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Final 5-year report of BIONYX comparing the thin-composite wire-strut zotarolimus-eluting stent versus ultrathin-strut sirolimus-eluting stent

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Abstract

Background: The BIONYX randomized trial is the first study to evaluate the Resolute Onyx durable polymer-coated zotarolimus-eluting stent (ZES) in all-comers. Furthermore, it is the first trial to assess safety and efficacy of this stent versus the Orsiro biodegradable-polymer sirolimus-eluting stent (SES) in all-comers, paying particular attention to patients with diabetes. It has previously shown promising results until 3 years of follow-up.

Aims: We aimed to assess long-term clinical outcome after percutaneous coronary intervention (PCI) with Onyx ZES versus Orsiro SES at 5-year follow-up.

Methods: The main composite endpoint was target vessel failure (TVF): cardiac death, target vessel myocardial infarction, or target vessel revascularization. Time to primary and secondary endpoints was assessed using Kaplan–Meier methods, applying the log-rank test for between-group comparison.

Results: Follow-up was available in 2414/2488 (97.0%) patients. After 5 years, TVF showed no significant difference between Onyx ZES and Orsiro SES (12.7% vs. 13.7%, hazard ratio [HR] 0.94, 95% confidence interval [CI] [0.75–1.17], $p_{log\text{-}rank} = 0.55$). Landmark analysis between 3- and 5-year follow-up found a lower target lesion revascularization rate for Onyx ZES (1.1% vs. 2.4%, HR 0.47, 95% CI [0.24–0.93], $p_{log\text{-}rank} = 0.026$). A prespecified subgroup analysis showed no significant between-stent difference in clinical outcome among patients with

Abbreviations: DES, drug-eluting stent; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; SES, sirolimus-eluting stent; TLF, target lesion failure; TVF, target vessel failure; TVR, target vessel revascularization; ZES, zotarolimus-eluting stent.

CLINICAL TRIAL REGISTRATION: https://clinicaltrials.gov/study/NCT02508714

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diabetes. After treatment with Onyx ZES, patients aged ≥75 years had significantly lower rates of TVF (13.8% vs. 21.9%, HR 0.60, 95% CI [0.39–0.93], $p_{\text{log-rank}} = 0.023$). **Conclusions:** The final 5-year analysis of the randomized BIONYX trial showed favorable and similar long-term outcomes of safety and efficacy for Onyx ZES and Orsiro SES in both all-comers and patients with diabetes.

KEYWORDS
coronary artery disease, drug-eluting stent, long-term follow-up, percutaneous coronary intervention, randomized controlled trial

1 | INTRODUCTION

The refinement of drug-eluting stents (DESs) is an ongoing process, with the Onyx stent being the latest iteration of the zotarolimus-eluting stent (ZES).[1–3] This stent is designed from a thin composite-wire strut that has a platinum-iridium core to enhance radiographic visibility.[1–3] Patients may benefit from this stent feature, in particular when undergoing challenging percutaneous coronary interventions (PCIs) in scenarios with limited radiographic visibility, for instance due to obesity or severe lesion calcification.[4] In the contemporary PCI population, such patient and lesion characteristics are increasingly present due to the rising prevalence of diabetes and the increase in elderly PCI patients. Patients with diabetes are known to have more diffuse coronary artery disease with a higher coronary plaque burden that results, on average, in a smaller lumen diameter.[5–7] In addition, the Onyx ZES is available in small stent diameters, which may be particularly useful in patients with diabetes.

The BIONYX[1] randomized trial compares the Onyx ZES versus the Orsiro ultrathin-strut biodegradable polymer-coated sirolimus-eluting stent (SES), a widely used DES that has achieved excellent results in previous clinical trials.[8–10] At 1-year follow-up of the BIONYX trial, the Onyx ZES was noninferior to the Orsiro SES in terms of patient safety and device efficacy, and at 3-year follow-up both stents showed good clinical results.[11,12] Only few other randomized all-comer trials have reported 5-year outcomes after PCI with one of the study stents. So far, *no* 5-year results have been published for the Onyx ZES, while a few all-comer trials have reported 5-year outcomes for the Orsiro SES.[13–15]

Therefore, in this final report of the BIONYX trial, we analyzed for the first time the 5-year follow-up data, comparing all-comers treated with Onyx ZES versus Orsiro SES. In addition, we performed a prespecified subgroup analysis in patients with known diabetes.

