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

Jung-Min Ahn, MD; Duk-Woo Park, MD; Young-Hak Kim, MD; HaeGeun Song, MD; Young-Rak Cho, MD; Won-Jang Kim, MD; Jong-Young Lee, MD; Soo-Jin Kang, MD; Seung-Whan Lee, MD; Cheol Whan Lee, MD; Seong-Wook Park, MD; Sung-Cheol Yun, PhD; Seungbong Han, PhD; Sung Yun Lee, MD; Bong-Ki Lee, MD; Jang-Hyun Cho, MD; Tae-Hyun Yang, MD; Nae-Hee Lee, MD; Joo-Young Yang, MD; Jong-Seon Park, MD; Won-Yong Shin, MD; Moo Hyun Kim, MD; Jang Ho Bae, MD; Myeong-Kon Kim, MD; Junghan Yoon, MD; Seung-Jung Park, MD

Background—Procedural and clinical outcomes still remain unfavorable for patients with long coronary lesions who undergo stent-based coronary interventions. Therefore, we compared the relative efficacy and safety of resolute zotarolimus-eluting stents (R-ZES) and sirolimus-eluting stents (SES) for patients with de novo long coronary lesions.

Methods and Results—This randomized, multicenter, prospective trial, called the Percutaneous Treatment of LONG Native Coronary Lesions With Drug-Eluting Stent-IV (LONG-DES IV) trial, compared long R-ZES and SES in 500 patients with long (≥25 mm) native coronary lesions. The primary end point of the trial was in-segment late luminal loss at 9-month angiographic follow-up. The baseline characteristics were not different between R-ZES and SES groups, including lesion lengths (32.4±13.5 mm versus 31.0±13.5 mm, *P*=0.27). At 9-month angiographic follow-up, the R-ZES was noninferior to the SES with respect to in-segment late luminal loss, the primary study end point (0.14±0.38 mm versus 0.12±0.43 mm, *P* for noninferiority=0.03, *P* for superiority=0.68). In addition, in-stent late luminal loss (0.26±0.36 mm versus 0.24±0.42 mm, *P*=0.78) and the rates of in-segment (5.2% versus 7.2%, *P*=0.44) and in-stent (4.0% versus 6.0%, *P*=0.41) binary restenosis were not significantly different between the 2 groups. There were no significant between-group differences in the rate of adverse clinical events (death, myocardial infarction, stent thrombosis, target-lesion revascularization, and composite outcomes).

Conclusions—For patients with de novo long coronary artery disease, R-ZES implantation showed noninferior angiographic outcomes as compared with SES implantation.

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Key Words: angioplasty ■ coronary disease ■ stents

Currently, the widespread use of drug-eluting stents (DES) has resulted in remarkable success in the effective reduction of neointimal hyperplasia and subsequent restenosis after percutaneous coronary intervention (PCI).[1] However, despite the strong antirestenotic efficacy of DES, the benefits of DES are often attenuated in patients with long coronary artery lesions, which are associated with an additional risk of adverse clinical outcomes.[2] Furthermore, the first-generation DES were associated with delayed arterial healing and potential inflammation, which has potential propensity for late thrombosis, especially in high-risk lesions such as long coronary segments.[3]

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From the Department of Cardiology (J.M.A., D.W.P., Y.H.K., H.G.S., Y.R.C., W.J.K., J.Y.L., S.J.K., S.W.L., C.W.L., S.W.P., S.J.P.) and Division of Biostatistics (S.C.Y., S.B.H.), Center for Medical Research and Information, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; Inje University Ilsan Paik Hospital, Goyang, Korea (S.Y.L.); Kangwon National University Hospital, Chuncheon, Korea (B.K.L.); St Carollo Hospital, Suncheon, Korea (J.H.C.); Inje University Pusan Paik Hospital, Pusan, Korea (T.H.Y.); Soonchunhyang University Bucheon Hospital, Bucheon, Korea (N.H.L.); National Health Insurance Corporation Ilsan Hospital, Goyang, Korea (J.Y.Y.); Yeungnam University Medical Center, Daegu, Korea (J.S.P.); Soonchunhyang University Hospital Cheonan, Cheonan, Korea (W.Y.S.); Dong-A Medical Center, Pusan, Korea (M.H.K.); Konyang University Hospital, Daejeon, Korea (J.H.B.); Kyunghee University Medical Center, Seoul, Korea (M.K.K.); and Wonju Christian Hospital, Wonju, Korea (J.H.Y.).

