Comparison of Resolute zotarolimus-eluting and Xience everolimus-eluting stents in patients with de novo long coronary artery lesions: a randomized LONG-DES VI trial

Do-Yoon Kang[a,*], Cheol Hyun Lee[a,*], Pil Hyung Lee[a], Jung-Min Ahn[a], Seung-Whan Lee[a], Young-Hak Kim[a], Seong-Wook Park[a], Chang Wook Nam[e], Yun Seok Choi[b], Seung-Woon Rha[c], Jang Hyun Cho[g], Weon Kim[d], Sung-Ho Her[h], Myung Ho Jeong[i], Joo-Young Yang[j], Bong-Ki Lee[k], Hun Sik Park[f], Duk-Woo Park[a] and Seung-Jung Park[a]

Background **Outcomes for stent-based coronary intervention of lesions with long diseased segments remain relatively unfavorable. This study sought to compare the efficacy of Resolute zotarolimus-eluting stents (R-ZES) and Xience everolimus-eluting stents (EES) for very long coronary lesions.**

Methods and results **This randomized, multicenter, prospective trial compared the use of R-ZES with EES for very long (≥50 mm) native coronary lesions. The primary end point was in-segment late luminal loss at 12-month angiographic follow-up. A total of 400 patients were needed to assess the primary end point. However, owing to very slow enrollment of patients, this trial was early terminated (302 patients were enrolled), and thus, this report provides descriptive information on primary and secondary end points. The R-ZES and EES groups had similar baseline characteristics. Lesion length was 49.6 ± 10.2 and 50.6 ± 13.3 mm in the R-ZES and EES groups, respectively ($P = 0.47$). The number of stents used at the target lesion was 2.1 ± 0.3 and 2.2 ± 0.5, respectively. Twelve-month angiographic follow-up was performed in 50% of eligible patients. In-segment late luminal loss did not significantly differ between the R-ZES and EES groups (0.17 ± 0.57 vs. 0.09 ± 0.43 mm, $P = 0.32$). In-segment binary restenosis rates were 8.1 and 5.3% in the R-ZES and EES groups, respectively ($P = 0.49$). There were no significant between-group differences in the rate of adverse events (death, myocardial infarction, stent thrombosis, target lesion revascularization, and composite outcomes).**

Conclusion **For patients with very long native coronary artery disease, R-ZES and EES implantation showed comparable angiographic and clinical outcomes through 1 year of follow-up.** *Coron Artery Dis* **30:59–66**

Coronary Artery Disease 2019, **30**:59–66

Keywords: angioplasty, coronary disease, stents

[a]Asan Medical Center, Heart Institute, University of Ulsan College of Medicine, [b]Department of Internal Medicine, Division of Cardiology, Yeouido St Mary's Hospital, [c]Cardiovascular Center, Korea University Guro Hospital, [d]Cardiovascular Center, Division of Cardiology, Kyunghee University Hospital, Seoul, [e]Department of Medicine, Keimyung University Dongsan Medical Center, [f]Department of Internal Medicine, Kyungpook National University Hospital, Daegu, [g]Cardiovascular Center, St Carollo General Hospital, Soonchun, [h]The Catholic University of Korea, Daejeon St Mary's Hospital, Daejeon, [i]Department of Cardiology, Chonnam National University Medical School, Gwangju, [j]Department of Internal Medicine, National Health Insurance Corporation Ilsan Hospital, Goyang and [k]Department of Internal Medicine, Kangwon National University Hospital, Chuncheon, South Korea

Correspondence to Seung-Jung Park, MD, PhD, Asan Medical Center, Heart Institute, University of Ulsan, 388-1 Pungnap-dong, Songpa-gu, Seoul 138-736, South Korea
Tel: +82 230 104 812; fax: +82 2486 5918; e-mail: sjpark@amc.seoul.kr

*Dr Do-Yoon Kanga and Dr Cheol Hyun Lee contributed equally to the writing of this article.

Received 13 June 2018 **Revised** 17 October 2018 **Accepted** 21 October 2018

Introduction

The widespread use of drug-eluting stents (DES) has significantly reduced the incidence of restenosis and the need for repeat revascularization [1]. Nevertheless, the benefits are often attenuated in patients with long coronary artery lesions, who remained at a higher risk of adverse clinical outcomes [2–6]. With improved design and performance, newer-generation and second-generation DES demonstrated their potential advantage in interventions for long coronary lesions [5–9]. Resolute zotarolimus-eluting stents (R-ZES) have a polymer design for improved biocompatibility and controlled drug release over a long period. A low-profile thin-strut, cobalt-alloy stent was developed to further enhance deliverability and clinical safety [10,11]. These devices have shown promising clinical and angiographic outcomes in large registry and randomized trials [12–15]. The Xience cobalt–chromium everolimus-eluting stent (EES) is made on the thin multi-link stent platform for

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.coronary-artery.com.

DOI: 10.1097/MCA.0000000000000680

improved conformability, showing superior clinical outcomes than other DESs [16–18]. Until recently, there have been limited data comparing the benefits of these two DES for the treatment of very long coronary lesions, which have been most commonly used DES in contemporary clinical practice. We conducted a prospective randomized Long Drug-Eluting Stent (LONG-DES) VI trial to compare the efficacy of R-ZES and EES for de novo native very long (≥50 mm) coronary lesions.