2 | METHODS

2.1 | Study design and participants

Patients were enrolled between October 2015 and December 2016, and they were eligible if aged 18 years or older and presenting with any type of coronary syndrome that required a PCI, suitable for treatment with Onyx ZES or Orsiro SES. Any lesion length or type, reference vessel size, and number of target lesions or coronary arteries to be treated was permitted. A more detailed description of the study design can be found in previously published reports.[1] All patients provided written informed consent. The study complied with the CONSORT 2010 Statement and Declaration of Helsinki.[16,17] It was approved by the Medical Ethics Committee Twente and the institutional review boards of all participating centers.

2.2 | Randomization, procedures, and follow-up

After being enrolled in the study, patients were randomly allocated (1:1) to Onyx ZES or Orsiro SES, *stratified by sex* and *diabetes* (Supporting Information: Figure 1 and Table 1). Both patients and assessors were blinded for the randomly allocated stent. The study stents were: Resolute Onyx (Medtronic), available in diameters ranging from 2.0 to 5.0 mm, and Orsiro (Biotronik), available in diameters ranging from 2.25 to 4.0 mm. More details of both study devices have previously been reported.[1] PCI was performed by experienced interventional cardiologists in consonance with current international guidelines. During 5-year follow-up, clinical events were assessed annually after the first PCI at a visit to an outpatient clinic, by questionnaires and/or telephone follow-up.

2.3 | Clinical outcomes

Purpose of this 5-year analysis of BIONYX was to establish the long-term safety and the efficacy of the novel Onyx ZES compared to the Orsiro SES. Safety and efficacy were evaluated by the main endpoint target vessel failure (TVF), a composite of cardiac death, target vessel myocardial infarction (MI), or target vessel revascularization (TVR). Secondary study endpoints were: the composite endpoint target lesion failure (TLF; cardiac death, target vessel MI, or target lesion revascularization) as well as its individual components; major adverse cardiac events (all-cause death, any MI, or clinically indicated target lesion revascularization); and stent thrombosis. The study was *independently monitored*. All potential adverse clinical events were *adjudicated by an external clinical event committee* consisting of interventional cardiologists affiliated with the University of

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Amsterdam (Amsterdam, the Netherlands). Subgroup analyses were performed in patients with medically treated diabetes mellitus at the time of study inclusion.

2.4 | Statistical analysis

Pearson's chi-square test or Fisher's exact test were used to compare categorical variables, and the Student's *t*-test was used for the comparison of continuous variables. In all analyses, the intention-to-treat principle was applied. Time to primary and secondary endpoints was assessed using Kaplan–Meier methods, and the log-rank test was applied for between-group comparisons. The Cox proportional hazards regression model was used to compute hazard ratios (HRs) with two-sided confidence intervals (CIs). If patients were lost to follow-up, died, or withdrew their consent, they were censored at the time of last contact or time of death.

Multivariate analyses were performed to adjust for any possible confounders. The multivariate model was created with stratification factors diabetes and sex, and all baseline variables showing a between-stent association with TVF ($p < 0.15$). After using step-wise backward selection, the model included sex, diabetes, hyper-tension, multivessel treatment, and stent diameter < 2.75 mm. For patients 75 years and older, the model included only the stratification factors. Landmark analyses were performed at 3-year, providing insights into the adverse clinical events that occurred from 3- to 5-year follow-up.[12] In a prespecified analysis, clinical endpoints were assessed in patients with medically treated diabetes mellitus. The main endpoint TVF was assessed in prespecified subgroups. A two-sided *p*-value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS statistics version 24.0 (IBM Corp.).

3 | RESULTS

3.1 | Baseline characteristics

Overall, 2488 patients with 3239 target lesions had been enrolled in the trial, and 1243 study participants (1646 target lesions) had been randomly allocated to treatment with Onyx ZES and 1245 (1593 target lesions) to treatment with Orsiro SES. Of all patients, 23.9% were female, 20.5% had medically treated diabetes, 70.9% presented with an acute coronary syndrome, and 51.2% were initially treated for an acute MI. Baseline characteristics of study participants, target lesions, and the performed interventional procedures are described in Supporting Information: Table 2.