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Correspondence to Seung-Jung Park, MD, Department of Cardiology, University of Ulsan College of Medicine, Cardiac Center, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul, 138–736, Korea. E-mail sjpark@amc.seoul.kr

Resolute zotarolimus-eluting stents (R-ZES), in which the antiproliferative agent is released over a long period of time from a novel 3-component durable polymer to a low-profile, thin-strut, cobalt-alloy stent, were developed to further enhance the clinical safety and efficacy of stenting.[4,5] These devices have shown promising clinical and angiographic outcomes in large registry and randomized trials.[6–8] To date, there have been limited data comparing R-ZES with the first-generation sirolimus-eluting stents (SES). Because long coronary artery lesions may be a practical target to compare the performance of early and newer devices in terms of pronounced antirestenotic efficacy,[9] we therefore conducted this prospective, multicenter, randomized study, called the Percutaneous Treatment of LONG Native Coronary Lesions With Drug-Eluting Stent-IV (LONG-DES IV) trial, to compare angiographic and clinical outcomes of R-ZES and SES for native long coronary artery lesions.

WHAT IS KNOWN

- Although first-generation drug-eluting stents reduced neointimal hyperplasia and restenosis, these stents were associated with delayed arterial healing and vascular inflammation. This finding provided some mechanistic insight to understand the potential propensity for late thrombosis following first-generation drug-eluting stents, especially in high-risk lesions such as long coronary segments.
- Resolute zotarolimus-eluting stents, in which the antiproliferative agent is released over a long period of time from a novel 3-component durable polymer onto a low-profile, thin-strut, cobalt-alloy stent, were developed to further enhance the clinical safety and efficacy of stenting. These devices have shown promising clinical and angiographic outcomes in large registry and randomized trials.
- To date, there have been limited data comparing Resolute zotarolimus-eluting stents with the first-generation sirolimus-eluting stents in the treatment of long coronary artery disease segments.

WHAT THE STUDY ADDS

- In this prospective, randomized trial involving patients with long coronary artery lesions, Resolute zotarolimus-eluting stents were noninferior to sirolimus-eluting stents as assessed by 9-month angiographic in-segment late luminal loss.
- Both stent platforms were associated with comparable low rates of clinical end points at 12 months, suggesting that both stents are equally effective at 1 year in the treatment of long coronary artery lesions.

Methods

Study Design and Population

The LONG-DES IV trial was a prospective, randomized, single-blind, controlled study conducted in 13 major cardiac centers in South Korea, between March 2009 and July 2010. 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. The sponsor of this study contributed to study design but had no role in data collection, monitoring, analysis, or interpretation, or in writing the article.

This study consecutively enrolled eligible patients, aged ≥18 years, with stable angina, acute coronary syndromes, or inducible ischemia, who had at least 1 native long coronary lesion suitable for stent implantation. Angiographic eligibility for inclusion consisted of a target lesion with a diameter stenosis ≥50%, visual vessel diameter ≥2.5 mm, a visual lesion length ≥25 mm, and a planned total stent length ≥28 mm. Exclusion criteria were acute ST-segment elevation myocardial infarction necessitating primary PCI; severely compromised ventricular dysfunction (ejection fraction <30%) or cardiogenic shock; allergy to antiplatelet drugs, heparin, stainless steel, contrast agents, zotarolimus, or sirolimus; left main coronary artery disease (defined as >50% stenosis); renal dysfunction (serum creatinine concentration ≥2.0 mg/dL) or dependence on dialysis; terminal illness; elective surgery planned within 6 months after the procedure, necessitating antiplatelet agent discontinuation; participation in a study of another coronary device; or inability to follow the protocol. All patients meeting the inclusion and exclusion criteria were studied and none fulfilling the criteria were excluded.

Randomization, Procedures, and Adjunct Drug Therapy

Patients who met the inclusion and exclusion criteria were randomized 1:1 after diagnostic angiography and before PCI to treatment with R-ZES (Endeavor Resolute, Medtronic, Santa Rosa, CA) or SES (Cypher Select Plus; Cordis, Johnson & Johnson) by means of an interactive web response system. The allocation sequence was computer-generated, stratified according to participating center, and blocked with block sizes of 6 and 10 varying randomly. 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 2.5, 2.75, 3.0, 3.5, and 4.0 mm and in lengths of 12, 14, 15, 18, 22, 26, 30, 34, and 38 mm; SES were available in diameters of 2.5, 2.75, 3.0, and 3.5 mm and in lengths of 8, 13, 18, 23, 28, and 33 mm. In patients with multiple lesions who fulfilled the inclusion and exclusion criteria, the operator determined the hierarchy of lesions and declared the target lesion for each patient before the procedure. 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 1 or several stents.