Methods

Study design and population

The LONG-DES VI trial (*http://www.clinicaltrials.gov*; identifier NCT01489761) is a prospective, randomized, single-blind controlled study conducted in 15 centers in South Korea between March 2012 and October 2016. Patients with very long coronary artery disease of diameter stenosis of at least 50% and visual lesion length of at least 50 mm who planned to implant at least two DES were enrolled in the study. Exclusion criteria included acute ST-segment elevation myocardial infarction (MI) necessitating primary percutaneous coronary intervention (PCI); severely compromised ventricular dysfunction (ejection fraction < 30%) or cardiogenic shock; renal dysfunction (serum creatinine level ≥ 2.0 mg/dl) or dependence on dialysis; contraindications to the use of zotarolimus, everolimus, or antiplatelet drugs; and a life expectancy less than 1 year.

The study protocol was approved by the Ethics Committee at each participating center and was conducted according to the principles of the Declaration of Helsinki regarding investigations in humans. All patients provided written informed consent for participation in this trial.

Randomization, procedures, and adjunct drug therapy

Patients who met the inclusion and exclusion criteria were randomly assigned on a 1 : 1 fashion after diagnostic angiography for PCI with R-ZES (Resolute Integrity or Onyx; Medtronic, Minneapolis, Minnesota, USA) or EES (Xience Prime, Xpedition or Alpine; Abbott Vascular, Santa Clara, California, USA). The allocation was performed using an interactive web response system. Random sequence was generated with block sizes of 4 or 6, stratified according to participating center. In patients with multiple lesions who fulfilled the inclusion and exclusion criteria, the treating physician determined the target lesion for each patient before randomization. Patients, but not investigators, were unaware of the treatment assignment.

Stent implantation was performed according to standard techniques. R-ZES were available in diameters of 2.25, 2.5, 2.75, 3.0, 3.5, and 4.0 mm and lengths of 9, 12, 15, 18, 22, 26, 30, 34, and 38 mm; EES were available in diameters of 2.25, 2.5, 2.75, 3.0, 3.5, and 4.0 mm and lengths of 8, 12, 15, 18, 23, 28, 33, and 38 mm. The same randomly assigned stent had to be implanted in all lesions in patients requiring multilesion interventions, except when the assigned stent could not be inserted, in which case crossover to another device was allowed. Full lesion coverage was attempted by implanting two or more stents.

Before or during the procedure, all patients received at least 200 mg of aspirin and a 300–600 mg loading dose of clopidogrel. After the procedure, all patients received 100 mg/day of aspirin indefinitely, as well as 75 mg/day clopidogrel for at least 12 months.

Study end points and definitions

The primary end point was in-segment late luminal loss at 12 months after the index procedure (defined as the difference in the minimal luminal diameter assessed immediately after the procedure and at angiographic follow-up, measured within the margins, 5-mm proximal and 5-mm distal to the stent). Secondary angiographic end points were in-stent and in-segment binary restenosis and in-stent late luminal loss at 12 months. Secondary clinical end points included death, MI, ischemia-driven target lesion revascularization, ischemia-driven target vessel revascularization, stent thrombosis, major adverse cardiac events – a composite of death, MI, and target vessel revascularization – within 13 months, and device success.

All deaths were considered to have been from cardiac causes unless a noncardiac cause could be identified. A diagnosis of MI was based on the presence of new Q waves in at least two contiguous leads on an ECG or an elevation of creatine kinase (CK)-MB more than three times the normal upper limit in at least two blood samples. Periprocedural MI was defined as an elevation of CK-MB more than three times the normal upper limit in at least two blood samples with a normal range in the baseline value within 48 h of the procedure. If the baseline CK-MB values were above the normal upper limits, periprocedural MI was diagnosed when a CK-MB was elevated 50% greater than the most recent preprocedural level, with documentation that the values were stable or falling before PCI. Revascularization of the target lesion and target vessel was considered to be ischemia driven if there was stenosis of at least 50% of the diameter of the treated lesion or vessel by quantitative coronary analysis at the independent core laboratory in the presence of ischemic signs (i.e. positive functional tests) or symptoms, or a target vessel (or lesion) diameter stenosis of 70% or greater with or without documented ischemia [12]. Stent thrombosis was defined as definite or probable thrombosis by the Academic Research Consortium definitions [19]. Device success was defined as a final stenosis of less than 30% of the vessel diameter after implantation of the assigned stent only.

Patient follow-up and data management

A 12-lead ECG was obtained for each patient, and serum concentrations of CK-MB were measured before stenting, 8–16 h after the procedure, and again 18–24 h after the procedure. Clinical follow-up visits were scheduled at

30 days, 6, and 13 months after the procedure and, and all eligible patients were asked to have angiographic follow-up at 12 months after the procedure, or earlier, if anginal symptoms occurred. The patients' clinical status, all interventions, and adverse events were recorded at each visit.

All data were collected using a web-based dedicated case report form. Members of the academic coordinating center (Clinical Research Center, Asan Medical Center, Seoul, Korea) periodically performed monitoring and verification of the registry data in the participating hospitals. All outcomes of interests were confirmed by source documentation and were centrally adjudicated by an independent Clinical Events Committee whose members were blinded to the assigned stent. An independent Data and Safety Monitoring Board periodically reviewed the data to identify potential safety issues.

