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CORONARY

Thin Composite-Wire-Strut Zotarolimus-Eluting Stents Versus Ultrathin-Strut Sirolimus-Eluting Stents in BIONYX at 2 Years

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ABSTRACT

OBJECTIVES The aim of this study was to assess 2-year safety and efficacy of the current-generation thin composite-wire-strut durable-polymer Resolute Onyx zotarolimus-eluting stent (ZES), compared with the ultrathin-strut biodegradable-polymer Orsiro sirolimus-eluting stent (SES) in all-comers and a pre-specified small-vessel subgroup analysis.

BACKGROUND The Resolute Onyx ZES is widely used in clinical practice, but no follow-up data beyond 1 year have been published. The randomized BIONYX (Bioresorbable Polymer-Coated Orsiro Versus Durable Polymer-Coated Resolute Onyx Stents) trial (NCT02508714) established the noninferiority of ZES versus SES regarding target vessel failure (TVF) rates.

METHODS A total of 2,488 all-comer patients were treated at 7 coronary intervention centers in Belgium, Israel, and the Netherlands. The main endpoint, TVF, was a composite of safety (cardiac death or target vessel–related myocardial infarction) and efficacy (clinically indicated target vessel revascularization). Two-year follow-up data were analyzed using Kaplan-Meier methods.

RESULTS Two-year follow-up data were available for 2,460 of 2,488 patients (98.9%). TVF occurred in 93 of 1,243 patients (7.6%) assigned to ZES versus 87 of 1,245 patients (7.1%) assigned to SES (log-rank $p = 0.66$). There was no significant between-stent difference in individual components of this endpoint. The incidence of definite-or-probable stent thrombosis was low for both treatment arms (0.4% vs. 1.1%; log-rank $p = 0.057$). In patients stented in small vessels, there was no between-stent difference (TVF 8.2% vs. 8.7% [log-rank $p = 0.75$], target lesion revascularization 4.0% vs. 4.4% [log-rank $p = 0.77$]).

CONCLUSIONS At 2-year follow-up, the novel thin composite-wire-strut durable-polymer Resolute Onyx ZES showed in all-comers similar safety and efficacy compared with the ultrathin cobalt-chromium-strut biodegradable-polymer Orsiro SES. The analysis of patients who were treated in small vessels also suggested no advantage for either stent. (J Am Coll Cardiol Intv 2020;13:1100–9) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Zotarolimus-eluting coronary stents showed favorable clinical outcomes in several randomized clinical trials in all-comers (1–4). Nevertheless, a recent study in patients with small target vessels suggested an increased repeated target lesion revascularization risk with the previous-generation thin-strut durable-polymer zotarolimus-eluting device compared with an ultrathin-strut biodegradable-polymer sirolimus-eluting stent (SES; Orsiro, Biotronik, Bülach, Switzerland) (5). The newest generation zotarolimus-eluting stent (ZES; Resolute Onyx, Medtronic, Santa Rosa, California) has a refined design and is based on a thin metallic stent platform, made from a strut with an outer layer of cobalt-chromium alloy and a dense platinum-iridium core wire (6). This "composite-wire strut" has enhanced radiographic visibility and allows reduced strut thickness, while radial and longitudinal strength is maintained. These novel features of the current Resolute Onyx ZES, together with the wider range of available stent diameters, may have the potential to reduce adverse clinical events after percutaneous coronary intervention, which may be most pronounced in small target vessels.

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The primary outcome of the randomized BIONYX (Bioresorbable Polymer-Coated Orsiro Versus Durable Polymer-Coated Resolute Onyx Stents) trial (6) showed noninferiority of the Resolute Onyx ZES versus the Orsiro SES regarding target vessel failure (TVF) at 12 months in all-comers. No data on longer term follow-up have been published, although the Resolute Onyx ZES is widely used in clinical practice. The present analysis is the first to report 2-year clinical outcomes of this trial and the first to report 2-year clinical outcomes of the Resolute Onyx ZES in all-comers. In addition, we performed a pre-specified subgroup analysis in patients with small target vessels.

METHODS

STUDY DESIGN AND PATIENT POPULATION. BIONYX is an international, prospective, investigator-initiated, patient- and assessor-blinded, randomized noninferiority trial (NCT02508714), conducted at 7 specialized cardiac centers in Belgium, Israel, and the Netherlands. Details on trial design and 1-year clinical outcomes have been reported (6). In brief, all-comer patients with any coronary syndrome, de novo or restenotic target lesions, any lesion length, any reference vessel size, and any number of lesions or vessels to be treated were enrolled from October 2015 to December 2016. Only very few exclusion criteria were applied (Supplemental Appendix). All patients provided written informed consent. The trial complied with the Declaration of Helsinki, and was approved by the Medical Ethics Committee Twente and the Institutional Review Boards of all participating centers. Patients were randomly assigned (1:1) to ZES or SES, which were available in diameters ranging for ZES from 2.0 to 5.0 mm and for SES from 2.25 to 4.0 mm (further details in Supplemental Figure 1).

