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ORIGINAL ARTICLE
Coronary Intervention

First Report of 3-Year Clinical Outcome After Treatment With Novel Resolute Onyx Stents in the Randomized BIONYX Trial

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Background: At 1 year, the international randomized BIONYX trial (ClinicalTrials.gov:NCT02508714) established non-inferiority regarding safety and efficacy of the novel Resolute Onyx zotarolimus-eluting stent (RO-ZES) vs. the Orsiro sirolimus-eluting stent (O-SES). Although the RO-ZES is used in daily practice, no clinical results have been published beyond 2 years.

Methods and Results: We assessed 3-year clinical outcomes of 2,488 all-comers after percutaneous coronary intervention (PCI) with RO-ZES vs. O-SES. The main endpoint was target vessel failure (TVF), a composite of cardiac death, target vessel myocardial infarction (MI), or target vessel revascularization. Time-to-endpoints was assessed by Kaplan-Meier methods and between-group comparisons by log-rank tests. Follow-up was available in 2,433/2,488 (97.8%) patients. There was no significant between-stent difference in TVF (RO-ZES 112/1,243 [9.2%] vs. O-SES 109/1,245 [8.9%], hazard ratio [HR]: 1.03, 95% confidence interval [CI] 0.79–1.34; $P_{log\text{-}rank}$=0.85) and its individual components. The all-cause mortality was significantly lower after PCI with RO-ZES (3.7% vs.5.4%, HR: 0.67, 95% CI 0.46–0.97; $P_{log\text{-}rank}$=0.034), but cardiac mortality did not differ significantly (1.1% vs.1.9%, HR: 0.56, 95% CI 0.28–1.11; $P_{log\text{-}rank}$=0.09). Definite-or-probable stent thrombosis rates were low for both groups (0.6% vs.1.2%, HR: 0.46, 95% CI 0.19–1.14; $P_{log\text{-}rank}$=0.09).

Conclusions: This first 3-year randomized assessment of the RO-ZES showed a favorable rate of TVF that matched the outcomes of patients treated with O-SES. We observed a lower rate of all-cause death in the RO-ZES group, but long-term clinical follow-up is of interest.

Key Words: All-comer trials; Drug-eluting stents; Percutaneous coronary intervention; Randomized controlled trials

Innovations in drug-eluting stent (DES) design have enabled the use of thinner stent struts while maintaining or improving radial force and radiographic visibility. Such refinements of DES may improve clinical outcomes following percutaneous coronary intervention (PCI). A recently introduced contemporary DES is the Resolute Onyx zotarolimus-eluting stent (RO-ZES), which has thin composite-wire-struts with adequate radiographic visibility due to a dense platinum–iridium core, covered by an outer layer of cobalt–chromium alloy.[1] In the BIONYX randomized trial, we compared the RO-ZES to the ultrathin-strut Orsiro sirolimus-eluting stent (O-SES) in an all-comer population. At 1-year follow-up, the trial established the non-inferiority of RO-ZES vs. O-SES regarding the primary endpoint of safety and efficacy,[1] and at 2 years, the trial showed outcomes that were favorable for both devices.[2]

Both stents are used in routine clinical practice, yet for the RO-ZES no outcome data beyond 2 years have been

