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Comparison of a Novel Biodegradable Polymer Sirolimus-Eluting Stent With a Durable Polymer Everolimus-Eluting Stent

Results of the Randomized BIOFLOW-II Trial

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Background—Biodegradable polymers for release of antiproliferative drugs from drug-eluting stents aim to improve vascular healing. We assessed noninferiority of a novel ultrathin strut drug-eluting stent releasing sirolimus from a biodegradable polymer (Orsiro, O-SES) compared with the durable polymer Xience Prime everolimus-eluting stent (X-EES) in terms of the primary end point in-stent late lumen loss at 9 months.

Methods and Results—A total of 452 patients were randomly assigned 2:1 to treatment with O-SES (298 patients, 332 lesions) or X-EES (154 patients, 173 lesions) in a multicenter, noninferiority trial. The primary end point was in-stent late loss at 9 months. O-SES was noninferior to X-EES for the primary end point (0.10±0.32 versus 0.11±0.29 mm; difference=0.00063 mm; 95% confidence interval, −0.06 to 0.07; $P_{\text{noninferiority}}<0.0001$). Clinical outcome showed similar rates of target-lesion failure at 1 year (O-SES 6.5% versus X-EES 8.0%; hazard ratio=0.82; 95% confidence interval, 0.40–1.68; log-rank test: $P=0.58$) without cases of stent thrombosis. A subgroup of patients (n=55) underwent serial optical coherence tomography at 9 months, which demonstrated similar neointimal thickness among lesions allocated to O-SES and X-EES (0.10±0.04 mm versus 0.11±0.04 mm; −0.01 [−0.04, −0.01]; $P=0.37$). Another subgroup of patients (n=56) underwent serial intravascular ultrasound at baseline and 9 months indicating a potential difference in neointimal area at follow-up (O-SES, 0.16±0.33 mm^2 versus X-EES, 0.43±0.56 mm^2; $P=0.04$).

Conclusions—Compared with durable polymer X-EES, novel biodegradable polymer–based O-SES was found noninferior for the primary end point in-stent late lumen loss at 9 months. Clinical event rates were comparable without cases of stent thrombosis throughout 1 year of follow-up.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01356888.

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Drug-eluting stents (DESs) have mitigated the issue of restenosis inherent to bare metal stents.[1] In addition, new-generation DESs have addressed concerns of very late stent thrombosis (ST) previously observed with early-generation devices.[2–5] Notwithstanding, very late lumen loss (LLL) referred to as catch-up phenomenon as evidenced during serial angiographic follow-up continues to be observed with new-generation DES.[6] Moreover, case reports of hypersensitivity reactions after new-generation DES implantation maintain concerns over durable polymer biocompatibility.[7] Finally, neoatherosclerosis with emergence of atherosclerotic lesions within the stented segment gives rise to both restenosis and plaque rupture/erosion and seems related to a differential healing response after DES implantation.[8,9] In view of the above

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WHAT IS KNOWN

- New-generation durable polymer–based drug-eluting stents have improved outcomes compared with early-generation drug-eluting stents.
- Biodegradable polymers aim to further improve the long-term vascular healing to prevent late angiographic catch-up of late lumen loss and neoatherosclerosis.
- The Orsiro stent is a novel ultrathin (60 μm) cobalt–chromium–based platform releasing sirolimus from biodegradable poly-L lactic acid polymer.

WHAT THE STUDY ADDS

- The biodegradable polymer–based Orsiro stent provides similar effectiveness as the durable polymer–based Xience stent at 9-month angiographic follow-up.
- Intracoronary imaging using both optical coherence tomography and intravascular ultrasound imaging indicates a high rate of covered and apposed struts at 9 months.

considerations, continued efforts to improve DES technology are warranted.

The Orsiro stent is a novel platform releasing sirolimus from biodegradable poly-L lactic acid polymer, which completely degrades during a period of 12 to 24 months. The metallic stent platform consists of ultrathin (60 μm) Cobalt-chromium L605 struts covered with an amorphous silicon carbide layer (Figure 1). The passive coating seals the stent surface and reduces interaction between the metal stent and the surrounding tissue by acting as a diffusion barrier.[10] This thin-layer, amorphous silicon carbide coating is deposited onto the surface of the stent through a plasma-enhanced chemical vapor deposition technique. In vitro studies have shown ≤96% reduction of metal ion release when the stent surface is coated with silicon carbide.[11] Pharmacokinetic studies attested to adequate drug release and tissue retention in vivo, and experimental studies showed inflammatory scores comparable to bare metal stents during long-term follow-up throughout 6 months.[12] Following results of a first-in-man study comprising 30 patients,[13] the Biotronik-Safety and Clinical Performance of the Drug Eluting Orsiro Stent in the Treatment of Subjects With Single De Novo Coronary Artery Lesions-II (BIOFLOW-II) trial was designed to directly compare the angiographic efficacy of the novel biodegradable polymer–based sirolimus-eluting Orsiro stent (O-SES) with the durable polymer–based everolimus-eluting Xience Prime stent (X-EES) platform in a randomized, multicenter, assessor-blind, noninferiority trial. Our primary hypothesis was that O-SES is not inferior to X-EES in terms of the primary end point LLL at 9 months. Owing to the limited number of studies with O-SES, we decided to use a 2:1 allocation ratio to gather more information on the newer study stent. Predefined subgroups underwent additional investigations by serial optical coherence tomography (OCT) and intravascular ultrasound.

Methods

Study Design

The BIOFLOW-II trial was a randomized, multicenter, assessor-blind, noninferiority trial comparing the biodegradable polymer–based O-SES with the durable polymer–based X-EES in patients with stable or unstable coronary artery disease undergoing percutaneous coronary intervention registered at ClinicalTrials.gov (NCT01356888). Patients were recruited between July 2011 and March 2012 in 24 centers in 8 European countries. The trial was sponsored by Biotronik AG, Bülach, Switzerland. The study complied with the declaration of Helsinki and was approved by all institutional ethics committees. Patients provided written, informed consent.

Patient Population

Patients who were ≥18 and <80 years of age with stable or unstable angina pectoris, silent ischemia, or clinical evidence of myocardial ischemia were eligible in the presence of de novo coronary lesions ≤26 mm in length in native vessels with a reference vessel diameter ranging from 2.25 to 4.0 mm suitable for coronary stent implantation. The most important exclusion criteria encompassed evidence of myocardial infarction within 72 hours prior to the procedure, or elevated biomarkers within 24 hours of the procedure, unprotected left main or 3 vessel coronary artery disease, and left ventricular function <30%.

