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Long-term clinical outcomes after bioresorbable and permanent polymer drug-eluting stent implantation: final five-year results of the CENTURY II randomised clinical trial

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KEYWORDS

- clinical trials
- drug-eluting stent
- multiple vessel disease
- single vessel disease

Abstract

Aims: The aim of this study was to establish the long-term safety and efficacy of a sirolimus-eluting stent with bioresorbable polymer (BP-SES; Ultimaster) by comparison with an everolimus-eluting stent with permanent polymer (PP-EES; XIENCE).

Methods and results: CENTURY II (Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease) is a large-scale, prospective, multicentre, randomised single-blind, controlled, non-inferiority trial conducted at 58 study sites globally, including Europe, Japan and Korea, powered to prove non-inferiority for freedom from target lesion failure (TLF: cardiac death, target vessel-related myocardial infarction [MI] and target lesion revascularisation) at nine months. Patients requiring a percutaneous coronary intervention (PCI) were randomised (1:1) to BP-SES (n=551) or PP-EES (n=550). Freedom from TLF at five years was 90.0% in the BP-SES and 91.1% in the PP-EES group (p=0.54). The patient-oriented composite endpoint (all death, any MI, any revascularisation) was 24.1 and 25.6% (p=0.57) with BP-SES and PP-EES, respectively. The very late stent thrombosis rate from one to five years was especially low at 0.2% in both arms.

Conclusions: This randomised clinical trial showed that the BP-SES stent was non-inferior to the benchmark PP-EES stent for TLF. Safety and efficacy measures were comparable up to five-year follow-up after PCI.

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Abbreviations

ACS	acute coronary syndrome
BARC	Bleeding Academic Research Consortium
BMS	bare metal stent
BP-SES	bioresorbable polymer sirolimus-eluting stent
CAD	coronary artery disease
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
MI	myocardial infarction
(N)STEMI	(non-)ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
PP-EES	permanent polymer everolimus-eluting stent
ST	stent thrombosis
TLF	target lesion failure
TLR	target lesion revascularisation
TVF	target vessel failure
TVR	target vessel revascularisation
(VL)ST	(very late) stent thrombosis

Introduction

Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) significantly reduced neointimal proliferation and restenosis risk, when compared to bare metal stents (BMS)[1]. Concerns were raised when, after DES treatment, reports of a higher risk of (very) late stent thrombosis (VLST) appeared in a few studies[2,3]. Delayed vessel healing and stent endothelialisation, linked to a lack of biocompatibility of stent polymers used in first-generation DES, were identified as the main culprits of increased ST[4].

Since then, major advances have taken place in stent design, including changes in platform structure, use of antiproliferative agents and polymer composition. The Ultimaster® stent (Terumo Corp., Tokyo, Japan) belongs to this new generation of DES systems. It comprises a thin-strut cobalt-chromium platform, with gradient, abluminal, bioresorbable coating (a polymeric matrix carrier with incorporated sirolimus drug)[5].

The CENTURY II trial (Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease study) was designed to assess, in a general population of coronary artery disease (CAD) patients referred for PCI, whether Ultimaster (BP-SES) achieves similar (non-inferiority study design) clinical outcomes to the gold standard, everolimus-eluting XIENCE stent (Abbott Vascular, Santa Clara, CA, USA), which has a circumferential (biocompatible) permanent polymer (PP-EES) coating. The trial reached the primary endpoint of freedom from target lesion failure (TLF: a composite of cardiac death, target vessel-related myocardial infarction [MI] and target lesion revascularisation) at nine months. In the per-protocol analysis, 95.6% of patients treated with BP-SES and 95.1% patients treated with PP-EES were free from TLF at nine months, with an absolute risk difference of 0.55% in favour of the BP-SES group ($p_{non\text{-}inferiority}<0.0001$)[6].

The present study reports long-term clinical safety and efficacy data and compares five-year clinical outcomes in both treatment arms.

Methods

Detailed methods can be found in the **Supplementary Appendix 1**.

STUDY DESIGN

The CENTURY II trial is a prospective multicentre randomised, single-blind, controlled, non-inferiority two-arm clinical trial, comparing BP-SES with PP-EES (study registration number: UMIN000006940). Details of the study design have been reported elsewhere[6].

STUDY POPULATION AND RANDOMISATION

A total of 1,119 eligible CAD patients, scheduled for PCI, were enrolled at 58 centres in Europe (42 sites), Japan (15 sites) and Korea (one site) (see list in **Supplementary Appendix 2**.). Patients were randomly assigned in a 1:1 proportion to undergo PCI with either BP-SES or PP-EES. Randomisation was stratified for cohort JR (Japanese requirements: the subset of patients matching requirements for DES in Japan) and balanced for diabetes mellitus, acute coronary syndrome (ACS) and multivessel disease. Detailed inclusion and exclusion criteria have been reported previously[6]. The study complied with the Declaration of Helsinki and was approved by the institutional review board at each participating centre and the competent authority of each participating country. All patients provided written informed consent before undergoing any study-specific procedure.

STUDY DEVICES

The bioresorbable polymer-containing sirolimus-eluting Ultimaster stent (BP-SES) uses a cobalt-chromium metal platform with thin struts (80 µm) with bioresorbable PDLLA-PCL (poly D,L-lactide-co-caprolactone) polymer. The permanent polymer everolimus-eluting stent XIENCE (PP-EES) is a second-generation DES, based on a cobalt-chromium alloy platform with a strut thickness of 81 µm.

ENDPOINTS AND DEFINITIONS

Clinical outcomes at one-year and five-year follow-up include: (i) freedom from TLF, a device-oriented composite endpoint (cardiac death, MI not clearly attributable to a non-target vessel, and clinically driven target lesion revascularisation [TLR]); (ii) rate of target vessel failure (TVF), defined as a composite of cardiac death and MI not clearly attributable to a non-target vessel, and clinically driven target vessel revascularisation (TVR); (iii) patient-oriented composite endpoint composed of all deaths, all MI and all coronary revascularisations; (iv) rates of TLR, TVR, ST, cardiac death, MI; (v) composite of cardiac death and MI; (vi) rate of bleeding and vascular complications according to Bleeding Academic Research Consortium (BARC) definitions[7]. The endpoints are defined as per Academic Research Consortium recommendations[8].

STATISTICAL ANALYSIS

Differences between randomisation arms were assessed by the Student's t-test, analysis of variance, or non-parametric test (i.e., Mann-Whitney), as appropriate. The Kaplan-Meier method

was used to estimate event rates for time-to-event outcomes, and data were compared with the log-rank test. A landmark Kaplan-Meier analysis was performed at one year. To explore whether TLF with BP-SES vs. PP-EES was consistent across subgroups, logistic regression analysis was performed. All analyses were carried out using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

BASELINE PATIENT AND PROCEDURAL CHARACTERISTICS

Out of 1,119 patients (intention-to-treat), 1,101 patients (551 in the BP-SES and 550 in the PP-EES arm) were included in the per-protocol analysis **(Figure 1)**. The main baseline characteristics were similar in both arms **(Table 1)**. The frequency of cardiovascular risk factors was similar in both groups **(Table 1)**, apart from a slightly higher frequency of arterial hypertension in the BP-SES arm. A total of 1,427 lesions were treated (711 in BP-SES and 716 in PP-EES). Type B2/C lesions were frequently present and most lesions were treated through the radial access **(Table 2)**. The per-protocol analysis in the cohort with Japanese requirements (cohort JR) included 362 patients treated with BP-SES and 353 patients treated with PP-EES **(Supplementary Table 1, Supplementary Table 2)**.