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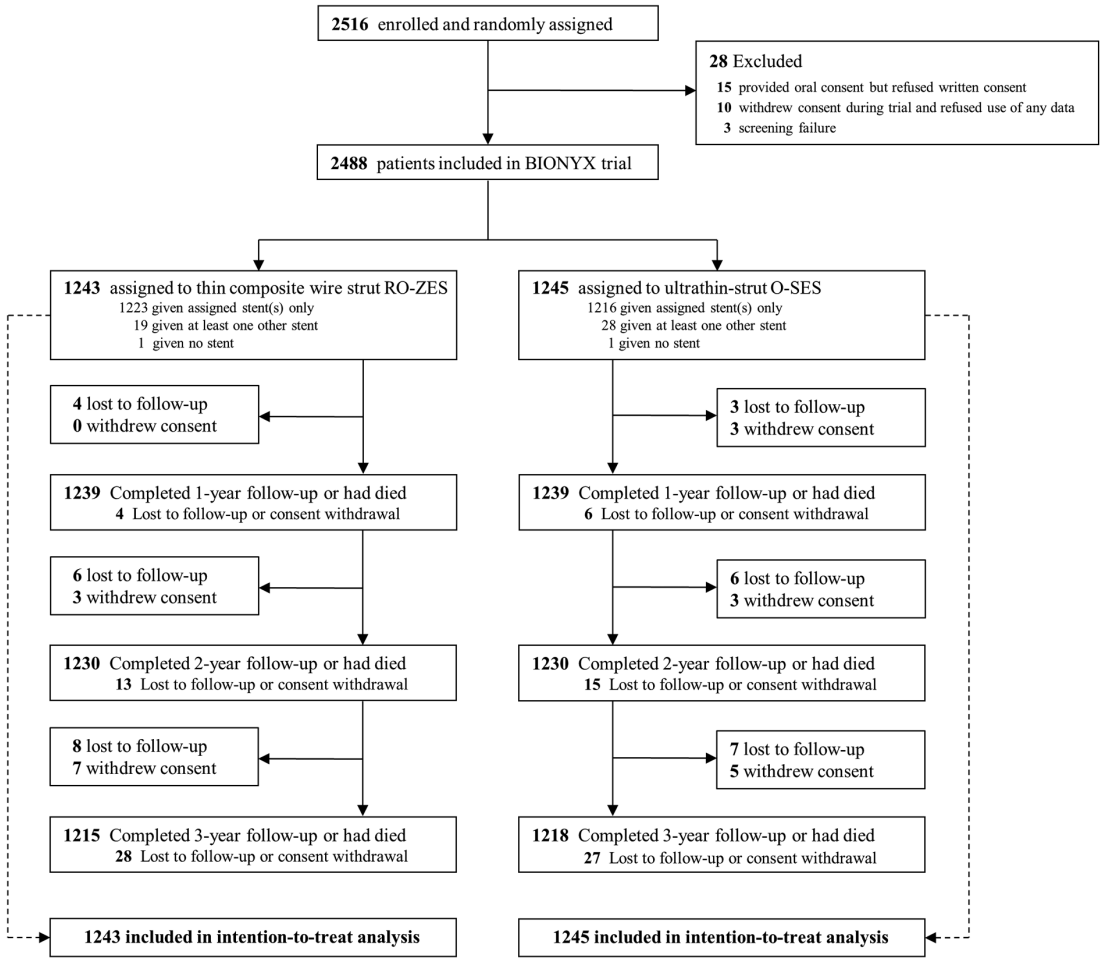


Figure 1. Study flow diagram. O-SES, Orsiro sirolimus-eluting stent; RO-ZES, Resolute Onyx zotarolimus-eluting stent.

published. Among contemporary DES, assessed in randomized clinical trials with broad study populations, the O-SES is the only stent that showed more favorable 3-year outcomes.[3,4] Therefore, it is of particular interest to evaluate whether the RO-ZES matches the clinical results achieved with the O-SES. The current analysis reports for the first time the 3-year results of the BIONYX trial, assessing in all-comers the safety and efficacy of the RO-ZES vs. the O-SES.

Methods

Study Design and Participants

Details of the study design and methods of the BIoresorbable polymer-coated Orsiro versus durable polymer-coated RESOLUTE ONYX stents (BIONYX – ClinicalTrials.gov: NCT02508714) trial have been reported.[1] Patients requiring PCI for any coronary syndrome, any lesion length, type, or size, and any number of lesions or vessels were enrolled between October 2015 and December 2016 at 7 cardiac centers in the Netherlands, Belgium, and Israel. To ensure an all-comers population, there were very few exclusion criteria. All patients provided written informed consent. The trial complied with the Declaration of Helsinki and was approved by the Medical Ethics Committee Twente and institutional review boards of all participating centers. Patients were randomly (1 : 1) assigned to RO-ZES or O-SES, stratified for sex and diabetes. Details of the RO-ZES (Medtronic, Santa Rosa, CA, USA) and O-SES (Biotronik, Bülach, Switzerland) have been reported.[1] Coronary interventions were performed in accordance with standard techniques and international guidelines. Patients and assessors were blinded to allocated stents, but the treating clinicians were not. In general, dual antiplatelet therapy (DAPT) was prescribed for at least 6 months in clinically stable patients and for 12 months after acute coronary syndromes. Follow-up was obtained at patient visits to outpatient clinics, by telephone, or by medical questionnaire. The main 3-year analysis of the BIONYX trial was prespecified, and follow-up will be performed up to 5 years after the index procedure.