Quantitative coronary angiography

Coronary angiograms were digitally recorded at baseline, immediately after the procedure, and at follow-up and assessed offline in the angiographic core laboratory (Asan Medical Center, Seoul, Korea) using CAAS V automated edge-detection system (Pie Medical Imaging, Maastricht, The Netherlands). All measurements were performed on angiograms recorded after the intracoronary administration of nitroglycerin. Standard qualitative and quantitative analyses and definitions were used for angiographic analysis [20]. The reference diameter was determined by interpolation.

All quantitative angiographic measurements were obtained within the stented segment (in-stent) and over the entire segment including the stent and its 5-mm proximal and distal margins (in-segment). Angiographic variables included absolute lesion length, stent length, reference vessel diameter, minimum lumen diameter, percent diameter stenosis, binary restenosis rate, acute gain, late loss, and patterns of restenosis. Binary restenosis was defined as percent diameter stenosis of 50% or greater on follow-up angiography, and patterns of angiographic restenosis were quantitatively assessed with the Mehran classification [21].

Statistical analysis

The primary objective of the study was to assess whether the angiographic outcome of treatment with R-ZES was not inferior to the outcome of treatment with EES. To calculate the sample size, in-segment late luminal loss of 0.20 ± 0.40 mm in EES was assumed based on the previous trials [7]. Calculation of the study sample size was based on a margin of noninferiority for in-segment late luminal loss of 0.08 mm, which was equal to 60% of an assumed mean $\pm$ SD late luminal loss of EES. Using α level of 0.05 and a statistical power of 80%, we estimated that 176 patients per group were needed to demonstrate noninferiority of the R-ZES. Expecting that $\sim$15% of patients would not receive follow-up angiography, 400 patients (200 patients per group) were needed to fulfill the primary end point. Sample size was calculated with using PASS software (NCSS, Kaysville, Utah, USA).

All analyses were based on the intention-to-treat principle. Differences between treatment groups were evaluated by Student's t-test for continuous variables and by χ^2 or Fisher's exact test for categorical variables. Cumulative event curves were generated using the Kaplan–Meier method. The noninferiority hypothesis was assessed statistically with Z test, by which P values for noninferiority were calculated to compare differences between groups with margins of noninferiority [22]. Statistical analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, New York, USA) and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). All P values are two sided, apart from those from noninferiority testing of the primary end point.

Table 1 Baseline clinical characteristics of the patients

Characteristics	Zotarolimus-eluting stent ($N = 153$)	Everolimus-eluting stent ($N = 149$)	P value
Age (years)	65.8 ± 8.6	65.9 ± 10.0	0.94
Sex (male) [n (%)]	115 (75.2)	109 (73.2)	0.69
BMI (kg/m^2)	25.1 ± 3.3	25.1 ± 3.3	0.89
Diabetes mellitus [n (%)]	73 (47.7)	62 (41.6)	0.36
Hypertension [n (%)]	109 (71.2)	96 (64.4)	0.30
Hyperlipidemia [n (%)]	114 (74.5)	107 (71.8)	0.82
Current smoker [n (%)]	32 (20.9)	32 (21.5)	0.83
Previous coronary angioplasty [n (%)]	16 (10.5)	10 (6.7)	0.27
Previous bypass surgery [n (%)]	1 (0.7)	5 (3.4)	0.09
Previous myocardial infarction [n (%)]	9 (5.9)	5 (3.4)	0.32
Previous peripheral vascular disease [n (%)]	5 (3.3)	5 (3.4)	0.94
Left ventricular ejection fraction (%)	62.3 ± 8.5	59.0 ± 9.3	0.01
Multivessel disease [n (%)]	107 (69.9)	95 (63.8)	0.37
Clinical presentation [n (%)]			0.63
Stable angina or silent ischemia	95 (62.1)	86 (57.7)	
Unstable angina	45 (29.4)	46 (30.9)	
Non-ST elevation myocardial infarction	13 (8.5)	17 (11.4)	

Data are given for the intention-to-treat population.

Results

Baseline characteristics and procedural results

Owing to very slow enrollment of study patients, this trial was prematurely terminated and thus this report provides descriptive information on primary and secondary study end points. A total of 302 patients were randomized to receive R-ZES ($n=153$) or EES ($n=149$) as treatment for very long lesions. Most of the baseline characteristics were similar between the R-ZES and EES group, except that mean ejection fraction was significantly lower in the EES group (Table 1). Table 2 shows the lesion and procedural characteristics of the study populations. Most lesion and procedural characteristics were similar between the two groups except for the number of stents used at the target lesion. The mean ± SD number of stents implanted in the target lesion was 2.1 ± 0.4, and the mean total length of the stents was 63.5 ± 13.2 mm. The rate of device success was 97.3% in R-ZES and 96.0% in EES group, whereas 2.6 and 0.7% were implanted with nonallocated stents, respectively (Fig. 1).