3.2 | 5-year clinical outcomes

At 5-year follow-up, outcome data were available in 2414/2488 (follow-up rate: 97.0%) of the initially enrolled patients: 46 patients were lost to follow-up and 28 withdrew consent. There were no significant differences in the main endpoint TVF (HR 0.94, 95% CI [0.75–1.17], $p_{\text{log-rank}} = 0.55$) or its individual components (Table 1 and Figure 1). The rate of cardiac death in patients treated with Onyx ZES was 2.7% and in those treated with Orsiro SES 4.1% (HR 0.66, 95% CI [0.42–1.03], $p_{\text{log-rank}} = 0.063$). Furthermore, the rates of the two other components of the primary endpoint, target vessel MI and TVR (4.8% vs. 4.4%, and 8.6% vs. 9.0%, respectively), were similar for both groups. The rates of any death showed no significant between-stent difference (8.6% vs. 10.6%, $p_{\text{log-rank}} = 0.09$). The incidence of definite stent thrombosis remained low and without a significant difference between Onyx ZES and Orsiro SES (1.0% vs. 1.3%, $p_{\text{log-rank}} = 0.54$) (Figure 2).

Landmark analyses between 3- and 5-year follow-up are displayed in Table 1. While target lesion revascularization (TLR) showed no significant between-stent difference over the entire follow-up period of 5 years, TLR was found to occur less often in patients treated with Onyx ZES during the last 2 years of follow-up (1.1% vs. 2.4%, HR 0.47, 95% CI [0.24–0.93], $p_{\text{log-rank}} = 0.026$). After adjusting for confounders in a multivariate analysis, the association remained significant ($p = 0.047$).

3.3 | Subgroup analyses

A total of 510/2488 (20.5%) trial participants were known to have medically treated diabetes, and 182 (35.7%) of them were treated with insulin. Table 2 shows the 5-year clinical outcomes of all patients with medically treated diabetes. No statistically significant between-stent difference was found in patients with diabetes. The results of the subgroup analyses for TVF are shown in Table 3. Among patients aged 75 years and older, TVF occurred less often in those who were treated with Onyx ZES (13.8% vs. 21.9%, HR 0.60, 95% CI [0.39–0.93], $P_{\text{log-rank}} = 0.023$). In a multivariate analysis, age ≥75 years showed an independent association with TVF ($p = 0.018$, adjusted HR 0.59, 95% CI [0.38–0.91]). Other subgroups showed no significant between-stent difference in TVF (Table 3).

4 | DISCUSSION

4.1 | Main findings

BIONYX is the first to evaluate the long-term safety and efficacy of the thin composite-wire-strut durable polymer-coated Onyx ZES versus the ultra-thin strut biodegradable polymer-coated Orsiro SES. Neither the main endpoint TVF nor its individual components showed a significant difference between the two stent groups. While the event rates of most other clinical endpoints were numerically somewhat lower in patients treated with Onyx ZES, there was no statistically significant between-stent difference. Subgroup analyses in patients with diabetes revealed no significant between-stent difference.

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TABLE 1 Five-year clinical outcomes in all study patients.