Procedures

Patients were randomly allocated to treatment with O-SES (Orsiro, Biotronik, Bülach, Switzerland) or X-EES (Xience Prime, Abbott, IL) to achieve a 2:1 randomization ratio. Central randomization was performed after all inclusion criteria had been met in the absence of exclusion criteria and after diagnostic angiography but prior to percutaneous coronary intervention, with concealment of allocation ensured by means of a web-based system. The allocation sequence was computer generated in randomly varying blocks and stratified by center and diabetic status. Both stent types were available in diameters of 2.25, 2.5, 2.75, 3.0, 3.5, and 4.0 mm. Available stent lengths were 8, 12, 15, 18, 23, 28, 33, and 38 mm for X-EES and 9, 13, 15, 18, 22, 26, and 30 mm for O-SES. Balloon angioplasty and coronary stent implantation were performed using standard techniques. Prior to stent implantation, predilatation with a balloon somewhat smaller in diameter than the reference vessel diameter was recommended but

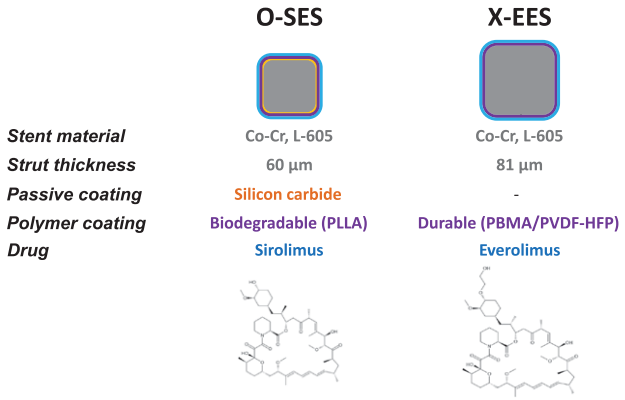

Figure 1. Stent material, strut thickness, passive and polymer coating, and antiproliferative drug components of the stent platforms (biodegradable polymer–based sirolimus-eluting stents and durable polymer–based everolimus-eluting stents) used in the Biotronik-Safety and Clinical Performance of the Drug Eluting Orsiro Stent in the Treatment of Subjects With Single De Novo Coronary Artery Lesions-II (BIOFLOW-II) trial. O-SES indicates sirolimus-eluting Orsiro stent; PBMA, poly n-butyl methacrylate; PLLA, poly-l lactic acid; PVDF-HFP, poly vinylidene fluoride co-hexafluoropropylene; and X-EES, Xience Prime everolimus-eluting stent.

not mandatory. Stent length was expected to cover the entire target lesion to assure full lesion coverage with a single stent. It was advised to avoid stent overlap with the exception for bailout or if the first stent did not completely cover the target lesion.

Acetylsalicylic acid at a dose of 75 to 100 mg during ≥3 days prior to the procedure or 250 to 500 mg during the procedure was given. Clopidogrel was given with a loading dose of 300 to 600 mg per os within 6 hours prior or during the procedure except for those patients who were on clopidogrel 75 mg per day for ≥7 days. Dual antiplatelet therapy consisting of acetylsalicylic acid and clopidogrel was prescribed for the duration of ≥6 months in all patients. The use of novel P2Y12 inhibitors was allowed if clinically indicated. During the procedure, intravenous unfractionated heparin or low-molecular-weight heparin according to local practice was given to all patients. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. Creatine kinase, creatine kinase-MB, and troponin were assessed at admission and within 6 to 24 hours after the procedure or at discharge whichever came first. In case of elevated cardiac enzymes after the procedure, creatine kinase, creatine kinase-MB, and troponin measurements were continued every 8 hours until the peak of the biomarkers had been defined. A 12-lead ECG was performed prior to the procedure, within 6 to 24 hours after the procedure, at discharge, and in case of recurrent signs of ischemia.

Data Management

Independent study monitors verified source data according to a prespecified monitoring plan. Data were stored in a central database (e-capture.net/Belgium), which was maintained by a contract research organization (e-novex bvba, Antwerp, Belgium). Follow-ups were scheduled at 30 days and 6, 9, and 12 months, and patients were questioned about the occurrence of angina, any adverse events, hospitalization, and antithrombotic medication intake and were asked to complete the EQ-5D quality-of-life questionnaire. All patients were asked to return for an angiographic follow-up study at 9 months. Any death, myocardial infarction, revascularization, and ST were independently adjudicated by a blinded clinical event committee.

Quantitative Coronary Angiography

Coronary angiograms were digitally recorded at baseline, immediately after the procedure, and at follow-up and were assessed at the angiographic core laboratory of MedStar Health Research Institute, Washington, DC. Angiogram readers were blinded to the assigned study stent.

Angiograms were recorded in 2 orthogonal views with matching projections taken before and after the procedure and at 9-month follow-up, and the average of those views was taken for all subjects. Orthogonal views with the highest resolution and no foreshortening or overlap of the vessel had to be taken by the investigators. In case only one orthogonal view of sufficient quality was available for the analysis, evaluation was based on this 1 view.

Measurements were performed on the cineangiograms after maximum vasodilatation with nitroglycerin, and the contrast-filled, nontapered catheter tip was used for calibration (≥6F guiding catheter). Digital angiograms were analyzed with the help of an automated edge-detection system (QAngio XA, Version 7.1.14.0; Medis Medical Imaging Systems, Leiden, The Netherlands). Quantitative measurements included the diameter of the reference vessel, the minimal luminal diameter, percent diameter stenosis (difference between reference vessel diameter and minimal luminal diameter/reference diameter × 100), and LLL (difference between minimal lumen diameter after the procedure and minimal lumen diameter at follow-up). Binary restenosis was defined as stenosis of ≥50% of the minimal lumen diameter in the target lesion at angiographic follow-up. All angiographic measurements of the target lesion were obtained within the stented segment (in-stent) and over the entire segment comprising the stent and its 5 mm proximal and distal margins (in-segment).