Clinical Endpoints

Clinical endpoints were prespecified according to the Academic Research Consortium.[5,6] The main endpoint, target vessel failure (TVF), was a composite of cardiac

Table 1. 3-Year Clinical Outcomes With 1-Year Landmarks

	Resolute Onyx (n=1,243)	Orsiro (n=1,245)	HR (95% CI)	$P_{log\text{-}rank}$
Adverse events up to 3-years' follow-up				
Target vessel failure	112 (9.2)	109 (8.9)	1.03 (0.79–1.34)	0.85
Target lesion failure	88 (7.2)	91 (7.5)	0.97 (0.72–1.30)	0.82
Major adverse cardiac events	130 (10.5)	147 (11.9)	0.88 (0.70–1.12)	0.30
Any death	45 (3.7)	67 (5.4)	0.67 (0.46–0.97)	0.034
Cardiac death	13 (1.1)	23 (1.9)	0.56 (0.28–1.11)	0.09
Vascular death	5 (0.4)	10 (0.8)	0.50 (0.17–1.45)	0.19
Non-cardiovascular death	27 (2.2)	34 (2.8)	0.79 (0.48–1.30)	0.35
Any myocardial infarction	55 (4.5)	54 (4.5)	1.01 (0.70–1.47)	0.95
Target vessel myocardial infarction	39 (3.2)	38 (3.1)	1.02 (0.65–1.60)	0.92
Any revascularization	133 (11.0)	137 (11.4)	0.96 (0.76–1.22)	0.75
Target vessel revascularization	84 (6.9)	75 (6.2)	1.12 (0.82–1.52)	0.49
Target lesion revascularization*	57 (4.7)	55 (4.6)	1.03 (0.71–1.50)	0.86
Definite-or-probable stent thrombosis	7 (0.6)	15 (1.2)	0.46 (0.19–1.14)	0.09
Definite stent thrombosis	7 (0.6)	13 (1.1)	0.53 (0.21–1.34)	0.17
Adverse events between 1- and 3-years' follow-up				
Target vessel failure	57 (4.9)	51 (4.4)	1.12 (0.77–1.63)	0.57
Target lesion failure	40 (3.4)	47 (4.0)	0.85 (0.56–1.30)	0.45
Major adverse cardiac events	69 (5.9)	90 (7.7)	0.76 (0.56–1.05)	0.09
Any death	25 (2.1)	41 (3.4)	0.60 (0.37–0.99)	0.045
Cardiac death	6 (0.5)	10 (0.8)	0.60 (0.22–1.64)	0.31
Vascular death	3 (0.3)	5 (0.4)	0.59 (0.14–2.49)	0.47
Non-cardiovascular death	16 (1.3)	26 (2.2)	0.61 (0.33–1.14)	0.12
Any myocardial infarction	35 (3.0)	34 (2.9)	1.02 (0.64–1.64)	0.93
Target vessel myocardial infarction	21 (1.8)	20 (1.7)	1.04 (0.57–1.93)	0.89
Any revascularization	68 (6.0)	67 (5.9)	1.00 (0.72–1.40)	0.99
Target vessel revascularization	45 (3.9)	37 (3.2)	1.21 (0.78–1.87)	0.39
Target lesion revascularization*	26 (2.2)	31 (2.7)	0.84 (0.50–1.41)	0.50
Definite-or-probable stent thrombosis	6 (0.5)	6 (0.5)	0.99 (0.32–3.06)	0.98
Definite stent thrombosis	6 (0.5)	6 (0.5)	0.99 (0.32–3.06)	0.98

Data are n (%). *One additional patient of the Resolute Onyx group experienced a target lesion revascularization that was adjudicated as not clinically indicated. CI, confidence interval; HR, hazard ratio.

death, target vessel-related myocardial infarction (MI), or target vessel revascularization. The secondary composite endpoint, target lesion failure (TLF), consisted of cardiac death, target vessel-related MI, or target lesion revascularization. Major adverse cardiac events consisted of all-cause death, any MI, or clinically indicated target lesion revascularization. Other secondary endpoints include all-cause death, the individual components of TVF, and stent thrombosis (ST). The trial was monitored (Diagram, Zwolle, the Netherlands), and clinical events were adjudicated by an independent clinical event committee (University of Amsterdam, The Netherlands). Quantitative coronary angiographic measurements were performed by analysts at an angiographic core laboratory (QAngio XA version 7.3, Medis, Leiden, the Netherlands).