PROCEDURES AND FOLLOW-UP. Coronary interventions were performed according to standard techniques, and concomitant medical treatment was prescribed according to medical guidelines. The stent platform of the Resolute Onyx ZES is made from a swaged shape composite wire of platinum-iridium, surrounded by a cobalt-chromium alloy. The uncoated struts of stents with diameters ≤4.0 mm (81 μm) are 10 μm thinner than the struts of its predecessor and circumferentially covered with a 5.6-μm-thick polymer blend that elutes zotarolimus for 6 months. ZES with diameters ≥4.5 mm have a strut thickness of 91 μm, matching the strut thickness of its predecessor. The stent platform of the Orsiro SES is made from a

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
HR = hazard ratio
MI = myocardial infarction
SES = sirolimus-eluting stent(s)
TVF = target vessel failure
ZES = zotarolimus-eluting stent(s)

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

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TABLE 1 2-Year Clinical Outcome in All Patients (N = 2,488)

	ZES (n = 1,243)	SES (n = 1,245)	Hazard Ratio (95% CI)	Log-Rank p Value
Any death	35 (2.8)	47 (3.8)	0.74 (0.48–1.15)	0.18
Cardiac death	12 (1.0)	20 (1.6)	0.60 (0.29–1.22)	0.15
Any MI	40 (3.3)	39 (3.2)	1.02 (0.66–1.59)	0.93
Target vessel MI	34 (2.8)	28 (2.3)	1.21 (0.73–2.00)	0.45
Any revascularization	106 (8.7)	105 (8.6)	1.00 (0.77–1.31)	0.99
Target vessel revascularization	66 (5.4)	57 (4.7)	1.16 (0.81–1.65)	0.43
Target lesion revascularization*	48 (3.9)	41 (3.4)	1.17 (0.77–1.78)	0.46
Target vessel failure†	93 (7.6)	87 (7.1)	1.07 (0.80–1.43)	0.66
Target lesion failure	76 (6.2)	71 (5.8)	1.07 (0.78–1.48)	0.68
Major adverse cardiac events	102 (8.3)	107 (8.6)	0.95 (0.73–1.25)	0.73
Patient-oriented composite endpoint	152 (12.3)	161 (13.0)	0.94 (0.75–1.17)	0.56
Definite or probable stent thrombosis	5 (0.4)	13 (1.1)	0.38 (0.14–1.07)	0.057
Definite stent thrombosis	5 (0.4)	11 (0.9)	0.45 (0.16–1.30)	0.13

2-year follow-up information was obtained from 2,460 of all 2,488 study patients (98.9%) and analyzed using the Kaplan-Meier method, so the percentages may differ slightly from straightforward "nominator divided by denominator" calculations. *1 additional patient in the ZES group experienced a target lesion revascularization that was adjudicated as not being clinically indicated. †Main composite endpoint including cardiac death, target vessel–related MI, and clinically indicated target vessel revascularization.

CI = confidence interval; MI = myocardial infarction; SES = sirolimus-eluting stent; ZES = zotarolimus-eluting stent.

cobalt-chromium alloy with a strut thickness of 60 μm (in stents ≤3.0 mm) or 80 μm (in stents ≥3.5 mm), covered in an asymmetrical biodegradable polymer that elutes sirolimus within 4 months (6).

Clinical follow-up was obtained at visits to outpatient clinics or by telephone questionnaire. Clinical endpoints were pre-specified according to the Academic Research Consortium (7,8). The main endpoint was TVF, a composite of cardiac death, target vessel-related myocardial infarction (MI), or clinically indicated target vessel revascularization. Secondary endpoints included the individual components of TVF, target lesion failure, and target lesion revascularization. Stent thrombosis was defined according to Academic Research Consortium definitions (7,8). The Supplemental Appendix provides further details on the definition of clinical endpoints. The trial was monitored (Diagram, Zwolle, the Netherlands), and event adjudication was performed by an independent external clinical event committee, consisting of experienced interventional cardiologists (University of Amsterdam, Amsterdam, the Netherlands), who were blinded to assigned stent type. Angiographic analyses and quantitative coronary angiographic measurements were done by analysts at an angiographic core laboratory according to current standards QAngio XA version 7.3, (Medis, Leiden, the Netherlands). Patients with reference vessel diameters <2.5 mm were included in the small-vessel subgroup analysis; this cutoff value was based on previous clinical research (9).

STATISTICAL ANALYSIS. Analyses were done according to the intention-to-treat principle. Differences in categorical variables between groups were examined using Pearson's chi-square test, and for comparisons of continuous variables Student's *t*-test or the Wilcoxon rank sum test, as appropriate, was used. Time to endpoints was assessed using the Kaplan-Meier method, and the log-rank test was applied for between-group comparisons. Patients were censored (at the moment of dropout) if they were lost to follow-up, withdrew their consent, or died. Hazard ratios (HRs) with 2-sided confidence intervals (CIs) were computed using Cox proportional hazards analysis. Landmark analyses were performed using the 1-year landmark. In a pre-specified subgroup analysis, we assessed clinical outcomes in patients with small coronary target vessels, defined as a reference vessel diameter <2.5 mm. The main endpoint was also assessed in other pre-specified subgroups, and we used a Wald test for interaction between each subgroup and randomized stent. A 2-sided p value < 0.05 was considered to indicate statistical significance. Statistical analyses were done using SPSS version 24.0 (IBM, Armonk, New York).