Optical Coherence Tomography

The OCT substudy was performed at 6 of 24 sites in 65 patients at baseline. OCT of the stented segment was performed at baseline and follow-up using the frequency domain C7 console of Lightlab (St Jude, Westford, MA) with a nonocclusive imaging technique as previously described. Offline OCT data analysis was undertaken by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) blinded to stent type allocation, clinical, and procedural characteristics of the patients. Analysis of contiguous cross-sections at 1 mm longitudinal intervals within the stented segment was performed using offline software QIVUS (MEDIS, Leiden, The Netherlands). Stent and lumen areas were traced semiautomatically. Neointima area was defined as the difference between stent minus lumen area. This definition was used for frames without any malapposition area. In frames with malapposition, this was adjusted accordingly. The number of stent struts was determined in each cross section. Thickness (μm) of the tissue coverage on the luminal side of each strut was measured at the middle of the long axis of the strut. A linear measurement line was drawn from the endoluminal leading edge perpendicular to the long axis of the strut toward the luminal leading edge of the strut. Struts were classified as apposed (when the strut was in contact with the vessel wall) or malapposed if protruding into the lumen at a distance greater than the strut thickness.

Intravascular Ultrasound

The intravascular ultrasound study (IVUS) substudy was performed at 5 of 24 sites in 66 patients at baseline. Intravascular ultrasound imaging was performed after intracoronary administration of i.c. nitroglycerin using motorized pullback (0.5 mm/s). Sites used either Volcano or Boston Scientific IVUS consoles and catheters. All follow-up examinations at 9 months were performed with the same type of console and catheter as at baseline. Images were continuously recorded throughout the stent and ≥5 mm distal and proximal to the stent. Offline IVUS data analysis was undertaken by an independent core laboratory (MedStar Health Research Institute, Washington, DC) blinded to stent type allocation, clinical, and procedural characteristics of the patients. Using computerized planimetry, the reference segment external elastic membrane, stent, and lumen were measured every 1.0 mm within the stent. Neointima was calculated as stent minus lumen measures. Incomplete stent apposition was defined as ≥1 stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut without overlapping side branches.

Study End Points and Definitions

The primary end point of the study was in-stent LLL at 9 months after stent implantation as assessed by quantitative coronary angiography in an independent core laboratory (Medstar, Washington, DC). Secondary angiographic end points included in-segment LLL and in-stent and in-segment minimal luminal diameter, percent diameter stenosis, and binary restenosis.

Prespecified end points of patients included into the OCT substudy comprised neointimal hyperplasia, strut coverage, and stent apposition at 9 months. Prespecified end points of patients included into the IVUS substudy comprised neointimal hyperplasia and incomplete stent apposition at 9 months. We also addressed clinical events at 1 year as secondary end points. The definition of cardiac death included any death due to proximate cardiac cause (eg, myocardial infarction, low-output failure, and fatal arrhythmia), procedure-related deaths, including those related to concomitant treatment, unwitnessed death, and death of unknown cause. Myocardial infarction was adjudicated and reported according to both the Joint ESC/ACCF/AHA/WHF Task Force universal definition of myocardial infarction[14] and on the basis of the Academic Research Consortium extended historical definition of myocardial infarction. Target-lesion revascularization (TLR) was defined as any repeat percutaneous coronary intervention within the stent or within the 5-mm borders adjacent to the stent or bypass surgery of the target vessel. Revascularization of the target lesion and vessel was regarded as clinically driven, if the stenosis on any target lesion or vessel was ≥50% of the diameter of the vessel on the basis of

quantitative coronary angiography in the presence of recurrent angina or objective signs of ischemia or if the stenosis was ≥70% of the diameter of the vessel even in the absence of ischemic signs and symptoms. Target-lesion failure was defined as the composite of cardiac death, target-vessel myocardial infarction, coronary artery bypass grafting, or clinically driven TLR, and target-vessel failure was defined as the composite of cardiac death, target-vessel myocardial infarction, coronary artery bypass grafting, or clinically driven target-vessel revascularization. ST was defined according to the Academic Research Consortium definition as definite, probable, or possible.[15] Device success was defined as a final residual diameter stenosis of <30% by quantitative coronary angiography, using the assigned device. Procedure success was defined as a final residual diameter stenosis of <30% by quantitative coronary angiography, using any percutaneous method, without the occurrence of death, myocardial infarction, or repeat revascularization of the target lesion during the hospital stay. All adverse events were adjudicated by an independent clinical event committee.

Statistical Analysis

This was a noninferiority trial, which was powered for noninferiority on the primary end point in-stent LLL at 9 months. Based on available results on LLL in Everolimus-eluting stents (SPIRIT III Trial[16]: in-stent LLL at 8 months=0.16±0.41 mm; Resolute All Comers Trial[17]: in-stent LLL at 13 months=0.19±0.40 mm), we assumed a mean in-stent LLL at 9 months of 0.16±0.40 mm for both stents. Sample size calculation assumed a noninferiority margin of 0.16 mm as the acceptable difference between O-SES and X-EES, where the difference is defined as LLL (O-SES) minus LLL (X-EES), an average number of lesions per subject of 1.3, a design factor of 1.1 to account for the clustering of lesions within patients, an angiographic follow-up rate of 80%, and an allocation ratio of 2:1 for O-SES and X-EES. Under these assumptions, we estimated that a total of 440 patients (293 in the Orsiro group and 147 in the Xience Prime group) or 352 subjects with angiographic follow-up (234 in the Orsiro group and 118 in the Xience Prime group) will yield a power of 1-β=80% at a 2-sided α=5%. Analyses were performed by a statistician of an academic clinical trials unit (CTU Bern, Bern University Hospital, Switzerland) in Stata (Stata Inc., College Station, TX). For the noninferiority and superiority analysis of angiographic end points we used mixed maximum-likelihood logistic and linear regression models that allowed for correlation of multiple lesions within patients. We used the Cox proportional-hazard model to estimate hazard ratios and 95% confidence intervals (CIs) for between-group comparison of clinical outcomes and the log-rank test to calculate corresponding *P* values. All patients who underwent randomization were included in the analysis of primary outcome and secondary clinical outcomes in the groups to which they were originally allocated to, regardless of the treatment actually received (intention-to-treat principle). OCT and IVUS substudies were performed with 2 separate subgroups of patients. OCT and IVUS end points are means calculated at lesion level. OCT and IVUS continuous variables are presented as mean±SD, and comparison was performed by unpaired *t* test between the randomized groups. All *P* values and CIs are 2-sided. No adjustments were made for multiple comparisons. The analysis was performed by a statistician at the Clinical Trials Unit at Bern University Hospital who had full access to the data and was independent of the sponsor. The sponsor of the study was involved in the design of the study but not in the data management and analysis of the data.

