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ORIGINAL ARTICLE

Randomized comparison between 2-link cell design biolimus A9-eluting stent and 3-link cell design everolimus-eluting stent in patients with de novo true coronary bifurcation lesions: the BEGIN trial

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Abstract

The appropriate stent platform for treating coronary bifurcation lesions (CBLs) remains controversial. Previous bench tests have demonstrated the superiority of a 2-link cell design to 3-link cell design for creating inter-strut dilation at the side branch ostium. This randomized multicenter prospective BEGIN trial compared the biodegradable polymer-based biolimus A9-eluting stent (2-link BES) with the durable polymer-based cobalt chromium everolimus-eluting stent (3-link EES) in 226 patients with de novo CBLs. Patients with true bifurcations, defined as > 50% stenosis in the main vessel and side branch (SB) and an SB diameter > 2.25 mm, were enrolled. Guide wire re-crossing to the distal cell (near the carina) in the jailed SB and final kissing inflation were recommended. The SB angiographic endpoint was < 50% stenosis diameter. Left-main CBLs (13.5% vs. 13.0%) and 2-stent technique (30.6% vs. 22.6%) rates were similar. The primary endpoints (minimum lumen diameter at the SB ostium measured at an independent core laboratory at the 8-month follow-up) were comparable (1.64 ± 0.50 mm vs. 1.63 ± 0.51 mm, $p = 0.976$). There was no significant difference in composite outcomes of cardiac death, myocardial infarction, or target vascular revascularization at 12 months (7.4% vs. 8.0%, $p = 0.894$). Two-link BES and 3-link EES showed similar 8-month angiographic and 1-year clinical outcomes for true CBLs.

Keywords Randomized study · Coronary bifurcation lesions · Drug-eluting stent · Biolimus A9-eluting stent · Everolimus-eluting stent

Introduction

Percutaneous coronary intervention (PCI) for coronary bifurcation lesions (CBLs) remains challenging even in the drug-eluting stent (DES) era. Tubular stents are usually implanted in CBLs by modifying their struts' shape to cover both the main vessel (MV) and the side branch (SB) using various techniques [1]. Therefore, the identification of the appropriate stent design for this particular anatomy is greatly needed.

First-generation DESs are related to delayed atrial healing and potential inflammation as well as the propensity for delayed catch-up and thrombosis [2]. Furthermore, an increased number of links connecting to metal hoops (i.e., 6-link cell design, Cypher) has been associated with limited side-cell expansion at the SB ostium (SBO) and a higher likelihood of restenosis after complex CBL stenting [3]. In contrast, the second-generation DES platform is based on a thinner strut structure with a 1.5–3-link cell design that

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creates large side cells after SB balloon dilation. Recent bifurcation studies demonstrated the superiority of second-generation DES over first-generation DES with respect to angiographic enlargement at the SBO and long-term clinical outcomes [4, 5]. However, a randomized trial comparing second-generation DESs in the management of CBLs is lacking. Previous bench tests demonstrated the superiority of a 2-link cell design over a 3-link cell design for reducing incomplete stent apposition (ISA) at the SBO; however, 2-link design can lead to stent deformation by overdilation of hugging final kissing inflation (FKI) balloons in the proximal MV, resulting in decreased efficacy due to polymer injury or decreased drug penetration [6, 7]. Differences in DES designs in the bench test may translate to different angiographic outcomes; thus, prospective randomized trials in CBLs is warranted [4].

Nobori (Terumo, Tokyo, Japan), a biolimus-eluting stent (BES) made of stainless steel with an abluminal biodegradable polymer, is a 2-link DES. Different from global design (3.5 mm 3-link with 9 crowns, Biomatrix), inter-strut dilation diameter in the Japanese design (3.5 mm 2-link with 10 crowns) is the maximum at 4.2 mm [8]. Xience (Abbott Vascular, Santa Clara, CA, USA), an everolimus-eluting stent (EES) made of cobalt chrome component with durable polymer, is a 3-link platform well recognized as a standard DES used in daily practice [9–13].

Hence, here we conducted a prospective multicenter randomized trial to evaluate and compare the 8-month angiographic outcomes at the SBO after implantation of 2-link BES and 3-link EES, to determine the appropriate DES platform for CBLs.

