EuroIntervention 2019;15:e1006-e1013 published online June 2019 ■ published online e-edition December 2019

BIOFLOW-IV, a randomised, intercontinental, multicentre study to assess the safety and effectiveness of the Orsiro sirolimus-eluting stent in the treatment of subjects with de novo coronary artery lesions: primary outcome target vessel failure at 12 months

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-18-01214

KEYWORDS

- clinical trials
- drug-eluting stent
- miscellaneous

Abstract

Aims: The BIOFLOW-IV clinical trial was designed for regulatory submission in Japan. It assessed the safety and efficacy of a new third-generation sirolimus-eluting stent system with bioresorbable polymer (Orsiro, BP-SES) compared with an everolimus-eluting stent system with permanent polymer (XIENCE Prime/Xpedition, PP-EES).

Methods and results: This prospective, international, multicentre, 2:1 randomised, non-inferiority trial enrolled 575 patients (385 BP-SES and 190 PP-EES) with 659 stenotic *de novo* lesions. Of these, 137 patients (23.8%) were Japanese. Follow-up until five years is ongoing. We herein report outcomes at 12 months. Baseline parameters were well balanced. Device success was 98.9% for BP-SES versus 99.6% for PP-EES, p=0.670. Non-inferiority related to 12-month target vessel failure was met ($p_{non\text{-}inferiority}$ <0.001). Further, there was no significant difference in clinical outcomes between the groups. The target vessel failure rate was 5.5% for BP-SES and 7.5% for PP-EES, the target lesion failure rate was 4.2% versus 5.4%, and the definite or probable stent thrombosis rate was 0.8% versus 0%.

Conclusions: The randomised BIOFLOW-IV trial provides further evidence on the safety and efficacy of the Orsiro BP-SES and its non-inferiority to the current benchmark, an everolimus-eluting permanent polymer stent. ClinicalTrials.gov: NCT01939249

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SUBMITTED ON 20/12/2018 - REVISION RECEIVED ON 1st 17/04/2019 / 2nd 04/06/2019 - ACCEPTED ON 21/06/2019

DOI: 10.4244/EIJ-D-18-01214

Abbreviations

BP-SES	bioresorbable polymer sirolimus-eluting stent
CABG	coronary artery bypass grafting
DAPT	dual antiplatelet therapy
DES	drug-eluting stent(s)
MI	myocardial infarction
PP-EES	permanent polymer everolimus-eluting stent
TLF	target lesion failure
TLR	target lesion revascularisation
TVF	target vessel failure
TVR	target vessel revascularisation

Introduction

First-generation drug-eluting stents (DES) led to a reduction of restenosis compared to bare metal stents, but at the cost of elevated stent thrombosis rates. The annual rate of definite very late stent thrombosis was 0.6-0.7% and the major adverse cardiac events rate increased constantly by 2.6% per year[1]. Second-generation DES with thinner struts and an improved polymer-drug combination improved results, particularly of very late stent thrombosis[2,3]. The Orsiro bioresorbable polymer sirolimus-eluting stent (BP-SES) (Biotronik AG, Bülach, Switzerland) is a third-generation DES which is based on an ultra-thin cobalt-chromium stent. According to a recent state-of-the-art paper, it currently has the thinnest struts of marketed DES[4]. It has a unique hybrid coating consisting of a bioresorbable drug-polymer combination which – after bioresorption – only leaves the bare metal stent in the vessel, which is covered by a passive coating layer of amorphous silicon carbide[5].

Numerous studies have been conducted with this novel device with more than 30,000 patients enrolled so far; however, enrolment was predominantly in Europe. The aim of the randomised BIOFLOW-IV trial was to provide further evidence on the safety and efficacy of the device, including Japanese centres where BP-SES was an investigational device and used for the first time. From the study initiation onwards, the study was set up to meet the Japanese regulatory requirements and organised to meet the data integrity from the Good Clinical Practice conformity perspectives. Subsequently, data from BIOFLOW-IV were used as the primary data set for the Japanese market approval.

Methods

STUDY DESIGN AND RANDOMISATION

BIOFLOW-IV is a prospective, intercontinental, multicentre, randomised controlled, non-inferiority trial, comparing BP-SES with permanent polymer everolimus-eluting stents (PP-EES). The details of the study design are available at ClinicalTrials.gov (NCT01939249). Subjects were randomised in a 2:1 ratio to either the BP-SES Orsiro or the PP-EES XIENCE Prime/Xpedition (Abbott Vascular, Santa Clara, CA, USA). The randomisation was performed intraprocedurally once all inclusion and exclusion criteria were verified, using an electronic data capture system to assign patients to treatment groups, a block size of 3, and stratification by site and diabetes status. Subjects were informed about the treatment allocation after the index procedure. The trial was conducted in accordance with the Declaration of Helsinki, Japanese Good Clinical Practice, and local and national regulations. The study was monitored including 100% source document verification. A clinical events committee (CEC) adjudicated all serious adverse events and a core laboratory (MedStar Health Research Institute, Washington, DC, USA) assessed the baseline and procedural angiographic parameters. Follow-up assessments were scheduled at 1, 6, and 12 months; annual follow-up up to five years is ongoing. An office visit was only required for the 12-month follow-up visit; the remaining visits could be conducted by phone.

PARTICIPANTS

A total of 575 eligible coronary artery disease (CAD) patients were enrolled at 46 sites in Japan (n=12), Europe (n=29), Australia (n=2), and Israel (n=3). Main inclusion criteria were CAD with stenotic *de novo* lesions in up to two separate native coronary arteries with a reference vessel diameter ≥2.50 mm and ≤3.75 mm, lesion length ≤26 mm, and target vessel Thrombolysis In Myocardial Infarction (TIMI) flow ≥2. Main exclusion criteria were evidence of myocardial infarction (MI) within 72 hours prior to the procedure, left ventricular ejection fraction ≤30%, impaired renal function (i.e., serum creatinine >2.5 mg/dl), planned intervention of the target vessel(s) after the index procedure and planned intervention of the non-target vessel within 30 days after the index procedure, life expectancy less than 12 months, three-vessel CAD at the time of the procedure, and the target lesion being located in the left main, located or supplied by a bypass graft, involving a side branch >2.0 mm, being an ostial lesion, being heavily calcified, or containing a thrombus. Subjects were deemed eligible after they had signed the consent and all inclusion and exclusion criteria had been fulfilled.