Results

Patient flow and trial profile are summarized in Figure 2. Between July 2011 and March 2012, 452 patients were randomly assigned 2:1 to treatment with O-SES (298 patients, 332 lesions) or X-EES (154 patients, 173 lesions). A total of 298 patients allocated to O-SES and 154 patients allocated to X-EES received ≥1 stent. Eleven patients (3.7%) allocated to O-SES and 6 patients allocated to X-EES (4.5%) were lost to follow-up before reaching 1 year.

Baseline clinical characteristics are summarized in Table 1 and were balanced in both groups including risk factors for coronary artery disease, clinical presentation, and left ventricular function. The mean age of all patients was 63.4±10.0 years, 77% were men, and 28% had diabetes mellitus. Procedural characteristics including number of treated lesions and vessels per patient, the frequency distribution in terms of lesion location, preprocedural Thrombolysis in Myocardial Infarction grade flow, and average lesion and stent length were similar for both groups (Table 2). All subjects received the allocated study stent. Device (100% versus 100%, *P*=1.00) and procedural success (97.4% versus 97.5%, *P*=1.00) were comparable for the 2 devices as were the angiographic lesion measurements before and immediately after stent implantation (Table 2).

Angiographic Outcomes

Angiographic follow-up at 270±14 days was completed in 385 of 452 patients (85%) with 427 of 505 lesions (85%; Table 3). A total of 253 patients (85%) allocated to O-SES and 132 patients (86%) allocated to X-EES underwent follow-up angiography. Among patients undergoing angiographic follow-up, clinical baseline characteristics were similar between O-SES and X-EES with the exception of age (62.7±10.4 versus 64.8±9.2, *P*=0.04).

According to the prespecified noninferiority margin of 0.16 mm, O-SES was noninferior to X-EES for the primary angiographic end point in-stent LLL at 9 months (0.10±0.32 versus 0.11±0.29 mm; difference=0.00063 mm; 95% CI, −0.06 to 0.07, $P_{\text{noninferiority}}$<0.0001). A post hoc test derived from the CI for the primary end point indicates that noninferiority would have been declared at an α level of 5% with a more stringent margin of 0.07 mm. The cumulative frequency of in-stent LLL for the 2 stent groups at the time of follow-up angiography is shown in Figure 3. In-segment LLL amounted to 0.09±0.35 mm for O-SES and 0.09±0.33 mm for X-EES (*P*=0.86). Other angiographic measures including in-stent and in-segment minimal lumen diameter and percent diameter stenosis were comparable for the 2 stent types (Table 3). In-segment binary restenosis was 4.0% among lesions allocated to the O-SES and 4.7% among lesions allocated to the X-EES (*P*=0.93). Figure 4 shows the results of a stratified analysis for the primary end point LLL. Results were consistent irrespective of age, diabetes mellitus, lesion length, reference vessel diameter, and lesion location.

Clinical Outcomes

The use of dual antiplatelet therapy was high in both the O-SES and X-EES groups. The rate of dual antiplatelet therapy at discharge was 99.3% versus 98.7% (*P*=0.12), at 30 days 99.3% versus 99.3% (*P*=1.00), at 6 months 83.6% versus 81.0% (*P*=0.23), and at 12 months 67.6% versus 62.6% (*P*=0.30).

Clinical event rates at 1-year follow-up are summarized in Table 4. The device-related composite end point target-lesion failure occurred with similar frequency among patients in the O-SES and X-EES group (O-SES 6.5% versus X-EES 8.0%; hazard ratio=0.82; 95% CI, 0.40–1.68; *P*=0.58; Figure 5A). Rates of cardiac death (0.7% versus 0.7%, *P*=0.98), target-vessel myocardial infarction (2.7% versus 2.6%, *P*=0.95), and clinically indicated TLR (3.5% versus 4.7%, *P*=0.54)

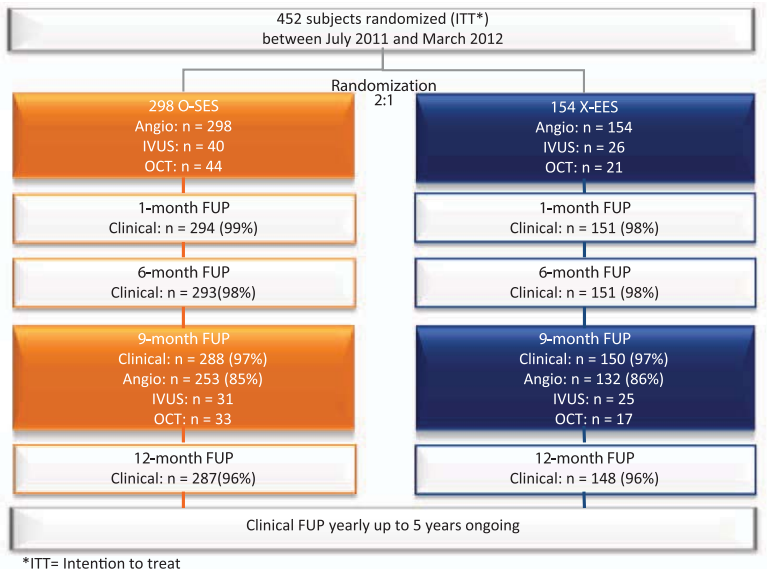

Figure 2. Trial profile and flow chart of the patients. A total of 452 patients underwent percutaneous coronary intervention with either sirolimus-eluting Orsiro stent (O-SES) or Xience Prime everolimus-eluting stent (X-EES) platform at 24 international sites during the inclusion period. FUP indicates follow-up; IVUS, intravascular ultrasound study; and OCT, optical coherence tomography.

were comparable for patients in the O-SES and X-EES group (Figure 5). There was no case of ST irrespective of definition with either stent type throughout the follow-up period (Table 4).

OCT Findings

Forty-four patients allocated to O-SES and 21 patients allocated to X-EES were included into the prespecified OCT substudy at baseline and underwent OCT using the non-occlusive technique. Baseline clinical characteristics of patients undergoing OCT were comparable for both stent groups. At the time of angiographic follow-up, 36 lesions (from 33 patients) allocated to O-SES and 19 lesions (from 17 patients) allocated to X-EES underwent OCT. In lesion-based analyses, mean neointimal thickness was similar in O-SES and X-EES (0.10±0.04 versus 0.11±0.04 mm; *P*=0.37; Table 5). There were no differences in terms of lumen and stent area between stent types. Strut-based analysis showed a low proportion of malapposed (1.11±2.32% versus 0.77±2.04%; difference 0.34 [−0.95, 1.62]; *P*=0.43) and uncovered struts (1.98±3.71% versus 2.71±3.31%; difference −0.73 [−2.80, 1.34]; *P*=0.48) in the O-SES and X-EES groups during follow-up.