RESULTS

BASELINE CHARACTERISTICS OF ALL PATIENTS. Of the 2,488 trial participants ranging in age from 30 to 96 years (mean 64.0 ± 11.0 years), 1,894 (76.1%) were men and 594 (23.9%) were women. Of these all-comer patients, 1,765 (70.9%) presented with acute coronary syndromes (Supplemental Table 1).

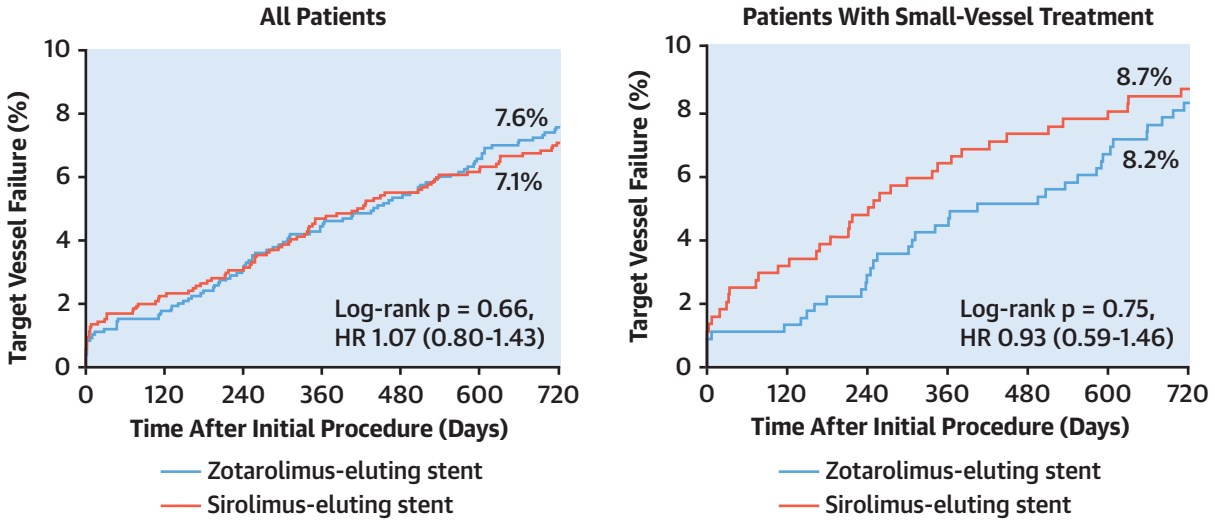
2-YEAR CLINICAL OUTCOMES IN ALL PATIENTS. Follow-up was available in 2,460 of 2,488 patients (98.9%); 19 patients were lost to follow-up and 9 withdrew their consent and were censored at moment of dropout (Supplemental Figure 2). **Table 1** presents 2-year clinical outcomes; event rates are based on Kaplan-Meier estimates. The main endpoint, TVF, occurred in 93 of 1,243 patients (7.6%) assigned to ZES and 87 of 1,245 patients (7.1%) assigned to SES (HR: 1.07, 95% CI: 0.80 to 1.43; p = 0.66) (**Central Illustration**). There were no significant between-stent differences in the incidence of the individual TVF components of cardiac death, target vessel-related MI, and clinically indicated target vessel revascularization (**Figure 1**). In both groups, the use of dual-antiplatelet therapy at 2 years was low (15.2% vs 14.7%) (Supplemental Table 2), as

CENTRAL ILLUSTRATION **2-Year Summary of Thin Composite-Wire-Strut Zotarolimus-Eluting Stents Versus Ultrathin-Strut Sirolimus-Eluting Stents in BIONYX**

2,488 All-Comer Patients Randomized in BIONYX

Resolute Onyx (n = 1,243)		Orsiro (n = 1,245)
Cobalt-chromium, platinum-iridium core wire	Stent material	Cobalt-chromium
81/91 μm*	Strut thickness	60/80 μm†
Zotarolimus, 6 months	Drug, elution time	Sirolimus, 3.3 months
Durable	Polymer coating	Biodegradable