Statistical Analysis

Time-to-endpoints was assessed by Kaplan-Meier methods, and the log-rank test was applied for between-group comparisons. Hazard ratios (HR) with 2-sided confidence intervals (CI) were computed by Cox proportional hazards analysis. Landmark analyses were performed using the 1-year landmark. A two-sided P value <0.05 was considered significant, and statistical analyses were done with SPSS 24.0 (IBM Corp, Armonk, NY, USA).

Results

The 3-year follow-up data were available for 2,433/2,488 (97.8%) patients (34 lost to follow-up; 21 withdrew consent). The study flow diagram is shown in **Figure 1**. Baseline patient, lesion, and procedural characteristics are detailed in the **Supplementary Table**. Patients were on average 64.0±11.0 years old, 23.9% of patients were female, and 20.5% had diabetes. One-third of all patients were current smokers (30.6%), and approximately half of them had hypertension (51.5%). Patients presented with acute coronary syndrome in 70.9% of cases.

At 3-year follow-up, the main endpoint TVF did not differ significantly between stent arms: RO-ZES 112/1,243 (9.2%) vs. O-SES 109/1,245 (8.9%) (HR: 1.03, 95% CI 0.79–1.34; $P_{log\text{-}rank}$=0.85; **Table 1**). Furthermore, there were no significant between-stent differences in the individual components of TVF (**Figure 2**). Definite-or-probable ST rates were low for both groups and showed no between-group difference (0.6% vs. 1.2%, HR: 0.46, 95% CI 0.19–1.14; $P_{log\text{-}rank}$=0.09). The all-cause mortality rate was significantly lower in RO-ZES-treated patients (45/1,243

