Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable-Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularization: 2-Year Results of the BIOSCIENCE Trial

Rainer Zbinden, MD;* Raffaele Piccolo, MD;* Dik Heg, PhD; Marco Roffi, MD; David J. Kurz, MD; Olivier Muller, MD; André Vuilliomenet, MD; Stéphane Cook, MD; Daniel Weilenmann, MD; Christoph Kaiser, MD; Peiman Jamshidi, MD; Anna Franzone, MD; Franz Eberli, MD; Peter Jüni, MD; Stephan Windecker, MD; Thomas Pilgrim, MD

Background—No data are available on the long-term performance of ultrathin strut biodegradable polymer sirolimus-eluting stents (BP-SES). We reported 2-year clinical outcomes of the BIOSCIENCE (Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularisation) trial, which compared BP-SES with durable-polymer everolimus-eluting stents (DP-EES) in patients undergoing percutaneous coronary intervention.

Methods and Results—A total of 2119 patients with minimal exclusion criteria were assigned to treatment with BP-SES (n=1063) or DP-EES (n=1056). Follow-up at 2 years was available for 2048 patients (97%). The primary end point was target-lesion failure, a composite of cardiac death, target-vessel myocardial infarction, or clinically indicated target-lesion revascularization. At 2 years, target-lesion failure occurred in 107 patients (10.5%) in the BP-SES arm and 107 patients (10.4%) in the DP-EES arm (risk ratio [RR] 1.00, 95% CI 0.77–1.31, *P*=0.979). There were no significant differences between BP-SES and DP-EES with respect to cardiac death (RR 1.01, 95% CI 0.62–1.63, *P*=0.984), target-vessel myocardial infarction (RR 0.91, 95% CI 0.60–1.39, *P*=0.669), target-lesion revascularization (RR 1.17, 95% CI 0.81–1.71, *P*=0.403), and definite stent thrombosis (RR 1.38, 95% CI 0.56–3.44, *P*=0.485). There were 2 cases (0.2%) of definite very late stent thrombosis in the BP-SES arm and 4 cases (0.4%) in the DP-EES arm (*P*=0.423). In the prespecified subgroup of patients with ST-segment elevation myocardial infarction, BP-SES was associated with a lower risk of target-lesion failure compared with DP-EES (RR 0.48, 95% CI 0.23–0.99, *P*=0.043, $P_{interaction}$=0.026).

Conclusions—Comparable safety and efficacy profiles of BP-SES and DP-EES were maintained throughout 2 years of follow-up.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT01443104. (***J Am Heart Assoc***. 2016;5: e003255 doi: 10.1161/JAHA.116.003255)

Key Words: biodegradable polymer • drug-eluting stent • everolimus-eluting stent • percutaneous coronary intervention • sirolimus-eluting stent

Newer generation drug-eluting stents (DESs) represent the standard of care in patients undergoing percutaneous coronary intervention (PCI) and are recommended for all patient and lesion subsets.[1,2] The crucial shortcoming of early generation DESs was a delayed healing response of the stented coronary artery, resulting in an increase in late

thrombotic events.[3] Newer generation DESs were developed featuring biocompatible or biodegradable polymers that release -limus analogues at lower dosages.[4,5] These refinements resulted not only in a remarkable reduction in the risk of stent thrombosis (ST) compared with early generation DESs but also improved efficacy (lower risk of repeat revascularization) and safety (lower risk of death and myocardial infarction [MI]).[6]

The biodegradable-polymer sirolimus-eluting stent (BP-SES; Orsiro; Biotronik AG) represents a further iteration of DES technology by combining a biodegradable polymer with an ultrathin-strut cobalt–chromium platform (60 μm for stent diameters up to 3.0 mm, 80 μm for stent diameters >3 mm). In the BIOSCIENCE (Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularisation) trial, the BP-SES was noninferior to the durable-polymer everolimus-eluting stent (DP-EES) with respect to the primary composite safety and efficacy end point of target-lesion failure at 12 months.[7] Nevertheless, long-term comparative data on biodegradable- and durable-polymer newer generation DESs are sparse and limited mainly to thick-strut biodegradable-polymer DESs (BP-DESs). Consequently, the purpose of the present study was to report the long-term clinical outcomes of patients included in the BIOSCIENCE trial over 2 years of follow-up.

Methods

Study Design and Patient Population

BIOSCIENCE was an investigator-initiated, single-blind, multicenter, randomized noninferiority trial with minimal exclusion criteria (ClinicalTrials.gov, NCT01443104). The study design and the principal features of the study devices have been detailed previously.[8] Study enrollment was performed between February 2012 and May 2013 at 9 centers in Switzerland. Patients were randomly assigned to treatment with BP-SES or DP-EES (Xience Prime or Xpedition stent; Abbott Vascular). There were no restrictions on the number of treated lesions, the number of vessels, or the lesion length. Main exclusion criteria were intolerance to aspirin, clopidogrel, or DES components and planned surgery within 6 months at the time of index PCI. The study complied with the Declaration of Helsinki and was approved by the institutional ethics committees of all participating sites. All patients provided written informed consent for participation in the trial.

Randomization and Procedures

After diagnostic angiography, patients were randomly allocated at a 1:1 ratio to treatment with BP-SES or DP-EES using a centralized, Web-based randomization system. Randomization was stratified according to center and to presence or absence of ST-segment elevation MI (STEMI). Study participants and outcome assessors were masked to the allocated DES, whereas treating physicians were not.

PCI was performed according to current guidelines. Lesion predilation, direct stenting, and postdilatation were done at the operator's discretion. During the procedure, patients were given unfractionated heparin at a dose of at least 5000 IU or 70–100 IU/kg. The use of glycoprotein IIb/IIIa inhibitors or bivalirudin during PCI was left to the discretion of the operator. Antiplatelet treatment was initiated before or at the time of PCI and consisted of acetylsalicylic acid (>250 mg) in combination with a loading dose of clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. Dual antiplatelet therapy was recommended for a duration of 12 months after stent implantation and consisted of acetylsalicylic acid 100 mg daily and a $P2Y_{12}$ inhibitor (75 mg clopidogrel once per day, 10 mg prasugrel once per day, or 90 mg ticagrelor twice per day), followed by acetylsalicylic monotherapy indefinitely.

