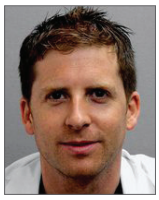
Biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents for primary percutaneous coronary revascularisation of acute myocardial infarction



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KEYWORDS

- acute myocardial infarcation
- biodegradable polymer
- durable polymer
- everolimus-eluting stents
- sirolimus-eluting stents

Abstract

Aims: Our aim was to compare the safety and efficacy of a novel, ultrathin strut, biodegradable polymer sirolimus-eluting stent (BP-SES) with a thin strut, durable polymer everolimus-eluting stent (DP-EES) in a pre-specified subgroup of patients with acute ST-segment elevation myocardial infarction (STEMI) enrolled in the BIOSCIENCE trial.

Methods and results: The BIOSCIENCE trial is an investigator-initiated, single-blind, multicentre, randomised non-inferiority trial (NCT01443104). Randomisation was stratified according to the presence or absence of STEMI. The primary endpoint, target lesion failure (TLF), is a composite of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularisation within 12 months. Between February 2012 and May 2013, 407 STEMI patients were randomly assigned to treatment with BP-SES or DP-EES. At one year, TLF occurred in seven (3.4%) patients treated with BP-SES and 17 (8.8%) patients treated with DP-EES (RR 0.38, 95% CI: 0.16-0.91, p=0.024). Rates of cardiac death were 1.5% in the BP-SES group and 4.7% in the DP-EES group (RR 0.31, 95% CI: 0.08-1.14, p=0.062); rates of target vessel myocardial infarction were 0.5% and 2.6% (RR 0.18, 95% CI: 0.02-1.57, p=0.082), respectively, and rates of clinically indicated target lesion revascularisation were 1.5% in the BP-SES group versus 2.1% in the DP-EES group (RR 0.69, 95% CI: 0.16-3.10, p=0.631). There was no difference in the risk of definite stent thrombosis.

Conclusions: In this pre-specified subgroup analysis, BP-SES was associated with a lower rate of target lesion failure at one year compared to DP-EES in STEMI patients. These findings require confirmation in a dedicated STEMI trial.

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Introduction

Acute ST-segment elevation myocardial infarction (STEMI) confers an increased risk of adverse outcome compared to stable coronary artery disease which extends beyond the periprocedural phase of primary percutaneous coronary intervention (PCI). Plaque characteristics of culprit lesions, thrombus burden and persistent inflammation are hallmarks of STEMI patients which increase the risk of delayed arterial healing and vessel remodelling, as reflected by higher rates of incomplete stent strut coverage[1,2] and malapposition[3].

Biodegradable polymer-based metallic drug-eluting stents (BP-DES) have been observed to reduce the rate of major adverse cardiac events (MACE) compared to bare metal stents (BMS) among patients with STEMI undergoing primary PCI at one year[4]. BP-DES have also been associated with a favourable healing response in intravascular imaging studies[5], and demonstrated a lower incidence of MACE throughout long-term follow-up compared to early-generation durable polymer drug-eluting stents among patients with STEMI[6,7]. A randomised comparison of durable polymer everolimus-eluting stents (DP-EES) versus BMS failed to show superiority of DP-EES with regard to the patient-oriented primary composite endpoint of all-cause death, recurrent myocardial infarction, and repeat revascularisation at one year. However, rates of target lesion revascularisation and definite and probable stent thrombosis were significantly lower in patients treated with DP-EES compared with BMS[8].

New-generation DES with cobalt-chromium platforms, reduced stent strut thickness and biocompatible polymers have been shown to be safe and effective in unselected patient populations and represent the current standard of care in patients undergoing PCI[9]. The combination of biodegradable polymers with thin strut cobalt-chromium platforms represents the next iteration of technological progress. In the randomised controlled BIOSCIENCE (biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation) trial, an ultrathin strut cobalt-chromium stent releasing sirolimus from a biodegradable poly-L-lactic acid (PLLA) polymer (BP-SES) was non-inferior compared to a thin strut DP-EES in a patient population reflecting routine clinical practice[10]. We present the results of a pre-specified subgroup analysis of patients with STEMI enrolled into the BIOSCIENCE trial.

Methods

STUDY DESIGN AND PATIENTS

The BIOSCIENCE trial is an investigator-initiated, single-blind, multicentre, randomised non-inferiority trial comparing an ultrathin strut (60 µm for stent diameters up to 3.0 mm, 80 µm for stent diameters >3.0 mm) cobalt-chromium L605 stent platform covered with an amorphous silicon-carbide layer and a biodegradable PLLA polymer releasing sirolimus (Orsiro; Biotronik AG, Bülach, Switzerland) with a thin strut cobalt-chromium, durable polymer everolimus-eluting stent (XIENCE PRIME/Xpedition®; Abbott Vascular, Santa Clara, CA, USA) in a patient population with minimal exclusion criteria in nine centres in Switzerland. In summary, all patients aged 18 years or older with at least one coronary lesion with >50% diameter *de novo* stenosis or restenosis in a native coronary artery or a bypass graft suitable for stent implantation were eligible for inclusion. There were no restrictions in terms of number of vessels or lesions treated. Inclusion and exclusion criteria as well as detailed characteristics of the study devices have been reported previously[11]. The study was approved by the institutional ethics committees of all participating sites and complied with the Declaration of Helsinki. All study participants provided written informed consent. The trial is registered with ClinicalTrials.gov (NCT01443104). The trial was supported by an unrestricted grant from Biotronik, Bülach, Switzerland. The funding source had no role in the study design, data collection, data monitoring, data analysis, or data interpretation.

RANDOMISATION

Patients were randomly allocated in a 1:1 ratio to BP-SES or DP-EES immediately after diagnostic angiography and prior to PCI. Randomisation was computer generated and stratified according to the presence or absence of STEMI, per site. Sequentially numbered, opaque, sealed envelopes were used as a back-up in case of malfunction of the web-based randomisation system.