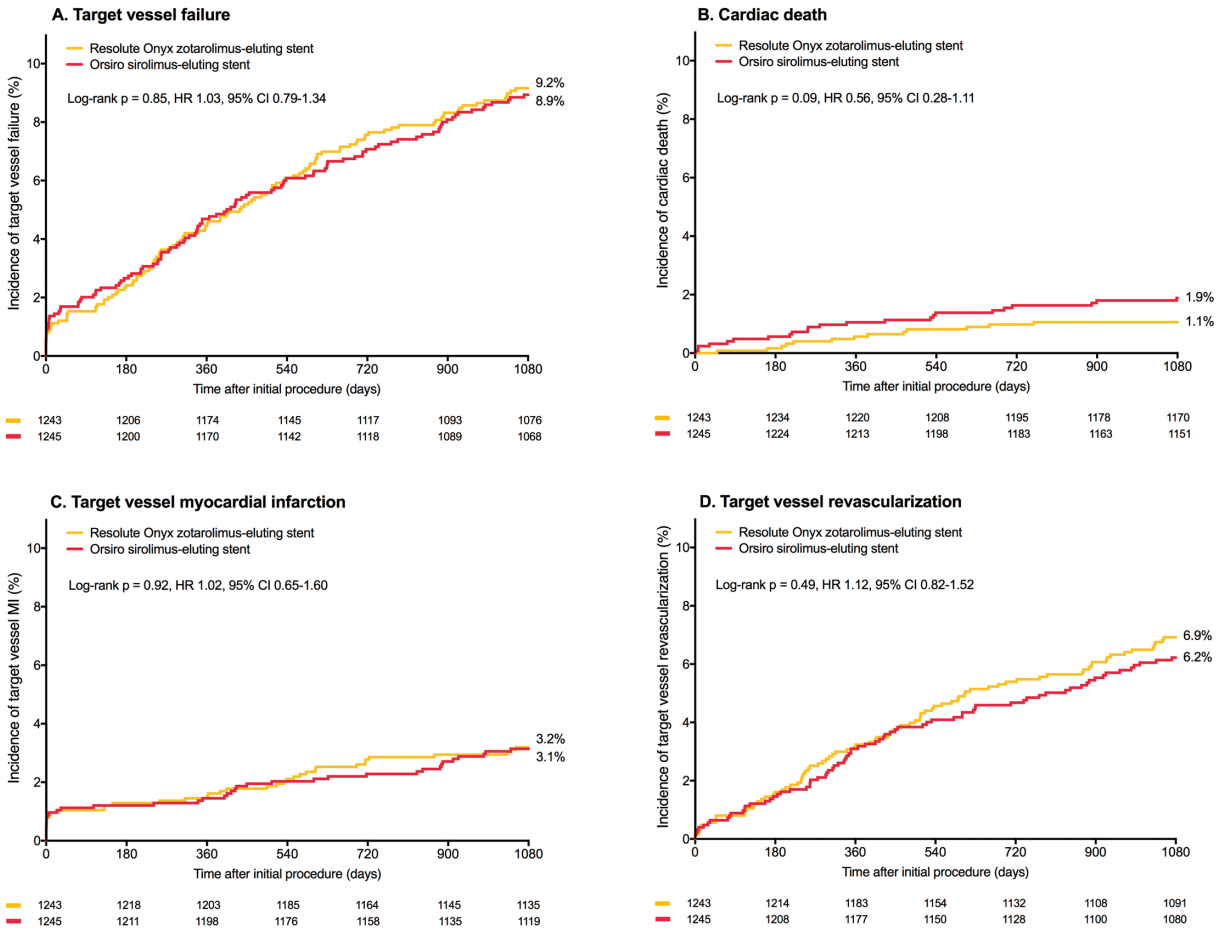


Figure 2. Kaplan-Meier event curves of target vessel failure and its individual components at 3-year follow-up. (**A**) Target vessel failure, (**B**) cardiac death, (**C**) target vessel myocardial infarction, (**D**) target vessel revascularization. CI, confidence interval; HR, hazard ratio.

[3.7%] vs. 67/1,245 [5.4%], HR: 0.67, 95% CI 0.46–0.97; $P_{log\text{-}rank}$=0.034). This was not driven by a specific cause of death: cardiac (1.1% vs. 1.9%), vascular (0.4% vs. 0.8%), and non-cardiovascular death rates (2.2% vs. 2.8%) tended to be slightly and non-significantly lower in the RO-ZES group. All findings were consistent after adjustment for stratification factors. Event rates of the main composite endpoint were consistent across subgroups (**Table 2**) and there was no ethnicity-based difference. The rate of DAPT at 3 years was 9.7% in RO-ZES and 11.0% in O-SES (P=0.32; **Table 3**). There was also no significant difference in the rate of direct oral anticoagulant (8.0% vs. 8.7%; P=0.58) or vitamin K antagonist use (6.7% vs. 5.8%; P=0.35).

Table 1 shows the landmark analyses. The difference in 3-year all-cause death in favor of the RO-ZES was mainly based on events during the 2nd and 3rd years of follow-up (HR: 0.60, 95% CI 0.37–0.99; $P_{log\text{-}rank}$=0.045). In addition, the landmark analysis showed no significant between-stent difference in TVF (HR: 1.12, 95% CI 0.77–1.63; $P_{log\text{-}rank}$= 0.57), or its individual components. The rates of very late ST were equal (0.5% vs. 0.5%, HR: 0.99, 95% CI 0.32–3.06; $P_{log\text{-}rank}$=0.98).