Clinical End Points

The primary end point of target-lesion failure (TLF) was a composite of cardiac death, target-vessel MI, and clinically indicated target-lesion revascularization at 12 months. The definition of cardiac death included any death due to immediate cardiac cause, deaths related to the procedure, unwitnessed death, and death from unknown cause. MI was differentiated into Q-wave and non–Q-wave MI. Spontaneous MI was documented in case of a typical rise and fall of creatinine kinase-MB fraction or troponin in the presence of ≥1 of the following conditions: ischemic symptoms, new pathological Q waves, ischemic electrocardiographic changes, or pathological evidence of acute MI. Target vessel–related MI was considered in cases in which the MI was related to the target vessel or the MI was not clearly related to another vessel. Target-lesion revascularization was defined as any repeated percutaneous or surgical intervention due to a stenosis or occlusion within the stent or within the 5-mm borders proximal or distal to the stent. ST was categorized according to the definitions provided by the Academic Research Consortium.[9] A revascularization was considered to be clinically indicated if the stenosis of the treated lesion was at least 50% of the lumen diameter in the presence of signs or symptoms of ischemia or if the diameter stenosis was at least 70% of the lumen diameter, regardless of the presence or absence of ischemic signs and symptoms. Target-vessel failure was a composite of cardiac death, MI that could not be clearly attributed to a vessel other than the target vessel, and target-vessel revascularization. Secondary end points were clinically indicated and not clinically indicated target-lesion revascularization; clinically indicated and not clinically indicated target-vessel revascularization; target-vessel failure; cardiac death; all

death; MI; definite ST; and definite or probable ST. All data were stored in a central database (Cardiobase; Clinical Trials Unit and Department of Cardiology at Bern University Hospital and 2mT Software GmbH). Follow-up visits were performed at 30 days, 12 months, and 24 months. Patients were questioned about the occurrence of angina, any adverse events, hospital admissions, and cardiovascular medication intake. Electrocardiographs were systematically collected at baseline, after the procedure, at 12-month follow-up, and in case of recurrent signs or symptoms of ischemia. All serious adverse events were blinded and submitted to the Clinical Trials Unit of the University of Bern. Any death, reinfarction, revascularization, ST, cerebrovascular accident, and bleeding event was independently adjudicated by a clinical events committee blinded to treatment allocation.

Statistical Analysis

The trial was powered for noninferiority of BP-SES compared with DP-EES with respect to the primary clinical end point, TLF, at 12 months. With a noninferiority margin of 3.5%, the enrollment of 2060 patients was calculated to provide >80% power to detect noninferiority at a 1-sided type 1 error of 0.05. For this prespecified analysis, we calculated the 2-sided 95% CI and 2-sided *P*-value for superiority for all end points. Specifically, we used the Mantel–Cox method to calculate risk ratio (RR) with 95% CI from the log-rank test. We used time to first event for each type of outcome throughout and reported Kaplan–Meier estimates of event rates. A landmark analysis was performed by using the 1-year landmark. For each type of event, patients were censored at the time of the first event: A patient who experienced an event contributing to the primary composite end point during 365 days, for example, was censored at the time of the event and excluded from the analysis after the landmark point. *P* values for characteristics recorded at the patient level are from unpaired t tests, χ^2 tests, or Fisher exact tests, except when specified. *P* values for characteristics that were recorded at the lesion level are from general or generalized linear mixed models to account for the nonindependence of lesions in the same patient. We prespecified stratified analyses of the primary end point for the following subgroups: diabetes, acute coronary syndrome status, STEMI, sex, age ≥65 years, obesity, and renal failure. To identify interactions between groups and for each of these characteristics on the effect size, we approximated Mantel–Haenszel χ^2 tests for effect modification. All patients who were randomly assigned and provided written informed consent were included in the analyses of end points according to the intention-to-treat principle. Analyses were done by a statistician at the Clinical Trials Unit of the University of Bern and carried out with Stata statistical software release 13 (StataCorp LP).

Results

A total of 2129 patients with coronary artery disease were randomized to treatment with BP-SES (1066 patients) or DP-EES (1063 patients). After exclusion of 10 patients who did not confirm their initial consent, 1063 patients with 1594 lesions who were randomly assigned to BP-SES and 1056 patients with 1545 lesions who were randomly assigned to DP-EES remained for the final analysis. Overall, 39 patients (3.7%) allocated to BP-SES and 32 (3%) allocated to DP-EES were lost to follow-up or withdrew consent before reaching 24 months, without between-group differences (Figure 1). Baseline patient characteristics have been shown previously.[7] In brief, parameters were well balanced between the 2 treatment arms with respect to age, sex, cardiovascular risk factors, and previous revascularization procedures. More than 50% of the patients presented with an acute coronary syndrome. There was a significant difference with regard to stent length, which was significantly longer in the DP-EES arm compared with the BP-SES arm (27.5±16.8 mm versus 25.9±15.4 mm; *P*=0.01).

Table shows clinical outcomes at 2 years. At 2 years, we established noninferiority of BP-SES for the primary end point, with an absolute risk difference of −0.07% and the upper limit of the 1-sided 95% CI of 2.50% (*P*=0.0032 in 1-sided noninferiority analysis). Subsequent superiority testing for the primary end point did not yield significant differences between BP-SES and DP-EES (10.5% versus 10.4%, respectively; RR 1.00, 95% CI 0.77–1.31, *P*=0.979) (Figure 2A).

The rates of the individual components of the primary end point, including cardiac death, target-vessel MI, and clinically indicated target-lesion revascularization, were comparable for the 2 treatment arms and are illustrated in Figure 2B through 2D. Similarly, no significant differences were noted for any of the secondary end points (Table). Of note, there was a higher rate of all-cause death in patients treated with BP-SES compared with DP-EES (6.0% versus 4.0%; *P*=0.047) because of an excess of noncardiovascular deaths in the BP-SES arm (Table S1). In a landmark analysis for the primary end point and its components with the landmark set at 1 year, we found no difference in late events between 1 and 2 years (Figure 3). The landmark analysis for all study end points is presented in Table S2. The rate of definite ST was similar in the 2 treatment arms (1.1% versus 0.8%, *P*=0.485) (Table). Very late definite ST occurred in 2 (0.2%) versus 4 (0.4%) patients allocated to BP-SES and DP-EES, respectively (Table S2). At 2 years of follow-up, 15.2% of the patients allocated to BP-SES and 14.5% of patients allocated to DP-EES were still on dual antiplatelet therapy (*P*=0.66).

