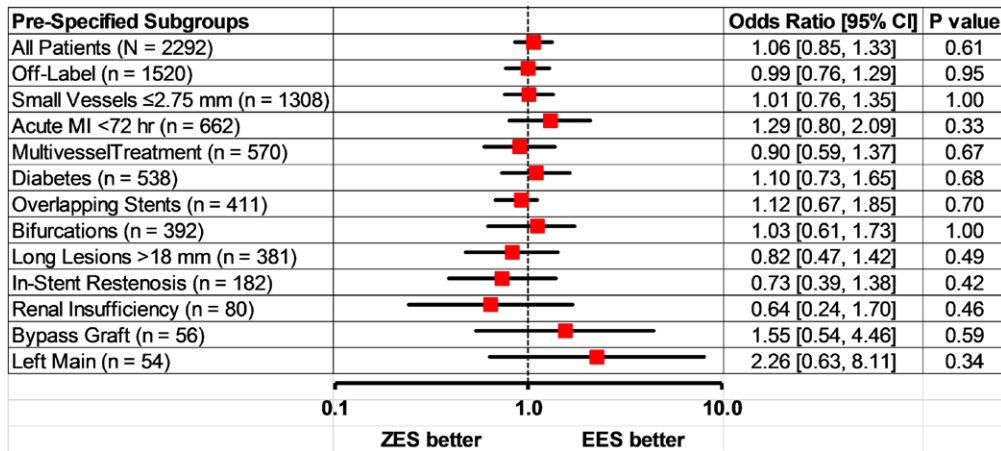
Figure 3. Forest plot showing prespecified subgroups analysis comparing zotarolimus- and everolimus-eluting stents for target lesion failure at 5-year follow-up. Zotarolimus- and everolimus-eluting stents had similar device-oriented composite end point (DoCE) or target lesion failure (TLF), including combination of cardiac death, myocardial infarction (MI) not clearly attributable to a nontarget vessel, and clinically indicated target lesion revascularization. Error bars indicate a point-wise 2-sided 95% confidence interval (1.96 SD). Standard error based on the Greenwood Formula. EES indicates everolimus-eluting stents; and ZES, zotarolimus-eluting stents.

in either patient-oriented and device-oriented end points or stent thrombosis.

The DES are the main stay in treating patients with flow-limiting coronary lesions.[16,17] First-generation DES showed a substantial improvement reduction in restenosis and need for repeat revascularization compared with bare metal stents.[6,7] However, these first-generation devices failed in adding a major gain in terms of long-term mortality[18] and a major concern remained on long-term safety, in particular, related to late stent thrombosis.[8,9,19–24] The second-generation DES, with novel stent design/material, improved polymer biocompatibility, and novel antiproliferative drugs were developed to improve acute performance and long-term outcomes.[11,14]

ZES and EES have previously been shown to be equivalent in terms of procedural success, angiographic late lumen loss, and short-/midterm clinical outcomes.[13,25,26] Our data confirms that they remain comparable over a long follow-up period of 5 years. These results are consistent with reports from other trials and registries.[27,28] The Real-World Endeavor Resolute Versus Xience V Drug-Eluting Stent Study in Twente (TWENTE) trial randomly assigned patients to ZES (n=697) or EES (n=694) and found no difference in patient-oriented composite end point (ZES 16.4% versus EES 17.1%, P=0.75) and target vessel failure (ZES 10.8% versus EES 11.6, P=0.65) at 2-year follow-up.[27] It has also been shown that there is no difference in outcomes between the 2 stents when used for patients with complex coronary disease,[29,30] long lesions requiring overlapping stents,[31] unprotected left main stem,[32] small diameter (<2.7 mm) vessels,[33] and bifurcation lesions.[34] Our findings from stratified analyses corroborate these studies.

The incidence of stent thrombosis in ZES- or EES-treated patients in this study was similar and comparable to other studies. In the LEADERS trial, the incidence of definite/probable stent thrombosis at 5 year for second-generation biolimus eluting stent was 3.6%. In the TWENTE trial, 95% patients were asked to discontinue dual antiplatelet therapy after 12 months. Two-year rates of definite or probable stent thrombosis were similar (ZES 1.2% versus EES 1.4%, P=0.63).[27]

ZES (cobalt-chromium platform) has been reported to be equivalent to the newer platinum-chromium (Pt-Cr)– based EES (Promus Element, Boston Scientific Ltd),[35,36] whereas Pt-Cr–based (Promus Element) and cobalt-chromium–based (Xience-V) EES are also comparable in outcomes.[37] HOST-ASSURE trial randomized 3755 all-comer patients undergoing percutaneous coronary intervention to PtCr-EES or ZES. At 1-year, the primary end point of TLF occurred in 2.9% and 2.9% of the population in the PtCr-EES and ZES groups, respectively (superiority P=0.98, noninferiority P=0.025). There were no significant differences in the individual components of TLF, as well as the patient-oriented clinical outcome.[35] Another recently reported all-comer trial (n=1811 patients) comparing cobalt-chromium–based ZES (n=906) against Promus Element (Pt-Cr EES, n=905) has shown no difference in the primary end point of target vessel failure or its individual components at 12-month follow-up. There was also no difference in stent thrombosis (ZES 0.3% versus Promus Element 0.7%, P=0.34).[36] There was also no difference in the outcomes for patients presenting with ST-elevation myocardial infarction.[36]

Limitations
This study's powered primary end point was target lesion failure at 1 year, and the clinical outcome at the final 5-year follow-up is a secondary end point. However, it was a prespecified secondary end point, with all events adjudicated by an independent Clinical Events Committee.

Conclusions
ZES and EES offered similar patient- and device-related end points at 5-year follow-up. Both ZES and EES are the most widely used DES at the moment, and our results indeed confirm that these stents have equally good outcomes during a long-term follow-up.

Sources of Funding

Disclosures

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