Angiographic outcomes

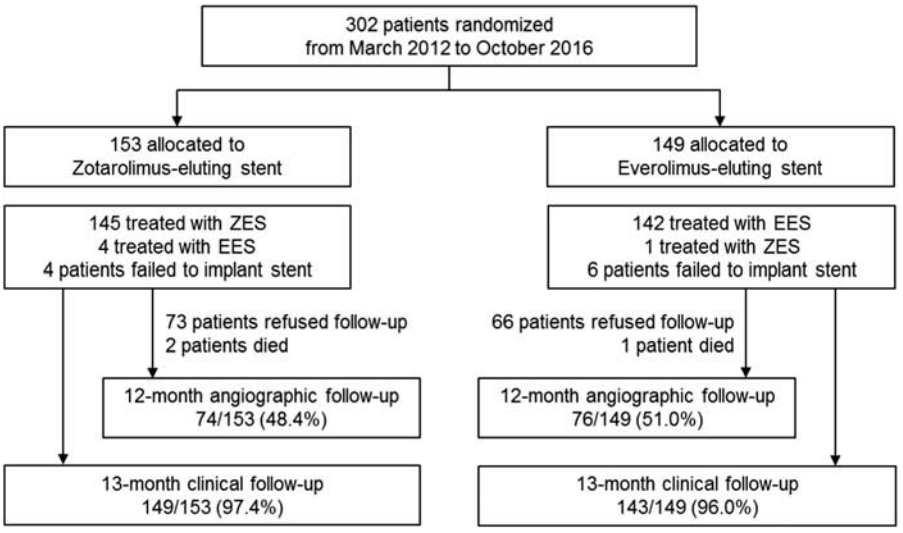
Quantitative angiographic results at baseline, immediately after the procedure, and 12-month follow-up are shown in Table 3. Angiographic measurements of lesions before and after the procedure were similar in the groups. Follow-up

Table 2 Baseline lesions and procedural characteristics

Characteristics	Zotarolimus-eluting stent ($N=153$)	Everolimus-eluting stent ($N=149$)	P value
Lesion characteristics [*n* (%)]			
Target vessel			0.98
Left anterior descending	111 (72.5)	105 (70.5)	
Left circumflex	10 (6.7)	9 (6.3)	
Right coronary	28 (18.3)	28 (18.8)	
TIMI flow grade 0 or 1	23 (15.0)	17 (11.4)	0.47
Bifurcation lesions	34 (22.2)	29 (19.5)	0.94
Thrombus	2 (1.3)	1 (0.7)	0.58
Severe tortuosity	2 (1.3)	2 (1.3)	0.98
Severe calcification	38 (24.8)	36 (24.2)	0.88
Ulceration	11 (7.2)	11 (7.4)	0.96
Procedural characteristics			
Number of stents used at the target lesion	2.1 ± 0.3	2.2 ± 0.5	0.007
Length of stents used at the target lesion (mm)	61.8 ± 11.3	65.2 ± 14.7	0.03
Average stent diameter at the target lesion (mm)	3.1 ± 0.3	3.0 ± 0.4	0.63
Maximal pressure at stent deployment (atm)	12.2 ± 3.5	12.6 ± 4.0	0.29
Direct stenting [*n* (%)]	2 (1.3)	2 (1.3)	0.96
Post-additional balloon inflation [*n* (%)]	54 (35.3)	50 (33.6)	0.86
Intravascular ultrasound guidance [*n* (%)]	96 (62.7)	92 (60.1)	0.89
Glycoprotein IIb/IIIa antagonists [*n* (%)]	2 (1.3)	5 (3.4)	0.23

Data are given for the intention-to-treat population.

Fig. 1



Patient flow and follow-up in the long drug-eluting stent (LONG-DES) VI trial. No reliable data are available on the assessment criteria for patient eligibility. EES, everolimus-eluting stent; ZES, zotarolimus-eluting stent.

Table 3 Quantitative angiographic analysis

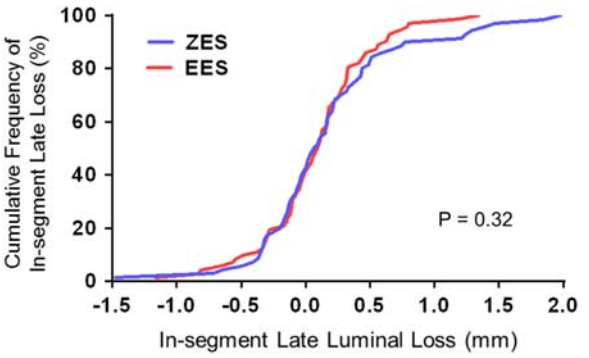
Characteristics	Zotarolimus-eluting stent ($N=153$)	Everolimus-eluting stent ($N=149$)	P value
Before procedure			
Lesion length (mm)	49.6±10.2	50.6±13.3	0.47
Reference vessel diameter (mm)	3.13±0.41	3.09±0.47	0.47
Minimal luminal diameter (mm)	0.73±0.40	0.75±0.45	0.67
Diameter stenosis (%)	76.7±12.9	75.8±13.5	0.60
Immediately after procedure			
Minimal luminal diameter (mm)			
In segment	1.91±0.59	1.93±0.55	0.76
In stent	2.19±0.59	2.18±0.56	0.90
Proximal margin	3.01±0.88	3.10±0.85	0.41
Distal margin	1.88±0.56	1.92±0.56	0.57
Diameter stenosis (%)			
In segment	20.7±11.8	19.0±10.4	0.21
In stent	13.3±11.2	14.1±10.4	0.56
Proximal margin	12.4±10.5	12.0±9.6	0.76
Distal margin	17.2±11.3	16.1±10.8	0.42
Acute gain (mm)			
In segment	1.21±0.57	1.22±0.63	0.90
In stent	1.49±0.58	1.47±0.60	0.77
Follow-up at 12 months [*n* (%)]	74 (48.4)	76 (51.0)	0.65
Minimal luminal diameter (mm)			
In segment	1.84±0.54	1.95±0.47	0.20
In stent	1.96±0.53	2.03±0.47	0.48
Proximal margin	2.97±0.60	3.18±0.54	0.03
Distal margin	2.00±0.37	2.03±0.40	0.69
Diameter stenosis (%)			
In segment	27.8±20.5	25.1±13.7	0.35
In stent	27.1±20.6	25.4±14.8	0.57
Proximal margin	16.2±10.2	13.5±10.0	0.10
Distal margin	16.0±11.8	13.9±11.3	0.27
Late luminal loss (mm)			
In segment (primary end point)	0.17±0.57	0.09±0.43	0.32
In stent	0.33±0.50	0.27±0.35	0.45
Proximal margin	0.14±0.38	0.05±0.34	0.16
Distal margin	0.07±0.34	0.01±0.40	0.39
Angiographic restenosis [*n* (%)]			
In segment	6 (8.1)	4 (5.3)	0.49
In stent	6 (8.1)	4 (5.3)	0.49
Proximal margin	0	0	NA
Distal margin	2 (2.7)	1 (1.3)	0.54