PROCEDURES

PCI was performed according to current guidelines. Thrombus aspiration, predilation, and post-dilatation were performed according to the discretion of the operator. Staged repeat revascularisation procedures with the assigned study stent were scheduled within three months of the index procedure. Patients were treated with unfractionated heparin with a dose of 5,000 IU or 70-100 IU/kg body weight during the procedure. The administration of bivalirudin instead of unfractionated heparin was allowed. Administration of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. Antiplatelet therapy was initiated upstream or at the time of primary PCI. Acetylsalicylic acid (≥250 mg) was combined with clopidogrel (loading dose 600 mg, maintenance dose 75 mg QD), prasugrel (loading dose 60 mg, maintenance dose 10 mg QD), or ticagrelor (loading dose 180 mg, maintenance dose 90 mg BID). After a recommended dual antiplatelet therapy of 12 months duration, monotherapy with acetylsalicylic acid was continued indefinitely.

DEFINITIONS AND DATA MANAGEMENT

Definitions of primary and secondary endpoints have been outlined previously[11]. Target lesion failure was the pre-specified primary endpoint and was a composite of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularisation (TLR) within 12 months. Cardiac death was defined as any death due to an immediate cardiac cause, death related to the procedure, unwitnessed death, and death of unknown cause. Spontaneous myocardial infarction was recorded in case of a typical rise and fall of creatinine kinase MB fraction or troponin in

the presence of at least one of the following: ischaemic symptoms, new pathologic Q-waves, ischaemic electrocardiographic changes or pathological evidence of acute myocardial infarction. Periprocedural myocardial reinfarction in the setting of evolving myocardial infarction was defined as recurrent chest pain lasting >20 minutes (or new ECG changes consistent with myocardial infarction) in combination with a >50% increase of peak CK (or CK-MB in the absence of CK) level above the previous level measured within 24 hours after the event. In case elevated CK (or CK-MB) levels from the index infarction were falling or had returned to normal, a reinfarction was diagnosed in case of new elevation of CK >2x the upper limit of normal (ULN) if the CK level had returned to <ULN, or a rise by >50% above the previous nadir level if the CK level had not returned to <ULN. A myocardial infarction was related to the target vessel if it could not be clearly related to another vessel. TLR was documented in case of any repeat percutaneous or surgical intervention secondary to a stenosis within the stent or within the 5 mm borders proximal or distal to the stent. TLR was regarded as clinically indicated if the stenosis of the treated lesion was ≥50% of the lumen diameter in the presence of signs or symptoms of ischaemia, or if the diameter stenosis was ≥70% irrespective of the presence or absence of ischaemic signs and symptoms.

All data were entered into a web database held at the Clinical Trials Unit and the Department of Cardiology in Bern, Switzerland. Regular follow-up was performed at 30 days and one year. Electrocardiograms were systematically recorded at baseline, after the procedure, at 12-month follow-up and in case of recurrent signs or symptoms of ischaemia. Data monitoring and event adjudication have been described previously.

STATISTICAL ANALYSIS

The BIOSCIENCE trial was powered for non-inferiority on the primary clinical endpoint, target lesion failure at 12 months, in the overall population but not in the pre-specified subgroup of STEMI patients. Based on event rates reported from COMPARE[12], RESOLUTE All-Comers[9], and the LESSON registry[13], a TLF rate of 8% at 12 months was assumed in both treatment arms. Using a margin of 3.5% for non-inferiority of BP-SES vis-à-vis DP-EES, enrolment of 2,060 patients was calculated to provide at least 80% power to detect non-inferiority at a one-sided type I error of 0.05.

The STEMI population was a pre-specified subgroup with a significant interaction effect (STEMI yes or no vs. randomised stent) reported for the primary outcome[10], which warranted a more in-depth assessment of clinical outcomes reported here. Clinical endpoints were analysed according to the intention-to-treat principle. We used the Mantel-Cox method to calculate rate ratios (RR), two-sided 95% confidence intervals (CI) and corresponding two-sided p-values for superiority from the log-rank test. We used time to first event for each type of outcome throughout, and report Kaplan-Meier estimates of event rates. All analyses of endpoints were performed according to the intention-to-treat principle. Analyses were undertaken by a statistician of the Clinical Trials Unit Bern in Stata version 13 (StataCorp LP, College Station, TX, USA). All p-values and CIs are reported two-sided. P-values for characteristics recorded at the patient level are from unpaired t-tests, chi-square tests, or Fisher's exact tests, except when specified. P-values for characteristics that were recorded at the lesion level are from general or generalised linear mixed models to account for the non-independence of lesions within the same patient.

Results

Among 2,119 patients randomly assigned to treatment with BP-SES or DP-EES between February 2012 and May 2013, 407 patients (19%) presented with STEMI. Two hundred and eleven STEMI patients with 289 lesions were allocated to treatment with BP-SES, and 196 STEMI patients with 267 lesions were allocated to treatment with DP-EES **(Figure 1)**.

Baseline clinical characteristics were comparable between the two treatment arms **(Table 1)**. The time interval from pain onset to presentation was ≤6 hours in 111 (70%) patients with BP-SES and 89 (61%) patients with DP-EES. The median door-to-balloon time amounted to 53 (interquartile range [IQR] 32-93) minutes in the BP-SES group and 51 (IQR 33-95) minutes in the DP-EES group, respectively. More than 98% of patients were in Killip class I or II in both treatment groups at the time of primary PCI. Angiographic and procedural features were similar between the two treatment arms with the exception of a higher number of small vessels per lesion among patients treated with DP-EES as compared with BP-SES (84 [32%] versus 57 [21%], p=0.01) and a smaller maximal stent diameter (3.1±0.5 mm versus 3.2±0.5 mm, p=0.01), respectively **(Table 2)**. Medical treatment during the procedure and throughout follow-up is summarised in **Table 3** without significant differences. There were no differences in periprocedural antiplatelet and antithrombotic therapy between groups. The majority of patients were loaded with a novel $P2Y_{12}$ inhibitor primarily, or in addition to clopidogrel. Glycoprotein IIb/IIIa inhibitors were used in 24.2% of patients treated with BP-SES and 16.3% of patients treated with DP-EES (p=0.06). Periprocedural antithrombotic treatment consisted of unfractionated heparin in the overwhelming majority of patients.

