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A randomized, prospective, intercontinental evaluation of a bioresorbable polymer sirolimus-eluting coronary stent system: the CENTURY II (Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease) trial

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Aim The aim of this study was to establish safety and efficacy of a new sirolimus-eluting stent with bioresorbable polymer, Ultimaster (BP-SES). Sirolimus-eluting stent with bioresorbable polymer was compared with everolimus-eluting, permanent polymer, Xience stent (PP-EES) in the frame of a CENTURY II clinical trial designed to make global clinical data compliant with regulatory requirements in Europe and Japan.

Methods and results The CENTURY II is a prospective, multicentre, randomized (1 : 1), single blind, controlled, non-inferiority clinical trial conducted at 58 study sites in Japan, Europe, and Korea. A total of 1123 patients requiring a percutaneous coronary intervention (PCI) procedure, with implantation of drug-eluting stent (DES), were enrolled [total population (TP)]. Randomization of patients was stratified for the subset of patients matching requirements for DES in Japan (Cohort JR, $n = 722$). Baseline patient demographic and angiographic characteristics were similar in both study arms, with minimal differences between the TP and Cohort JR. The primary endpoint, freedom from target lesion failure (TLF) at 9 months—TLF [composite of cardiac death, target-vessel-related myocardial infarction (MI) and target lesion revascularization]—was 95.6% with BP-SES and 95.1% with PP-EES ($P_{\text{non-inferiority}} < 0.0001$). Composite of cardiac death and MI rate was 2.9 and 3.8% ($P = 0.40$) and target vessel revascularization was 4.5% with BP-SES and 4.2% with PP-EES ($P = 0.77$). The stent thrombosis rate was 0.9% in both arms. In Cohort JR, freedom from TLF was 95.9 and 94.6% ($P_{\text{non-inferiority}} < 0.0005$) with BP-SES and PP-EES, respectively.

Conclusion The new bioresorbable polymer sirolimus-eluting stent showed safety and efficacy profiles similar to durable polymer everolimus-eluting stent at 9-month follow-up.

Study registration number UMIN000006940.

Keywords Bioresorbable polymer • Drug-eluting stent • Sirolimus • Everolimus • Randomized trial

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Introduction

Drug-eluting stents (DES) have improved the outcomes of coronary intervention mostly through profound reduction in angiographic and clinical restenosis, better quality of life, and reduced need for repeat revascularization.[1–3] In the long-term, however, extensive clinical use of earlier generation DES was associated with unfavourable effects such as stent thrombosis (ST) and late failure.[4–11] Those findings have led to the development of several new DES with different design concepts all aiming at improving long-term safety and efficacy.[12–15]

The newly developed Ultimaster DES (Terumo Corporation, Tokyo, Japan) incorporates several innovative features such as bioresorbable polymer (resorbed within 3–4 months) and abluminal gradient coating that are expected to translate into the positive clinical outcome.

Inspired by the regulatory harmonization principles, we set out to conduct a large-scale randomized study in Japan and Europe comparing this newly developed bioresorbable polymer sirolimus-eluting stent (BP-SES) with the permanent polymer everolimus-eluting stent (PP-EES). The trial was powered to evaluate non-inferiority in terms of a clinical outcome. The study design has incorporated usage pattern of DES in Europe and in Japan on a pre-specified cohort's basis. As such the CENTURY II study is one of the first intercontinental efforts to develop global clinical trials in Europe and Japan and to provide regulatory bodies with meaningful clinical data thereby addressing gaps in timely access to new technology across the world.

Methods

Study design and patients

CENTURY II (Clinical Evaluation of New TerUmo dRug-eluting coronarY stent system in the treatment of patients with coronary artery disease) is a prospective, multicentre, randomized (1 : 1), single blind, controlled, non-inferiority, two-arm trial of BP-SES and PP-EES. Patients scheduled for PCI using DES in 58 participating centres from Europe, Japan, and Korea (Supplementary material online, Appendix) were enrolled. Patients with ischaemic heart disease due to stenotic lesions of coronary arteries with reference vessel diameter suitable for treatment with stents ≥2.5 and ≤4.0 mm (≤3.5 mm in Japan) were considered for the study. Randomization of patients was stratified by general inclusion and exclusion criteria [total population (TP)] and by criteria matching regulatory requirements and approved indications for DES in Japan (Cohort JR) (*Figure 1*).

Eligible patients were aged 18 years or older, good candidates for PCI using DES and acceptable candidates for CABG. They also must have clinical evidence of ischaemic heart disease and/or a positive functional study.

General exclusion criteria were life expectancy of <1 year; allergy/intolerance to sirolimus, everolimus, dual antiplatelet treatment (DAPT) and other PCI-related materials; left ventricular ejection fraction <25%; bleeding diathesis or coagulopathy; cardiogenic shock; renal failure requiring dialysis; inability to provide written informed consent. Additional exclusion criteria for Cohort JR were age <20 years (in Japan only); acute MI within 48 h before baseline procedure; previous PCI with stenting (within 30 days); previous stenting within the target lesion; bifurcation lesion that requires stenting of main and side branch, ostial lesion; target lesion located in- or supplied by- an arterial or venous bypass graft; target lesion requires vessel preparation other

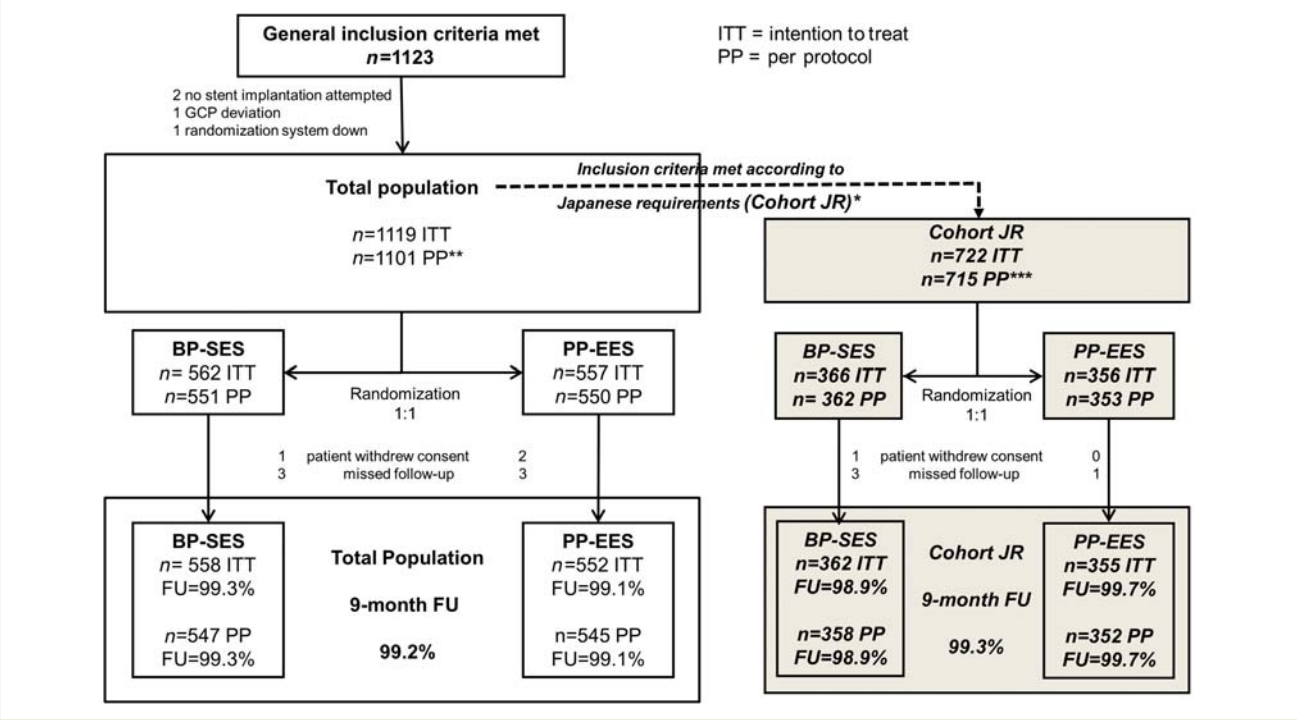

Figure 1 Study flowchart. *Japanese requirement (JR): patients who met criteria matching approved indication for drug-eluting stent in Japan; **1101 patients analysed per protocol for total population − 22 major protocol deviations (details in Supplementary material online, Appendix); ***715 patients analysed per protocol for cohort JR − 9 major protocol deviations.

than balloon-pre-dilation; left main stenosis; more than one lesion per vessel and >2 vessels requiring treatment.

The study complied with the Declaration of Helsinki and was approved by the institutional review board at each participating centre. All patients provided written informed consent before undergoing any study-specific procedures.

Randomization

Patients were randomly assigned (1 : 1) to undergo PCI with either BP-SES or PP-EES. Randomization was performed at each site using an interactive web response system, or alternatively using a telephone allocation service. Randomization of patients was stratified for Cohort JR, the subset of patients matching requirements for DES in Japan, and balanced for diabetes mellitus, high-risk acute coronary syndrome (STEMI and NSTEMI) and multivessel disease.

Procedures

Coronary interventions were performed according to standard hospital practice. After randomized stent assignment, all further procedures, lesion pre-dilation, stenting or post-stenting dilation, as well as usage of imaging modalities for result optimization or GP IIb/IIIa inhibitors, were left at operator's discretion. All patients received DAPT according to hospital practice. Protocol recommended continuation of DAPT for at least 6 months. Antiplatelet therapy beyond 6 months was at discretion of treating physician considering prevailing guidelines.[16] All patients were to be followed up at 1, 4, and 9 months and yearly up to 5 years.

Table 1 Baseline patient characteristics

	Cohort JR 715 patients			Total population 1101 patients		
	BP-SES (*n* = 362)	PP-EES (*n* = 353)	*P*-value	BP-SES (*n* = 551)	PP-EES (*n* = 550)	*P*-value
Age (years), mean ± SD	65 ± 11	66 ± 10	0.65	65 ± 11	66 ± 11	0.61
Male gender, %	74.59	80.74	0.05	78.58	82.36	0.11
Body mass index, mean ± SD	26.74 ± 4.36	26.23 ± 4.31	0.08	26.94 ± 4.17	26.86 ± 5.79	0.28
Silent ischaemia, %	16.02	19.26	0.26	14.88	18.36	0.12
Stable angina, %	58.01	58.07	0.99	49.00	46.00	0.32
Unstable angina, %	13.54	11.61	0.44	13.61	10.91	0.17
High-risk ACS, %	12.43[a]	11.05[a]	0.57	22.50	24.73	0.39
STEMI, %	1.93	0.85	0.22	5.26	5.64	0.79
NSTEMI, %	10.50	10.20	0.90	17.24	19.09	0.43
Diabetes, %	35.91	33.71	0.54	31.94	30.91	0.71
IDDM, %	16.92	10.92	0.17	16.48	14.71	0.65
NIDDM, %	83.08	89.08	0.17	83.52	85.29	0.65
Dyslipidaemia, %	69.83	72.57	0.42	70.30	69.56	0.79
Hypertension, %	76.39	69.52	0.04	73.31	67.82	0.05
Current smoking, %	19.03	21.26	0.46	22.16	23.89	0.50
Previous smoking, %	49.15	45.69	0.36	46.74	42.04	0.12
Family history of CV disease, %	30.61	30.35	0.94	30.75	32.06	0.66
History of PCI, %	32.32	30.68	0.64	37.21	35.04	0.45
History of CABG, %	3.04	2.27	0.53	4.54	3.65	0.46
History of MI, %	23.20	19.83	0.27	28.31	27.64	0.80
Charlson comorbidity index, mean ± SD	1.22 ± 1.43	1.14 ± 1.29	0.51	1.24 ± 1.51	1.20 ± 1.42	0.77
Vessels diseased, %						
1-	66.57	66.57	0.78	60.98	59.45	0.20
2-	26.52	25.21		29.58	27.82	
3-	6.91	8.22		9.07	12.55	
Vessels treated, %			0.40			0.59
1-	85.36	87.54		84.03	83.27	
2-	14.64	12.46		15.43	15.64	
3-	NA	NA		0.54	1.09	
Syntax score, mean ± SD	8.28 ± 5.89	8.26 ± 5.78	0.78	9.26 ± 7.04	9.33 ± 6.38	0.36

[a]Acute MI >48 h before procedure.
All values are available for all patients.
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; SD, standard deviation.

