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# Three-year clinical outcome of biodegradable hybrid polymer Orsiro sirolimus-eluting stent and the durable biocompatible polymer Resolute Integrity zotarolimus-eluting stent: A randomized controlled trial

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**Abstract**

**Aims:** We compared long-term clinical outcomes between patients treated with Orsiro sirolimus-eluting stent (O-SES) and those treated with durable biocompatible polymer Resolute Integrity zotarolimus-eluting stent (R-ZES).

**Methods and Results:** The ORIENT trial was a randomized controlled noninferiority trial to compare angiographic outcomes between O-SES and R-ZES. We performed a post hoc analysis of 3-year clinical outcomes and included 372 patients who were prospectively enrolled and randomly assigned to O-SES ( $n = 250$ ) and R-ZES ( $n = 122$ ) groups in a 2:1 ratio. The primary endpoint was target lesion failure defined as a composite of cardiac death, nonfatal myocardial infarction, and target lesion revascularization. At 3 years, target lesion failure occurred in 4.7% and 7.8% of O-SES and R-ZES groups, respectively (hazard ratio, 0.58; 95% confidence intervals, 0.24–1.41;

**Abbreviations:** DES, drug-eluting stents; EES, everolimus-eluting stent; LLL, late lumen loss; MI, myocardial infarction; O-SES, Orsiro sirolimus-eluting stent; PCI, percutaneous coronary intervention; R-ZES, Resolute Integrity zotarolimus-eluting stent; TLF, target lesion failure; TLR, target lesion revascularization; TVR, target vessel revascularization.

Soo-Hyun Kim and Si-Hyuck Kang contributed equally to this study.

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$p = .232$  by log-rank test). Secondary endpoints including cardiac death, myocardial infarction, and target lesion revascularization showed no significant differences between the groups. Stent thrombosis occurred in two patients in R-ZES group (0.0% vs. 1.6%,  $p = .040$ ).

**Conclusion:** This study confirms long-term safety and efficacy of the two stents. We found a trend for lower target lesion failure with O-SES compared to R-ZES, although statistically insignificant.

#### KEYWORDS

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

## 1 | INTRODUCTION

Current-generation drug-eluting stents (DES) have shown high efficacy and safety,<sup>1–3</sup> and contemporary guidelines recommend DES as the preferred treatment option over bare metal stents, regardless of clinical situations.<sup>4,5</sup> Although DES have reduced the need for repeat revascularization in the short term, late stent failure remains a concern. First-generation DES have shown to be associated with a continuous accumulation of late adverse events including target lesion revascularization (TLR) and very late stent thrombosis.<sup>6–8</sup> In second-generation DES, despite the improved performance and better patient outcomes with lower risk of late thrombotic events, stent failure still occurs.<sup>9,10</sup> Previous studies have suggested that in-stent neoatherosclerosis contributes to late vascular complications.<sup>11,12</sup> However, there are still limited long-term data on newer-generation DES.<sup>13</sup>