	Onyx ZES (*n* = 1243)	Orsiro SES (*n* = 1245)	Hazard ratio (95% CI)	$p_{log\text{-}rank}$	Adjusted HR[a] (95% CI)	*p* Value
Adverse events up to 5-year follow-up						
Target vessel failure	153 (12.7)	163 (13.7)	0.94 (0.75–1.17)	0.55	0.93 (0.74–1.16)	0.51
Target lesion failure	125 (10.4)	141 (11.8)	0.87 (0.69–1.11)	0.30	0.88 (0.69–1.12)	0.29
Major adverse cardiac events	211 (17.2)	233 (19.1)	0.90 (0.75–1.08)	0.26	0.89 (0.74–1.08)	0.24
Any death	105 (8.6)	129 (10.6)	0.80 (0.62–1.04)	0.09	0.79 (0.61–1.02)	0.07
Cardiac death	32 (2.7)	48 (4.1)	0.66 (0.42–1.03)	0.063	0.65 (0.42–1.02)	0.062
Vascular death	7 (0.6)	13 (1.1)	0.53 (0.21–1.33)	0.17	0.51 (0.20–1.27)	0.15
Noncardiovascular death	66 (5.5)	68 (5.8)	0.96 (0.68–1.34)	0.80	0.94 (0.67–1.33)	0.72
Any MI	80 (6.7)	73 (6.2)	1.09 (0.79–1.49)	0.61	1.10 (0.80–1.51)	0.57
Target vessel MI	57 (4.8)	52 (4.4)	1.09 (0.75–1.59)	0.66	1.09 (0.75–1.59)	0.66
Any revascularization	157 (13.1)	168 (14.1)	0.92 (0.74–1.15)	0.47	0.94 (0.75–1.17)	0.57
Target vessel revascularization	103 (8.6)	106 (9.0)	0.97 (0.74–1.27)	0.80	0.94 (0.73–1.26)	0.75
Target lesion revascularization	69 (5.7)	80 (6.8)	0.86 (0.62–1.18)	0.34	0.85 (0.61–1.18)	0.33
Definite-or-probable stent thrombosis	12 (1.0)	17 (1.4)	0.70 (0.33–1.46)	0.34	0.69 (0.33–1.45)	0.33
Definite stent thrombosis	12 (1.0)	15 (1.3)	0.79 (0.37–1.69)	0.54	0.78 (0.37–1.68)	0.53
Adverse events between 3- and 5-year follow-up						
Target vessel failure	41 (3.9)	54 (5.2)	0.75 (0.50–1.13)	0.17	0.78 (0.52–1.18)	0.24
Target lesion failure	37 (3.4)	50 (4.7)	0.73 (0.48–1.11)	0.14	0.76 (0.49–1.17)	0.21
Major adverse cardiac events	81 (7.4)	86 (8.1)	0.92 (0.68–1.25)	0.61	0.94 (0.69–1.28)	0.70
Any death	60 (5.1)	62 (5.4)	0.95 (0.67–1.35)	0.77	0.94 (0.66–1.35)	0.75
Cardiac death	19 (1.7)	25 (2.2)	0.74 (0.41–1.35)	0.33	0.76 (0.41–1.39)	0.37
Vascular death	2 (0.2)	3 (0.3)	0.66 (0.11–3.93)	0.64	0.66 (0.11–3.95)	0.65
Noncardiovascular death	39 (3.4)	34 (3.0)	1.13 (0.71–1.78)	0.62	1.10 (0.69–1.76)	0.69
Any MI	25 (2.3)	19 (1.8)	1.30 (0.71–2.36)	0.39	1.34 (0.73–2.47)	0.34
Target vessel MI	18 (1.3)	14 (1.3)	1.27 (0.63–2.55)	0.50	1.35 (0.66–2.76)	0.41
Any revascularization	24 (2.3)	31 (3.1)	0.75 (0.44–1.28)	0.30	0.79 (0.46–1.36)	0.39
Target vessel revascularization	19 (1.8)	31 (3.0)	0.60 (0.34–1.07)	0.08	0.63 (0.35–1.13)	0.12
Target lesion revascularization	12 (1.1)	25 (2.4)	0.47 (0.24–0.93)	0.026	0.49 (0.24–0.99)	0.047
Definite-or-probable stent thrombosis	5 (0.4)	2 (0.2)	2.44 (0.47–12.55)	0.27	2.29 (0.44–11.89)	0.32
Definite stent thrombosis	5 (0.4)	2 (0.2)	2.44 (0.47–12.55)	0.27	2.29 (0.44–11.89)	0.32

Note: Numbers are *n*/*N* (%). In addition sex and diabetes were included in the model because randomization was stratified for these variables.

Abbreviations: CI, confidence interval; MI, myocardial infarction; SES, sirolimus-eluting stent; ZES, zotarolimus-eluting stent.

[a]Multivariate models included variables that significantly differed between groups at baseline and had a significant association with the primary endpoint target vessel failure. The variables are: hypertension, multivessel treatment and stent diameter < 2.75 mm.

4.2 | Other findings in perspective

The 5-year rate of definite stent thrombosis was very low for both stents. At 1-year follow-up, a statistically significant difference in the incidence of stent thrombosis was seen in favor of the Onyx ZES,[1] but that did not persist at long-term follow-up. At 3-year follow-up, all-cause mortality was found to be significantly lower in patients treated with Onyx ZES, which then was considered to be a play of chance.[12] Our current 5-year data corroborate that assumption, as all-cause mortality showed no significant between-stent difference at long-term follow-up.