Table 2 Baseline lesion and procedural characteristics

	Cohort JR 814 lesions			Total population 1427 lesions		
	BP-SES (*n* = 417)	PP-EES (*n* = 397)	*P*-value	BP-SES (*n* = 711)	PP-SES (*n* = 716)	*P*-value
Lesions detected, mean ± SD	1.68 ± 1.02	1.66 ± 1.01	0.66	1.97 ± 1.34	1.99 ± 1.29	0.68
Lesions treated, mean ± SD	1.15 ± 0.37	1.12 ± 0.33	0.33	1.29 ± 0.57	1.30 ± 0.57	0.62
Lesion location, %			0.29			0.25
RCA	27.10	28.72		28.41	30.59	
LAD	46.52	48.61		43.32	43.16	
LCX	26.38	22.67		26.44	24.72	
LM	0.0	0.0		1.27	1.40	
Graft	0.0	0.0		0.56	0.14	
Ostial, %	3.10[a]	5.58[a]	0.08	5.95	8.39	0.08
Calcification, %			0.75			0.70
None/mild	80.95	83.25		78.52	82.34	
Moderate	14.05	12.44		14.80	12.45	
Severe	5.00	4.31		6.68	5.21	
Thrombus present, %	2.62	0.76	0.04	3.92	4.05	0.90
Bifurcation, %	14.87	15.62	0.77	13.78	14.39	0.74
ACC/AHA			0.31			0.13
Classification, %						
A	5.24	4.31		4.35	3.91	
B1	14.29	15.99		13.64	15.20	
B2	49.52	54.57		48.33	52.97	
C	30.95	25.13		33.67	27.93	
Access site, %			0.79			0.55
Femoral	22.38	22.38		26.68	25.64	
Radial	75.14	75.64		71.69	73.09	
Brachial	2.49	1.98		1.63	1.27	
Pre-dilation, %	82.49	80.35	0.43	77.36	77.37	0.99
Post-dilation, %	58.99	56.93	0.55	53.53	54.71	0.66
Stents per lesion, mean ± SD	1.18 ± 0.43	1.17 ± 0.42	0.90	1.18 ± 0.43	1.20 ± 0.44	0.32
Stents per patient, mean ± SD	1.36 ± 0.62	1.32 ± 0.63	0.20	1.51 ± 0.78	1.55 ± 0.86	0.94
Total stent length per lesion (mm), mean ± SD	23.05 ± 10.62	22.83 ± 9.94	0.67	22.96 ± 10.55	22.94 ± 10.39	0.55
Total stent length per patient (mm), mean ± SD	26.55 ± 14.04	25.68 ± 13.77	0.25	29.46 ± 17.04	29.61 ± 18.06	0.66
Delivery success, %	99.40	99.57	0.70	99.05	99.53	0.23
Procedure success, %	98.34	98.30	0.96	98.00	98.18	0.83
QCA lesion characteristics	*n* = 420	*n* = 394		*n* = 689	*n* = 691	
Pre-procedure						
Lesion length (mm), mean ± SD	16.37 ± 8.79	15.61 ± 7.96	0.29	16.92 ± 9.73	15.85 ± 8.69	0.07
Lesion length distribution, %			0.41			0.02
<10 mm	5.01	2.81		4.82	5.27	
>10 to <20 mm	51.79	59.44		51.53	57.69	
>20 mm	43.20	37.76		43.65	37.04	
RVD (mm), mean ± SD	2.64 ± 0.54	2.70 ± 0.56	0.11	2.62 ± 0.55	2.66 ± 0.55	0.14
MLD (mm), mean ± SD	0.89 ± 0.36	0.91 ± 0.37	0.25	0.86 ± 0.37	0.87 ± 0.40	0.35
% Diameter stenosis, mean ± SD	66.31 ± 11.58	66.15 ± 11.63	0.56	67.35 ± 12.18	67.38 ± 13.36	0.33
Post-procedure						
MLD (mm), mean ± SD						
In-stent	2.54 ± 0.42	2.60 ± 0.46	0.14	2.53 ± 0.43	2.56 ± 0.47	0.28

Continued

Table 2 *Continued*

	Cohort JR 814 lesions			Total population 1427 lesions		
	BP-SES (*n* = 417)	**PP-EES (*n* = 397)**	***P*-value**	**BP-SES (*n* = 711)**	**PP-SES (*n* = 716)**	***P*-value**
In-segment	2.21 ± 0.53	2.28 ± 0.53	0.07	2.19 ± 0.54	2.22 ± 0.56	0.20
% Diameter stenosis						
In-stent	12.32 ± 6.47	11.54 ± 6.07	0.06	12.42 ± 6.63	12.02 ± 6.72	0.14
In-segment	22.70 ± 9.67	21.33 ± 9.39	0.04	22.91 ± 9.86	22.25 ± 10.19	0.14
Acute gain (mm)						
In-stent	1.65 ± 0.45	1.69 ± 0.46	0.48	1.67 ± 0.46	1.70 ± 0.50	0.53
In-segment	1.32 ± 0.52	1.36 ± 0.51	0.27	1.33 ± 0.53	1.36 ± 0.56	0.63

[a]Results by core laboratory while eligibility was assessed by visual assessment of operator.
ACC/AHA, American College of Cardiology/American Heart Association; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex; LM, left main; MLD, minimal luminal diameter; RVD, reference vessel diameter.

Angiography at 9-month follow-up visit was scheduled for 400 patients from Cohort JR (minimum of 200 patients enrolled in Japan).

Study devices

Detailed technical description of Ultimaster BP-SES and comparator device, Xience PP-EES is given in Supplementary material online, Appendix.

Endpoints and definitions

The primary endpoint was 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 revascularization (TLR) at 9-month post-stent implantation for TP and for Cohort JR. Secondary endpoints were (i) 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 revascularization (TVR); (ii) patient-oriented composite endpoint composed of all deaths, all MI and all coronary revascularizations; (iii) rate of TLR, TVR; ST, cardiac death, MI; (iv) composite of cardiac death and MI; and (v) rate of bleeding and vascular complications according to Bleeding Academic Research Consortium (BARC) definitions.[17] Main angiographic endpoints included angiographic in-stent and in-segment binary restenosis rates (≥50% diameter stenosis) and in-stent and in-segment late loss (LL) at 9-month post-procedure. The endpoints are defined as per Academic Research Consortium (ARC) recommendations as listed in Supplementary material online, Appendix.[18]

Quantitative coronary angiography

All baseline and follow-up angiograms of the patients in angiographic subgroup were assessed by independent core laboratory (K.I.C. co Ltd, Kanagawa, Japan) using dedicated software (qAngio XA ver. 7.1, Medis, the Netherlands). Main angiographic parameters at baseline were minimum lumen diameter (MLD) before and after procedure, per cent diameter stenosis (DS%), acute gain (defined as the change in MLD from baseline to the final procedural angiogram), and at 9-month follow-up, angiographic binary restenosis rate (≥50% diameter stenosis), MLD, %DS and LL in-stent and in-segment (calculated as the difference in MLD between measurements noted immediately after the procedure and at follow-up).

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 Event Committee (CEC) reviewed and adjudicated all major adverse cardiac events. The members of the committees were not affiliated with the study sponsor and were not participating in the trial. The study was managed by independent contract research organizations responsible for monitoring, data management, and analysis. Data were collected and stored on an independent electronic data collection platform (Merge, USA). In keeping with regulatory requirements in Japan and Europe, all data on case report forms were 100% verified on-site vs. source documents.

Blinding

Members of DMC, CEC, Steering committee, and Core laboratory were blinded to patient assignment, while investigators and study personnel were not blinded. Patients were not informed about the type of the device they were treated with.

Sample size and statistical analysis

The CENTURY II randomized trial was powered for non-inferiority of BP-SES compared with PP-EES for the primary endpoint of 9-month TLF. In SPIRIT III,[2] a pivotal PP-EES study, with more restrictive inclusion criteria than CENTURY II, reported TVF rate was 7.2%. Based on the higher complexity of the population to be included in CENTURY II, the TLF event-free rate for BP-SES was estimated at 90% in the TP. A *P*-value <0.05 would indicate non-inferiority of BP-SES and would correspond to the upper limit of the one-sided 95% confidence interval (CI) of the difference not exceeding 5.5%. With a 5.5% non-inferiority margin, accounting for type I error at 0.05 (one-sided), with a 90% statistical power, 1 : 1 sampling ratio (BP-SES : PP-EES) and an expected 10% dropout rate, sample size was calculated at 560 patients in each group for the TP (total of 1120 patients). In agreement with Pharmaceuticals and Medical Devices Agency in Japan, the TLF event-free rate for Ultimaster in Cohort JR was estimated at 94% implying that 345 patients should be included in each group (total of 690 patients).

Categorical variables were compared using the χ^2 statistics or Fisher's exact test, Cochran–Mantel–Haenszel test. Continuous variables were compared using the Student's *t*-test or non-parametric test (i.e. Mann–Whitney or Kruskal–Wallis test for multiple groups comparison). Dichotomous secondary clinical endpoints were tested using the χ^2

test or Fisher's exact method. The Kaplan–Meier method was used to estimate event rates for time—to event outcomes, and data were compared with the long-rank test. For the continuous secondary endpoints, the following summary statistics are presented: number, mean, median, standard deviation, and reference range (95%). The difference between randomization 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 pre-specified clinical and angiographic subgroups, logistic regression analysis with interaction testing was performed. For the primary endpoint, both per-protocol and intent-to-treat analyses are presented.[19] All other endpoints were analysed in the per-protocol and the intention-to-treat population. Intent-to-treat analyses are available as Supplementary material online. All analyses were carried out using the SAS software, version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient characteristics and procedural outcomes

From 27 February 2012 to 10 January 2013, 1123 patients with 1464 lesions were enrolled at 58 sites in 13 countries: Europe (42 sites), Japan (15 sites), and South Korea (1 site). Patient flow and compliance with follow-up is shown in *Figure 1*. In total, 1119 patients were included in the intention-to-treat analysis (562 patients in BP-SES and 557 patients in PP-EES) and 1101 patients were included in the per-protocol analysis, 551 in BP-SES, and 550 in PP-EES (protocol deviations shown in Supplementary material online, Appendix).

In the TP, the mean patient age was 65 years, 20% were women, 31% had diabetes mellitus, and 36% of patients presented with acute coronary syndrome. Baseline clinical characteristics of the randomized study groups were similar in both TP and Cohort JR, except for a higher prevalence of arterial hypertension requiring treatment in the BP-SES group (*Table 1*). The population in Cohort JR had lower representation of high-risk acute coronary syndrome patients (consistent with eligibility criteria) and higher prevalence of diabetes mellitus. The lesion characteristics and complexity were similar in both cohorts and in both study arms (*Table 2*). More than 80% of the lesions were classified as B2 or C, 14% were located at bifurcation, 7% were ostial, and 5% totally occluded.

In 16% of patients, multiple vessels and in 25%, multiple lesions were treated. Device and procedure success were similar in both arms. Except for higher representation of longer lesions in the BP-SES arm, there were no significant differences in angiographic and procedural characteristics (*Table 2*). Overall, >40% of the lesions were longer than 20 mm and the mean reference vessel diameter was 2.64 mm.

Clinical outcomes

At 30 days, there was a comparable rate of death (0.2% in both arms), MI (1.8% in BP-SES and 2.2% in PP-EES), and TLR (0.5% BP-SES and 0.4% PP-EES) in TP. The findings were similar in Cohort JR. All analyses in the intention-to-treat population show identical findings.

Primary endpoint

In TP, 95.6% of patients in BP-SES and 95.1% of patients in PP-EES were free from TLF at 9 months (*Table 3* and *Figure 2*). Results indicate

Table 3 Non-inferiority primary endpoint calculation

	Cohort JR 715 patients				Total population 1101 patients			
Per protocol population	**BP-SES (*n* = 362)**	**PP-EES (*n* = 353)**	**Difference (95% CI)**	***P*-value**	**BP-SES (*n* = 551)**	**PP-EES (*n* = 550)**	**Difference (95% CI)**	***P*-value**
Freedom from TLF	95.86% (347/362)	94.62% (334/353)	1.24% (−2.10%; 4.58%)	0.0005	95.64% (527/551)	95.09% (523/550)	0.55% (−2.07%; 3.18%)	<0.0001
Intention-to-treat population	**722 patients**				**1119 patients**			
	BP-SES (*n* = 366)	**PP-EES (*n* = 356)**	**Difference (95% CI)**	***P*-value**	**BP-SES (*n* = 562)**	**PP-EES (*n* = 557)**	**Difference (95% CI)**	***P*-value**
Freedom from TLF	95.90% (351/366)	94.66% (337/356)	1.24% (−2.08%;4.55%)	0.0004	95.37% (536/562)	94.97% (529/557)	0.40% (−2.22%; 3.02%)	0.0001

Estimated non-inferiority margin of 5.5%.
TLF, target lesion failure; defined as composite of cardiac death, target vessel-related MI and clinically indicated TLR; TLR, target lesion revascularization.

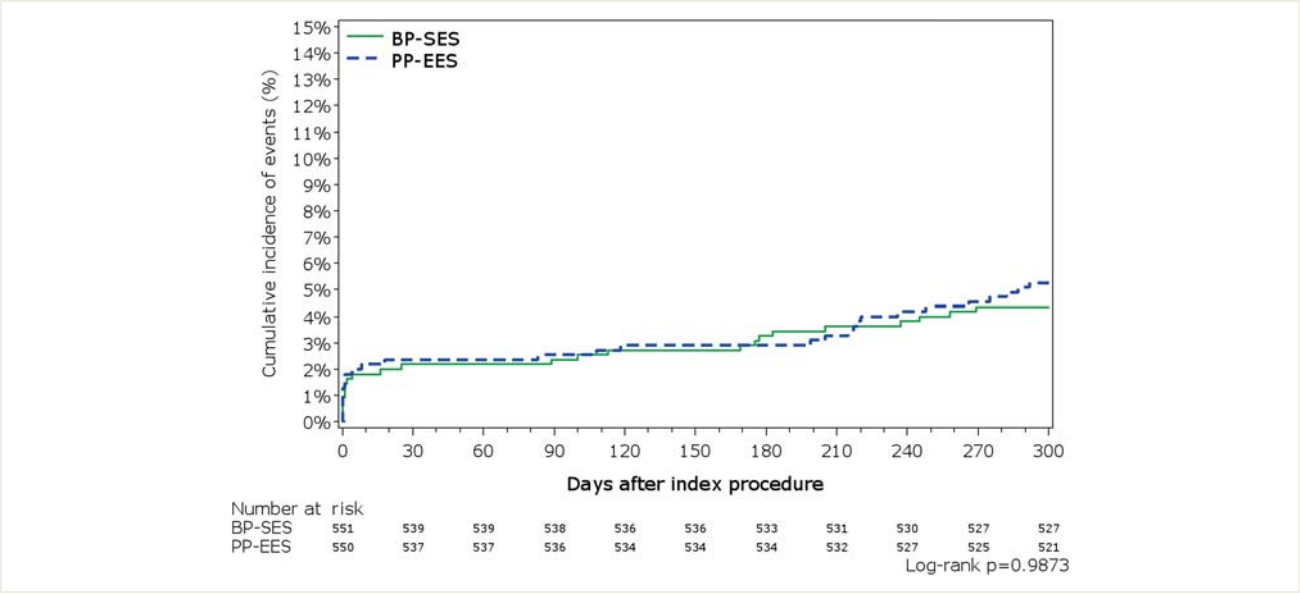

Figure 2 Century II Cumulative event rates for target lesion failure composite.

non-inferiority of the BP-SES, with an absolute risk difference of 0.55% in favour of the BP-SES group and with the lower limit of the one-sided 95% CI of 2.07% ($P < 0.0001$ in one-sided non-inferiority analysis). In Cohort JR, the freedom from TLF was 95.9 and 94.6% in BP-SES and PP-EES, respectively, and non-inferiority was also confirmed with an absolute difference of 1.24% in favour of BP-SES and with lower limit of one-sided 95% CI of -2.1% ($P < 0.0005$). The results were similar by intention-to-treat population (*Table 3*). At 9 months, 93% of patients in BP-SES and 92% of patients in PP-EES were angina free. There were no significant differences detected in any of the secondary endpoints. The rate of TLR per lesion up to 9 months was 1.7% (12/711) in BP-SES and 2.1% (15/716) in PP-EES ($P = 0.56$). For secondary endpoint analysis, findings in Cohort JR were similar to the TP (*Table 4*).

In the TP, ST through 9-month follow-up occurred in five patients in each group. All of them were adjudicated as definite ST with a rate at 0.9% ($P = 0.99$). No probable or possible ST was detected during the follow-up. In the PP-EES group, one patient suffered two ST episodes at Days 83 and 94, while one patient had simultaneous ST in all three lesions treated at baseline. In Cohort JR, there were three definite ST, one in the BP-SES arm (0.28%), and two in the PP-EES arm (0.57%) ($P = 0.55$). All patients suffering ST in the BP-SES arm were on DAPT at the time of event, while one patient in the PP-EES group experienced ST 3 days after stopping both aspirin and clopidogrel.

Bleeding and vascular complications were reported in 6.0% of patients in BP-SES and in 9.0% of patients in the PP-EES arm ($P = 0.06$). Most of the bleedings were adjudicated as Type 1 and Type 2 according to BARC criteria.

Angiographic subset analysis

Angiographic follow-up was performed in 429 patients (484 lesions). In-stent LL was 0.18 mm in PP-EES vs. 0.26 mm in BP-SES ($P = 0.003$); in-segment LL (0.10 mm in PP-EES vs. 0.09 mm in BP-SES; $P = 0.59$) was not different, nor was the binary restenosis rate (1.27 vs. 1.21% in-stent and 3.80 vs. 2.83% in-segment in PP-EES and BP-SES, respectively) (*Table 5*).

Subgroup analysis

No significant interactions between treatment assignment and outcomes at 9 months were found among nine subgroups tested by logistic regression analysis (*Figure 3*).