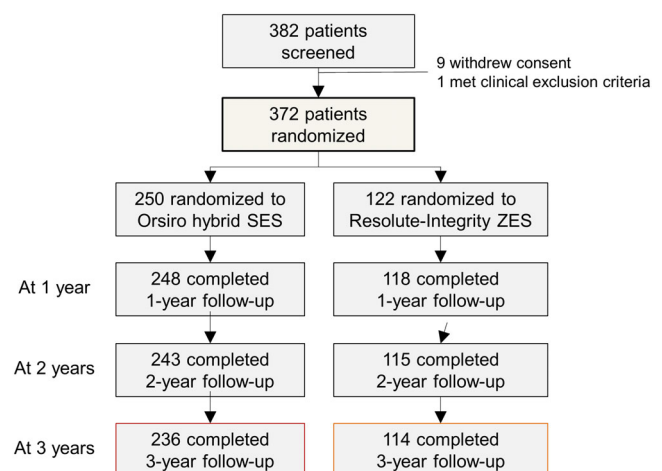
Orsiro Hybrid sirolimus-eluting stent (O-SES; Biotronik AG, Bulach, Switzerland) and Resolute Integrity zotarolimus-eluting stent (R-ZES; Medtronic Cardiovascular, Santa Rosa, CA) are among the widely used second-generation DES with their good performance.<sup>14–17</sup> O-SES has an ultrathin strut (60  $\mu\text{m}$ ) and unique hybrid coating of passive and active bioabsorbable polymer components. R-ZES has a relatively thick strut (91  $\mu\text{m}$ ) and durable polymer, but has the advantage of good flexibility and conformability with round strut and continuous sinusoid technology. We previously reported the 9-month angiographic outcomes of the two stents in a prospective randomized controlled trial of all-comers with coronary artery disease.<sup>18,19</sup> In-stent late loss at 9 months was 0.06 and 0.12 mm for O-SES and R-ZES respectively, which did not differ significantly. Adverse clinical event rates were low for both stents at 12 months. In the present study, we report 3-year clinical outcomes of the trial to assess long-term safety and efficacy of contemporary second-generation DES.

## 2 | METHODS

The ORIENT (the Orsiro Hybrid sirolimus-eluting stent and Resolute Integrity zotarolimus-eluting stent in a prospective randomized controlled trial of all-comers with coronary artery disease) was a

multicenter, randomized, open-label, all-comer, noninferiority trial. The design and results have been reported previously in detail.<sup>18,19</sup> In brief, the study participants were enrolled in eight centers in the Republic of Korea between October 2013 and June 2014. A total of 372 patients undergoing percutaneous coronary intervention for coronary artery disease were randomly assigned to O-SES or R-ZES in a 2:1 ratio, via a web-based online randomization system. Coronary artery disease included stable angina as well as acute coronary syndrome. Percutaneous coronary intervention (PCI) was performed using standard techniques and routine protocols. Dual antiplatelet therapy was recommended for at least 12 months unless contraindicated. The study protocol was approved by the review boards of the participating institutions. All participating patients provided written informed consent for enrollment. The study complied with the provisions of the Declaration of Helsinki. After the index PCI, clinical follow-up data were obtained from outpatient clinic visit or telephone at 1, 3, 9, and 12 months and extended annually thereafter up to 3 years.

The 9-month angiographic results, in-stent late lumen loss (LLL), have been published previously.<sup>18</sup> The main outcome of the present



**FIGURE 1** Flow diagram of the study population. SES, sirolimus-eluting stent; ZES, zotarolimus-eluting stent [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

study was target lesion failure (TLF) at 3 years, a composite of cardiac death, TLR, and target vessel-related myocardial infarction (MI). The secondary endpoints included target vessel failure, patient-oriented

composite endpoint, a composite of cardiac death and nonfatal MI, all-cause and cardiac death, nonfatal MI (target or nontarget vessel-related), clinically driven TLR, clinically driven target vessel