Before or during the procedure, all patients received at least 200 mg of aspirin and a 300- to 600-mg loading dose of clopidogrel. Heparin was administered throughout the procedure to maintain an activated clotting time ≥250 seconds. Administration of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. After the procedure, all patients received 100 mg/day of aspirin indefinitely, as well as 75 mg/day clopidogrel for at least 12 months. Use of the standard post-intervention care was recommended.[10]

Intravascular ultrasound (IVUS) was performed using standard technique, as described previously. The performance of IVUS and the response to the IVUS findings were at the discretion of the treating physician.[11,12]

Study End Points and Definitions

The primary end point was in-segment late luminal loss 9 months after the index procedure, defined as the difference in minimal luminal diameter assessed immediately after the procedure and at angiographic follow-up, measured within the margins, and 5 mm proximal and distal to the stent. Secondary angiographic end points were in-stent and in-segment binary restenosis and in-stent late loss at 9 months. Secondary clinical end points included death, myocardial infarction, ischemia-driven target-lesion revascularization, ischemia-driven target-vessel revascularization, stent thrombosis, a composite of major adverse cardiac events (ie, death, myocardial infarction,

and target-vessel revascularization) within 12 months, and device success.

All deaths were considered to be of cardiac causes unless a noncardiac cause could be identified. A diagnosis of myocardial infarction was based on the presence of new Q waves in at least 2 contiguous leads on an ECG or an elevation of creatine kinase-MB fraction or troponin I concentration >3 times the normal upper limit in at least 2 blood samples. Revascularization of the target-lesion and vessel was considered ischemia-driven if there was ≥50% stenosis of the diameter of the treated lesion or vessel by quantitative coronary analysis at an independent core laboratory, as well as ischemic signs (ie, positive functional tests) or symptoms, or a target vessel (or lesion) diameter stenosis ≥70% with or without documented ischemia.[13] Stent thrombosis was defined as definite or probable by Academic Research Consortium definitions.[14] Device success was defined as a final stenosis of <30% of the vessel diameter after implantation of the assigned stent only.

Patient Follow-Up and Data Management

A 12-lead ECG was obtained and serum concentrations of creatine kinase and its MB isoenzyme were measured before stenting, 8 to 16 hours, and again 18 to 24 hours after the procedure. Clinical follow-up visits were scheduled at 30 days, 9 months, and 12 months. In addition, we monitored clinical status, rehospitalizations, recatheterization, cardiac-related medications, and occurrence of adverse events throughout follow-up. All eligible patients were asked to return for an angiographic follow-up 9 months after the procedure, or earlier if anginal symptoms occurred. Figure 1 shows the flow of patients during follow-up.

Clinical, angiographic, procedural, and outcome data were collected using a dedicated, electronic case report form by specialized personnel at the clinical data-management center who were unaware of treatment assignments. All outcomes of interest were confirmed by source documentation collected at each hospital 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 reviewed the data periodically to identify potential safety issues, but there were no formal stopping rules.

Quantitative Coronary Angiography

Coronary angiograms were digitally recorded at baseline, immediately after the procedure, and at follow-up, and were assessed offline in the angiographic core laboratory (Asan Medical Center, Seoul, Korea) using an automated edge-detection system (CASS V, Pie Medical Imaging) by experienced assessors unaware of the allocated stent. All measurements were performed on cineangiograms recorded after the intracoronary administration of nitroglycerin. Standard qualitative and quantitative analyses and definitions were used for angiographic analysis.[15] 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, immediate gain, and patterns of recurrent restenosis. In-segment late luminal loss, primary study end point, was calculated in the way of analysis segment late loss method.[16] Binary restenosis was defined as ≥50% diameter stenosis on follow-up angiography and patterns of angiographic restenosis were quantitatively assessed with the Mehran classification.[17]

Statistical Analysis

The primary objective of the study was to assess whether the angiographic outcome of R-ZES was not inferior to that of SES. To calculate study sample size, we assumed an in-segment late luminal loss of 0.24±0.38 mm for SES based on the results of the LONG-DES II trial.[9] Calculation of the study sample size was based on a margin of noninferiority for in-segment late luminal loss of 0.10 mm, which was equal to 40% of an assumed mean (±SD) late luminal loss of SES. Using an α level 0.05 and a statistical power of 80%, we estimated that 180 patients per group were needed to demonstrate noninferiority of the R-ZES. Expecting that ≈30% of patients would not undergo follow-up angiography, we determined that 500 patients (250 per group) were needed to fulfill the primary end point. Sample size was calculated using PASS software (NCSS, Kaysville, UT).

