내과학박사 학위논문

생분해성 폴리머 스텐트인 **Orsiro** 하이브리드 약물 방출 스텐트와 생체 적합성 폴리머 스텐트인 **Resolute Integrity** 약물 방출 스텐트의 관상 동맥 조영술상 재협착률에 대한 다기관 무작위 배정 연구

2020년 **2**월

서울대학교 대학원

내과학교실

강 시 혁

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지도교수 연 태 진

이 논문을 내과학박사 학위논문으로 제출함

2019년 **11**월

서울대학교 대학원

내과학교실

강 시 혁

강시혁의 박사 학위논문을 인준함

2020년 **1**월

위 원 장 진 호 준 **(인)**

부 위 원 장 연 태 진 **(인)**

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요약(국문초록)

생분해성 폴리머 스텐트인 Orsiro 하이브리드 약물 방출 스텐트와 생체적합성 폴리머 스텐트인 Resolute Integrity 약물 방출 스텐트의 관상동맥 조영술상 재협착률에 대한 다기관 무작위 배정 연구

연구 목적: 본 연구는 최근에 도입된 두가지 약물방출관상동맥스텐트의 영상학적 재협착을 평가하기 위해 설계되었다. Resolute-Integrity zotarolimus-eluting stents (R-ZES)는 폴리머가 내구성을 가지고 있으며 선행 연구를 통해 그 성적이 잘 증명되어 있다. Orsiro sirolimus-eluting stents (O-SES) 는 더 최근에 개발된 스텐트로 생체분해성 폴리머와 영구폴리머가 두 개층으로 코팅된 독특한 디자인을 가지고 있다.

연구 절차와 결과: 관상동맥성형술이 계획된 372명의 환자가 본 연구에 등록되어 2:1의 비율로 O-SES군(250명)와 R-ZES군(122명)에 배정되었다. 연구의 1차 종료점은 9개월째 관상동맥조영술을 통해 평가한 재협착 정도(in-stent late lumen loss)였는데, O-SES군에서는 중간값 0.06 mm (4분위수간 영역, -0.09 to 0.24 mm)였고 R-ZES군에서는 중간값 0.12 mm (-0.07 to 0.32 mm)으로 나타났다. 통계적으로는 비열등성을 만족하였다 (p for noninferiority <0.001; p for superiority = 0.205). 영상학적 재협착율은 O-SES 군에서 15.0% (10.0% to 20.0%), R-ZES 군에서 20.0% (13.3% to 26.0%)로 통계적인 차이가 있는 것으로 나타났다 (p = 0.002). 목표 병변 실패사건(target lesion failure)은 양군에서 2.4%와 3.3% 발생하였다 (p = 0.621). 하위집단분석 상 당뇨 하위군을 제외하고는 모든 하위군에서 두 스텐트의 성적은 차이를 보이지 않는 것으로 나타났다.

결론: 본 연구 결과 O-SES는 R-ZES와 비교하여 영상학적으로 평가한 9개월 째 재협착 측면에서 비열등한 것이 확인되었다. 재협착과 임상사건 측면 모두에서 두 스텐트는 매우 훌륭한 성적을 보여주었다. 본 연구 결과는 현존하는 두 스텐트의 효능과 안전성을 확인해주었다.

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주요어 : 관상동맥질환, 관상동맥성형술, 관상동맥스텐트, 무작위배정임상연구, 영상학적협착, 임상사건

학 번 : 2015-30552

Abstract

Angiographic outcomes of Orsiro biodegradable polymer sirolimus-eluting stents and Resolute Integrity durable polymer zotarolimus-eluting stents: results of the ORIENT trial

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Aims: We performed a randomized controlled open-label noninferiority trial to compare angiographic outcomes between the ultrathin strut, biodegradable hybrid polymer Orsiro sirolimus-eluting stents (O-SES) and the durable biocompatible polymer Resolute-Integrity zotarolimus-eluting stents (R-ZES).

Methods and results: A total of 372 patients planned to undergo percutaneous coronary revascularization were randomly assigned 2:1 to treatment with O-SES or R-ZES (250 and 122 patients, respectively). O-SES was noninferior to R-ZES for the primary endpoint, in-stent late lumen loss at 9 months [median 0.06 mm (interquartile ranges, -0.09 to 0.24 mm) versus 0.12 mm (-0.07 to 0.32 mm); p for noninferiority <0.001; p for superiority = 0.205]. Percent diameter stenosis was significantly lower in the O-SES group than in the R-ZES group [15.0 (10.0 to 20.0) versus 20.0 (13.3 to 26.0); p = 0.002]. Target lesion failure occurred in 2.4% and 3.3% of the O-SES and R-ZES groups, respectively (p = 0.621). Subgroup analyses showed consistently similar outcomes between the two groups in terms of the primary endpoint, except for the diabetic subgroup.

Conclusions: O-SES was noninferior to R-ZES in terms of in-stent late loss at 9 months. Angiographic restenosis and clinical adverse events were low in both groups. This study confirms the excellent safety and efficacy profiles of both the contemporary coronary stents.

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keywords: coronary artery disease, percutaneous coronary revascularization, coronary stent, randomized controlled trial, angiographic restenosis, clinical outcomes

Student Number : 2015-30552

Introduction

Drug-eluting stents (DES) have become an indispensable component in percutaneous coronary revascularization.[1, 2] Although the advent of DES reduced the need for repeat revascularization, concerns have been raised as studies reported an increased propensity for very late stent thrombosis with DES use compared to bare metal stents (BMS).[3-5] This has provoked numerous innovations in DES design.