**TABLE 1** Baseline characteristics

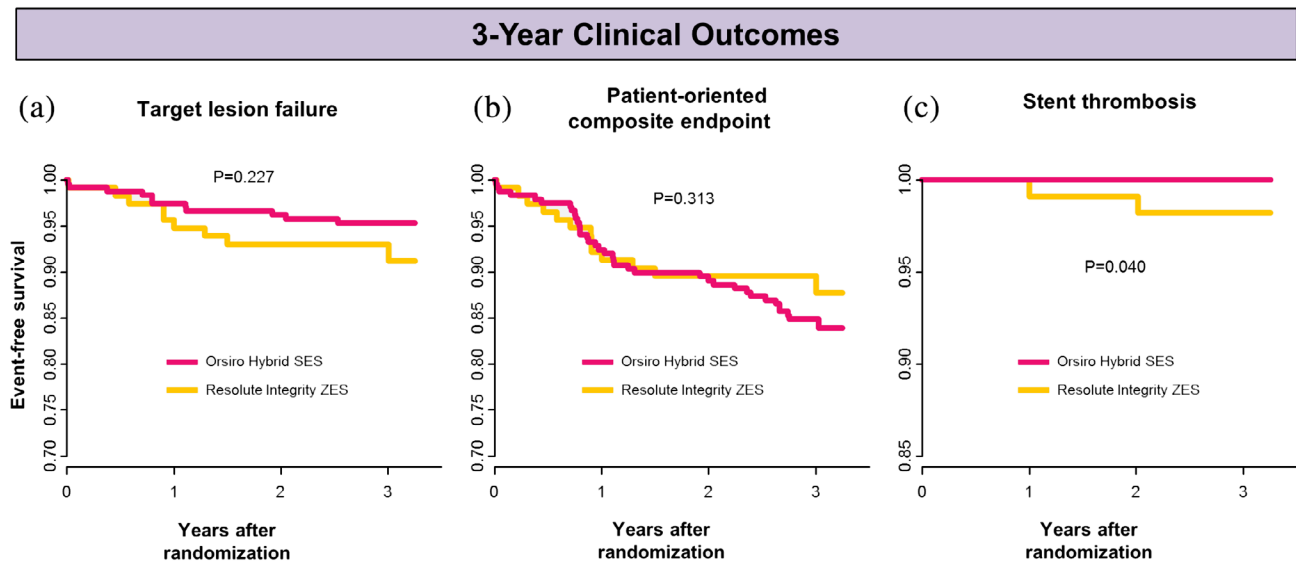
	Total	Orsiro Hybrid SES (N = 250)	Resolute Integrity ZES (N = 122)
Age	65.1 ± 11.6	65.2 ± 11.9	64.8 ± 11.0
Sex (male)	266 (71.5)	180 (72.0)	86 (70.5)
Body mass index (kg/m <sup>2</sup> )	24.7 ± 3.4	24.8 ± 3.5	24.5 ± 3.1
Hypertension	244 (65.6)	163 (65.2)	81 (66.4)
Diabetes	97 (26.1)	63 (25.2)	34 (27.9)
Dyslipidemia	200 (53.8)	134 (53.6)	66 (54.1)
Current smoker	102 (27.4)	67 (26.8)	35 (28.7)
Chronic renal failure	10 (2.7)	7 (2.8)	3 (2.5)
History of stroke	33 (8.9)	25 (10.0)	8 (6.6)
Peripheral artery disease	8 (2.2)	4 (1.6)	4 (3.3)
Previous PCI	52 (14.0)	34 (13.6)	18 (14.8)
Previous bypass surgery	2 (0.5)	2 (0.8)	0 (0.0)
Chronic lung disease	12 (3.2)	9 (3.6)	3 (2.5)
Clinical diagnosis			
Stable angina	200 (53.8)	133 (53.2)	67 (54.9)
Unstable angina	87 (23.4)	62 (24.8)	25 (20.5)
NSTEMI	53 (14.2)	33 (13.2)	20 (16.4)
STEMI	32 (8.6)	22 (8.8)	10 (8.2)
Discharge medications			
Aspirin	363 (97.6)	243 (97.2)	120 (98.4)
Clopidogrel	361 (97.0)	243 (97.2)	118 (96.7)
ACE inhibitors	138 (37.1)	92 (36.8)	46 (37.7)
Angiotensin receptor blockers	122 (32.8)	82 (32.8)	40 (32.8)
β-Blockers	245 (65.9)	158 (63.2)	87 (71.3)
Calcium channel blockers	118 (31.7)	76 (30.4)	42 (34.4)
Statins	342 (91.9)	224 (89.6)	118 (96.7)

Abbreviations: ACE, angiotensin-converting enzyme; NSTEMI, Non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SES, sirolimus-eluting stent; STEMI, ST-elevation myocardial infarction; ZES, zotarolimus-eluting stent.