All analyses were based on the intention-to-treat principle. Differences between treatment groups were evaluated by Student *t* test for continuous variables and by the χ^2 or Fisher exact test for categorical variables. Cumulative event curves were generated using the Kaplan-Meier method. The noninferiority hypothesis was assessed statistically with a Z test, by which *P* values for noninferiority were calculated to compare differences between groups with margins of noninferiority.[18] For the primary end point (in-segment late loss between SES and R-ZES), a hypothesis of noninferiority was tested. All other tests were conducted under a superiority hypothesis. Trial data were held by the trial coordination center at the Asan Medical Center. Analyses were performed using SAS software, version 9.1

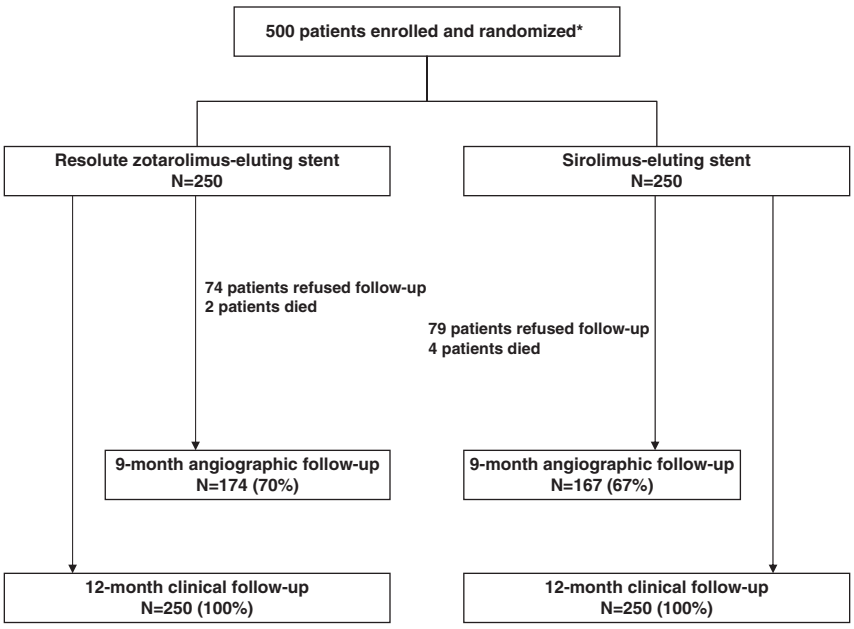

Figure 1. Patient flow and follow-up in Percutaneous Treatment of LONG Native Coronary Lesions With Drug-Eluting Stent-IV (Long-DES IV). *We have no reliable data for patients assessed for eligibility.

(SAS Institute, Cary, NC) by a statistical analyst who was unaware of the type of stent implanted. All *P* values are 2-sided, apart from those of noninferiority testing of the primary end point. Dr S.J. Park had full access to the data and vouches for its integrity and analysis.

Results

Baseline Characteristics and Procedural Results

Between March 2009 and July 2010, 500 patients were randomized to receive PCI with the R-ZES (n=250) or SES (n=250). Baseline clinical, lesions, and procedural characteristics are shown in Tables 1 and 2. Most of these characteristics were similar between the R-ZES group and the SES group, except for the number and diameter of stents implanted into the target lesion and maximal pressure because of inherent available device length and nominal pressure. The mean (±SD) number of stents implanted in the target lesion was 1.6±0.7 and the mean total length of the stents was 45.4±17.0 mm. The rate of device success was 99.8% in both groups.

Angiographic Outcomes

Quantitative angiographic results at baseline, immediately after the procedure, and at 9 month follow-up are shown in Table 3. Angiographic measurements of lesions before and immediately after the procedure were similar in the 2 groups. Follow-up angiography was performed in 174 patients (70%) in the R-ZES group and 167 patients (67%) in the SES group (*P*=0.50). The median durations of angiographic follow-up were 8.8 months (interquartile range, 7.9 and 9.7 months). Patients undergoing angiographic follow-up were younger (*P*<0.01), more likely to be male (*P*=0.02), less likely to have diabetes mellitus (*P*<0.01), and more likely to have hyperlipidemia (*P*=0.002) and to undergo PCI using IVUS (*P*<0.001) than those who did not return for angiographic follow-up (online-only Data Supplement Tables I and II).