Findings for the primary end point were consistent across major subgroups such as age, sex, diabetes, acute coronary syndrome, body mass index, and renal failure (Figure 4). In
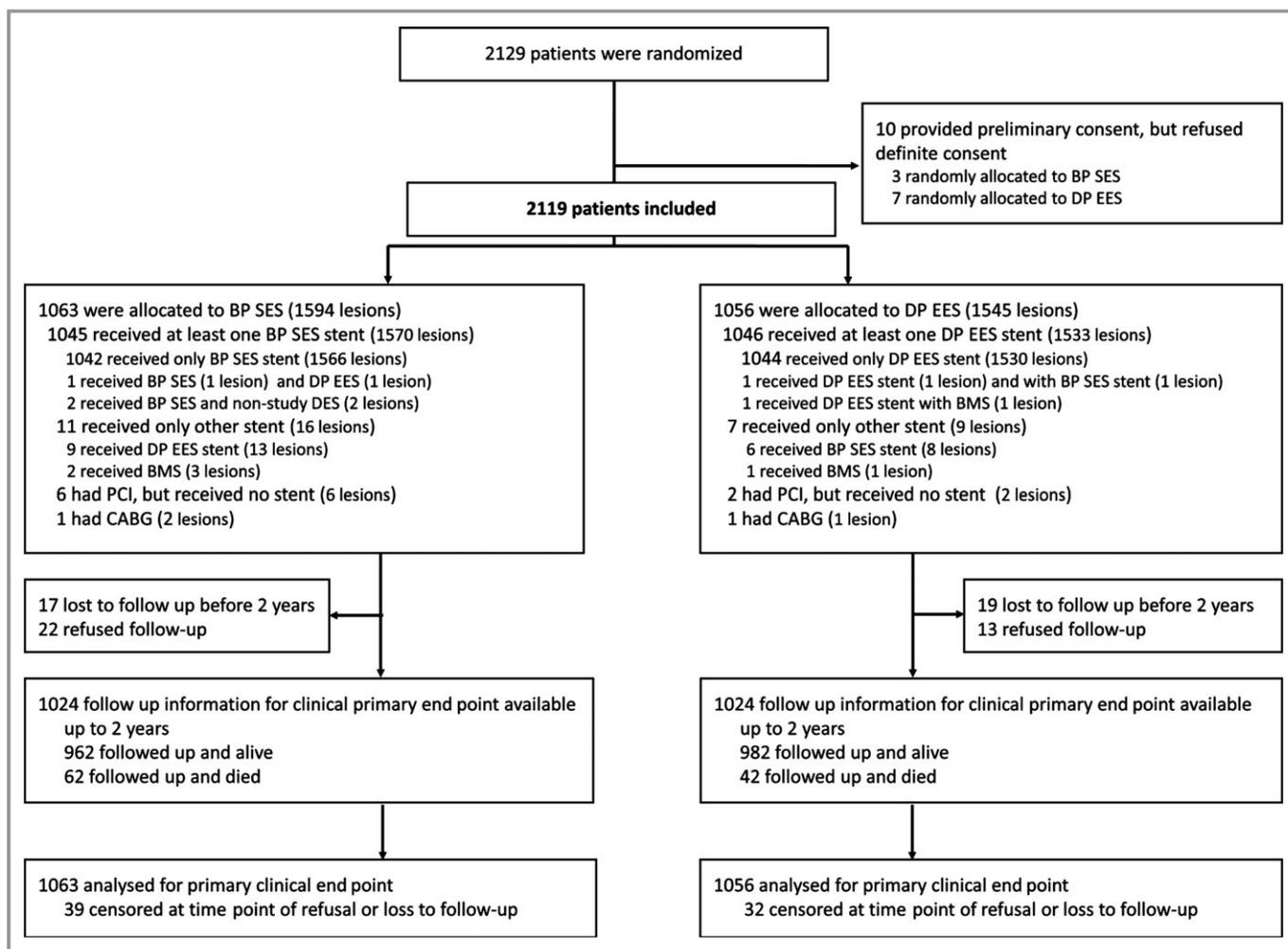
Figure 1. Patient flow according to the CONSORT statement. BMS indicates bare-metal stent; BP-SES, biodegradable-polymer sirolimus-eluting stent; CABG, coronary artery bypass grafting; DES, drug-eluting stent; DP-EES, durable-polymer everolimus-eluting stent; PCI, percutaneous coronary intervention.

the prespecified subgroup of patients presenting with STEMI, patients treated with BP-SES were documented to have a lower risk of TLF than patients allocated to DP-EES (RR 0.48, 95% CI, 0.23–0.99, *P*=0.043), with a significant interaction between the type of stent and the presence or absence of STEMI (*P*=0.026).

Discussion

To the best of our knowledge, this study is the first report of 2-year clinical outcomes of newer generation DESs combining a biodegradable polymer with an ultrathin cobalt–chromium platform compared with DP-EES from a randomized controlled trial. The 2-year results of the BIOSCIENCE trial corroborate the primary end point results at 1 year[7] and demonstrate comparable rates of clinical outcomes throughout 2 years of follow-up in a patient population with minimal exclusion criteria treated with BP-SES or DP-EES.

Newer generation DESs were developed with the aim of overcoming the limitations of early generation DESs that were associated with a higher risk of late thrombotic events compared with bare-metal stents. The increased risk of very late ST resulted from incomplete strut endothelialization related to a persistent inflammatory reaction caused by a hypersensitivity reaction to the polymer. Current evidence suggests better safety and efficacy profiles for both biodegradable- and durable-polymer newer-generation DESs compared with early generation DESs.[2,4] The 5-year follow-up of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) trial showed a significant reduction of the risk of very late ST and associated clinical end points in patients treated with biodegradable-polymer biolimus-eluting stents (BP-BES) compared with patients treated with early generation sirolimus-eluting stents.[10] At this time, it is controversial whether the safety profile of the BP-BES, which represents the most studied BP-DES, is equivalent to the