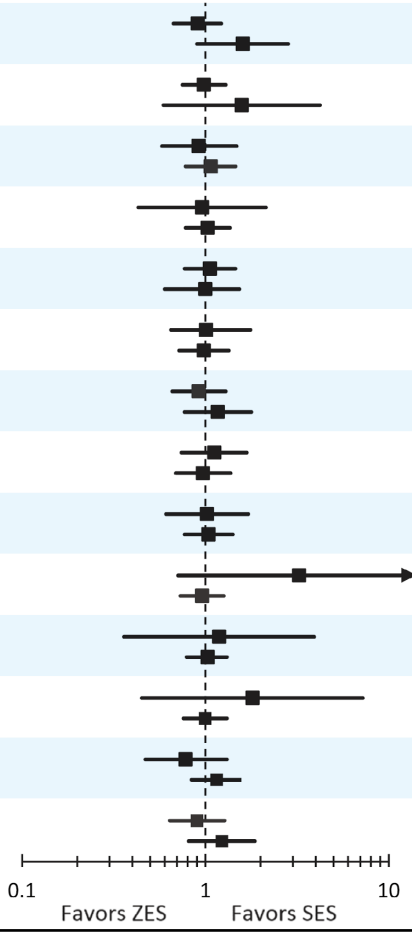
Discussion

This large-scale international randomized trial is the first to report 3-year clinical outcomes of patients treated with the RO-ZES, and demonstrated maintenance of the safety and efficacy of the RO-ZES vs. the O-SES at 3-year follow-up. Furthermore, no between-stent difference was found for the individual endpoints of TVF. Yet, the rate of all-cause mortality in the RO-ZES group was lower as compared with the O-SES group – a difference that was mainly based on deaths that occurred during the 2nd and 3rd years of follow-up. For the other endpoints there was no difference in the occurrence of events between 1 and 3 years.

Two other randomized studies that assessed the O-SES have reported conflicting results.[3,7] The BIOSCIENCE trial found a higher 5-year rate of all-cause mortality in patients treated with O-SES as compared with patients treated with durable polymer everolimus-eluting stents (EES: 14.1% vs. 10.3%), which was mainly driven by cancer-related deaths.[7] We also found a higher mortality rate for O-SES in the current study, but we did not observe a specific cause of death as the driver of that difference. Another trial that reported 3-year follow-up of the O-SES is the BIOLFOW

Table 2. Subgroup Analyses for the 3-Year Rates of Target Vessel Failure

	RO-ZES (n=1,243)	O-SES (n=1,245)	Forest plot	HR (95% CI)	P value	P interaction
Men	82/946 (8.7)	90/948 (9.5)		0.91 (0.67–1.22)	0.53	0.09
Women	30/297 (10.1)	19/297 (6.4)		1.60 (0.90–2.83)	0.10	
European	100/1,176 (8.5)	103/1,194 (8.6)		0.98 (0.75–1.29)	0.92	0.37
Other ethnicity	12/67 (17.9)	6/51 (11.8)		1.58 (0.59–4.22)	0.36	
Diabetes	34/260 (13.1)	35/250 (14.0)		0.92 (0.58–1.48)	0.76	0.62
No diabetes	78/983 (7.9)	74/995 (7.4)		1.07 (0.78–1.46)	0.68	
Renal insufficiency	12/83 (14.5)	12/83 (14.5)		0.96 (0.43–2.14)	>0.99	0.86
No renal insufficiency	100/1,160 (8.6)	97/1,162 (8.3)		1.03 (0.78–1.36)	0.81	
Acute coronary syndrome	77/880 (8.8)	73/885 (8.2)		1.06 (0.77–1.46)	0.71	0.74
Stable angina/silent ischemia	35/363 (9.6)	36/360 (10.0)		1.00 (0.60–1.53)	0.87	
Multivessel treatment	35/236 (14.8)	28/205 (13.7)		1.01 (0.65–1.76)	0.73	0.77
Single-vessel treatment	77/1,007 (7.6)	81/1,040 (7.8)		0.98 (0.72–1.34)	0.90	
Small vessel <2.75 mm	67/675 (9.9)	67/626 (10.7)		0.92 (0.66–1.29)	0.65	0.38
No small vessel	45/568 (7.9)	42/619 (6.8)		1.17 (0.77–1.78)	0.45	
Bifurcation	48/485 (9.9)	44/496 (8.9)		1.12 (0.74–1.68)	0.58	0.60
No bifurcation	64/758 (8.4)	65/749 (8.7)		0.97 (0.69–1.37)	0.87	
Lesion length >27 mm	27/245 (11.0)	30/278 (10.8)		1.02 (0.61–1.71)	0.93	0.95
Lesion length ≤27 mm	85/998 (8.5)	79/967 (8.2)		1.04 (0.77–1.41)	0.78	
In-stent restenosis	10/44 (22.7)	2/27 (7.4)		3.25 (0.71–14.83)	0.09	0.12
No in-stent restenosis	102/1,199 (8.5)	107/1,218 (8.8)		0.96 (0.73–1.26)	0.81	
Bypass graft	5/17 (29.4)	6/23 (26.1)		1.19 (0.36–3.92)	0.82	0.81
No bypass graft	107/1,226 (8.7)	103/1,222 (8.4)		1.03 (0.79–1.35)	0.79	
Left main	6/25 (24.0)	3/22 (13.6)		1.81 (0.45–7.22)	0.37	0.41
No left main	106/1,218 (8.7)	106/1,223 (8.7)		1.00 (0.76–1.31)	0.98	
Age ≥75 years	25/224 (11.2)	35/251 (13.9)		0.78 (0.47–1.31)	0.36	0.21
Age <75 years	87/1,019 (8.5)	74/994 (7.4)		1.15 (0.84–1.57)	0.37	
Only stents ≤3.00 mm	62/685 (9.1)	67/674 (9.9)		0.90 (0.64–1.27)	0.58	0.26
Not only stents ≤3.00 mm	49/557 (8.8)	41/570 (7.2)		1.23 (0.81–1.86)	0.32	