DUAL ANTIPLATELET THERAPY

Table 3 gives the number of patients in each treatment arm using DAPT at 1, 4, 9 months, 1- and 5-year follow-up. The use of DAPT in the cohort JR is shown in **Supplementary Table 3**.

LONG-TERM CLINICAL OUTCOMES

One-year clinical outcomes **(Table 4)** showed no significant difference between BP-SES and PP-EES in all-cause death, any MI, revascularisations or any of the composite endpoints. Rates of ST, bleeding and vascular complications were similar between the two arms. These findings were observed in the total population and in the cohort JR **(Supplementary Table 4)**.

Figure 2 shows the TLF-free rates at five-year follow-up. No differences were found between the two treatment arms (90.0% for BP-SES versus 91.1% for PP-EES; p=0.54 in the total population). At five-year follow-up, all-cause death, any MI or revascularisations did not differ **(Table 5)** in the total population or in the cohort JR **(Supplementary Table 5)**. At five years, the composite safety endpoint of cardiac death and MI was 5.8% for BP-SES and 7.1% for PP-EES (p=0.39), and the patient-oriented composite endpoint was 24.1% for BP-SES and 25.6% for PP-EES (p=0.57) **(Table 5, Figure 3)**. Rates of ST were also similar in both arms **(Table 5)**. Bleeding and vascular complications at five-year follow-up were reported in 19.2% of patients in the BP-SES arm and 19.1% of patients in the PP-EES arm (p=0.95).

Results of a landmark analysis between one and five years are reported in **Supplementary Table 6** and **Supplementary Figure 1**.

SUBGROUP ANALYSIS

Figure 4 shows the relative risk of five-year TLF in high-risk subgroups including diabetes, patients with long lesions (>25 mm),

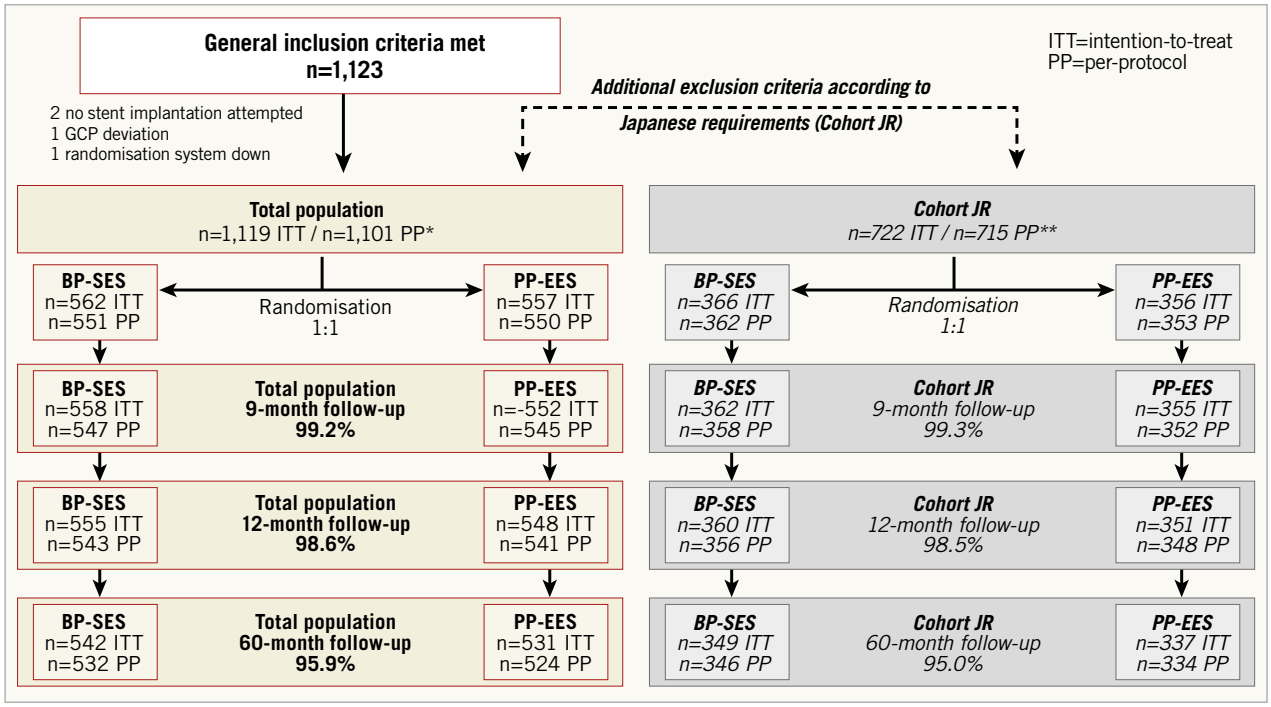

Figure 1. *Study flow chart. *1,101 patients analysed per protocol for total population: 22 major protocol deviations. **715 patients analysed per protocol for cohort JR: nine major protocol deviations. Japanese requirement (JR): patients who met criteria matching approved indication for drug-eluting stents in Japan. BP-SES: bioresorbable polymer sirolimus-eluting stent; PP-EES: permanent polymer everolimus-eluting stent*

Table 1. Baseline patient characteristics.

		BP-SES n=551	PP-EES n=550	*p*-value
Age, years		65.2±10.5	65.5±10.6	0.61
Male gender		78.6 (433/551)	82.4 (453/550)	0.11
Body mass index, kg/m²		26.9±4.2	26.9±5.8	0.28
Silent ischaemia		14.9 (82/551)	18.4 (101/550)	0.12
Stable angina		49.0 (270/551)	46.0 (253/550)	0.32
Unstable angina		13.6 (75/551)	10.9 (60/550)	0.17
High-risk ACS		22.5 (124/551)	24.7 (136/550)	0.39
STEMI		5.3 (29/551)	5.6 (31/550)	0.79
NSTEMI		17.2 (95/551)	19.1 (105/550)	0.43
Diabetes		31.9 (176/551)	30.9 (170/550)	0.71
IDDM		16.5 (29/176)	14.7 (25/170)	0.65
NIDDM		83.5 (147/176)	85.3 (145/170)	0.65
Dyslipidaemia		70.3 (381/542)	69.6 (377/542)	0.79
Hypertension		73.3 (401/547)	67.8 (371/547)	0.05
Smoking, current		22.2 (119/537)	23.9 (129/540)	0.50
Smoking, previous		46.7 (251/537)	42.0 (227/540)	0.12
Family history of CAD disease		30.8 (155/504)	32.1 (159/496)	0.66
History of PCI		37.2 (205/551)	35.0 (192/548)	0.45
History of CABG		4.5 (25/551)	3.7 (20/548)	0.46
History of MI		28.3 (156/551)	27.6 (152/550)	0.80
Charlson Comorbidity Index		1.2±1.5	1.2±1.4	0.77
Vessels diseased	1	61.0 (336/551)	59.5 (327/550)	0.27
	2	29.6 (163/551)	27.8 (153/550)	
	3	9.1 (50/551)	12.6 (69/550)	
Vessels treated	1	84.0 (463/551)	83.3 (458/550)	0.59
	2	15.4 (85/551)	15.6 (86/550)	
	3	0.5 (3/551)	1.1 (6/550)	
SYNTAX score		9.3±7.0	9.3±6.4	0.36

Values are mean±SD or % (number). Data for the JR cohort are available in Supplementary Table 1. (N)IDDM: (non-) insulin-dependent diabetes mellitus

Table 2. Baseline lesion and procedural characteristics.