Table. Clinical Outcomes

	BP-SES	DP-EES	Risk Difference, BP-SES vs DP-EES, %	RR, BP-SES vs DP-EES	
	n=1063	n=1056	(95% CI)	(95% CI)	P Value
All-cause death	62 (6.0)	42 (4.0)	1.86 (0.02 to 3.69)	1.48 (1.00–2.20)	0.047
Cardiac death	33 (3.2)	33 (3.2)	−0.02 (−1.50 to 1.46)	1.01 (0.62–1.63)	0.984
Myocardial infarction	62 (6.1)	73 (7.2)	−1.08 (−3.16 to 1.00)	0.85 (0.60–1.19)	0.344
Q-wave	12 (1.2)	11 (1.1)	0.09 (−0.80 to 0.97)	1.09 (0.48–2.48)	0.831
Non Q-wave	51 (5.0)	63 (6.2)	−1.17 (−3.09 to 0.75)	0.81 (0.56–1.17)	0.258
Target-vessel MI	42 (4.1)	46 (4.5)	−0.40 (−2.10 to 1.29)	0.91 (0.60–1.39)	0.669
Q-wave	12 (1.2)	8 (0.8)	0.37 (−0.45 to 1.19)	1.50 (0.61–3.68)	0.369
Non–Q-wave	30 (2.9)	38 (3.7)	−0.78 (−2.28 to 0.72)	0.79 (0.49–1.27)	0.327
Cardiac death or MI	92 (8.9)	101 (9.8)	−0.91 (−3.36 to 1.54)	0.91 (0.69–1.21)	0.518
Repeat revascularisation	126 (12.6)	113 (11.2)	1.15 (−1.54 to 3.85)	1.14 (0.88–1.47)	0.320
Percutaneous repeat revascularization	123 (12.3)	111 (11.0)	1.06 (−1.61 to 3.73)	1.13 (0.87–1.46)	0.348
Surgical repeat revascularization	5 (0.5)	7 (0.7)	−0.19 (−0.83 to 0.45)	0.72 (0.23–2.26)	0.566
TLR	64 (6.4)	58 (5.8)	0.53 (−1.45 to 2.51)	1.12 (0.78–1.60)	0.539
Clinically indicated TLR	59 (6.0)	51 (5.1)	0.72 (−1.17 to 2.61)	1.17 (0.81–1.71)	0.403
Percutaneous TLR	56 (5.7)	49 (4.9)	0.63 (−1.22 to 2.48)	1.16 (0.79–1.70)	0.451
Surgical TLR	4 (0.4)	4 (0.4)	−0.00 (−0.52 to 0.52)	1.00 (0.25–4.02)	0.995
TVR	81 (8.1)	75 (7.5)	0.52 (−1.71 to 2.74)	1.10 (0.80–1.50)	0.568
Clinically indicated TVR	77 (7.7)	68 (6.8)	0.80 (−1.35 to 2.95)	1.15 (0.83–1.59)	0.399
Percutaneous TVR	74 (7.4)	67 (6.7)	0.62 (−1.51 to 2.74)	1.12 (0.81–1.56)	0.496
Surgical TVR	4 (0.4)	4 (0.4)	−0.00 (−0.52 to 0.52)	1.00 (0.25–4.02)	0.995
Cerebrovascular event	19 (1.9)	20 (2.0)	−0.11 (−1.25 to 1.04)	0.95 (0.51–1.79)	0.883
Transient ischemic attack	5 (0.5)	4 (0.4)	0.09 (−0.46 to 0.65)	1.26 (0.34–4.68)	0.733
Stroke*	15 (1.5)	17 (1.7)	−0.20 (−1.24 to 0.84)	0.89 (0.44–1.77)	0.731
Ischemic stroke	13 (1.3)	17 (1.7)	−0.39 (−1.39 to 0.62)	0.77 (0.37–1.58)	0.469
Target-lesion failure[†]	107 (10.5)	107 (10.4)	−0.07 (−2.63 to 2.50)	1.00 (0.77–1.31)	0.979
Target-vessel failure[‡]	124 (12.2)	127 (12.3)	−0.36 (−3.11 to 2.39)	0.98 (0.77–1.26)	0.882
Death, MI, or repeat revascularization[§]	197 (19.1)	176 (17.0)	1.87 (−1.38 to 5.11)	1.13 (0.92–1.39)	0.237
Definite stent thrombosis	11 (1.1)	8 (0.8)	0.28 (−0.53 to 1.08)	1.38 (0.56–3.44)	0.485
Definite or probable stent thrombosis	40 (3.9)	50 (4.9)	−0.97 (−2.69 to 0.75)	0.80 (0.53–1.21)	0.287
Bleeding event					
BARC type 3 to 5	36 (3.5)	36 (3.5)	−0.02 (−1.57 to 1.52)	1.00 (0.63–1.59)	0.999
BARC type 2	25 (2.5)	31 (3.0)	−0.58 (−1.95 to 0.78)	0.80 (0.47–1.36)	0.417
BARC type 3a	17 (1.7)	10 (1.0)	0.65 (−0.30 to 1.61)	1.71 (0.78–3.72)	0.175
BARC type 3b	12 (1.2)	22 (2.1)	−0.95 (−2.02 to 0.12)	0.54 (0.27–1.10)	0.085
BARC type 3c	4 (0.4)	2 (0.2)	0.19 (−0.27 to 0.64)	2.01 (0.37–11.08)	0.411
BARC type 4	1 (0.1)	1 (0.1)	−0.00 (−0.26 to 0.26)	1.00 (0.06–15.88)	0.998
BARC type 5a	1 (0.1)	1 (0.1)	−0.00 (−0.26 to 0.26)	1.01 (0.06–15.95)	0.996
BARC type 5b	3 (0.3)	1 (0.1)	0.19 (−0.18 to 0.56)	3.01 (0.31–29.12)	0.318

Number of first events and cumulative incidence percentage are reported. RR (95% CI) is estimated using the Mantel–Cox method with 2-sided *P* values from log-rank test. Continuity corrected RR with Fisher exact test for zero outcomes. BARC indicates Bleeding Academic Research Consortium; BP-SES, biodegradable-polymer sirolimus–eluting stent; DP-EES, durable-polymer everolimus–eluting stent; MI, myocardial infarction; RR, risk ratio; TLR, target-lesion revascularization; TVR, target-vessel revascularization.

*Includes ischemic stroke, intracerebral hemorrhagic stroke, and unclear etiology cerebrovascular event.

[†]Primary end point, defined as the composite of cardiac death, target-vessel Q-wave or non–Q wave MI, and clinically indicated TLR.

[‡]Defined as the composite of cardiac death, any Q-wave or non–Q wave MI, and any TVR.