Data are n/n (%). Ethnicity was self-reported. European ethnicity included Israeli Jewish ethnicity. Other ethnicities included North African, African, Surinamese, Caribbean, Asian, Israeli Arab, and other non-Western ethnicities. CI, confidence interval; HR, hazard ratio; O-SES, Orsiro sirolimus-eluting stent; RO-ZES, Resolute Onyx zotarolimus-eluting stent.

Table 3. Use of Antiplatelet and Oral Anticoagulant Therapy at 3-Year Follow-up

	Resolute Onyx (n=1,171/1,243*)	Orsiro (n=1,154/1,245*)	P value
Aspirin	957 (81.7)	928 (80.4)	0.42
Dual antiplatelet therapy	114 (9.7)	127 (11.0)	0.32
Clopidogrel	64 (5.5)	80 (6.9)	0.14
Ticagrelor	45 (3.8)	39 (3.4)	0.55
Prasugrel	5 (0.4)	8 (0.7)	0.40
Single P2Y12 inhibitor therapy	43 (3.7)	51 (4.4)	0.36
Clopidogrel	32 (2.7)	29 (2.5)	0.74
Ticagrelor	10 (0.9)	20 (1.3)	0.06
Prasugrel	1 (0.1)	2 (0.2)	0.56
Direct oral anticoagulant	94 (8.0)	100 (8.7)	0.58
Vitamin K antagonist	79 (6.7)	67 (5.8)	0.35

Values are n (%). *Data available in 2,325/2,488 (93.4%) patients.

V trial,[3] which showed favorable 3-year outcomes of O-SES vs. EES for target lesion revascularization and target vessel MI, but found no difference in all-cause mortality. In that trial,[3] the all-cause mortality rate of O-SES (3.1%) was lower than in our study (5.4%), possibly due to the somewhat more complex patient population (i.e., less exclusion criteria) in BIONYX. All things considered, we feel that most likely the lower rate of all-cause mortality for RO-ZES in our study was a play of chance, but long-term follow-up will be of interest. In BIOFLOW V, the rate of target lesion revascularization for O-SES (3.2%) was numerically lower than in our study (4.6%), yet the rate of target vessel MI was numerically higher (5.0%, and 4.6% in BIONYX). This may be due to the inclusion of patients with ST-elevation MI (STEMI) in BIONYX as opposed to BIOFLOW V, as the ongoing ischemia in the setting of an acute MI generally prevents detection of a potential periprocedural MI. Nevertheless, the 3-year adverse event rates of O-SES in that trial are mostly in line with the results of the current analysis.

The randomized BIOSTEMI trial has shown superiority in TLF of O-SES over durable polymer EES in 1,300 patients who presented with STEMI,[8] combined with historical prior information of the BIOSCIENCE STEMI-subgroup[9] in a Bayesian approach. However, analyzing both STEMI subgroups separately showed a numerically lower rate of target vessel MI and cardiac death for patients enrolled in the BIOSCIENCE trial, and a numerically lower rate of target lesion revascularization was seen only for patients enrolled in the BIOSTEMI trial. Thus, the driver of the significantly lower rate of TLF differed between these 2 groups, raising the question of the mechanism by which treatment with the O-SES results in more favorable outcomes in STEMI patients.[10] Nevertheless, in light of these results and the results of the BIOFLOW V trial,[3] the O-SES has certainly shown favorable outcomes as compared with the durable polymer EES. In our present study there was no between-stent difference in the main outcome for patients who presented with an acute coronary syndrome (**Table 2**), and a previous subgroup analysis of patients with an acute MI at 2-year follow-up also showed no between-stent difference.[11] Hence, in our study the RO-ZES matched the results achieved by the so far 'best in class' O-SES. This may be related to refinements of specific stent features, such as the increased visibility of the RO-ZES due to its platinum–iridium core, the wide range of available stent diameters preventing over- or under-sizing, or its swaged-shaped stent design that might facilitate endothelialization of the struts. However, based on our trial data it is impossible to pinpoint which of these features finally results in the favorable clinical outcomes.

