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ORIGINAL RESEARCH

Final 5-Year Report of the Randomized BIO-RESORT Trial Comparing 3 Contemporary Drug-Eluting Stents in All-Comers

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BACKGROUND: In a previous trial, higher 5-year mortality was observed following treatment with biodegradable polymer Orsiro sirolimus-eluting stents (SES). We assessed 5-year safety and efficacy of all-comers as well as patients with diabetes treated with SES or Synergy everolimus-eluting stents (EES) versus durable polymer Resolute Integrity zotarolimus-eluting stents (ZES).

METHODS AND RESULTS: The randomized BIO-RESORT (Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population) trial enrolled 3514 all-comer patients at 4 Dutch cardiac centers. Patients aged ≥18 years who required percutaneous coronary intervention were eligible. Participants were stratified for diabetes and randomized to treatment with SES, EES, or ZES (1:1:1). The main end point was target vessel failure (cardiac mortality, target vessel myocardial infarction, or target vessel revascularization). Five-year follow-up was available in 3183 of 3514 (90.6%) patients. The main end point target vessel failure occurred in 142 of 1169 (12.7%) patients treated with SES, 130 of 1172 (11.6%) treated with EES, versus 157 of 1173 (14.1%) treated with ZES (hazard ratio [HR], 0.89 [95% CI, 0.71–1.12], $P_{log\text{-}rank}$=0.31; and HR, 0.82 [95% CI, 0.65–1.04], $P_{log\text{-}rank}$=0.10, respectively). Individual components of target vessel failure showed no significant between-stent difference. Very late definite stent thrombosis rates were low and similar (SES, 1.1%; EES, 0.6%; ZES, 0.9%). In patients with diabetes, target vessel failure did not differ significantly between stent-groups (SES, 19.8%; EES, 19.2%; versus ZES, 21.1% [$P_{log\text{-}rank}$=0.69 and $P_{log\text{-}rank}$=0.63]).

CONCLUSIONS: Orsiro SES, Synergy EES, and Resolute Integrity ZES showed similar 5-year outcomes of safety and efficacy, including mortality. A prespecified stent comparison in patients with diabetes also revealed no significant differences in 5-year clinical outcomes.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01674803.

Key Words: biodegradable polymer ■ drug-eluting stent ■ durable polymer ■ percutaneous coronary intervention ■ randomized clinical trial

Different drug-eluting stents (DES) have shown similar long-term efficacy in preventing recurrence of lumen obstruction following percutaneous coronary intervention (PCI).[1–3] Nevertheless, throughout the years, there have been studies showing that DES can differ in long-term safety.[4–6] Consequently, assessing long-term

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CLINICAL PERSPECTIVE

What Is New?

- Between Orsiro and Resolute Integrity stents, we found no significant differences in safety and efficacy, including all-cause mortality.
- This randomized study presents the first 5-year follow-up data of the biodegradable polymer Synergy stent, showing in all-comer patients safety and efficacy similar to the durable polymer Resolute Integrity stent.

What Are the Clinical Implications?

- All-comer patients and patients with diabetes can be safely and effectively treated with Orsiro, Synergy, and Resolute Integrity drug-eluting stents.

Nonstandard Abbreviations and Acronyms

BIOFLOW III	BIOTRONIK—Safety and Performance Registry for an All-comers Patient Population With the Limus Eluting Orsiro Stent System Within Daily Clinical Practice III
BIO-RESORT	Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population
BIOSCIENCE	Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularization
DES	drug-eluting stent
DUTCH PEERS	Third-Generation Zotarolimus-Eluting and Everolimus-Eluting Stents in All-Comer Patients Requiring a Percutaneous Coronary Intervention
EES	everolimus-eluting stent
EVOLVE II	The EVOLVE II Clinical Trial to Assess the SYNERGY Stent System for the Treatment of Atherosclerotic Lesion(s)
RESOLUTE US	Clinical Evaluation of the Medtronic Resolute Zotarolimus-Eluting Coronary Stent System in the Treatment of De Novo Lesions in Native Coronary Arteries With a Reference Vessel Diameter of 2.25 mm to 4.2 mm
SES	sirolimus-eluting stents
ZES	zotarolimus-eluting stents

safety of novel DES is of interest and may reveal clinically relevant differences, both in all-comers and in high-risk subgroups, such as patients with diabetes. Previously, the 1-year safety and efficacy was similar in patients treated with the very thin-strut biodegradable polymer Synergy everolimus-eluting stent (EES) and ultrathin-strut biodegradable polymer Orsiro sirolimus-eluting stents (SES) versus the thin-strut durable polymer Resolute Integrity zotarolimus-eluting stents (ZES) assessed in the randomized BIO-RESORT (Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population) trial.[7] So far, only 1 randomized clinical trial assessed the 5-year outcome of treatment with the Synergy EES, showing no difference versus a thin-strut durable polymer DES in target lesions of low to moderate complexity.[8]

Recently, an all-comer study with SES showed a higher 5-year mortality rate as compared with a thin-strut durable polymer DES.[6] This finding was driven by cancer-related mortality, but there is no valid explanation of why this SES would be carcinogenic. In addition, a subgroup analysis revealed a 5-year mortality rate of >20% in SES-treated patients with diabetes.[9] Five-year reports of randomized studies with Orsiro SES are scarce; therefore, it is important to evaluate the long-term mortality of SES-treated patients in another randomized trial. Here, we assessed the 5-year outcome of the randomized BIO-RESORT trial,[7] which compared 3 new-generation DES in all-comers: Orsiro SES and Synergy EES versus Resolute Integrity ZES. In addition, we report the findings of a prespecified subgroup analysis in patients with diabetes.

METHODS

Data that support the findings of this study may be made available upon reasonable request. Detailed requests can be made to Cardiovascular Research and Education Enschede and will be evaluated by an independent review committee, identified for this purpose.

Study Design and Participants

The study design of the BIO-RESORT trial, including details regarding sample size, was previously reported.[7] In brief, this investigator-initiated, patient- and assessor-blinded, noninferiority (3.5% noninferiority margin, 2.5% one-sided α level), randomized clinical trial was executed in 4 cardiac centers in the Netherlands (ClinicalTrials.gov NCT01674803). A total of 3514 all-comer patients requiring PCI with DES were randomly assigned in a 1:1:1 fashion to treatment with either Orsiro SES (Biotronik), Synergy EES (Boston Scientific), or Resolute Integrity ZES (Medtronic). Randomization was performed via web-based allocation and was stratified for diabetes.[7] There were few exclusion criteria, which included known intolerance

to dual antiplatelet therapy, known pregnancy, and life expectancy of <1 year. There was no limit for reference vessel size, lesion length, and number of lesions or vessels to be treated. Patients presenting with any coronary syndrome could participate, and any type of lesion (eg, de novo, restenotic, or coronary bypass lesion) was permitted. The trial was approved by the medical ethics committee Twente and the institutional review boards of all participating centers. In addition, the trial complied with the Declaration of Helsinki. All patients provided written informed consent.

Stents

The Orsiro SES elutes sirolimus within 3 months from a circumferential coating. The 60-μm (for ≤3.0-mm stents) or 80-μm (for >3.0-mm stents) cobalt-chromium struts with a thin passive coating of amorphous silicon carbide are asymmetrically covered with a biodegradable polymer coating that is thicker on the abluminal side (7.4 μm) than on the luminal side (3.5 μm).[7] The biodegradable poly[L-lactide] acid is fully resorbed within ≈24 months. The Synergy EES elutes everolimus within 3 months from a 4-μm poly (lactic-co-glycolic acid) coating, located only on the abluminal side of 74-μm (for stents ≤2.5 mm), 79-μm (for 3.0–3.5 mm stents), or 81-μm (for 4.0 mm stents) platinum chromium struts. The poly (lactic-co-glycolic acid) coating is resorbed within 4 months.[7] The Resolute Integrity ZES elutes zotarolimus during the first 6 months and has thin, round-shaped, 91-μm cobalt-chromium struts that are circumferentially covered by a 6-μm blend of 3 durable polymers.[7]

Procedures, Clinical Follow-Up, and Event Adjudication

Coronary interventional procedures were performed according to standard techniques. The choice of concomitant medication and type and duration of antiplatelet therapy was based on routine clinical practice, current international guidelines, and operator's judgment. Cardiovascular Research and Education Enschede (Enschede, the Netherlands) performed trial and data management. The research staff was blinded to the assigned stent type. Clinical follow-up was obtained by telephone, questionnaires, or visits to the outpatient clinic. An independent clinical research organization (Diagram, Zwolle, the Netherlands) performed data monitoring, processing of clinical outcome data, and independent clinical event adjudication. At all times, the clinical event committee was blinded to the assigned stent type. No routine angiographic follow-up was performed.

Clinical End Points

Clinical end points were centrally assessed and prespecified according to definitions of the Academic Research Consortium.[10,11] The main end point at 5-year follow-up was target vessel failure (TVF), a composite of cardiac death, target vessel–related myocardial infarction, or clinically indicated target vessel revascularization. Prespecified secondary end points included the individual components of TVF, all-cause mortality, target lesion revascularization, and stent thrombosis. Other secondary composite end points included target lesion failure (cardiac death, target vessel–related myocardial infarction, or clinically driven target lesion revascularization); major adverse cardiac events (all-cause death, any myocardial infarction, or clinically indicated target lesion revascularization); and the patient-oriented composite end point (all-cause mortality, any myocardial infarction, or any repeat coronary revascularization).

Statistical Analysis

Differences in categorical variables were assessed with chi-square or Fisher exact tests, and continuous variables were compared with ANOVA. Time to main and secondary end points was assessed by Kaplan–Meier analyses, and the approximate log-rank test (Mantel-Cox test) was applied for between-group comparisons. Hazard ratios (HRs) were calculated using Cox proportional hazards analysis. Landmark analyses between 1 and 5 years were performed using 1-year landmarks. Cox regression was performed in order to test for interaction between subgroups and DES type regarding the main clinical end point. The trial was designed to assess the 1-year noninferiority of the primary end point. The 80% power was used to show noninferiority with a margin of 2.5% and an α of 0.05 (1-sided). *P* values and CIs were 2-sided, and a *P* value <0.05 was considered significant. Holm-Bonferroni correction was used to correct for testing between multiple groups. Statistical analyses were performed with SPSS version 24 (IBM) and Holm-Bonferroni Sequential Correction (Justin Gaetona, 2013).

RESULTS

All Patients

Between December 2012 and August 2015, 3514 all-comer patients were enrolled and included in the intention-to-treat analysis. Five-year follow-up was available in 3183 of 3514 (90.6%) patients; 88 patients were lost to follow-up, while 244 patients withdrew consent (Figure 1). Trial participants were aged 63.9±10.8 years, ranging from 32 to 93 years; 72.5% were men and 69.7% presented with an acute coronary syndrome. Baseline patient, lesion, and procedural characteristics are presented in Table S1. Dual antiplatelet therapy use at 5 years was low and similar

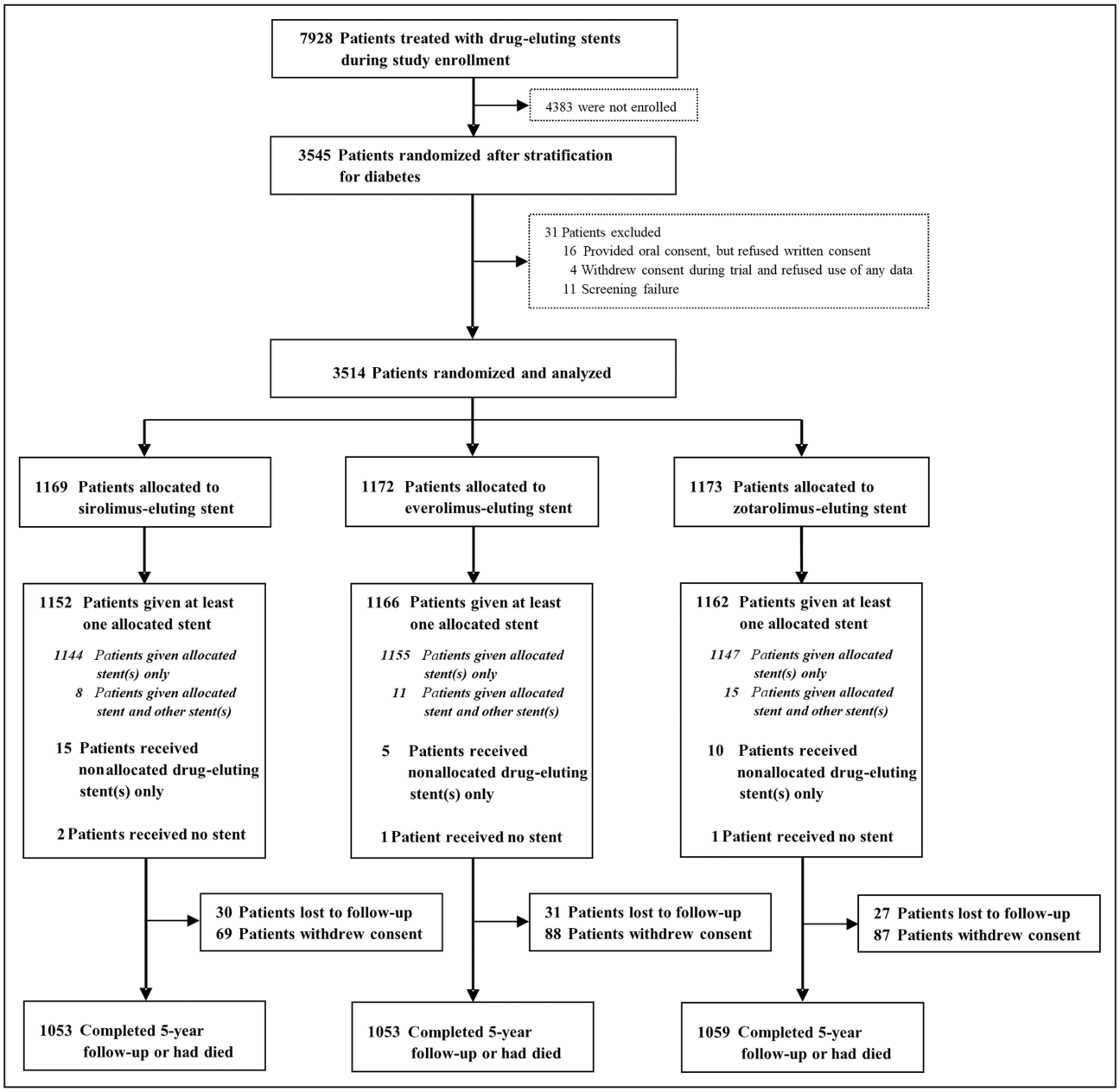

Figure 1. Trial profile.

for all 3 stent groups (SES 5.9%, EES 3.8%, ZES 4.4%) (Table S2). In addition, ≈15% of the study population used oral anticoagulants.

Five-year clinical outcome is presented in Table 1 (Holm-Bonferroni–corrected *P* values are presented in Table S3). TVF occurred in 142 of 1169 (12.7%) patients assigned to SES, 130 of 1172 (11.6%) patients assigned to EES, and 157 of 1173 (14.1%) patients assigned to ZES (SES versus ZES: HR, 0.89 [95% CI, 0.71–1.12], $P_{\text{log-rank}}$=0.31; EES versus ZES: HR, 0.82 [95% CI, 0.65–1.04], $P_{\text{log-rank}}$=0.10). There was no significant between-stent difference in the individual components of TVF (Figure 2) and other secondary clinical end points. The incidence of definite stent thrombosis (16 of 1169 [1.5%], 11 of 1172 [1.0%], and 13 of 1173 [1.2%], respectively) did not differ significantly (SES versus ZES: HR, 1.22 [95% CI, 0.59–2.54], $P_{\text{log-rank}}$=0.60; EES versus ZES: HR, 0.84 [95% CI, 0.38–1.88], $P_{\text{log-rank}}$=0.68). Patients treated with SES had a risk for clinical adverse events that was similar to patients treated with EES during 5-year follow-up (Table S4).The landmark analyses between 1- and 5-year follow-up also showed no statistically significant difference in the main and secondary end points for SES versus ZES and EES

Table 1. Clinical Events During 5-Year Follow-Up

	SES (n=1169)	EES (n=1172)	ZES (n=1173)	HR (95% CI) SES vs ZES	$P_{log\text{-}rank}$ SES vs ZES†	HR (95% CI) EES vs ZES	$P_{log\text{-}rank}$ EES vs ZES†
Death, any	92 (8.2)	85 (7.6)	106 (9.5)	0.86 (0.65–1.14)	0.28	0.80 (0.60–1.06)	0.12
Cardiac death	33 (3.0)	31 (2.8)	40 (3.6)	0.82 (0.52–1.30)	0.39	0.77 (0.48–1.24)	0.28
MI, any	66 (6.0)	56 (5.0)	60 (5.4)	1.09 (0.77–1.56)	0.62	0.93 (0.65–1.34)	0.70
Target vessel MI	50 (4.5)	44 (3.9)	50 (4.5)	1.00 (0.67–1.47)	0.98	0.88 (0.59–1.31)	0.52
Coronary revascularization, any	153 (14.0)	139 (12.7)	164 (15.0)	0.92 (0.74–1.14)	0.44	0.84 (0.67–1.05)	0.13
Target vessel revascularization	91 (8.3)	79 (7.2)	101 (9.3)	0.88 (0.67–1.17)	0.40	0.78 (0.58–1.04)	0.09
Target lesion revascularization	55 (5.0)	50 (4.6)	62 (5.7)	0.88 (0.61–1.26)	0.47	0.80 (0.55–1.16)	0.24
Nontarget vessel revascularization	86 (8.0)	79 (7.8)	85 (7.3)	1.08 (0.80–1.47)	0.62	1.08 (0.79–1.46)	0.64
Target vessel failure*	142 (12.7)	130 (11.6)	157 (14.1)	0.89 (0.71–1.12)	0.31	0.82 (0.65–1.04)	0.10
Target lesion failure	113 (10.1)	109 (9.7)	128 (11.5)	0.87 (0.68–1.12)	0.28	0.85 (0.66–1.09)	0.20
Major adverse cardiac events	178 (15.8)	174 (15.4)	198 (17.6)	0.88 (0.72–1.08)	0.23	0.87 (0.71–1.07)	0.19
Patient-oriented composite end point	256 (22.6)	237 (21.0)	270 (23.9)	0.93 (0.79–1.11)	0.42	0.87 (0.73–1.03)	0.11
Definite or probable stent thrombosis	20 (1.8)	15 (1.4)	19 (1.8)	1.05 (0.56–1.96)	0.89	0.79 (0.40–1.55)	0.49
Definite stent thrombosis	16 (1.5)	11 (1.0)	13 (1.2)	1.22 (0.59–2.54)	0.60	0.84 (0.38–1.88)	0.68
Probable stent thrombosis	4 (0.4)	4 (0.3)	6 (0.6)	0.66 (0.19–2.35)	0.52	0.67 (0.19–2.36)	0.53

Data are expressed as number (percentage). EES indicates everolimus-eluting stent; HR, hazard ratio; MI, myocardial infarction; SES, sirolimus-eluting stent; and ZES, zotarolimus-eluting stent.

*Main clinical end point of cardiac death, target vessel–related MI, or clinically indicated target vessel revascularization.

†See Table S3 for *P* values corrected with Holm-Bonferroni correction.

versus ZES (Table 2) (Holm-Bonferroni–corrected *P* values are presented in Table S5). Subgroup analyses showed no between-stent difference in the 5-year TVF rate (Figure 4 and Figure 5).

Noninferiority of the EES versus ZES at 5-year follow-up was confirmed with an absolute risk difference of –2.3% (97.5% CI, –5.3 to 0.7) and an upper limit of the 1-sided 97.5% CI of 0.4% ($P_{noninferiority}$=0.005). Moreover, noninferiority of the SES versus ZES at 5-year follow-up was confirmed with an absolute risk difference of –1.2% (97.5% CI, –4.3 to 1.9) and an upper limit of the 1-sided 97.5% CI of 1.5% ($P_{noninferiority}$=0.006).

Patients With Diabetes

Of all 3514 trial participants, 624 (17.8%) had diabetes, without any difference between stent groups. Of all patients with diabetes, 211 were treated with SES, 203 with EES, and 210 with ZES. Baseline patient, lesion, and procedural characteristics of these patients are presented in Table S6. Patients with diabetes were aged 65.5±10.1 years, 67.9% were men, and 22.8% were current smokers. At 5-year follow-up, 6.5% of the patients with diabetes used dual antiplatelet therapy and 21.9% used oral anticoagulants.

TVF occurred in 39 of 211 (19.8%) patients treated with SES, 37 of 203 (19.2%) treated with EES, and 41 of 210 (21.1%) treated with ZES (SES versus ZES: HR, 0.91 [95% CI, 0.59–1.42], $P_{log\text{-}rank}$=0.69; EES versus ZES: HR, 0.90 [95% CI, 0.58–1.40], $P_{log\text{-}rank}$=0.63) (Figure 3). All-cause and cardiac mortality were lower in patients with diabetes assigned to SES versus ZES (HR, 0.53 [95% CI, 0.30–0.93], $P_{log\text{-}rank}$=0.026; and HR, 0.35 [95% CI, 0.14–0.90], $P_{log\text{-}rank}$=0.030), but this was not statistically significant after applying the Holm-Bonferroni correction to adjust for testing between multiple groups (Table S7). In addition, no statistically significant difference in all-cause or cardiac mortality was found for treatment with EES versus ZES (HR, 0.71 [95% CI, 0.43–1.20], $P_{log\text{-}rank}$=0.20; and HR, 0.49 [95% CI, 0.21–1.14], $P_{log\text{-}rank}$=0.10). There was also no significant between-stent difference in other clinical end points (Table 3). Patients treated with EES had a similar risk for clinical adverse events than patients treated with SES during 5-year follow-up. (Table S4).

In addition, no significant between-stent difference in clinical outcome was found between patients with insulin-dependent and noninsulin-dependent diabetes, except for a higher rate of definite or probable stent thrombosis in patients with insulin-dependent diabetes treated with ZES as compared with EES (Table S8) (Holm-Bonferroni–corrected *P* values are presented in Table S9).

DISCUSSION

Main Findings

Five years after PCI, both the novel Orsiro SES and Synergy EES showed no significant difference in the main end point TVF as compared with the Resolute Integrity ZES. In addition, for all 3 stents, similar outcomes were found regarding mortality, myocardial infarction, and repeated revascularization. A landmark analysis between 1- and 5-year follow-up also

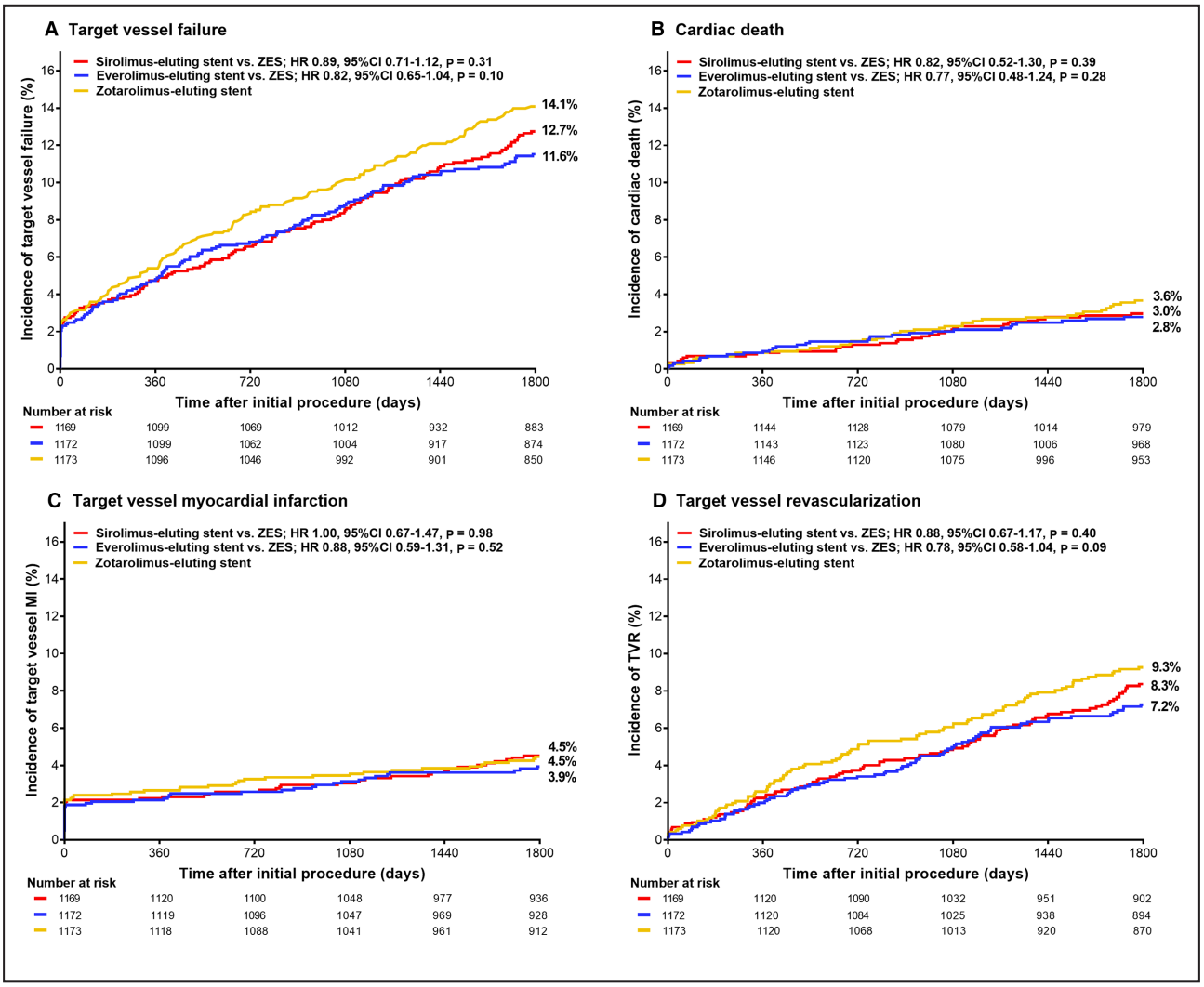

Figure 2. Kaplan–Meier curves for the main end point target vessel failure and its individual components at 5-year follow-up. Cumulative incidence of (**A**) target vessel failure (main composite end point) and its individual components (**B**) cardiac death, (**C**) target vessel–related MI, and (**D**) TVR. HR indicates hazard ratio; MI, myocardial infarction; TVR, target vessel revascularization; and ZES, zotarolimus-eluting stent.

showed no significant between-stent difference in the occurrence of the main end point and its components. Furthermore, in all 3 DES, a low incidence of very late stent thrombosis was found. The favorable long-term safety and efficacy of the 3 stents was consistent in various subgroups. A prespecified analysis of the diabetes subgroup revealed that cardiac mortality was numerically but not significantly lower in patients treated with Orsiro SES or Synergy EES versus Resolute Integrity ZES (3.0% or 4.2% versus 8.3%). Among patients with diabetes, there was no significant between-stent difference in the main end point and secondary end points other than mortality.

Five-Year Clinical Outcome in All-Comers

For Orsiro SES, 5-year follow-up has been reported by only 1 study, the BIOSCIENCE (Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularization) trial (n=2119). It assessed this SES versus a thin-strut durable polymer EES (Xience, Abbott Vascular) in all-comers and showed no difference in 5-year target lesion failure rate (20.2% versus 18.8%).[6] However, 2 other trials with a shorter follow-up and dissimilar study populations showed superiority in target lesion failure of the Orsiro SES versus the Xience EES.[12,13] One of these 2 trials had a follow-up of 2 years and was performed in patients with ST-segment–elevation myocardial infarction (STEMI),[12] while the other study with a follow-up of 3 years was performed in patients with any clinical syndrome except STEMI.[13] Our present analysis did not find such a difference; yet, there may be too many dissimilarities between the studies

Table 2. Landmark Analysis of Clinical Events Between 1- and 5-Year Follow-Up

	SES (n=1169)	EES (n=1172)	ZES (n=1173)	HR (95% CI) SES vs ZES	$P_{log\text{-}rank}$ SES vs ZES†	Difference (95% CI) EES vs ZES	$P_{log\text{-}rank}$ EES vs ZES†
Death, any	73 (6.4)	65 (5.7)	87 (7.6)	0.83 (0.61-1.13)	0.23	0.74 (0.54–1.02)	0.07
Cardiac death	23 (2.0)	21 (1.8)	30 (2.6)	0.76 (0.44-1.30)	0.31	0.60 (0.40–1.22)	0.20
MI, any	37 (3.3)	31 (2.8)	29 (2.6)	1.26 (0.77-2.05)	0.35	1.06 (0.64–1.76)	0.81
Target vessel MI	24 (2.1)	19 (1.7)	19 (1.7)	1,24(0.68-2.27)	0.48	0.99 (0.53–1.88)	0.98
Coronary revascularization, any	104 (9.5)	99 (9.0)	112 (10.2)	0.90 (0.69-1.18)	0.45	0.87 (0.66–1.14)	0.31
Target vessel revascularization	65 (5.8)	56 (5.0)	71 (6.3)	0.90 (0.64-1.25)	0.50	0.78 (0.55–1.11)	0.16
Target lesion revascularization	37 (3.3)	33 (2.9)	45 (4.0)	0.81 (0.52-1.24)	0.33	0.73 (0.46–1.14)	0.16
Nontarget vessel revascularization	62 (5.5)	67 (6.0)	57 (5.1)	0.70 (1.07-1.54)	0.70	1.18 (0.83–1.67)	0.37
Target vessel failure*	87 (7.9)	74 (6.7)	94 (8.6)	0.90 (0.67-1.21)	0.48	0.78 (0.57–1.05)	0.10
Target lesion failure	66 (6.0)	59 (5.3)	75 (6.8)	0.86 (0.62-1.19)	0.36	0.78 (0.55–1.09)	0.15
Major adverse cardiac events	119 (10.8)	114 (10.3)	137 (12.4)	0.85 (0.66-1.08)	0.18	0.82 (0.64–1.06)	0.13
Patient-oriented composite end point	169 (15.7)	156 (14.4)	180 (16.7)	0.91 (0.74-1.13)	0.40	0.85 (0.69–1.06)	0.15
Definite or probable stent thrombosis	15 (1.3)	10 (0.9)	13 (1.1)	1.14 (0.54-2.40)	0.73	0.77 (0.34–1.75)	0.52
Definite stent thrombosis	12 (1.1)	7 (0.6)	10 (0.9)	1.18 (0.51-2.74)	0.69	0.70 (0.27–1.84)	0.47
Probable stent thrombosis	3 (0.3)	3 (0.3)	3 (0.3)	0.99 (0.20-4.90)	0.99	1.00 (0.20–4.94)	0.997

Data are expressed as number (percentage). EES indicates everolimus-eluting stent; HR, hazard ratio; MI, myocardial infarction; SES, sirolimus-eluting stent; and ZES, zotarolimus-eluting stent.

*Main clinical end point of cardiac death, target vessel–related MI, or clinically indicated target vessel revascularization.

†See Table S5 for *P* values corrected with Holm-Bonferroni correction.

(eg, reference device, length of follow-up, and clinical syndrome at presentation) to justify a direct comparison. In addition, in BIO-RESORT, the 5-year target lesion failure rate for the Orsiro SES was substantially lower (10.1%) than in BIOSCIENCE (20.2%),[6] driven by lower cardiac mortality and target lesion revascularization rates. Dissimilarities in patient age and the proportion of patients with diabetes and with a history of previous coronary artery bypass grafting may have contributed to the outcome differences between trials.

The Synergy EES has been previously assessed in the EVOLVE II (The EVOLVE II Clinical Trial to Assess the SYNERGY Stent System for the Treatment of Atherosclerotic Lesion[s]) study (n=1684) in which no difference was found for the main end point target lesion failure versus the thin-strut durable polymer Promus Element EES (Boston Scientific).[8] At 5-year follow-up of that study, the target lesion failure rate for Synergy EES was 14.3%, which is slightly higher than the rate of 9.6% observed in the current analysis. This is surprising because that trial did not assess patients with acute STEMI and certain high-risk lesion criteria. In addition, at 5-year follow-up of the EVOLVE II trial, the use of dual antiplatelet therapy was disproportionately high (36.4%, versus 4.7% in BIO-RESORT). Nevertheless, the exclusion of patients with STEMI may in fact lead to higher event rates, as patients with STEMI are on average younger and have fewer comorbidities than patients who initially present with stable or unstable angina, in whom atherosclerosis may be more advanced.[14] Comparison of the patient characteristics at baseline supports this thought as the EVOLVE II patient population had more cardiovascular risk factors.

The Resolute Integrity ZES has been previously assessed in the DUTCH PEERS (Third-Generation Zotarolimus-Eluting and Everolimus-Eluting Stents in All-Comer Patients Requiring a Percutaneous Coronary Intervention) randomized trial, which compared it with the Promus Element EES in all-comers.[15] The trial found no difference in 5-year TVF rate, which in the 906 Resolute Integrity ZES–treated patients was comparable to the rate in ZES-treated patients in the present analysis (13.2% and 14.1%).

New-generation DES other than the study stents were compared in several other randomized trials, which also found no between-stent difference in clinical outcome at 5-year follow-up.[1,2,16] The results of the current analysis add to the body of evidence that shows in all-comers no significant difference between contemporary stents in 5-year clinical safety and efficacy.

Five-Year Clinical Outcome of Patients With Diabetes

Patients with diabetes have an increased risk of adverse events following PCI,[17–19] and it is clinically relevant to assess the long-term outcome of patients with diabetes, treated with contemporary DES. Previously, a subgroup analysis of the BIOSCIENCE trial in all-comer patients with diabetes showed no difference in target lesion failure between Orsiro SES and Xience EES

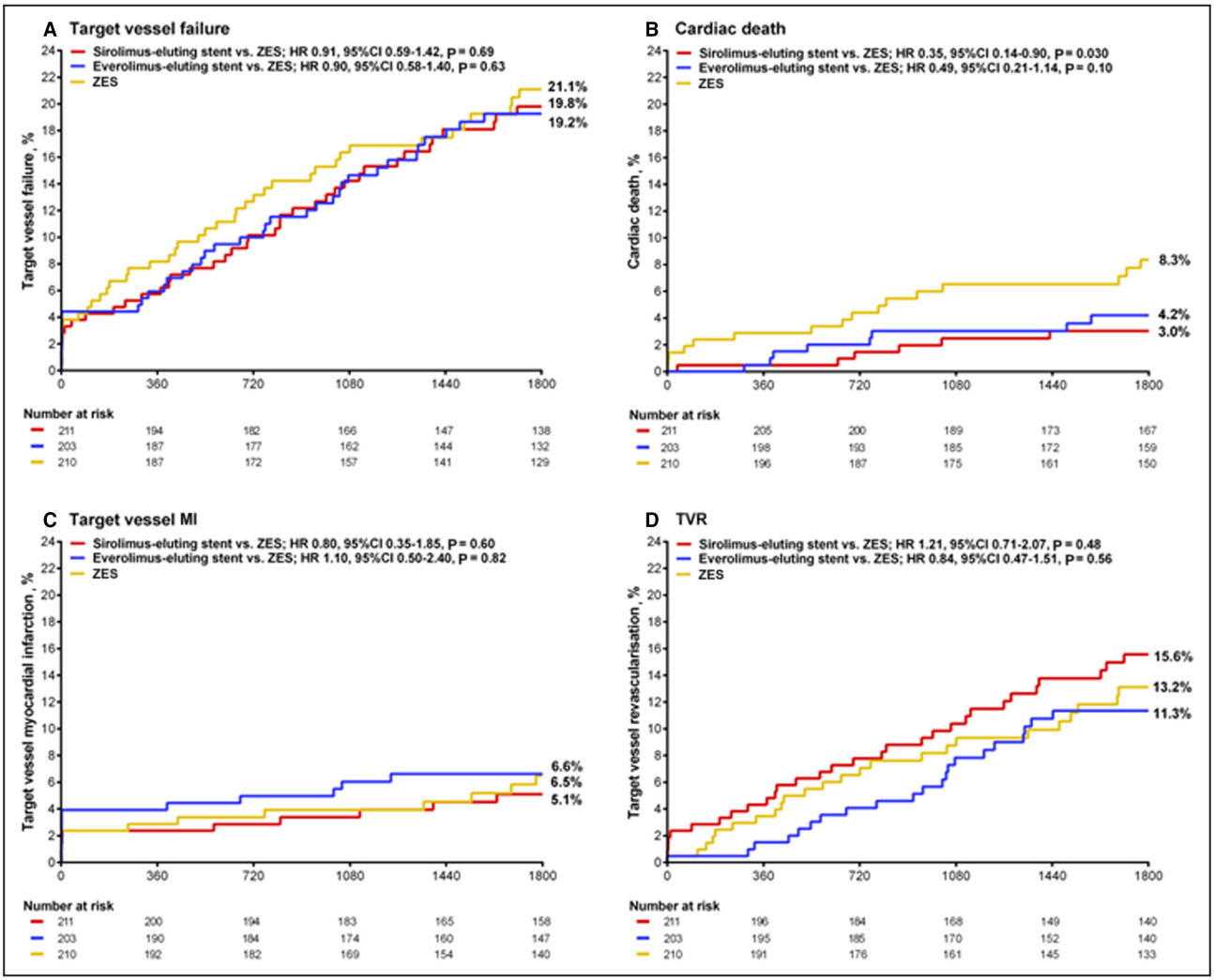

Figure 3. Kaplan–Meier curves for target vessel failure and its individual components in patients with diabetes at 5-year follow-up.
Cumulative incidence of (**A**) target vessel failure and its individual components (**B**) cardiac death, (**C**) target vessel-related MI, and (**D**) TVR. HR indicates hazard ratio; MI, myocardial infarction; TVR, target vessel revascularization; and ZES, zotarolimus-eluting stent.

(31.0% versus 25.8%).[9] In that study, the target lesion failure rates were higher than in the present analysis (SES, 14.7%; EES, 15.5%; ZES, 17.7%), as well as in several other studies. For example, the 5-year target lesion failure rate was 14.0% in 402 patients with diabetes who were treated with Orsiro SES in the BIOFLOW III (BIOTRONIK––Safety and Performance Registry for an All-comers Patient Population With the Limus Eluting Orsiro Stent System Within Daily Clinical Practice III) registry,[20] and it was 17.0% in 463 patients treated with Synergy EES in the EVOLVE II diabetes substudy.[8] In the RESOLUTE US (Clinical Evaluation of the Medtronic Resolute Zotarolimus-Eluting Coronary Stent System in the Treatment of De Novo Lesions in Native Coronary Arteries With a Reference Vessel Diameter of 2.25 mm to 4.2 mm) observational study, patients with diabetes (n=461) also showed a 5-year target lesion failure rate (16.9%) that was comparable to the target lesion failure rate of ZES-treated patients in the present analysis.[21]

Five-Year Mortality

Previous trials reported varying 5-year mortality rates following treatment with the study stents. For Synergy EES–treated patients, 5-year mortality in the EVOLVE II trial was similar to the mortality of Promus Element EES–treated patients (6.9% versus 7.4%).[8] EVOLVE II trial participants with diabetes, treated with Synergy EES, also had a low mortality rate (10.3%). These rates are comparable to the all-cause mortality of Synergy EES in our present trial, both in all-comers (7.6%) and in patients with diabetes (13.0%).

Table 3. Clinical Events During 5-Year Follow-Up in Patients With Diabetes

	SES (n=211)	EES (n=203)	ZES (n=210)	HR (95% CI) SES vs ZES	$P_{log\text{-}rank}$ SES vs ZES†	HR (95% CI) EES vs ZES	$P_{log\text{-}rank}$ EES vs ZES†
Death, any	19 (9.4)	25 (13.0)	34 (17.1)	0.53 (0.30–0.93)	*0.026*	0.71 (0.43–1.20)	0.20
Cardiac death	6 (3.0)	8 (4.2)	16 (8.3)	0.35 (0.14–0.90)	*0.030*	0.49 (0.21–1.14)	0.10
MI, any	16 (8.3)	15 (7.6)	14 (7.6)	1.10 (0.54–2.25)	0.80	1.09 (0.52–2.25)	0.83
Target vessel MI	10 (5.1)	13 (6.6)	12 (6.5)	0.80 (0.35–1.85)	0.60	1.10 (0.50–2.40)	0.82
Coronary revascularization, any	45 (23.6)	35 (18.5)	39 (21.0)	1.11 (0.73–1.71)	0.63	0.86 (0.55–1.36)	0.53
Target vessel revascularization	30 (15.6)	21 (11.3)	24 (13.2)	1.21 (0.71–2.07)	0.48	0.84 (0.47–1.51)	0.56
Target lesion revascularization	18 (9.2)	13 (6.9)	14 (7.8)	1.25 (0.62–2.51)	0.54	0.91 (0.43–1.93)	0.80
Nontarget vessel revascularization	22 (11.9)	20 (10.5)	18 (9.7)	1.15 (0.62–2.17)	0.66	1.08 (0.57–2.05)	0.81
Target vessel failure*	39 (19.8)	37 (19.2)	41 (21.1)	0.91 (0.59–1.42)	0.69	0.90 (0.58–1.40)	0.63
Target lesion failure	29 (14.7)	30 (15.5)	34 (17.7)	0.82 (0.50–1.34)	0.43	0.89 (0.54–1.49)	0.63
Major adverse cardiac events	45 (22.2)	48 (25.6)	52 (26.0)	0.83 (0.56–1.24)	0.37	0.93 (0.63–1.37)	0.71
Patient-oriented composite end point	65 (32.2)	64 (32.7)	69 (34.3)	0.90 (0.64–1.26)	0.54	0.92 (0.65–1.29)	0.62
Definite or probable stent thrombosis	8 (4.1)	4 (2.1)	8 (4.4)	0.96 (0.36–2.56)	0.94	0.49 (0.15–1.63)	0.24
Definite stent thrombosis	7 (3.6)	3 (1.6)	2 (1.1)	3.38 (0.70–16.25)	0.13	1.47 (0.25–8.81)	0.67
Probable stent thrombosis	1 (0.5)	1 (0.5)	6 (3.3)	0.16 (0.02–1.31)	0.09	0.16 (0.02–1.35)	0.09

Data are expressed as number (percentage). EES indicates everolimus-eluting stent; HR, hazard ratio; MI, myocardial infarction; SES, sirolimus-eluting stent; and ZES, zotarolimus-eluting stent.

*Main clinical end point of cardiac death, target vessel–related MI, or clinically indicated target vessel revascularization.

†See Table S7 for *P* values corrected with Holm-Bonferroni correction.

For Orsiro SES–treated patients, previous studies reported conflicting results. The BIOSCIENCE trial found a higher mortality for Orsiro SES than for Xience EES (14.1% versus 10.3%), but that difference was driven by cancer-related mortality.[6] In addition, in a diabetes substudy of BIOSCIENCE (n=486) the mortality rate was 20.9% in

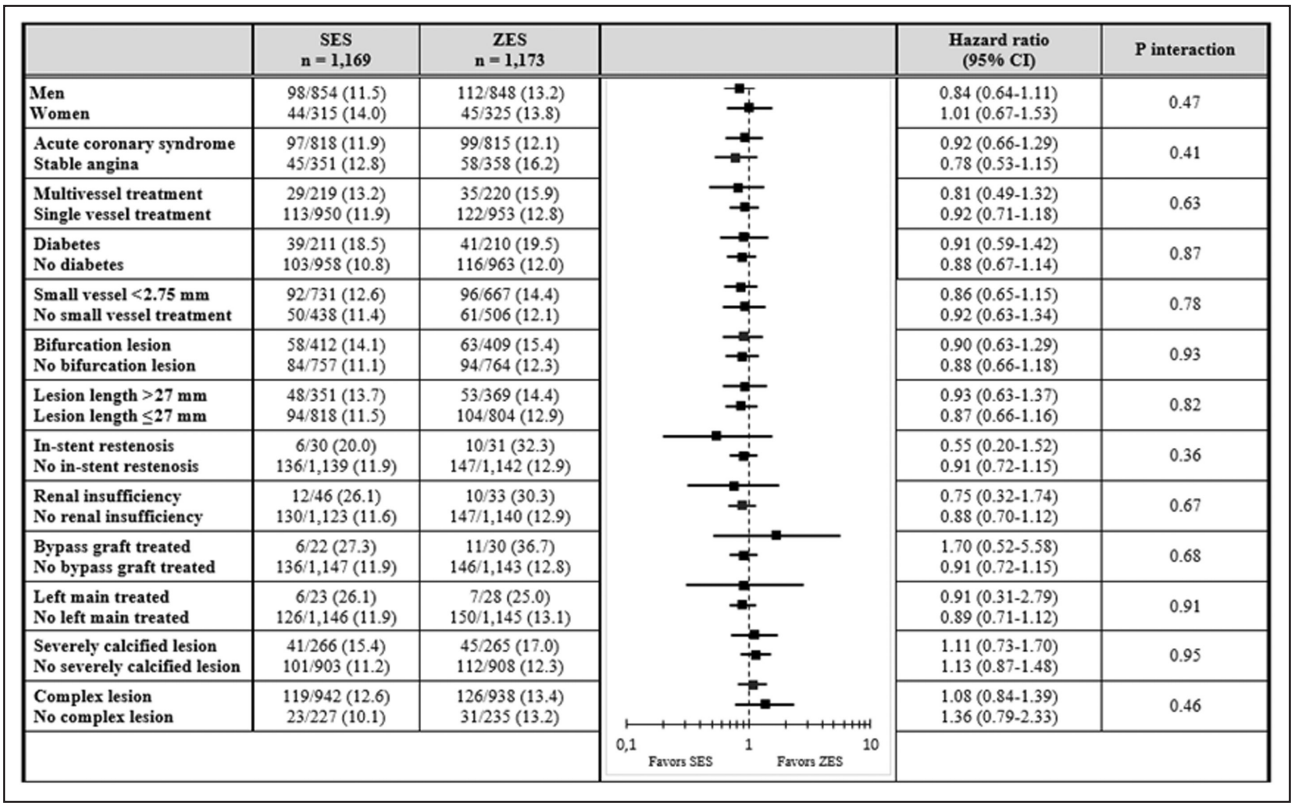

Figure 4. Subgroup analyses for target vessel failure at 5 years for SES versus ZES.
Data are expressed as n/N (percentage). SES indicates sirolimus-eluting stents; and ZES, zotarolimus-eluting stents.

	EES n = 1,172	ZES n = 1,173	Hazard ratio (95% CI)	P interaction
Men	97/845 (11.5)	112/848 (13.2)	0.86 (0.65-1.13)	0.55
Women	33/327 (10.1)	45/325 (13.8)	0.73 (0.47-1.14)	
Acute coronary syndrome	78/816 (9.6)	99/815 (12.1)	0.78 (0.58-1.04)	0.53
Stable angina	52/356 (14.6)	58/358 (16.2)	0.90 (0.62-1.31)	
Multivessel treatment	33/201 (16.4)	35/220 (15.9)	1.01 (0.63-1.62)	0.36
Single vessel treatment	97/971 (10.0)	122/953 (12.8)	0.78 (0.60-1.01)	
Diabetes	37/203 (18.2)	41/210 (19.5)	0.90 (0.58-1.40)	0.64
No diabetes	93/969 (9.6)	116/963 (12.0)	0.79 (0.60-1.04)	
Small vessel <2.75 mm	84/680 (12.4)	96/667 (14.4)	0.85 (0.63-1.14)	0.69
No small vessel treatment	46/492 (9.3)	61/506 (12.1)	0.77 (0.52-1.12)	
Bifurcation lesion	50/415 (12.0)	63/409 (15.4)	0.77 (0.53-1.11)	0.65
No bifurcation lesion	80/757 (10.6)	94/764 (12.3)	0.86 (0.64-1.15)	
Lesion length >27 mm	40/353 (11.3)	53/369 (14.4)	0.77 (0.51-1.16)	0.69
Lesion length ≤27 mm	90/819 (11.0)	104/804 (12.9)	0.85 (0.64-1.13)	
In-stent restenosis	5/28 (17.9)	10/31 (32.3)	0.51 (0.17-1.48)	0.37
No in-stent restenosis	125/1,144 (10.9)	147/1,142 (12.9)	0.84 (0.66-1.07)	
Renal insufficiency	8/25 (27.6)	10/28 (30.3)	0.85 (0.34-2.15)	0.97
No renal insufficiency	122/1,143 (10.7)	147/1,140 (12.9)	0.82 (0.65-1.04)	
Bypass graft treated	10/18 (55.6)	11/30 (36.7)	1.79 (0.76-4.22)	0.10
No bypass graft treated	120/1,154 (10.4)	146/1,143 (12.8)	0.81 (0.63-1.03)	
Left main treated	5/25 (20.0)	7/28 (25.0)	0.82 (0.65-1.04)	0.88
No left main treated	125/1,147 (10.9)	150/1,145 (13.1)	0.83 (0.65-1.05)	
Severely calcified lesion	34/252 (13.5)	45/265 (17.0)	0.78 (0.50-1.21)	0.75
No severely calcified lesion	96/920 (10.4)	112/908 (12.3)	0.84 (0.64-1.11)	
Complex lesion	104/903 (11.5)	126/938 (13.4)	0.85 (0.66-1.11)	0.57
No complex lesion	26/269 (9.7)	31/235 (13.2)	0.72 (0.43-1.21)	

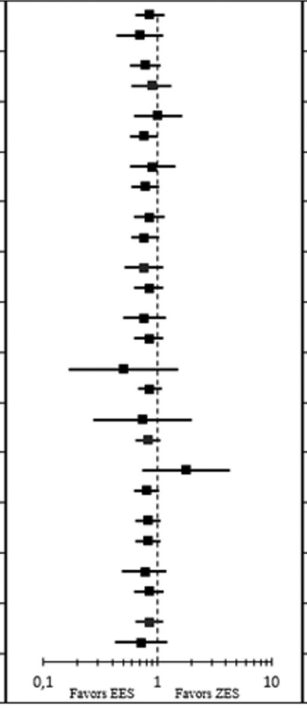

Figure 5. Subgroup analyses for target vessel failure at 5 years of EES versus ZES.
Data are expressed as n/N (percentage). EES indicates everolimus-eluting stents; and ZES, zotarolimus-eluting stents.

patients treated with Orsiro SES and 13.8% with Xience EES (*P*=0.053).[9] Furthermore, a registry of diabetic patients with any clinical syndrome except STEMI observed a 5-year mortality of 15.5% in Orsiro SES–treated patients.[20] In our present analysis, all-comer patients treated with Orsiro SES had a relatively low mortality rate (8.2%), and in patients with diabetes we found a mortality rate that was also low and lower than in patients treated with Resolute Integrity ZES (9.4% versus 17.1%).

Notably, the lack of difference in 5-year mortality rates of Orsiro SES– and Resolute Integrity ZES–treated patients in BIO-RESORT challenge the findings of the BIOSCIENCE trial, which suggest an increased mortality in patients treated with Orsiro SES, driven by cancer-related death.[6] The poly-L-lactic acid polymer-coating of Orsiro SES gradually degrades into carbon dioxide and hydrogen,[22] which both have no systemic carcinogenic effects. Consequently, we cannot think of any reasonable explanation for a higher or lower all-cause mortality risk associated with the Orsiro SES. We feel that the higher mortality rate in the all-comers of BIOSCIENCE may have resulted from a play of chance.

Limitations

The current analysis has some limitations. Although various adverse events (and not only the main end point) were independently adjudicated by a clinical event committee, this large-scale randomized clinical trial was not powered to assess secondary end points. Hence, such findings should be considered hypothesis generating. Furthermore, residual confounding cannot be excluded, but it may be limited by the fact that multiple patient-, target lesion–, interventional procedure–, and medical therapy–related parameters were assessed. Follow-up was not available in 2% (87 of 3514) of patients because of loss to follow-up and in 7% (244 of 3514) consent withdrawal, without any between-stent difference. Of note, a follow-up of 5 years was intended from the very beginning of the current trial. However, as funding was initially not guaranteed beyond 3-year follow-up, the medical ethics committee did not permit consenting patients for a follow-up of 5 years but demanded reconsenting every patient after 3 years, once additional funding was granted. Regrettably, 4% of the study participants refused to reconsent and these patients were classified as "consent withdrawal." Nevertheless, with only 2% (87 of 3514) of patients, the actual loss to follow-up during all 5 years was low. In addition, the 91% completeness of 5-year follow-up is similar to that of various other randomized stent trials with conventional clinical follow-up.[4,7,16,23]

CONCLUSIONS

Orsiro SES, Synergy EES, and Resolute Integrity ZES showed similar 5-year outcomes of safety and efficacy, including mortality. A prespecified stent comparison in patients with diabetes also revealed no significant differences in 5-year clinical outcomes.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Tables S1–S9

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Supplemental Material

Table S1. Baseline patient, lesion and procedural characteristics of all patients

	All patients n = 3,514	SES n = 1,169	EES n = 1,172	ZES n = 1,173
Age, yrs	63.9 ± 10.8	64.2 ± 10.7	64.0 ± 10.7	63.6 ± 10.9
Male	2547 (72.5)	854 (73.1%)	845 (72.1%)	848 (72.3%)
Body mass index, kg/m^2	27.4 ± 4.2	27.4 ± 4.2	27.6 ± 4.2	27.3 ± 4.0
Current smoker	1,031/3,422 (30.1)	341/1,144 (29.8)	336/1,135 (29.6)	354/1,143 (31.0)
Medical history				
Family history of CAD	1,557/3,372 (46.2)	516/1,120 (46.1)	512/1,114 (46.0)	529/1,138 (46.5)
Diabetes, medically treated	624 (17.8)	211 (18.0)	203 (17.3)	210 (17.9)
Hypertension	1624 (46.2)	550 (47.0)	520 (44.4)	554 (47.2)
Hypercholesterolemia	1335 (38.0)	463 (39.6)	422 (36.0)	450 (38.4)
Previous MI	649 (18.5)	209 (17.9)	192 (16.4)	248 (21.1)
Previous PCI	626 (17.8)	214 (18.3)	214 (18.3)	198 (16.9)
Previous CABG	267 (7.6)	80 (6.8)	91 (7.8)	96 (8.2)
Previous stroke	231 (6.6)	76 (6.5)	74 (6.3)	81 (6.9)
Renal insufficiency*	108 (3.1)	46 (3.9)	29 (2.5)	33 (2.8)
Clinical presentation				
Acute coronary syndrome	2449 (69.7)	818 (70.0)	816 (69.6)	815 (69.5)
Stable angina	1065 (30.3)	351 (30.0)	356 (30.4)	358 (30.5)
Lesion characteristics				
At least 1 complex lesion	2783 (79.2)	942 (80.6)	903 (77.0)	938 (80.0)
At least 1 bifurcation lesion	1236 (35.2)	412 (35.2)	415 (35.4)	409 (34.9)
At least 1 chronic total occlusion	139 (4.0)	47 (4.0)	44 (3.8)	48 (4.1)
At least 1 bypass graft lesion	70 (2.0)	22 (1.9)	18 (1.5)	30 (2.6)
At least 1 ostial lesion	252 (7.2)	74 (6.3)	97 (8.3)	81 (6.9)
At least 1 severely calcified lesion	783 (22.3)	266 (22.8)	252 (21.5)	265 (22.6)
Procedural details				
Implantation of assigned stents only	3,446 (98.1)	1,144 (97.9)	1,155 (98.5)	1,147 (97.8)
Total stent length per patient, mm	31 (20-50)	30 (18-49)	32 (20-48)	30 (22-52)
Direct stenting	589 (16.8)	207 (17.7)	208 (17.7)	174 (14.8)
Postdilation	2833 (80.6)	946 (80.9)	960 (81.9)	927 (79.0)
Multivessel treatment	640 (18.2)	219 (18.7)	201 (17.2)	220 (18.8)
Radial approach	1597 (45.4)	530 (45.3)	523 (44.6)	544 (46.4)
IVUS	62 (1.8)	20 (1.7)	20 (1.7)	22 (1.9)
OCT	21 (0.6)	9 (0.8)	7 (0.6)	5 (0.4)
FFR	391 (11.1)	131 (11.2)	133 (11.3)	127 (10.8)

Values are mean ± SD, n (%) or median (interquartile range, 25th-75th percentile). *Defined as an estimated glomerular filtration rate of < 30 ml/min/1.73m^2 or the need for dialysis.
Abbreviations: CAD = coronary artery disease; CABG = coronary artery bypass grafting; EES = everolimus-eluting stent; FFR = Fractional Flow Reserve; IVUS = Intravasculair Ultra Sound; MI = myocardial infarction; OCT = Optical Coherence tomography; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent; ZES = zotarolimus-eluting stent.

Table S2. Medication at 5-year follow-up for all patients and for patients with diabetes

	All patients n = 2,950	**SES n = 994**	**EES n = 982**	**ZES n = 974**	**p-value**
Aspirin	2,288 (77.6)	779 (78.4)	751 (76.5)	758 (77.8)	0.58
DAPT	139 (4.7)	59 (5.9)	37 (3.8)	43 (4.4)	0.07
With clopidogrel	103 (3.5)	39 (3.9)	30 (3.1)	34 (3.5)	0.58
With prasugrel or ticagrelor	36 (1.2)	20 (2.0)	7 (0.7)	9 (0.9)	*0.02*
Oral anticoagulation	467 (15.8)	161 (16.2)	161 (16.2)	145 (14.9)	0.62
Oral anticoagulation with $P2Y_{12}$ inhibitor	23 (0.8)	12 (1.2)	3 (0.3)	8 (0.8)	0.07
	Patients with diabetes n = 493	**SES n = 168**	**EES n = 169**	**ZES n = 156**	**p-value**
Aspirin	346 (70.2)	118 (70.2)	122 (72.2)	106 (67.9)	0.71
DAPT	32 (6.5)	16 (9.5)	8 (4.7)	8 (5.1)	0.14
With clopidogrel	25 (5.1)	11 (6.5)	7 (4.1)	7 (4.5)	0.56
With prasugrel or ticagrelor	7 (1.4)	5 (3.0)	1 (0.6)	1 (0.6)	0.11
Oral anticoagulation	108 (21.9)	37 (22.0)	26 (21.3)	35 (22.4)	0.97
Oral anticoagulation with $P2Y_{12}$ inhibitor	5 (1.0)	1 (0.6)	1 (0.6)	3 (1.9)	0.39

Numbers are n (%). Data available in 2,950/3,514 patients (SES 994/1,169; EES 982/1,172; ZES 974/1,173), and 493/624 patients with diabetes (SES 168/211; EES 169/203; ZES 156/210).
Abbreviations: DAPT = dual Antiplatelet Therapy; EES = everolimus-eluting stent; SES = sirolimus-eluting stent; ZES = zotarolimus-eluting stent.

Table S3. Holm-Bonferroni corrected p-values of 5-year clinical outcomes

	Hazard ratio (95% CI) SES *vs* ZES	$P'_{log\text{-}rank}$ † SES *vs* ZES	Hazard ratio (95% CI) EES *vs* ZES	$P'_{log\text{-}rank}$ † EES *vs* ZES
Death, any	0.86 (0.65-1.14)	0.28	0.80 (0.60-1.06)	0.24
Cardiac death	0.82 (0.52-1.30)	0.39	0.77 (0.48-1.24)	0.56
Myocardial infarction, any	1.09 (0.77-1.56)	1.00	0.93 (0.65-1.34)	0.70
Target vessel myocardial infarction	1.00 (0.67-1.47)	0.98	0.88 (0.59-1.31)	1.00.
Coronary revascularization, any	0.92 (0.74-1.14)	0.44	0.84 (0.67-1.05)	0.26
Target vessel revascularization	0.88 (0.67-1.17)	0.40	0.78 (0.58-1.04)	0.18
Target lesion revascularization	0.88 (0.61-1.26)	0.47	0.80 (0.55-1.16)	0.48
Non-target vessel revascularization	1.08 (0.80-1.47)	1.00	1.08 (0.79-1.46)	0.64
Target vessel failure*	0.89 (0.71-1.12)	0.31	0.82 (0.65-1.04)	0.20
Target lesion failure	0.87 (0.68-1.12)	0.28	0.85 (0.66-1.09)	0.40
Major adverse cardiac events	0.88 (0.72-1.08)	0.23	0.87 (0.71-1.07)	0.38
Patient-oriented composite endpoint	0.93 (0.79-1.11)	0.42	0.87 (0.73-1.03)	0.22
Definite-or-probable stent thrombosis	1.05 (0.56-1.96)	0.89	0.79 (0.40-1.55)	0.98
Definite stent thrombosis	1.22 (0.59-2.54)	1.00	0.84 (0.38-1.88)	0.68
Probable stent thrombosis	0.66 (0.19-2.35)	1.00	0.67 (0.19-2.36)	0.53

†P'-values are corrected with Holm-Bonferroni correction. *Main clinical endpoint of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization.
Abbreviations: EES = everolimus-eluting stent; SES = sirolimus-eluting stent; ZES = zotarolimus-eluting stent.

Table S4. Clinical events during 5-year follow-up, comparison SES vs EES in all-comer patients and in diabetes patients

All-comer patients.				
	SES n = 1,169	**EES n = 1,172**	**Hazard ratio (95% CI) EES *vs* SES**	**$P_{log\text{-}rank}$ EES *vs* SES**
Death, any	92 (8.2)	85 (7.6)	0.93 (0.69-1.25)	0.63
Cardiac death	33 (3.0)	31 (2.8)	0.94 (0.58-1.54)	0.82
Myocardial infarction, any	66 (6.0)	56 (5.0)	0.85 (0.60-1.21)	0.37
Target vessel myocardial infarction	50 (4.5)	44 (3.9)	0.88 (0.59-1.32)	0.54
Coronary revascularization, any	153 (14.0)	139 (12.7)	0.91 (0.73-1.15)	0.44
Target vessel revascularization	91 (8.3)	79 (7.2)	0.88 (0.65-1.18)	0.39
Target lesion revascularization	55 (5.0)	50 (4.6)	0.92 (0.62-1.34)	0.65
Non-target vessel revascularization	86 (8.0)	79 (7.8)	1.00 (0.74-1.35)	0.98
Target vessel failure*	142 (12.7)	130 (11.6)	0.92 (0.73-1.17)	0.50
Target lesion failure	113 (10.1)	109 (9.7)	0.97 (0.75-1.26)	0.83
Major adverse cardiac events	178 (15.8)	174 (15.4)	0.99 (0.80-1.22)	0.90
Patient-oriented composite endpoint	256 (22.6)	237 (21.0)	0.93 (0.78-1.11)	0.43
Definite-or-probable stent thrombosis	20 (1.8)	15 (1.4)	0.75 (0.39-1.47)	0.40
Definite stent thrombosis	16 (1.5)	11 (1.0)	0.69 (0.32-1.49)	0.34
Probable stent thrombosis	4 (0.4)	4 (0.3)	1.00 (0.25-4.00)	1.00
Patients with diabetes				
	SES n = 211	**EES n = 203**	**Hazard ratio (95% CI) EES *vs* SES**	**$P_{log\text{-}rank}$ SES *vs* ZES**
Death, any	19 (9.4)	25 (13.0)	1.36 (0.75-2.46)	0.32
Cardiac death	6 (3.0)	8 (4.2)	1.38 (0.48-4.00)	0.55
Myocardial infarction, any	16 (8.3)	15 (7.6)	0.98 (0.49-1.99)	0.96
Target vessel myocardial infarction	10 (5.1)	13 (6.6)	1.37 (0.60-3.11)	0.47
Coronary revascularization, any	45 (23.6)	35 (18.5)	0.78 (0.50-1.22)	0.27
Target vessel revascularization	30 (15.6)	21 (11.3)	0.70 (0.40-1.22)	0.21
Target lesion revascularization	18 (9.2)	13 (6.9)	0.73 (0.36-1.49)	0.39
Non-target vessel revascularization	22 (11.9)	20 (10.5)	0.95 (0.52-1.74)	0.86
Target vessel failure*	39 (19.8)	37 (19.2)	0.98 (0.63-1.54)	0.93
Target lesion failure	29 (14.7)	30 (15.5)	1.08 (0.65-1.80)	0.77
Major adverse cardiac events	45 (22.2)	48 (25.6)	1.11 (0.74-1.67)	0.62

Patient-oriented composite endpoint	65 (32.2)	64 (32.7)	1.02 (0.73-1.45)	0.90
Definite-or-probable stent thrombosis	8 (4.1)	4 (2.1)	0.51 (0.15-1.69)	0.26
Definite stent thrombosis	7 (3.6)	3 (1.6)	0.44 (0.11-1.69)	0.22
Probable stent thrombosis	1 (0.5)	1 (0.5)	1.04 (0.07-16.61)	0.98

Data are n (%). *Main clinical endpoint of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization.
Abbreviations: CI = confidence interval; EES = everolimus-eluting stent; SES = sirolimus-eluting stent; ZES = zotarolimus-eluting stent

Table S5. Holm-Bonferroni corrected p-values of landmark analysis between 1 and 5-year follow-up

	Hazard ratio (95% CI) SES *vs* ZES	$P'_{log\text{-}rank}$ † SES *vs* ZES	Difference (95% CI) EES *vs* ZES	$P'_{log\text{-}rank}$ † EES *vs* ZES
Death, any	1.21 (0.89-1.65)	0.23	0.74 (0.54-1.02)	0.14
Cardiac death	1.32 (0.77-2.28)	0.31	0.60 (0.40-1.22)	0.40
Myocardial infarction, any	0.79 (0.49-1.29)	0.70	1.06(0.64-1.76)	0.81
Target vessel myocardial infarction	0.80 (0.44-1.47)	0.98	0.99 (0.53-1.88)	0.98
Coronary revascularization, any	1.11 (0.85-1.45)	0.45	0.87 (0.66-1.14)	0.62
Target vessel revascularization	1.12 (0.80-1.57)	0.50	0.78 (0.55-1.11)	0.32
Target lesion revascularization	1.24 (0.80-1.92)	0.33	0.73 (0.46-1.14)	0.32
Non-target vessel revascularization	0.93 (0.65-1.33)	0.70	1.18 (0.83-1.67)	0.74
Target vessel failure*	1.11 (0.83-1.49)	0.48	0.78 (0.57-1.05)	0.20
Target lesion failure	1.17 (0.84-1.62)	0.36	0.78 (0.55-1.09)	0.30
Major adverse cardiac events	1.18 (0.93-1.51)	0.18	0.82 (0.64-1.06)	0.26
Patient-oriented composite endpoint	1.10 (0.89-1.35)	0.40	0.85 (0.69-1.06)	0.30
Definite-or-probable stent thrombosis	0.88 (0.42-1.84)	0.73	0.77 (0.34-1.75)	1.00
Definite stent thrombosis	0.85 (0.37-2.00)	0.69	0.70 (0.27-1.84)	0.94
Probable stent thrombosis	1.01 (0.20-5.01)	1.00	1.00 (0.20-4.94)	0.997

†P'-values are corrected with Holm-Bonferroni correction. *Main clinical endpoint of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization.
Abbreviations: EES = everolimus-eluting stent; SES = sirolimus-eluting stent; ZES = zotarolimus-eluting stent.

Table S6. Baseline patient, lesion and procedural characteristics of patients with diabetes

	All patients with diabetes n = 624	SES n = 211	EES n = 203	ZES n = 210	p-value
Age, yrs	66.5 ± 10.1	67.1 ± 9.6	66.7 ± 9.6	65.5 ± 10.9	0.25
Male	424 (67.9)	146 (69.2)	142 (70.0)	136 (64.8)	0.47
Body mass index, kg/m^2	29.3 ± 4.7	29.7 ± 4.4	29.3 ± 4.9	29.1 ± 4.7	0.41
Current smoker	136/597 (22.8)	46/201 (22.9)	39/195 (20.0)	51/201 (25.4)	0.44
Medical history					
Family history of CAD	250/577 (43.3)	86/193 (44.6)	79/185 (42.7)	85/199 (42.7)	0.91
Hypertension	423 (67.8)	146 (69.2)	133 (65.5)	144 (68.6)	0.69
Hypercholesterolemia	321 (51.4)	109 (51.7)	102 (50.2)	110 (52.4)	0.91
Previous MI	149 (23.9)	54 (25.6)	40 (19.7)	55 (26.2)	0.23
Previous PCI	157 (25.2)	56 (26.5)	57 (28.1)	44 (21.0)	0.21
Previous CABG	81 (13.0)	27 (12.8)	29 (14.3)	25 (11.9)	0.77
Previous stroke	68 (10.9)	29 (13.7)	18 (8.9)	21 (13.7)	0.25
Renal insufficiency*	42 (6.7)	18 (8.5)	7 (3.4)	17 (8.1)	0.07
Clinical presentation					
Acute coronary syndrome	380 (60.9)	129 (61.1)	127 (62.6)	124 (59.0)	0.76
Stable angina	244 (39.1)	82 (38.9)	76 (37.4)	86 (41.0)	0.76
Lesion characteristics†					
At least 1 complex lesion	493 (79.0)	174 (82.5)	151 (74.4)	168 (80.0)	0.12
At least 1 bifurcation lesion	235 (37.7)	74 (35.1)	74 (36.5)	87 (41.4)	0.37
At least 1 chronic total occlusion	33 (5.3)	13 (6.2)	12 (5.9)	8 (3.8)	0.50
At least 1 bypass graft lesion	19 (3.0)	5 (2.4)	5 (2.5)	9 (4.3)	0.44
At least 1 ostial lesion	47 (7.5)	15 (7.1)	18 (8.9)	14 (6.7)	0.67
At least 1 severely calcified lesion	162 (26.0)	54 (25.6)	53 (26.1)	55 (26.2)	0.99
Procedural details					
Implantation of assigned stents only	611 (97.9)	209 (99.1)	199 (98.0)	203 (96.7)	0.23
Total stent length per patient, mm	39 (18-49)	38 (18-45)	38 (20-50)	40 (22-52)	0.50
Direct stenting	91 (14.6)	33 (15.6)	33 (16.3)	25 (11.9)	0.40
Postdilation	487 (78.0)	167 (79.1)	152 (74.9)	168 (80.0)	0.41
Multivessel treatment	113 (18.1)	34 (16.1)	31 (15.3)	48 (22.9)	0.09
Radial approach	321 (51.4)	114 (54.0)	108 (53.2)	99 (47.1)	0.31

Values are mean ± SD, n (%) or median (interquartile range, 25th-75th percentile). *Defined as an estimated glomerular filtration rate of < 30 ml/min/1.73m^2 or the need for dialysis. †Details and definitions of lesion characteristics have been previously reported.
Abbreviations: CAD = coronary artery disease; CABG = coronary artery bypass grafting; EES = everolimus-eluting stent; MI = myocardial infarction; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent; ZES = zotarolimus-eluting stent.

Table S7. Holm-Bonferroni corrected p-values for 5-year clinical outcome of patients with diabetes

	Hazard ratio (95% CI) SES *vs* ZES	P'$_{log\text{-}rank}$ † SES *vs* ZES	Hazard ratio (95% CI) EES *vs* ZES	P'$_{log\text{-}rank}$ † EES *vs* ZES
Death, any	0.53 (0.30-0.93)	*0.052*	0.71 (0.43-1.20)	0.20
Cardiac death	0.35 (0.14-0.90)	*0.060*	0.49 (0.21-1.14)	0.10
Myocardial infarction, any	1.10 (0.54-2.25)	1.00	1.09 (0.52-2.25)	0.83
Target vessel myocardial infarction	0.80 (0.35-1.85)	1.00	1.10 (0.50-2.40)	0.82
Coronary revascularization, any	1.11 (0.73-1.71)	0.63	0.86 (0.55-1.36)	1.00
Target vessel revascularization	1.21 (0.71-2.07)	0.96	0.84 (0.47-1.51)	0.56
Target lesion revascularization	1.25 (0.62-2.51)	1.00	0.91 (0.43-1.93)	0.80
Non-target vessel revascularization	1.15 (0.62-2.17)	1.00	1.08 (0.57-2.05)	0.81
Target vessel failure*	0.91 (0.59-1.42)	0.69	0.90 (0.58-1.40)	1.00
Target lesion failure	0.82 (0.50-1.34)	0.86	0.89 (0.54-1.49)	0.63
Major adverse cardiac events	0.83 (0.56-1.24)	0.74	0.93 (0.63-1.37)	0.71
Patient-oriented composite endpoint	0.90 (0.64-1.26)	1.00	0.92 (0.65-1.29)	0.62
Definite-or-probable stent thrombosis	0.96 (0.36-2.56)	0.94	0.49 (0.15-1.63)	0.48
Definite stent thrombosis	3.38 (0.70-16.25)	0.26	1.47 (0.25-8.81)	0.67
Probable stent thrombosis	0.16 (0.02-1.31)	0.18	0.16 (0.02-1.35)	0.09

†P'-values are corrected with Holm-Bonferroni correction. *Main clinical endpoint of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization.
Abbreviations: EES = everolimus-eluting stent; SES = sirolimus-eluting stent; ZES = zotarolimus-eluting stent.

Table S8. Five-year clinical outcome of patients with insulin-dependent diabetes and non-insulin-dependent diabetes

Patients with insulin-dependent diabetes					
	SES n = 70	**EES n = 74**	**ZES n = 76**	**$P_{log\text{-}rank}$ † SES *vs* ZES**	**$P_{log\text{-}rank}$ † EES *vs* ZES**
Death, any	7 (10.4)	8 (11.2)	14 (19.8)	0.12	0.12
Cardiac death	2 (3.1)	2 (2.8)	7 (10.3)	0.10	0.07
Myocardial infarction, any	8 (12.6)	8 (11.0)	5 (7.8)	0.39	0.40
Target vessel myocardial infarction	4 (6.1)	8 (11.0)	5 (7.8)	0.77	0.40
Coronary revascularization, any	19 (30.3)	15 (21.4)	14 (21.9)	0.35	0.88
Target vessel revascularization	11 (17.2)	10 (14.3)	11 (17.6)	0.98	0.59
Target lesion revascularization	9 (14.1)	5 (7.0)	8 (12.6)	0.79	0.30
Target vessel failure*	14 (21.4)	18 (25.2)	17 (24.8)	0.56	0.95
Target lesion failure	13 (20.1)	14 (19.4)	15 (21.9)	0.71	0.81
Major adverse cardiac events	20 (29.9)	20 (27.7)	21 (29.3)	0.90	0.78
Definite-or-probable stent thrombosis	4 (6.1)	0	6 (9.1)	0.55	0.010
Definite stent thrombosis	4 (6.1)	0	1 (1.4)	0.17	0.32
Patients with non-insulin-dependent diabetes					
	SES n = 141	**EES n = 129**	**ZES n = 134**	**$P_{log\text{-}rank}$ † SES *vs* ZES**	**$P_{log\text{-}rank}$ † EES *vs* ZES**
Death, any	12 (8.8)	17 (13.9)	20 (15.6)	0.10	0.65
Cardiac death	4 (3.0)	6 (5.0)	9 (7.3)	0.12	0.45
Myocardial infarction, any	8 (6.1)	7 (5.7)	9 (7.5)	0.69	0.65
Target vessel myocardial infarction	6 (4.6)	5 (4.0)	7 (5.9)	0.67	0.58
Coronary revascularization, any	26 (20.2)	20 (16.6)	25 (20.6)	0.93	0.48
Target vessel revascularization	19 (14.7)	11 (9.3)	13 (10.8)	0.35	0.70
Target lesion revascularization	9 (6.8)	8 (6.8)	6 (5.3)	0.51	0.55
Target vessel failure*	25 (18.9)	19 (15.6)	24 (19.2)	0.97	0.47
Target lesion failure	16 (11.9)	16 (13.2)	19 (15.5)	0.48	0.67
Major adverse cardiac events	25 (18.3)	28 (22.6)	31 (24.2)	0.30	0.80
Definite-or-probable stent thrombosis	4 (3.1)	4 (3.3)	2 (1.7)	0.47	0.40
Definite stent thrombosis	3 (2.4)	3 (2.5)	1 (1.0)	0.36	0.31

Data are n (%).†P-values are corrected with Bonferroni correction (α=0.025). See Table S9 for p-values corrected with Holm-Bonferroni correction.*Main clinical endpoint of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization.
Abbreviations: EES = everolimus-eluting stent; SES = sirolimus-eluting stent; ZES = zotarolimus-eluting stent.

Table S9. Holm-Bonferroni corrected p-values for 5-year clinical outcome of patients with insulin-dependent diabetes and non- insulin-dependent diabetes

Patients with insulin-dependent diabetes		
	P'$_{log\text{-}rank}$ † SES *vs* ZES	**P'$_{log\text{-}rank}$ † EES *vs* ZES**
Death, any	0.24	0.12
Cardiac death	0.10	0.14
Myocardial infarction, any	0.78	0.40
Target vessel myocardial infarction	0.77	0.80
Coronary revascularization, any	0.70	0.88
Target vessel revascularization	0.98	1.00
Target lesion revascularization	0.79	0.60
Target vessel failure*	1.00	0.95
Target lesion failure	1.00	0.81
Major adverse cardiac events	0.90	1.00
Definite-or-probable stent thrombosis	0.55	0.020
Definite stent thrombosis	0.34	0.32
Patients with non-insulin-dependent diabetes		
	P'$_{log\text{-}rank}$ † SES *vs* ZES	**P'$_{log\text{-}rank}$ † EES *vs* ZES**
Death, any	0.20	0.65
Cardiac death	0.24	0.45
Myocardial infarction, any	0.69	1.00
Target vessel myocardial infarction	0.67	1.00
Coronary revascularization, any	0.93	0.96
Target vessel revascularization	0.70	0.70
Target lesion revascularization	1.00	0.55
Target vessel failure*	0.97	0.94
Target lesion failure	0.96	0.67
Major adverse cardiac events	0.60	0.80
Definite-or-probable stent thrombosis	0.47	0.80
Definite stent thrombosis	0.36	0.62

†P'-values are corrected with Holm-Bonferroni correction. *Main clinical endpoint of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization.
Abbreviations: EES = everolimus-eluting stent; SES = sirolimus-eluting stent; ZES = zotarolimus-eluting stent.