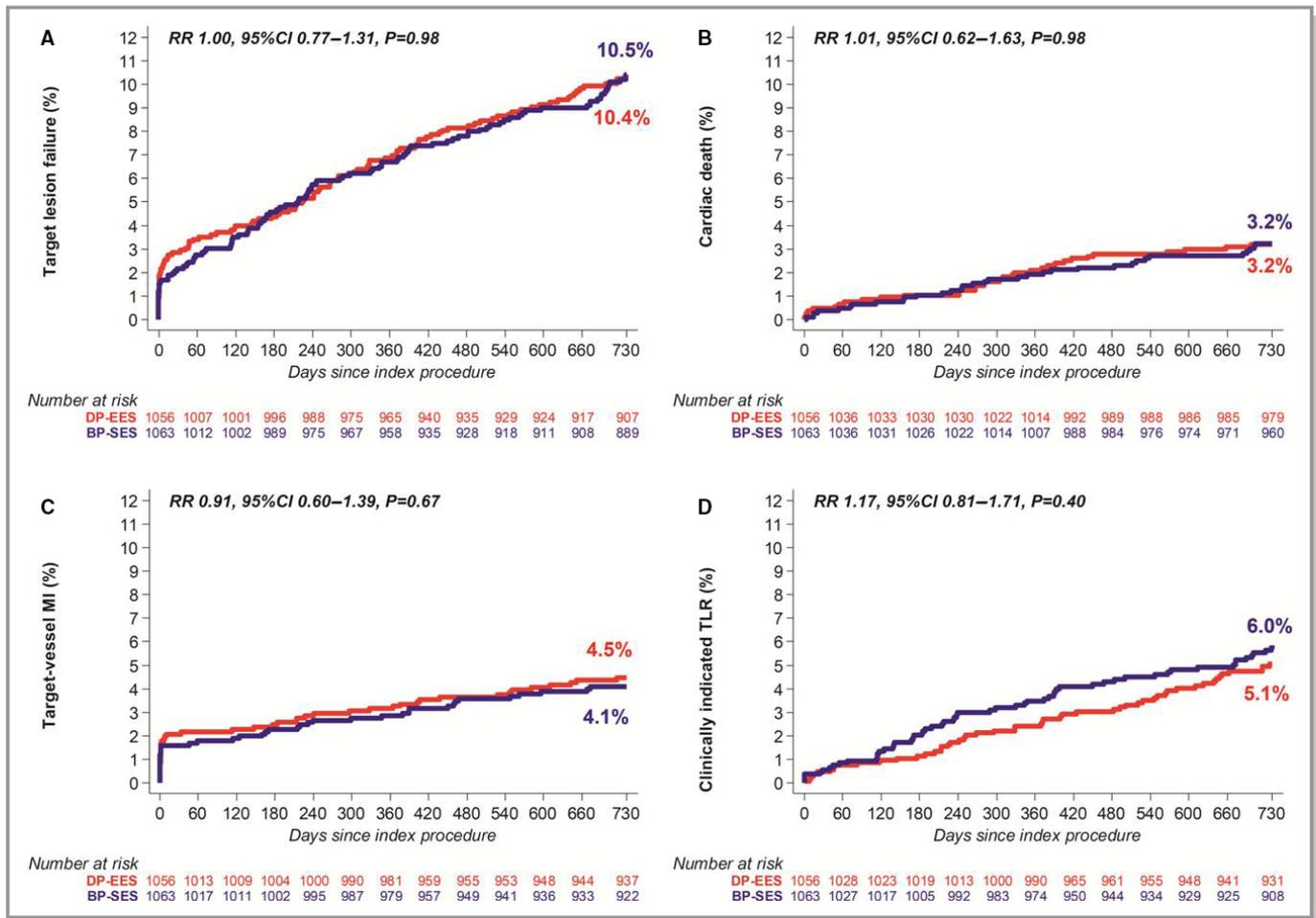[§]Patient-oriented composite end point.

Figure 2. Kaplan-Meier curves for the primary end point (panel A) and its compenents (panels B-D) at 2-year follow-up. The blue line shows the BP-SES, and the red line shows the DP-EES. BP-SES indicates biodegradable-polymer sirolimus-eluting stent; DP-EES, durable-polymer everolimus-eluting stent; RR, risk ratio; TLR, target-lesion revascularization.

safety profile of the DP-EES. In direct randomized comparisons, the BP-BES had a safety profile equivalent to that of the DP-EES, with a similar risk of MI and ST[11–14]; however, individual head-to-head comparisons were not powered to assess differences in MI and ST, and data from network meta-analyses suggest a lower safety profile of the BP-BES. In a network meta-analysis including 63 242 patients, Navarese and colleagues reported a significant increase in the odds of MI with the BP-BES compared with the DP-EES.[15] Another network meta-analysis documented a higher risk of ST among patients treated with the BP-BES compared with the DP-EES; the difference was driven by an increased risk of early ST (within the first 30 days).[16] In this context, it is noteworthy that the BP-BES is based on a relatively thick-strut stainless steel platform with a strut thickness of 120 μm and uses an abluminally distributed polymer of 10-μm thickness.[17] In comparison, both BP-SES and DP-EES use thinner strut (60 or 80 μm and 81 μm, respectively) and polymer (7 and 8 μm, respectively) coating thicknesses.[2] It

has been reported that strut thickness and geometry greatly modulate stent thrombogenicity, particularly during the early phase after stent implantation.[18] These observations may in part explain the results of the SORT OUT (Scandinavian Organization for Randomized Trials with Clinical Outcome) VII trial, which compared the thin-strut BP-SES with the thick-strut BP-BES among 2525 patients undergoing PCI.[19] At 12 months, the study found a significantly lower rate of definite ST with the BP-SES (0.4% versus 1.2%), with an excess of ST cases in the BP-BES arm during the early period following PCI.

In a large network meta-analysis, Bangalore and colleagues reported a higher risk of target-vessel revascularization and late mortality with BP-DES compared with new-generation DP-DES.[20] It is noteworthy that 17 different BP-DES devices were included under the same node,[20] bringing into question whether the results of various BP-DESs should be interpreted as a single category rather than individually. In view of the recent evidence, it seems appropriate to disentangle at least
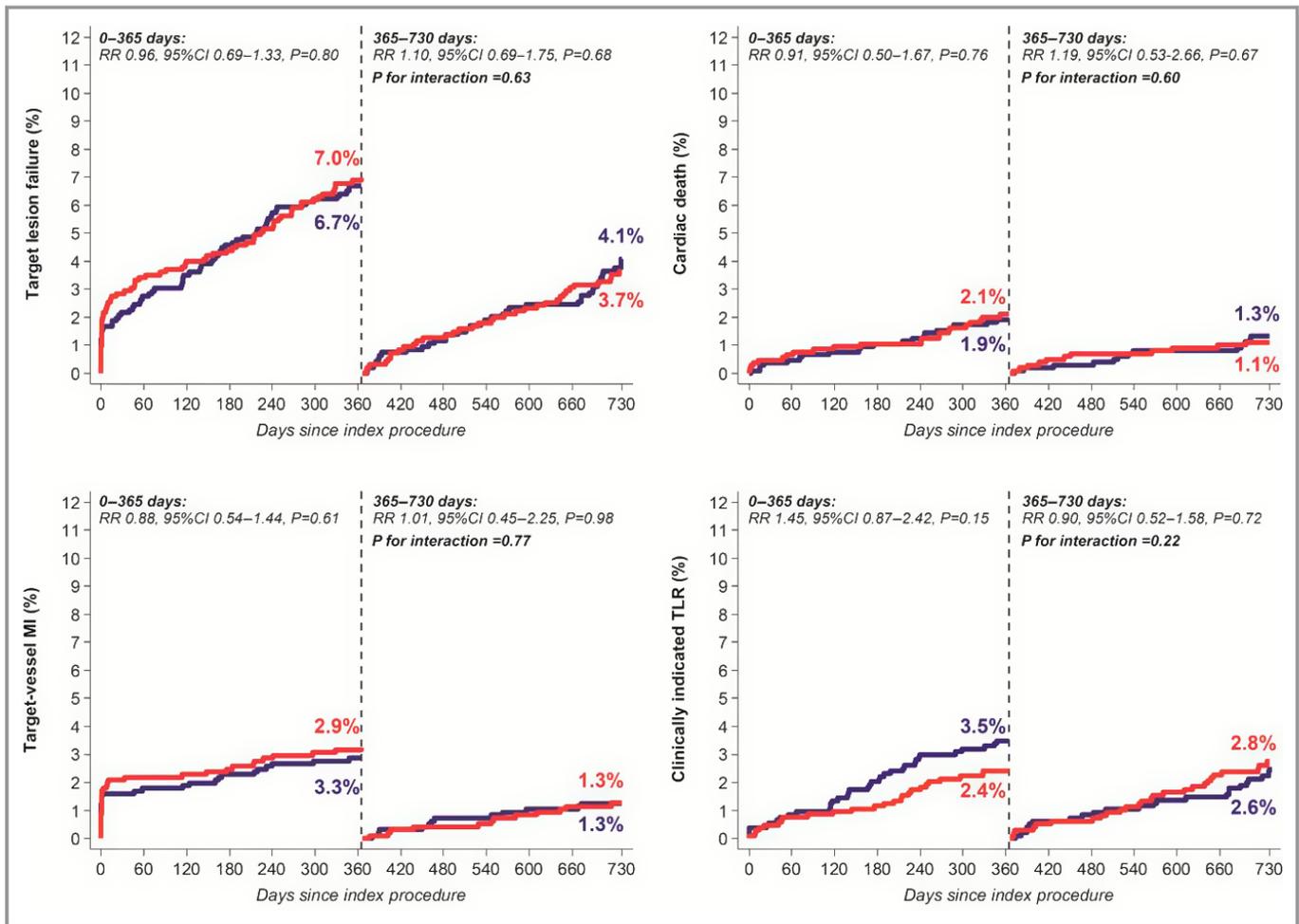
Figure 3. Kaplan–Meier curves for the landmark analyses of the primary end point and its components. The blue line shows the BP-SES, and the red line shows the DP-EES. TLR indicates target-lesion revascularization; TV, target vessel.