NA, not available.

angiography was performed in 74 (49%) patients in the R-ZES group and 76 (51%) patients in the SES group ($P=0.65$). The median duration of angiographic follow-up was 12.8 months (interquartile range: 11.9–13.5) in the R-ZES group and 12.7 months (interquartile range: 11.9–14.0) in the EES group ($P=0.75$). Patients who underwent angiographic follow-up were more likely to have previous coronary angioplasty ($P=0.01$) and intravascular ultrasound guidance for index procedure ($P=0.001$) than those who did not return for angiography (Supplementary Tables 1 and 2, Supplemental digital content 1, *http://links.lww.com/MCA/A209*).

At the 12-month angiographic follow-up, in-segment late luminal loss (the primary endpoint) of the R-ZES was not significantly different with that of the EES (0.17±0.57 vs. 0.09±0.43 mm, $P=0.32$; Fig. 2 and Table 3). The

Fig. 2



Cumulative rates of in-segment late luminal loss at follow-up angiography. Late luminal loss was defined as the difference between the minimal luminal diameter at the end of the procedure and the minimal luminal diameter at follow-up. EES, everolimus-eluting stent; ZES, zotarolimus-eluting stent.

Table 4 Angiographic pattern of restenosis[a]

Characteristics	Zotarolimus-eluting stent ($N=74$)	Everolimus-eluting stent ($N=76$)	P value
Overall number of in-stent restenosis cases	6	4	0.49
Focal [*n* (%)]			
IA (gap)	2 (33.3)	0	
IB (margin)	1 (16.7)	0	
IC (focal body)	2 (33.3)	3 (75.0)	
ID (multifocal)	0	0	
Diffuse [*n* (%)]			
II (intra-stent)	1 (16.7)	1 (25.0)	
III (proliferative)	1 (16.7)	0	
IV (total occlusion)	0	0	

[a]Classified using the Mehran criteria [13].

rates of in-segment binary restenosis were 8.1% in the R-ZES group and 5.3% in the EES group ($P=0.49$), and the patterns of in-stent restenosis are shown in Table 4. The extent of in-stent late luminal loss (0.33±0.50 vs. 0.27±0.35 mm, $P=0.45$) and rates of in-stent binary restenosis (8.1 vs. 5.3%, $P=0.49$) were also similar between the groups.

Clinical outcomes

Major clinical events during follow-up are summarized in Table 5. The 13-month clinical follow-up was completed in 292 (97%) patients. At 1 and 13 months, the incidence of individual and composite clinical outcomes did not differ significantly between the two groups. The overall 13-month cumulative rate of MACE was 18.8% in R-ZES group and 19.6% in EES group ($P=0.86$, Fig. 3). The most common clinical event was periprocedural MI, and no significant difference in its incidence was observed (14.1 vs. 16.8%, $P=0.53$). After excluding periprocedural MI, the incidence of death, spontaneous MI, and target-vessel revascularization also did not differ (5.4 vs. 3.5%,

Table 5 Clinical events at follow-up

Clinical outcomes	Zotarolimus-eluting stent ($N=149$)	Everolimus-eluting stent ($N=143$)	P value
Follow-up at 1 month			
Death	1 (0.7)	0	>0.99
Cardiac	1 (0.7)	0	>0.99
Noncardiac	0	0	NA
MI	21 (14.1)	25 (17.5)	0.43
Periprocedural	21 (14.1)	24 (16.8)	0.53
Q wave	0	1 (0.7)	0.49
Non-Q wave	21 (14.1)	24 (16.8)	0.53
Death or MI	22 (14.8)	25 (17.5)	0.53
Stent thrombosis, definite or probable	0	2 (1.4)	0.24
Repeat revascularization			
All types	0	1 (0.7)	0.49
Target lesion	0	1 (0.7)	0.49
Target vessel	0	1 (0.7)	0.49
Follow-up at 13 months			
Death	3 (2.0)	1 (0.7)	0.62
Cardiac	3 (2.0)	0	0.25
Noncardiac	0	1 (0.7)	0.49
MI	22 (14.8)	25 (17.5)	0.53
Q wave	0	1 (0.7)	0.49
Non-Q wave	22 (14.8)	24 (16.8)	0.75
Death or MI	24 (16.1)	26 (18.2)	0.64
Stent thrombosis, definite or probable	0	2 (1.4)	0.24
Repeat revascularization			
All types	10 (6.7)	11 (7.7)	0.75
Target lesion	6 (4.0)	3 (2.1)	0.34
Target vessel	7 (4.7)	4 (2.8)	0.54
Composite of death, MI, or TLR	28 (18.8)	28 (19.6)	0.86
Composite of death, MI, or TVR[a]	28 (18.8)	28 (19.6)	0.86
Composite of death, MI excluding periprocedural MI, or TVR	8 (5.4)	5 (3.5)	0.42
Target lesion failure, defined post-hoc[b]	28 (18.8)	28 (19.6)	0.86