Target Vessel Failure at 2 years



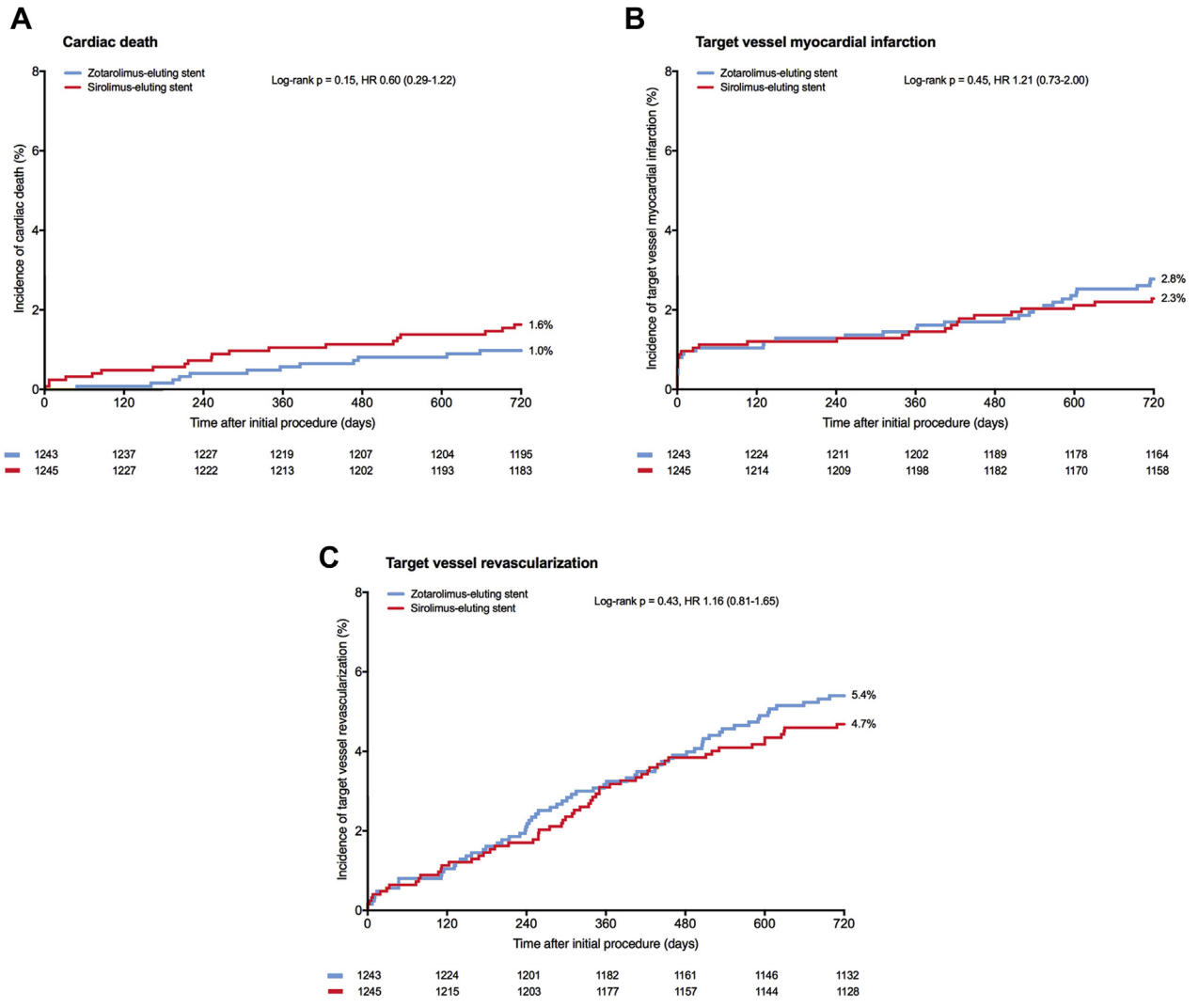
Resolute Onyx vs. Orsiro:
Similar 2-year safety and efficacy in all-comers

Buiten, R.A. et al. J Am Coll Cardiol Intv. 2020;13(9):1100–9.

Target vessel failure was the main composite clinical endpoint, consisting of cardiac death, target vessel myocardial infarction, and clinically indicated target vessel revascularization. *Strut thickness 81 μm for stents ≤4.0 mm and 91 μm for stents ≥4.5 mm. †Strut thickness 60 μm for stents ≤3.0 mm and 80 μm for stents ≥3.5 mm. BIONYX = Bioresorbable Polymer-Coated Orsiro Versus Durable Polymer-Coated Resolute Onyx Stents.

was the incidence of definite or probable stent thrombosis (5 of 1,243 [0.4%] vs. 13 of 1,245 [1.1%]; HR: 0.38; 95% CI: 0.14 to 1.07; p = 0.057) (**Figure 2**, Supplemental Table 3). Landmark analyses between 1 and 2 years revealed no between-stent difference (**Figure 3**). In addition, results for the main endpoint were consistent across various subgroups (Supplemental Figure 3).