Intravascular Ultrasound Findings

Forty patients allocated to Orsiro and 26 patients allocated to Xience Prime were included into the prespecified IVUS substudy at baseline with similar baseline clinical characteristics for both stent groups. At the time of angiographic follow-up, 31 lesions (from 31 patients) allocated to O-SES and 25 lesions (from 25 patients) allocated to X-EES underwent IVUS follow-up. Mean neointimal area was somewhat smaller among lesions allocated to O-SES compared with those allocated to X-EES (0.16±0.33 versus 0.43±0.56 mm^2; *P*=0.04; Table 6). There were no differences in terms of stent and vessel area between stent types. No case of stent malapposition was observed in either group.

Table 1. Baseline Clinical Characteristics

	Biodegradable Polymer Sirolimus-Eluting Stent	Durable Polymer Everolimus-Eluting Stent
No. of patients, n	298	154
Age, y (SD)	62.72±10.39	64.82±9.21
Male sex, n (%)	233 (78.19)	115 (74.68)
Cardiac risk factors		
Diabetes mellitus, n (%)	84 (28.19)	44 (28.57)
of which insulin-requiring diabetes mellitus	18 (21.43)	15 (34.09)
Hypertension, n (%)	231 (77.78)	119 (77.27)
Hypercholesterolaemia, n (%)	202 (68.01)	113 (73.38)
Current smoking, n (%)	87 (29.19)	37 (24.03)
History of myocardial infarction, n (%)	90 (30.20)	31 (20.13)
Left ventricular ejection fraction, % (SD)	62.33±11.07	63.96±11.17
Long lesions (>20 mm; n [%])	51 (17.11)	27 (17.53)
Average no. of lesions per patient, n (SD)	1.1±0.32	1.12±0.33

Values are mean±SD or n (%).

Table 2. Procedural Results

	Biodegradable Polymer Sirolimus-Eluting Stent	Durable Polymer Everolimus-Eluting Stent	*P* Value
No. of lesions, n	332	173	
Preprocedural results			
Lesion length, mm (SD)	13.36±6.82	13.65±5.58	0.64
Reference vessel diameter, mm (SD)	2.78±0.49	2.75±0.49	0.54
Minimal lumen diameter, mm (SD)	0.93±0.46	0.96±0.46	0.64
Stenosis, % lumen diameter (SD)	66.73±14.27	65.34±14.52	0.44
Target-lesion localization			0.10
Left main, n (%)	1 (0.30)	0 (0.00)	
Left anterior descending artery, n (%)	148 (44.71)	69 (39.88)	
Left circumflex artery, n (%)	73 (22.05)	55 (31.79)	
Right coronary artery, n (%)	109 (32.93)	49 (28.32)	
Type of stent			
Biodegradable polymer O-SES	360	0	
Durable polymer X-EES	0	186	
Other drug-eluting stent	0	0	
Procedural results			
No. of study stents per patient, n (SD)	1.22±0.52	1.21±0.45	0.83
Maximal stent diameter per patient, mm (SD)	3.13±0.47	3.07±0.47	0.16
Total stent length per patient, mm (SD)	22.3±12.0	21.2±8.3	0.33
Direct stenting, n (%)	155 (46.4)	72 (41.6)	0.30
Implantation of study stent, n (%)			
Device success, n (%)	332(100)	173 (100)	1.00
Procedure success, n (%)	297 of 305 (97.4)	154 of 158 (97.5)	1.00
Minimal lumen diameter, mm (SD)			
In-stent	2.62±0.45	2.58±0.41	0.35
In-segment	2.33±0.48	2.31±0.45	0.54
Diameter stenosis, % (SD)			
In-stent	6.91±7.25	7.07±7.70	0.81
In-segment	17.44±7.00	17.42±6.64	0.95
Acute gain, mm (SD)			
In-stent	1.69±0.47	1.62±0.46	0.15
In-segment	1.40±0.49	1.35±0.48	0.26

Values are mean±SD or n (%). O-SES indicates sirolimus-eluting Orsiro stent; and X-EES, Xience Prime everolimus-eluting stent.

Discussion

In the randomized, multicenter, assessor-blind, noninferiority BIOFLOW-II trial, the novel biodegradable polymer–based O-SES fulfilled the prespecified noninferiority criteria for the primary end point in-stent LLL at 9 months compared with the durable polymer–based X-EES. Findings were robust across all angiographic measures of stent efficacy, including minimal lumen diameter, percent diameter stenosis, and binary restenosis. Subgroups—notably lesions in small vessels and diabetic patients—showed similar angiographic efficacy outcomes, and results were supported using intracoronary imaging by means of OCT and IVUS.

The efficacy of the novel biodegradable polymer–based O-SES is notable by matching one of the most effective devices, the durable polymer–based X-EES. The latter DES platform has been shown to more effectively reduce the risk of TLR not only compared with paclitaxel-eluting stents[18,19] but also early-generation sirolimus-eluting Cypher stents,[20] and it marks the current standard of care in terms of safety and efficacy. In addition, the angiographic potency of the O-SES with an in-stent LLL of 0.10±0.32 mm at 9 months compares well with other new-generation DES.[21–28] The O-SES platform has several distinguishing characteristics. First, the strut thickness of the device is reduced to 60 μm (Figure 1). Thin as compared with thick struts have been reported to reduce arterial injury and angiographic restenosis in case of bare metal stents,[29] but it remains to be shown whether differences in strut thickness are clinically meaningful when applied to new-generation DES. Second, the Orsiro sirolimus-eluting stent has a circumferential stent coating consisting of silicon carbide. Whether the additional silicon carbide layer portends any advantage particularly during the

Table 3. Angiographic Follow-Up Results at 9 Months (Primary End Point)