MI, myocardial infarction; NA, not available; TLR, target lesion revascularization; TVR, target-vessel revascularization.
[a]Prespecified major adverse cardiac events were defined as a composite of all-cause death, MI, and ischemia-driven TVR.
[b]Target-lesion failure, defined post hoc, was a composite of death from cardiac causes, any MI (not clearly attributable to a nontarget vessel), and ischemia-driven TLR.

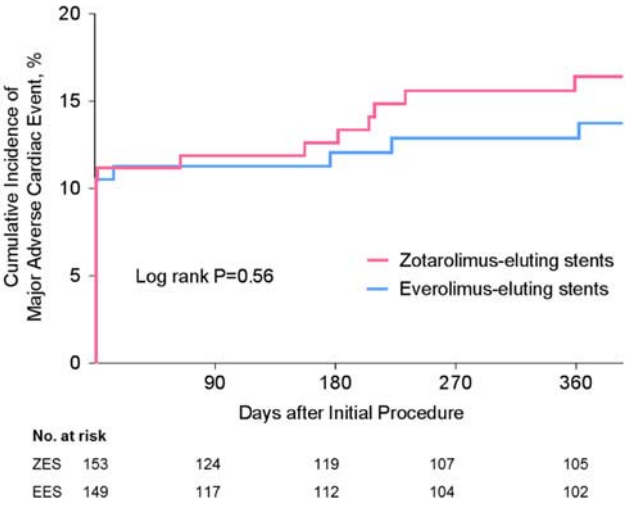
$P=0.42$). During the 12-month period, there were two cases of definite stent thrombosis (the day of the procedure and 14 days after procedure) after use of the EES and no case after R-ZES.

Discussion

This randomized trial was designed to compare the efficacy of contemporary R-ZES and EES for very long (≥50 mm) native coronary lesions. The R-ZES and EES demonstrated similar degree of in-segment late luminal loss at 12-month angiographic follow-up. Moreover, clinical outcomes of both stents were comparable, suggesting that both DESs are equally effective for treatment of long coronary artery lesions.

Long lesion is a major determinant of poor prognostic outcomes after PCI with stenting that might comprise more than 20% of current PCI [23,24]. Thus, investigating the

Fig. 3



Kaplan–Meier 12-month actuarial incidence of major adverse cardiac events. Major adverse cardiac events were defined as a composite of death, myocardial infarction, or ischemic-driven target-vessel revascularization. EES, everolimus-eluting stent; ZES, zotarolimus-eluting stent.

safety and efficacy of various types of DESs in this high-risk lesion subset has important clinical implication and might provide helpful information to select the optimal type of DES for such complex lesions. The LONG-DES registry and LONG-DES II randomized trial showed that Cypher (Cordis, Johnson and Johnson, New Brunswick, New Jersey, USA) sirolimus-eluting stent may be more effective than Taxus (Boston Scientific, Natick, Massachusetts, USA) paclitaxel-eluting stents in reducing angiographic restenosis in long coronary artery disease [25]. The LONG-DES III trial found that Cypher sirolimus-eluting stent showed significantly lesser in-segment late loss compared with Promus EESs, with a particularly beneficial effect at the proximal margin [7]. The LONG-DES IV trial compared Cypher sirolimus-eluting stent and R-ZES, whereas the LONG-DES V trial compared Nobori (Terumo Corporation, Japan) biolimus A9-eluting stent and Promus EES, resulting in comparable angiographic and clinical outcomes [8,9].

In this LONG-DES VI trial, we compared most widely used, contemporary DES (R-ZES and EES) for very long coronary lesion requiring at least two DES implantations. The major advantage of R-ZES is its polymer coating enabling longer and more controlled drug elution, and continuous sinusoid technology of Integrity bare-metal stent providing powerful performance. Xience EES using thin cobalt–chromium strut based on multi-link platform provides improved conformability, showing the best clinical outcomes in randomized trials and meta-analysis [1,16, 17,26]. Recently, all-comer randomized DUTCH PEERS trial [Durable Polymer-based STent CHallenge of Promus

Element vs. ReSolute Integrity in an All Comers Population (DUTCH PEERS); NCT01331707] and HOST-ASSURE trial [Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis – SAfety and EffectiveneSS of Drug-ElUting Stents & Anti-platelet Regimen (HOST-ASSURE); NCT01267734] showed that R-ZES was as effective as EES regarding clinical outcomes [14,27]. Consistent with previous reports, both R-ZES and EES showed excellent angiographic and clinical outcomes for very long lesions in this trial. To our knowledge, our investigation provides the first comparison of two contemporary DES platforms for treatment of very long (≥50 mm) coronary artery disease. Overall results showed efficacy and safety of multiple stenting in long lesions and excellent angiographic outcomes of overlapping DES. In addition, longest available 38-mm stents would reduce the number of stents in this situation, and our study also suggested the acceptable performance of 38-mm longest stents which were commonly used in this trial. However, given that this trial was powered to detect difference of angiographic surrogate marker, but not clinical end points, our findings warrant substantiation with larger trial adopting clinical events as the primary end point.