Clinical outcome is summarised in **Table 4** and illustrated in **Figure 2**. Among STEMI patients, the primary endpoint TLF occurred in seven (3.4%) patients treated with BP-SES and 17 (8.8%) patients treated with DP-EES at one year (RR 0.38, 95% CI: 0.16-0.91, p=0.024). The rates of the individual components of the composite endpoint TLF are summarised in **Figure 2**. There was a non-significant trend towards lower rates of cardiac death (BP-SES three [1.5%] versus DP-EES nine [4.7%], RR 0.31, 95% CI: 0.08-1.14, p=0.062) and target vessel myocardial infarction (BP-SES one [0.5%] versus DP-EES five [2.6%], RR 0.18, 95% CI: 0.02-1.57, p=0.082) in patients treated with BP-SES. Rates of clinically indicated TLR were 1.5% in the BP-SES group versus 2.1% in the DP-EES group (RR 0.69, 95% CI: 0.16-3.10, p=0.631). Rates of definite, probable, and possible stent thrombosis (ST) at

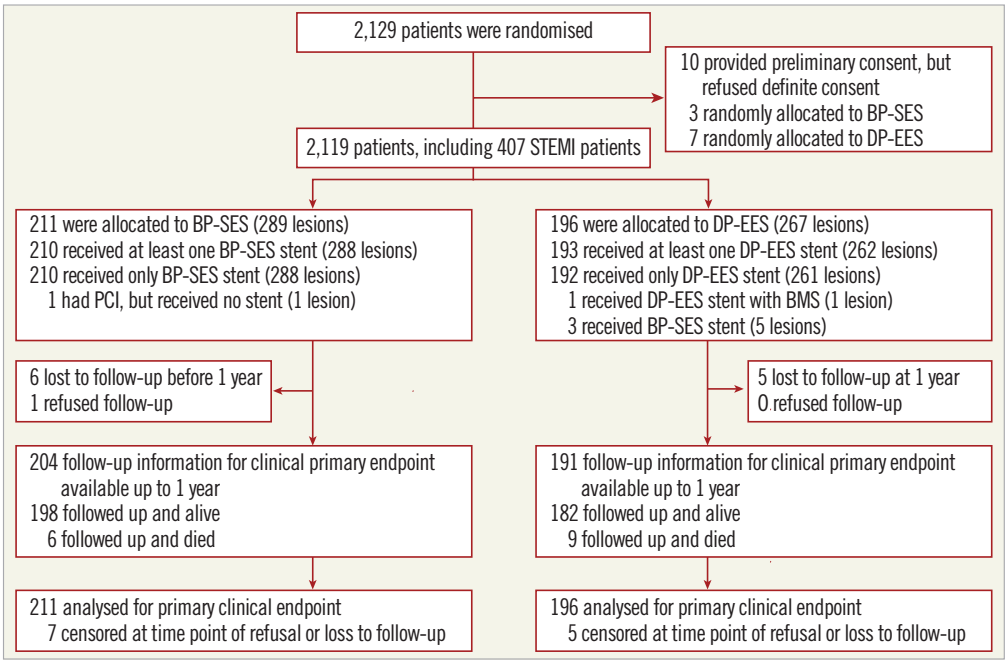

Figure 1. *Patient flow according to the CONSORT statement. BP-SES: biodegradable polymer sirolimus-eluting stent; DP-EES: durable polymer everolimus-eluting stent*