Table 1. Baseline Clinical Characteristics of the Patients*

Characteristics	R-ZES (250 Patients)	SES (250 Patients)	*P* Value
Age, y	62.8±9.7	62.7±9.8	0.85
Male sex, no. (%)	184 (73.6)	181 (72.4)	0.76
Body-mass index	25.1±3.1	25.2±2.9	0.82
Diabetes mellitus, no. (%)	68 (27.2)	76 (30.4)	0.43
Hypertension, no. (%)	150 (60.0)	135 (54.0)	0.18
Hyperlipidemia, no. (%)	141 (56.4)	136 (54.4)	0.65
Current smoker, no. (%)	68 (27.2)	71 (28.4)	0.77
Family history of CAD, no. (%)	23 (9.2)	23 (9.2)	>0.99
Previous coronary angioplasty, no. (%)	17 (6.8)	14 (5.6)	0.58
Previous bypass surgery, no. (%)	4 (1.6)	4 (1.6)	>0.99
Previous myocardial infarction, no. (%)	3 (1.2)	5 (2.0)	0.51
Left ventricular ejection fraction, %	59.1±7.9	59.9±7.9	0.40
Multivessel disease	124 (49.6)	122 (48.8)	0.86
Clinical indication, no. (%)			0.48
Stable angina	160 (64.0)	160 (64.0)	
Unstable angina	71 (28.4)	64 (25.6)	
NSTEMI	19 (7.6)	26 (10.4)	

R-ZES indicates resolute zotarolimus-eluting stents; SES, sirolimus-eluting stents; CAD, coronary artery disease; NSTEMI, non-ST-elevation myocardial infarction.

*Plus-minus values are means±SDs. Data are given for the intention-to-treat population.

Table 2. Baseline Lesions and Procedural Characteristics*

Characteristics	R-ZES (250 Patients)	SES (250 Patients)	*P* Value
Lesion characteristics			
Target vessel, no. (%)			0.61
Left anterior descending	156 (62.4)	147 (58.8)	
Left circumflex	31 (12.4)	33 (13.2)	
Right coronary	62 (24.8)	70 (28.0)	
Ramus intermedius	1 (0.4)	0	
TIMI flow grade=0 or 1, no. (%)	27 (10.8)	21 (8.4)	0.36
Bifurcation lesions, no. (%)	91 (36.4)	86 (34.4)	0.64
Thrombus, no. (%)	2 (0.8)	8 (3.2)	0.11
Tortuosity, no. (%)			0.96
None or mild	242 (96.8)	243 (97.2)	
Moderate	7 (2.8)	6 (2.4)	
Severe	1 (0.4)	1 (0.4)	
Calcification, no. (%)			0.27
None or mild	182 (72.8)	197 (78.8)	
Moderate	31 (12.4)	22 (8.8)	
Severe	37 (14.8)	31 (12.4)	
SYNTAX score	14.0±7.5	14.0±7.5	0.98
Procedural characteristics			
No. of stents used at the target lesion			0.11
1 stent	102 (40.8)	128 (51.2)	
2 stents	120 (48.0)	103 (41.2)	
3 stents	26 (10.4)	17 (6.8)	
4 stents	2 (0.8)	2 (0.8)	
Mean	1.7±0.7	1.6±0.7	0.02
Length of stents used at the target lesion, mm	45.9±17.1	44.8±16.9	0.49
Average stent diameter at the target lesion, mm	3.3±0.4	3.2±0.3	0.03
Maximal pressure, atm	13.1±3.9	15.1±4.2	<0.001
Direct stenting, no. (%)	23 (9.2)	26 (10.4)	0.65
Post-additional balloon inflation	172 (68.8)	187 (74.8)	0.14
Intravascular ultrasound utilization, no. (%)	201 (80.4)	205 (82.0)	0.65
Glycoprotein IIb/IIIa antagonists, no. (%)	3 (1.2)	5 (2.0)	0.72

R-ZES indicates resolute zotarolimus-eluting stents; SES, sirolimus-eluting stents; TIMI, Thrombolysis In Myocardial Infarction; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery.

*Plus-minus values are means±SDs.