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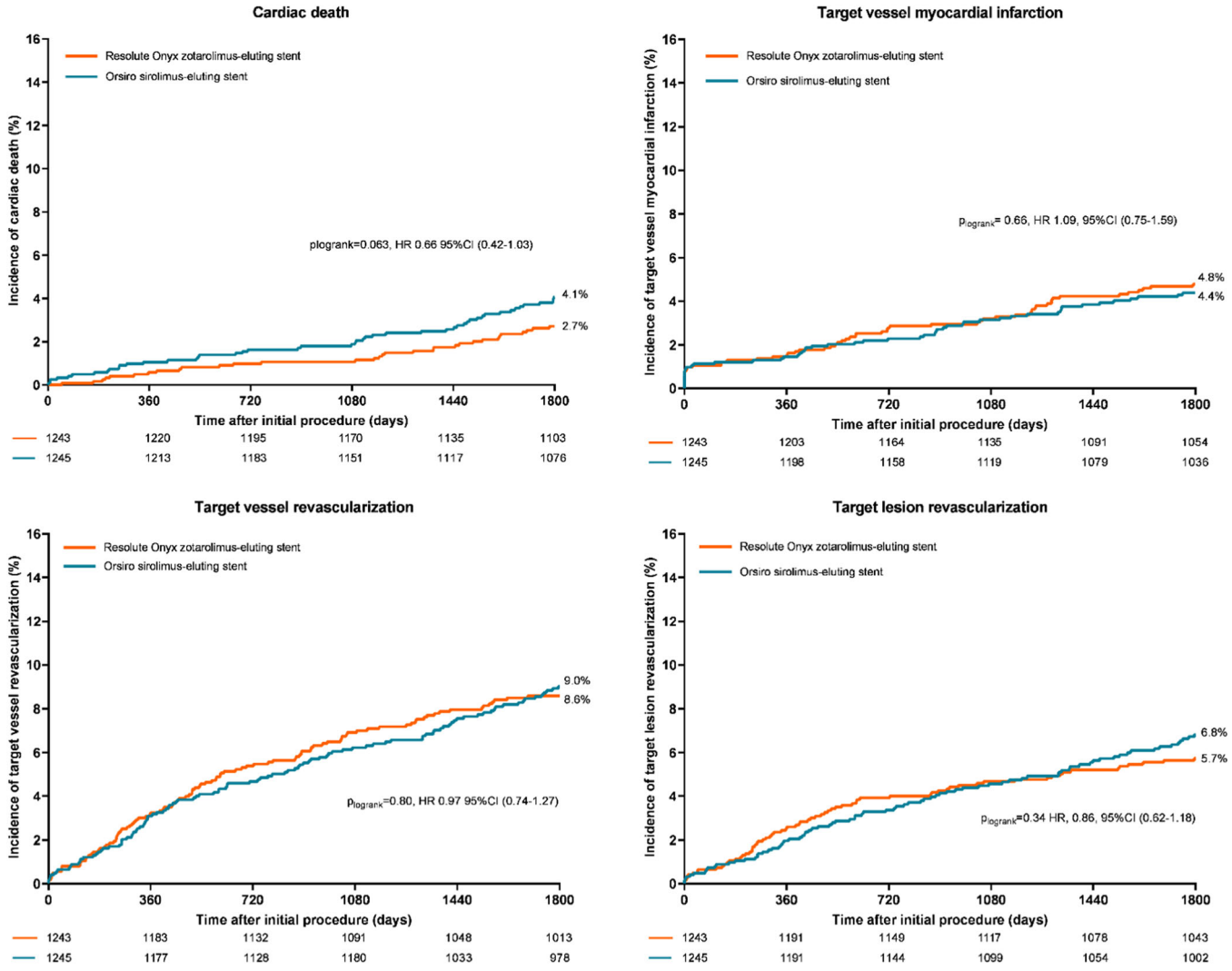

FIGURE 1 Kaplan–Meier time to event curves of the incidence of the individual components of the primary endpoint target vessel failure in all study patients: Cardiac death (A), target vessel myocardial infarction (B), and target vessel revascularization (C). (D) The secondary endpoint target lesion revascularization. [Color figure can be viewed at wileyonlinelibrary.com]

Among trial participants aged 75 years and older, patients treated with Onyx ZES showed *significantly* lower 5-year rates of the main endpoint TVF (13.8% vs. 21.9%). This favorable hypothesis-generating observation may trigger further prospective research with the Onyx ZES in elderly patient populations.

4.3 | Previous studies with the study stents

The BIONYX trial is the only all-comers study with the Onyx ZES and the first trial to ever report 5-year follow-up data after treatment with this DES. The Onyx ONE trial has compared the Onyx ZES versus the polymer-free biolimus-eluting stent (Biosensors) in a high bleeding risk population, treated with only 1 month of DAPT. At 1-year and the final 2-year follow-up of that trial, Onyx ZES was found to be noninferior to the biolimus-eluting stent with regard to both safety and efficacy.[18,19] Our observation of a lower TLR rate in Onyx ZES between 3- and 5-year follow-up of BIONYX cannot be compared with findings of previous randomized studies due to the lack of long-term data with this stent.