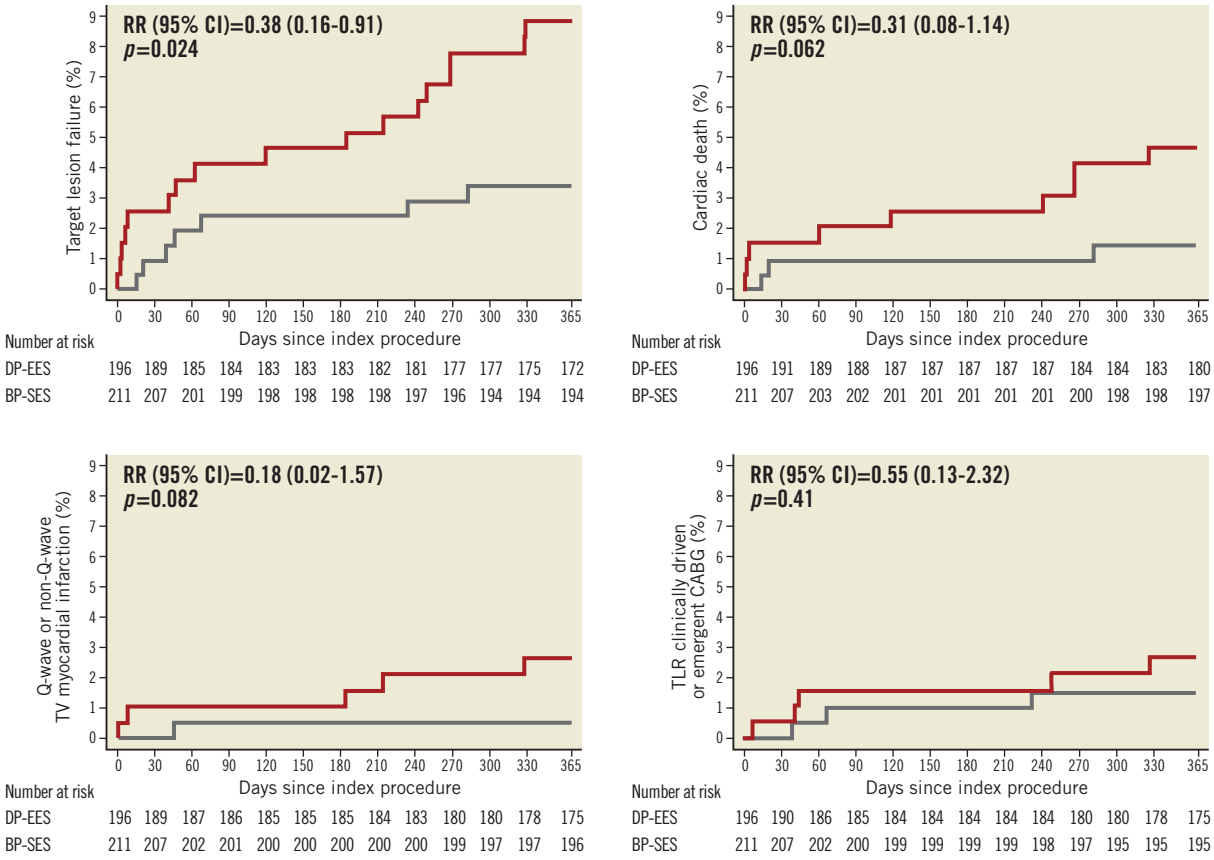

Figure 2. *Time-to-event curves for the composite endpoint target lesion failure and individual components of the primary endpoint up to 12 months of follow-up. A) Target lesion failure. B) Cardiac death. C) Target vessel (TV) myocardial infarction. D) Clinically indicated target lesion revascularisation (TLR) or emergent coronary artery bypass surgery (CABG). Blue lines indicate BP-SES, red lines indicate DP-EES.*

Table 1. Baseline clinical characteristics.

	Biodegradable polymer sirolimus-eluting stent n=211	Durable polymer everolimus-eluting stent n=196	*p*-value
Age, years (SD)	61.3±12.4	61.7±12.7	0.75
Male gender, n (%)	170 (80.6%)	151 (77.0%)	0.40
Body mass index, kg/m^2	27.0±4.3*	27.0±4.3**	0.94
Diabetes mellitus, n (%)	30 (14.2%)	27 (13.8%)	1.00
Hypertension, n (%)	102 (48.6%)$^{\Delta}$	98 (50.3%)$^{\Delta\Delta}$	0.77
Hypercholesterolaemia, n (%)	110 (52.1%)	101 (51.5%)	0.92
Current smoker, n (%)	93 (44.1%)	77 (39.5%)$^{\Delta\Delta}$	0.37
Family history of CAD, n (%)	42 (20.1%)*	45 (23.0%)	0.55
Previous MI, n (%)	10 (4.7%)	9 (4.6%)	1.00
Previous PCI, n (%)	12 (5.7%)	8 (4.1%)	0.50
Previous CABG, n (%)	5 (2.4%)	1 (0.5%)	0.22
Previous stroke or TIA, n (%)	2 (0.9%)	3 (1.5%)	0.68
Peripheral vascular disease, n (%)	3 (1.4%)	2 (1.0%)	1.00
Renal failure (GFR <60 ml/min), n (%)	15 (7.7%)‡	17 (9.6%)‡‡	0.58
Left ventricular ejection fraction,%	49.5±10.9¶	48.3±11.1¶¶	0.32
Clinical presentation			
Time to balloon inflation (from symptom onset), min	248 (165-470)$^{\#}$	284 (162-534)$^{\#\#}$	0.48
Pain onset to balloon			0.12
0-6 hrs	111 (70.3%)$^{\#}$	89 (61.4%)$^{\#\#}$	
>6-12 hrs	24 (15.2%)	38 (26.2%)	
>12-24 hrs	21 (13.3%)	17 (11.7%)	
>24 hrs	2 (1.3%)	1 (0.7%)	
Time from arrival at hospital to balloon inflation, min	53 (32-94)	51 (33-95)	0.87
Killip class			0.77
Killip class I	181 (85.8%)	168 (87.5%)	
Killip class II	26 (12.3%)	21 (10.9%)	
Killip class III	3 (1.4%)	3 (1.6%)	
Killip class IV	1 (0.5%)	0 (0.0%)	
Baseline medications, n (%)			
Aspirin	41 (19.8%)§	31 (16.3%)§§	0.43
Clopidogrel	2 (1.0%)§	4 (2.1%)§§	0.43
Prasugrel	1 (0.5%)§	4 (2.1%)§§	0.20
Ticagrelor	4 (1.9%)§	2 (1.1%)§§	0.69
Any dual antiplatelet treatment	6 (2.9%)§	8 (4.2%)§§	0.58
Oral anticoagulants - vitamin K antagonists	1 (0.5%)§	2 (1.1%)§§	0.61
Novel oral anticoagulants	0 (0.0%)$^{\lozenge}$	0 (0.0%)§§	
Any antithrombotic treatment	1 (0.5%)§	2 (1.1%)§§	0.61
Statins	34 (16.5%)$^{\lozenge}$	35 (18.4%)§§	0.69
ACE inhibitors or receptor blockers	27 (13.1%)$^{\lozenge}$	23 (12.1%)§§	0.88
Beta-blockers	28 (13.6%)$^{\lozenge}$	34 (17.9%)§§	0.27

Data expressed as n (%), means±standard deviation or medians (25%-75% interquartile range). p-values from Fisher's tests, unpaired t-tests and Mann-Whitney U tests, respectively. *n: 209; $^{\Delta}$n: 210; ‡n: 196; ¶n: 167; $^{\#}$n: 158; §n: 207; $^{\lozenge}$n: 206; **n: 193; $^{\Delta\Delta}$n: 195; ‡‡n: 177; ¶¶n: 157; $^{\#\#}$n: 145; §§n: 190.

different time points are summarised in **Table 5**. Whereas there were no differences in rates of definite ST, rates of definite or probable ST were numerically more frequent in the DP-EES treatment arm at one year.