Table 3. Quantitative Angiographic Analysis*

Characteristics	R-ZES (250 Patients)	SES (250 Patients)	*P* Value†
Before procedure			
Lesion length, mm	32.4±13.5	31.0±13.5	0.27
Reference vessel diameter, mm	3.25±0.47	3.21±0.49	0.36
Minimal luminal diameter, mm	0.92±0.46	0.95±0.49	0.54
Diameter stenosis, %	71.4±14.3	70.4±14.3	0.46
Immediately after procedure			
Minimal luminal diameter, mm			
In segment	2.36±0.49	2.33±0.52	0.56
In stent	2.67±0.47	2.66±0.49	0.78
Proximal margin	3.31±0.56	3.24±0.59	0.20
Distal margin	2.37±0.51	2.34±0.52	0.53
Diameter stenosis, %			
In segment	18.8±9.4	19.3±10.7	0.58
In stent	10.4±7.2	10.8±8.3	0.58
Proximal margin	9.9±8.6	10.4±9.6	0.54
Distal margin	17.2±9.4	18.1±10.6	0.30
Acute gain, mm			
In segment	1.44±0.64	1.38±0.66	0.36
In stent	1.76±0.64	1.72±0.64	0.51
Follow-up at 9 months, % in eligible patients	174 (70%)	167 (67%)	0.50
Minimal luminal diameter, mm			
In segment	2.24±0.49	2.27±0.58	0.65
In stent	2.45±0.52	2.47±0.59	0.74
Proximal margin	3.12±0.65	3.11±0.62	0.91
Distal margin	2.34±0.45	2.380.49	0.44
Diameter stenosis, %			
In segment	23.4±13.3	24.7±15.0	0.39
In stent	19.5±13.0	20.0±15.9	0.74
Proximal margin	14.7±13.3	15.0±12.6	0.85
Distal margin	17.7±9.5	18.5±10.6	0.48
Late luminal loss, mm			
In segment (primary end point)	0.14±0.38	0.12±0.43	0.68
In stent	0.26±0.36	0.24±0.42	0.78
Proximal margin	0.23±0.47	0.20±0.42	0.67
Distal margin	0.06±0.29	0.02±0.30	0.24
Angiographic restenosis, no. (%)			
In segment	9 (5.2)	12 (7.2)	0.44
In stent	7 (4.0)	10 (6.0)	0.41
Proximal margin	3 (1.7)	2 (1.2)	>0.99
Distal margin	0	1 (0.6)	0.49

R-ZES indicates resolute zotarolimus-eluting stents; and SES, sirolimus-eluting stents.

*Plus-minus values are means±SDs.

†All tests were conducted under a superiority hypothesis.

At 9 months of angiographic follow-up, the in-segment late luminal loss, as the primary study end point, of the

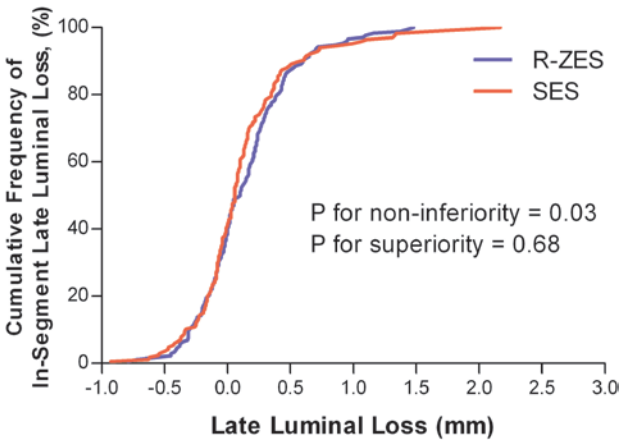

Figure 2. Cumulative rates of in-segment late luminal loss at follow-up angiography. Late luminal loss was defined as the difference between the minimal luminal diameter at the end of the procedure and the minimal luminal diameter at follow-up. R-ZES indicates resolute zotarolimus-eluting stents; and SES, sirolimus-eluting stents.

R-ZES was not inferior to that of the SES (0.14±0.3 mm versus 0.12±0.43 mm, *P* for noninferiority=0.03 and *P* for superiority=0.68; Figure 2; Table 3). The rates of in-segment binary restenosis in these 2 groups were 5.2% and 7.2%, respectively (*P*=0.44), and there was no significant difference for the patterns of restenosis between the groups (Table 4). In addition, we could not detect significant differences for the degree of in-stent late luminal loss (0.26±0.36 mm versus 0.24±0.42 mm, *P*=0.78) and the rates of in-stent binary restenosis (4.0% versus 6.0%, *P*=0.41) between the R-ZES and SES groups.