thin-strut from thick-strut BP-DESs for the interpretation of clinical data.

The BIOSCIENCE trial showed excellent safety and efficacy profiles for both the BP-SES and the DP-EES, without any difference in late adverse events between 1 and 2 years. The rate of very late ST was low for both BP-SES and DP-EES (0.2% and 0.4%), and target-vessel MI occurred in 1.3% of patients in both treatments arms beyond 1 year. Moreover, the sustained similar efficacy in terms of target-lesion revascularization for BP-SES and DP-EES at 2 years (6.0% versus 5.1%) is in line with the excellent late lumen loss found in the BIOFLOW (Biotronik-Safety and Clinical Performance of the Drug Eluting Orsiro Stent in the Treatment of Subjects With Single De Novo Coronary Artery Lesions) II trial at 9-month angiographic follow-up (0.10±0.32 versus 0.11±0.29 mm for BP-SES versus DP-EES).[21]

We found a higher risk of all-cause death in the BP-SES arm compared with the DP-EES arm. The difference was due to an excess in noncardiovascular death in the BP-SES arm and may result from chance.

Recently, 2 randomized trials powered for a clinical primary end point reported the results of thin-strut BP-DES versus DP-EES. The CENTURY (Clinical Evaluation of New TerUmo dRug-eluting coronary stent) II trial allocated 1123 PCI patients to receive the Ultimaster BP-SES (Terumo Corporation) or DP-EES.[22] At 9 months, noninferiority with regard to the primary end point of TLF was established, without any significant difference in secondary end points between the 2 treatment arms.[22] Similarly, the EVOLVE (A Prospective Randomized Multicenter Single-blind Noninferiority Trial to Assess the Safety and Performance of the Evolution Everolimus-Eluting Monorail Coronary Stent System for the Treatment of a De novo Atherosclerotic Lesion) II trial compared a thin-strut BP-EES with DP-EES in a relatively lower risk PCI cohort of 1684 patients.[23] At 12 months, the BP-EES was noninferior to DP-EES with respect to the primary end point of TLF[23]; however, longer follow-up data beyond the first year are still forthcoming for these studies.

A potential benefit of BP-SES compared with DP-EES in the subgroup of patients presenting with STEMI observed at
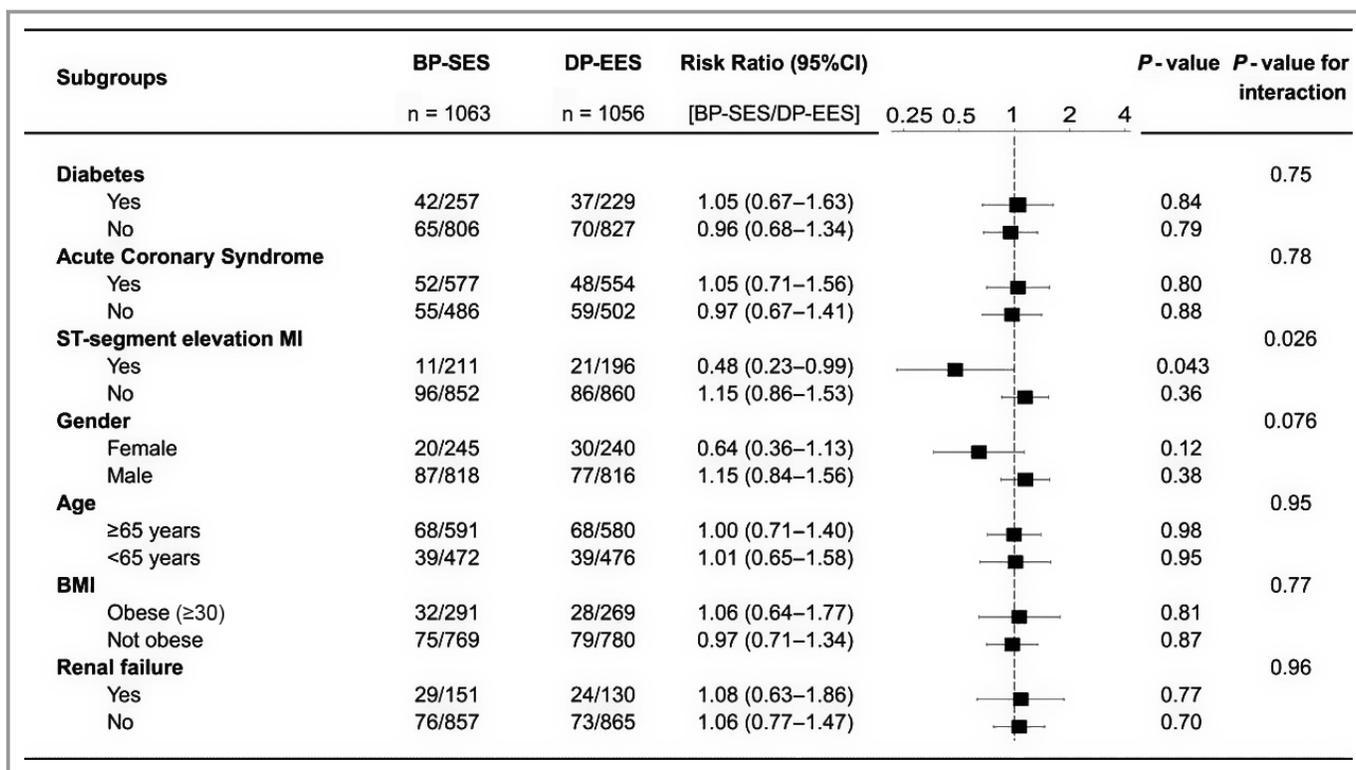
Subgroups	BP-SES	DP-EES	Risk Ratio (95%CI)		P-value	P-value for interaction
	n = 1063	n = 1056	[BP-SES/DP-EES]	0.25 0.5 1 2 4		
Diabetes						0.75
Yes	42/257	37/229	1.05 (0.67–1.63)		0.84	
No	65/806	70/827	0.96 (0.68–1.34)		0.79	
Acute Coronary Syndrome						0.78
Yes	52/577	48/554	1.05 (0.71–1.56)		0.80	
No	55/486	59/502	0.97 (0.67–1.41)		0.88	
ST-segment elevation MI						0.026
Yes	11/211	21/196	0.48 (0.23–0.99)		0.043	
No	96/852	86/860	1.15 (0.86–1.53)		0.36	
Gender						0.076
Female	20/245	30/240	0.64 (0.36–1.13)		0.12	
Male	87/818	77/816	1.15 (0.84–1.56)		0.38	
Age						0.95
≥65 years	68/591	68/580	1.00 (0.71–1.40)		0.98	
<65 years	39/472	39/476	1.01 (0.65–1.58)		0.95	
BMI						0.77
Obese (≥30)	32/291	28/269	1.06 (0.64–1.77)		0.81	
Not obese	75/769	79/780	0.97 (0.71–1.34)		0.87	
Renal failure						0.96
Yes	29/151	24/130	1.08 (0.63–1.86)		0.77	
No	76/857	73/865	1.06 (0.77–1.47)		0.70	