Discussion

In the pre-specified subgroup analysis of the randomised BIOSCIENCE trial, BP-SES was associated with a lower rate of the primary endpoint TLF at one year compared to DP-EES. Differences

Table 2. Angiographic and procedural characteristics.

No. of patients	Biodegradable polymer sirolimus-eluting stent n=211	Durable polymer everolimus-eluting stent n=196	*p*-value
Lesions, n	n=289	n=267	
Target vessel location per lesion$^{\Delta}$, n (%)	n=289	n=267	0.10
Left main artery	6 (2.1%)	4 (1.5%)	
Left anterior descending artery	109 (37.7%)	115 (43.1%)	
Left circumflex artery	47 (16.3%)	55 (20.6%)	
Right coronary artery	124 (42.9%)	93 (34.8%)	
Saphenous vein graft	3 (1.0%)	0 (0.0%)	0.25
No. of treated lesions per patient¶	1.37±0.73	1.36±0.62	0.95
Number of treated lesions per patient$^{\Delta}$, n (%)	n=211	n=196	0.95
One	155 (73.5%)	140 (71.4%)	
Two	41 (19.4%)	41 (20.9%)	
Three	10 (4.7%)	15 (7.7%)	
≥Four	5 (2.4%)	0 (0.0%)	
Type of intervention per lesion, n (%)**	n=289	n=267	0.36
Stent implantation	276 (95.5%)	259 (97.0%)	
PTCA	12 (4.2%)	8 (3.0%)	
Failed PCI	1 (0.3%)	0 (0.0%)	
Baseline TIMI flow per lesion, n (%)	n=282	n=263	0.23
0 or 1	163 (57.8%)	136 (51.7%)	
2	37 (13.1%)	47 (17.9%)	
3	82 (29.1%)	80 (30.4%)	
TIMI flow post intervention per lesion, n (%)	n=287	n=267	0.79
0 or 1	2 (0.7%)	3 (1.1%)	
2	7 (2.4%)	5 (1.9%)	
3	278 (96.9%)	259 (97.0%)	
Thrombus aspiration per lesion, n (%)	115 (39.8%)	92 (34.7%)$^{\#}$	0.22
Number of stents per lesion, mean (SD)	1.42±0.71$^{\lozenge}$	1.39±0.71$^{\lozenge\lozenge}$	0.71
Total stent length per lesion, mm	29.49±17.83$^{\lozenge}$	30.52±18.99$^{\lozenge\lozenge}$	0.51
Maximum stent diameter per lesion, mm	3.18±0.48$^{\lozenge}$	3.06±0.52$^{\lozenge\lozenge}$	0.01
Maximum pressure per lesion, atm	13.86±3.36$^{\lozenge}$	13.39±3.20$^{\lozenge\lozenge}$	0.11
Overlapping stents per lesion, n (%)	83 (30.1%)$^{\lozenge}$	62 (23.9%)$^{\lozenge\lozenge}$	0.14
Direct stenting per lesion, n (%)	78 (28.3%)$^{\lozenge}$	68 (26.3%)$^{\lozenge\lozenge}$	0.62
Long lesion per lesion (>20 mm), n (%)	171 (62.0%)$^{\lozenge}$	170 (65.6%)$^{\lozenge\lozenge}$	0.38
Small vessel per lesion (<2.75 mm), n (%)	57 (20.7%)$^{\lozenge}$	84 (32.4%)$^{\lozenge\lozenge}$	0.01
Type of stent per lesion$^{\Delta}$, (%)			0.053$^{\Delta\Delta}$
Study stent BP-SES	276 (100.0%)	5 (1.9%)	
Study stent DP-EES	0 (0.0%)	254 (98.1%)	
Other drug-eluting stent	0 (0.0%)	0 (0.0%)	
Bare metal stent	0 (0.0%)	1 (0.4%)	
IABP per patient, n (%)	1 (0.5%)	0 (0.0%)	1.00$^{\Delta}$
Vasopressors per patient, n (%)	4 (1.9%)	1 (0.5%)	0.24

Data expressed as n (%) or means±standard deviation. *p*-values from ¶Poisson regression and $^{\Delta}$chi-square tests or Fisher's test; otherwise, *p*-values from mixed models for the per-lesion analyses, accounting for lesions nested within patients: general linear mixed models for continuous variables, generalised linear mixed models for counts no. Long lesion: total stent length >20 mm. Small vessel: minimum stent diameter <2.75 mm. ** In one patient randomised to stent DP-EES one lesion, the intervention was aborted. $^{\Delta\Delta}$ One patient randomised to stent DP-EES contained stent DP-EES and BMS within same lesion. *p*-value for any non-randomised stent implanted per patient. $^{\lozenge}$n: 276; $^{\#}$n: 265; $^{\lozenge\lozenge}$n: 259.

Table 3. Medical treatment.