		BP-SES	PP-EES	*p*-value
Lesions detected		1.97±1.34	1.99±1.29	0.67
Lesions treated		1.29±0.57	1.30±0.57	0.62
Lesion location (per lesion)	RCA	28.4 (202/711)	30.6 (219/716)	0.25
	LAD	43.3 (308/711)	43.2 (309/716)	
	CFX	26.4 (188/711)	24.7 (177/716)	
	LM	1.3 (9/711)	1.4 (10/716)	
	Graft	0.6 (4/711)	0.1 (1/716)	
Ostial (per lesion)		6.0 (41/689)	8.4 (58/691)	0.08
Calcification (per lesion)	None/mild	78.5 (541/689)	82.3 (569/691)	0.70
	Moderate	14.8 (102/689)	12.5 (86/691)	
	Severe	6.7 (46/689)	5.2 (36/691)	
Thrombus present (per lesion)		3.9 (27/689)	4.1 (28/691)	0.90
Bifurcation (per lesion)		13.8 (98/711)	14.4 (103/716)	0.74
ACC/AHA classification	A	4.4 (30/689)	3.9 (27/691)	0.13
	B1	13.6 (94/689)	15.2 (105/691)	
	B2	48.3 (333/689)	53.0 (366/691)	
	C	33.7 (232/689)	27.9 (193/691)	
Access site (per patient)	Femoral	26.7 (147/551)	25.6 (141/550)	0.55
	Radial	71.7 (395/551)	73.1 (402/550)	
	Brachial	1.6 (9/551)	1.3 (7/550)	
Predilatation (per lesion)		77.4 (550/711)	77.4 (554/716)	0.99
Post-dilatation (per lesion)		53.5 (379/708)	54.7 (389/711)	0.66
No. of stents implanted per lesion		1.2±0.4	1.2±0.4	0.32
No. of stents implanted per patient		1.5±0.8	1.6±0.9	0.94
Total implanted stent length per lesion, mm		23.0±10.6	22.9±10.4	0.55
Total implanted stent length per patient, mm		29.5±17.0	29.6±18.1	0.66
Delivery success (per stent)		99.1 (832/840)	99.5 (852/856)	0.23
Procedure success (per patient)		98.0 (540/551)	98.2 (540/550)	0.83

Values are mean±SD or % (number). Data for the JR cohort are available in Supplementary Table 2. CFX: circumflex; LAD: left anterior descending; LM: left main; RCA: right coronary artery

Table 3. Dual antiplatelet therapy.

	BP-SES	PP-EES	*p*-value
DAPT at 1 month	98.4 (539/548)	98.2 (536/546)	0.81
DAPT at 4 months	97.5 (534/548)	96.3 (525/545)	0.29
DAPT at 9 months	89.9 (483/537)	86.9 (459/528)	0.12
DAPT at 1 year	66.1 (355/537)	64.7 (341/527)	0.63
DAPT at 5 years	15.7 (77/491)	13.6 (66/485)	0.36

Values are % (number). Data for the JR cohort are available in Supplementary Table 3. DAPT: dual antiplatelet therapy

bifurcation, high-risk ACS and multivessel disease. No significant differences were observed between treatment arms.

Discussion

We report the longest available clinical data concerning safety and efficacy following bioresorbable polymer sirolimus-eluting stent implantation, showing comparable clinical outcomes to the current benchmark device, a durable polymer everolimus-eluting stent, up to five years of follow-up. Rates of VLST are remarkably low, showing excellent safety of both investigated devices.

OVERALL DEVICE PERFORMANCE

The principal findings of this analysis are that device-related events (TLF) were low and comparable with both stents up to five years of follow-up (10.0% [BP-SES] vs. 8.9% [PP-EES]; p=0.54). The low incidence of device-related events with bioresorbable

Table 4. One-year clinical outcomes.

	BP-SES n=551	PP-EES n=550	*p*-value
All-cause death	1.3 (7/551)	2.6 (14/550)	0.12
Cardiac death	0.9 (5/551)	1.5 (8/550)	0.40
All MI	2.4 (13/551)	2.7 (15/550)	0.70
Target vessel MI	1.3 (7/551)	2.2 (12/550)	0.25
Clinically indicated revascularisations			
TLR*	3.4 (19/551)	3.6 (20/550)	0.87
TV non-TLR	2.5 (14/551)	2.0 (11/550)	0.55
TVR	5.3 (29/551)	4.0 (22/550)	0.32
All revascularisations (clinically and non-clinically driven)			
TLR*	4.2 (23/551)	4.4 (24/550)	0.88
TV non-TLR	2.9 (16/551)	2.7 (15/550)	0.86
TVR	6.2 (34/551)	5.5 (30/550)	0.61
Composite endpoints			
TLF	5.4 (30/551)	5.5 (30/550)	0.99
TVF	7.4 (41/551)	7.1 (39/550)	0.82
Cardiac death and MI	3.3 (18/551)	4.0 (22/550)	0.52
Patient-oriented composite endpoint	10.7 (59/551)	14.2 (78/550)	0.08
Stent thrombosis			
Total	1.1 (6/551)	1.1 (6/550)	0.99
Definite	1.1 (6/551)	0.9 (5/550)	0.76
Probable	0.0 (0/551)	0.2 (1/550)	0.32
Possible	0.0 (0/551)	0.0 (0/550)	–
Definite + probable	1.1 (6/551)	1.1 (6/550)	0.99
Bleeding or vascular complications	10.5 (58/551)	13.3 (73/550)	0.16
Any bleeding	8.0 (44/551)	10.9 (60/550)	0.10
Bleeding BARC type 2 to 5	4.5 (25/551)	6.7 (37/550)	0.12
Bleeding BARC type 3 to 5	1.5 (8/551)	2.6 (14/550)	0.20

Values are % (number). *Totalled TLR: comprising more than one TLR per patient. BARC: Bleeding Academic Research Consortium; MI: myocardial infarction; TLF: target lesion failure; TLR: target lesion revascularisation; TV: target vessel; TVF: target vessel failure; TVR: target vessel revascularisation

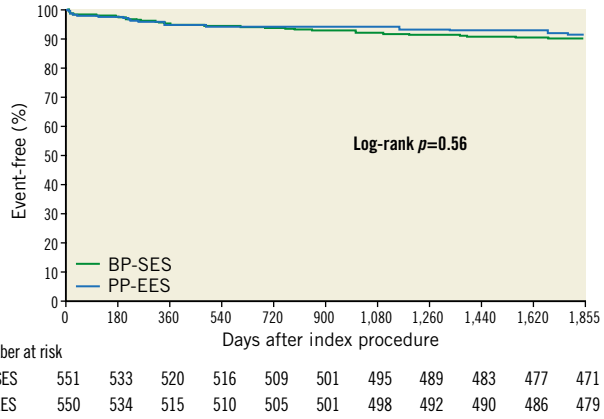

Figure 2. *Kaplan-Meier curve for target lesion failure-free event rate (%) at five-year follow-up. BP-SES: bioresorbable polymer sirolimus-eluting stent; PP-EES: permanent polymer everolimus-eluting stent*

Table 5. Five-year clinical outcomes.