FIGURE 1 Kaplan-Meier Cumulative Event Curves for Individual Components of the Main Endpoint, Target Vessel Failure, at 2-Year Follow-Up, in All Patients



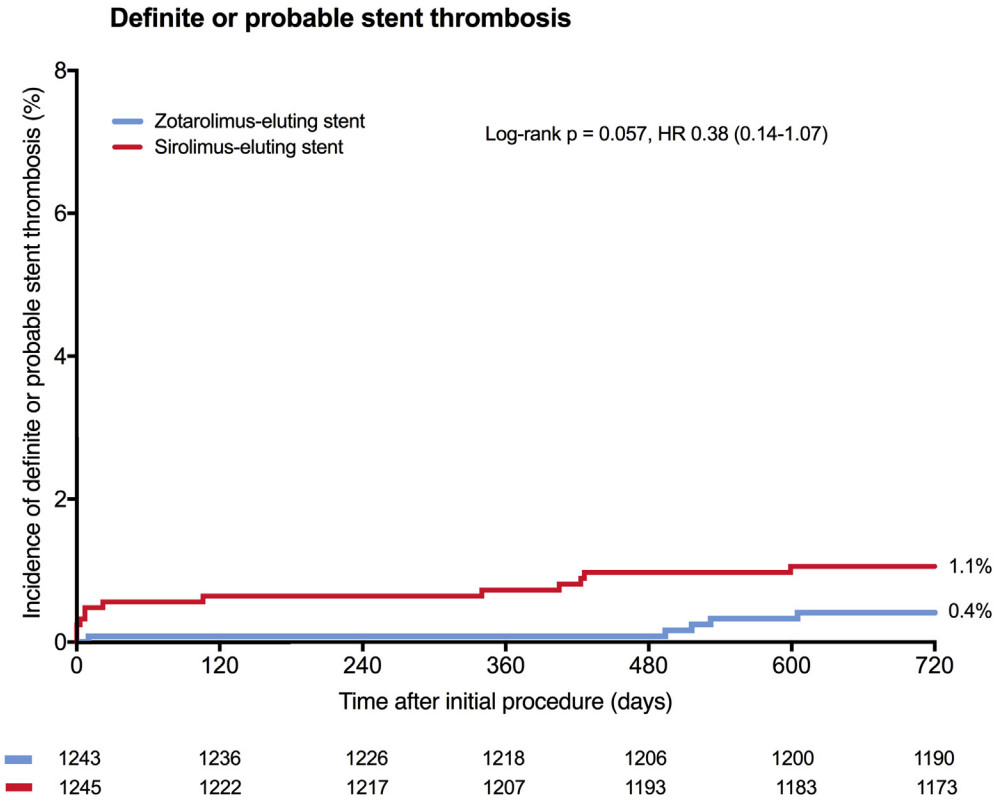
Cardiac death **(A)**, target vessel–related myocardial infarction **(B)**, and clinically indicated target vessel revascularization **(C)**. HR = hazard ratio.

SMALL-VESSEL SUBGROUP. A total of 898 patients (36.1%) were treated in at least 1 small vessel (reference vessel diameter <2.50 mm). Patients assigned to ZES were slightly older and less often smokers but otherwise had comorbidities similar to patients assigned to SES (Supplemental Table 4). There were 21 of 454 ZES patients (4.6%) who were treated with the 2.0-mm ZES, while 6 of 444 patients assigned to SES received 2.0-mm ZES (crossover). Adverse clinical event rates in these patients were similar to rates in the entire study population. Between ZES and SES, there was no significant difference in the incidence of TVF (37 of 454 [8.2%] vs. 38 of 444 [8.7%]; HR: 0.93; 95% CI: 0.59 to 1.46; p = 0.75) (**Central Illustration**) and repeat target lesion revascularizations (18 of 454 [4.0%] vs. 19 of 444 [4.4%]; HR: 0.91; 95% CI: 0.48 to 1.73; p = 0.77) (Supplemental Figure 4). There were no significant between-stent differences in other secondary endpoints or landmark analyses in patients with small-vessel treatment (**Table 2**).

DISCUSSION

MAIN FINDINGS. In this first randomized comparison of the thin composite-wire-strut durable-polymer Resolute Onyx ZES versus the ultrathin-strut biodegradable-polymer Orsiro SES in all-comers, we found low and similar 2-year clinical event rates. There was

FIGURE 2 Incidence of Definite or Probable Stent Thrombosis at 2 Years, in All Patients



HR = hazard ratio.

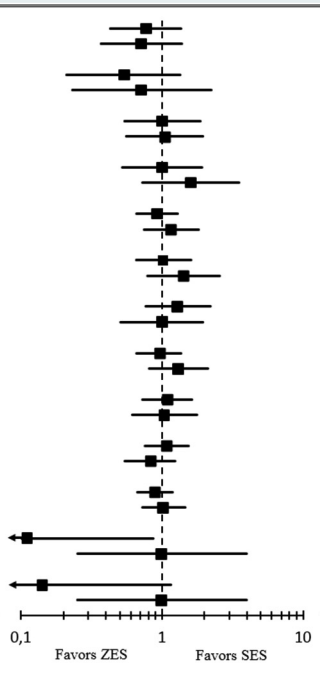
no difference in the incidence of the main clinical endpoint, TVF, and its individual components at 2 years. In addition, although the study was not powered to assess infrequent adverse events such as stent thrombosis, the incidence of stent thrombosis was found to be low in both groups, which may indicate favorable safety characteristics. Stent thrombosis risk was particularly low in patients treated with the Resolute Onyx, which is of interest given the fact that this is the first report on 2-year clinical outcomes with this stent; previous studies reported favorable clinical outcomes for the Resolute Onyx after 8 to 12 months (10–12). Notably, in patients stented in small vessels (<2.5 mm), we observed no between-stent difference in clinical outcomes. The results of the present 2-year analysis of BIONYX are remarkable, given the fact that the Resolute Onyx competes with an ultrathin-strut biodegradable polymer-coated SES that has demonstrated in 2 clinical trials superiority versus the cobalt-chromium fluoropolymer-coated everolimus-eluting Xience stent (Abbott Vascular, Santa Clara, California) (13–15), a device that for many years was considered the "gold standard" for drug-eluting stents.