STUDY DEVICES

The BP-SES is an ultra-thin cobalt-chromium alloy platform (60 µm struts for stent sizes with 3.0 mm diameter and below) with a hybrid coating: the passive coating with amorphous silicon carbide encapsulates the stent surface by covalently binding to the metal stent surface[5,6]. It reduces ion release from the metal stent platform and minimises the interaction between the stent platform and the surrounding tissue. It also reduces the release of allergenic metal ions by 96%, which accordingly leads to a lower rate of corrosion and a lower risk of tissue inflammation[7,8]. The active coating consists of a biodegradable poly-L-lactic acid polymer from which sirolimus is released[9]. PP-EES is a cobalt-chromium metal platform (81 µm struts) with a durable polymer (poly-n-butyl-methacrylate [PBMA]) which adheres to the stent and drug coating. The co-polymer consisting of vinylidine fluoride and hexafluoropropylene (PVDF-HFP) serves as drug matrix and releases everolimus[1].

INTERVENTION

BP-SES was an investigational device in Japan and therefore, instead of the device name, the code BTR-1131 was used in

compliance with Japanese Good Clinical Practice. Both stents were available in diameters of 2.5, 2.75, 3.0, and 3.5 mm, and PP-EES additionally in a 3.25 mm diameter. Stent lengths were 9, 13, 15, 18, 22, 26, and 30 mm for BP-SES and 8, 12, 15, 18, 23, 28, and 33 mm for PP-EES. For the mandatory predilatation, only balloon angioplasty was allowed. Multiple focal lesions were considered as a single lesion if they could be covered by one stent. Implantation technique had to follow the respective instructions for use; the stent should extend beyond the lesion by a minimum of 2 mm both proximally and distally. More than one study stent was not allowed except in case of suboptimal results or bail-out situations. Post-dilatation was allowed at the discretion of the investigator. Post intervention, acetylsalicylic acid life-long and dual antiplatelet therapy (DAPT) for at least six months was recommended.

ENDPOINTS AND DEFINITIONS

The primary endpoint was non-inferiority to PP-EES for 12-month target vessel failure (TVF), defined as a composite of cardiac death, target vessel Q-wave or non-Q-wave MI[10], emergent coronary artery bypass grafting (CABG), or clinically driven target vessel revascularisation (TVR) and presented as frequency. Secondary clinical endpoints were TVF, target lesion failure (TLF), defined as a composite of cardiac death, target vessel Q-wave or non-Q-wave myocardial infarction (MI), and clinically driven target lesion revascularisation (TLR); MI[10]; clinically driven TLR; clinically driven TVR; all-cause mortality; cardiac and non-cardiac death; a composite of death and MI; a composite of death, MI, and TVR; rate of probable or definite stent thrombosis[11], and cerebrovascular events. Device success was defined as final residual diameter stenosis <30% by quantitative coronary angiography (QCA), using the assigned device only and including successful delivery of the stent at the target lesion, appropriate stent deployment, and successful removal of the stent delivery system. Procedural success was defined as final diameter stenosis <30% by QCA using any percutaneous method, without TLF during the hospital stay.

STATISTICAL ANALYSIS

The sample size was calculated using the Equation 1 Fleiss formula and was based on the following criteria: expected 12-month BP-SES TVF frequency of 5.4%, expected PP-EES TVF frequency of 5.4%, 6.0% non-inferiority margin, one-sided significance level of 0.025, power of 0.80, and an expected withdrawal/drop-out rate of 10%. Per calculation, 555 patients were required (370 BP-SES, 185 PP-EES).

The current analysis is based on the modified intention-to-treat population, meaning that subjects were allocated to the group they were randomised to irrespective of stent placement. Subjects who were randomised but did not receive a study stent were followed up to 12 months only. The visit time window was used for respective analysis (for 12-month outcomes, the time interval up to 379 days was considered). Continuous variables are presented as mean±standard deviation (SD) and categorical variables as n (%). Chi-square, Fisher's and Wilcoxon tests were used for comparison between the treatment groups. The secondary clinical endpoints were presented as Kaplan-Meier estimates including 95% confidence intervals, and groups were compared using the log-rank test. The statistical analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

BASELINE PATIENT AND PROCEDURAL CHARACTERISTICS

From September 2013 to January 2015, 575 patients with 659 lesions were enrolled **(Figure 1)**. Of these, the 137 Japanese patients were enrolled from September 2013 until June 2014, and the remaining non-Japanese patients from February 2014 until January 2015. Enrolment per country is displayed in **Supplementary Figure 1**.

Baseline parameters were well balanced amongst the BP-SES and PP-EES groups **(Table 1)**. Mean age was 64.7±9.6 years, 74.1% were male, 30.6% had diabetes, and 30.6% a history of MI.

Vascular access was predominantly radial (66.3%), followed by femoral (31.3%) and brachial (2.4%) access. Predilatation was performed in 84.0% of BP-SES and 80.1% of PP-EES lesions (p=0.216) and post-dilatation in 41.3% versus 46.3% (p=0.225). Mean stent length was 18.6±5.4 mm versus 18.2±6.2 mm, and mean stent diameter was 3.03±0.38 mm versus 3.04±0.38 mm. Device success was 98.9% (467/472 stents) for BP-SES and 99.6% for PP-EES (227/228 stents) (p=0.670) and clinical procedural success based on the universal definition for MI was 96.1% (370/385) versus 95.8% (182/190) (p=0.856). Patients were discharged at 1.5±2.2 days post procedure on average, ranging from 0 to 32 days. Lesion characteristics assessed by the core laboratory indicated no significant differences between BP-SES and PP-EES; lesion details are provided in **Table 2**.

Table 1. Patient characteristics.

	BP-SES N=385	PP-EES N=190
Age, years	64.8±9.6	64.4±9.8
Age ≥75 years	65 (16.9)	33 (17.4)
Male	280 (72.7)	146 (76.8)
Smoking history	221 (57.4)	115 (60.5)
Current smoker	82 (21.3)	53 (27.9)
Ex-smoker	139 (36.1)	62 (32.6)
Hypertension	296 (76.9)	136 (71.6)
Hypercholesterolaemia	261 (67.8)	136 (71.6)
Diabetes mellitus	117 (30.4)	59 (31.1)
insulin-dependent	23 (6.0)	17 (8.9)
History of myocardial infarction	114 (29.6)	62 (32.6)
History of stroke or TIA	35 (9.1)	19 (10.0)
Previous coronary interventions	169 (43.9)	88 (46.3)

Data are displayed as mean±SD or n (%). BP-SES: bioresorbable polymer sirolimus-eluting stent; PP-EES: permanent polymer everolimus-eluting stent; TIA: transient ischaemic attack

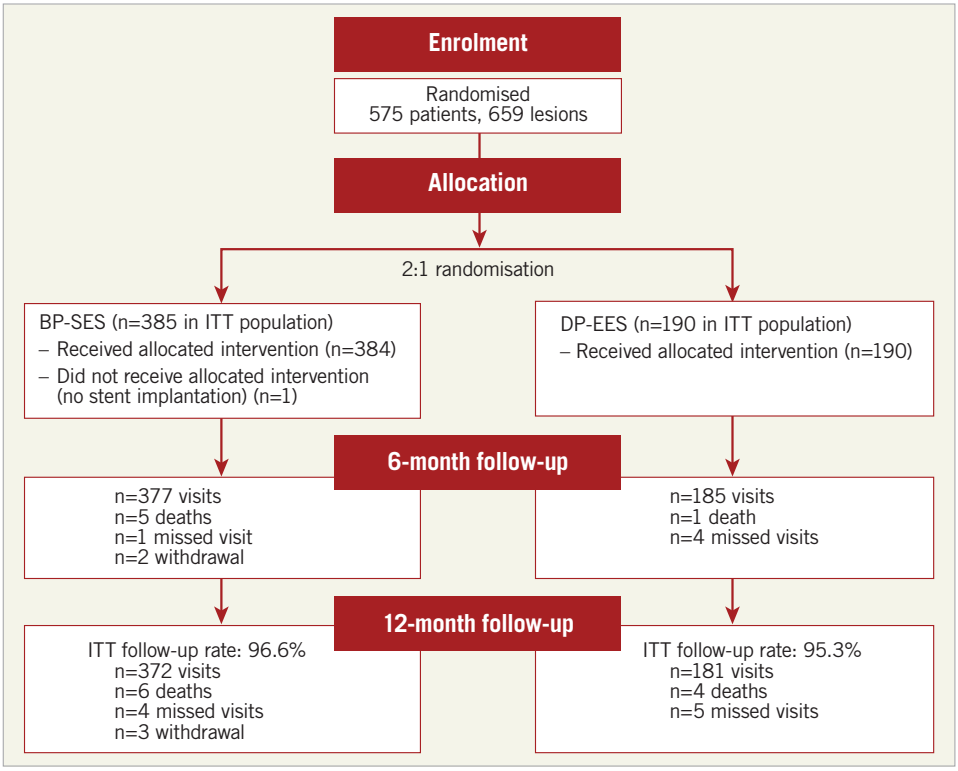

Figure 1. *Patient flow chart.*

Table 2. Lesion characteristics based on core laboratory assessment.

		BP-SES N=441	PP-EES N=214
Vessel	RCA	160 (36.3)	67 (31.3)
	LAD	174 (39.5)	87 (40.7)
	LCX	106 (24.0)	59 (27.6)
	Left main	1 (0.2)	1 (0.5)
Lesion class*	Type A	74 (17.3)	38 (18.2)
	Type B1	208 (48.7)	92 (44.0)
	Type B2	69 (16.2)	44 (21.1)
	Type C	76 (17.8)	35 (16.8)
Bifurcation lesion		20 (4.5)	12 (5.6)
Thrombus present		8 (1.8)	2 (0.9)
Lesion length, mm		13.7±6.1	13.4±6.3
Reference vessel diameter, mm		2.75±0.49	2.78±0.46
Minimum lumen diameter, mm		0.93±0.40	0.97±0.40
Diameter stenosis, %		66.3±12.7	65.2±12.5
Post procedure			
Minimum lumen diameter, mm	In-stent	2.57±0.41	2.59±0.40
	In-segment	2.27±0.46	2.28±0.42
Diameter stenosis, %	In-stent	6.9±7.5	7.2±8.1
	In-segment	18.5±7.0	18.8±6.9

Data are displayed as mean±SD or n (%). *Data not evaluable in all patients. BP-SES: bioresorbable polymer sirolimus-eluting stent; LAD: left anterior descending artery; LCX: left circumflex artery; PP-EES: permanent polymer everolimus-eluting stent; RCA: right coronary artery

CARDIAC MEDICATIONS

At six months, 85.9% (BP-SES) versus 84.9% (PP-EES) of the patients were on DAPT, and, at 12 months, 59.1% (BP-SES) versus 46.4% (PP-EES) of the total population. Statin use was nearly identical in BP-SES and PP-EES patients, ranging from 83.4% to 83.9% up to 12-month follow-up.

FOLLOW-UP RATES AND CLINICAL OUTCOMES

The follow-up rate at 12 months was 96.6% in the BP-SES group and 95.3% in the DP-EES group (median follow-up duration was 367 days for all patients and 365 for those patients who did not reach 379 days).

The primary endpoint, 12-month TVF frequency using the universal definitions[10], was observed in 5.1% of BP-SES patients versus 6.6% of PP-EES patients (difference –2.27% and 95% CI: –6.83, 2.29). Non-inferiority of BP-SES versus PP-EES was confirmed ($p<0.001$). There was no significant difference in relation to clinical outcomes. The secondary endpoints, Kaplan-Meier failure estimates at 12 months, were as follows: TVF was 5.5% for BP-SES and 7.5% for PP-EES, TLF was 4.2% versus 5.4%, and clinically driven TLR was 2.1% versus 1.8% **(Figure 2, Table 3)**. Cardiac death was 0.0% in the BP-SES group and 0.5% in the PP-EES group. This event was one sudden death during swimming on day 202. The autopsy did not reveal any suspicion of myocardial infarction or stent thrombosis.

Three stent thromboses were adjudicated by the CEC in the BP-SES group **(Supplementary Appendix 1)**. Case 1 had a heavily

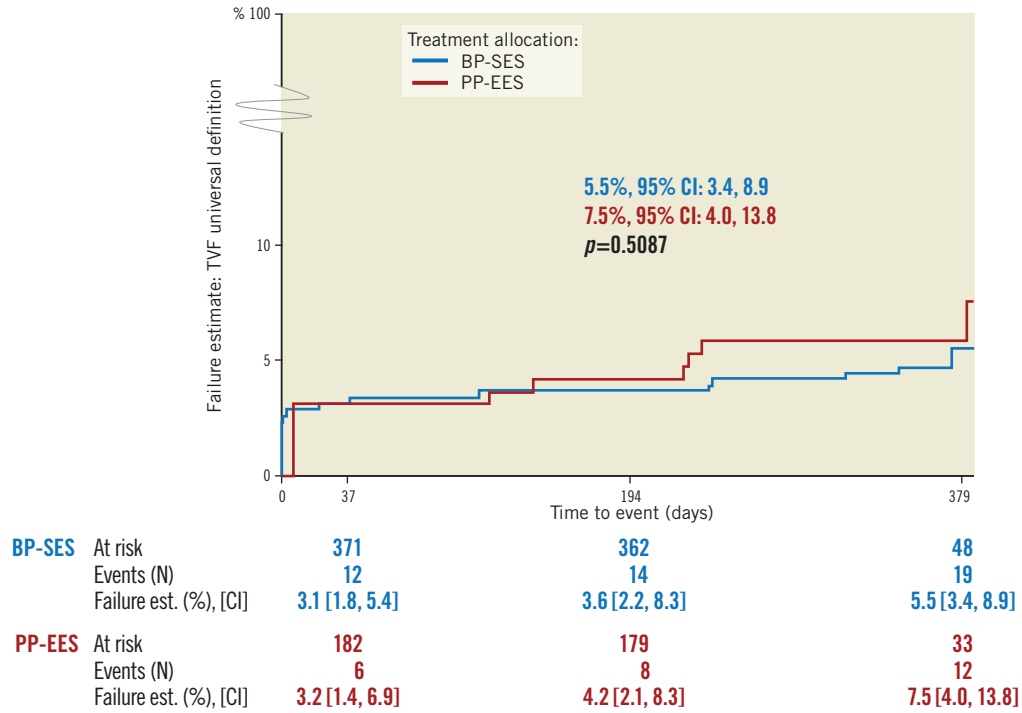

Figure 2. *Kaplan-Meier failure estimates for target vessel failure in BP-SES versus PP-EES up to 12-month follow-up. CI: confidence interval; BP-SES: bioresorbable polymer sirolimus-eluting stent; PP-EES: permanent polymer everolimus-elutng stent; TVF: target vessel failure*

calcified left anterior descending artery and extensive dissection after predilatation. The stent thrombosis of case 2 was associated with high on-treatment clopidogrel resistance as measured by VerifyNow, and case 3 had continued elevation of ST and cardiac enzymes before the index procedure. The rates of definite or probable stent thrombosis were 0.8% (BP-SES) versus 0.0% (PP-EES) with no significant difference between the treatment groups (p=0.554).

REGIONAL ANALYSIS

The characteristics of the patient baseline, procedural and clinical outcomes in the Japanese versus the non-Japanese group were assessed in order to verify the applicability of intercontinental data for regulatory approval in Japan.

Japanese patients were significantly older, had more hypertension and hypercholesterolaemia, a higher incidence of prior stroke or transient ischaemic attack, more previous coronary interventions and less lesion calcification compared to non-Japanese **(Supplementary Table 1)**. During the procedure, predilatation and post-dilatation were more frequent (98.6% and 78.8%) in Japanese subjects compared to 78.2% and 32.7% in non-Japanese subjects (p<0.001). Less pressure was applied for dilatation, and inflation time was longer in Japanese patients. Furthermore, the average stent length was longer in the Japanese cohort. During follow-up, more Japanese patients were on DAPT: 95.5% of Japanese subjects compared to 82.5% of non-Japanese subjects at six months (p<0.001) and 81.1% versus 46.8% at 12 months (p<0.001). No significant difference was observed in the clinical endpoints comparing Japanese versus non-Japanese subjects and between the

Table 3. Kaplan-Meier failure estimate rates at 12 months.

	12 months		*p*-value
	BP-SES N=372	PP-EES N=181	
TVF	19 (5.5) [3.4, 8.9]	12 (7.5) [4.0, 13.8]	0.509
TLF	14 (4.2) [2.4, 7.4]	8 (5.4) [2.5, 11.7]	0.755
Composite of death, MI, TVR	28 (7.9) [5.4, 11.5]	15 (9.8) [5.6, 16.6]	0.806
Composite of death and MI	19 (5.0) [3.2, 7.7]	10 (6.0) [3.1, 11.3]	0.859
Death	6 (1.6) [0.7, 3.5]	4 (2.9) [1.0, 8.2]	0.628
Cardiac death	0	1 (0.5) [0.1, 3.8]	0.330
MI	14 (3.7) [2.2, 6.1]	6 (3.2) [1.4, 6.9]	0.772
TV-MI	13 (3.4) [2.0, 5.8]	6 (3.2) [1.4, 6.9]	0.893
Clinically driven TVR	12 (3.7) [2.0, 6.9]	5 (3.9) [1.4, 10.5]	0.718
Clinically driven TLR	6 (2.1) [0.8, 5.3]	1 (1.8) [0.2, 11.8]	0.273
Definite or probable stent thrombosis	3 (0.8) [0.3, 2.4]	0	0.554
Cerebrovascular disease	6 (1.6) [0.7, 3.5]	6 (3.2) [1.4, 7.0]	0.205

Data are displayed as number of events (Kaplan-Meier failure estimates % and [95% CI]). Time interval up to 379 days was considered for the 12-month follow-up visit. MI: myocardial infarction; TLF: target lesion failure; TLR: target lesion revascularisation; TV: target vessel; TVF: target vessel failure; TVR: target vessel revascularisation

BP-SES and PP-EES groups in Japanese patients **(Supplementary Table 2-Supplementary Table 4, Supplementary Figure 2, Supplementary Figure 3)**.

Discussion

The main findings of the BIOFLOW-IV randomised trial are very good clinical outcomes in the BP-SES and the PP-EES groups without statistically significant differences between them. The primary endpoint, non-inferiority of BP-SES to PP-EES, was met with p<0.001.

The clinical outcomes of the BP-SES group are consistent with several randomised controlled trials comparing BP-SES with the PP-EES stents, mainly in a European population. They univocally report similar outcomes amongst both stents. TVF at 12 months was 5.0% compared to 4.0% in Korean patients enrolled in the ORIENT trial, 5% in BIO-RESORT, 7% in BIOFLOW-V, 8.1% in BIOSCIENCE and 9.3% in BIOFLOW-II[12-16]. TLF at 12 months was 4.2% compared to 2.4% in ORIENT, 4% in BIO-RESORT, 5.1% in BIOFLOW-III, 6% in BIOFLOW-V, 6.5% in BIOFLOW-II, and 6.7% in BIOSCIENCE[12-17]. Definite or probable stent thrombosis at 12 months was 0.8% compared to 0% in the ORIENT and BIOFLOW-II studies, and <1% in BIO-RESORT and BIOFLOW-V. The recent publication of the BIOFLOW-V randomised trial included not only centres from Europe, but also centres from the USA, Canada, Australia, New Zealand, South Korea and Israel, and reported superior TLF and myocardial infarction rates for BP-SES compared to PP-EES[12]. Aside from these trials, randomised trials also showed similar results of BP-SES compared to durable polymer zotarolimus-eluting stents[13,14], and everolimus-eluting or biolimus-eluting biodegradable polymer stents[13,18].

Likewise, the 12-month outcomes of BIOFLOW-IV are similar to the nine-month outcomes of the CENTURY-II randomised trial, comparing another sirolimus-eluting biodegradable polymer stent (Ultimaster®; Terumo Corp., Tokyo, Japan) with the PP-EES in 1,101 patients[19]. Specifically, TVF at 12 months was 5.0% for BP-SES in our series compared to 6.0% at nine months for the Ultimaster in CENTURY-II, and definite or probable stent thrombosis was 0.8% compared to 0.9%, respectively. Comparing outcomes in Japanese patients only, in our study, the TVF rate at 12 months in Japanese patients was 2.2% for BP-SES as compared to 5.0% in 100 patients of the RESOLUTE Japan trial treated with a permanent polymer zotarolimus-eluting stent[20]. Definite or probable stent thrombosis was absent in the latter, but a 4.0% myocardial infarction rate was observed.

Long-term follow-up is required to clarify the influence of differences in patient baseline and procedural characteristics and DAPT on TVF and stent thrombosis between Japanese and non-Japanese subjects. Even though the 12-month TLF rate is numerically higher in the non-Japanese group, this has to be interpreted carefully as the study was not designed to detect differences in clinical endpoints between Japanese and non-Japanese subjects.

Additionally, long-term follow-up observation is expected to elucidate further the potential benefits of the passive coating of the BP-SES stent[9]. The already available five-year clinical results of the BIOFLOW-II study[21], the BIOFLOW-III registry[22] and of the BIOSCIENCE study[23] support the concept of reduced release of allergenic metallic ions and reduction of tissue inflammation because of the passive coating method with a 0% definite or probable stent thrombosis rate at five years in BIOFLOW-II and 0.7% in BIOFLOW-III, as well as a five-year stent thrombosis rate of 1.6% in BIOSCIENCE.

Limitations

The study has several limitations. Inclusion and exclusion criteria were restrictive, excluding patients with acute myocardial infarction for Japanese regulatory purposes. Therefore, results only apply to the specific patient population presented herein. Additionally, the study was not powered to detect differences between the Japanese and non-Japanese populations and therefore respective conclusions are speculative. The pre-defined non-inferiority margin seemed high at 6.0%; however, results clearly show that the difference in TVF rates between the treatment arms was much narrower and well within the non-inferiority margin of 6%. Investigators, the CEC and the independent core laboratory were not blinded to the treatment allocation which could have introduced a bias.

Conclusions

The randomised BIOFLOW-IV trial provides further evidence on the safety and efficacy of the BP-SES with biodegradable polymer and its non-inferiority to a current state-of-the-art everolimus-eluting permanent polymer stent. The data further indicate its safety and efficacy in the Japanese population. Long-term observation of the BIOFLOW-IV subjects is expected to assess further the potential clinical benefits of the BP-SES.

Impact on daily practice

The ultra-thin cobalt-chromium alloy platform BP-SES, Orsiro, demonstrated similar safety and efficacy outcomes at 12 months to the current benchmark PP-EES in this study. The occurrence of stent thrombosis was low with no late stent thrombosis, supporting the safe use of the ultra-thin strut stent in daily practice. Patient baseline characteristics and procedural differences observed between Japan and Europe did not translate into differences in clinical endpoints and, ultimately, BIOFLOW-IV led to device approval in Japan.

Acknowledgements

We would like to thank Stephanie Sauter and Barbara Widmann (employees of Biotronik AG) for their help in preparing the manuscript.

Funding

The BIOFLOW-IV study was funded by Biotronik AG, Switzerland.

Conflict of interest statement

R. Tölg declares receiving speaker's honoraria from Biotronik. B. Witzenbichler declares having received financial support from Biotronik for study coordinator's labour costs. M. Haude reports study grants and personal fees from Biotronik, Abbott Vascular, Cardiac Dimensions, and Philips. T. Slagboom declares having a personal consultancy agreement with Biotronik before and during the study. R. Waksman reports grants and personal fees from Abbott Vascular, AstraZeneca, Biosensors, Biotronik, Boston Scientific and Chiesi, personal fees from Amgen, Corindus, Lifetech Medical, Medtronic, Philips Volcano and Pi-Cardia Ltd, being an investor in MedAlliance, and receiving grants from Edwards Lifesciences. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Details of stent thrombosis cases.

Supplementary Figure 1. Enrolment per country.

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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-18-01214

Supplementary data

Supplementary Appendix 1. Details of stent thrombosis cases.

Subject 1

Gender/age: male, 55 years

Medical history/risk factors: current smoker; diabetic (non-insulin-dependent); hypertension; hypercholesterolaemia; respiratory disease; previous MI (type of most recent MI: NSTEMI)

Other relevant risk factors: arteriosclerosis of renal artery

Previous surgeries of vessels: stenting with BMS of mid CX as treatment of MI

Target lesion: prox LAD, lesion length: 21 mm, diameter: 2.5 mm

BP-SES was deployed: diameter: 2.50 mm, length: 26 mm

Narrative: during the index procedure, a heavily calcified proximal LAD was treated (diffusely diseased vessel periphery). After several predilatations, extensive dissection was seen. The implanted stent probably did not cover the distal dissection and did not seem to be fully expanded in the middle part.

Shortly after the procedure, the patient complained about heavy chest pain; the ECG showed ST-elevation in the anterior wall. The patient received re-angiography, the target vessel was now occluded, a repeat angioplasty did not restore flow. The patient was transferred to the operating room for CABG.

Action taken: balloon dilation, CABG

Resolved

CEC adjudication:

Acute stent thrombosis (<=24 hours)

Periprocedural MI (univ. def.), periprocedural MI (ext. def.) caused by target vessel

Clinically driven TLR, CABG

Subject 2

Gender/age: male, 71 years

Medical history/risk factors: ex-smoker; diabetic (non-insulin-dependent); hypertension; hypercholesterolaemia

No previous surgeries

Target lesion: proximal LAD, lesion length: 26 mm, diameter: 3 mm

BP-SES was deployed: diameter: 3.00 mm, length: 30 mm

Narrative (site): the patient underwent PCI of proximal LAD due to 75% stenosis. The procedure was completed uneventfully. The following morning the patient complained of chest pain. ST elevation was noted in the ECG and emergency PCI was performed. During the procedure, stent thrombosis was noted. The thrombus was aspirated and, after balloon inflation, the PCI was completed. The event most likely occurred because of clopidogrel resistance.

Action taken: non-medication therapy, PCI

Outcome: resolved - stopped at 1 day

Periprocedural MI (univ. def.), periprocedural MI (ext. def.) caused by target vessel

Core laboratory confirmed clinically driven TLR and resolution of event. Testing showed clopidogrel resistance.

CEC adjudication:

Acute stent thrombosis (<=24 hours)

Periprocedural MI (univ. def.), periprocedural MI (ext. def.) caused by target vessel

Testing showed clopidogrel resistance

Clinically driven TLR and resolution of event

Subject 3

Gender/age: male, 76 years

Medical history/risk factors: hypertension; hypercholesterolaemia; previous MI

Previous surgeries of vessel:

Stenting with DES (TAXUS Liberté) for mid RCA with angina pectoris

Stenting with DES (CYPHER, Resolute) for mid LAD indication with angina pectoris

Stenting with DES (CYPHER) for proximal CX indication with angina pectoris

Stenting with DES (CYPHER) for distal CX indication with angina pectoris

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Target lesion: distal RCA, lesion length: 18 mm, diameter: 3.5 mm

BP-SES was deployed: diameter: 3.50 mm, length: 22 mm

Narrative (site):

The patient underwent PCI of the distal RCA. After returning to the room the patient felt chest pain. ECG showed ST elevations. An emergency coronary angiography was performed and acute stent thrombosis was diagnosed. The thrombus was aspirated and PCI was performed.

Action taken: non-medication therapy, XIENCE Xpedition (3.5/18 mm) implanted

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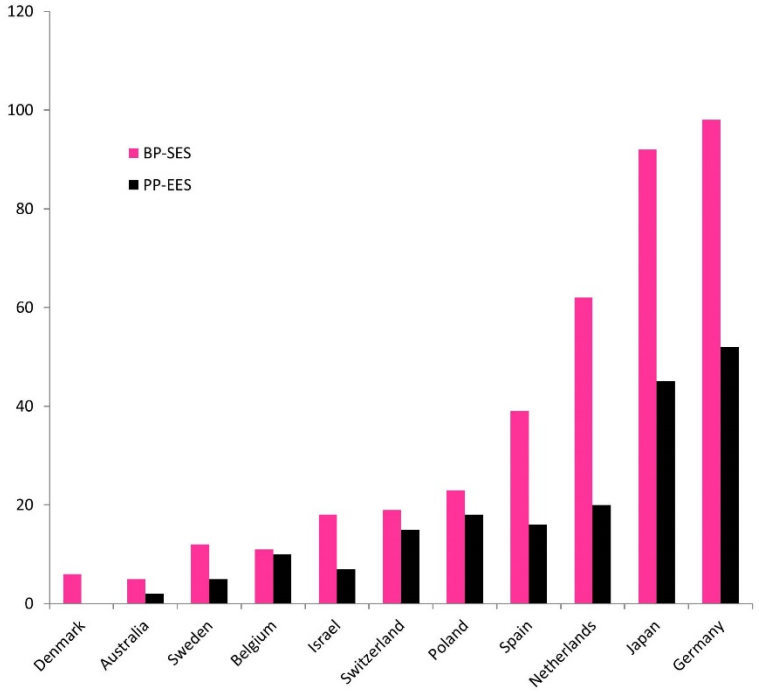
CEC adjudication:

Acute stent thrombosis (<=24 hours)

Periprocedural MI (univ. def.), periprocedural MI (ext. def.) caused by target vessel

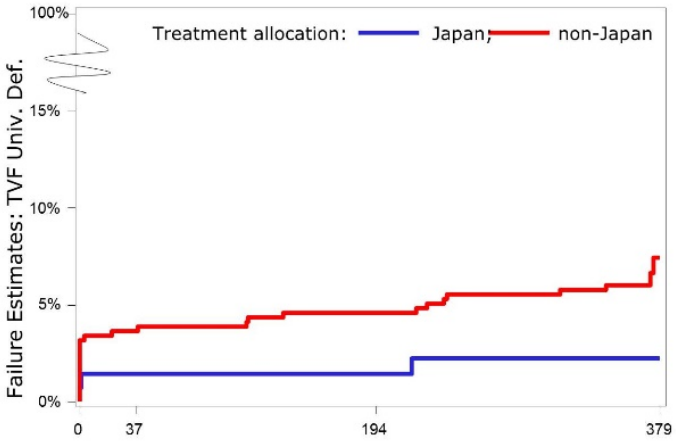
Clinically driven TLR and resolution of event

Supplemental Figure 1: Enrollment per country



BP-SES: biosorbable polymer sirolimus-eluting stent, PP-EES: permanent polymer everolimus-eluting stent

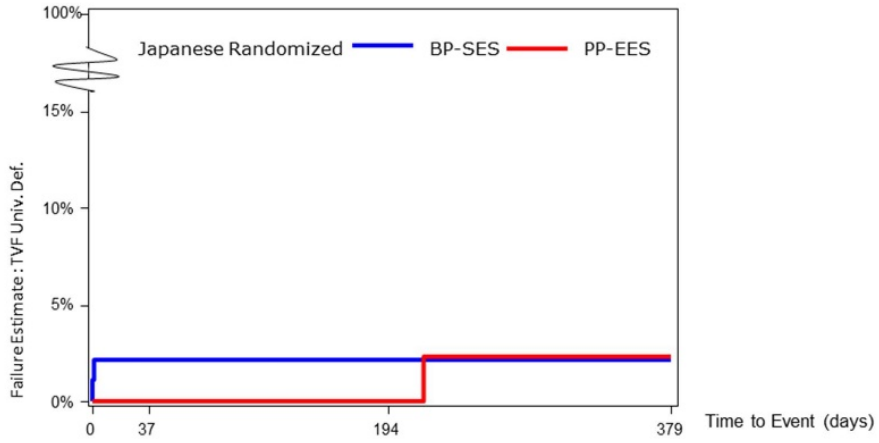
Supplemental Figure 2: Target vessel failure estimate in Japanese versus non-Japanese patients



Japan			
	At risk	133	19
	Events (N)	2	13
	Failure Est (%), [CI]	1.5 [0.4; 5.7]	2.2 [0.7; 6.7]
Non-Japan			
	At risk	408	62
	Events (N)	20	28
	Failure Est (%), [CI]	4.6 [3.0, 7.0]	7.5 [5.0, 11.1]

CI = Confidence interval, TVF = Target vessel failure

Supplemental Figure 3: Target vessel failure estimate in Japanese patients randomized to BP-SES versus PP-EES



BP-SES			
	At risk	88	88
	Events (N)	2	2
	Failure Est (%), [CI]	2.2 [0.5; 8.4]	2.2 [0.5; 8.4]
PP-EES			
	At risk	45	11
	Events (N)	0	1
	Failure Est (%), [CI]	0.0[0.0, 0.0]	2.3 [0.3; 15.1]

BP-SES: Bioresorbable Polymer Sirolimus Eluting Stent, PP-EES: Permanent Polymer Everolimus Eluting Stent, CI = Confidence interval, TVF= Target vessel failure

Supplementary Table 1. Baseline characteristics in Japanese versus non-Japanese patients.

	Japanese	**Non-Japanese**	**Overall**	***p*-value#**
	N=137	**N=438**	**N=575**	
Age, years	67.1±9.1	63.9±9.7	64.7±9.6	**<0.001**
Male	107 (78.1)	319 (72.8)	426 (74.1)	0.219
Smoking history	87 (63.5)	249 (56.8)	336 (58.4)	0.168
Hypertension	118 (86.1)	314 (71.7)	432 (75.1)	**<0.001**
Hypercholesterolaemia	117 (85.4)	280 (63.9)	397 (69.0)	**<0.001**
Diabetes mellitus	46 (33.6)	130 (29.7)	176 (30.6)	0.388
History of stroke or TIA	26 (19.0)	28 (6.4)	54 (9.4)	**<0.001**
History of myocardial infarction	39 (28.5)	137 (31.3)	176 (30.6)	0.533
Previous coronary interventions	73 (53.3)	184 (42.0)	257 (44.7)	**0.021**
Lesions	**N=146**	**N=513**	**N=659**	
Calcification*				**<0.001**
None	107 (73.3)	260 (50.7)	367 (55.7)	
Mild	29 (19.9)	166 (32.4)	195 (29.6)	
Moderate	10 (6.8)	81 (15.8)	91 (13.8)	
Severe	0	6 (1.2)	6 (0.9)	
Lesion class				0.122
Type A	24 (16.4)	88 (17.3)	112 (17.1)	
Type B1	61 (41.8)	239 (47.0)	300 (45.8)	
Type B2	33 (22.6)	80 (15.7)	113 (17.8)	
Type C	27 (18.5)	84 (16.5)	111 (16.9)	

Unknown	1 (0.7)	18 (3.5)	19 (2.9)	
Lesion length, mm	13.9±6.4	13.5±6.1	13.6±6.2	0.508
Minimum lumen diameter, mm	1.0±0.4	0.9±0.4	0.9±0.4	0.502
Diameter stenosis, %	65.6±11.4	66.0±13.0	66.0±12.6	0.768

Data are displayed as mean±SD or n (%).