**TABLE 2** Medications at 1, 2, and 3 years

	Total	Orsiro Hybrid SES (N = 250)	Resolute Integrity ZES (N = 122)	p values
At 1 year	(n = 363)	(n = 246)	(n = 117)	
Aspirin	82.9 (301/363)	83.7 (206/246)	81.2 (95/117)	.599
Clopidogrel	74.9 (272/363)	76.0 (187/246)	72.6 (85/117)	.785
Dual antiplatelet therapy	61.7 (224/363)	64.2 (158/246)	56.4 (66/117)	.316
At 2 years	(n = 350)	(n = 238)	(n = 112)	
Aspirin	73.7 (258/350)	75.6 (180/238)	69.6 (78/112)	.167
Clopidogrel	54.0 (189/350)	52.9 (126/238)	56.2 (63/112)	.726
Dual antiplatelet therapy	36.9 (129/350)	37.8 (90/238)	34.8 (39/112)	.671
At 3 years	(n = 349)	(n = 237)	(n = 112)	
Aspirin	66.8 (233/349)	68.8 (163/237)	62.5 (70/112)	.085
Clopidogrel	47.6 (166/349)	46.0 (109/237)	50.9 (57/112)	.689
Dual antiplatelet therapy	27.5 (96/349)	27.8 (66/237)	26.8 (30/112)	.812

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



**FIGURE 2** 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 [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

revascularization (TVR), stroke, bleeding, and definite or probable stent thrombosis. Target vessel failure was defined as a composite of cardiovascular death, target vessel MI, or TVR. Patient-oriented composite endpoint was defined as a composite of all-cause mortality, any stroke, MI, or revascularization. The definitions of clinical events followed the recommendations of the Academic Research Consortium and the Forth Universal Definition of MI.<sup>20,21</sup> Only spontaneous MI was included, while index procedure-related type 4a MI was not considered. Bleeding events were defined according to the PLATO (Platelet Inhibition and Patient Outcomes) criteria.<sup>22</sup> All clinical events were adjudicated by an independent clinical event adjudication committee.

Categorical variables were compared using the chi-square or Fisher's exact test, and continuous variables were compared using the independent *t*-test or Wilcoxon's signed-rank test as appropriate. The study outcomes were assessed throughout 3 years since enrolment. The survival curves were constructed for time-to-event variables using Kaplan–Meier estimates and were compared using the log-rank test.

Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional-hazards models for between-group comparison of clinical outcomes.

All probability values were two-sided, and  $p < .05$  was considered statistically significant. Statistical analyses were performed using R programming, version 3.4.2 (The R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org>).

### 3 | RESULTS

As shown in Figure 1, 98.4%, 96.2%, and 94.1% (350 out of 372) completed clinical follow-up at 1, 2, and 3 years after coronary stent implantation, respectively. The baseline characteristics have been reported previously<sup>18</sup> and are reproduced in Table 1. There were no

significant differences between the two groups. The mean age was 65 years, and male sex accounted for 71.5% of the study population. The proportion of hypertension, diabetes, and current smoking was 65.5%, 26.1%, and 27.4%, respectively. Approximately half of the study population (47%) was clinically diagnosed with acute coronary syndrome. Dual antiplatelet therapy was maintained in 61.7%, 36.9%, and 27.5% at 1, 2, and 3 years, respectively (Table 2).

TLF occurred in 4.7% and 7.8% at 3 years in the O-SES and R-ZES groups, respectively (log-rank  $p = .227$ ) (Figure 2a). The occurrence of patient-oriented composite endpoint did not differ between the two groups (15.6% and 11.3%; log-rank  $p = .313$ ) (Figure 2b). Table 3 summarizes the cumulative event rates at 1, 2, and 3 years. No significant differences were observed between the two groups in terms of death, MI, repeat revascularization, stroke, and bleeding.

No cases of stent thrombosis were reported in the O-SES group, while two patients experienced stent thrombosis in the R-ZES arm (log-rank  $p = .040$ ) (Figure 2c), 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 7 days. Regarding the other case, the index lesion was chronic total occlusion of the right coronary artery, and long stenting was performed. Dual antiplatelet therapy was switched to aspirin alone at 1 year, and stent thrombosis developed at 736 days. Subgroup analysis showed no significant effect modification across subgroups (Figure 3).