PREVIOUS STUDIES. The Resolute Onyx ZES has been studied in only a few clinical trials, with BIONYX being the first trial in all-comers (6,11,12,16). A prospective single-arm trial (11) in which 75 patients underwent coronary stenting with the Resolute Onyx showed noninferiority of 8 month angiographic outcomes compared with historical data from the RESOLUTE-US trial. Eight-month target lesion failure and target lesion revascularization rates were higher than in the present study (6.7% and 4.0%, respectively), which might be related to the lack of routine angiographic follow-up in our study.

One-year clinical outcomes of the randomized Onyx ONE noninferiority trial were recently presented (16). This study randomized 1,996 patients at high bleeding risk to the Resolute Onyx ZES or a polymer-free biolimus A9-drug-coated stent (BioFreedom, BioSensors Europe, Morges, Switzerland), and all patients received 1 month of dual-antiplatelet therapy,

FIGURE 3 Forest Plot Showing the Landmark Analysis With the 1-Year Landmark, in All Patients

	ZES n = 1,243	SES n = 1,245	Forest plot	Hazard ratio (95% CI)	P-logrank
Any death 0-1 year	20 (1.6)	26 (2.1)		0.77 (0.43–1.37)	0.37
Any death 1-2 years	15 (1.2)	21 (1.7)		0.71 (0.37-1.38)	0.31
Cardiac death 0-1 year	7 (0.6)	13 (1.1)		0.54 (0.21–1.34)	0.18
Cardiac death 1-2 years	5 (0.4)	7 (0.6)		0.71 (0.23-2.24)	0.56
Any myocardial infarction 0-1 year	20 (1.6)	20 (1.6)		1.00 (0.54–1.86)	0.97
Any myocardial infarction 1-2 years	20 (1.7)	19 (1.6)		1.04 (0.56-1.96)	0.89
Target vessel myocardial infarction 0-1 year	18 (1.5)	18 (1.5)		1.00 (0.52–1.92)	1.00
Target vessel myocardial infarction 1-2 years	16 (1.3)	10 (0.8)		1.59 (0.72-3.51)	0.25
Any revascularization 0-1 year	65 (5.3)	70 (5.7)		0.92 (0.66–1.29)	0.64
Any revascularization 1-2 years	41 (3.6)	35 (3.1)		1.16 (0.74-1.82)	0.52
Target vessel revascularization 0-1 year	39 (3.2)	38 (3.1)		1.02 (0.66–1.60)	0.92
Target vessel revascularization 1-2 years	27 (2.3)	19 (1.6)		1.42 (0.79-2.55)	0.24
Target lesion revascularization 0-1 year	31 (2.5)	24 (2.0)		1.29 (0.76–2.20)	0.35
Target lesion revascularization 1-2 years	17 (1.4)	17 (1.4)		1.00 (0.51-1.96)	1.00
Target vessel failure 0-1 year	**55 (4.5)**	**58 (4.7)**		**0.95 (0.66–1.37)**	**0.77**
Target vessel failure 1-2 years	**38 (3.3)**	**29 (2.5)**		**1.31 (0.81-2.12)**	**0.27**
Target lesion failure 0-1 year	48 (3.9)	44 (3.6)		1.09 (0.72–1.64)	0.68
Target lesion failure 1-2 years	28 (2.4)	27 (2.3)		1.04 (0.61-1.76)	0.89
Major adverse cardiac events 0-1 year	61 (4.9)	57 (4.6)		1.07 (0.75–1.54)	0.71
Major adverse cardiac events 1-2 years	41 (3.5)	50 (4.2)		0.82 (0.54-1.24)	0.34
Patient-oriented composite endpoint 0-1 year	91 (7.3)	102 (8.2)		0.89 (0.67–1.18)	0.41
Patient-oriented composite endpoint 1-2 years	61 (5.3)	59 (5.2)		1.02 (0.72-1.46)	0.90
Definite-or-probable stent thrombosis 0-1 year	1 (0.1)	9 (0.7)		0.11 (0.01–0.87)	0.01
Definite-or-probable stent thrombosis 1-2 years	4 (0.3)	4 (0.3)		0.99 (0.25-3.96)	0.99
Definite stent thrombosis 0-1 year	1 (0.1)	7 (0.6)		0.14 (0.02–1.16)	0.03*
Definite stent thrombosis 1-2 years	4 (0.3)	4 (0.3)		0.99 (0.25-3.96)	0.99