Figure 4. Stratified analysis of target-lesion failure at 2 years across prespecified subgroups. Number of first events and percentages are reported. Rate ratios with 95% CIs are estimated using the Mantel–Cox method with 2-sided P values from log-rank test. Renal failure indicates a creatinine-estimated glomerular filtration rate of <60 mL/min using the Modification of Diet in Renal Disease formula. BMI indicates body mass index; BP-SES, biodegradable-polymer sirolimus-eluting stent; DP-EES, durable-polymer everolimus-eluting stent.

1 year was maintained throughout 2 years of follow-up; however, the effect at 2 years (RR 0.48, 95% CI 0.23–0.99) was attenuated compared with the effect at 1 year (RR 0.38, 95% CI 0.16–0.91).[7,24] The observation is relevant because of previous concerns related to DP-SES[25,26] and is consistent with data from thick-strut BP-DES.[27,28] In an individual data–pooled analysis of 497 STEMI patients from 3 randomized controlled trials comparing thick-strut stainless steel BP-DESs with early generation SESs, the difference in favor of BP-DES emerged in the first year after PCI and remained stable thereafter.[28] Biodegradable polymers may enhance arterial healing in the inflammatory milieu of STEMI and reduce the number of uncovered struts; however, the results in STEMI patients were at variance with patients with non–ST-segment elevation acute coronary syndrome, in whom the risk of TLF trended higher with BP-SES compared with DP-EES (RR 1.52, 95% CI 0.94–2.48, *P*=0.086). Along with this limitation, the relatively modest sample size of STEMI patients (n=407) represents a further reason to use caution in interpreting the findings observed in this subgroup that may well be related to chance.

Our results should be interpreted in light of the following limitations. First, we are unable to report the number of eligible patients not included in the trial during the study period because the protocol did not regulate the use of a screening log. Second, the study was powered for the primary composite end point of TLF; therefore, our analysis remains underpowered to detect differences in the individual components of the primary end point or in rare events, such as very late ST. Third, the biodegradable polymer of the BP-SES degrades over a period of 12 to 24 months. Consequently, potential differences between BP-SES and DP-EES may unfold only during very long-term follow-up. Fourth, some adverse events may be related to previously implanted stents und unrelated to the study devices; however, all potential events were adjudicated by a blinded clinical events committee and classified according to their relation to the assigned study stent. Finally, although the greater benefit with BP-SES in the subgroup of patients with STEMI persisted after 2 years of follow-up, this finding should be considered hypothesis generating and warrants further study.

In conclusion, the 2-year follow-up of the BIOSCIENCE trial confirms equivalent safety and efficacy profiles of BP-SES and DP-EES. The rate of adverse events beyond 1 year was low and comparable for both treatment arms, with a low rate of very late ST. Whether differences in clinical outcomes emerge beyond 2 years needs to be further investigated.

Sources of Funding

Disclosures

References

1. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35:2541–2619.

2. Piccolo R, Giustino G, Mehran R, Windecker S. Stable coronary artery disease: revascularisation and invasive strategies. *Lancet*. 2015;386:702–713.

3. Windecker S, Meier B. Late coronary stent thrombosis. *Circulation*. 2007;116:1952–1965.

4. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. *N Engl J Med*. 2013;368:254–265.

5. Piccolo R, Stefanini GG, Franzone A, Spitzer E, Blochlinger S, Heg D, Juni P, Windecker S. Safety and efficacy of resolute zotarolimus-eluting stents compared with everolimus-eluting stents: a meta-analysis. *Circ Cardiovasc Interv*. 2015;8:e002223.

6. Windecker S, Stortecky S, Stefanini GG, da Costa BR, Rutjes AW, Di Nisio M, Silletta MG, Maione A, Alfonso F, Clemmensen PM, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head S, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter D, Schauerte P, Sousa Uva M, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A, Kolh P, Juni P. Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. *BMJ*. 2014;348:g3859.

7. Pilgrim T, Heg D, Roffi M, Tuller D, Muller O, Vuilliomenet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Fahrni T, Moschovitis A, Noble S, Eberli FR, Wenaweser P, Juni P, Windecker S. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial. *Lancet*. 2014;384:2111–2122.

8. Pilgrim T, Roffi M, Tuller D, Muller O, Vuilliomenet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Heg D, Juni P, Windecker S. Randomized comparison of biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents for percutaneous coronary revascularization: rationale and design of the BIOSCIENCE trial. *Am Heart J*. 2014;168:256–261.

9. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research C. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351.

10. Serruys PW, Farooq V, Kalesan B, de Vries T, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, Rademaker-Havinga T, van Es GA, Meier B, Juni P, Windecker S. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, noninferiority trial. *JACC Cardiovasc Interv*. 2013;6:777–789.

