

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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This paper also includes supplementary data published online at: http://www.pcronline.com/eurointervention/110th_issue/265

KEYWORDS

- biodegradable polymer
- coronary artery disease
- drug-eluting stents
- percutaneous coronary intervention

Abstract

Aims: We performed a randomised controlled open-label non-inferiority trial to compare angiographic outcomes between the ultra-thin strut, biodegradable hybrid polymer Orsiro sirolimus-eluting stent (O-SES) and the durable biocompatible polymer Resolute Integrity zotarolimus-eluting stent (R-ZES).

Methods and results: A total of 372 patients planned to undergo percutaneous coronary revascularisation were randomly assigned 2:1 to treatment with O-SES or R-ZES (250 and 122 patients, respectively). O-SES was non-inferior to R-ZES for the primary endpoint, in-stent late lumen loss at nine months (median 0.06 mm [interquartile range, -0.09 to 0.24 mm] versus 0.12 mm [-0.07 to 0.32 mm]; p for non-inferiority <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 non-inferior to R-ZES in terms of in-stent late loss at nine months. Angiographic restenosis and clinical adverse events were low in both groups. This study confirms the good safety and efficacy profiles of both contemporary coronary stents.

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Introduction

Drug-eluting stents (DES) have become an indispensable component in percutaneous coronary revascularisation^{1,2}. Although the advent of DES has reduced the need for repeat revascularisation, concerns have been raised as studies have reported an increased propensity for very late stent thrombosis with DES use as compared to bare metal stents (BMS)³⁻⁵. This has provoked numerous innovations in DES design, for example changes in the polymer composition. As studies have suggested polymer as a culprit for thrombogenicity^{6,7}, biocompatible durable polymers (DP) and biodegradable polymers (BP) have replaced previous polymers. Another innovation is thinner strut 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 characteristics, and antiproliferative drugs⁸.

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 of DP-DES^{9,10}. The Orsiro biodegradable polymer sirolimus-eluting stent (O-SES; Biotronik AG, Bulach, Switzerland) is a novel DES with an ultra-thin 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 to date (60 µm), and thus provides good flexibility and deliverability. Previous studies have shown promising angiographic and clinical outcomes after implantation of O-SES¹¹⁻¹³.

The 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 V[®] everolimus-eluting stent (Abbott Vascular, Santa Clara, CA, USA)¹⁴. In addition, recent studies have shown good performance of R-ZES^{15,16}. In this study, we performed a randomised 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-comers trial with limited exclusion criteria.

Methods

STUDY DESIGN

The Orsiro Hybrid sirolimus-eluting stent and Resolute Integrity zotarolimus-eluting stent in all-comers with coronary artery disease (ORIENT) trial is a prospective randomised open-label multicentre trial. The study design has been described previously¹⁷. The study participants were enrolled in eight centres in the Republic of Korea between October 2013 and June 2014. This trial was initiated by investigators, and grant support was provided by BIOTRONIK Korea Co., Ltd., Seoul, Republic of Korea. Data were managed by a contract research organisation (T&W

software, Seoul, Republic of 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 revascularisation modality was based on the current recommendations of the ACC/AHA/SCAI and ESC/EACTS guidelines or the clinical judgement 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 minimise exclusion of patients, thus reflecting the real-world population at large (**Online Table 1**).

TREATMENT AND RANDOMISATION

Patients who were planned to undergo PCI after diagnostic angiography were randomly assigned in a 2:1 ratio to either the O-SES or the R-ZES group. Randomisation was carried out via a web-based online randomisation system. The randomisation 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 nine months post PCI. Clinical follow-up was performed at one, three, nine, 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 nine months, as measured by quantitative coronary angiography. Secondary angiographic endpoints included in-segment LLL, percentage diameter stenosis, and binary restenosis at nine months. Quantitative analysis of coronary angiographic images (QCA) was performed by specialised 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 software (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 death, clinically driven target lesion revascularisation (TLR), clinically driven target vessel revascularisation (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 nine-month LLL was compared using the Student's t-test. Assuming a mean LLL of 0.30 ± 0.54 mm for both stents²⁰, 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 non-inferiority 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 non-inferiority 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 generalised 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 carried out on the primary endpoint, which was intended for descriptive purposes. Secondary clinical endpoints were compared with the Cox proportional hazards model. Kaplan-Meier survival curves were constructed. Binary variables were compared with the use of the χ^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 1 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.