	BP-SES n=551	PP-EES n=550	*p*-value
All-cause death	7.6 (42/551)	7.6 (42/550)	0.99
Cardiac death	2.9 (16/551)	3.5 (19/550)	0.60
All MI	3.3 (18/551)	3.8 (21/550)	0.62
Target vessel MI	1.8 (10/551)	2.4 (13/550)	0.52
Clinically indicated revascularisations			
TLR*	6.5 (36/551)	6.2 (34/550)	0.81
TV non-TLR	4.2 (23/551)	3.3 (18/550)	0.43
TVR	8.5 (47/551)	6.7 (37/550)	0.26
All revascularisations (clinically and non-clinically driven)			
TLR*	9.4 (52/551)	8.2 (45/550)	0.46
TV non-TLR	6.0 (33/551)	5.6 (31/550)	0.80
TVR	11.8 (65/551)	9.8 (54/550)	0.29
Composite endpoints			
TLF	10.0 (55/551)	8.9 (49/550)	0.54
TVF	12.5 (69/551)	11.3 (62/550)	0.52
Cardiac death and MI	5.8 (32/551)	7.1 (39/550)	0.39
Patient-oriented composite endpoint	24.1 (133/551)	25.6 (141/550)	0.57
Stent thrombosis			
Total	1.3 (7/551)	1.3 (7/550)	0.99
Definite	1.3 (7/551)	1.1 (6/550)	0.78
Probable	0.0 (0/551)	0.2 (1/550)	0.32
Possible	0.0 (0/551)	0.0 (0/550)	–
Definite + probable	1.3 (7/551)	1.3 (7/550)	0.99
Stent thrombosis (definite or probable)			
Acute	0.0 (0/551)	0.0 (0/550)	–
Subacute	0.5 (3/551)	0.5 (3/550)	0.99
Late	0.5 (3/551)	0.5 (3/550)	0.99
Very late	0.2 (1/551)	0.2 (1/550)	0.99
Bleeding or vascular complications	19.2 (106/551)	19.1 (105/550)	0.95
Any bleeding	15.1 (83/551)	15.1 (83/550)	0.99
Bleeding BARC type 2 to 5	11.3 (62/551)	11.1 (61/550)	0.93
Bleeding BARC type 3 to 5	4.7 (26/551)	4.7 (26/550)	0.99

Values are % (number). *Totalled TLR: comprising more than one TLR per patient. BARC: Bleeding Academic Research Consortium; MI: myocardial infarction; TLF: target lesion failure; TLR: target lesion revascularisation; TV: target vessel; TVF: target vessel failure; TVR: target vessel revascularisation

polymer is in line with prior analyses of this subclass of devices. In the ISAR-TEST 4 trial, TLF at five years was not significantly different between BP-DES and PP-EES (20.5% vs. 19.5%, respectively, hazard ratio [HR] 1.04, 95% CI: 0.84-1.29; p=0.71)[9]. In the COMPARE II trial (Abluminal Biodegradable Polymer Biolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent), TLF rates at five years for BP-biolimus-eluting stents and PP-EES were comparable (respectively, 13.4% vs. 11.5%; p=0.17)[10], and similar to this report. Five-year results from the NEXT trial

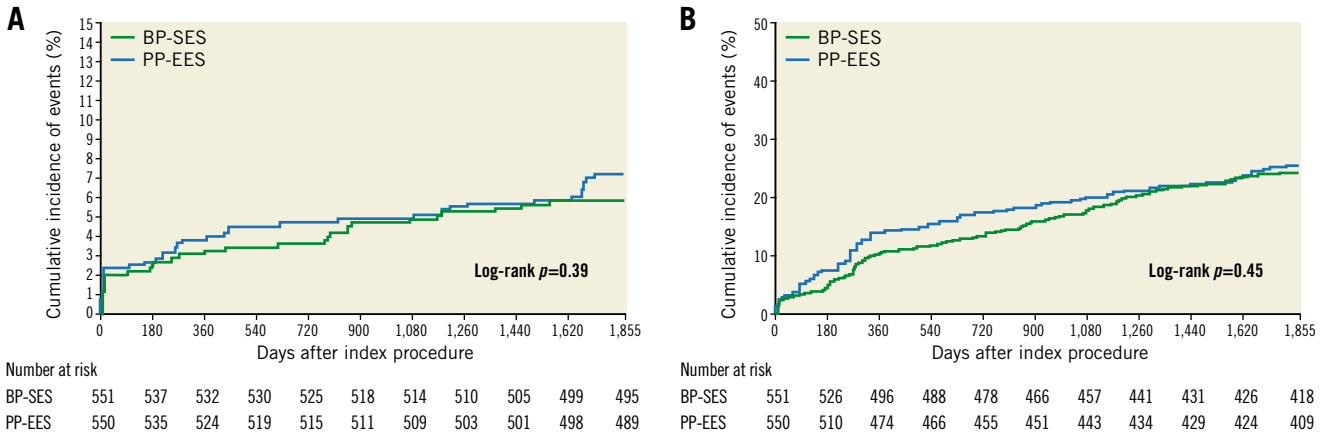

Figure 3. *Kaplan-Meier curves for five-year safety endpoints. Composite of cardiac death and MI (A) and patient-oriented composite endpoint (POCE) of any death, any MI and any coronary revascularisation (B). BP-SES: bioresorbable polymer sirolimus-eluting stent; PP-EES: permanent polymer everolimus-eluting stent*

confirm these findings, showing comparable TLF rates of 13.9% vs. 13.6% (p=0.84) for BP-BES vs. PP-EES[11].

Since then, the XIENCE stent has built up a favourable efficacy and safety profile during short-, medium- and long-term follow-up and is considered to be the benchmark device for evaluation of emerging new DES[9]. Hence, the observed clinical performance of the Ultimaster stent resembles that of XIENCE at all analysed time points and places it alongside the best-in-class DES.