No. of patients		Biodegradable polymer sirolimus-eluting stent n=211	Durable polymer everolimus-eluting stent n=196	*p*-value
During primary PCI, n (%)	Aspirin	209 (99.1%)	194 (99.0%)	1.00
	Clopidogrel	69 (32.7%)	64 (32.7%)	1.00
	Prasugrel	141 (66.8%)	141 (71.9%)	0.28
	Ticagrelor	46 (21.8%)	35 (17.9%)	0.39
	Unfractionated heparin	206 (97.6%)	193 (98.5%)	0.73
	Low-molecular-weight heparin (LMWH)	8 (3.8%)	10 (5.1%)	0.63
	Bivalirudin	3 (1.4%)	3 (1.5%)	1.00
	Glycoprotein IIb/IIIa inhibitors	51 (24.2%)	32 (16.3%)	0.06
At discharge, n (%)	Aspirin	209 (99.1%)*	195 (100.0%)¶	0.50
	Clopidogrel	17 (8.1%)*	15 (7.7%)¶	1.00
	Prasugrel	145 (68.7%)*	145 (74.4%)¶	0.23
	Ticagrelor	48 (22.7%)*	36 (18.5%)¶	0.33
	Any dual antiplatelet treatment	207 (98.1%)*	195 (100.0%)¶	0.12
	Vitamin K oral anticoagulants	9 (4.3%)*	7 (3.6%)¶	0.80
	Non-vitamin K oral anticoagulants (NOAC)	1 (0.5%)*	1 (0.5%)¶	1.00
	Any antithrombotic treatment	10 (4.7%)*	8 (4.1%)¶	0.81
	Statin	207 (98.1%)*	190 (97.4%)¶	0.74
	ACE inhibitor	181 (85.8%)*	162 (83.1%)¶	0.49
	Beta-blocker	187 (88.6%)*	178 (91.3%)¶	0.41
At 30-day follow-up, n (%)	Aspirin	204 (99.0%)‡	191 (99.5%)‡‡	1.00
	Clopidogrel	23 (11.2%)‡	19 (9.9%)‡‡	0.75
	Prasugrel	140 (68.0%)‡	141 (73.4%)‡‡	0.27
	Ticagrelor	43 (20.9%)‡	32 (16.7%)‡‡	0.31
	Any dual antiplatelet treatment	203 (98.5%)‡	190 (99.0%)‡‡	1.00
	Oral anticoagulants	11 (5.3%)‡	7 (3.6%)‡‡	0.48
	Novel oral anticoagulants	0 (0.0%)‡	1 (0.5%)‡‡	0.48
	Any antithrombotic treatment	11 (5.3%)‡	8 (4.2%)‡‡	0.64
	Statin	200 (97.1%)‡	183 (95.3%)‡‡	0.43
	ACE inhibitor	165 (80.1%)‡	143 (74.5%)‡‡	0.19
	Beta-blocker	179 (86.9%)‡	173 (90.1%)‡‡	0.35
At 1-year follow-up, n (%)	Aspirin	192 (97.0%)#	177 (97.3%)##	1.00
	Clopidogrel	30 (15.2%)#	23 (12.6%)##	0.55
	Prasugrel	122 (61.6%)#	112 (61.5%)##	1.00
	Ticagrelor	31 (15.7%)#	29 (15.9%)##	1.00
	Any dual antiplatelet treatment	178 (89.9%)#	158 (86.8%)##	0.42
	Oral anticoagulants	8 (4.0%)#	7 (3.8%)##	1.00
	Novel oral anticoagulants	1 (0.5%)#	2 (1.1%)##	0.61
	Any antithrombotic treatment	9 (4.5%)#	9 (4.9%)##	1.00
	Statin	183 (92.9%)#	174 (95.6%)##	0.28
	ACE inhibitor	140 (70.7%)#	112 (61.9%)##	0.08
	Beta-blocker	156 (78.8%)#	158 (86.8%)##	0.04

*n: 194; ¶n: 195; ‡n: 206; #n: 198; ‡‡n: 192; ##n: 182.

in the primary endpoint were driven by non-significant, numerical differences in cardiac death and target vessel myocardial infarction, whereas there was no difference in repeat revascularisation.

The antirestenotic efficacy of early-generation durable polymer sirolimus-eluting stents (DP-SES) in the setting of STEMI came at the expense of an excess in late thrombotic events[14]. In the LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial[15], which compared biodegradable polymer biolimus-eluting stents (BP-BES) with early-generation DP-SES, a lower rate of the primary endpoint MACE among BP-BES treated patients was documented in the subgroup of STEMI at nine months, a finding which was maintained during

Table 4. Clinical outcomes at 12 months after stent implantation.

	Biodegradable polymer sirolimus-eluting stent n=211	Durable polymer everolimus-eluting stent n=196	Rate ratio [SES/EES] (95% CI)	*p*-value
All-cause death	6 (2.9)	9 (4.7)	0.62 (0.22-1.74)	0.357
Cardiac death	3 (1.5)	9 (4.7)	0.31 (0.08-1.14)	0.062
Reinfarction (any)	3 (1.5)	5 (2.6)	0.55 (0.13-2.32)	0.412
Q-wave	0 (0.0)	3 (1.6)	0.13 (0.01-2.50)	0.111
Non-Q-wave	3 (1.5)	2 (1.1)	1.40 (0.23-8.42)	0.710
Target vessel reinfarction	1 (0.5)	5 (2.6)	0.18 (0.02-1.57)	0.082
Q-wave	0 (0.0)	3 (1.6)	0.13 (0.01-2.50)	0.111
Non-Q-wave	1 (0.5)	2 (1.1)	0.47 (0.04-5.12)	0.522
Cardiac death or MI	6 (2.9)	14 (7.3)	0.39 (0.15-1.03)	0.048
Any repeat revascularisation	10 (4.9)	9 (4.7)	1.02 (0.41-2.51)	0.964
Any target lesion revascularisation	3 (1.5)	5 (2.7)	0.55 (0.13-2.31)	0.410
Clinically indicated TLR	3 (1.5)	4 (2.1)	0.69 (0.16-3.10)	0.631
Clinically indicated TVR	6 (3.0)	5 (2.7)	1.12 (0.34-3.66)	0.857
Any target vessel revascularisation	6 (3.0)	6 (3.2)	0.92 (0.30-2.87)	0.891
Clinically indicated TLR or clinically indicated surgical TVR	3 (1.5)	5 (2.7)	0.55 (0.13-2.32)	0.412
Cerebrovascular event*	4 (2.0)	4 (2.1)	0.93 (0.23-3.71)	0.913
Target lesion failure**	7 (3.4)	17 (8.8)	0.38 (0.16-0.91)	0.024
Target vessel failure***	10 (4.9)	18 (9.3)	0.51 (0.24-1.11)	0.082
Death, MI, or any repeat revascularisation****	17 (8.3)	19 (9.8)	0.82 (0.43-1.59)	0.563
BARC bleeding events type 3-5	9 (4.4)	10 (5.2)	0.83 (0.34-2.06)	0.694
BARC bleeding type 3a	4 (1.9)	3 (1.6)	1.24 (0.28-5.56)	0.777
BARC bleeding type 3b	4 (2.0)	7 (3.7)	0.53 (0.15-1.80)	0.299
BARC bleeding type 3c	0 (0.0)	0 (0.0)		
BARC bleeding type 4	1 (0.5)	0 (0.0)	2.79 (0.11-68.08)	1.000
BARC bleeding type 5a	0 (0.0)	0 (0.0)		
BARC bleeding type 5b	0 (0.0)	0 (0.0)		