Although the Orsiro SES has been thoroughly investigated, only few studies have assessed the long-term clinical outcome after PCI with this stent in all-comers: The most recently published randomized clinical trial that reported 5-year follow-up data (SORT OUT VII) compared the Orsiro SES with the Nobori biodegradable polymer biolimus-eluting stent (Terumo Corporation).[13] In that trial, the composite primary endpoint TLF did not differ between the Orsiro SES and Nobori biolimus-eluting stent groups (12.4% vs. 13.1%), and it was similar to our findings in the Orsiro SES group (12.0%). The randomized BIOSCIENCE trial,[14] comparing Orsiro SES with the Xience thin cobalt-chromium strut durable polymer everolimus-eluting stent (Abbott Vascular), also showed no between-stent difference in the main endpoint TLF.

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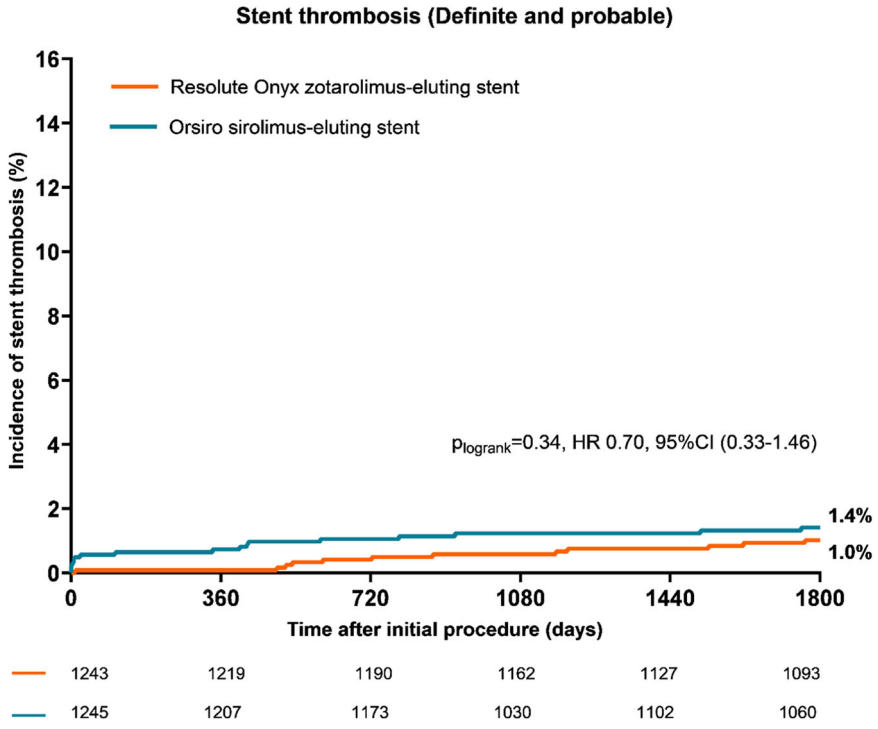

FIGURE 2 Kaplan–Meier time to event curves of the incidence of definite and probable stent thrombosis in all study patients. CI, confidence interval; HR, hazard ratio. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Five-year clinical outcomes in patients *with known diabetes mellitus* (*n* = 510).

	Onyx ZES (*n* = 260)	Orsiro SES (*n* = 250)	Hazard ratio (95% CI)	$p_{\text{log-rank}}$
Target vessel failure	51 (20.6)	54 (23.6)	0.88 (0.60–1.29)	0.51
Target lesion failure	44 (17.8)	47 (20.5)	0.87 (0.58–1.32)	0.51
Major adverse cardiac event	68 (26.7)	75 (31.1)	0.84 (0.60–1.17)	0.29
Any death	36 (14.2)	41 (17.0)	0.82 (0.53–1.29)	0.39
Cardiac death	17 (7.0)	16 (7.1)	0.99 (0.50–1.97)	0.98
Vascular death	4 (1.6)	4 (1.7)	0.94 (0.24–3.77)	0.93
Noncardiovascular death	15 (6.2)	21 (9.1)	0.67 (0.35–1.30)	0.23
Any myocardial infarction	25 (10.4)	30 (13.2)	0.77 (0.45–1.31)	0.33
Target vessel myocardial infarction	17 (7.0)	21 (9.3)	0.75 (0.40–1.43)	0.39
Any revascularization	47 (19.4)	46 (20.4)	0.96 (0.64–1.44)	0.84
Target vessel revascularization	30 (12.4)	35 (15.9)	0.80 (0.49–1.30)	0.37
Target lesion revascularization	22 (9.0)	27 (12.3)	0.76 (0.43–1.34)	0.3
Definite-or-probable stent thrombosis	4 (1.7)	6 (2.6)	0.62 (0.18–2.20)	0.46
Definite stent thrombosis	4 (1.7)	5 (2.2)	0.74 (0.20–2.77)	0.66

Note: Numbers are *n*/*N* (%).