### 4 | DISCUSSION

In this study, we report 3-year clinical outcomes of patients who were randomly assigned to O-SES and R-ZES. The risk of adverse events

**TABLE 3** Clinical outcomes up to 3 years

	Orsiro Hybrid SES	Resolute Integrity ZES	OR (95% CI)	p values
<b>Events at 1 year</b>				
All-cause death	4 (1.6)	3 (2.5)	0.63 (0.11–4.37)	.686
Cardiovascular death	2 (0.8)	2 (1.7)	0.47 (0.03–6.59)	.597
Myocardial infarction	0 (0.0)	2 (1.7)	–	.103
Repeat revascularization	19 (7.7)	7 (6.0)	1.31 (0.51–3.81)	.666
Target lesion revascularization	6 (2.4)	4 (3.4)	0.71 (0.16–3.47)	.733
Target vessel revascularization	9 (3.6)	5 (4.2)	0.85 (0.25–3.31)	.776
Stroke	1 (0.4)	0 (0.0)	–	1.000
Bleeding	7 (2.8)	5 (4.2)	0.66 (0.17–2.68)	.534
Major, life-threatening	0 (0.0)	1 (0.9)	–	.320
Major, others	1 (0.4)	1 (0.9)	0.47 (0.01–37.5)	.542
Minor	6 (2.5)	3 (2.6)	0.94 (0.20–5.92)	1.000
Cardiac death or myocardial infarction	2 (0.8)	3 (2.6)	0.31 (0.03–2.77)	.334
TLF (cardiac death, MI, TLR)	8 (3.2)	6 (5.0)	0.63 (0.19–2.25)	.395
TVF (cardiac death, MI, TVR)	11 (4.4)	8 (6.7)	0.64 (0.23–1.90)	.450
POCE (death, MI, RR)	23 (9.3)	10 (8.4)	1.11 (0.49–2.72)	.848
<b>Events at 2 years</b>				
All-cause death	5 (2.0)	3 (2.0)	0.78 (0.15–5.14)	.715
Cardiovascular death	2 (0.8)	2 (1.7)	0.47 (0.03–6.56)	.596
Myocardial infarction	0 (0.0)	3 (2.6)	–	.032
Repeat revascularization	22 (9.0)	9 (7.8)	1.17 (0.50–2.99)	.841
Target lesion revascularization	8 (3.3)	6 (5.2)	0.62 (0.18–2.22)	.391
Target vessel revascularization	11 (4.5)	7 (6.0)	0.73 (0.25–2.29)	.605
Stroke	2 (0.8)	0 (0.0)	–	1.000
Bleeding	7 (2.9)	6 (5.2)	0.54 (0.15–1.99)	.363
Major, life threatening	0 (0.0)	1 (0.9)	–	.319
Major, others	1 (0.4)	1 (0.9)	0.47 (0.01–37.3)	.540
Minor	6 (2.5)	4 (3.6)	0.70 (0.16–3.42)	.732
Cardiac death or myocardial infarction	2 (0.8)	4 (3.5)	0.23 (0.02–1.64)	.087
TLF (cardiac death, MI, TLR)	10 (4.1)	8 (6.9)	0.58 (0.20–1.74)	.302
TVF (cardiac death, MI, TVR)	14 (5.8)	10 (8.6)	0.65 (0.26–1.69)	.366
POCE (death, MI, RR)	28 (11.5)	12 (10.3)	1.13 (0.53–2.54)	.858
<b>Events at 3 years</b>				
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)	.336
Myocardial infarction	1 (0.4)	3 (2.6)	0.16 (0.00–2.03)	.106
Repeat revascularization	28 (12.0)	9 (7.8)	1.59 (0.70–3.98)	.271
Target lesion revascularization	9 (3.8)	6 (5.2)	0.73 (0.22–2.55)	.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)	.402
Major, life threatening	1 (0.4)	1 (0.9)	0.49 (0.01–38.4)	.548
Major, others	1 (0.4)	1 (0.9)	0.49 (0.01–37.3)	.551
Minor	6 (2.6)	4 (3.6)	0.72 (0.17–3.56)	.734
Cardiac death or myocardial infarction	3 (1.3)	5 (4.4)	0.29 (0.04–1.50)	.121
TLF (cardiac death, MI, TLR)	11 (4.7)	9 (7.8)	0.59 (0.21–1.66)	.327