Methods

Study design

The BEGIN (Bifurcation stEntinG using 2lInk stent: Nobori vs. 3link steNt: Xience) trial is a prospective multicenter open-label randomized trial comparing 2-link BES and 3-link EES in CBLs in Japan (NCT01574586).

A web-based allocation system was used for randomization. The statisticians (AC Medical Inc., Tokyo, Japan), steering committee, clinical research organization (Kurashiki Central Hospital Clinical Research Center, Kurashiki, Japan), clinical event committee, angiographic core laboratory (Japan Cardiovascular Imaging Core Laboratory [JCICL], Tokyo, Japan), and sponsor (TERUMO Japan, Tokyo) were blinded to the study group assignments. The study protocol was approved by the institutional review board of each participating center. Written informed consent was obtained from all patients.

Study protocol

The study protocol was confirmed in March 2012. Forty-six Japanese centers participated, of which 34 enrolled patients (Supplemental Table 1). Inclusion criteria were as follows: Patients ≥ 20 years with (1) de novo and true CBLs, ≥ 50% diameter stenosis (DS) in the MV and SB belonging to Medina classes (1.1.1), (1.0.1), and (0.1.1); (2) visually estimated target lesion reference vessel diameter (RVD), 2.5–5.0 mm in the MV, and ≥ 2.25 mm in the SB; (3) target CBLs treatable with one or two stents in both branches (treatable within 4 stents in lesions including CBLs); and (4) Thrombolysis in Myocardial Infarction (TIMI) grade ≥ 1 flow in both branches. CBLs were defined as lesions 10 mm proximal from the carina to the MV or 5 mm distal from the carina to the MV or SB on angiography. For the left main coronary artery (LMCA) lesions, PCI consensus was obtained after discussion between the cardiologists and cardiac surgeons. One target CBL per patient treated with the study device was enrolled. Exclusion criteria included pregnancy, life expectancy < 1 year, acute myocardial infarction (MI) within 1 week, left ventricular ejection fraction < 30%, scheduled for elective treatment requiring antiplatelet drug withdrawal, 3-vessel diseases, and serum creatinine level ≥ 2.0 mg/dL. Vascular morphological restriction criteria included lesions proximal to coronary artery bypass graft anastomotic site (visual estimation ≤ 5.0 mm) or including a part of the coronary artery bypass grafting, in-stent restenosis, and severe calcification or usage of debulking device (rotablator or directional coronary atherectomy).

Procedure

After a baseline angiogram was obtained, the patients were randomly assigned in a 1:1 ratio to one of the two devices: 2-link BES (Nobori, TERUMO, Tokyo) and 3-link EES (Xience V, Prime, Xpedition, Abbott Vascular). Xience (2.5–3.5 mm) has a 3-link cobalt chromium platform with everolimus and a durable polymer. Stent lengths of 8, 12, 15, 18, 23, 28, 33, and 38 mm were available (33 and 38 mm were available when the Xience Prime or Xpedition were used). The Nobori 2.5–3.0 mm has a 2-link stainless steel platform with biolimus A9 and abluminal biodegradable polymer. Stent lengths of 8, 14, 18, 24, and 28 mm were available. The global design of the Nobori 3.5 mm has a 3-link, 9-crown design, while the Japanese design has a 2-link, 10-crown design; therefore, the Nobori platform used in this trial had a 2-link design. Provisional SB stenting or an elective 2-stent strategy was performed at the operator's discretion depending on

bifurcation morphology. After wires were inserted into both branches, pre-dilation was recommended for the MV. After crossover stent deployment, re-wiring to jailed SB was performed. To confirm guidewire re-crossing to the distal cell (near the carina), a double-lumen catheter (DLC; Crusaide, Kaneka Medix Corporation, Osaka, Japan or Sasuke ASAHI INTECC, Nagoya, Japan) or the assessment of re-crossing point by the manual pull-back of intravascular ultrasonography (IVUS) in the MV was strongly recommended. Final kissing-balloon inflation (FKI) was recommended as a mandatory step. Pre- and post-procedure IVUS-guided stent optimization was also recommended, but post-procedure minimum stent/lumen diameter and reduction of incomplete stent apposition (ISA) were determined at the operator`s discretion. In provisional SB stenting, stent implantation in the SB was allowed by the culottes technique or T-stent technique only when at least one of the following conditions was met: (1) residual stenosis > 50%, (2) dissection of type B or worse or (3) TIMI ≤ 2. Additional stent implantation in either branch was allowed to obtain whole-lesion coverage or in cases of dissection. Only culottes and the T-stent technique were recommended for the elective 2-stent strategy. In this trial, other stent techniques (e.g., simultaneous kissing stent, crush, mini-crush, double kissing crush technique) were not recommended for elective or bail-out use. Pre-dilation for SB and the proximal optimization technique (POT) were performed at the operator's discretion. All patients were pretreated with aspirin and either ticlopidine or clopidogrel. A 300-mg loading dose of clopidogrel was administered before the index procedure, if patients were not pretreated. During the procedure, patients received intravenous unfractionated heparin to maintain an activated clotting time > 250 s. Maximum creatine kinase (CK) and CK-MB isoform cardiac enzymes were recorded at 8–28 h after the procedure. After discharge, aspirin (≥ 81 mg daily) therapy was continued indefinitely, while clopidogrel (75 mg daily) or ticlopidine (200 mg daily) was continued for at least 12 months.