Number of first events and percentages are reported. Rate ratios (RR; 95% CI) are estimated using the Mantel-Cox method with two-sided *p*-values from log-rank test. All events were censored beyond 365 days. Continuity corrected RR with Fisher's exact test for zero outcomes. MI: myocardial infarction; TLR: target lesion revascularisation; TVR: target vessel revascularisation. *Includes ischaemic stroke, intracerebral haemorrhage and unclear aetiology CVE. **Primary endpoint, defined as the composite of cardiac death, target vessel Q-wave or non-Q-wave MI, clinically indicated TLR and clinically indicated surgical TVR. ***Defined as the composite of cardiac death, any Q-wave or non-Q-wave MI, and any TVR. ****Patient-oriented composite endpoint.

long-term follow-up throughout five years[16]. The present study may extend the potential benefit of biodegradable polymer-based DES among STEMI patients observed with early-generation thick-strut stainless steel DES to newer-generation thin-strut cobalt-chromium DES. Noteworthy, cobalt-chromium DP-EES currently represent the benchmark for safety and efficacy in STEMI patients undergoing primary PCI, as suggested by recent network meta-analyses[17,18].

An individual patient-data, pooled analysis of 497 patients with STEMI from three trials randomly comparing thick-strut stainless steel BP-DES with early-generation, thick-strut DP-SES observed a benefit of BP-DES with a difference emerging within one year after primary PCI (BP-DES 27 [9.4%] versus early-generation DP-SES 32 [15.8%], HR 0.58, 95% CI: 0.35-0.93, p=0.03), whereas there was no difference in the period between one and four years (BP-DES 13 [5.2%] versus early-generation DP-SES 14 [8.6%], HR 0.62, 95% CI: 0.29-1.31, p=0.21). In contrast to the present analysis, the effect within the first year was driven by a lower rate of repeat revascularisation (TLR: BP-DES 12 [4.4%] versus early-generation DP-SES 19 [9.7%], HR 0.43, 95% CI: 0.21-0.89, p=0.02), while no difference was observed in rates of cardiac death or myocardial infarction[6]. A trend towards a lower rate of definite stent thrombosis in the first year after stent implantation documented in the pooled analysis (BP-DES eight [2.9%] versus early-generation DP-SES 13 [6.5%], HR 0.43, 95% CI: 0.18-1.03, p=0.06) was also seen in the present subgroup analysis[6]. Five-year outcomes of the LEADERS trial showed significantly improved safety and

Table 5. Stent thrombosis.

		Biodegradable polymer sirolimus-eluting stent n=211	Durable polymer everolimus-eluting stent n=196	Rate ratio [SES/EES] (95% CI)	*p*-value
Definite stent thrombosis¶	0 to 30 days	0 (0.0)	1 (0.5)	0.31 (0.01-7.56)	0.482
	>30 days to 12 months	0 (0.0)	1 (0.5)	0.31 (0.01-7.56)	0.480
	0 days to 12 months	0 (0.0)	2 (1.0)	0.19 (0.01-3.93)	0.231
Probable stent thrombosis	0 to 30 days	2 (1.0)	4 (2.0)	0.46 (0.08-2.51)	0.358
	>30 days to 12 months	1 (0.5)	3 (1.6)	0.31 (0.03-2.96)	0.280
	0 days to 12 months	3 (1.4)	7 (3.6)	0.39 (0.10-1.53)	0.163
Possible stent thrombosis	0 to 30 days	0 (0.0)	0 (0.0)		
	>30 days to 12 months	1 (0.5)	5 (2.6)	0.19 (0.02-1.59)	0.085
	0 days to 12 months	1 (0.5)	5 (2.6)	0.19 (0.02-1.59)	0.085
Definite or probable stent thrombosis	0 to 30 days	2 (1.0)	5 (2.6)	0.37 (0.07-1.89)	0.212
	>30 days to 12 months	1 (0.5)	4 (2.2)	0.23 (0.03-2.05)	0.150
	0 days to 12 months	3 (1.4)	9 (4.7)	0.31 (0.08-1.13)	0.060

Number of first events and percentages are reported. Rate ratios (RR) are estimated using the Mantel-Cox method with two-sided *p*-values from log-rank test, except ¶ continuity corrected RR with *p*-values from Fisher's test. Possible stent thrombosis cannot occur by definition within 30 days. Landmark used at 30 days for >30 days to 12 months analyses, and note that the risk set for each risk difference calculation changes accordingly.

efficacy outcomes in patients with STEMI treated with BP-BES as compared to early-generation DP-SES, driven by a lower rate of cardiac death (BP-BES four [3%] versus DP-SES 16 [11.4%], p=0.007) and revascularisation (BP-BES 14 [17.8%] versus 37 [26.4%], p=0.049)[7]. It remains to be determined whether these findings are a class effect of biodegradable polymer DES in general, or whether the properties are inherent to individual stents specifically.

Biodegradable polymers may have favourable results on arterial healing after DES implantation. In the optical coherence tomography substudy of the LEADERS trial[5], a favourable healing response was observed with BP-BES compared with early-generation DP-SES at nine months. The effect of an enhanced healing response may be augmented in the inflammatory milieu of STEMI. Evidence of adverse arterial remodelling among patients with STEMI has been shown by a greater degree of incomplete DES apposition and delayed tissue coverage compared to patients with stable or unstable angina in optical coherence tomography studies[1,19]. However, while sirolimus is released over a period of 12 to 14 weeks, the PLLA polymer matrix degrades over a period of 12 to 24 months, and may not fully account for the observed difference. In addition to the biodegradable polymer, the reduced strut thickness of the novel stent platform as well as the passive stent coating may play a role when implanted into lesions of patients with STEMI, by reducing acute arterial injury and the risk for peripheral embolisation as well as affording a more rapid re-endothelialisation. A reduction of strut thickness in the case of BMS has been associated with a lower risk of restenosis[20] and attenuated thrombogenicity[21].