One is changes in the polymer compositions. Biocompatible durable polymers (DP) and biodegradable polymers (BP) have replaced previous polymers. The polymer matrix of early-generation DES has been shown to elicit an inflammatory response. Histopathologic analysis of very late stent thrombosis specimens showed evidence of localized hypersensitivity reactions with eosinophilic infiltrates and aggregates of giant cells around polymer fragments.[6] A prolonged inflammatory response to the polymer has hence been associated with delayed vascular healing with impaired stent strut endothelialization and pathologic vessel remodeling resulting in coronary evaginations with secondary incomplete stent apposition.[7] Biocompatible durable polymers (DP) and biodegradable polymers (BP) have been introduced to overcome concerns over delayed arterial healing that might result in very late stent thrombosis and restenosis. Biocompatible DP has shown to induce less activated monocyte adhesion and to cause less inflammatory reactions. BP coating degrades when the active drug is eluted, at which the remaining stent backbone resembles that of a bare metal stent. Another innovation is thinner-strutted devices. Recent evidence suggests that the safety profile of a coronary stent is determined not only by the property

of the polymers, but by an optimal combination of stent geometry, strut thickness, polymer characters, and antiproliferative drugs.[8]

The safety profile of earlier models of BP-DES was not as good as expected. The rate of stent thrombosis of BP biolimus-eluting stents was lower than that of first-generation DES, but higher than that of everolimus-eluting stents (EES), which is a second generation DP-DES.[9, 10] The Orsiro biodegradable polymer sirolimus-eluting stent (O-SES, Biotronik AG, Bulach, Switzerland) is a novel DES with an ultrathin strut. Its hybrid coating ensures degradation of the biodegradable poly-L lactic acid polymer and blockade of metallic surface exposure to the surrounding tissue. O-SES has the thinnest strut thickness till date (60 μm), and thus provides excellent flexibility and deliverability. Previous studies have shown promising angiographic and clinical outcomes after implantation of O-SES.[11-13]

Resolute Integrity zotarolimus-eluting stent (R-ZES, Medtronic Cardiovascular, Santa Rosa, CA, USA) is one of the most widely used contemporary DP-DES. The RESOLUTE All Comers trial showed equivalent outcomes of the Endeavor Resolute ZES, a previous version of R-ZES, with the Xience everolimus-eluting stents.[14] In addition, recent studies have shown excellent performance of R-ZES.[15, 16] In this study, we performed a randomized controlled trial comparing angiographic outcomes of O-SES with the R-ZES in subjects undergoing percutaneous coronary intervention (PCI) for coronary artery disease. This study was an all-comer trial with limited exclusion criteria.

Methods

Study Design

The Orsiro Hybrid sirolimus-eluting stents and Resolute Integrity zotarolimus-eluting stents in all-comers with coronary artery disease (ORIENT) trial is a prospective randomized open-label multicenter trial. The study design has been described previously.[17] The study participants were enrolled in 8 centres in Korea between October 2013 and June 2014. This trial was initiated by investigators, and grant support was provided by Biotronik Korea Co, Korea. Data were managed by a contract research organization (T&W software, Seoul, Korea). The data analysis was performed by the investigators. The authors are solely responsible for the design and execution of the trial, related statistical analyses, and all aspects of manuscript preparation, including drafting, editing, and final content. The study protocol was approved by the local institutional review board at each participating centre and registered at www.clinicaltrials.gov (NCT01826552).

Study Patients

Subjects aged 18 years or older, presenting with symptomatic coronary artery disease and coronary lesions >50%, and indicated for PCI with DES implantation were eligible for enrolment. The decision on the revascularization modality was based on the current recommendations of the ACC/AHA/SCAI and ESC/EACTS guidelines or the clinical judgment of the interventional cardiologist.[1, 2] Coronary artery disease included stable angina as well as acute coronary syndrome. All participating patients provided

written informed consent. Inclusion and exclusion criteria were graded to minimize exclusion of patients, thus reflecting the real-world population at large (table 1).

Table 1. Eligibility criteria of the trial

Inclusion criteria
• Patient age ≥18 years • Ability to acknowledge verbally the risks, benefits and treatment ramifications in receiving the Orsiro Hybrid® or Resolute Integrity® stent • Written informed consent given by legally authorized agent prior to any study-related procedure • Indication for use of drug-eluting stent based on ACC/AHA/SCAI and ESC/EACTS guidelines and/or clinical judgment of interventional cardiologist. • Target lesion(s) in coronary artery or graft vessel with estimated reference diameter ≥2.5 mm and ≤5.0 mm • Target lesion(s) amenable to percutaneous coronary intervention
Exclusion criteria
• Known hypersensitivity or contraindication to any of the following agents: heparin, aspirin, clopidogrel, sirolimus, • zotarolimus, cobalt chromium or contrast mediaa • Inability to tolerate aspirin or clopidogrel for 1-year duration of study • Systemic (intravenous) use of sirolimus or zotarolimus within 12 months • Females with childbearing potential (unless negative by a recent pregnancy test) or anticipating pregnancy following study enrollment • History of bleeding diathesis, known coagulopathy (including heparin-induced thrombocytopenia), or refusal of blood transfusions • Gastrointestinal or genitourinary bleeding within prior 3 months, or major surgery within 2 months • Planned major non-cardiac surgery within designated study period • Cardiogenic shock (Killip class IV) • Symptomatic heart failure, precluding coronary angiography in a supine position • Non-cardiac co-morbid conditions limiting life expectancy (to <1 year) or potentially undermining protocol compliance (as judged by the site investigator) • Active participation in another drug- or device-related investigational study where the primary endpoint follow-up is ongoing • Unwillingness or inability to comply with protocol procedures

Treatment and Randomization

Patients who were planned to undergo PCI after diagnostic angiography were randomly assigned in a 2:1 ratio to either the O-SES or R-ZES group. Randomization was done via a web-based online randomization system. The randomization was stratified by the participating centres. PCI was performed using standard techniques. Dual antiplatelet therapy was recommended for at least 12 months, but was not mandatory. All patients were recommended to undergo angiographic follow-up at 9 months post-PCI. Clinical follow-up was performed at 1, 3, 9, and 12 months after the index PCI. Patients were followed up by office visits or telephone contacts.

Study Endpoints

The primary endpoint of the trial was in-stent late lumen loss (LLL) at 9 months, as measured by performing quantitative coronary angiography. Secondary angiographic endpoints included in-segment LLL, percentage diameter stenosis, and binary restenosis at 9 months. Quantitative analysis of coronary angiographic images (QCA) was performed by specialized technicians who were unaware of the purpose of this study. The analysis was performed at Seoul National University Bundang Hospital Cardiovascular Center. The Cardiovascular Angiography Analysis System 5.9.2 QCA system (Pie Medical Imaging, Maastricht, the Netherlands) was used for automated contour detection and quantification. All QCA measurements of the target lesion were obtained within the stented segment (in-stent), and over the entire segment comprising the stent and its proximal and distal margins (in-segment) up to 5 mm. Secondary clinical endpoints included all-cause and cardiac deaths, clinically driven target lesion revascularization (TLR),

clinically driven target vessel revascularization (TVR), myocardial infarction (MI) (target or non-target vessel-related), definite or probable stent thrombosis, and target lesion failure (TLF, a composite of cardiac death, TLR and target vessel-related MI) at 12 months. Clinical events were defined according to the recommendations of the Academic Research Consortium and the Third Universal Definition of MI.[18, 19]

Statistical analysis

The primary endpoint of the 9-month LLL was compared by using Student's t-test. Assuming a mean LLL of 0.30±0.54 mm for both stents,[20] we calculated that the enrolment of 375 patients (250 and 125 for the O-SES and R-ZES groups, respectively) would provide a 90% statistical power to confirm the noninferiority margin of 0.20 mm at a one-sided significance level of 0.05 and an expected dropout rate of 30%.[21] Sequential superiority testing was performed when the null hypothesis of noninferiority was rejected. The primary endpoint analysis was performed on the basis of the index lesion, which was determined randomly before the angiographic analysis. Per-lesion and per-treatment analyses were also performed. For the per-lesion analysis, a generalized estimating equations model that used an exchangeable working correlation matrix was used to assess the treatment effect by taking into account the clustering effect within a patient.