Several meta-analyses have compared ultrathin-strut DES, such as the O-SES, to thicker strut (durable polymer-coated) 2nd-generation DES.[12–17] In 4 meta-analyses, the ultrathin-strut DES showed a lower risk of MI,[12–15] and 2 analyses also showed a lower risk of ST.[12,13] It is as yet unknown whether these more favorable outcomes of ultrathin-strut (<70 μm or <80 μm) DES can be met by the 'new-generation' thin strut (81 μm) RO-ZES.

The ST rates in our trial were very low in both stent arms, yet particularly low in the RO-ZES arm with 7 cases in 1,243 patients. Notably, the 3-year rate of DAPT did not differ between groups (RO-ZES 9.7% vs. O-SES 11.0%) and was comparable or lower than in various other randomized trials.[3,18–22] In previous research, a preclinical study showed superior thromboresistance and equivalent endothelial healing of the RO-ZES as compared with a polymer-free biolimus-eluting stent (BioFreedom, Biosensors, Newport Beach, CA, USA) in porcine arteriovenous shunts and a flow-loop model.[23] The low ST rate found in our trial may be related to these qualities in preclinical assessment and may make the RO-ZES compatible with short-term DAPT. This has been the focus of the large-sized randomized Onyx One trial.[24] That study demonstrated in 1,996 high bleeding risk (HBR) patients who were treated with 1 month of DAPT, a non-inferior safety and efficacy of the RO-ZES vs. the polymer-free BioFreedom stent.[24] In addition, it showed no between-stent difference in the risk of ST. Another analysis that included 1,506 HBR patients, who did not have any major adverse events during the first month, confirmed the safety and efficacy of the RO-ZES following 1 month of DAPT by meeting the prespecified performance goal.[25] In the O-SES group of our study, the 3-year rate of definite-or-probable ST (1.2%) was in line with that of other all-comer trials.[18,26] Looking at all the available evidence, the RO-ZES appears to be associated with a particularly low risk of ST. However, we must note that there have been no studies that were adequately powered to properly investigate this infrequent adverse event, and the underlying mechanism of the low ST risk remains

largely unclear.

Only a few trials have assessed the RO-ZES,[1,24,27,28] and so far, there has not been a report of 3-year clinical results; thus, we cannot compare our results with other studies. Preclinical studies evaluated the RO-ZES and the O-SES and directly compared some of the stent features. As compared with the O-SES, the RO-ZES is somewhat more flexible and more radiopaque, which may be favorable in certain challenging lesions,[29,30] but the O-SES shows less elastic recoil,[29] which is a stent feature that is also considered advantageous. Furthermore, a study that evaluated the overexpansion of 4.0-mm stents found a 145% increase in cell opening diameter in O-SES and in RO-ZES a 104% increase.[31] Although a greater increase in cell opening diameter facilitates access to the side branches, it may also promote prolapse of underlying plaque and may reduce the antiproliferative properties of the DES.[31] Thus far, in our all-comer patient population, none of these DES features have yet translated into a significant improvement in clinical outcomes for either stent, but dedicated studies in specific subgroups may reveal further insights.

Study Limitations

This study was not adequately powered to assess secondary endpoints, and in particular, infrequent adverse events such as ST. Therefore, findings of the secondary endpoints and the landmark analysis should be considered as hypothesis generating. In addition, 3-year follow-up information was missing for 55/2,488 (2.3%) patients, but there was no difference between stent arms.

Conclusions

This first 3-year randomized assessment of the RO-ZES showed a favorable rate of TVF that matched the outcome of patients treated with the O-SES. We observed a lower rate of all-cause death in the Resolute Onyx group, but long-term follow-up of mortality and other clinical endpoints will be of interest.

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IRB Information

Medical Ethical Committee Twente, reference no. P15-19.

Disclosures

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Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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