VERY LATE STENT THROMBOSIS

One of the most noteworthy findings was the very low rate of VLST with both stents (0.2% vs. 0.2%, respectively; p=0.99). Following landmark publications such as the LEADERS trial (Limus Eluted From A Durable Versus ERodable Stent Coating) and network meta-analysis, concerns were raised about the long-term safety of first-generation DES. Increased VLST rates were intuitively attributed to persistent inflammatory stimulus arising from the mere presence of durable polymer, long after complete drug elution[12]. LEADERS was the first randomised trial to show long-term benefit of BP-DES over first-generation PP-DES. At five years, the BP-DES stent was statistically non-inferior to the PP-DES stent for the primary composite endpoint of cardiac death, MI, and clinically indicated TVR, with observed rates of 22.3% and 26.1%, respectively. One of the most notable findings of the study was the increased safety of the BP-DES, due to a significant reduction in VLST, with event cases continuing to accumulate from one (2.2%) to five years (4.2%) in the PP-DES group only, while almost plateauing in BP-DES patients during the same period (2.0% to 2.6%). Similar findings came from a pooled analysis of 4,062 patients from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS study evaluating four-year clinical outcomes. The risk of ST was lower with BP-DES than with PP-DES controls, predominantly due to a significantly lower risk of VLST (HR 0.22, 95% CI: 0.08-0.61; p=0.004)[13].

	BP-SES	PP-EES	*p*-value	RR (95% CI)	Int. *p*-value
Diabetes	24/176 (13.6%)	20/170 (11.8%)	0.60	1.159 [0.666;2.018]	0.86
No diabetes	31/375 (8.3%)	29/380 (7.6%)	0.75	1.083 [0.666;1.761]	
Lesions >25 mm	13/100 (13.0%)	10/78 (12.8%)	0.97	1.014 [0.470;2.189]	0.81
Lesions ≤25 mm	42/451 (9.3%)	39/472 (8.3%)	0.57	1.127 [0.743;1.709]	
Bifurcation	7/92 (7.6%)	11/97 (11.3%)	0.38	0.671 [0.272;1.656]	0.22
No bifurcation	48/459 (10.5%)	38/453 (8.4%)	0.29	1.247 [0.831;1.870]	
High-risk ACS	14/124 (11.3%)	13/136 (9.6%)	0.65	1.181 [0.578;2.414]	0.87
No high-risk ACS	41/427 (9.6%)	36/414 (8.7%)	0.65	1.104 [0.721;1.692]	

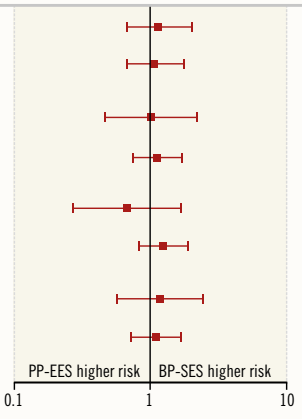

Figure 4. *Subgroup analysis: relative risk with 95% confidence interval (CI) of target lesion failure (TLF) at five years. Int. p-value: p-value for interaction*

It was hypothesised that bioresorbable polymer leaving an inert bare metallic platform following optimal drug release would prevent VLST. Results from NOBORI-1 showed some superiority to first-generation PP-DES with rates of definite and probable ST of 0.0% vs. 3.2% with bioresorbable and durable polymer stents, respectively (p=0.01)[14]. However, as Kang et al concluded in their meta-analysis, further all-round refinements in device design, reduced strut thickness and optimised elution process with reduced drug concentration and shortened elution periods may also have contributed to the observed findings[15]. Initial reports of randomised studies between BP-DES and new-generation PP-DES did not reproduce observed differences in early studies with respect to short- and medium-term safety outcomes[16-18]. However, the expected advantage of BP-DES was to be detected during longer observation periods, which are needed to elucidate the true value of biodegradable technology in contemporary PCI practice. Long-term reports of COMPARE II, ISAR-TEST 4 and EVOLVE failed to show any significant advantage in long-term safety of BP-DES compared to new-generation, biocompatible PP-DES[9,10,19]. Rates of ST were low and comparable in treatment groups, with just a few events occurring after 12 months across all studied populations. Further to this, the recent meta-analysis that included 16 RCTs, comprising 19,886 patients, addressed the effect of BP-DES design characteristics such as strut thickness, polymer degradation time and metallic platform material. None of the above proved to contribute to improved safety and efficacy compared to new PP-DES[20]. It is possible that active bioresorption during polymer elimination causes inflammation, making late benefit barely noticeable[21]. Very thin durable polymer DES designs also minimise metallic stimulus for thrombogenicity[22] and increase the biocompatibility of new polymers, causing little or no inflammation[23]. Finally, given the current very low rates of VLST, none of the above-mentioned trials was powered to detect such minute differences in late safety outcomes.

Study limitations

This study has a number of limitations. First, the study was powered for non-inferiority of BP-SES over PP-DES, in terms of TLF at nine months. This long-term report mainly provides hypothesis-generating insights. Second, the observed findings may not be applicable to all subgroups of this all-comer population. The overall SYNTAX score of 9 is low, mainly due to the additional exclusion criteria required in Japanese patients. In the overall population, patients with high-risk ACS, bifurcation lesions, left main and ostial lesions were included, adding evidence to the generalisability of our findings to an everyday population of CAD patients.

Conclusions

Biodegradable polymer and permanent polymer DES showed comparable clinical outcomes at five years. The observed rates of VLST were remarkably low, confirming the excellent safety of both investigated devices.

Impact on daily practice

This report presents the longest available clinical data regarding efficacy and safety following bioresorbable polymer sirolimus-eluting stent implantation, showing that comparable clinical outcomes to the current benchmark device, a durable polymer everolimus-eluting stent, are maintained up to five years. Notably, observed rates of very late stent thrombosis are remarkably low, supporting the safe use of this thin-strut stent in routine clinical PCI practice.

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Conflict of interest statement

B. Merkely reports personal fees from Abbott, Biotronik, Boston Scientific and Medtronic during the conduct of the study. Except for the institutional research grant received in the framework of the CENTURY II study, the other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Appendix 2. CENTURY II investigators.

Supplementary Figure 1. Kaplan-Meier curve for landmark analysis of target lesion failure-free event rate (%) up to one-year follow-up and between one-year and five-year follow-up.

Supplementary Table 1. Baseline patient characteristics of cohort JR.

Supplementary Table 2. Baseline lesion and procedural characteristics of cohort JR.

Supplementary Table 3. Dual antiplatelet therapy of cohort JR.

Supplementary Table 4. One-year clinical outcomes of cohort JR.

Supplementary Table 5. Five-year clinical outcomes of cohort JR.

Supplementary Table 6. Landmark analysis between 1 year and 5 years.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/136th_issue/60

Supplementary data

Supplementary Appendix 1. Methods.

Study population and randomisation

A total of 1,119 eligible CAD patients, scheduled for PCI, were enrolled and followed up at 58 participating centres in Europe (42 sites), Japan (15 sites) and Korea (1 site). Patients were randomly assigned in a 1:1 proportion to undergo PCI with either BP-SES or PP-EES, using an interactive web response system, or alternatively using a telephone allocation service. Randomisation of patients was stratified for Cohort JR (Japanese requirements: the subset of patients matching requirements for DES in Japan) and balanced for diabetes mellitus, acute coronary syndrome (ACS) and multivessel disease. Detailed inclusion and exclusion criteria have been reported previously [6]. Briefly, patients were eligible for enrolment in the study if they were 18 years or older, constituted good candidates for PCI using DES, were acceptable candidates for CABG and had clinical evidence of ischaemic heart disease and/or a positive functional test. Exclusion criteria for the general population were limited. Additional exclusion criteria applied to Cohort JR were age 20 years; acute MI within 48 hrs before baseline procedure; previous PCI with stenting; previous stenting within the target lesion; bifurcation lesion that required stenting of main and side branch, ostial lesion; target lesion located in a bypass graft; target lesion requiring vessel preparation other than balloon predilation; left main; more than one lesion per vessel and more than two vessels requiring treatment. The study complied with the Declaration of Helsinki and was approved by the institutional review board at each participating centre and the competent authority of each participating country. All patients provided written informed consent before undergoing any study-specific procedures.

Study devices

The bioresorbable polymer-containing sirolimus-eluting Ultimaster stent (BP-SES) uses a cobalt-chromium (Co-Cr) bare metal platform with thin struts (80 µm) with bioresorbable poly (DL-lactic acid-poly caprolactone) polymer with incorporated sirolimus drug (3.9 µg/mm stent length). The polymer is gradient, is coated on the abluminal side only and degrades within 3-4 months following implantation. The permanent polymer everolimus-eluting stent XIENCE (PP-EES) is a second-generation DES, based on a cobalt-chromium alloy stent with a strut thickness of 81 µm. Its coating consists of a permanent, non-erodable fluorinated copolymer, loaded with 100 µg/cm^2 of the antiproliferative drug everolimus.

Endpoints and definitions

Clinical outcomes at one-year and five-year follow-up include (i) freedom from target lesion failure (TLF), a device-oriented composite endpoint (cardiac death, MI not clearly attributable to a non-target vessel, and clinically driven target lesion revascularisation [TLR]); (ii) rate of target vessel failure (TVF) defined as composite of cardiac death and MI not clearly attributable to a non-target vessel, and clinically driven target vessel revascularisation (TVR); (iii) patient-oriented composite endpoint composed of all-cause death, all MI and all coronary revascularisations; (iv) rates of TLR, TVR, ST, cardiac death, MI; (v) composite of cardiac death and MI; (vi) rate of bleeding and vascular complications according to Bleeding Academic Research Consortium (BARC) definitions [7] for the total population and for cohort JR. The endpoints are defined as per Academic Research Consortium (ARC) recommendations [8].

Data management and quality assurance

A data monitoring committee (DMC) was responsible for the review of all data and identification of potential safety issues. An independent clinical events committee (CEC) reviewed and adjudicated all major endpoint-related adverse events. Members of the DMC, CEC and core laboratory were blinded to patient assignment, while investigators and study personnel were not blinded. Patients were not informed about the type of device they were treated with.

Statistical analysis

Categorical variables were compared using the chi^2 statistics (binary variables) and Cochran–Mantel–Haenszel test (multinomial variables). Continuous variables were compared using non-parametric tests: the Mann-Whitney U test was used for 2-group comparisons and the Kruskal-Wallis test for multiple group comparisons. Dichotomous secondary clinical endpoints were tested using the chi^2 test. The Kaplan-Meier method was used to estimate event rates for time-to-event outcomes, and data were compared with the log-rank test. The difference between randomisation arms was assessed by Student's t-test, analysis of variance, or non-parametric test (i.e., Mann-Whitney), as appropriate. To explore whether TLF with BP-SES vs. PP-EES was consistent across subgroups, logistic regression analysis was performed. All endpoints were analysed in the per-protocol and the intention-to-treat population. All analyses were carried out using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Appendix 2. CENTURY II investigators.

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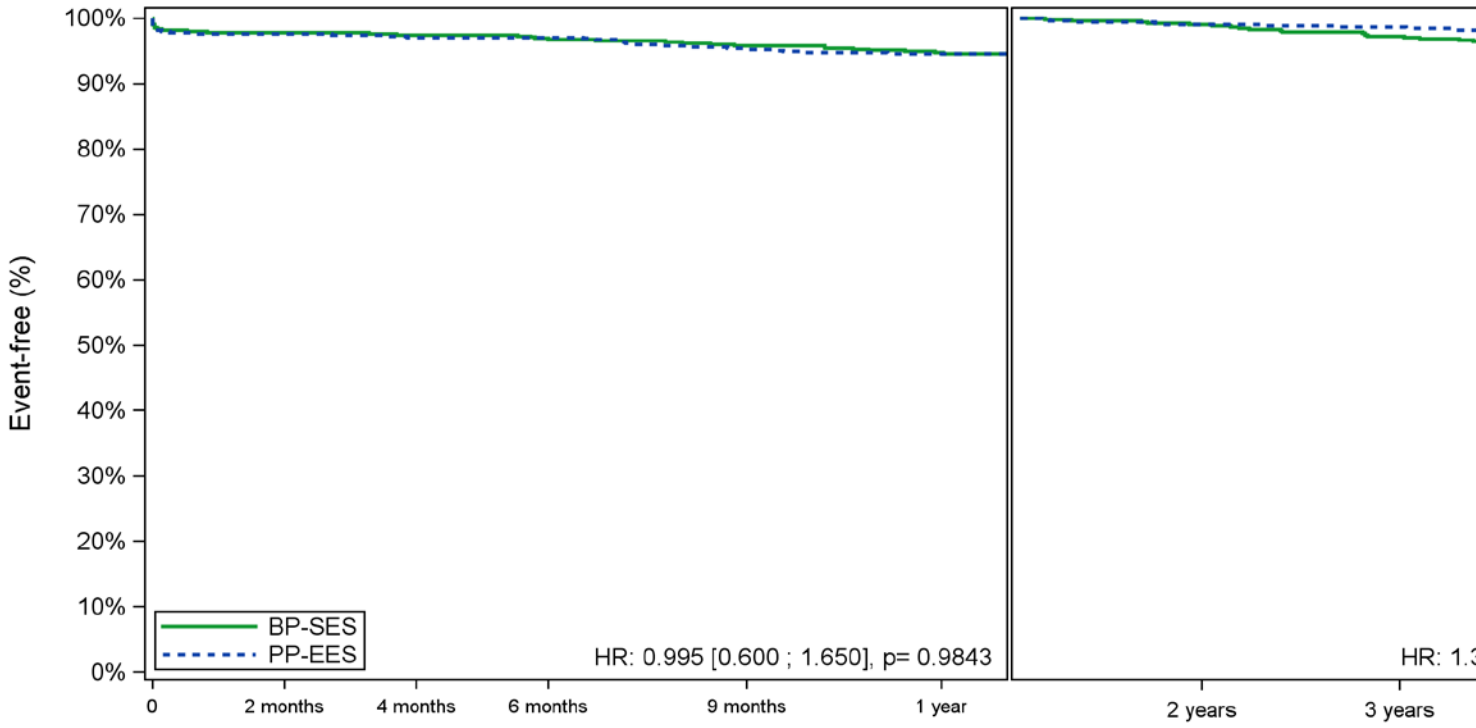
Supplementary Figure 1. Kaplan-Meier curve for landmark analysis of target lesion failure-free event rate (%) up to one-year follow-up (left panel) and between one-year and five-year follow-up (right panel).

BP-SES: bioresorbable polymer sirolimus-eluting stent; PP-EES: permanent polymer everolimus-eluting stent; TLF: target lesion failure


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Event-free (%)
BP-SES
PP-EES
HR: 0.995 [0.600 ; 1.650], p= 0.9843
HR: 1.3
0
2 months
4 months
6 months
9 months
1 year
2 years
3 years

Supplementary Table 1. Baseline patient characteristics of Cohort JR.

	BP-SES n=362	PP-EES n=353	*p*
Age, years	65.4±10.6	65.7±10.4	0.65
Male gender	74.6 (270/362)	80.7 (285/353)	0.05
Body mass index, kg/m²	26.7±4.4	26.2±4.3	0.08
Silent ischaemia	16.0 (58/362)	19.3 (68/353)	0.26
Stable angina	58.0 (210/362)	58.1 (205/353)	0.99
Unstable angina	13.5 (49/362)	11.6 (41/353)	0.44
High-risk ACS	12.4 (45/362)	11.1 (39/353)	0.57
STEMI	1.9 (7/362)	0.9 (3/353)	0.22
NSTEMI	10.5 (38/362)	10.2 (36/353)	0.90
Diabetes	35.9 (130/362)	33.7 (119/353)	0.54
IDDM	16.9 (22/130)	10.9 (13/119)	0.17
NIDDM	83.1 (108/130)	89.1 (106/119)	0.17
Dyslipidaemia	69.8 (250/358)	72.6 (254/350)	0.42
Hypertension	76.4 (275/360)	69.5 (244/351)	0.04
Smoking, current	19.0 (67/352)	21.3 (74/353)	0.46
Smoking, previous	49.2 (173/352)	45.7 (159/348)	0.36
Family history of CAD disease	30.6 (101/330)	30.4 (95/313)	0.94
History of PCI	32.3 (117/362)	30.7 (108/352)	0.64
History of CABG	3.0 (11/362)	2.3 (8/352)	0.53
History of MI	23.2 (84/362)	19.8 (70/353)	0.27
Charlson Comorbidity Index	1.2±1.4	1.1±1.3	0.51
Vessels diseased			0.78
1	66.6 (241/362)	66.6 (235/353)	
2	26.5 (96/362)	25.2 (89/353)	
3	6.9 (25/362)	8.2 (29/353)	
Vessels treated			0.40
1	85.4 (309/362)	87.5 (309/353)	
2	14.6 (53/362)	12.5 (44/353)	
3	NA	NA	
SYNTAX score	8.3±5.9	8.3±5.8	0.78

Values are mean±SD or % (number).
Cohort JR (Japanese requirements): patients who met criteria matching approved indication for drug-eluting stents in Japan. ACS: acute coronary syndrome; CABG: coronary artery bypass graft; CV: cardiovascular; MI: myocardial infarction; (N)IDDM: (non-) insulin-dependent diabetes mellitus; (N)STEMI: (non-) ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention

Supplementary Table 2. Baseline lesion and procedural characteristics of cohort JR.

	BP-SES	PP-EES	*p*
Lesions detected	1.68±1.02	1.66±1.01	0.68
Lesions treated	1.15±0.37	1.12±0.33	0.33
Lesion location (per lesion)			0.29
RCA	27.1 (113/417)	28.7 (114/397)	
LAD	46.5 (194/417)	48.6 (193/397)	
CFX	26.4 (110/417)	22.7 (90/397)	
LM	0.0 (0/417)	0.0 (0/397)	
Graft	0.0 (0/417)	0.0 (0/397)	
Ostial (per lesion)	3.1 (13/420)	5.6 (22/394)	0.08
Calcification (per lesion)			0.75
None/mild	81.0 (340/420)	83.3 (328/394)	
Moderate	14.1 (59/420)	12.4 (49/394)	
Severe	5.0 (21/420)	4.3 (17/394)	
Thrombus present (per lesion)	2.6 (11/420)	0.8 (3/394)	0.04
Bifurcation (per lesion)	14.9 (62/417)	15.6 (62/397)	0.77
ACC/AHA classification			0.30
A	5.2 (22/420)	4.3 (17/394)	
B1	14.3 (60/420)	16.0 (63/394)	
B2	49.5 (208/420)	54.6 (215/394)	
C	31.0 (130/420)	25.1 (99/394)	
Access site (per patient)			0.79
Femoral	22.4 (81/362)	22.4 (79/353)	
Radial	75.1 (272/362)	75.6 (267/353)	
Brachial	2.5 (9/362)	2.0 (7/353)	
Predilatation (per lesion)	82.5 (344/417)	80.4 (319/397)	0.43
Post-dilatation (per lesion)	59.0 (246/417)	56.9 (226/397)	0.55
No. of stents implanted per lesion	1.2±0.4	1.2±0.4	0.90
No. of stents implanted per patient	1.4±0.6	1.3±0.6	0.20
Total implanted stent length per lesion, mm	23.1±10.6	22.8±9.9	0.67
Total implanted stent length per patient, mm	26.6±14.0	25.7±13.8	0.25
Delivery success (per stent)	99.4 (493/496)	99.6 (466/468)	0.70
Procedure success (per patient)	98.3 (356/362)	98.3 (347/353)	0.96

Values are mean±SD or % (number).
Cohort JR (Japanese requirements): patients who met criteria matching approved indication for drug-eluting stent in Japan. ACC/AHA: American College of Cardiology/American Heart Association; LAD: left anterior descending; LCX: left circumflex; LM: left main; RCA: right coronary artery

Supplementary Table 3. Dual antiplatelet therapy of Cohort JR.

	BP-SES	PP-EES	*p*
DAPT at 1 month	98.9 (356/360)	97.4 (341/350)	0.15
DAPT at 4 months	97.5 (351/360)	95.1 (332/349)	0.09
DAPT at 9 months	90.3 (317/351)	85.6 (290/339)	0.05
DAPT at 1 year	68.6 (242/353)	67.0 (227/339)	0.65
DAPT at 5 years	15.8 (51/323)	16.8 (53/316)	0.74

Values are % (number).

Cohort JR (Japanese requirements): patients who met criteria matching approved indication for drug-eluting stent in Japan

Supplementary Table 4. One-year clinical outcomes of cohort JR.