All primary and secondary endpoints were analysed on an intention-to-treat basis. Per-treatment analyses were done on the primary endpoint, which was intended for descriptive purposes. Secondary clinical endpoints were compared with the Cox proportional hazard model.

Kaplan–Meier survival curves were constructed. Binary variables were compared with the use of the $\chi 2$-test or Fisher's exact test, and continuous variables were compared with an independent t-test or Wilcoxon's signed rank test when appropriate. Exploratory subgroup analysis was performed. Statistical analyses were performed by using R programming version 3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org). A two-sided p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

Among a total of 372 patients enrolled, 250 were assigned to the O-SES group and 122 to the R-ZES group (Figure 1). Table 2 shows the baseline characteristics of the study population. There were no significant differences in patient characteristics between the assigned groups. The mean age was 65 years, and 71% were male. Sixty six percent had hypertension, and 26% had diabetes mellitus. The clinical diagnosis was acute coronary syndrome in 47% of the patients, including 9% with ST-segment elevation myocardial infarction.

Figure 1. Study Flow.

SES denotes sirolimus-eluting stent; ZES, zotarolimus-eluting stent.

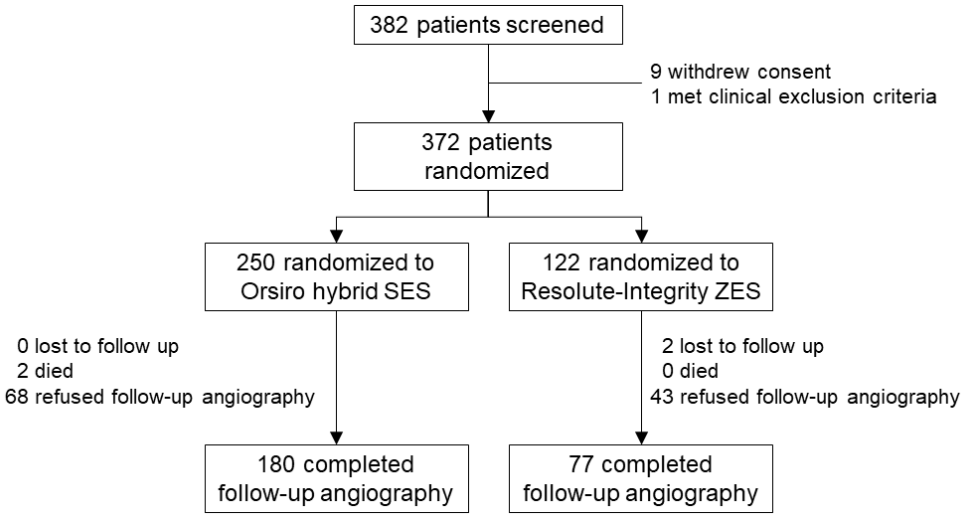


Table 2. Baseline clinical characteristics.

	Orsiro SES (N=250)	Resolute-Integrity ZES (N=122)	P-values
Age	65.2±11.9	64.8±11.0	0.759
Sex	180 (72.0)	86 (70.5)	0.762
Body mass index (kg/m2)	24.8±3.5	24.5±3.1	0.481
Hypertension	162 (64.8)	81 (66.4)	0.762
Diabetes	63 (25.2)	33 (27.0)	0.702
Dyslipidemia	134 (53.6)	66 (54.1)	0.928
Current smoker	66 (26.4)	35 (28.7)	0.641
Chronic kidney disease	7 (2.8)	3 (2.5)	0.849
History of stroke	25 (10.0)	8 (6.6)	0.273
Peripheral artery disease	4 (1.6)	4 (3.3)	0.295
Previous PCI	34 (13.6)	18 (14.8)	0.763
Previous bypass surgery	2 (0.8)	0 (0.0)	0.322
Chronic lung disease	9 (3.6)	3 (2.5)	0.559
Clinical diagnosis			0.643
Stable Angina	136 (53.3)	70 (55.1)	
Unstable Angina	62 (24.3)	25 (19.7)	
NSTEMI	33 (12.9)	21 (16.5)	
STEMI	24 (9.4)	11 (8.7)	
Discharge medications			
Aspirin	243 (97.2)	120 (98.4)	0.494
Clopidogrel	243 (97.2)	117 (95.9)	0.506

ACE inhibitors	92 (36.8)	45 (36.9)	0.987
Angiotensin receptor blockers	82 (32.8)	40 (32.8)	0.998
β-blockers	158 (63.2)	87 (71.3)	0.121
Calcium channel blockers	75 (30.0)	42 (34.4)	0.388
Statins	224 (89.6)	118 (96.7)	0.018

SES denotes sirolimus-eluting stent; ZES, zotarolimus-eluting stent; PCI, percutaneous coronary intervention; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; ACE, angiotensin converting enzyme. Chronic kidney disease was defined as a decreased eGFR <60 ml/min/1.73 m^2, calculated by the 4-component MDRD (Modification of Diet in Renal Disease) study equation incorporating age, race, sex, and serum creatinine.

Table 3 shows the data on baseline lesion and procedural characteristics of all treated lesions. Among a total of 521 lesions, left main coronary artery comprised 5% and left anterior descending artery 47%. Seventy four percent of the lesions met the B2/C criteria according to the American College of Cardiology-American Heart Association (ACC-AHA) classification. Adjunctive intracoronary imaging study was done in 20%, and bifurcation stenting was required in 17% of the lesions. No significant differences between the groups were present in terms of lesion and procedural factors.

Table 3. Lesion and procedural characteristics.