Table 2 shows the data on baseline lesion and procedural characteristics of all treated lesions. Among a total of 521 lesions, the left main coronary artery comprised 5% and the 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) classifica-

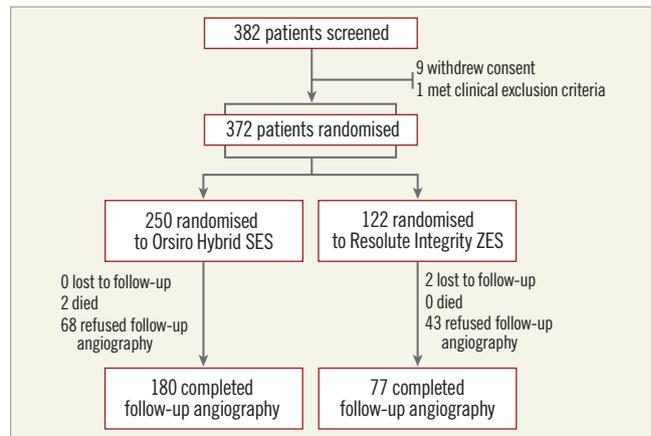


Figure 1. Study flow chart. SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent

tion. An adjunctive intracoronary imaging study was carried out 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.

ANGIOGRAPHIC OUTCOMES

Angiographic analyses of the index lesions before and after the index procedure and at nine-month follow-up are shown in Table 3. There were no significant differences before and after

Table 1. Baseline characteristics.

	Orsiro SES (N=250)	Resolute Integrity ZES (N=122)	p-value
Clinical characteristics			
Age	65.2±11.9	64.8±11.0	0.759
Male sex	180 (72.0)	86 (70.5)	0.762
Body mass index (kg/m ²)	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
Dyslipidaemia	134 (53.6)	66 (54.1)	0.928
Current smoker	66 (26.4)	35 (28.7)	0.641
Chronic renal failure	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
Clinical diagnosis			
Stable angina	136 (53.3)	70 (55.1)	0.643
Unstable angina	62 (24.3)	25 (19.7)	
NSTEMI	33 (12.9)	21 (16.5)	
STEMI	24 (9.4)	11 (8.7)	
NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; SES: sirolimus-eluting stent; STEMI: ST-segment elevation myocardial infarction; ZES: zotarolimus-eluting stent			

Table 2. Lesion and procedural characteristics.

	Orsiro SES (N=345)	Resolute Integrity ZES (N=176)	p-value
Lesion location			
Left main	20 (5.8)	5 (2.8)	0.084
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			
A	15 (4.3)	10 (5.7)	0.714
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
Procedural success (per patient)	249 (99.6)	121 (99.2)	0.603

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

the procedures in terms of lesion parameters. Before the 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.

Follow-up angiography was carried out in 69% of the patients after a median of 302 days following the index PCI. The median in-stent LLL, the primary endpoint, was 0.06 mm (interquartile range [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 non-inferiority margin of 0.20 mm (p for non-inferiority <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 nine months post PCI was lower in the O-SES group

Table 3. Angiographic outcomes at 9 months after index procedure.

	Orsiro SES (N=250)	Resolute Integrity ZES (N=122)	p-value
Before procedure			
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			
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			
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 as median (interquartile range) or number (%). p-values were calculated with the use of Wilcoxon signed-rank tests or Fisher's exact test. MLD: minimal lumen diameter; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent

than in the R-ZES group, significantly for in-stent and marginally for in-segment measurements. The binary restenosis rate was low in both of the groups.

Per-lesion analyses are shown in **Online Table 2**. 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). **Online Table 3** 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).

CLINICAL OUTCOMES

Table 4 shows a comparison of 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, non-fatal MI, and TLF, occurred in 2.4%