Clinical Outcomes

Major clinical events during follow-up are summarized in Table 5. At 1 month, the incidences of individual and composite clinical outcomes were not different in the 2 groups. All patients completed the 12-month clinical follow-up. At 12 months, the incidence of individual and composite clinical outcomes did not significantly differ between the 2 groups. The overall 12-month cumulative rate of major adverse cardiac events was illustrated in Figure 3 (*P*=0.65). During the 12 months, only 2 SES-treated patients experienced stent thrombosis (1 and 3 days after the procedure), compared with none of the R-ZES-treated patients.

Discussion

In this prospective, randomized trial involving patients with long coronary artery lesions, R-ZES implantation was noninferior to SES implantation as assessed by 9-month angiographic in-segment late luminal loss. Furthermore, both stent platforms were associated with comparable low rates of clinical end points for 12 months, suggesting that both stents are equally effective in the treatment of long coronary artery lesions.

Long coronary artery lesions comprises up to 20% of current PCI practice and it was a major determinant of worse prognostic outcomes after stent implantation.[2,6,19] Therefore, investigating the relative efficacies of particular DES has

Table 4. Angiographic Pattern of Restenosis*

Characteristics	R-ZES (250 Patients)	SES (250 Patients)	*P* Value
Overall No.ISR	9	12	0.86
Focal, no. (%)			
IA (gap)	0	0	
IB (margin)	2 (33.3)	3 (25.0)	
IC (focal body)	4 (44.4)	7 (58.3)	
ID (multifocal)	0	0	
Diffuse, no. (%)			
II (intrastent)	2 (22.2)	2 (16.7)	
III (proliferative)	0	0	
IV (total occlusion)	0	0	

R-ZES indicates resolute zotarolimus-eluting stents; SES, sirolimus-eluting stents; ISR, angiographic in-segment retenosis; NA, not available.

*Classified using the Mehran criteria (13).

Table 5. Clinical Events at Follow-up*

Clinical Outcomes	R-ZES (250 Patients)	SES (250 Patients)	*P* Value
Follow-up at 1 mo			
Death	1 (0.4)	3 (1.2)	0.62
Cardiac	1 (0.4)	2 (0.8)	>0.99
Noncardiac	0	1 (0.4)	>0.99
Myocardial infarction	29 (11.6)	33 (13.2)	0.59
Q-wave	0	3 (1.2)	0.25
Non-Q-wave	29 (11.6)	30 (12.0)	0.89
Death or myocardial infarction	30 (12.0)	35 (14.0)	0.51
Stent thrombosis, definite or probable	0	2 (0.8)	0.50
Repeat revascularization			
All type	0	2 (0.8)	0.50
Target-lesion	0	2 (0.8)	0.50
Target-vessel	0	2 (0.8)	0.50
Follow-up at 12 mo			
Death	2 (0.8)	4 (1.6)	0.41
Cardiac	1 (0.4)	2 (0.8)	>0.99
Noncardiac	1 (0.4)	2 (0.8)	>0.99
Myocardial infarction	29 (11.6)	34 (13.6)	0.50
Q-wave	0	3 (1.2)	0.25
Non-Q-wave	29 (11.6)	31 (12.4)	0.78
Death or myocardial infarction	31 (12.4)	35 (14.0)	0.60
Stent thrombosis, definite or probable	0	2 (0.8)	0.50
Repeat revascularization			
All type	7 (2.8)	10 (4.0)	0.46
Target-lesion	4 (1.6)	6 (2.4)	0.75
Target-vessel	5 (2.0)	6 (2.4)	>0.99
Composite of death, myocardial infarction, or target-vessel revascularization†	35 (14.0)	40 (16.0)	0.53
Composite of death, myocardial infarction, or target-lesion revascularization	36 (14.4)	40 (16.0)	0.62
Target-lesion failure, defined post hoc‡	34 (14.0)	39 (16.0)	0.53

R-ZES indicates resolute zotarolimus-eluting stents; SES, sirolimus-eluting stents; NA, not available.

*Percentages are from the intention-to-treat analysis. *P* values were calculated using the χ^2 test or Fisher exact test, as appropriate.

†Prespecified major adverse cardiac events were defined as a composite of all-cause death, myocardial infarction, and ischemia-driven target-vessel revascularization.