	Orsiro SES (N=345)	Resolute-Integrity ZES (N=176)	P-values
Lesion location			0.084
Left main	20 (5.8)	5 (2.8)	
Left anterior descending	158 (45.8)	85 (48.3)	
Left circumflex	93 (27.0)	36 (20.5)	
Right coronary	74 (21.4)	50 (28.4)	
ACC/AHA lesion classification			0.714
A	15 (4.3)	10 (5.7)	
B1	75 (21.7)	33 (18.8)	

B2	108 (31.3)	52 (29.5)	
C	147 (42.6)	81 (46.0)	
Chronic total occlusion	31 (9.0)	11 (6.3)	0.419
Ostial lesion	24 (7.0)	9 (5.1)	0.379
Bifurcation lesion	79 (22.9)	42 (23.9)	0.864
Restenotic lesion	4 (1.2)	4 (2.3)	0.368
Calcification	38 (11.0)	22 (12.5)	0.313
Stent number (per lesion)	1.14±0.43	1.13±0.43	0.715
Stent number (per patient)	1.58±0.90	1.63±0.85	0.592
Stent diameter - mm	2.98±0.46	3.00±0.45	0.618
Stent length (per lesion) - mm	26.1±12.8	27.3±14.9	0.414
Stent length (per patient) - mm	36.1±22.5	39.3±24.2	0.216
Performance of adjunctive ballooning	257 (74.5)	124 (70.5)	0.528
Nominal diameter - mm	3.03±0.51	2.98±0.49	0.278
Balloon pressure - atm	16.5±7.6	15.6±4.0	0.177
Expected balloon diameter - mm	3.34±1.01	3.33±1.43	0.854
IVUS or OCT	71 (20.6)	34 (19.3)	0.806
Bifurcation stenting	60 (17.4)	30 (17.0)	0.887
Device success (per lesion)	343 (99.4)	174 (98.9)	0.519
Procedureal success (per patient)	249 (99.6)	121 (99.2)	0.603

SES denotes sirolimus-eluting stent; ZES, zotarolimus-eluting stent; ACC, American College of Cardiology; AHA, American Heart Association; IVUS, intravascular ultrasound; OCT, optical coherence tomography.

Angiographic outcomes

Angiographic analyses of the index lesions before and after the index procedure and at the 9-month follow-up are shown in Table 4. There were no significant differences before and after the procedures in terms of lesion parameters. Before procedures, the reference diameter was 2.92 mm, minimal lumen diameter 0.90 mm, and diameter stenosis 74%. Acute gain after PCI was 1.62 ± 0.45 mm, which was similar in both groups.

Table 4. Angiographic outcomes at 9 months after index procedure.

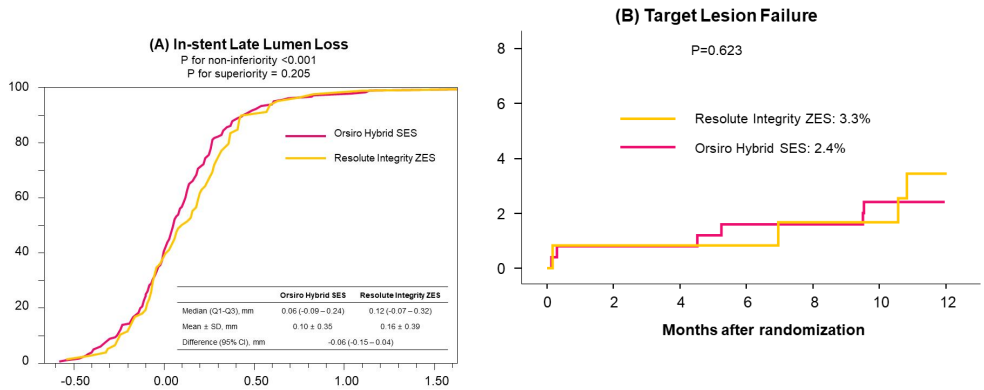
	Orsiro SES	Resolute-Integrity ZES	P-values
Before procedure	(N=250)	(N=122)	
Reference vessel diameter (mm)	2.85 (2.54-3.20)	2.80 (2.60-3.10)	0.692
Lesion length (mm)	18.0 (13.0-24.0)	18.2 (14.0-24.9)	0.464
MLD (mm)	0.88 (0.63-1.13)	0.88 (0.58-1.14)	0.778
Diameter stenosis (%)	72.0 (62.5-84.0)	72.0 (63.0-83.0)	0.648
Immediately after procedure	(N=250)	(N=122)	
MLD (mm)			
In-stent	2.48 (2.22-2.81)	2.46 (2.21-2.72)	0.617
In-segment	2.48 (2.22-2.81)	2.46 (2.21-2.72)	0.643
Diameter stenosis (%)			
In-stent	13.0 (9.0-18.0)	14.0 (9.0-18.0)	0.749
In-segment	12.0 (9.0-17.0)	12.5 (8.3-17.0)	0.725
Acute gain (mm)			
In-stent	1.58 (1.32-1.90)	1.58 (1.31-1.90)	0.619
In-segment	1.58 (1.31-1.90)	1.59 (1.31-1.82)	0.640
Follow-up at 9 months	(N=180)	(N=77)	
MLD (mm)			
In-stent	2.40 (2.12-2.77)	2.39 (2.07-2.66)	0.568
In-segment	2.39 (2.11-2.75)	2.39 (2.07-2.66)	0.668
Diameter stenosis (%)			
In-stent	15.0 (10.0-20.0)	20.0 (13.3-26.0)	0.002
In-segment	15.5 (9.8-20.3)	18.0 (12.0-26.0)	0.011
Late lumen loss (mm)			
In-stent	0.06 (-0.09-0.24)	0.12 (-0.07-0.32)	0.205
In-segment	0.06 (-0.08-0.26)	0.12 (-0.07-0.32)	0.305
Binary restenosis (n, %)			
In-stent	3 (1.7)	1 (1.3)	0.827
In-segment	5 (2.8)	1 (1.3)	0.472

Values are presented in median (interquartile ranges) or number (%). P value were calculated with the use of Wilcoxon signed-rank tests or Fisher's exact test.
SES denotes sirolimus-eluting stent; ZES, zotarolimus-eluting stent; MLD, minimal lumen diameter.

Follow-up angiography was done in 69% of the patients after a median of 302 days since the index PCI. The median of in-stent LLL, the primary endpoint, was 0.06 mm (interquartile ranges [IQR], -0.09 to 0.24 mm) and 0.12 mm (IQR, -0.07 to 0.32 mm) in the O-SES and R-ZES groups,

respectively. Figure 2A shows the hypothesis testing for the primary endpoint. The upper margin of the difference was within the predefined noninferiority margin of 0.20 mm (p for noninferiority <0.001). Superiority testing did not show a statistically significant difference (p for superiority = 0.283). In-segment LLL showed similar patterns. Diameter stenosis at 9 months post-PCI was lower in the O-SES group than in the R-ZES group significantly for in-stent and marginally for in-segment measurements. Binary restenosis rate was low in both of the groups.