Limitations

The present analysis has several limitations. First, the BIOSCIENCE trial was not powered to assess differences in clinical outcome among patients with STEMI and therefore findings may be due to chance alone. However, randomisation was prespecified for the presence or absence of STEMI and there were no differences in evidence-based medical therapy. Furthermore, event rates were consistent with event rates of recent STEMI trials **(Table 6)**. Second, patients in the DP-EES treatment arm had a higher proportion of small vessel disease and a smaller

Table 6. Event rates in recent STEMI trials (%).

	MULTISTRATEGY[22]** (BMS/SES)	DEDICATION[23]** (DES/BMS)	HORIZONS[24]* (PES/BMS)	EXAMINATION[8]* (EES/BMS)	COMFORTABLE[4]* (BES/BMS)	BIOSCIENCE* (SES/EES)
Death	2.2/1.3	5.2/2.6	3.5/3.5	3.5/3.5	3.2/4.1	2.9/4.7
Cardiac death	–	4.2/1.6	2.4/2.7	3.2/2.8	2.9/3.5	1.5/4.7
Reinfarction	2.7/1.3	1.0/1.9	3.7/4.5	1.3/2.0	2.0/3.7	1.5/2.6
TV reinfarction	–	–	–	1.1/2.0	0.5/2.7	0.5/2.6

* follow-up to 12 months; ** follow-up to 8 months; TV: target vessel

maximum stent diameter that may have affected clinical outcome. Moreover, there was a trend towards a more frequent administration of glycoprotein IIb/IIIa inhibitors in the group of patients treated with BP-SES. Third, the STEMI patients included in the BIOSCIENCE trial were rather low risk based on Killip class; generalisability to a higher-risk population therefore requires confirmation in registries including higher-risk patients. Finally, the duration of follow-up was limited to 12 months, which may not suffice to assess the efficacy of BP-SES beyond complete degradation of the biodegradable polymer.

Conclusion

In conclusion, BP-SES may be associated with improved clinical outcomes compared with DP-EES among STEMI patients undergoing primary PCI. The findings are hypothesis-generating and have to be reproduced in a dedicated, randomised trial in order to substantiate the potential benefit of BP-SES in patients with STEMI.

Impact on daily practice

The use of a thin-strut biodegradable polymer sirolimus-eluting stent (Orsiro BP-SES) in patients with acute ST-segment elevation myocardial infarction (STEMI) is safe and effective. In this pre-specified analysis of the BIOSCIENCE trial, the BP-SES had a similar performance compared with the durable polymer everolimus-eluting stents, with a significant reduction in the risk of target lesion failure. This finding needs confirmation at long-term follow-up and warrants further clinical evaluation in an appropriate randomised trial. However, the Orsiro BP-SES is currently a reasonable alternative when implanted in the STEMI setting.

Appendix. Contributors

T. Pilgrim, R. Piccolo, D. Heg, P. Jamshidi and S. Windecker conceived the study. T. Pilgrim, D. Heg, P. Jamshidi, and S. Windecker had responsibility for the design of the study. T. Pilgrim, R. Piccolo, D. Heg, M. Roffi, D. Tüller, A. Vuilliomenet, O. Muller, S. Cook, D. Weilenmann, C. Kaiser, A. Khattab, M. Taniwaki, F. Rigamonti, S. Blöchlinger, P. Wenaweser, P. Jüni, S. Windecker were responsible for the acquisition of data. D. Heg did the analysis and interpreted the results in collaboration with T. Pilgrim, R. Piccolo, P. Jüni, S. Windecker and all other authors. T. Pilgrim, R. Piccolo, D. Heg and S. Windecker wrote the first draft of the report. All authors critically revised the report for important intellectual content and approved the final version.

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Conflict of interest statement

T. Pilgrim has received travel expenses and payment for lectures from Biotronik and Medtronic. R. Piccolo received a research grant from Veronesi Foundation. M. Roffi has received grants from Boston Scientific, Abbott Vascular, Medtronic, and Biosensors, and payment for lectures from Lilly-Daiichi Sankyo. D. Tüller has received travel expenses from Biotronik, Biosensors, Terumo, and Medtronic. S. Cook has received grants and personal fees from Boston Scientific, grants from Medtronic and Cordis, and personal fees from St. Jude Medical. C. Kaiser has received grants from B. Braun, Biotronik, Abbott Vascular, Terumo, Daiichi Sankyo, Eli Lilly, personal fees from Eli Lilly, AstraZeneca, Abbott Vascular, GE Healthcare, Eli Lilly, Daiichi Sankyo. P. Wenaweser has received personal fees from Biotronik and Cordis, grants and personal fees from Medtronic, Edwards Lifesciences, Symetis, and Boston Scientific, and grants from JenaValve, NVT and St. Jude Medical. P. Jüni is an unpaid steering committee or statistical executive committee member of trials funded by Abbott Vascular, Biosensors, Medtronic and Johnson & Johnson. CTU Bern, which is part of the University of Bern, has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by Abbott Vascular, Ablynx, Amgen, AstraZeneca, Biosensors, Biotronik, Boehringer Ingelheim, Eisai, Eli Lilly, Exelixis, Geron, Gilead Sciences, Nestlé, Novartis, Novo Nordisc, Padma, Roche, Schering-Plough, St. Jude Medical, and Swiss Cardio Technologies. S. Windecker has received research contracts to the institution from Biotronik and St. Jude. The other authors have no conflicts of interest to declare.

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