‡Target-lesion failure, defined post hoc, was a composite of death from cardiac causes, any myocardial infarction (not clearly attributable to a nontarget vessel), or ischemia-driven target-lesion revascularization.

important clinical implications for selecting the most effective therapy in these high-risk lesion subsets. The LONG-DES registry and LONG-DES II randomized trial showed that SES may be more effective than paclitaxel-eluting stents in reducing angiographic restenosis in these patients.[9,20] Recently, the LONG-DES III trial found that SES showed significantly lesser in-segment late loss compared with everolimus-eluting stents, with a particularly beneficial effect at the proximal margin.[21] Coincide with continuing concept of previous LONG-DES trial series comparing early and newer DES, we performed LONG-DES IV trial, which is powered to evaluate the new DES of R-ZES and the old standard DES of the SES in terms of angiographic parameters such as late luminal loss and restenosis.

The major advance of R-ZES compared with the earlier version of ZES is its polymer coating, which is composed of 3 hydrophilic and hydrophobic polymeric elements, while preserving the flexible stent platform, drug property, and dose. As a result, R-ZES has demonstrated higher biocompatibility, superior drug-release kinetics, and enhanced antirestenotic efficacy when compared with its precursor.[4,5,22] Recent Resolute All Comers trial showed that R-ZES was as effective as everolimus-eluting stents at 1 year. In addition, a deterioration in endothelialization offsetting higher antirestenotic efficacy was not observed, a finding supported by optical coherence tomography.[6,23] The favorable results were also documented in severe registry studies including unselected, complex clinical and anatomic subsets.[8,19] Consistent with these previous findings, the current study demonstrated that the angiographic and clinical outcomes of R-ZES were excellent and were comparable to those of SES, which had been the most effective stent in the first-generation DES, in complex lesion subsets of long coronary lesions. However, because this trial was adequately powered to detect significant difference of angiographic surrogate marker, but not clinical end points, our findings should be confirmed or refuted through larger clinical trial adopting clinical end points as the primary outcomes.

Our trial had several limitations. First, we assessed angiographic surrogate end point of in-segment late loss, and this trial was not designed or powered to assess binary restenosis rate, which could have been a better surrogate end point for clinical relevance. Larger, long-term clinical comparative studies are therefore required to confirm or rebut our findings. Another limitation of our study was the relatively short follow-up period of 12 months. Durable polymers of early-generation DES have been associated with chronic inflammation of the arterial wall, with the potential for delayed

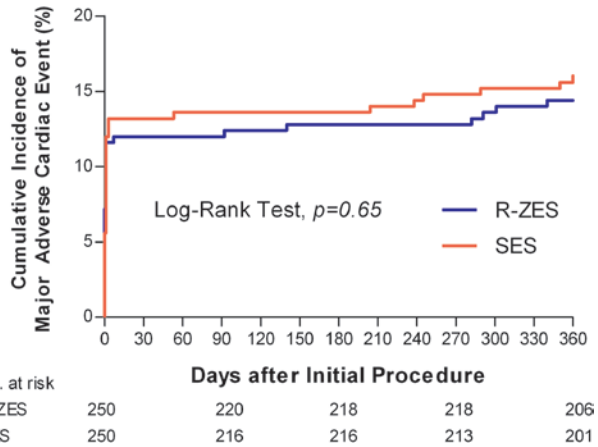

Figure 3. Kaplan-Meier 12-month actuarial incidence of major adverse cardiac events. Major adverse cardiac events were defined as the composite of death, myocardial infarction, or ischemic-driven target-vessel revascularization. R-ZES indicates resolute zotarolimus-eluting stents; SES, sirolimus-eluting stents.

restenosis. Therefore, longer term follow-up might be needed to confirm the long-term durability of the newer devices. Third, the angiographic follow-up rate was 68.2%, which was lower than the protocol-based estimated rate. Fourth, our study population was relatively at low angiographic lesion complexity including low degree of tortuosity. Fifth, IVUS examination and response to the IVUS findings were left at the physician's discretion, yet it may potentially skew outcomes in a randomized study. Finally, there were some imbalances in procedural characteristics, as shown by differences in the total number and diameter of stents and the maximal pressure for achieving a similar poststent lumen diameter. These differences may have been due to original differences between the 2 stent types in stent length, size, and nominal pressure. Nevertheless, considering the directionality of these potential effects, our overall findings would likely not change.

In conclusion, R-ZES implantation in patients with native long coronary artery lesions resulted in noninferior 9-month angiographic in-segment late loss compared with SES implantation without significant differences in death, myocardial infarction, angiographic restenosis, or stent thrombosis during 1 year of follow-up.

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