In BIOSCIENCE, the 5-year rates of any death in the Orsiro and Xience stent groups were 14.1% and 10.3%, ($p_{\text{log-rank}}$ = 0.017).[14] In BIONYX patients treated with Orsiro SES, the rate of any death was somewhat lower (10.6%). When comparing the study populations of both trials, we did not notice any clear difference in patient or lesion characteristics. A between-stent difference in mortality, found in the BIOSCIENCE trial, was explained by a difference in cancer-related deaths. Yet, such difference was not seen in BIONYX that observed somewhat more cardiovascular deaths in patients of the Orsiro SES group. In the 5-year report of BIOFLOW V, a randomized trial that compared Orsiro SES versus Xience everolimus-eluting stents, the rate of any death was 6.8% and 6.4%, respectively.[10] The overall lower mortality in BIOFLOW V may reflect a difference in study population from the aforementioned all-comer trials: BIOFLOW V

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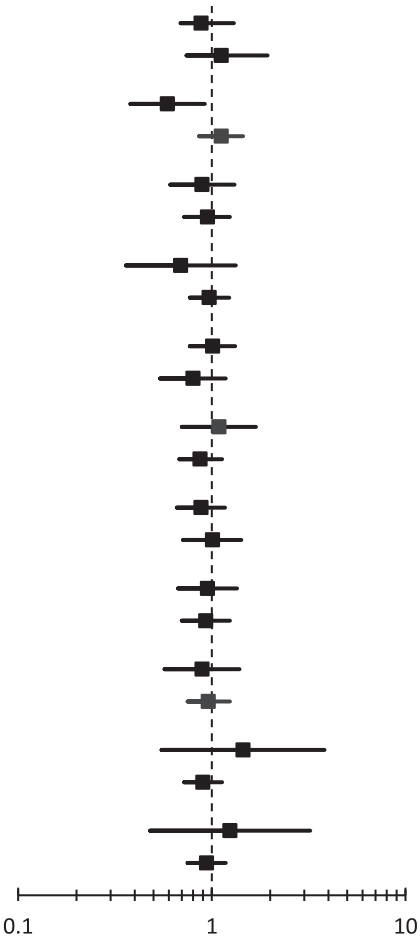
TABLE 3 Subgroup analyses for target vessel failure at 5-year follow-up.

	Onyx ZES (*n* = 1243)	Orsiro SES (*n* = 1245)	Hazard ratio (95% CI)	*p* Value	*P* Interaction
Men	117/946 (12.4)	132/948 (13.9)	0.88 (0.69–1.13)	0.32	0.32
Women	36/261 (13.8)	31/297 (10.4)	1.16 (0.72–1.88)	0.52	
Age ≥ 75 years	31/224 (13.8)	55/251 (21.9)	0.60 (0.39–0.93)	0.023	0.018
Age < 75 years	122/1019 (12.0)	108/994 (10.9)	1.11 (0.86–1.44)	0.44	
Diabetes	51/260 (19.6)	54/250 (21.6)	0.88 (0.60–1.29)	0.58	0.77
No diabetes	102/983 (10.4)	109/995 (11.0)	0.95 (0.72–1.24)	0.68	
Renal insufficiency	16/83 (19.3)	21/83 (25.3)	0.70 (0.36–1.33)	0.35	0.36
No renal insufficiency	137/1160 (11.8)	142/1162 (12.2)	0.97 (0.76–1.22)	0.76	
Acute coronary syndrome	107/880 (12.2)	107/885 (12.1)	1.00 (0.77–1.31)	0.97	0.36
Stable angina	46/363 (12.7)	56/360 (15.6)	0.80 (0.54–1.19)	0.27	
Multivessel treatment	45/236 (19.1)	35/205 (17.1)	1.1 (0.71–1.71)	0.59	0.37
Single-vessel treatment	108/1007 (10.7)	128/1040 (12.3)	0.87 (0.67–1.12)	0.26	
Small vessel <2.75 mm	91/675 (13.5)	96/626 (15.3)	0.87 (0.65–1.16)	0.34	0.52
No small vessel	62/568 (10.9)	67/619 (10.8)	1.01 (0.71–1.42)	0.96	
At least 1 bifurcation	60/485 (12.4)	64/496 (12.9)	0.95 (0.67–1.36)	0.80	0.89
No bifurcation	93/758 (12.3)	99/749 (13.2)	0.92 (0.70–1.23)	0.58	
At least 1 lesion >27 mm	34/245 (13.9)	44/278 (15.8)	0.87 (0.55–1.36)	0.53	0.68
No lesion >27 mm	119/998 (11.9)	119/967 (12.3)	0.97 (0.75–1.25)	0.80	
In stent restenosis	13/44 (29.5)	6/27 (22.2)	1.45 (0.55–3.82)	0.50	0.34
No in stent restenosis	140/1199 (11.7)	157/1218 (12.9)	0.90 (0.72–1.13)	0.36	
Bypass graft treated	8/17 (47.1)	9/23 (39.1)	1.28 (0.49–3.32)	0.62	0.52
No bypass graft	145/1226 (11.8)	154/1222 (12.6)	0.93 (0.74–1.17)	0.56	