Regional analysis

To further confirm global applicability of intercontinental data for regulatory approval purposes, we have compared baseline patient characteristics, procedural particularities, and the clinical outcome of patients treated in Japan vs. outside Japan, irrespective of stent type (detailed data not shown). The patients in Japan were older with lower body mass index, higher prevalence of overall diabetes mellitus, but significantly less insulin-dependent diabetes mellitus and higher frequency of dyslipidaemia and hypertension. The lesion characteristics were similar, but the number of lesions treated was lower. The procedures through radial access were more frequent in Japan with significantly more pre- and post-dilations performed. Up to 9-month, there were no significant differences in any individual or composite endpoints between the populations treated in and outside Japan.

Discussion

The principal finding from the present study, representing the 9-month outcomes from the prospective, multicentre, multinational, intercontinental, randomized, controlled CENTURY II trial, is that primary clinical endpoint was met by showing non-inferiority of the novel sirolimus-eluting Co-Cr (Ultimaster) stent, to everolimus-eluting (Xience) stent when used in patients with broad inclusion criteria. Furthermore, ischaemia-driven TLR (clinical restenosis) occurred infrequently, with similar rates in both study groups. Short-term safety was demonstrated with both study stents,

Table 4 Clinical outcomes at 9 months

	Cohort JR 715 patients			Total population 1101 patients		
	BP-SES ($n = 362$)	PP-EES ($n = 353$)	*P*-value	BP-SES ($n = 551$)	PP-EES ($n = 550$)	*P*-value
All cause death, %	0.83 (3/362)	2.27 (8/353)	0.12	1.27 (7/551)	1.64 (9/550)	0.61
Cardiac death, %	0.83 (3/362)	1.42 (5/353)	0.46	0.91 (5/551)	1.09 (6/550)	0.76
All MI, %	1.93 (7/362)	2.27 (8/353)	0.76	2.00 (11/551)	2.73 (15/550)	0.43
Q-wave MI, %	0.55 (2/362)	0.00 (0/353)	0.16	0.54 (3/551)	0.18 (1/550)	0.32
Non-Q-wave MI, %	0.28 (1/362)	0.57 (2/353)	0.55	0.18 (1/551)	0.91 (5/550)	0.10
Target vessel MI, %	1.38 (5/362)	1.70 (6/353)	0.73	1.27 (7/551)	2.18 (12/550)	0.25
Certain or suspected target vessel MI, %	1.93 (7/362)	2.27 (8/353)	0.76	1.81 (10/551)	2.73 (15/550)	0.31
Clinically indicated revascularization, %	3.59 (13/362)	6.52 (23/353)	0.07	4.54 (25/551)	5.64 (31/550)	0.41
TLR, %	1.66 (6/362)	1.98 (7/353)	0.75	2.18 (12/551)	1.64 (9/550)	0.51
TLR-PCI, %	1.66 (6/362)	1.70 (6/353)	0.97	2.0 (11/551)	1.45 (8/550)	0.49
TLR-CABG, %	0.0 (0/362)	0.28 (1/353)	0.31	0.18 (1/551)	0.36 (2/550)	0.56
TV non-TLR, %	2.21 (8/362)	1.98 (7/353)	0.83	2.00 (11/551)	1.82 (10/550)	0.83
TVR, %	3.59 (13/362)	3.68 (13/353)	0.95	3.81 (21/551)	3.09 (17/550)	0.51
All revascularizations (clinically and non-clinically indicated), %	4.97 (18/362)	8.22 (29/353)	0.08	5.63 (31/551)	7.82 (43/550)	0.15
TLR, %	2.21 (8/362)	2.27 (8/353)	0.96	2.72 (15/551)	2.18 (12/550)	0.56
TV non-TLR, %	2.49 (9/362)	2.55 (9/353)	0.96	2.18 (12/551)	2.36 (13/550)	0.84
TVR, %	4.42 (16/362)	4.53 (16/353)	0.94	4.54 (25/551)	4.18 (23/550)	0.77
Composite endpoints						
TLF, %	4.14 (15/362)	5.38 (19/353)	0.44	4.36 (24/551)	4.91 (27/550)	0.66
TVF, %	6.08 (22/362)	7.08 (25/353)	0.59	5.99 (33/551)	6.36 (35/550)	0.80
Cardiac death and MI, %	2.76 (10/362)	3.68 (13/353)	0.49	2.90 (16/551)	3.82 (21/550)	0.40
Patient-oriented composite endpoint, %	7.46 (27/362)	11.90 (42/353)	0.05	8.35 (46/551)	10.91 (60/550)	0.15
Stent thrombosis, %	0.28 (1/362)	0.57 (2/353)	0.55	0.91 (5/551)	0.91 (5/550)[a]	0.99
Definite	0.28 (1/362)	0.57 (2/353)	0.55	0.91 (5/551)	0.91 (5/550)	0.99
Probable	0.00 (0/362)	0.00 (0/353)	1.0	0.00 (0/551)	0.00 (0/550)	1.0
Possible	0.00 (0/362)	0.00 (0/353)	1.0	0.00 (0/551)	0.00 (0/550)	1.0
Stent thrombosis, %						
Acute	0.00 (0/362)	0.00 (0/353)	1.0	0.00 (0/551)	0.00 (0/550)	1.0
Subacute	0.28 (1/362)	0.28 (1/353)	1.0	0.54 (3/551)	0.36 (2/550)	0.65
Late	0.00 (0/362)	0.28 (1/353)	0.31	0.36 (2/551)	0.54 (3/550)	0.65
DAPT use at 9 months, %	89.74 (315/351)	85.55 (290/339)	0.09	89.57 (481/537)	86.74 (458/528)	0.15

[a]One patient had two definite ST at 83 and 94 days in two separate lesions treated at baseline.
MI, myocardial infarction; patient-oriented composite endpoint is defined as all deaths, MI and revascularizations; TLF, target lesion failure, defined as composite of cardiac death, target vessel-related MI and clinically indicated TLR; TLR, target lesion revascularization; 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 revascularization.

with non-significant differences in 9-month rates of cardiac death, MI, and ST.