Figure 2. Primary angiographic and secondary clinical endpoint analysis. (A) In-stent late lumen loss at 9 months, and (B) target lesion failure at 12 months after index procedure.



The purple line represents the Orsiro biodegradable polymer sirolimus-eluting stent, while the yellow line does Resolute Integrity durable polymer zotarolimus-eluting stent.

Per-lesion analyses are shown in table 5. In-stent LLL was 0.06 mm (IQR, -0.10 to 0.24 mm) and 0.12 mm (IQR, -0.07 to 0.30 mm) in the O-SES and R-ZES groups, respectively (p = 0.163). Table 6 shows the

per-treatment analyses, in which in-stent LLL was shown to be 0.06 mm (IQR, -0.10 to 0.23 mm) and 0.13 mm (IQR, -0.06 to 0.31 mm) (p = 0.140).

Table 5. Per-lesion analysis of angiographic outcomes at 9 months after index procedure.

	Orsiro SES	Resolute-Integrity ZES	P-values
Before procedure	(N=351)	(N=184)	
Reference vessel diameter (mm)	2.80 (2.50-3.20)	2.77 (2.55-3.10)	0.847
Lesion length (mm)	17.8 (13.0-24.0)	18.2 (14.0-24.8)	0.097
Minimal lumen diameter (mm)	0.89 (0.67-1.18)	0.88 (0.62-1.15)	0.649
Diameter stenosis (%)	70.0 (61.0-82.0)	71.0 (63.0-82.0)	0.832
Immediately after procedure	(N=351)	(N=184)	
Minimal lumen diameter (mm)			
in stent	2.46 (2.18-2.77)	2.44 (2.20-2.73)	0.654
in segment	2.46 (2.18-2.75)	2.44 (2.20-2.73)	0.694
Diameter stenosis (%)			
in stent	13.0 (9.0-18.0)	14.0 (9.0-18.0)	0.587
in segment	13.0 (9.0-17.0)	13.0 (8.0-17.5)	0.521
Acute gain (mm)			
in stent	1.52 (1.26-1.83)	1.54 (1.29-1.82)	0.909
in segment	1.53 (1.26-1.83)	1.54 (1.29-1.82)	0.966
Follow-up at 9 months	(N=255)	(N=112)	
Minimal lumen diameter (mm)			
in stent	2.36 (2.10-2.70)	2.34 (1.99-2.64)	0.142
in segment	2.36 (2.10-2.69)	2.34 (1.99-2.64)	0.197
Diameter stenosis (%)			
in stent	15.0 (10.0-20.3)	20.0 (13.0-26.0)	0.004
in segment	15.0 (9.8-22.0)	18.0 (12.0-27.0)	0.017
Late lumen loss (mm)			
in stent	0.06 (-0.10-0.24)	0.12 (-0.07-0.30)	0.163
in segment	0.07 (-0.09-0.26)	0.13 (-0.07-0.30)	0.221
Binary restenosis (n, %)			
in stent	6 (2.4)	4 (3.6)	0.551
in segment	8 (3.1)	4 (3.6)	0.882

Values are presented in median (interquartile ranges) or number (%).

SES denotes sirolimus-eluting stent; ZES, zotarolimus-eluting stent.

Table 6. Per-treatment analysis of angiographic outcomes at 9 months after index procedure.

	Orsiro SES	Resolute-Integrity ZES	P-values
Before procedure	(N=339)	(N=170)	
Reference vessel diameter (mm)	2.82 (2.50-3.20)	2.78 (2.59-3.10)	0.996
Lesion length (mm)	18.0 (13.0-24.0)	17.7 (14.0-24.2)	0.249
Minimal lumen diameter (mm)	0.89 (0.66-1.18)	0.88 (0.63-1.16)	0.465
Diameter stenosis (%)	70.0 (61.0-82.0)	70.0 (63.0-81.0)	0.751
Immediately after procedure	(N=339)	(N=170)	
Minimal lumen diameter (mm)			
in stent	2.46 (2.19-2.78)	2.48 (2.21-2.76)	0.871
in segment	2.46 (2.19-2.77)	2.48 (2.22-2.76)	0.944
Diameter stenosis (%)			
in stent	13.0 (9.0-18.0)	14.0 (9.0-17.0)	0.789
in segment	13.0 (9.0-17.0)	13.0 (8.0-17.0)	0.663
Acute gain (mm)			
in stent	1.53 (1.28-1.83)	1.55 (1.31-1.83)	0.776
in segment	1.53 (1.28-1.83)	1.55 (1.31-1.83)	0.740
Follow-up at 9 months	(N=249)	(N=103)	
Minimal lumen diameter (mm)			
in stent	2.38 (2.11-2.72)	2.36 (2.04-2.66)	0.332
in segment	2.37 (2.10-2.71)	2.36 (2.04-2.66)	0.423
Diameter stenosis (%)			
in stent	15.0 (10.0-20.0)	19.0 (12.5-26.0)	<0.001
in segment	15.0 (10.0-21.0)	17.0 (11.5-26.0)	0.006
Late lumen loss (mm)			
in stent	0.06 (-0.10-0.23)	0.13 (-0.06-0.31)	0.140
in segment	0.06 (-0.10-0.26)	0.13 (-0.06-0.31)	0.189
Binary restenosis (n, %)			
in stent	5 (2.0)	3 (2.9)	0.667
in segment	7 (2.8)	3 (2.9)	0.961

Values are presented in median (interquartile ranges) or number (%).

SES denotes sirolimus-eluting stent; ZES, zotarolimus-eluting stent.

Clinical outcomes at 12 months

Table 7 compares clinical outcomes of the study groups within 12 months. No significant differences were present in terms of clinical endpoints. As shown in Figure 2B, TLF, a composite of cardiac death, nonfatal MI, and TLF, occurred in 2.4% and 3.3% of the patients in the O-SES and R-ZES groups, respectively ($p = 0.621$). There were no cases of stent thrombosis identified.

Table 7. Clinical outcomes at 12 months after index procedure.

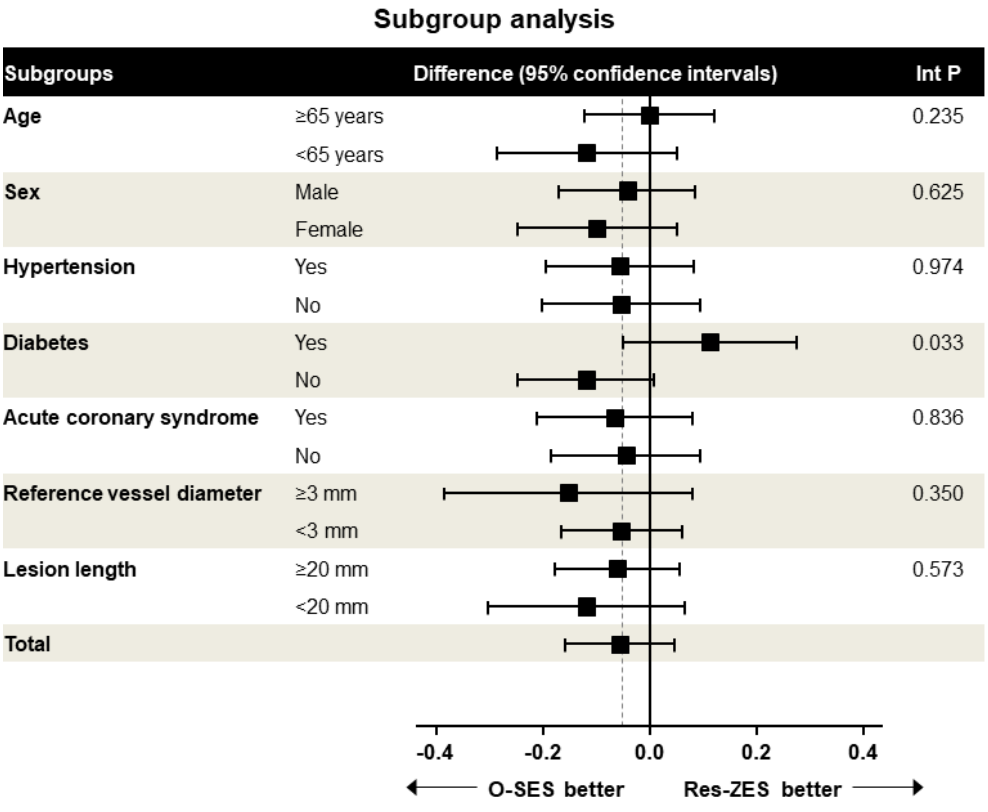
	Orsiro hybrid SES (N=250)	Resolute-Integrity ZES (N=122)	HR (95% CI)	P-values
All-cause death	4 (1.6)	1 (0.8)	1.94 (0.22-17.33)	0.529
Cardiovascular death	3 (1.2)	1 (0.8)	1.45 (0.15-13.98)	0.738
Myocardial infarction	0 (0.0)	1 (0.8)	-	0.134
Repeat revascularization	14 (5.6)	6 (4.9)	1.12 (0.43-2.91)	0.817
Target lesion revascularization	3 (1.2)	3 (2.5)	0.48 (0.10-2.38)	0.374
Target vessel revascularization	7 (2.8)	4 (3.3)	0.84 (0.25-2.86)	0.780
Stent thrombosis	0 (0.0)	0 (0.0)	-	-
Ischemic stroke	1 (0.4)	0 (0.0)	-	0.378
Hemorrhagic stroke	0 (0.0)	0 (0.0)	-	-
Bleeding	6 (2.4)	3 (2.5)	0.96 (0.24-3.83)	0.951
Major, life-threatening	0 (0.0)	1 (0.8)	-	0.125
Major, others	0 (0.0)	0 (0.0)	-	-
Minor	5 (2.0)	2 (1.6)	1.20 (0.23-6.20)	0.823
Cardiac death or myocardial infarction	3 (1.2)	1 (0.8)	1.45 (0.15-13.98)	0.738
TLF (cardiac death, MI, TLR)	6 (2.4)	4 (3.3)	0.72 (0.20-2.56)	0.621
TVF (cardiac death, MI, TVR)	10 (4.0)	5 (4.1)	0.96 (0.33-2.82)	0.944
POCE (death, MI, RR)	18 (7.2)	7 (5.7)	1.24 (0.52-2.96)	0.629

SES denotes sirolimus-eluting stent; ZES, zotarolimus-eluting stent; HR, hazard ration; CI, confidence interval; TLF, target lesion failure; MI, myocardial infarction; TLR, target lesion revascularion; TVF, target vessel failure; TVR, target vessel revascularization; POCE, patient-oriented clinical endpoint; RR, repeat revascularization.

Subgroup analysis

Subgroup analyses for the primary endpoint, in-stent LLL, are shown in Figure 3. The difference in LLL did not vary significantly according to the clinical and angiographic characteristics except for the diabetic subgroup. R-ZES tended to outperform in diabetes, while O-SES tended to be better in the non-diabetic subgroup with a significant interaction (P for interaction = 0.033). The median in-stent LLL in the diabetic subgroup was 0.14 mm (IQR, 0.05 to 0.35 mm) and 0.08 (IQR, -0.08 to 0.348 mm) in the O-SES and R-ZES groups, respectively (p = 0.169), while it was 0.02 (IQR, -0.11 to 0.21 mm) and 0.13 (-0.05 to 0.31 mm) in the non-diabetic subgroup (p = 0.066).

Figure 3. Subgroup analysis.



Stratified analyses for several subgroups of the primary endpoint of in-stent late lumen loss. Differences are the mean of the Orsiro biodegradable polymer sirolimus-eluting stent (O-SES) minus Resolute Integrity durable polymer zotarolimus-eluting stent (R-ZES). Horizontal lines represent 95% confidence intervals. Int P denotes interaction P values.

3-year clinical outcomes

Three-year clinical outcome was collected in a post-hoc analysis. TLF occurred in 4.7% and 7.8% at 3 years in the O-SES and R-ZES groups, respectively (log-rank P=0.227) (Figure 4A). The occurrence of patient-oriented composite endpoint did not differ between the two groups (15.6% and 11.3%; log-rank P=0.313) (Figure 4B). Table 8 summarizes the cumulative event rates at 1, 2, and 3 years. No significant differences were observed between the 2 groups in terms of death, MI, repeat revascularization, stroke, and bleeding.

At 1 year, 224 out of 363 patients (61.7%) were on dual antiplatelet therapy. The rate were similar between the 2 groups (64.2% vs. 56.4; P=0.316). No significant differences in clinical outcomes were present with regard to dual antiplatelet therapy at 1 year (hazard ratio, 1.19; 95% CI, 0.22-6.48; P=0.843).