11. Natsuaki M, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, Akasaka T, Igarashi K, Tanabe K, Morino Y, Ishikawa T, Nishikawa H, Awata M, Abe M, Okada H, Takatsu Y, Ogata N, Kimura K, Urasawa K, Tarutani Y, Shiode N, Kimura T; Investigators N. Biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent: a randomized, controlled, noninferiority trial. *J Am Coll Cardiol*. 2013;62:181–190.

12. Danzi GB, Piccolo R, Galasso G, Piscione F. Nobori biolimus-eluting stent vs. permanent polymer drug-eluting stents in patients undergoing percutaneous coronary intervention. *Circ J*. 2014;78:1858–1866.

13. Vlachojannis GJ, Smits PC, Hofma SH, Togni M, Vazquez N, Valdes M, Voudris V, Puricel S, Slagboom T, Goy JJ, den Heijer P, van der Ent M. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with coronary artery disease: three-year follow-up of the COMPARE II (Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent) trial. *EuroIntervention*. 2015;11:272–279.

14. Natsuaki M, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, Akasaka T, Igarashi K, Tanabe K, Morino Y, Ishikawa T, Nishikawa H, Awata M, Abe M, Okada H, Takatsu Y, Ogata N, Kimura K, Urasawa K, Tarutani Y, Shiode N, Kimura T. Final 3-year outcome of a randomized trial comparing second-generation drug-eluting stents using either biodegradable polymer or durable polymer: NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial. *Circ Cardiovasc Interv*. 2015;8:e002817 doi: 10.1161/CIRCINTERVENTIONS.115.002817.

15. Navarese EP, Tandjung K, Claessen B, Andreotti F, Kowalewski M, Kandzari DE, Kereiakes DJ, Waksman R, Mauri L, Meredith IT, Finn AV, Kim HS, Kubica J, Suryapranata H, Aprami TM, Di Pasquale G, von Birgelen C, Kedhi E. Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis. *BMJ*. 2013;347:f6530.

16. Kang SH, Park KW, Kang DY, Lim WH, Park KT, Han JK, Kang HJ, Koo BK, Oh BH, Park YB, Kandzari DE, Cohen DJ, Hwang SS, Kim HS. Biodegradable-polymer drug-eluting stents vs. bare metal stents vs. durable-polymer drug-eluting stents: a systematic review and Bayesian approach network meta-analysis. *Eur Heart J*. 2014;35:1147–1158.

17. Piccolo R, Nicolino A, Danzi GB. The Nobori biolimus-eluting stent: update of available evidence. *Expert Rev Med Devices*. 2014;11:275–282.

18. Kolandaivelu K, Swaminathan R, Gibson WJ, Kolachalama VB, Nguyen-Ehrenreich KL, Giddings VL, Coleman L, Wong GK, Edelman ER. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. *Circulation*. 2011;123:1400–1409.

19. Jensen LO, Thayssen P, Maeng M, Ravkilde J, Krussel L, Tilsted H, Junker A, Terkelsen CJ, Vein KT, Kaltoft A, Villadsen AB, Aaroe J, Berencsi K, Jensen SE, Hansen KN, Kristensen SD, Madsen M, Botker HE, Hansen HS, Raungaard B, Lassen JF, Christiansen EH. Randomised comparison of a sirolimus-eluting stent with a biolimus-eluting stent in patients treated with PCI: the SORT OUT VII trial. Presented at EuroPCR 2015, Paris. 2015. Available at: http://www.pcronline.com/Lectures/2015/Randomised-comparison-of-a-sirolimus-eluting-stent-with-a-biolimus-eluting-stent-in-patients-treated-with-PCI-the-SORT-OUT-VII-trial. Accessed November 30, 2015.

20. Bangalore S, Toklu B, Amoroso N, Fusaro M, Kumar S, Hannan EL, Faxon DP, Feit F. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. *BMJ*. 2013;347:f6625.

21. Windecker S, Haude M, Neumann FJ, Stangl K, Witzenbichler B, Slagboom T, Sabate M, Goicolea J, Barragan P, Cook S, Piot C, Richardt G, Merkely B, Schneider H, Bilger J, Erne P, Waksman R, Zaugg S, Juni P, Lefevre T. Comparison of a novel biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent: results of the randomized BIOFLOW-II trial. *Circ Cardiovasc Interv*. 2015;8:e001441 doi: 10.1161/CIRCINTERVENTIONS.114.001441.

22. Saito S, Valdes-Chavarri M, Richardt G, Moreno R, Iniguez Romo A, Barbato E, Carrie D, Ando K, Merkely B, Kornowski R, Eltchaninoff H, James S, Wijns W; Investigators CI. A randomized, prospective, intercontinental evaluation of a bioresorbable polymer sirolimus-eluting coronary stent system: the CENTURY II (Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease) trial. *Eur Heart J*. 2014;35:2021–2031.

23. Kereiakes DJ, Meredith IT, Windecker S, Lee Jobe R, Mehta SR, Sarembock IJ, Feldman RL, Stein B, Dubois C, Grady T, Saito S, Kimura T, Christen T, Allocco DJ, Dawkins KD. Efficacy and safety of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent: the EVOLVE II Randomized Trial. *Circ Cardiovasc Interv*. 2015;8:e002372 doi: 10.1161/CIRCINTERVENTIONS.114.002372.

24. Pilgrim T, Piccolo R, Heg D, Roffi M, Tüller D, Vuilliomenet A, Muller O, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Khattab AA, Taniwaki M, Rigamonti F, Nietlispach F, Blochlinger S, Wenaweser P, Jüni P, Windecker S. Biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents for primary percutaneous coronary revascularization of acute myocardial infarction. *EuroIntervention*. 2015;11(8).

25. Piccolo R, Cassese S, Galasso G, Niglio T, De Rosa R, De Biase C, Piscione F. Long-term clinical outcomes following sirolimus-eluting stent implantation in patients with acute myocardial infarction. A meta-analysis of randomized trials. *Clin Res Cardiol*. 2012;101:885–893.

26. Piscione F, Piccolo R, Cassese S, Galasso G, Chiariello M. Clinical impact of sirolimus-eluting stent in ST-segment elevation myocardial infarction: a meta-analysis of randomized clinical trials. *Catheter Cardiovasc Interv*. 2009;74:323–332.

27. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet*. 2008;372:1163–1173.

28. de Waha A, King LA, Stefanini GG, Byrne RA, Serruys PW, Meier B, Juni P, Kastrati A, Windecker S. Long-term outcomes of biodegradable versus durable polymer drug-eluting stents in patients with acute ST-segment elevation myocardial infarction: a pooled analysis of individual patient data from three randomised trials. *EuroIntervention*. 2015;10:1425–1431.