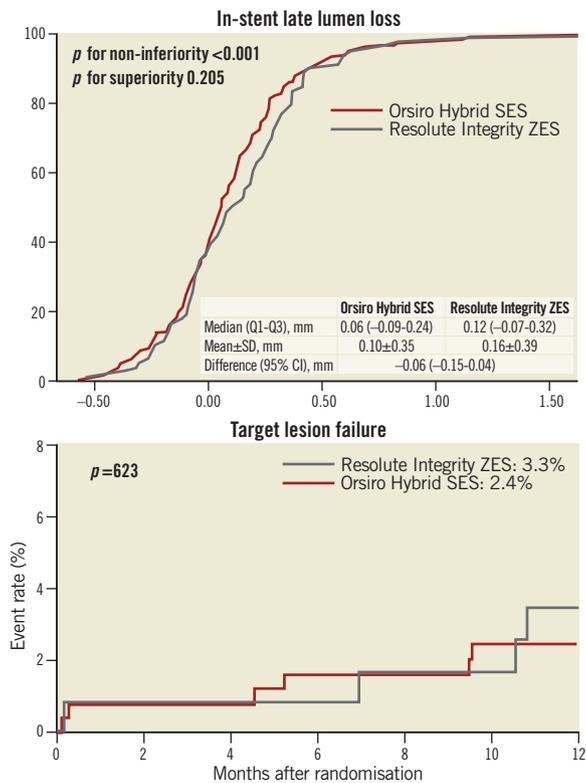


Figure 2. Primary angiographic and secondary clinical endpoint analysis. A) In-stent late lumen loss at nine months. B) Target lesion failure at 12 months after the index procedure. The red line represents the Orsiro biodegradable polymer sirolimus-eluting stent, while the grey line represents the Resolute Integrity durable polymer zotarolimus-eluting stent.

and 3.3% of the patients in the O-SES and R-ZES groups, respectively ($p=0.621$). No cases of stent thrombosis were identified.

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 diabetic patients, 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 ($p=0.066$).

Discussion

In this study, we showed that O-SES was non-inferior compared to R-ZES in terms of the primary angiographic endpoint, in-stent LLL at nine months. There were no significant differences in clinical outcomes between the two stents. Compared to the R-ZES group, the O-SES group showed a lower percentage of diameter stenosis at nine months.

Table 4. Clinical outcomes at 12 months after index procedure.

	Orsiro Hybrid SES (N=250)	Resolute Integrity ZES (N=122)	HR (95% CI)	p -value
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 revascularisation	14 (5.6)	6 (4.9)	1.12 (0.43-2.91)	0.817
Target lesion revascularisation	3 (1.2)	3 (2.5)	0.48 (0.10-2.38)	0.374
Target vessel revascularisation	7 (2.8)	4 (3.3)	0.84 (0.25-2.86)	0.780
Stent thrombosis	0 (0.0)	0 (0.0)	–	–
Ischaemic stroke	1 (0.4)	0 (0.0)	–	0.378
Haemorrhagic 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

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

The findings of this study confirm the good performance of both the O-SES and the R-ZES. R-ZES is one of the most widely used contemporary DES worldwide. The Integrity platform has been utilised in the Resolute Integrity instead of the Driver® bare metal stent platform (Medtronic), which was used in the previous versions. The Integrity stent platform has a 90 μ m 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 strength²². Otherwise, the R-ZES shares the same delivery drug (zotarolimus) and the same BioLinx™ biocompatible polymer (Medtronic) mounted on the same metal alloy (cobalt-chromium) with the previous version, the Endeavor® Resolute ZES (Medtronic). 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.

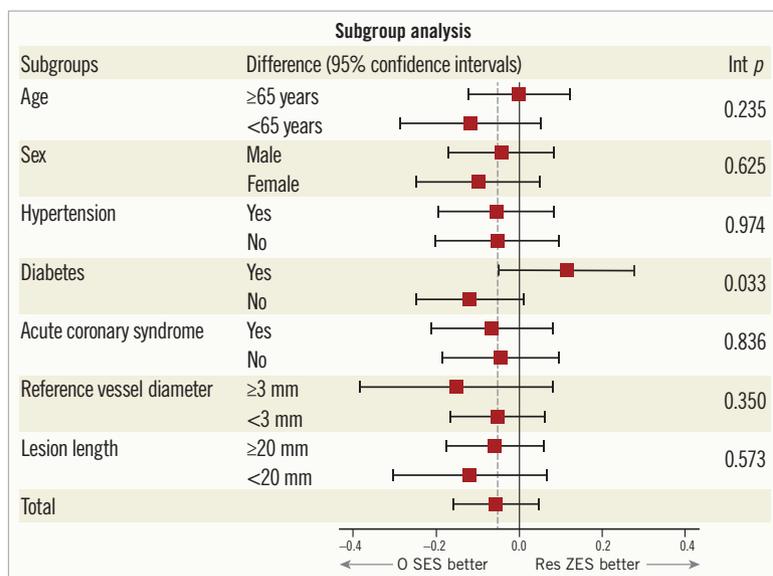


Figure 3. Subgroup analysis. Stratified analyses for several subgroups of the primary endpoint of in-stent late lumen loss. Differences are the mean of the Orsiro biodegradable polymer sirolimus-eluting stent (O-SES) minus Resolute Integrity durable polymer zotarolimus-eluting stent (R-ZES). The horizontal lines represent 95% confidence intervals. Int *p*: interaction *p*-values