	Mean±SD or n (%)		Difference	
	Biodegradable Polymer Sirolimus-Eluting Stent	Durable Polymer Everolimus-Eluting Stent	Estimate (95% CI)	*P* Value
No. of lesions, n	278	149		
Reference vessel diameter, mm	2.78±0.49	2.74±0.48	0.05 (–0.05 to 0.14)	0.35
Minimal lumen diameter, mm (SD)				
In-stent	2.52±0.56	2.48±0.50	0.04 (–0.06 to 0.15)	0.43
In-segment	2.25±0.55	2.22±0.56	0.03 (–0.08 to 0.14)	0.59
Diameter stenosis, % (SD)				
In-stent	9.52±13.49	9.43±10.78	0.18 (–2.50 to 2.86)	0.90
In-segment	19.48±12.89	19.28±12.25	0.07 (–2.64 to 2.79)	0.96
Late loss, mm (SD)				
In-stent	0.10±0.32	0.11±0.29	0.0006 (–0.06 to 0.07)	0.98
In-segment	0.09±0.35	0.09±0.33	0.007 (–0.07 to 0.08)	0.86
Binary restenosis, n (%)				
In-stent	6 (2.16)	2 (1.34)	1.78 (0.24–12.96)*	0.57
In-segment	11 (3.96)	7 (4.70)	0.83 (0.01–55.31)*	0.93

Crude mean±SD or counts (%) are reported for each randomized arm. Two-sided *P* values from superiority tests, differences, odds ratios, and 95% CIs are based on models; differences are the mean of the Orsiro arm minus the mean of the Xience arm. Continuous and categorical outcomes were analyzed at lesion level with mixed effects linear regression models or mixed effects logistic regression models that account for the nonindependence of multiple lesions within patients. Late loss is defined as minimal lumen diameter at the baseline post procedure minus minimal lumen diameter at 9 months of follow-up. CI indicates confidence interval.

*Odds ratios are reported for binary restenosis.

period after polymer biodegradation requires further study. Third, the antiproliferative drug used for drug release is the mammalian target of rapamycin inhibitor sirolimus. The drug is applied at a dose density of 1.4 µg/mm^2, which corresponds well to the one previously used with the sirolimus-eluting Cypher and Nevo stent platforms,[27,30] and is released during a period of 3 months with 50% of drug released during the first 30 days. Fourth, the drug is released from a biodegradable poly-L lactic acid layer, which degrades into carbon dioxide and water.[31] Several biodegradable polymers have been investigated in various DES to date including poly-lactic glycolic acid (Costar, Nevo, Micell, Synergy), poly-D,L-lactic acid (Biomatrix, Nobori), and poly-L lactic acid (Orsiro, Absorb). The concept of drug release from biodegradable polymers is attractive due to rare case reports of hypersensitivity reactions against components of durable polymer–based DES.[7,32,33]

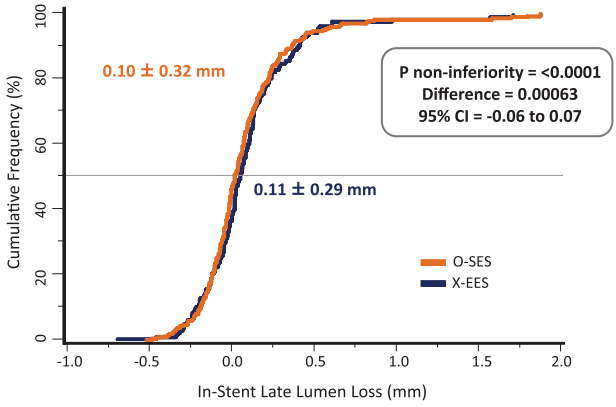

Figure 3. Cumulative distribution of the primary end point in-stent late lumen loss shown separately for the 2 stent types (sirolimus-eluting Orsiro stent [O-SES]=orange; Xience Prime everolimus-eluting stent [X-EES]=blue). The cumulative distribution curve of in-stent late loss is nearly superimposed indicating similar angiographic potency at 9-month angiographic follow-up. CI indicates confidence interval.

OCT-defined neointimal thickness was similar for the biodegradable polymer O-SES and the durable polymer X-EES stent without differences in terms of uncovered and malapposed struts. Due to its resolution, IVUS is not able to precisely measure the neointima thickness. It is, therefore, only possible to measure the neointima area. OCT and IVUS results were obtained from 2 separate subgroups, and neointimal area was somewhat lower with O-SES in the OCT and IVUS examination (*P*=0.03 and *P*=0.04, respectively). However, the *P* values are only marginally positive and should be interpreted with caution because this difference may be partly related to the differences observed in stent area between groups.

Clinical event rates were low in this patient population scheduled for angiographic follow-up. Extended follow-up to 1 year showed rates of clinically indicated TLR (3.5% versus 4.7%; *P*=0.54) to mirror angiographic efficacy results. Moreover, rates of death and myocardial infarction were low, and there was no case of ST in either group throughout 1 year. In this context, it is noteworthy that stent strut coverage and apposition as assessed by OCT was high in both groups, suggesting that the potent reduction in neointimal hyperplasia was not associated with adverse arterial healing.

Limitations

The present study with a primary angiographic end point and exploratory intracoronary imaging studies was performed