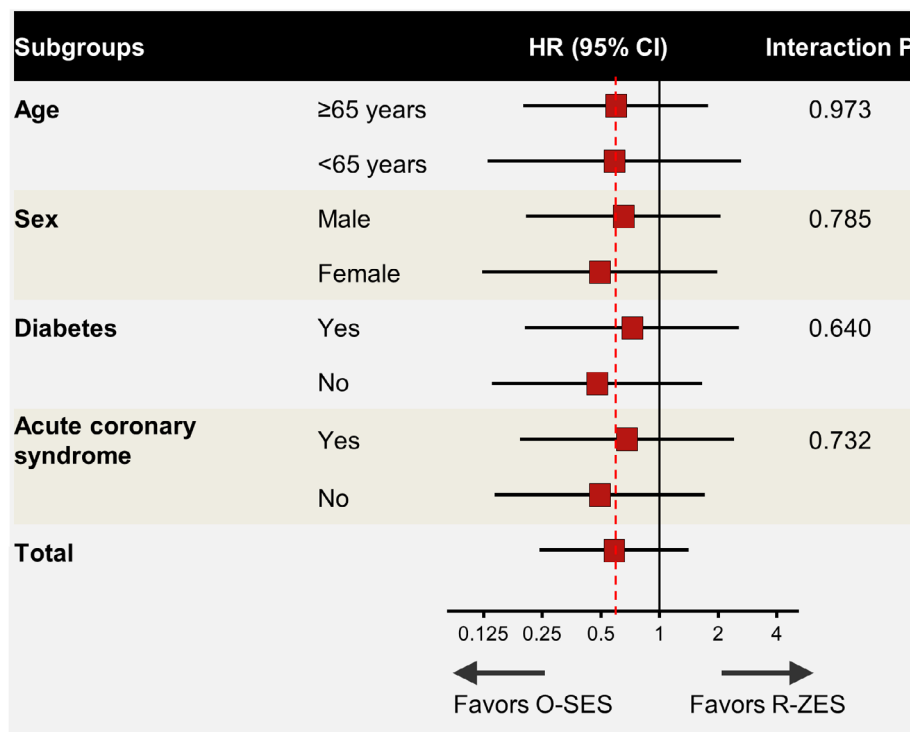
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**TABLE 3** (Continued)

	Orsiro Hybrid SES	Resolute Integrity ZES	OR (95% CI)	<i>p</i> values
TVF (cardiac death, MI, TVR)	18 (7.6)	11 (9.6)	0.79 (0.34–1.93)	.543
POCE (death, MI, RR)	37 (15.6)	13 (11.3)	1.45 (0.72–3.11)	.330

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

### Subgroup analysis



**FIGURE 3** Subgroup analysis for target lesion failure. Stratified analyses for several subgroups of target lesion failure. Horizontal lines represent 95% confidence intervals. HR, hazard ratio; O-SES, Orsiro sirolimus-eluting stent; R-ZES, Resolute Integrity zotarolimus-eluting stent [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

including target lesion failure did not differ significantly between the two stents up to 3 years. Two patients developed very late stent thrombosis, both of them were in the R-ZES arm.