O-SES represents a newer-generation BP-DES. Several features, such as an ultra-thin 60 μm strut, effective antiproliferative drug (sirolimus), and a hybrid design of passive protection of the metallic surface by a semi-conductive barrier and active drug release from a biodegradable polymer, support the performance as well as the safety of the O-SES. The BIOFLOW-I, a first-in-man trial, showed low in-stent neointimal hyperplasia and low cardiovascular event rates¹¹. The BIOFLOW-II, a randomised controlled clinical trial, proved the non-inferiority of O-SES compared to the XIENCE PRIME[®] 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-EES¹³. O-SES was shown to be non-inferior 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-comers trials that were powered to detect the differences in clinical event rates suggest equivalent efficacy of the two devices. The RESOLUTE All-Comers trial actually showed the same event rates between the R-ZES and the

X-EES groups^{24,25}. In addition, O-SES showed quite similar outcomes to the X-EES in the BIOSCIENCE trial¹³. Future studies that are currently underway will provide further insight into the safety and efficacy of the Orsiro SES²⁹.

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 PCI³⁰. The diabetic milieu attenuates the antirestenotic 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 status¹². A pre-specified subgroup analysis of the large-scale BIOSCIENCE trial also showed that the rates of clinical adverse events of O-SES and X-EES were similar in both diabetic and non-diabetic subgroups³³. Furthermore, there have been 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 were exploratory and only for hypothesis generation. This finding needs to be tested further in future studies.

Limitations

This study has several limitations. First, this study was designed to detect the non-inferiority margin of the angiographic endpoint. It was 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 on the market, namely the Resolute Onyx™ (Medtronic). However, its design is very similar to that of the Resolute Integrity except for improved visibility. We assume that there is a low probability that the performance of the Onyx version would be vastly different from that of the 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. Accordingly, from a retrospective viewpoint, our statistical assumption may have been too generous.

Conclusions

O-SES was non-inferior to R-ZES in terms of in-stent LLL at nine months. Angiographic restenosis and clinical adverse event rates were low in both groups. This study confirms the good performance profiles of both of these contemporary coronary stents.

Impact on daily practice

This study showed that the Orsiro Hybrid sirolimus-eluting stent was non-inferior to the Resolute zotarolimus-eluting stent in terms of angiographic outcomes. In addition, the two stents were associated with low angiographic restenosis and clinical adverse events. The results of this study support the safety and efficacy profiles of these two currently available coronary stents.

Funding

This work was supported by a grant from BIOTRONIK Korea Co., Ltd., Republic of Korea. Besides financial sponsorship, the company had no role in protocol development or the implementation, management, data collection, or analysis of this study.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Online Table 1. Eligibility criteria of the trial.

Online Table 2. Per-lesion analysis of angiographic outcomes at nine months after the index procedure.

Online Table 3. Per-treatment analysis of angiographic outcomes at nine months after the index procedure.

The supplementary data are published online at:
http://www.pcronline.com/eurointervention/110th_issue/265



Supplementary data

Online Table 1. Eligibility criteria of the trial.

Inclusion criteria
<ul style="list-style-type: none"> – 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 authorised 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 judgement 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
<ul style="list-style-type: none"> – Known hypersensitivity or contraindication to any of the following agents: heparin, aspirin, clopidogrel, sirolimus, zotarolimus, cobalt chromium or contrast media – 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 enrolment – 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 comorbid 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

Online Table 2. Per-lesion analysis of angiographic outcomes at nine months after the index procedure.

	Orsiro SES	Resolute Integrity ZES	p-value
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 as median (interquartile range) or number (%).
SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent

Online Table 3. Per-treatment analysis of angiographic outcomes at nine months after the index procedure.

	Orsiro SES	Resolute Integrity ZES	p-value
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 as median (interquartile range) or number (%).
SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent