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Sirolimus-eluting or everolimus-eluting stents for coronary artery disease: 5-year outcomes of the randomised BIOFLOW-IV trial

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Corrigendum

Figures 1A and 1C of this article have been replaced in the online version. DP-SES has been replaced with DP-EES. 17th January 2022.

Introduction

A large body of evidence is available for biodegradable polymer stents[1], but long-term data are scarce and predominantly evaluated for Caucasian subjects. The BIOFLOW-IV trial aimed to provide additional data, comparing the safety and effectiveness of the ultrathin Orsiro biodegradable polymer sirolimus-eluting stent (BP-SES; Biotronik) with the XIENCE Prime/XIENCE Xpedition durable polymer everolimus-eluting stent (DP-EES; Abbott). We herein report final 5-year data.

Methods

The BIOFLOW-IV study has been described previously[2], and is registered at ClinicalTrials.gov: NCT01939249. In brief, BIOFLOW-IV is a randomised controlled (2:1), intercontinental, multicentre, non-inferiority trial. Between September 2013 and January 2015, patients were enrolled at 46 sites in Japan, Europe, Israel and Australia. Eligible patients had stenotic *de novo* lesions in up to 2 separate native coronary arteries. Dual antiplatelet therapy (DAPT) was recommended for at least 6 months. Follow-up was scheduled at 30 days, 6 and 12 months, and annually thereafter up to 5 years. An independent clinical events committee adjudicated events. Endpoints beyond 12 months are listed in **Supplementary Table 1**.

The study was performed in accordance with ISO 14155:2011, Japanese Good Clinical Practice guidelines, the Declaration of Helsinki, local and national regulations and was approved by all institutional ethics committees. All patients provided written informed consent. The study was monitored with 100% source data verification.

The Orsiro BP-SES is based on an ultrathin cobalt-chromium stent combined with a unique hybrid coating. The passive coating reduces ion release from the stent and minimises the interaction between the stent and tissue, and the active coating releases sirolimus through a biodegradable polymer matrix[2].

The statistical methods are provided in the **Supplementary Appendix 1**.

Results

Data up to 12 months have been reported previously[2]. In brief, 385 patients were included in the BP-SES group and 190 patients

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in the DP-EES group. Core laboratory-assessed lesion lengths, reference vessel diameters and percent diameter stenosis were 13.6±6.2 mm, 2.76±0.48 mm, and 66.0±12.6 %, respectively.

At 60 months, 19.3% of patients (99/512) were on DAPT, and 8.2% (42/512) had additional antiplatelet or anticoagulation therapy. A total of 90.4% (463/512) were symptom free, and the remaining patients had predominantly stable angina.

Clinical information at 60 months was available for 94.8% in the BP-SES group and 96.3% in the DP-EES group. Outcomes were similar amongst the groups, with target vessel failure (TVF) estimates of 12.3% for the BP-SES group versus 10.8% for the DP-EES group (p=0.652) **(Table 1, Figure 1).**

A comparison between patients enrolled in Japan and those enrolled outside of Japan is provided in the **Supplementary Appendix 2** and **Supplementary Table 2**–**Supplementary Table 5**. **Figure 1** includes a comparison between BP-SES and DP-EES in the Japanese region. Patients enrolled in Japan were significantly older, had more hypertension, hypercholesterolaemia, prior stroke or transient ischaemic attack, more previous coronary interventions and were more frequently on DAPT at 60 months, while lesion parameters were similar across the regions.

Discussion

The BIOFLOW-IV randomised controlled trial demonstrated a sustained treatment effect at 60 months with very good clinical outcomes in both treatment groups. The 5-year TVF rate was 12.3% for the BP-SES group and 10.8% for the DP-EES group and is thus consistent with similar studies using contemporary drug-eluting stents, e.g., the EVOLVE II Trial with 5-year TVF rates of 18.2% and 18.1%[3] and the CENTURY II trial with TVF rates of 12.5% and 11.3%[4] for biodegradable and durable polymer stents, respectively.

The rate of symptom-free patients at 5 years was high at 90%, and the stent thrombosis rate was low, consistent with previous series. An individual patient data analysis of the BIOFLOW studies, encompassing 3,717 patients, reported only 13 cases of definite or probable stent thrombosis in 2,923 patients treated with the BP-SES[1]. The 3 cases of definite or probable stent thrombosis reported in the BP-SES group in BIOFLOW-IV were all acute (≤24 hours) and were not necessarily related to the stent itself: one occurred in a patient with extensive dissections after predilatation that was likely not fully covered by the stent, 1 patient was treated outside the protocol as he had continued ST-elevation and elevated cardiac enzymes prior to the procedure, and 1 patient had clopidogrel resistance. No further definite or probable stent thrombosis occurred up to 5 years.

Limitations

The study was powered for non-inferiority but not for differences between Japanese and non-Japanese centres, nor was it blinded. Further, inclusion and exclusion criteria were restrictive to comply with Japanese regulatory purposes. Lastly, the use of different definitions for myocardial infarction across studies hampers the comparison of outcomes.

Conclusions

The intercontinental, randomised controlled BIOFLOW-IV study demonstrated sustained safety and performance of the BP-SES and the DP-EES at 60 months, with low event rates that were similar amongst the groups and the absence of late or very late definite or probable stent thrombosis.

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Table 1. Kaplan-Meier failure estimates of clinical outcomes up to 60-month follow-up.

	24 months 730 days		36 months 1,095 days		48 months 1,460 days		60 months 1,825 days		Log-rank *p*-value
	BP-SES	DP-EES	BP-SES	DP-EES	BP-SES	DP-EES	BP-SES	DP-EES	
TVF, universal def	30 (7.9)	17 (9.1)	39 (10.4)	18 (9.6)	44 (11.8)	18 (9.6)	46 (12.3)	20 (10.8)	0.652
TLF, universal def	19 (5.0)	11 (5.9)	23 (6.1)	12 (6.4)	26 (6.9)	12 (6.4)	27 (7.2)	14 (7.6)	0.863
Death, MI, TVR	44 (11.5)	21 (11.1)	62 (16.3)	29 (15.4)	70 (18.5)	32 (17.0)	78 (20.6)	36 (19.2)	0.696
Death, MI	24 (6.3)	13 (6.9)	33 (8.7)	20 (10.7)	38 (10.0)	22 (11.7)	43 (11.4)	26 (13.9)	0.401
Death	11 (2.9)	5 (2.7)	15 (4.0)	11 (5.9)	19 (5.0)	14 (7.5)	21 (5.6)	15 (8.0)	0.269
Cardiac death	2 (0.5)	1 (0.5)	3 (0.8)	1 (0.5)	4 (1.1)	1 (0.5)	4 (1.1)	2 (1.1)	0.985
MI, universal def	15 (3.9)	8 (4.3)	21 (5.6)	9 (4.8)	23 (6.1)	9 (4.8)	26 (7.0)	12 (6.6)	0.856
TV-MI, universal def	14 (3.7)	7 (3.7)	16 (4.2)	8 (4.3)	17 (4.5)	8 (4.3)	17 (4.5)	9 (4.9)	0.856
CD-TVR	18 (5.9)	11 (6.0)	29 (7.8)	12 (6.5)	33 (8.9)	12 (6.5)	35 (9.5)	13 (7.1)	0.372
CD-TLR	19 (2.7)	3 (1.6)	25 (3.2)	3 (1.6)	28 (3.8)	3 (1.6)	15 (4.0)	3 (1.6)	0.137
Probable or definite ST	3 (0.8)	0 (0.0)	3 (0.8)	0 (0.0)	3 (0.8)	0 (0.0)	3 (0.8)	0 (0.0)	0.554
Cerebrovascular events	7 (1.8)	8 (4.3)	8 (2.1)	8 (4.3)	11 (3.0)	9 (4.9)	14 (3.8)	11 (6.0)	0.221

Data are displayed as n (Kaplan-Meier estimate in %). BP-SES: biodegradable polymer sirolimus-eluting stent; CD-TLR: clinically driven target lesion revascularisation; CD-TVR: clinically driven target vessel revascularisation; MI: myocardial infarction; DP-EES: durable polymer everolimus-eluting stent; ST: stent thrombosis; TLF: target lesion failure; TVF: target vessel failure, TV-MI: target vessel myocardial infarction

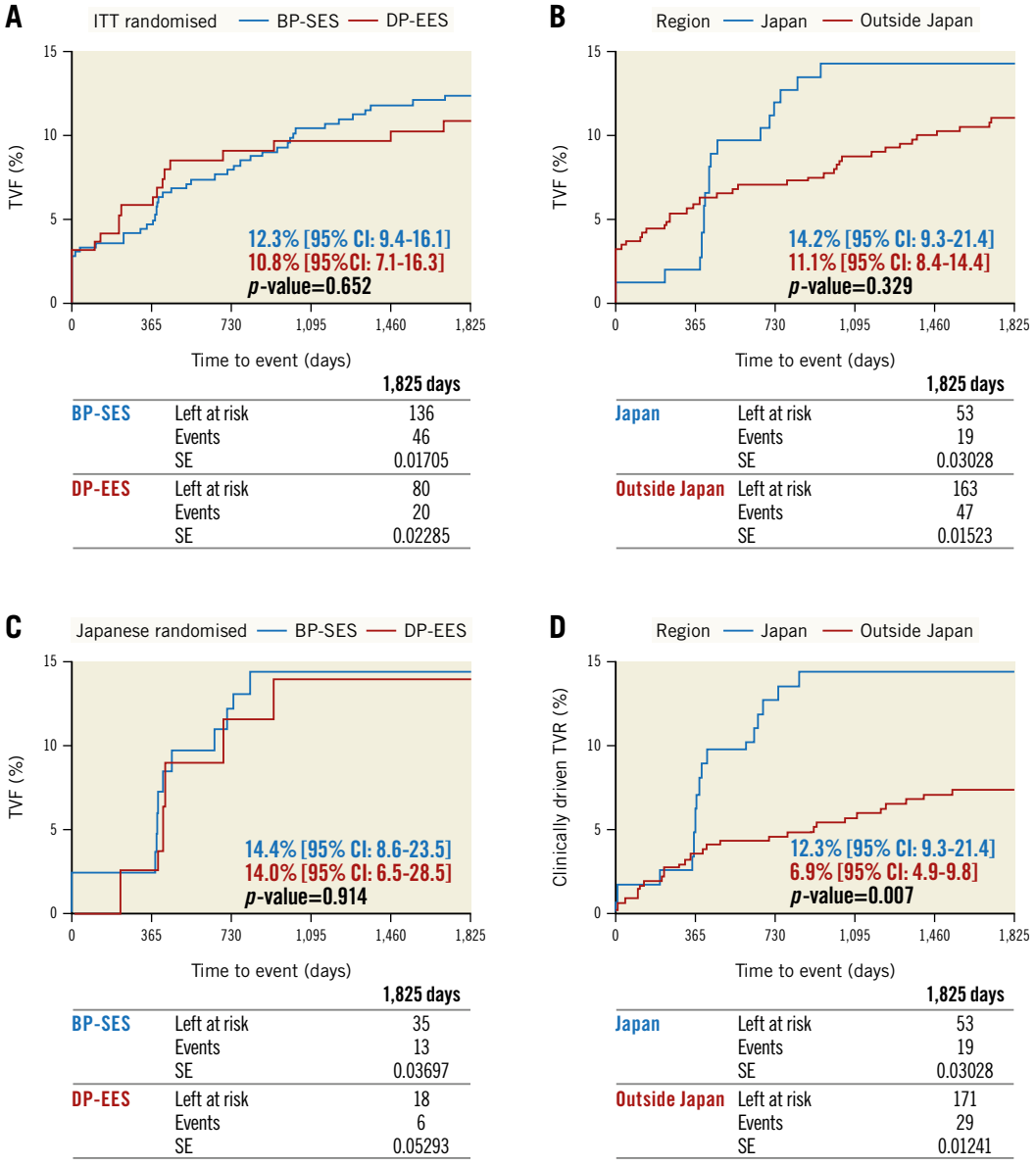

Figure 1. *Kaplan-Meier estimates for target vessel failure and clinically driven target vessel revascularisation. There was no significant difference in TVF between BP-SES and DP-EES (A), but comparing Japanese with non-Japanese centres, the Japanese centres had a non-significant trend towards a higher TVF rate as the curves rise steeply around 1 and 2 years (B). However, there was no difference in TVF amongst BP-SES and DP-EES within the Japanese region (C). The difference in TVF between Japan and outside of Japan was based on a significant trend towards higher CD-TVR (D), which was the underlying cause for all TVF. A likely explanation is that – although no diagnostic repeat angiographies were foreseen according to the study protocol – many Japanese centres performed routine angiographies, whereas in centres outside Japan the follow-up visits were mainly conducted by phone. This phenomenon might be caused by a difference in local practices, but also by the fact that the Orsiro BP-SES was not market approved in Japan at the time of enrolment, which usually triggers a more thorough follow-up, particularly as the device name was replaced with a code (BTR-1131). It is well known that routine angiographic follow-up increases revascularisation rates[5]. Additionally, there is a steep increase in TVR depicted for the Japanese cohort around 12 and 24 months, the time of angiographic follow-up and the CD-TVR was higher in patients with routine angiographic follow-up in Japan versus those without (14.6% vs 7.0%; p=0.211)* **(Supplementary Table 3)**. *BP-SES: biodegradable polymer sirolimus-eluting stent; CD-TVR: clinically driven target vessel revascularisation; CI: confidence interval; DP-EES: durable polymer everolimus-eluting stent; ITT: intention-to-treat; SE: standard error; TVF: target vessel failure*

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Conflict of interest statement

T. Slagboom declares having a personal consultancy agreement with BIOTRONIK before and during the study. R. Waksman reports grants

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Supplementary data

Supplementary Appendix 1. Statistical methods.

Supplementary Appendix 2. Regional differences in dual antiplatelet therapy (DAPT).

Supplementary Table 1. Endpoints beyond 12 months.

Supplementary Table 2. Key baseline and procedural parameters per region.

Supplementary Table 3. Impact of routine angiographic follow-up on revascularisation rates.

Supplementary Table 4. Kaplan-Meier failure estimates of clinical outcomes at 60-month follow-up per region.

Supplementary Table 5. Kaplan-Meier failure estimates of clinical outcomes at 60-month follow-up comparing patients enrolled in Japan.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00526

Supplementary data

Supplementary Appendix 1. Statistical methods.

The study was powered for non-inferiority relating to the primary endpoint TVF at 12 months. The current analysis is based on the modified intention-to-treat population, meaning that subjects were allocated to the group they were randomized to irrespective of stent placement, and that patients that did not receive a study device were followed for 12 months only. Continuous variables are presented as mean±standard deviation (SD) if normally distributed, as median with interquartile ranges (IQR) for not normally distributed variables, and as n (%) for categorical variables. Japanese patients were defined as those patients that were enrolled in centers in Japan. We compared continuous variables using the Wilcoxon tests and categorical variables using the Chi-square and Fisher's exact tests. The secondary clinical endpoints were presented as Kaplan-Meier estimates including 95% confidence intervals (CI), and groups were compared using the log-rank test. The statistical analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC, USA).

Supplementary Appendix 2. **Regional differences in dual antiplatelet therapy (DAPT).**

There was no significant difference amongst the treatment groups, but regional ones. Twice the number of Japanese patients (32.2%) were still on DAPT compared to non-Japanese subjects (15.5%), $p<0.001$. Moreover, there was a near significant trend towards less DAPT at 60 months subjects treated in Japan with the BP-SES compared to the DP-EES (27.2% versus 43.2%, $p=0.083$).

Supplementary Table 1. Endpoints beyond 12 months.

- Target vessel failure (TVF), defined as a composite of cardiac death, target vessel Q-wave or non-Q-wave myocardial infarction (MI), emergent coronary artery bypass grafting (CABG), and clinically driven target vessel revascularization (CD-TVR);
- Target lesion failure (TLF), defined as a composite of cardiac death, target vessel Q-wave or non-Q-wave MI,[1] and clinically driven target lesion revascularization (CD-TLR);
- MI according to universal definitions of myocardial infarctions
- CD-TLR;
- CD- TVR;
- All-cause mortality;
- Cardiac and non-cardiac death;
- Composite of death and MI;
- Composite of death, MI, and TVR;
- Probable or definite stent thrombosis according to the Academic Research Consortium criteria;
- Cerebrovascular events.

Supplementary Table 2. Key baseline and procedural parameters per region.

	Japan N=137	**Outside-Japan N=438**	**p-value**
Age, years	70 (61–64)	65 (57–72)	0.0004
Caucasian **Asian**	1 (0.7%) 136 (99.3%)[a]	434 (99.1%) 1 (0.2%)	-
Hypertension	118 (86.1%)	317 (71.7%)	0.0006
Hypercholesterolemia	117 (85.4%)	280 (63.9%	<0.0001
Diabetes	46 (33.6%)	130 (29.7%)	0.388
Previous coronary surgeries/interventions	73 (53.3%)	184 (42.0%)	0.021
History of stroke or TIA	26 (19.0%)	28 (6.4%)	<0.0001
Renal disease	17 (12.4%)	32 (7.3%)	0.062
Cancer	4 (2.9%)	35 (8.0%)	0.05
Ischemic status			0.024
Stable angina	100 (73.0%)	265 (60.5%)	
Unstable angina	20 (14.6%)	105 (24.0%)	
Doc. silent ischemia	17 (12.4%)	68 (15.5%)	
	Lesions N=146	**Lesions N=513**	**p-value**
ACC/ AHA classification			<0.0001
Type A	11 (7.5%)	168 (32.7%	
Type B1	57 (39.0%)	208 (40.5%)	
Type B2	44 (30.1%)	113 (22.0%)	
Type C	34 (23.3%)	23 (4.5%)	
Unknown	0 (0.0%)	1 (0.2%)	
Calcification			<0.0001
None	107 (73.3%)	260 (50.7%)	
Mild	29 (19.9%)	166 (32.4$)	
Moderate	10 (6.8%)	81 (15.8%	
Severe	0 (0.0%)	6 (1.2%)	
Lesion length, mm	14 (10-18)	14.7 ± 5.6	0.684
Vessel diameter, mm	3.0 (2.6−3.5)	3.0 (2.8 −3.5)	0.199
Pre-dilatation	144 (98.6%)	401 (78.2%)	<0.0001
Post-dilatation	115 (78.8%)	168 (32.7%)	<0.0001

Data are displayed and mean ±SD, median (interquartile range) or n (%). [a] all but one Asian patients were Japanese. TIA-transient ischemic attack. For continuous variables, Wilcoxon test was used and for categorical variables Chi-square (except Cancer and pre-dilatation, for which the Fisher's exact test was used) .

SupplementaryTable 3. Impact of routine angiographic follow-up on revascularisation rates.

	Japan[b] **N=137**	**Outside-Japan** **N=438**
Routine angiographic follow-up	82 patients 108 RA	20 patients 28 RA
CD-TVR after RA[a]	82 patients 12 (14.6%)[c]	20 patients 0 (0%)
CD-TVR in patients without RA[a]	43 patients 3 (7.0%) [c]	378 patients 28 (7.4%)

CD-TVR-clinically-driven TVR, RA-repeat angiography.
Follow-up angiography was not mandated per protocol and left to the discretion of the treating physician.
[a] CD-TVR that occurred prior to the repeat routine angiography were not counted. [b] In Japan, RA was predominantly performed during the 12-month time window. [c] Comparing patients in Japan with and without RA, there was a trend towards higher CD-TVR in the RA group (p=0.211 using Chi-Square test)

Supplementary Table 4. Kaplan-Meier failure estimates of clinical outcomes at 60-month follow-up per region.

	Japan **N=137**	**Outside Japan** **N=438**	**Log-rank** **p-value**
TVF, univ def	19 (14.2)	47 (11.1)	0.329
TLF, univ def	7 (5.2)	34 (8.0)	0.293
Death, MI, TVR	28 (20.9)	86 (19.9)	0.819
Death, MI	12 (9.0)	57 (13.2)	0.182
Death	6 (4.5)	30 (7.0)	0.310
Cardiac Death	0 (0.0)	6 (1.4)	0.344
MI, univ def	6 (4.5)	32 (7.5)	0.225
TV-MI, universal def	4 (3.0)	22 (5.1)	0.299
CD-TVR	19 (14.2)	29 (6.9)	0.007
CD-TLR	6 (4.5)	12 (2.9)	0.335
Probable or definite ST	2 (1.5)	1 (0.2)	0.081
Cerebrovascular events	7 (5.4)	18 (4.3)	0.639

Data are displayed as n (Kaplan-Meier estimate in %). CD-TLR-clinically driven target lesion revascularization, CD-TVR-clinically driven target vessel revascularization, MI-myocardial infarction, ST-stent thrombosis, TLF-target lesion failure, TVF-target vessel failure, TV-MI-target vessel myocardial infarction

Supplementary Table 5. Kaplan-Meier failure estimates of clinical outcomes at 60-month follow-up comparing patients enrolled in Japan.

	BP-SES (Japan, N=92)	DP-EES (Japan, N=45)	p-value
TVF, univ def	13 (14.4)	6 (14.0)	0.914
TLF, univ def	5 (5.5)	2 (4.8)	0.809
Death, MI, TVR	19 (20.9)	9 (20.9)	0.919
Death, MI	8 (8.8)	4 (9.5)	0.948
Death	3 (3.3)	3 (7.1)	0.343
Cardiac Death	0 (0.0)	0 (0.0)	-
MI, univ def	5 (5.6)	1 (2.4)	0.404
TV-MI, universal def	3 (3.3)	1 (2.4)	0.743
CD-TVR	13 (14.4)	6 (14.0)	0.914
CD-TLR	5 (5.5)	1 (2.3)	0.395
Probable or definite ST	2 (2.2)	0 (0.0)	>0.999
Cerebrovascular disease	6 (6.8)	1 (2.2)	0.323

Data are displayed as n (Kaplan-Meier estimate in %. CD-TLR-clinically driven target lesion revascularization, CD-TVR-clinically driven target vessel revascularization, MI-myocardial infarction, ST-stent thrombosis, TLF-target lesion failure, TVF-target vessel failure, TV-MI-target vessel myocardial infarction