Note: Numbers are *n*/*N* (%) Favors Onyx ZES Favors Orsiro SES.

included only patients undergoing planned PCI in de novo native coronary lesions in 1 or 2 vessels, while excluding patients with major bifurcation lesions, chronic total occlusions, or acute ST-segment elevation MI.[10]

Between 3- and 5-year follow-up, the present study observed a significantly lower incidence of TLR in patients treated with Onyx ZES (1.1% vs. 2.4%), while during the first 3 years there was no significant between-stent difference. The TLR rate of the Orsiro SES group in BIONYX is similar to that of the Orsiro SES group in BIOFLOW V (6.8% and 5.9%).[10] In the BIOFLOW V trial, after 3 years of follow-up, the rates of TLR were consistent in both stent groups; thereafter, the TLR rate doubled in the Orsiro SES group,[20] showing a similar pattern as seen in our present study. Notably, patient characteristics of the Orsiro SES groups in the BIONYX and BIOFLOW V trials were similar. Other randomized all-comer trials that assessed the Orsiro SES, such as BIO-RESORT[15] and SORT-OUT VII,[13] found 5-year TLR rates of 5.0% and 6.7%, respectively.

4.4 | Diabetes mellitus

A large meta-analysis found for various types of biodegradable polymer- and durable polymer-coated DES a similar safety and efficacy in diabetic patients.[21] Yet, the meta-analysis did not include

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any studies investigating the Onyx ZES. Due to the acclaimed low elastic recoil and high flexibility of this stent, one might expect favorable results after PCI with this stent in diabetic patients, who are more prone to develop small vessel-disease and challenging coronary lesions. Despite small numerical differences in favor of the Onyx ZES group, the diabetic subgroup analysis of BIONYX showed no significant between-stent difference in adverse events at 5-year follow-up. A previous analysis at 2-year follow-up had shown quite favorable outcomes in the diabetic subpopulation without a significant difference between Onyx ZES and Orsiro SES,[22] which has been corroborated at long-term by the findings of the present 5-year analysis.

So far, only one dedicated study investigated the clinical outcome of patients with diabetes treated with Onyx ZES. The SUGAR trial compared the Onyx ZES with the Cre8 EVO stent (Alvimedica) in patients with diabetes and found at 1-year follow-up lower TLF rates in the Cre8 EVO group, with possible superiority for that stent.[23] It has been suggested that this between-stent difference may be attributed to specific characteristics of the Cre8 EVO stent, such as its amphiphilic carrier to enhance drug diffusion. These device features may be of particular benefit in patients with diabetes, as patients with diabetes have been shown to have a dose-dependent resistance to antiproliferative drugs and require higher therapeutic drug concentrations.[24]

4.5 | Limitations

The current all-comers study has some limitations, and is formally not powered to assess secondary endpoints, landmark analyses, and subgroups. The results of these analyses should be considered hypothesis generating. Despite the assessment of many clinical, interventional procedure- and target lesion-related parameters as potential confounders, the presence of residual confounders cannot be excluded. After 5 years of follow-up, there was 3% loss of trial participants because of consent withdrawal and loss to follow-up (similar in both stent-arms). Nevertheless, in comparison with many other randomized stent trials, the 5-year follow-up rate of 97% is very high. Registration-based randomized trials may have even higher follow-up rates, yet at the price of other methodological limitations.

5 | CONCLUSION

The final 5-year analysis of the randomized BIONYX trial showed similar long-term outcomes of safety and efficacy for Onyx ZES and Orsiro SES, both in the entire study population of all-comers and among patients with known diabetes.

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CONFLICT OF INTEREST STATEMENT

Dr. Clemens von Birgelen has received research grants to the research department of Thoraxcentrum Twente from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. The remaining authors declare no conflict of interest.

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