Follow-up

Clinical follow-up was performed in out-patient clinic or via telephone at 8 and 12 months. Adverse events were monitored throughout the entire study period. Follow-up coronary angiography was scheduled at 8 months after the procedure for all patients unless necessary at an earlier time for clinical reasons. Figure 1 shows the patient flow during follow-up.

Quantitative coronary angiographic analysis

Angiographic analysis was performed by the JCICL. Matched orthogonal views (> 30°) were used for the quantitative coronary analysis (QCA) before and after treatment. Angiography was analyzed offline with a validated automated edge detection system with dedicated bifurcation software (QAngio XA ver 7.2; Medis Medical Imaging Systems BV, Leiden, the Netherlands). QCA was performed at baseline, after stent implantation, and at the 8-month follow-up. All parameters were calculated for the 5-mm lengths proximal and distal to the stented segment. In-segment restenosis was defined as a lumen diameter stenosis ≥ 50% at any of the

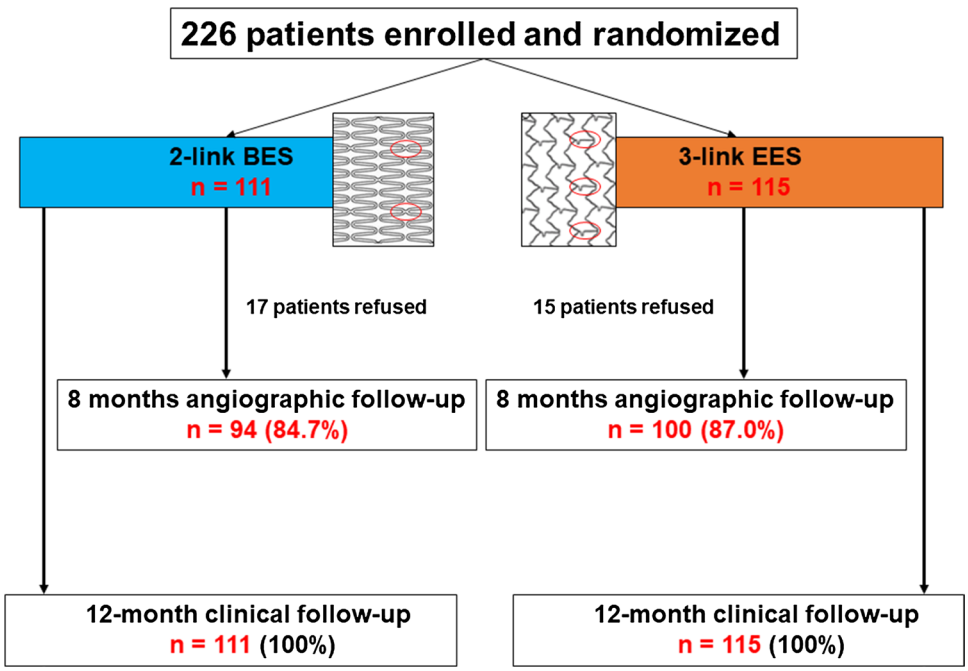

Fig. 1 Patient flow chart and 12-month clinical follow-up of the BEGIN trial. No reliable data are available on the assessment criteria for patient enrollment. *BES* biolimus A9-eluting stent, *EES* everolimus-eluting stent

following sites: (1) inside the stent; (2) within 5 mm proximal or distal to the stent; (3) within the proximal 5 mm of the non-stented SB; or (4) at the site of balloon inflation in the SB. In-stent late luminal loss was defined as the difference between minimal lumen diameter (MLD) immediately after the procedure and at 8 months later. TIMI frame counts at baseline, after crossover stenting in MV, and immediately after the procedure were measured at the JCICL.