No cases of stent thrombosis were reported in the O-SES group, while 2 patients experienced stent thrombosis in the R-ZES arm (log-rank P=0.040) (Figure 4C), which were confirmed as definite thrombosis on angiography. One of them developed thrombosis at 365 days since the index procedure, while the patient discontinued the dual antiplatelet therapy on his own for seven days. Regarding the other case, the index lesion was chronic total occlusion of the right coronary artery, and long stenting was performed.

Figure 4. Kaplan-Meier time-to-event curves for 3- year clinical outcomes: (A) target lesion failure, (B) patient-oriented composite endpoint and death, and (C) stent thrombosis

SES, sirolimus-eluting stent; ZES, zotarolimus-eluting stent.

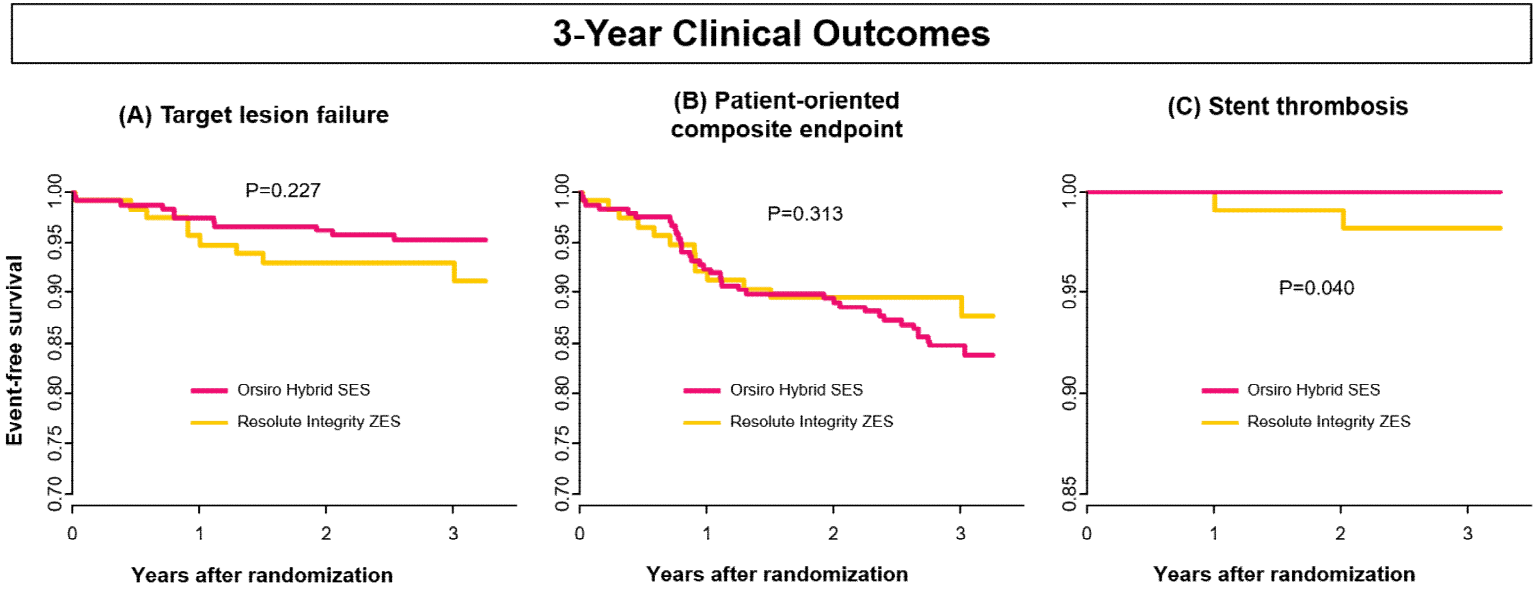


Table 3. Clinical outcomes up to 3 years

	Orsiro Hybrid SES	Resolute Integrity ZES	OR (95% CI)	P-values
Events at 2 years				
All-cause death	5 (2.0)	3 (2.0)	0.78 (0.15–5.14)	0.715
Cardiovascular death	2 (0.8)	2 (1.7)	0.47 (0.03–6.56)	0.596
Myocardial infarction	0 (0.0)	3 (2.6)	-	0.032
Repeat revascularization	22 (9.0)	9 (7.8)	1.17 (0.50–2.99)	0.841
Target lesion revascularization	8 (3.3)	6 (5.2)	0.62 (0.18–2.22)	0.391
Target vessel revascularization	11 (4.5)	7 (6.0)	0.73 (0.25–2.29)	0.605
Stroke	2 (0.8)	0 (0.0)	-	1.000
Bleeding	7 (2.9)	6 (5.2)	0.54 (0.15–1.99)	0.363
Major, life-threatening	0 (0.0)	1 (0.9)	-	0.319
Major, others	1 (0.4)	1 (0.9)	0.47 (0.01–37.3)	0.540
Minor	6 (2.5)	4 (3.6)	0.70 (0.16–3.42)	0.732
Cardiac death or myocardial infarction	2 (0.8)	4 (3,5)	0.23 (0.02–1.64)	0.087
TLF (cardiac death, MI, TLR)	10 (4.1)	8 (6.9)	0.58 (0.20–1.74)	0.302
TVF (cardiac death, MI, TVR)	14 (5.8)	10 (8.6)	0.65 (0.26–1.69)	0.366
POCE (death, MI, RR)	28 (11.5)	12 (10.3)	1.13 (0.53–2.54)	0.858
Events at 3 years				
All-cause death	9 (3.8)	4 (3.5)	1.09 (0.30–4.95)	1.000
Cardiovascular death	2 (0.8)	3 (2.6)	0.32 (0.03–2.86)	0.336
Myocardial infarction	1 (0.4)	3 (2.6)	0.16 (0.00–2.03)	0.106