Especially, in our study, the low incidence of clinical outcomes might be contributed in part by the more frequent use of the intravascular ultrasound for guiding PCI (62%) than described in registries and real-world setting. Previous studies reported that the intravascular imaging-guided PCI had significantly improved the clinical outcomes compared with angiography alone, especially for the long coronary lesions [28,29]. These provocative results may suggest that the long lesions is not truly high risk in the contemporary PCI setting with more advanced DES, PCI techniques, and adjunctive imagining tools for guidance of complex PCI.

Several limitations of this study deserve attention. First, this was a relatively limited-sized clinical trial, limiting meaningful analyses only to the angiographic outcomes but not clinical outcomes. Second, slow enrollment of this trial could introduce the enrollment bias (i.e. early termination of the study, significantly affecting the power of the study). Third, the rate of follow-up angiography at 12 months was suboptimal, thus limiting the interpretation of comparative angiographic efficacy. Fourth, some patients received nonallocated stents or failed to implant devices. However, per-protocol analysis showed concordant outcomes with those of intention-to-treat analysis (Supplementary Tables 3 and 4, Supplemental digital content 1, *http://links.lww.com/MCA/A209*). Finally, translation of angiographic end points to clinical outcomes was not guaranteed. However, we believe that late luminal loss at 12 months is a robust predictor for angiographic binary restenosis and hence target lesion revascularization. Larger long-term studies are needed to provide information regarding the clinical outcomes in these two groups.

Conclusion

Implantation of R-ZES and EES did not significantly differ regarding late luminal loss at 12 months in patients with de novo native very long coronary lesions. Both DES were equally effective and safe through 1 year of follow-up.

Acknowledgements

This study was supported by funds from the CardioVascular Research Foundation, Seoul, Korea.

Conflicts of interest

There are no conflicts of interest.

References

1 Palmerini T, Benedetto U, Biondi-Zoccai G, Della Riva D, Bacchi-Reggiani L, Smits PC, *et al.* Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 2015; **65**:2496–2507.

2 Suh J, Park DW, Lee JY, Jung IH, Lee SW, Kim YH, *et al.* The relationship and threshold of stent length with regard to risk of stent thrombosis after drug-eluting stent implantation. *JACC Cardiovasc Interv* 2010; **3**:383–389.

3 Claessen BE, Smits PC, Kereiakes DJ, Parise H, Fahy M, Kedhi E, *et al.* Impact of lesion length and vessel size on clinical outcomes after percutaneous coronary intervention with everolimus-versus paclitaxel-eluting stents pooled analysis from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) Randomized Trials. *JACC Cardiovasc Interv* 2011; **4**:1209–1215.

4 Yun KH, Ko JS, Rhee SJ, Lee EM, Yoo NJ, Kim NH, *et al.* Long-term predictors of clinical events after off-label use of drug-eluting stent beyond 1 year. *Korean Circ J* 2013; **43**:161–167.

5 Jim MH, Yiu KH, Ho HH, Chan WL, Ng AK, Siu CW, *et al.* Angiographic and clinical outcomes of everolimus-eluting stent in the treatment of extra long stenoses (AEETES). *J Interv Cardiol* 2013; **26**:22–28.

6 Li XT, Sun H, Zhang DP, Xu L, Ni ZH, Xia K, *et al.* Two-year clinical outcomes of patients with overlapping second-generation drug-eluting stents for treatment of long coronary artery lesions: comparison of everolimus-eluting stents with resolute zotarolimus-eluting stents. *Coron Artery Dis* 2014; **25**:405–411.

7 Park DW, Kim YH, Song HG, Ahn JM, Kim WJ, Lee JY, *et al.* Comparison of everolimus- and sirolimus-eluting stents in patients with long coronary artery lesions: a randomized LONG-DES-III (Percutaneous Treatment of LONG Native Coronary Lesions With Drug-Eluting Stent-III) Trial. *JACC Cardiovasc Interv* 2011; **4**:1096–1103.

8 Ahn JM, Park DW, Kim YH, Song H, Cho YR, Kim WJ, *et al.* Comparison of resolute zotarolimus-eluting stents and sirolimus-eluting stents in patients with de novo long coronary artery lesions: a randomized LONG-DES IV trial. *Circ Cardiovasc Interv* 2012; **5**:633–640.

9 Lee JY, Park DW, Kim YH, Ahn JM, Kim WJ, Kang SJ, *et al.* Comparison of biolimus A9-eluting (Nobori) and everolimus-eluting (Promus Element) stents in patients with de novo native long coronary artery lesions: a randomized Long Drug-Eluting Stent V trial. *Circ Cardiovasc Interv* 2014; **7**:322–329.

10 Mortier P, De Beule M, Segers P, Verdonck P, Verhegghe B. Virtual bench testing of new generation coronary stents. *EuroIntervention* 2011; **7**:369–376.