Data were analyzed using the Kaplan-Meier method, so the percentages may differ slightly from straightforward "nominator divided by denominator" calculations. Patients who were censored for each event during the first year were not included in the analyses from 1 to 2 years. *Because the log rank p value is based on Chi-square, it does not correspond with the 95% CI because of the very low event rate in the ZES group (p value based on Wald test: 0.07). CI = confidence interval; SES = sirolimus-eluting stent; ZES = zotarolimus-eluting stent.

followed by 11 months of single-antiplatelet therapy. The 1-year target lesion failure rates of both stent groups were similar (18.0% vs. 17.9%, respectively) but much higher than the 2-year rates in our present study, which may be attributed to the fact that Onyx ONE assessed patients at high bleeding risk only.

The smallest sized Resolute Onyx ZES (2.0 mm) was assessed in a prospective, single-arm, multicenter trial that included 101 patients with small target vessels and showed low target lesion failure rates and no case of stent thrombosis (12).

The Orsiro SES has been extensively studied in large randomized clinical stent trials and showed favorable results against well-established reference stents (4,17–21). Two randomized clinical trials showed significantly lower event rates with Orsiro SES versus Xience everolimus-eluting stents. This included the randomized BIOFLOW V trial, in which Orsiro outperformed Xience with regard to the composite endpoint, target lesion failure, in 1,334 patients (22). In BIOFLOW V, the 2-year target lesion failure rate of Orsiro was somewhat higher (7.5%) than in our present study, which might be related to differences in patient population. In addition, the recently published randomized BIOSTEMI trial showed at 1-year superiority of Orsiro versus Xience regarding target lesion failure in 1,300 patients presenting with ST-segment elevation MI (14). After 1 year of follow-up, target lesion failure occurred in 4% of these patients treated with Orsiro, which was comparable with the 1-year rate of target lesion failure (3.6%) in the all-comers population of BIONYX (6).

SMALL-VESSEL TREATMENT. Among patients in BIONYX who underwent small-vessel treatment, we found no between-stent differences in the incidence of various clinical endpoints. Yet target vessel MI occurred more often with the Resolute Onyx ZES during the second year of follow-up, but this might be due to chance. Notably, there was no difference in repeated target lesion revascularizations, which is in contrast to recent findings in 1,506 BIO-RESORT participants with small-vessel treatment (5). In that study, a higher incidence of repeated target lesion

TABLE 2 2-Year Clinical Outcomes in Patients With Small Vessel Treatment (N = 898)

	ZES (n = 454)	SES (n = 444)	Hazard Ratio (95% CI)	Log-Rank p Value
Events until 2 yrs				
Any death	10 (2.2)	17 (3.9)	0.57 (0.26–1.23)	0.15
Cardiac death	5 (1.1)	8 (1.8)	0.60 (0.20–1.84)	0.37
Any MI	19 (4.2)	17 (3.9)	1.08 (0.56–2.07)	0.82
Target vessel MI	16 (3.6)	12 (2.7)	1.29 (0.61–2.72)	0.51
Any revascularization	41 (9.1)	44 (10.2)	0.89 (0.58–1.36)	0.57
Target vessel revascularization	26 (5.8)	27 (6.3)	0.92 (0.54–1.57)	0.76
Target lesion revascularization	18 (4.0)	19 (4.4)	0.91 (0.48–1.73)	0.77
Target vessel failure*	37 (8.2)	38 (8.7)	0.93 (0.59–1.46)	0.75
Target lesion failure	29 (6.4)	30 (6.9)	0.93 (0.56–1.55)	0.78
Major adverse cardiac events	35 (7.8)	43 (9.8)	0.78 (0.50–1.22)	0.28
Patient-oriented composite endpoint	55 (12.2)	63 (14.3)	0.83 (0.58–1.19)	0.31
Definite or probable stent thrombosis	1 (0.2)	6 (1.4)	0.16 (0.02–1.34)	0.053
Definite stent thrombosis	1 (0.2)	5 (1.1)	0.19 (0.02–1.65)	0.09
Events between 1 and 2 yrs†				
Any death	5 (1.1)	6 (1.4)	0.80 (0.24–2.60)	0.70
Cardiac death	3 (0.7)	1 (0.2)	2.86 (0.30–27.49)	0.34
Any MI	11 (2.5)	7 (1.7)	1.50 (0.58–3.88)	0.40
Target vessel MI	9 (2.1)	2 (0.5)	4.31 (0.93–19.95)	0.06‡
Any revascularization	15 (3.5)	14 (3.6)	1.01 (0.49–2.09)	0.99
Target vessel revascularization	11 (2.6)	9 (2.2)	1.16 (0.48–2.79)	0.75
Target lesion revascularization	5 (1.2)	7 (1.7)	0.68 (0.22–2.15)	0.51
Target vessel failure	17 (4.0)	10 (2.5)	1.61 (0.74–3.52)	0.23
Target lesion failure	11 (2.6)	8 (2.0)	1.31 (0.53–3.27)	0.56
Major adverse cardiac events	14 (3.3)	18 (4.4)	0.74 (0.37–1.49)	0.40
Patient-oriented composite endpoint	22 (5.3)	20 (5.1)	1.03 (0.56–1.89)	0.92
Definite or probable stent thrombosis	1 (0.2)	1 (0.2)	0.95 (0.06–15.14)	0.97
Definite stent thrombosis	1 (0.2)	1 (0.2)	0.95 (0.06–15.14)	0.97