Numerous studies have been performed through the innovation of stent design and platform for better outcomes.<sup>23,24</sup> Biodegradable polymer has been adopted owing to concerns that durable polymer may trigger local inflammation and contribute to the development of late stent thrombosis.<sup>14,25,26</sup> Histopathological analysis in a porcine model of biodegradable polymer sirolimus stent implantation demonstrated favorable vascular healing, reductions in neointimal area, and low inflammatory responses.<sup>27</sup> Thinner struts, however, may be associated with more contribution to the lower risk of stent thrombosis by reducing arterial damage and facilitating reendothelialization.<sup>28–30</sup>

Recent studies have confirmed the efficacy and safety of O-SES, which is coated with biodegradable polymer and has ultra-thin strut. Several randomized controlled trials with O-SES showed comparable clinical outcomes with contemporary durable-polymer DES.<sup>14,16,31,32</sup> The recently published 5-year outcomes of the BIOSCIENCE (Sirolimus-eluting Stents With Biodegradable Polymer Versus an Everolimus-eluting Stents) trial showed that the long-term risk of TLF

was similar for O-SES and durable-polymer everolimus-eluting stent (EES).<sup>33</sup> In the meanwhile, O-SES outperformed durable-polymer EES in a complex patient population undergoing percutaneous coronary intervention in terms of TLF and target-vessel-related MI in the BIOFLOW V (Biotronik Prospective Randomized Multicenter Study to Assess the Safety and Effectiveness of the Orsiro Sirolimus-Eluting Coronary Stent System in the Treatment of Subjects with Up to Three De Novo or Restenotic Coronary Artery Lesions V) trial.<sup>34,35</sup> A recent meta-analysis of 10 randomized trials suggested a marginally lower risk of TLF and a significantly lower risk of MI with O-SES than second-generation thicker strut DES at 1 year.<sup>30</sup>

In this study, the results regarding stent thrombosis need judicious interpretation. Although the difference was statistically significant, there were only two cases of stent thrombosis. However, current studies have shown similar trends in the risk of stent thrombosis of O-SES. The 5-year outcomes of the BIOFLOW-II trial showed a marginally lower risk of stent thrombosis in patients treated with O-SES than in those treated with EES (0.7% vs. 2.8%; *p* = .088). In the BIOFLOW V trial, late/very late rates of both definite and definite/probable stent thrombosis were shown to be significantly lower in the

O-SES cohort.<sup>34,35</sup> The BIOSCIENCE trial also showed a marginal interaction of higher risk of stent thrombosis within 1 year and a lower risk of very late stent thrombosis between 1 and 5 years with O-SES (interaction  $p = .080$ ), although the overall cumulative incidence was similar in both O-SES and durable-polymer EES.<sup>33</sup>

However, caution is required as the BIONYX (Bioresorbable polymer-coated Orsiro versus durable polymer-coated Resolute Onyx stents) trial showed results contradictory.<sup>36</sup> O-SES was compared with the Resolute Onyx stent, which is the next iteration of Resolute Integrity ZES. Resolute Onyx has a very similar design as the previous version, except a metallic platform, which includes a platinum-iridium core intended to improve radiographic visibility. The overall 1-year risk of target vessel failure was similar between the two groups. However, definite or probable stent thrombosis occurred in a significantly lower rate in the Resolute Onyx group than that in the O-SES group (0.1% vs. 0.7%;  $p = .011$ ). Further clinical studies with longer-term follow-up are needed.

## 5 | LIMITATIONS

The trial was originally powered for the primary endpoint of 9-month in-stent restenosis. This is a report of a post hoc analysis; thus, the sample size is not adequately powered for comparison of clinical outcomes. Therefore, the results of this study should be considered as hypothesis generating. Second, there was a small number of events, especially regarding stent thrombosis. Even the lost in follow-up rate reached close to 6%. Third, medical treatment, including antiplatelet regimen was left at the discretion of the treating physicians. Lastly, while Resolute Integrity ZES was tested in this study, a newer version of Resolute Onyx™ (Medtronic) is being used in clinical practice.

## 6 | CONCLUSION

We report favorable outcomes of O-SES and R-ZES throughout 3 years after implantation. The present study confirmed the safety and efficacy profiles of the current generation DES. The rate of TLF did not significantly differ between the two stents.

### CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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