* Site assessed; the remaining values are core laboratory assessed.
# p-value for comparison Japanese vs non-Japanese subjects.

TIA: transient ischaemic attack

In Japanese patients, more predilatation was performed (98.6% versus 78.2%, p<0.001), less pressure was applied for predilatation (11.3±3.9 atm versus 13.5±3.3 atm, p<0.001), and the inflation time was longer (25.0±17.6 s versus 18.9±15.4 s, p<0.001). Implanted stents were longer (19.6±5.8 mm versus 18.2±5.6 mm, p=0.010), and were applied with less pressure (11.2±3.1 atm versus 14.4±3.1 atm, p<0.001) and longer inflation time (23.0±8.7 s versus 18.5±10.2 s, p<0.001). Furthermore, more post-dilatations were performed (78.8% versus 32.7%, p<0.001), also with less pressure applied (15.4±4.5 atm versus 18.2±5.0 atm, p<0.001) and longer inflation time (38.8±33.0 s versus 19.8±15.2 s, p<0.001).

Supplementary Table 2. Kaplan-Meier failure estimates at 12 months in Japanese versus non-Japanese patients.

	Japanese	Non-Japanese	*p*-value
TVF	3 (2.2)	28 (7.5)	0.060
TLF	2 (1.5)	20 (5.6)	0.103
Death	1 (0.7)	9 (2.3)	0.310
Cardiac death	0	1 (0.2)	>0.999
MI	2 (1.5)	18 (4.1)	0.140
TV-MI	2 (1.5)	17 (3.9)	0.167
Clinically driven TVR	3 (2.2)	14 (4.3)	0.559
Clinically driven TLR	2 (1.5)	5 (2.2)	0.730
Definite or probable stent thrombosis	2 (1.5)	1 (0.2)	0.081

Data are displayed as number of events (Kaplan-Meier failure estimates %).

Time interval up to 379 days was considered for the 12-month follow-up visit.

MI: myocardial infarction; TLF: target lesion failure; TLR: target lesion revascularisation; TV: target vessel; TVF: target vessel failure; TVR: target vessel revascularisation

Supplementary Table 3. Baseline characteristics in Japanese patients.

	BP-SES	PP-EES	All JPN patients	*p*-value
	N=92	N=45	N=137	
Age, years	68.1±8.5	65.0±10.0	67.1±9.1	0.092
Male	71 (77.2)	36 (80.0)	107 (78.1)	0.707
Smoking history	57 (62.0)	30 (66.7)	87 (63.5)	0.591
Hypertension	80 (87.0)	38 (84.4)	118 (86.1)	0.690
Hypercholesterolaemia	78 (84.8)	39 (86.7)	117 (85.4)	0.769
Diabetes mellitus	31 (33.7)	15 (33.3)	46 (33.6)	0.966
History of stroke or TIA	20 (21.7)	6 (13.3)	26 (19.0)	0.239
History of myocardial infarction	22 (23.9)	17 (37.8)	39 (28.5)	0.091
Previous coronary interventions	46 (50.0)	27 (60)	73 (53.3)	0.271
Lesions	**N=98**	**N=48**	**N=146**	
Calcification*				0.257
None	71 (72.4)	36 (75.0)	107 (73.3)	
Mild	18 (18.4)	11 (22.9)	29 (19.8)	
Moderate	9 (9.2)	1 (2.1)	10 (6.8)	
Severe	0	0	0	
Lesion class				0.303
Type A	13 (13.3)	11 (22.9)	24 (16.4)	
Type B1	46 (46.9)	15 (31.3)	61 (41.8)	
Type B2	20 (20.4)	13 (27.1)	33 (22.6)	
Type C	18 (18.4)	9 (18.8)	27 (18.5)	
Unknown	1 (1.0)	0	1 (0.7))	

Lesion length, mm	13.9±6.1	13.9±7.0	13.9±6.4	0.651
Minimum lumen diameter, mm	1.0±0.4	0.9±0.4	1.0±0.4	0.356
Diameter stenosis, %	64.9±11.5	67.2±11.0	65.6±11.4	0.276

Data are displayed as mean±SD or n (%).

p-value for comparison JPN vs non-JPN subjects.

*Site assessed; the remaining values are core laboratory assessed (four lesions were not available for core laboratory assessment).

BP-SES: bioresorbable polymer sirolimus-eluting stent; JPN: Japanese; PP-EES: permanent polymer everolimus-eluting stent; TIA: transient ischaemic attack

There was no difference in procedural techniques except that the BP-SES versus PP-EES had been applied with less pressure (10.6±3.0 atm versus 12.4±3.0 atm, $p<0.001$) and post-dilatation was applied with less pressure (14.8±4.3 atm versus 16.6±4.5 atm, $p=0.015$).

Supplementary Table 4. Kaplan-Meier failure estimates at 12 months in Japanese patients.

	BP-SES	PP-EES	*p*-value
TVF	2 (2.2)	1 (2.3)	0.993
TLF	2 (2.2)	0	>0.999
Death	1 (1.1)	0	>0.999
Cardiac death	0	0	-
MI	2 (2.2)	0	>0.999
TV-MI	2 (2.2)	0	>0.999
Clinically driven TVR	2 (2.2)	1 (2.3)	0.993
Clinically driven TLR	2 (2.2)	0	>0.999
Definite or probable stent thrombosis	2 (2.2)	0	>0.999

Data are displayed as number of events (Kaplan-Meier failure estimates %).

Time interval up to 379 days was considered for the 12-month follow-up visit.

BP-SES: bioresorbable polymer sirolimus-eluting stent; MI: myocardial infarction; PP-EES: permanent polymer everolimus-eluting stent; TLF: target lesion failure; TLR: target lesion revascularisation; TV: target vessel; TVF: target vessel failure; TVR: target vessel revascularisation