The rates of technical procedural success achieved with the two stents were similar and exceeded 99% in the study population (>80% of all lesions were classified as ACC/AHA class B2 or C) which shows both equivalent and high technical performance of both stents. Although the present study was not primarily designed to compare the technical characteristics of the two Co-Cr platforms, the similarity in performances and high success rate are important factors for practising physicians in the catheterization laboratory.[20]

The CENTURY II trial addressed a population with minimal exclusion criteria relying on the recommendation of the regulatory agencies and scientific associations that future trials should include patients who resemble a broad, unselected every-day clinical practice population.[21–22] These considerations have led to the enrolment of a large proportion of patients with acute coronary syndrome, diabetes mellitus, multivessel disease, bifurcation lesions, and diffuse, long lesions, representative of patients, and lesions undergoing PCI in contemporary practice.

The present study population is comparable with previously reported all-comers studies that compared PP-EES with either zotarolimus-eluting stent (Resolute all-comers) or biolimus-eluting stent (COMPARE II and NEXT).[15,23,24] Fewer patients with acute MI were included than in Resolute all-comers and COMPARE II

Table 5 Results of quantitative coronary angiography analysis in patients with 9 months angiographic follow-up

	BP-SES, 214 patients, 247 lesions	PP-EES, 215 patients, 237 lesions	*P*-value
Pre-procedure			
Lesion length, mm	16.62 ± 8.98	15.80 ± 8.13	0.30
RVD, mm	2.64 ± 0.52	2.67 ± 0.50	0.54
MLD, mm	0.87 ± 0.34	0.91 ± 0.34	0.29
Diameter stenosis, %	66.98 ± 10.66	66.12 ± 11.10	0.26
Post-procedure			
MLD, mm			
In-stent	2.56 ± 0.43	2.60 ± 0.47	0.50
In-segment	2.20 ± 0.58	2.27 ± 0.52	0.20
Diameter stenosis, %			
In-stent	11.94 ± 6.34	11.59 ± 6.26	0.28
In-segment	23.07 ± 10.27	21.28 ± 8.75	0.13
9-month			
MLD, mm			
In-stent	2.30 ± 0.50	2.42 ± 0.52	0.007
In-segment	2.11 ± 0.52	2.18 ± 0.56	0.18
Diameter stenosis, %			
In-stent	18.43 ± 10.29	15.75 ± 9.64	0.001
In-segment	23.77 ± 10.95	23.70 ± 11.55	0.73
Late loss, mm			
In-stent	0.26 ± 0.35	0.18 ± 0.31	0.003
In-segment	0.09 ± 0.45	0.10 ± 0.39	0.59
Late loss index, %			
In-stent	0.16 ± 0.21	0.11 ± 0.21	0.005
In-segment	−0.14 ± 1.86	0.03 ± 0.41	0.48
Binary restenosis, %			
In-stent	1.21	1.27	0.96
In-segment	2.83	3.80	0.55

All values are mean ± SD. MLD, minimal luminal diameter; RVD, reference vessel diameter.

trials, but more than in NEXT trial. The trend was opposite for the representation of patients with diabetes mellitus. Those differences are in line with eligibility criteria for Cohort JR (MI excluded) and proportion of patients enrolled in Japan (more diabetes).

Choice of comparator drug-eluting stent

Prior studies have shown, in a broad spectrum of patients undergoing PCI, that usage of PP-EES (Xience) resulted in low rates of TLF, a composite metric of safety and efficacy.[2,13–15] The Resolute All Comers study demonstrated similar TLF rate with PP-EES and zotarolimus-eluting stent but reduced definite or probable ST in patients treated with PP-EES (0.7 vs. 1.6% for ZES; $P = 0.05$).[23] Those findings have led to an increased adoption of PP-EES, presently one of the most frequently used DES in contemporary PCI practice around the world. This was the major reason to select PP-EES as a comparator stent to evaluate the performance of a new BP-SES. CENTURY II demonstrated short-term non-inferiority regarding the primary endpoint and similar rates of important clinical endpoints of the BP-SES stent. This confirms the working hypotheses behind its design. In addition to lesion characteristics and procedural techniques, early outcomes are primarily driven by stent deliverability, blood compatibility and drug release kinetics, being common to both platforms. Unique features of BP-SES are related to the use of bioresorbable polymer on a Co-Cr platform and its abluminal coating allowing for more rapid endothelialization. The links between stent struts are spared from coating which is intended to reduce the risk of polymer fracture. This bioresorbable polymer is expected to fully resorb within 3–4 months. The short polymer resorption time is possible through innovative co-polymerization technology that, at the same time, increases its elasticity, eliminates polymer delamination during stent expansion and further vessel wall injury.

Taking into account the complexity of the study population, the overall incidence of ST in the CENTURY II trial was low and similar to previous contemporary studies.[15,23,25] Whether the use of a bioresorbable instead of durable polymer, as a reservoir for drug release, will result in improved late outcomes remains to be determined.[26,27] In the LEADERS study[25] which examined a very complex patient population, important finding was the increased safety of the biodegradable polymer biolimus-eluting stent between 1 and 5 years, compared with the first-generation durable polymer sirolimus-eluting stent. In fact, the incidence of ST associated with the biodegradable polymer biolimus-eluting stent appeared to have almost plateaued after 1 year. This finding illustrates the potential importance of using a biodegradable polymer in order to reduce late hypersensitivity reactions, one of the most important pathophysiological mechanisms of late ST and DES failure.[28]

Quantitative coronary angiographic substudy

The anti-proliferative efficacy on neo-intima suppression was high for both study stents; yet, in-stent LL was significantly lower with PP-EES. As shown by Mauri *et al.*,[29] in-stent LL correlates tightly with restenosis rates and the need for re-intervention. In the present study, the observed differences in LL between the two stents did not translate in increased restenosis rates nor in any measurable difference in revascularization rates. TLR and TVR figures were extremely low in both groups in the presence of high-risk features (high representation of lesions longer than 20 mm, particularly in the BP-SES arm, the reference vessel diameter was 2.64 mm and >30% of patients had diabetes mellitus). Clinical restenosis, however, will only become apparent when in-stent LL reaches threshold values of ~0.6 mm, markedly higher than the observed figure. Accordingly, the per-lesion TLR rate was similar between the stent types and actually numerically lower at 1.7% with BP-SES vs. 2.1% with PP-SES. An exploratory subgroup analysis confirms comparable results in the most critical lesion subsets such as small vessels, long lesions, bifurcation lesions, and in patients with diabetes mellitus.