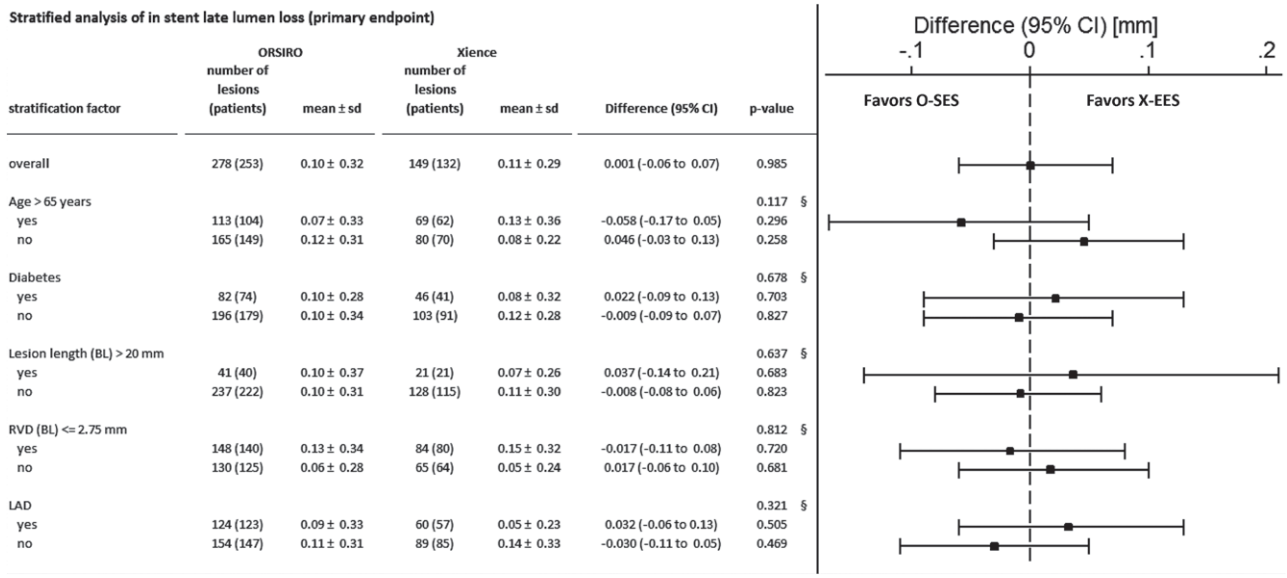

Figure 4. Stratified analyses for several subgroups of the primary angiographic end point in stent late lumen loss among patients randomized to treatment with sirolimus-eluting Orsiro stent (O-SES) or Xience Prime everolimus-eluting stent (X-EES). Differences are the mean of the Orsiro arm minus the mean of the Xience arm. Statistical analysis as described in Table 3, except for the stratification. *P* values for the difference are based on separate models for each stratum. *P* values for interaction (marked with §) between treatment group and corresponding stratification factor are based on a model that included all lesions. CI indicates confidence interval; LAD, left anterior descending artery; and RVD, reference vessel diameter.

in selected patients suitable for angiographic follow-up. Moreover, the study was not powered to assess clinical end points, specifically major safety end points such as death, myocardial infarction, and ST. Another limitation is the lack of follow-up beyond 1 year. Due to previous concerns of very LLL and ST, it will be of interest to perform long-term

Table 4. Clinical Outcomes

	Biodegradable Polymer Sirolimus-Eluting Stent	Durable Polymer Everolimus-Eluting Stent	Hazard Ratio (95% CI)	*P* Value
No. of patients, n	298	154		
Events at 1 y, n (%)				
Death	3 (1.0)	1 (0.7)	1.54 (0.16–14.84)	0.71
Cardiac death	2 (0.7)	1 (0.7)	1.03 (0.09–11.35)	0.98
Myocardial infarction*	9 (3.1)	4 (2.6)	1.17 (0.36–3.78)	0.80
TV myocardial infarction	8 (2.7)	4 (2.6)	1.04 (0.31–3.44)	0.95
Clinically indicated TLR	10 (3.5)	7 (4.7)	0.74 (0.28–1.94)	0.54
Any TLR	11 (3.8)	8 (5.4)	0.71 (0.29–1.76)	0.46
Clinically indicated TVR	19 (6.6)	10 (6.7)	1.00 (0.47–2.15)	1.00
Any TVR	22 (7.6)	13 (8.7)	0.89 (0.45–1.76)	0.73
Death or MI	12 (4.1)	5 (3.3)	1.24 (0.44–3.52)	0.69
Cardiac death or MI	11 (3.7)	5 (3.3)	1.14 (0.40–3.27)	0.81
Target-lesion failure	19 (6.5)	12 (8.0)	0.82 (0.40–1.68)	0.58
Target-vessel failure	27 (9.3)	15 (10.1)	0.94 (0.50–1.77)	0.85
Death, MI, or any revascularization	56 (19.2)	28 (18.7)	1.05 (0.67–1.66)	0.83
Definite ST	0 (0)	0 (0)		
Probable ST	0 (0)	0 (0)		

Number of events (Kaplan–Meier–based incidence rates [%]) are reported. Hazard ratios (O-SES/X-EES) are from Cox proportional-hazards models, and *P* values are 2-sided from superiority testing using log-rank tests. No coronary artery bypass grafting revascularization events were reported. Target-lesion failure is the composite of cardiac death, target-vessel myocardial infarction, coronary artery bypass grafting, or clinically driven TLR. Target-vessel failure is the composite of cardiac death, target-vessel myocardial infarction, coronary artery bypass grafting, or clinically driven TVR. CI indicates confidence interval; MI, myocardial infarction; ST, stent thrombosis; TLR, target-lesion revascularization; TV, target vessel; and TVR, target-vessel revascularization.

*Event rates for myocardial infarction in the table are reported according to the Joint ESC/ACCF/AHA/WHF Task Force universal definition of myocardial infarction.

