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Treating diabetic all-comers with contemporary drug-eluting stents: Prespecified comparisons from the BIO-RESORT and the BIONYX randomized trials

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ABSTRACT

Background: Patients with diabetes have more extensive coronary disease, resulting in higher risks of adverse clinical events following stenting. In all-comer patients, contemporary DES have shown excellent safety and efficacy, but data on diabetic patients are scarce. Separately for the BIO-RESORT and BIONYX trials, we assessed the 2-year clinical outcomes of diabetic patients, treated with various contemporary drug-eluting stents (DES).
Methods: We performed two prespecified secondary analyses of two randomized DES trials, which both stratified for diabetes. The main endpoint was target vessel failure (TVF), a composite of cardiac death, target vessel myocardial infarction, or target vessel revascularization. Follow-up was finished before the COVID-19 pandemic.
Results: In BIO-RESORT, 624/3514 (17.8%) had diabetes: 211 received Orsiro sirolimus-eluting stents (SES), 203 Synergy everolimus-eluting stents (EES), and 210 Resolute Integrity zotarolimus-eluting stents (RI-ZES). TVF did not differ between SES (10.2%) and EES (10.0%) versus RI-ZES (12.7%) (SES vs. RI-ZES HR:0.78, 95%-CI [0.44–1.40]; $p = 0.40$, EES vs. RI-ZES HR:0.79, 95%-CI [0.44–1.40]; $p = 0.42$). In BIONYX, 510/2488 (20.5%) patients had diabetes: 250 received SES and 260 Resolute Onyx zotarolimus-eluting stents (RO-ZES). There was no difference in TVF between SES (10.7%) versus RO-ZES (12.2%) (HR:0.88, 95%-CI [0.52–1.48]; $p = 0.63$).
Conclusions: There was no difference in 2-year clinical outcome among patients with diabetes, who were treated with SES, or EES, versus RI-ZES. In addition there was no difference in clinical outcome in diabetic patients, who were treated with SES versus RO-ZES. These findings may be considered as a signal of safety and efficacy of the studied DES in patients with diabetes.

1. Introduction

Patients with diabetes have more extensive coronary artery disease with a lumen size that is on average smaller than in patients without diabetes [1]. The coronary arteries of diabetic patients generally have more lipid-rich plaque with more macrophage infiltration and a greater plaque burden [2,3]. As a consequence of the more advanced atherosclerotic vascular changes, patients with diabetes have a higher risk of

Abbreviations: CI, confidence interval; DES, drug-eluting stent; EES, Synergy everolimus-eluting stent; HR, Hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; RI-ZES, Resolute Integrity zotarolimus-eluting stent; RO-ZES, Resolute Onyx zotarolimus-eluting stent; SES, Orsiro sirolimus-eluting stent; TVF, target vessel failure.

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adverse clinical events after percutaneous coronary intervention (PCI), such as repeat revascularization, stent thrombosis, and mortality [4,5].

Several randomized clinical trials have demonstrated the safety and efficacy of PCI with contemporary drug-eluting stents (DES) in *all-comer patients* [6–10]. However, *in patients with diabetes* there is limited evidence that supports the use of contemporary DES, such as the Orsiro sirolimus-eluting stent (SES; Biotronik, Bülach, Switzerland), the Synergy everolimus-eluting stent (EES; Boston Scientific, Marlborough, MA), and the Resolute Integrity zotarolimus-eluting stent (RI-ZES; Medtronic, Santa Rosa, CA) [11–17]. Furthermore, no outcome data have been published about the treatment of diabetic patients with the most recent iteration of the zotarolimus-eluting stent, the Resolute Onyx (RO-ZES; Medtronic).

The multicenter, randomized BIO-RESORT and BIONYX trials assessed these contemporary DES in all-comers [6,7]. Both studies, which established at 1-year follow-up non-inferiority of the respective novel DES, performed *stratification for diabetes* at the time of randomization and prespecified subgroup analyses in trial participants with diabetes. In this manuscript, we report the results of two separate *prespecified diabetes subgroup analyses of the BIO-RESORT and BIONYX trials* at 2-year follow-up, assessing the clinical safety and efficacy of contemporary DES in patients with known diabetes.

2. Methods

2.1. Study design and trial participants

The study design and details of the BIO-RESORT (Comparison of biodegradable polymer and durable polymer drug-eluting stents in an all-comers population; *NCT01674803*) and BIONYX (Bioresorbable polymer-coated Orsiro versus durable polymer-coated Resolute ONYX stents; *NCT025087140*) trials have been reported previously [6,7]. For both trials, patients were eligible for enrollment, if they were aged 18 years or older, capable of providing informed consent, and required PCI. There was no restriction for target lesion type (i.e., de novo, restenosis, or graft), lesion length, reference vessel size, clinical syndrome, and number of lesions or vessels to be treated. BIO-RESORT is a 3-arm, patient- and assessor-blinded study, performed at 4 cardiac centers in the Netherlands. Patients were randomized to treatment with the Orsiro SES (Biotronik), the Synergy EES (Boston Scientific) versus the RI-ZES (Medtronic) [6]. The international BIONYX trial is a patient- and assessor-blinded study that was performed in 7 specialized cardiac centers in the Netherlands, Belgium, and Israel. Patients were randomized to treatment with the RO-ZES (Medtronic) versus the Orsiro SES (Biotronik) [7]. In both trials, randomization was stratified for the presence of diabetes, and in BIONYX randomization was also stratified for sex. Fig. 1 displays the study flow diagrams for both studies. The trials complied with the Declaration of Helsinki and were approved by the Medical Ethics Committee Twente and the Institutional Review Boards of all participating centers. All patients provided written informed consent.

For the first time, we report in this manuscript the *pre-specified* subgroup analyses of both trials in patients with diabetes. Diabetes was defined as medically treated diabetes mellitus at inclusion. The 2-year outcomes of these subgroup analyses are reported separately for both, BIO-RESORT and BIONYX. Two-year outcomes of the entire all-comer populations have been published recently [18,19].

2.2. Procedures

All coronary interventions were performed according to international medical guidelines and the operator's judgement. Overall, a total of 4 types of contemporary DES were used. The SES elutes sirolimus within 4 months from a circumferential, asymmetrical

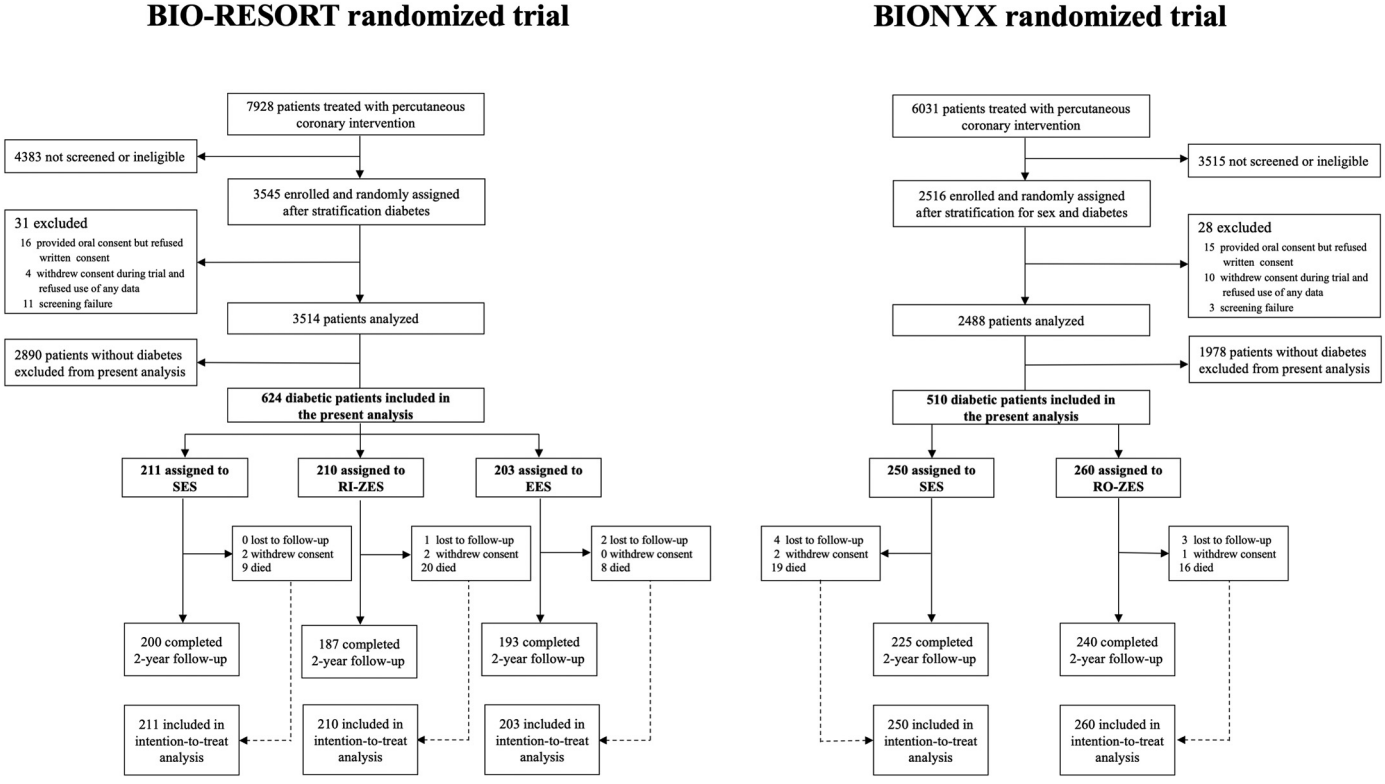

Fig. 1. Study flow diagrams of BIO-RESORT and BIONYX randomized trials. Abbreviations: EES = everolimus-eluting stent; RI-ZES = Resolute Integrity zotarolimus-eluting stent; RO-ZES = Resolute Onyx zotarolimus-eluting stent; SES = sirolimus-eluting stent.

Table 1
Baseline patient, lesion, and procedural characteristics in BIO-RESORT and BIONYX trial participants with known diabetes.

	BIO-RESORT patients with diabetes ($N = 624$)			BIONYX patients with diabetes ($N = 510$)	
	SES	RI-ZES	EES	SES	RO-ZES
Patients	$N = 211$	$N = 210$	$N = 203$	$N = 250$	$N = 260$
Age (years)	67.1 ± 9.6	65.5 ± 10.9	66.7 ± 9.6	66.0 ± 10.9	66.9 ± 9.7
Female	65 (30.8)	74 (35.2)	61 (30.0)	75 (30.0)	71 (27.3)
BMI (kg/m^2)	29.7 ± 4.4	29.1 ± 4.7	29.3 ± 4.9	29.3 ± 5.0	29.6 ± 5.0
Insulin-treated diabetes	70 (33.2)	76 (36.2)	74 (36.5)	87 (34.8)	95 (36.5)
Current smoker	46/201 (22.9)	51/201 (25.4)	39/195 (20.0)	71/243 (29.2)	55/253 (21.7)
Hypertension	146 (69.2)	144 (68.6)	133 (65.5)	188/247 (76.1)	192/259 (74.1)
Hypercholesterolemia	109 (51.7)	110 (52.4)	102 (50.2)	154/245 (62.9)	164/256 (64.1)
Chronic renal failure*	18 (8.5)	17 (8.1)	7 (3.4)	31 (12.4)	29 (11.2)
Peripheral vascular disease	20 (9.5)	28 (13.3)	30 (14.8)	30 (12.0)	35/259 (13.5)
LVEF <30%	5 (2.4)	6 (2.9)	4 (2.0)	8/247 (3.2)	4/257 (1.6)
Previous MI	54 (25.6)	55 (26.2)	40 (19.7)	56 (22.4)	56 (21.5)
Previous CVA/TIA	29 (13.7)	21 (10.0)	18 (8.9)	24 (9.6)	25 (9.6)
Previous PCI	56 (26.5)	44 (21.0)	57 (28.1)	76 (30.4)	83 (31.9)
Previous CABG	27 (12.8)	25 (11.9)	29 (14.3)	29 (11.6)	28 (10.8)
Clinical syndrome					
STEMI	38 (18.0)	34 (16.2)	43 (21.2)	43 (17.2)	38 (14.6)
NSTEMI	45 (21.3)	56 (26.7)	45 (22.2)	67 (26.8)	71 (27.3)
Unstable angina	46 (21.8)	34 (16.2)	39 (19.2)	52 (20.8)	61 (23.5)
Stable angina	82 (38.9)	86 (41.0)	76 (37.4)	88 (35.2)	90 (43.6)
At least 1 complex lesion	174 (82.5)	168 (80.0)	151 (74.4)	194 (77.6)	193 (74.2)
At least 1 bifurcated lesion	74 (35.1)	87 (41.4)	74 (36.5)	94 (37.6)	108 (41.5)
At least 1 severely calcified lesion	54 (25.6)	55 (26.2)	53 (26.1)	60 (24.0)	53 (20.4)
Direct stenting	33 (15.6)	25 (11.9)	33 (16.3)	49 (19.6)	56 (21.5)
Postdilation	167 (79.1)	168 (80.0)	152 (74.9)	176 (70.4)	168 (64.6)
Multivessel treatment	34 (16.1)	48 (22.9)	31(15.3)	45 (18.0)	59 (22.7)

This table presents details of the subgroups of patients with known diabetes in BIO-RESORT and BIONYX.
Data are *n* (%) or means ± SD. There were no significant differences between groups.
Abbreviations: BMI = body mass index; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; EES = Synergy everolimus-eluting stent; LVEF = left ventricular ejections fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RI-ZES = Resolute Integrity zotarolimus-eluting stent; RO-ZES = Resolute Onyx zotarolimus-eluting stent; SES = Orsiro sirolimus-eluting stent; STEMI = ST-segment elevation myocardial infarction.
* Renal insufficiency was defined as an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2 of body-surface area, creatinin ≥130 μmol/L, or the need for dialysis.

(thicker on abluminal side) biodegradable coating that is resorbed within 24 month; the SES has 60-μm (for ≤3.0-mm stents) or 80-μm (for >3.0-mm stents) cobalt-chromium struts that are covered by a thin passive coating of amorphous silicon carbide [6]. The EES elutes everolimus within 3 months from a poly(lactic-*co*-glycolic acid) coating that is located only on the abluminal side of 74-μm (for ≤2.5-mm stents), 79-μm (for 3.0- to 3.5-mm stents), or 81-μm (for 4.0-mm stents) platinum-chromium struts and is resorbed within 4 months. The RI-ZES has thin, round 91-μm cobalt-chromium struts that are circumferentially covered by a blend of three durable polymers, which elutes zotarolimus within 6 months [6]. Its iteration, the RO-ZES also elutes zotarolimus for 6 months from the same type of polymer-blend, covering 81-μm (for ≤4.0-mm stents) or 91-μm (for 4.5–5.0-mm stents) composite wire struts. The stent platform of RO-ZES is made from a single-strand of swaged shape cobalt-chromium wire with a platinum-iridium core that is manufactured into a sinusoidal waveform [7].

2.3. Follow-up, monitoring and clinical endpoints

For both trials, clinical follow-up was obtained at visits to outpatient clinics, by telephone, or by medical questionnaire. All follow-up data were obtained before the corona virus disease 2019 (COVID-19) pandemic. Thus, the event rates that we report, in particular the mortality rates, are unaffected by the COVID-19 pandemic. The trials were monitored (Diagram, Zwolle, Netherlands), and events were adjudicated by independent committees that were blinded for the assigned stent (Diagram, Zwolle, the Netherlands, or cardiologists of the University of Amsterdam, the Netherlands). Clinical endpoints were prespecified according to the Academic Research Consortium [20,21]. The main endpoint was target vessel failure (TVF), a composite of safety and efficacy consisting of cardiac death, target vessel-related myocardial infarction (MI), or clinically indicated target vessel revascularization. Secondary endpoints were also assessed, including target lesion failure (cardiac death, target vessel MI, or clinically indicated target lesion revascularization), target lesion revascularization, and both definite and definite-or-probable stent thrombosis.

2.4. Statistical analysis

Differences in categorical variables were examined with Pearson's χ^2 or Fisher's exact test, as appropriate, and differences in continuous variables with the t-test. Time to endpoints was assessed by the Kaplan-Meier method, 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. A two-sided p-value <0.05 was considered significant. To adjust for the stratification factor (sex), which was used at randomization in BIONYX, an additional analysis was performed that calculated an adjusted hazard ratio for the main outcome with a Cox model. Statistical analyses were done with SPSS version 24.0 (IBM, Armonk, NY).

3. Results

3.1. BIO-RESORT patients with diabetes

Of all 3514 BIO-RESORT trial participants, a total of 624 (17.8%) had diabetes. These patients were on average 66.5 ± 10.1 years old. Approximately one third of the diabetic patients was of female sex (32.1%). The

Table 2
Two-year clinical event rates in BIO-RESORT and BIONYX trial participants with known diabetes.

	BIO-RESORT patients with diabetes (N = 624)							BIONYX patients with diabetes (N = 510)			
	SES N = 211	RI-ZES N = 210	EES N = 203	Hazard ratio (95% CI) SES vs. RI-ZES	P-logrank SES vs. RI-ZES	Hazard ratio (95% CI) EES vs. RI-ZES	P-logrank EES vs. RI-ZES	SES N = 250	RO-ZES N = 260	Hazard ratio (95% CI) SES vs. RO-ZES	P-logrank SES vs. RO-ZES
Cardiac death	3 (1.5)	9 (4.4)	4 (2.0)	0.32 (0.09–1.19)	0.07	0.45 (0.14–1.44)	0.17	7 (2.9)	7 (2.8)	1.05 (0.37–2.99)	0.93
Target vessel myocardial infarction	6 (2.9)	7 (3.4)	10 (5.0)	0.84 (0.28–2.51)	0.76	1.48 (0.56–3.87)	0.43	11 (4.5)	11 (4.4)	1.05 (0.46–2.43)	0.90
Target vessel revascularization	16 (7.8)	13 (6.5)	8 (4.1)	1.21 (0.58–2.52)	0.61	0.60 (0.25–1.46)	0.26	14 (5.8)	20 (8.0)	0.73 (0.37–1.44)	0.36
Target lesion revascularization	10 (4.8)	6 (3.0)	7 (3.6)	1.65 (0.60–4.53)	0.33	1.17 (0.39–3.47)	0.78	9 (3.7)	15 (6.0)	0.62 (0.27–1.42)	0.25
Target vessel failure*	21 (10.2)	26 (12.7)	20 (10.0)	0.79 (0.44–1.40)	0.42	0.78 (0.44–1.40)	0.40	26 (10.7)	31 (12.2)	0.88 (0.52–1.48)	0.63
Target lesion failure	15 (7.2)	20 (9.7)	19 (9.5)	0.73 (0.38–1.43)	0.36	0.97 (0.52–1.83)	0.93	21 (8.7)	26 (10.2)	0.84 (0.47–1.50)	0.56
Definite-or-probable stent thrombosis	3 (1.4)	4 (1.9)	3 (1.5)	0.75 (0.17–3.34)	0.70	0.76 (0.17–3.38)	0.71	4 (1.6)	1 (0.4)	4.18 (0.47–37.43)	0.16
Definite stent thrombosis	3 (1.4)	1 (0.5)	3 (1.4)	2.99 (0.31–28.70)	0.32	2.00 (0.18–22.01)	0.57	3 (1.2)	1 (0.4)	3.14 (0.33–30.18)	0.30

Data are *n* (%).
Abbreviations: CI = confidence interval; EES = Synergy everolimus-eluting stent; RI-ZES = Resolute Integrity zotarolimus-eluting stent; RO-ZES = Resolute Onyx zotarolimus-eluting stent; SES = Orsiro sirolimus-eluting stent.
* Target vessel failure is the main endpoint consisting of cardiac death, target vessel myocardial infarction, or target vessel revascularization.

body mass index was 29.3 ± 4.7 kg/m2, and 35.3% were treated with insulin. Most patients (60.9%) presented with an acute coronary syndrome. Between stent groups, there was no significant difference in baseline patient, lesion, or procedural characteristics. Additional baseline patient, lesion, and procedural data are presented per stent group in Table 1.

Two-year follow-up was available in 617 (98.9%) diabetic patients: 3 were lost to follow-up and 4 withdrew their consent. Patients were censored at the last known contact (lost to follow-up), or at moment of drop-out (consent withdrawal). Table 2 presents clinical outcome for all diabetic patients at 2-year follow-up. The main endpoint TVF occurred in 10.2% of patients treated with SES, 12.7% treated with RI-ZES, and 10.0% treated with EES (SES vs. RI-ZES: HR 0.78, 95%-CI [0.44–1.40]; $p = 0.40$; and EES vs. RI-ZES HR 0.79, 95%-CI [0.44–1.40]; $p = 0.42$). There was no significant between-stent difference in the individual components of TVF; Kaplan Meier event curves showing event rates at 1- and 2-year follow-up are presented in Fig. 2. Definite-or-probable stent thrombosis rates were low and similar in all 3 stent groups (SES 1.4%, RI-ZES 1.9%, and EES 1.5%). Supplementary Table 1 presents the clinical outcome of diabetic patients with ($N = 220$) and without insulin-treatment ($N = 404$), showing no significant differences between stent groups.

3.2. BIONYX patients with diabetes

Of the 2488 participants in the BIONYX trial, 510 (20.5%) were known to have diabetes. Diabetic BIONYX trial participants were on average 66.4 ± 10.3 years old (female sex in 28.6%). Their body mass index was 29.5 ± 5.0 kg/m2, and medication included insulin in 35.7%. The majority of patients (65.1%) were treated for an acute coronary syndrome. There was no significant between-stent difference in baseline patient, lesion, or procedural characteristics. Table 1 presents additional baseline patient, lesion, and procedural data per stent group.

The 2-year follow-up was available in 500 (98.0%) patients: 7 were lost to follow-up and 3 withdrew their consent. Table 2 presents the 2-year clinical outcomes. The main endpoint TVF was reached in 10.7% of patients treated with SES versus 12.2% treated with RO-ZES (HR 0.88, 95%-CI [0.52–1.48]; $p = 0.63$). The individual components of TVF showed no significant between-stent difference, as can be seen in Fig. 3 which presents the Kaplan Meier event curves up to 2-year follow-up. In both stent groups, definite-or-probable stent thrombosis rates were low and showed no significant difference (SES 1.6% vs.RO-ZES 0.4%; Table 2). Supplementary Table 2 shows adverse event rates for 1978 non-diabetic patients, 328 diabetic patients without insulin treatment and 182 diabetic patients with insulin treatment. When all BIONYX trial participants were grouped according to their diabetic status, no significant between-stent difference was found.

The adjusted HR for TVF in BIONYX trial participants showed no significant between-stent difference, and differed only slightly from the unadjusted HR (adjusted HR 0.89 95%-CI [0.53–1.50], $p = 0.66$).

4. Discussion

4.1. Main findings

This manuscript reports *2 separate pre-specified* subgroup analyses in patients with known diabetes from the large-scale BIO-RESORT and BIONYX randomized trials, which assessed the clinical safety and efficacy of PCI with contemporary DES. As these stents differ in polymer-type, eluted drug, stent design and backbone, similar outcomes for all DES may not just be assumed. Yet, in both comparisons the adverse event rates were low and similar with the examined DES. Up to 2-year follow-up, for the main endpoint TVF there was no significant difference for SES or EES versus RI-ZES (BIO-RESORT; 10.2%, and 10.0%, versus 12.7%), and for SES versus RO-ZES (BIONYX; 10.7% versus 12.2%). In addition, there was no significant between-DES difference for the composite endpoint target lesion failure as well as for various individual endpoints of safety and efficacy. While in both stent trials during the second year of follow-up the majority of patients were not on dual antiplatelet therapy [18,19], definite-or-probable stent thrombosis rates were low in diabetic patients treated with any of the studied DES, ranging from 0.4% in RO-ZES in BIONYX to 1.9% in RI-ZES in BIO-RESORT. Although contemporary stents differ considerably in technical details, treatment of diabetic patients with all examined DES appears to be safe and efficacious, as in none of the trials a significant between-stent difference was found. This may suggest that concomitant medical therapy, stenting technique, and cardiovascular risk management may have

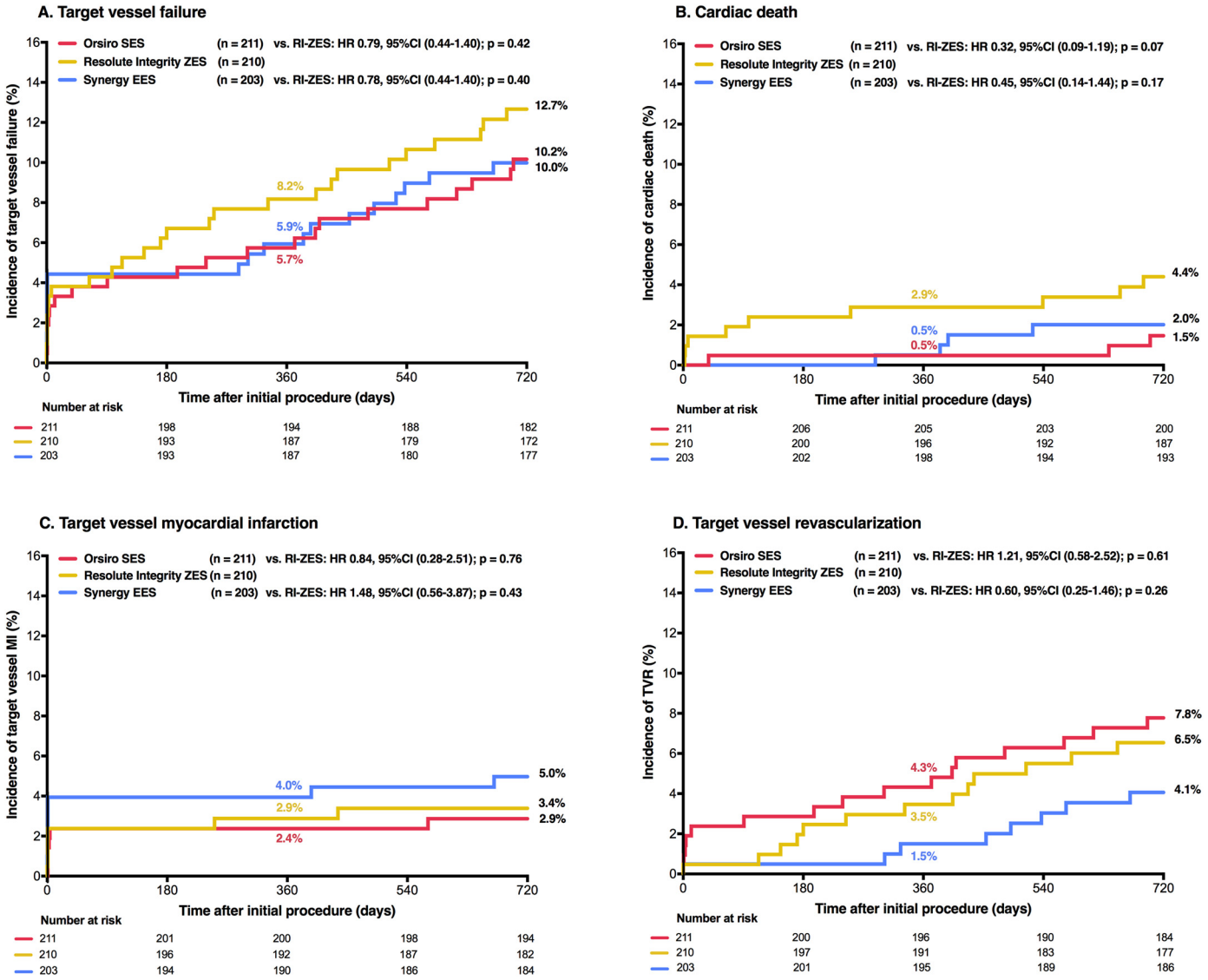

Fig. 2. Target vessel failure and components in BIO-RESORT patients with known diabetes until 2-year follow-up. Abbreviations: CI = confidence interval; EES = everolimus-eluting stent; HR = hazard ratio; MI = myocardial infarction; SES = sirolimus-eluting stent; TVR = target vessel revascularization; RI-ZES = Resolute Integrity zotarolimus-eluting stent.

a greater impact on the outcome of diabetic patients than the choice of contemporary DES.

4.2. Diabetic status and adverse event rates

Among BIO-RESORT trial participants who were treated with EES or RI-ZES, the 2-year TVF rates increased with the severity of diabetic status. Patients without diabetes had the lowest TVF rates (6.2% and 7.3%, respectively), followed by diabetic patients without insulin treatment (8.8% and 10.6%), and diabetic patients with insulin treatment had the highest rates (12.2% and 16.3%, respectively). Likewise, in the RO-ZES-treated BIONYX trial participants, the 2-year TVF rates were 6.4%, 11.1%, and 14.1%, respectively. Overall, the observed event rates and the relation between the rate and the diabetic status are in line with previous studies [14,17,22].

In the SES-arms of BIO-RESORT and BIONYX, the 2-year TVF rates were quite low in insulin-treated and non-insulin-treated diabetic patients (10.2% and 10.1%, as well as 8.3% and 11.8%, respectively). A previous study that assessed the SES in insulin-treated patients observed a dissimilar pattern with higher event rates in insulin-treated diabetic patients [12]. Subtle differences in procedural details (e.g. stent postdilation) or concomitant medication might have played a role. Furthermore, we cannot exclude that a play of chance might have contributed to the surprisingly low TVF rates in the two relatively small insulin-treated diabetic SES-patient subgroups of both trials.

4.3. Previous studies

As diabetic patients have a greater coronary plaque burden with a higher degree of lesion calcification, DES with very thin and ultrathin struts might have a theoretical disadvantage in plaque scaffolding, related to a slightly lower metal-to-artery ratio and radial force. The latter may be compensated for by refinements in strut material or shape, and in stent design. In addition, very thin and ultrathin struts may be advantageous in patients with smaller caliber coronary vessels, such as patients with diabetes, as the relative effect of strut size on lumen obstruction may be greater in small vessels. Furthermore, the use of biodegradable polymer coatings could be advantageous, as after polymer resorption only the metallic stent platform remains in the vessel, which may improve vascular healing [23]. Therefore, it is of interest to assess the clinical performance of contemporary DES in diabetic

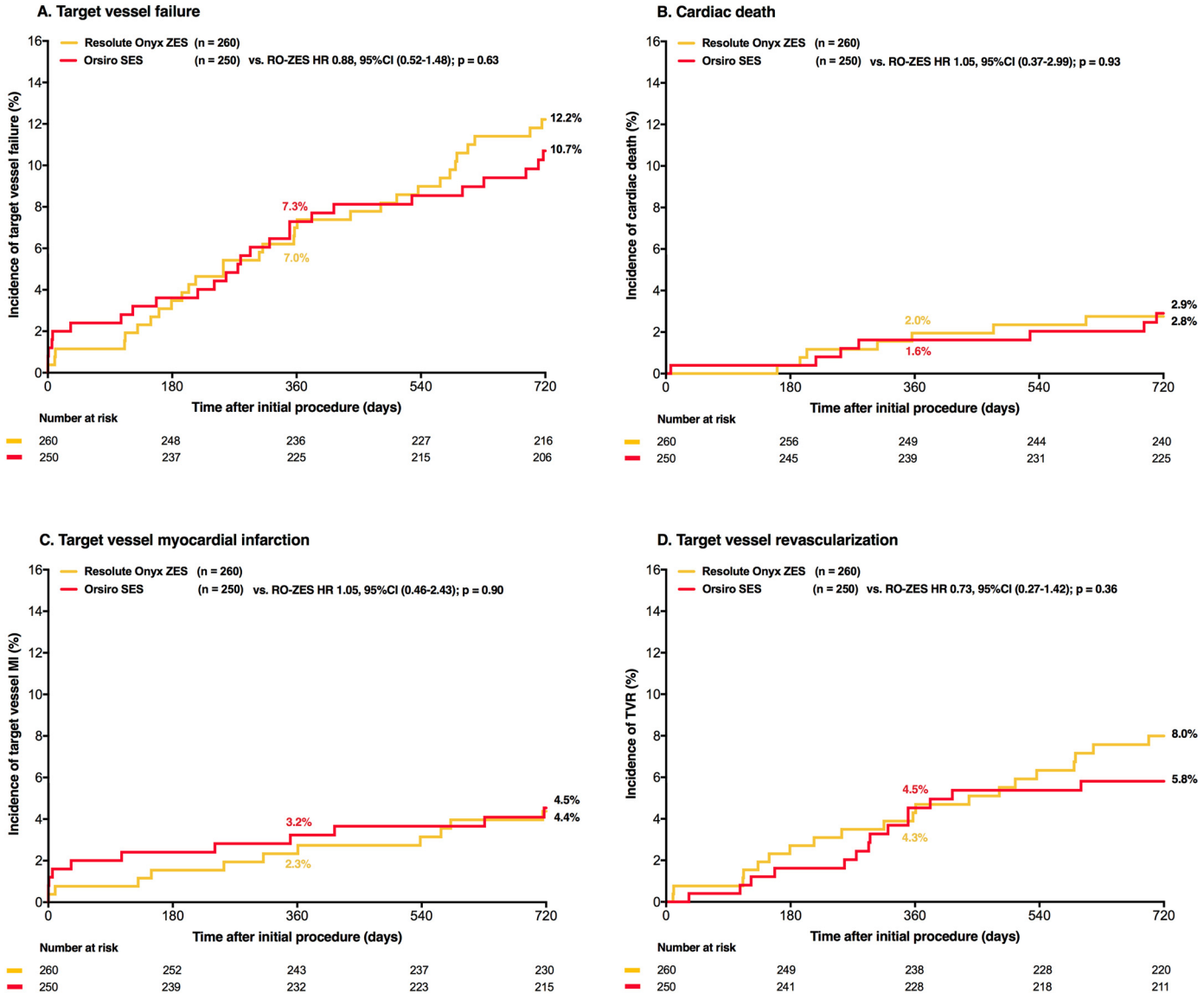

Fig. 3. Target vessel failure and components in BIONYX patients with known diabetes until 2-year follow-up. Abbreviations: CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; RO-ZES = Resolute Onyx zotarolimus-eluting stent; SES = sirolimus-eluting stent; TVR = target vessel revascularization.

patients. So far, only a small number of previous studies examined the devices that were assessed in the present analyses.

The present study is the first to report 2-year clinical outcomes of diabetic all-comer patients treated with RO-ZES. In addition, it is the first study to present 2-year results from a head-to-head comparison of the biodegradable polymer EES, as well as the ultrathin-strut biodegradable polymer SES, versus a reference stent in diabetic all-comers.

In a study that compared the ultrathin-strut SES with a thin strut durable polymer everolimus-eluting stent (Xience Prime/ Xpedition, Abbott Vascular) in 486 patients with known diabetes, similar 5-year target lesion revascularization rates were observed for both DES (16.9% vs. 15.8%, $p = 0.68$) [13]. Furthermore, a patient-level pooled analysis of three randomized trials (i.e., BIOFLOW II, IV, and V) that assessed the outcome of a total of 757 patients with diabetes found no difference in 1-year clinical outcome of patients treated with the SES versus the Xience Prime everolimus-eluting stent [12]. In the SORT OUT VII trial, the 2-year rate of the composite endpoint target lesion failure rate (i.e., cardiac death, target vessel MI, or target lesion revascularization) was 9.3% in 236 diabetic patients who were treated with SES, showing no difference as compared to a biodegradable polymer-coated biolimus-eluting stent [15]. In the present assessment of the ultrathin-strut SES, we observed a similarly low 2-year target lesion failure rate. Thus, both the previous studies as well as the current analysis reveal an excellent safety and efficacy of the ultrathin-strut SES in patients with diabetes.

The very thin strut biodegradable polymer EES was previously investigated in the diabetic patient subgroups of two clinical studies. Although the EVOLVE II diabetes substudy [11] assessed a somewhat more selected patient population than the present all-comer trials, the 2-year rate of target lesion revascularization (6.8%) was higher than in diabetic patients of the EES-group of BIO-RESORT (3.6%). In that study, the rates of safety endpoints were similar to our observations (target vessel MI 6.4% and 5.0%, cardiac death 1.5% and 2.0%, respectively). We can only speculate that differences in ischemia assessment, namely the measurement of fractional flow reserve, could have played a role in the observed difference in target lesion revascularization between diabetic patients of EVOLVE II [11] and BIO-RESORT. The SORT OUT VIII trial, a randomized public registry-based all-comers study, compared the very thin strut biodegradable polymer EES with a thicker strut biodegradable polymer biolimus-eluting stent, and included a total of 512

diabetic patients of whom at 1-year follow-up the biodegradable polymer EES-treated patients showed a non-significantly lower rate of target lesion failure (3.6% vs. 5.7%, respectively) [16]. Overall, diabetic patients treated with the very thin strut biodegradable polymer EES showed low event rates, suggesting its use is safe and efficacious in this high-risk subgroup.

Thus far, no outcome data was published of diabetic participants in a randomized clinical trial, who specifically were treated with the RO-ZES. Yet, there is limited pooled data available from patients treated with RO-ZES and a previous iterations of the ZES. The 2-year clinical outcomes of a total of 559 diabetic patients was reported by the randomized BIONICS trial that used ZES (RI-ZES or RO-ZES) as a reference device to assess another novel DES in a somewhat selected patient population [14]. In that study, the 275 ZES-treated patients had adverse event rates similar to the current analysis. For instance, the 2-year rate of target lesion failure was 10.5% in ZES-treated patients of that study [14], as compared to 9.7% for the RI-ZES and 10.2% for the RO-ZES treated patients in the present study. Furthermore, a previous iteration of the ZES, the Resolute ZES, was evaluated in a large pooled analysis of 878 patients with diabetes, which reported a 2-year target lesion failure rate of 9.5% [17], which matches quite well with the corresponding event rates of the two newer iterations in diabetic all-comers of the present analysis. The rates of other clinical endpoints of that registry were also in line with our current results in the next iterations of ZES. Nevertheless, it should be considered that in that registry the average complexity of patients and lesions was lower than in the current two all-comer trials; this interferes with a meaningful comparison of the event rates of both studies. A polymer-free amphilimus-eluting stent has previously shown promising results in diabetic patients with event rates that were comparable to those in non-diabetic patients and lower than with other DES [24–26]. However, in a randomized head-to-head comparison with the RI-ZES in 1491 all-comers, 1-year follow-up of the subgroup of diabetic patients showed no clinical advantage for either stent [27].

4.4. Limitations and strengths

While this manuscript reports two individual prespecified subgroup analyses in diabetic patients of two large-scale randomized DES trials which both stratified for the presence of diabetes, the sample sizes were insufficient to draw definite conclusions, and for that reason the findings are no more than hypothesis generating. Statistical power of these secondary analyses is limited, and we cannot exclude that small differences in outcome remained undetected due to sample size limitations. Nevertheless, the results provide a signal of safety and efficacy for treating this subset of patients with the contemporary DES that were examined in the trials. Despite some methodological limitations, a pooled data analysis of both trial's diabetic patient populations is of interest for future research. Considering the ongoing COVID-19 pandemic, for the time being the BIONYX trial may be the only source of unimpaired, monitored, 2-year outcome data in all-comers who were treated with RO-ZES. While event rates (specifically mortality rates) in this manuscript can be adequately compared to the rates of previous studies, future follow-up of this and other trials may be affected by the COVID-19 pandemic, which will make meaningful comparisons more challenging.

5. Conclusions

There was no difference in 2-year clinical outcome among patients with diabetes, who were treated with SES, or EES, versus RI-ZES. In addition there was no difference in clinical outcome in diabetic patients, who were treated with SES versus RO-ZES. These findings may be considered as a signal of safety and efficacy of the studied DES in patients with diabetes.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.10.051.

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