Global harmonization of device approval

Beyond the validation of new DES, this study is a valuable attempt to harmonize the generation of clinical evidence in support of

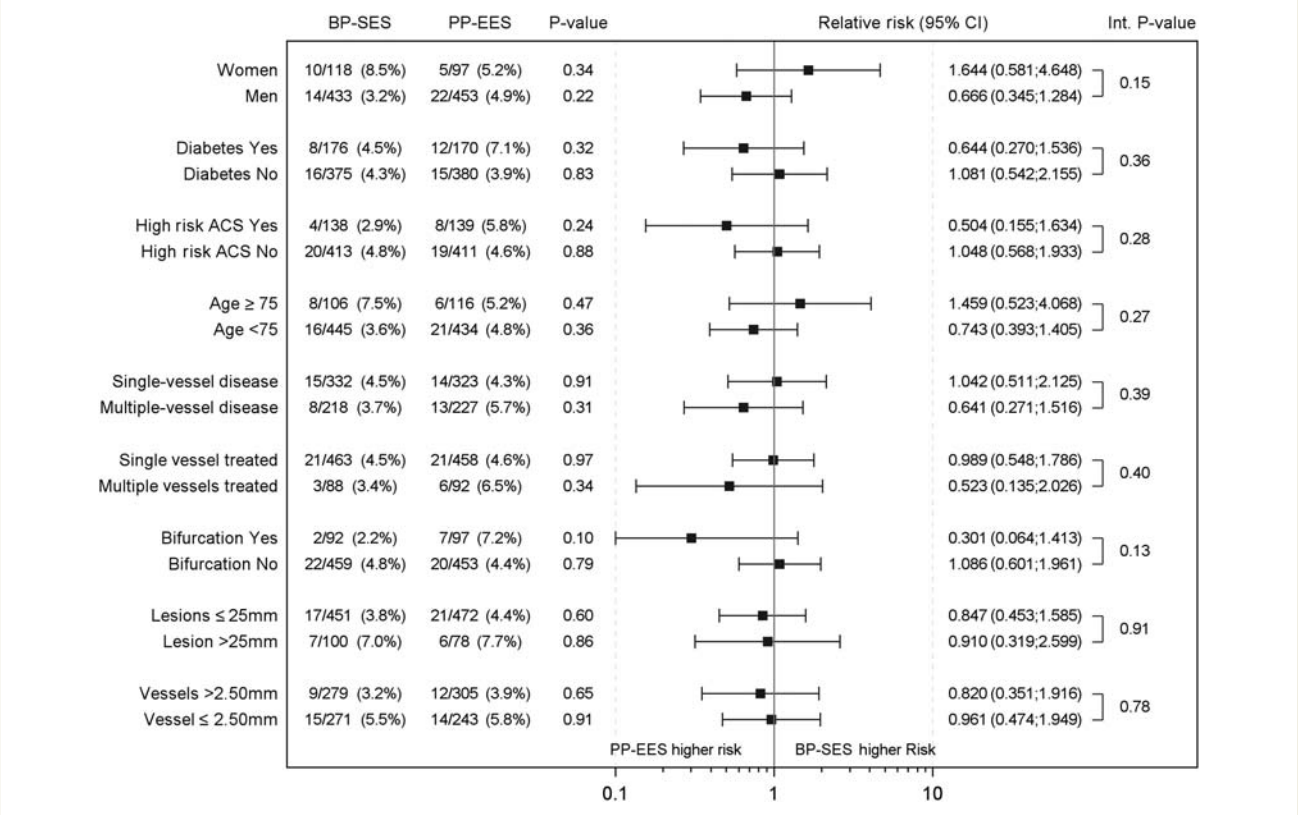

Figure 3 Subgroup analysis outcome: relative risk with 95% CI of target lesion failure composite (no. of events/no. of subjects, *P*-values).

regulatory approval of new devices across continents. Such synchronized efforts of academics, regulatory agencies and industry are paving the way to expedite patient access to novel technologies around the world.[22,30] Extensive rigour in data collection, follow-up compliance and 100% source data verification contribute to the validity of our results. Of note, small differences in baseline and procedural characteristics noted between patients enrolled in Japan and outside Japan did not translate into clinical outcome differences. The study of patients from a wide geographic area, involving different clinical and procedural practices provides additional useful information. Comparison of procedural outcomes using similar devices in different environments makes it possible to decipher to which extent practice patterns and procedural technique may influence clinical results. These observations demonstrate wide applicability of the present data for device approval purposes and the potential for optimization of PCI practice, further supporting the conduct of global clinical trials.

Study limitations

Currently, available data do not establish potential benefits of bioresorbable polymer coating. Long-term follow-up is required for a comprehensive evaluation of BP-SES, as planned by a study design up to 5 years. The CENTURY II trial excluded from Cohort JR acute MI patients, left main and bypass grafts stenosis. Hence, these subsets are less prevalent in the total study population. The study was not powered to detect differences in individual endpoints and rare events. The observed TLF rates were lower than the anticipated 10%, a reasonable estimate at the time of the study design. Considering that the objective of the study was to demonstrate the non-inferiority of the Ultimaster DES compared with the standard DES treatment, 5.5% non-inferiority was selected as an acceptable and clinically relevant difference for non-inferiority level between the two arms and applied for the two population-types cohorts.[19,31] Of note, if we would apply the most conservative method recommended in pharmaceutical trials, the so-called '95−95 method' would give a non-inferiority delta ~5% (when using 95 CI). Furthermore, although DMC, CEC, and core laboratory were blinded for patient's assignment, logistical considerations precluded blinding of study personnel. These limitations are of potential importance, but none is severe enough to cast doubts on the robustness of the main study findings.

Conclusion

The new sirolimus-eluting Co-Cr stent with bioresorbable polymer (Ultimaster BP-SES) was found to be as safe and as effective as everolimus-eluting Co-Cr stent with permanent polymer (Xience PP-EES) in this relatively complex patient population. Long-term follow-up of the patients enrolled in CENTURY II is expected to

provide further unambiguous assessment of the potential long-term clinical benefits of DES with a bioresorbable polymer.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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