11 Gogas BD, McDaniel M, Samady H, King SB 3rd. Novel drug-eluting stents for coronary revascularization. *Trends Cardiovasc Med* 2014; **24**:305–313.

12 Park DW, Kim YH, Yun SC, Kang SJ, Lee SW, Lee CW, *et al.* Comparison of zotarolimus-eluting stents with sirolimus- and paclitaxel-eluting stents for coronary revascularization: the ZEST (comparison of the efficacy and safety of zotarolimus-eluting stent with sirolimus-eluting and paclitaxel-eluting stent for coronary lesions) randomized trial. *J Am Coll Cardiol* 2010; **56**:1187–1195.

13 Tandjung K, Sen H, Lam MK, Basalus MWZ, Louwerenburg JHW, Stoel MG, *et al.* Clinical outcome following stringent discontinuation of dual antiplatelet therapy after 12 months in real-world patients treated with second-

generation zotarolimus-eluting resolute and everolimus-eluting Xience V stents: 2-year follow-up of the randomized TWENTE trial. *J Am Coll Cardiol* 2013; **61**:2406–2416.
14 von Birgelen C, Sen H, Lam MK, Danse PW, Jessurun GA, Hautvast RW, *et al*. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. *Lancet* 2014; **383**:413–423.
15 Park KW, Lee JM, Kang SH, Ahn HS, Kang HJ, Koo BK, *et al*. Everolimus-eluting Xience v/Promus versus zotarolimus-eluting resolute stents in patients with diabetes mellitus. *JACC Cardiovasc Interv* 2014; **7**:471–481.
16 Baber U, Mehran R, Sharma SK, Brar S, Yu J, Suh JW, *et al*. Impact of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. *J Am Coll Cardiol* 2011; **58**:1569–1577.
17 Kang SH, Park KW, Kang DY, Lim WH, Park KT, Han JK, *et al*. Biodegradable-polymer drug-eluting stents vs. bare metal stents vs. durable-polymer drug-eluting stents: a systematic review and Bayesian approach network meta-analysis. *Eur Heart J* 2014; **35**:1147–1158.
18 Gada H, Kirtane AJ, Newman W, Sanz M, Hermiller JB, Mahaffey KW, *et al*. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). *JACC Cardiovasc Interv* 2013; **6**:1263–1266.
19 Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, *et al*. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *J Am Coll Cardiol* 2015. 403–469.
20 Lansky AJ, Dangas G, Mehran R, Desai KJ, Mintz GS, Wu H, *et al*. Quantitative angiographic methods for appropriate end-point analysis, edge-effect evaluation, and prediction of recurrent restenosis after coronary brachytherapy with gamma irradiation. *J Am Coll Cardiol* 2002; **39**:274–280.
21 Mehran R, Mintz GS, Satler LF, Pichard AD, Kent KM, Bucher TA, *et al*. Treatment of in-stent restenosis with excimer laser coronary angioplasty: mechanisms and results compared with PTCA alone. *Circulation* 1997; **96**:2183–2189.
22 Chow SC, Liu JP. *Design and analysis of clinical trials*, 2nd edition. New York, NY: John Wiley and Son; 2004.
23 Kim WJ, Lee SW, Park SW, Kim YH, Yun SC, Lee JY, *et al*. Randomized comparison of everolimus-eluting stent versus sirolimus-eluting stent implantation for de novo coronary artery disease in patients with diabetes mellitus (ESSENCE-DIABETES): results from the ESSENCE-DIABETES trial. *Circulation* 2011; **124**:886–892.
24 Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, *et al*. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med* 2010; **363**:136–146.
25 Kim YH, Park SW, Lee SW, Park DW, Yun SC, Lee CW, *et al*. Sirolimus-eluting stent versus paclitaxel-eluting stent for patients with long coronary artery disease. *Circulation* 2006; **114**:2148–2153.
26 Bangalore S, Toklu B, Amoroso N, Fusaro M, Kumar S, Hannan EL, *et al*. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. *BMJ* 2013; **347**:f6625.
27 Park KW, Kang SH, Kang HJ, Koo BK, Park BE, Cha KS, *et al*. A randomized comparison of platinum chromium-based everolimus-eluting stents versus cobalt chromium-based Zotarolimus-Eluting stents in all-comers receiving percutaneous coronary intervention: HOST-ASSURE (harmonizing optimal strategy for treatment of coronary artery stenosis-safety & effectiveness of drug-eluting stents & anti-platelet regimen), a randomized, controlled, noninferiority trial. *J Am Coll Cardiol* 2014; **63**:2805–2816.
28 Buccheri S, Franchina G, Romano S, Puglisi S, Venuti G, D'Arrigo P, Francaviglia B, Scalia M, Condorelli A, Barbanti M, Capranzano P, Tamburino C, Capodanno D. Clinical outcomes following intravascular imaging-guided versus coronary angiography-guided percutaneous coronary intervention with stent implantation: a systematic review and Bayesian Network Meta-Analysis of 31 studies and 17,882 patients. *JACC Cardiovasc Interv* 2017; **10**:2488–2498.
29 Hong SJ, Kim BK, Shin DH, Nam CM, Kim JS, Ko YG, *et al*. IVUS-XPL investigators. effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: The IVUS-XPL randomized clinical trial. *JAMA* 2015; **314**:2155–2163.