	BP-SES n=362	PP-EES n=353	*p*
All-cause death	0.8 (3/362)	2.6 (9/353)	0.08
Cardiac death	0.8 (3/362)	1.4 (5/353)	0.46
All MI	2.2 (8/362)	2.3 (8/353)	0.96
Target vessel MI	1.4 (5/362)	1.7 (6/353)	0.73
Clinically indicated revascularisations			
TLR*	2.2 (8/362)	3.4 (12/353)	0.34
TV non-TLR	2.8 (10/362)	2.0 (7/353)	0.49
TVR	4.7 (17/362)	4.3 (15/353)	0.77
All revascularisations (clinically and non-clinically driven)			
TLR*	2.8 (10/362)	4.0 (14/353)	0.37
TV non-TLR	3.0 (11/362)	2.6 (9/353)	0.69
TVR	5.5 (20/362)	5.4 (19/353)	0.93
Composite endpoints			
TLF	4.7 (17/362)	5.7(20/353)	0.56
TVF	7.2 (26/362)	7.4 (26/353)	0.92
Cardiac death and MI	3.0 (11/362)	3.7 (13/353)	0.63
Patient-oriented composite endpoint	9.1 (33/362)	14.7 (52/353)	0.02
Stent thrombosis			
Total	0.6 (2/362)	0.8 (3/353)	0.63
Definite	0.6 (2/362)	0.6 (2/353)	0.98
Probable	0.0 (0/362)	0.3 (1/353)	0.31
Possible	0.0 (0/362)	0.0 (0/353)	-
Definite + probable	0.6 (2/362)	0.8 (3/353)	0.63
Bleeding or vascular complications	9.9 (36/362)	12.8 (45/353)	0.24
Any bleeding	7.7 (28/362)	11.3 (40/353)	0.10
Bleeding BARC type 2 to 5	4.1 (15/362)	7.4 (26/353)	0.06
Bleeding BARC type 3 to 5	1.4 (5/362)	2.8 (10/353)	0.18

Values are % (number).
*Totalled TLR: comprising more than one TLR per patient.
Cohort JR (Japanese requirements): patients who met criteria matching approved indication for drug-eluting stent in Japan. MI: myocardial infarction; patient-oriented composite endpoint is defined as all-cause death, MI and revascularisations; TLF: target lesion failure, defined as composite of cardiac death, target vessel-related MI and clinically indicated TLR; TLR: target lesion revascularisation; TV: target vessel; TVF: target vessel failure, defined as composite of clinically driven TVR, MI or cardiac death that could not be clearly attributed to a vessel other than the target vessel; TVR: target vessel revascularisation; BARC: Bleeding Academic Research Consortium (BARC) definitions

Supplementary Table 5. Five-year clinical outcomes of Cohort JR.

	BP-SES n=362	PP-EES n=353	*p*
All-cause death	6.6 (24/362)	5.7 (20/353)	0.59
Cardiac death	2.2 (8/362)	2.3 (8/353)	0.96
All MI	2.8 (10/362)	3.1 (11/353)	0.78
Target vessel MI	1.7 (6/362)	1.7 (6/353)	0.96
Clinically indicated revascularisations			
TLR *	5.0 (18/362)	6.5 (23/353)	0.38
TV non-TLR	4.4 (16/362)	2.8 (10/353)	0.26
TVR	7.7 (28/362)	6.5 (23/353)	0.53
All revascularisations (clinically and non-clinically driven)			
TLR*	8.0 (29/362)	8.5 (30/353)	0.81
TV non-TLR	5.5 (20/362)	5.4 (19/353)	0.93
TVR	10.8 (39/362)	9.1 (32/353)	0.45
Composite endpoints			
TLF	8.0 (29/362)	7.7 (27/353)	0.86
TVF	11.3 (41/362)	9.6 (34/353)	0.46
Cardiac death and MI	4.7 (17/362)	5.4 (19/353)	0.68
Patient-oriented composite endpoint	22.4 (81/362)	23.8 (84/353)	0.65
Stent thrombosis			
Total	0.8 (3/362)	1.1 (4/353)	0.68
Definite	0.8 (3/362)	0.8 (3/353)	0.98
Probable	0.0 (0/362)	0.3 (1/353)	0.31
Possible	0.0 (0/362)	0.0 (0/353)	-
Definite + probable	0.8 (3/362)	1.1 (4/353)	0.68
Stent thrombosis (definite or probable)			
Acute	0.0 (0/362)	0.0 (0/353)	-
Subacute	0.3 (1/362)	0.6 (2/353)	0.55
Late	0.3 (1/362)	0.3 (1/353)	0.99
Very late	0.3 (1/362)	0.3 (1/353)	0.99

Bleeding or vascular complications	16.6 (60/362)	18.7 (66/353)	0.46
Any bleeding	13.3 (48/362)	16.2 (57/353)	0.28
Bleeding BARC type 2 to 5	9.4 (34/362)	12.5 (44/353)	0.19
Bleeding BARC type 3 to 5	3.6 (13/362)	5.4 (19/353)	0.25

Values are % (number).
*Totalled TLR: comprising more than one TLR per patient.
Cohort JR (Japanese requirements): patients who met criteria matching approved indication for drug-eluting stent in Japan. MI: myocardial infarction; patient-oriented composite endpoint is defined as all-cause death, MI and revascularisations; TLF: target lesion failure, defined as composite of cardiac death, target vessel-related MI and clinically indicated TLR; TLR: target lesion revascularisation; TV: target vessel; TVF: target vessel failure, defined as composite of clinically driven TVR, MI or cardiac death that could not be clearly attributed to a vessel other than the target vessel; TVR: target vessel revascularisation

Supplementary Table 6. Landmark analysis between 1 year and 5 years.

	BP-SES	PP-EES	*p*
All-cause death	6.4 (35/544)	5.2 (28/536)	0.40
Cardiac death	2.0 (11/546)	2.0 (11/542)	0.99
All MI	0.9 (5/538)	1.1 (6/535)	0.75
Target vessel MI	0.6 (3/544)	0.2 (1/538)	0.32
Clinically indicated revascularisations			
TLR*	3.2 (17/531)	2.6 (14/531)	0.59
TV non-TLR	1.7 (9/537)	1.3 (7/539)	0.61
TVR	3.5 (18/522)	2.8 (15/528)	0.57
All revascularisations (clinically and non-clinically driven)			
TLR*	5.5 (29/527)	3.9 (21/527)	0.25
TV non-TLR	3.2 (17/535)	3.0 (16/535)	0.86
TVR	6.0 (31/517)	4.6 (24/520)	0.32
Composite endpoints			
TLF	4.8 (25/521)	3.7 (19/520)	0.36
TVF	5.5 (28/510)	4.5 (23/511)	0.47
Cardiac death and MI	2.6 (14/533)	3.2 (17/528)	0.57
Patient-oriented composite endpoint	15.0 (74/492)	13.4 (63/472)	0.45
Stent thrombosis			
Total	0.2 (1/545)	0.2 (1/544)	0.99
Definite	0.2 (1/545)	0.2 (1/545)	0.99
Probable	0	0	-
Possible	0	0	-
Definite + probable	0.2 (1/545)	0.2 (1/544)	0.99
Bleeding or vascular complications	9.7 (48/493)	6.7 (32/477)	0.09
Any bleeding	7.7 (39/507)	4.7 (23/490)	0.05
Bleeding BARC type 2 to 5	7.0 (37/526)	4.7 (24/513)	0.11
Bleeding BARC type 3 to 5	3.3 (18/543)	2.2 (12/536)	0.28

Values are % (number).
*Totalled TLR: comprising more than one TLR per patient.

MI: myocardial infarction; patient-oriented composite endpoint is defined as all-cause death, MI and revascularisations; TLF: target lesion failure, defined as composite of cardiac death, target vessel-related MI and clinically indicated TLR; TLR: target lesion revascularisation; TV: target vessel; TVF: target vessel failure, defined as composite of clinically driven TVR, MI or cardiac death that could not be clearly attributed to a vessel other than the target vessel; TVR: target vessel revascularisation; BARC: Bleeding Academic Research Consortium (BARC) definition