Repeat revascularization	28 (12.0)	9 (7.8)	1.59 (0.70–3.98)	0.271
Target lesion revascularization	9 (3.8)	6 (5.2)	0.73 (0.22–2.55)	0.580
Target vessel revascularization	15 (6.3)	7 (6.0)	1.04 (0.39–3.11)	1.000
Stroke	2 (0.9)	1 (0.9)	0.97 (0.05–57.9)	1.000
Bleeding	8 (3.4)	6 (5.2)	0.64 (0.19–2.31)	0.402
Major, life-threatening	1 (0.4)	1 (0.9)	0.49 (0.01–38.4)	0.548
Major, others	1 (0,4)	1 (0.9)	0.49 (0.01–37.3)	0.551
Minor	6 (2.6)	4 (3.6)	0.72 (0.17–3.56)	0.734
Cardiac death or myocardial infarction	3 (1.3)	5 (4.4)	0.29 (0.04–1.50)	0.121
TLF (cardiac death, MI, TLR)	11 (4.7)	9 (7.8)	0.59 (0.21–1.66)	0.327
TVF (cardiac death, MI, TVR)	18 (7.6)	11 (9.6)	0.79 (0.34–1.93)	0.543
POCE (death, MI, RR)	37 (15.6)	13 (11.3)	1.45 (0.72–3.11)	0.330

SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent;
CI: confidence interval; OR: odd ratio;
TLF: target lesion failure; TLR: target lesion revascularisation;
TVF: target vessel failure; TVR: target vessel revascularisation;
MI: myocardial infarction; POCE: patient-oriented clinical endpoint; RR: repeat revascularisation

Discussion

In this study, we showed that O-SES was noninferior compared to the Resolute Integrity ZES in terms of the primary angiographic endpoint, in-stent LLL at 9 months. There were no significant differences in clinical outcomes between the 2 stents. The O-SES group compared to the R-ZES group showed a lower percentage of diameter stenosis at 9 months.

The findings of this study confirm the excellent performance of both O-SES and R-ZES. R-ZES is one of the most widely used contemporary DES worldwide. The Integrity platform has been utilized in the Resolute Integrity instead of the Driver bare metal stent platform, which was used in the previous versions. The Integrity stent platform has a 90-μm strut thickness and a 1.12-mm crossing profile. The manufacturing process of the Continuous Sinusoidal Technology promises enhanced flexibility and deliverability, as well as radial and longitudinal strength.[22] Otherwise, the Resolute Integrity ZES shares the same delivery drug (zotarolimus) and the same BioLinx® biocompatible polymer mounted on the same metal alloy (cobalt chromium) with the previous version, the Endeavor Resolute ZES. The angiographic and clinical results of the R-ZES group in this study were comparable to the previous outcomes of Endeavor Resolute ZES.[20, 23-27] Until now, two large-scale clinical trials have been published investigating Integrity-platform R-ZES, the DUTCH PEERS and SORT OUT VI trials.[15, 16] The patient characteristics in this study were similar to those seen in the previous trials, except for a lower BMI, a higher rate of diabetes, and a lower frequency of acute coronary syndrome. Adverse clinical event rates were numerically lower in this study.

O-SES represents a newer generation BP-DES. Several features, such as an ultrathin 60 μm strut, effective antiproliferative drug (sirolimus), and a hybrid design of passive protection of the metallic surface by a semiconductive barrier and active drug release from a biodegradable polymer, support the performance as well as the safety of O-SES. The BIOFLOW-I, a first-in-man trial, showed low in-stent neointimal hyperplasia and low cardiovascular event rates.[11] The BIOFLOW-II, a randomized controlled clinical trial, proved the noninferiority of O-SES compared to the Xience everolimus-eluting stent (X-EES).[12] The recently published BIOSCIENCE trial enrolled a large number of patients and randomly assigned them to O-SES or X-EES.[13] O-SES was shown noninferior to the X-EES, which is considered to be the best among contemporary coronary stents.[9, 28] The rates of clinical adverse events seen in our study are lower than those seen in the previous reports, while neointimal hyperplasia, as assessed by angiography, was similar.[11, 12]

To the best of our knowledge, this is the first study comparing O-SES and R-ZES head to head. In this study, both stents showed good results. While in-stent and in-segment LLL showed no significant difference, percentage diameter stenosis was significantly lower in the O-SES group than in the R-ZES group. The difference became greater in the per-treatment analysis. However, the difference in this angiographic parameter can hardly be translated into an improvement in clinical outcomes. First, it needs to be stated that the percentage of diameter stenosis was not the primary endpoint of this study, but one of the secondary angiographic endpoints. Second, previous larger all-comer trials that were powered to detect the differences

in clinical event rates suggest equivalent efficacy of the two devices. The RESOLUTE All-Comers trial showed actually the same event rates between the R-ZES and the X-EES groups.[24, 25] In addition, O-SES showed quite similar outcomes with the X-EES in the BIOSCIENCE trial.[13] Future studies that are currently underway would provide further insight into the safety and efficacy of Orsiro SES.[29]

The significant interaction in the diabetic subgroup shown in this study needs further discussion. Patients with diabetes are at higher risk of adverse events after PCI.[30] The diabetic milieu attenuates the antirestenoic effects of DES, and the differential effects between different types of DES have attracted attention.[31, 32] In this study, O-SES compared to R-ZES tended to be associated with higher LLL in the diabetic subgroup. However, the BIOFLOW-II trial, in which O-SES and X-EES were compared, found no significant interaction between the stent types and diabetic status.[12] A prespecified subgroup analysis of the large-scale BIOSCIENCE trial also showed the rates of clinical adverse events of O-SES and X-EES were similar in both diabetic and nondiabetic subgroups.[33] Furthermore, there have no previous studies that proved differential effects among stents that elute rapamycin analogues according to diabetic status.[15, 16, 33] Subgroup analyses in this trial was exploratory and only for hypothesis generation. This finding needs to be further tested in future studies.

This study has several limitations. First, this study was designed to detect the noninferiority margin of the angiographic endpoint. It is underpowered to detect any difference in clinical endpoints. Findings for the secondary endpoints and in the subgroup analyses should be considered to be only of

a hypothesis-generating nature. Specifically, this study has limited power for comparison of clinical adverse events. Second, while we tested Resolute Integrity ZES in this study, a newer version of Resolute iterations has been launched in the market, namely Resolute Onyx. However, its design is very similar to that of the Resolute Integrity except improved visibility. We assume that there is a low probability that the performance of the Onyx version would be vastly different than that of R-ZES. Third, as the angiographic follow-up was only 69%, a selection bias could have been present. This is an innate drawback for such studies with angiographic endpoints. In addition, the rate of follow-up angiography was balanced between the study groups. Finally, the actual LLL was smaller than expected. According, from a retrospective viewpoint, our statistical assumption may have been too generous.

Conclusions

O-SES was noninferior to R-ZES in terms of in-stent LLL at 9 months. Angiographic restenosis and clinical adverse events rates were low in both groups. This study confirms the excellent performance profiles of both the contemporary coronary stents.

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