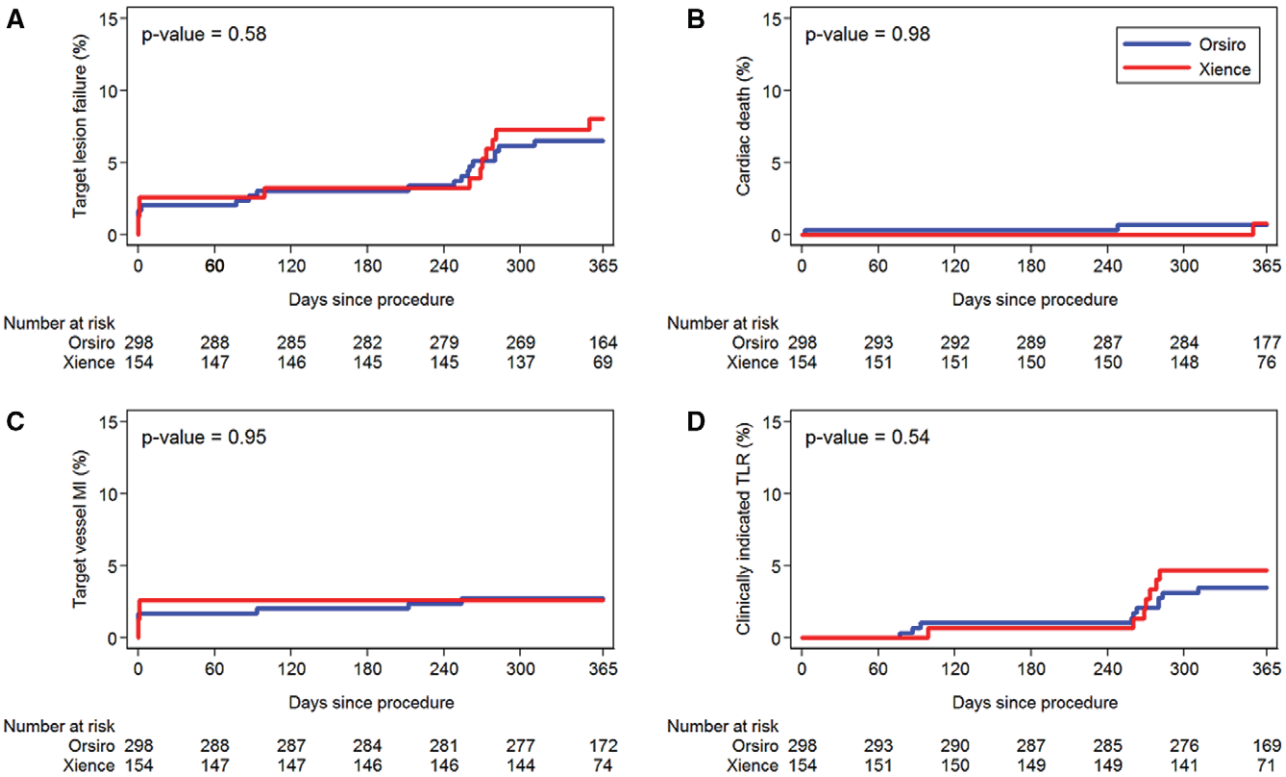

Figure 5. Kaplan–Meier curves for the clinical end point target-lesion failure (composite of cardiac death, target-vessel myocardial infarction, and clinically indicated target-lesion revascularization [TLR]) throughout 1 year (**A**), cardiac death (**B**), target-vessel myocardial infarction (**C**), and clinically indicated TLR (**D**) for patients receiving sirolimus-eluting Orsiro stent and Xience Prime everolimus-eluting stent. *P* values are 2-sided from log-rank tests. MI indicates myocardial infarction.

clinical, angiographic, and intracoronary imaging studies to appreciate potential differences between both stent platforms. LLL was lower than anticipated; therefore, the prespecified noninferiority margin might not have been fully appropriate. However, the SD of LLL was also lower than anticipated allowing for a more stringent margin. Therefore, a post hoc

Table 5. Optical Coherence Tomography Results at Baseline and 9 Months

	Biodegradable Polymer Sirolimus-Eluting Stent	Durable Polymer Everolimus-Eluting Stent	Difference (95% CI)	*P* Value
No. of lesion, n	36	19		
Baseline				
Stent area, mm^2	7.11±1.95	8.15±2.23	−1.04 (−2.23 to 0.15)	0.08
Lumen area, mm^2	6.90±1.97	7.86±2.04	−0.96 (−2.12 to 0.19)	0.10
Malapposed stent struts, %	6.35±9.65	5.59±8.82	0.76 (−4.65 to 6.17)	0.99
ISA distance, mm	0.08±0.05	0.10±0.08	−0.01 (−0.06 to 0.03)	0.57
ISA area, mm^2	0.13±0.27	0.16±0.39	−0.03 (−0.21 to 0.16)	0.98
Follow-up (9 mo)				
No. of lesion, n	36	19		
Stent area, mm^2	7.20±2.06	8.04±2.26	−0.84 (−2.07 to 0.40)	0.18
Lumen area, mm^2	6.53±2.17	7.09±2.19	−0.56 (−1.82 to 0.70)	0.37
Neointimal thickness, mm	0.10±0.04	0.11±0.04	−0.01 (−0.04 to 0.01)	0.37
Neointimal area, mm^2	0.75±0.40	1.00±0.44	−0.25 (−0.49 to −0.01)	0.03
Percent volume obstruction, %	10.97±6.73	11.54±5.69	−0.57 (−4.26 to 3.12)	0.64
Uncovered stent struts, %	1.98±3.71	2.71±3.31	−0.73 (−2.80 to 1.34)	0.48
Malapposed stent struts, %	1.11±2.32	0.77±2.04	0.34 (−0.95 to 1.62)	0.43
ISA distance, mm	0.35±0.13	0.39±0.19	−0.04 (−0.26 to 0.19)	0.71
ISA area, mm^2	0.07±0.15	0.05±0.16	−0.02 (−0.07 to 0.11)	0.17

CI indicates confidence interval; and ISA, incomplete stent apposition.

Table 6. Intravascular Ultrasound Study Results at Baseline and 9 Months

	Biodegradable Polymer Sirolimus-Eluting Stent	Durable Polymer Everolimus-Eluting Stent	*P* Value
Baseline			
No. of lesions	31	25	
Stent area, mm^2	7.50±2.50	7.28±2.17	0.73
Mean lumen area, mm^2	7.50±2.50	7.28±2.17	0.73
Minimal lumen area, mm^2	6.65±2.49	6.62±1.99	0.96
EEM area, mm^2	15.73±5.5*	15.95±5.06	0.88
Plaque area, mm^2	8.34±3.86*	8.67±3.27	0.74
Follow-up (9 mo)			
No. of lesions	31	25	
Stent area, mm^2	7.56±2.80	7.37±2.34	0.79
Mean lumen area, mm^2	7.40±2.79	6.95±2.34	0.52
Minimal lumen area, mm^2	6.64±2.68	6.22±1.97	0.51
EEM area, mm^2	15.54±5.46*	15.50±5.73†	0.98
Plaque area, mm^2	8.28±3.56*	8.57±3.80†	0.77
Neointimal area, mm^2	0.16±0.33	0.43±0.56	0.04
Change between baseline and follow-up			
Δ Stent area, mm^2	0.06±1.00	0.09±0.63	0.88
Δ Mean lumen area, mm^2	–0.10±1.03	–0.34±0.70	0.34
Δ Minimal lumen area, mm^2	–0.01±0.76	–0.40±0.61	0.04
Δ EEM (Vessel) area, mm^2	–0.19±3.23	–0.38±1.93	0.79
Δ Plaque area, mm^2	–0.07±2.99	–0.02±1.74	0.95

EEM indicates external elastic membrane.
*Parameter could not be analyzed for 2 lesions.
†Parameter could not be analyzed for 1 lesion.

noninferiority test based on the CI is reported in addition to the prespecified noninferiority test, which maintained the noninferiority hypothesis. Finally, results of the OCT and IVUS subgroups showed small differences which should be considered hypothesis generating and of unclear clinical significance. Intracoronary imaging results require confirmation with a cohort including more complex patients and lesion subsets.

Conclusions

In this randomized, multicenter, assessor-blind trial, the novel biodegradable polymer–based O-SES was noninferior for the primary end point in-stent LLL at 9 months compared with the durable polymer–based X-EES. Clinical event rates were comparable without cases of ST throughout 1-year follow-up.

Clinical Events Committee

Ralf Birkemeyer, MD (Chairman); Harald Rittger, MD; Zbigniew Siudak, MD

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