2-year follow-up information was obtained from 884 of 898 study patients with small-vessel treatment (98.4%) and analyzed using the Kaplan-Meier method, so the percentages may differ slightly from straightforward "nominator divided by denominator" calculations. *Main composite endpoint including cardiac death, target vessel–related MI, and clinically indicated target vessel revascularization. †Patients who were censored for each event during the first year were not included in this analysis. ‡P value based on Wald test because of the very low event rate in the SES group.

Abbreviations as in Table 1.

revascularizations was observed in patients with small-vessel treatment using the previous iteration of the ZES (Resolute Integrity) versus the ultrathin-strut Orsiro SES (5). The fact that no such signal was observed in the small vessel analysis of BIONYX is encouraging.

Given that with the Resolute Onyx, the eluted drug and the polymer type do not differ from the Resolute Integrity ZES (6), the more favorable results might be related to the lower strut thickness and the flattened ("swaged") strut shape of the current Resolute Onyx ZES, which might facilitate endothelialization of the struts. Hence, strut shape (besides strut thickness) could have an impact on the risk for repeated revascularization in small target vessels, but this hypothesis requires assessment in future studies.

In addition, we cannot exclude that the availability of a dedicated 2.0-mm size of the Resolute Onyx ZES might have contributed a bit to the favorable outcomes in the small-vessel subgroup. In fact, somewhat more patients assigned to ZES received 2.0-mm stents (21 patients in the ZES arm vs. 6 patients in the SES arm), but considering the small number of 2.0-mm stents used, one should be cautious and avoid overinterpretation.

STENT THROMBOSIS. During the first year of follow-up, there was a lower incidence of definite or probable stent thrombosis in the Resolute Onyx group (6). After 2-years, there was only a numeric difference in favor of the Resolute Onyx, which did not reach statistical significance. During the second year of the BIONYX trial, all definite stent thromboses (4 in each group) resulted in MI and target lesion revascularization, and there were no probable stent thromboses. Notably, 2 patients in the Resolute Onyx group were still on dual-antiplatelet therapy prior to the event, while in the Orsiro group, none of the patients were on dual-antiplatelet therapy (Supplemental Table 3). With the Resolute Onyx ZES, the 2-year definite stent thrombosis rate was 0.4%, which is very low for an all-comers study with a high proportion of acute coronary syndromes, especially when considering the low rate of dual-antiplatelet therapy, compared with

a series of studies with previous-generation ZES (1). The corresponding stent thrombosis rate with the Orsiro SES was low (0.9%) and matched well with previous trials (0.5% to 1.1%) (22–24). Data for the Resolute Onyx stent are certainly encouraging, but because of the very small number of stent thromboses, no definitive conclusions can be drawn. Considering the absence of follow-up data for Resolute Onyx ZES beyond 2 years, further long-term follow-up is of interest.

STUDY LIMITATIONS. The study was not powered to assess infrequent adverse events (e.g., stent thrombosis) and clinical outcomes in subgroups, such as patients with small vessels. The findings of the present study should be considered hypothesis generating. In addition, there was no routine angiographic follow-up, but this reflects current clinical routine.

CONCLUSIONS

At 2-year follow-up, the novel thin composite-wire-strut durable-polymer Resolute Onyx ZES showed in all-comers excellent safety and efficacy, similar to that of the ultrathin cobalt-chromium-strut biodegradable-polymer Orsiro SES. A pre-specified analysis of patients who were treated in small vessels also suggested no advantage for either stent.

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PERSPECTIVES

WHAT IS KNOWN? The durable-polymer Resolute Onyx stent has shown excellent clinical results until 1-year follow-up, but no data beyond 1 year of follow-up have been published.

WHAT IS NEW? This is the first report of the 2-year clinical follow-up of the international randomized BIONYX trial. All-comer patients had similar 2-year clinical event rates if treated with the Resolute Onyx (7.6%) versus the Orsiro (7.1%) stent (HR: 1.07; 95% CI: 0.80 to 1.43). Stenting small vessels suggested no advantage in outcomes for either stent.

WHAT IS NEXT? Treating all-comers with the novel ZES appears safe and effective until 2-year follow-up, and this includes patients treated in small coronary vessels.

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APPENDIX For supplemental Methods and Results, tables, and figures, please see the online version of this paper.