Study endpoints and definitions

The primary endpoint of the study was angiographic MLD at the SBO at 8 months. The secondary endpoint was the occurrence of major adverse cardiac events (MACE) defined as the composite of cardiac death, Q-wave or non-Q-wave MI, or target vessel revascularization (TVR) at 12 months. Q-wave MI was defined as the development of new pathological Q-waves in 2 or more contiguous leads with above-normal CK or CK-MB levels. Non-Q-wave MI was defined as an elevation of CK levels to ≥ 2 times the normal levels with elevated CK-MB in the absence of pathological Q waves. Stent thrombosis (ST) was defined as an MI attributable to the target vessel with angiographic documentation of thrombus or total occlusion at the target site that had been classified according to the Academic Research Consortium (ARC) definition. The protocol definition of ST in the current study corresponds with the ARC definition of definite ST. The clinical endpoints were adjudicated by an independent committee that was blinded to treatment allocation after review of the original source documentation.

Statistical analysis

The BEGIN trial was designed to evaluate the differences between 2-link and 3-link DES designs in terms of SB treatment for CBLs. To do this, angiographic MLD at the SBO 8 months after PCI was the primary endpoint. We hypothesized that the design of the 2-link BES platform, because of its higher possibility of dilating the side cells than that of the 3-link EES, could improve the angiographic results at the SB orifice. Until March 2012 when the BEGIN protocol was confirmed, no published data in the literature were available for mid-term QCA data regarding SB orifice after BES or EES, thus limiting the strength of the sample size calculations. Based on the previous CACTUS trial, the mid-term angiographic MLD at the SBO after contemporary DES implantation for CBLs was assumed to be 1.5 ± 0.5 mm. To achieve an 80% power to detect a 13.3% increase in MLD at the SBO using 2-link BES instead of 3-link EES at a level of significance of two-sided 5% using a 2-sample *t* test, we needed a sample size of 120 patients per group (240 total). The statistical analysis of the primary endpoint consisted of a total of 192 lesions/patients, which reduced the power of the study to 78.7%. Continuous variables are summarized as mean ± standard deviation (SD), and categorical variables are presented as frequency and percentage. For intergroup comparisons, a 2-sample t-test was used for continuous variables and Fisher's exact test was used for categorical variables. For time-to-event endpoints, the Kaplan–Meier method was used for the summary presentation and the log-rank test was used for 2-group comparisons. p values < 0.05 were considered statistically significant. All statistical analyses were performed by independent statisticians (AC Medical Inc., Tokyo, Japan) with the use of statistical software (SAS version 9.3; IBM, Cary, NC, USA).

Results

Patient characteristics and revascularization procedure

Between April 2012 and May 2014, a total of 226 patients were randomized to receive PCI with the 2-link BES ($n = 111$) or the 3-link EES ($n = 115$). The patients' baseline clinical characteristics are shown in Table 1. Most of these characteristics were similar between the two groups except for hypertension rate and warfarin intake, which were significantly higher in the 2-link BES group. Lesion and procedure characteristics are shown in Table 2. No difference was observed except for the use of the 2.75-mm stent (2-link BES vs. 3-link EES: 7.2% vs. 19.1%, $p = 0.008$) and stent inflation pressure in the MV (2-link BES vs. 3-link EES: 11.0 ± 3.4 vs. 12.0 ± 3.8 atm, $p = 0.045$). CBLs were similarly located between 2-link BES and 3-link EES in the LMCA (13.5% vs. 13.0%) as well as the left descending anterior artery (63.1% vs. 60.0%). Medina classification (1.1.1) was identically prevalent (2-link BES vs. 3-link EES: 70.3 vs. 67.0%, respectively). Almost patients underwent IVUS-guided bifurcation PCI both before and after the procedure (94.6% vs. 89.6%, $p = 0.539$). Single crossover stenting with FKI was the main strategy (66.7% vs. 73.0%). The 2-stent technique was similarly used (30.6% vs. 22.6%). FKI was similarly performed in both groups (97.3% vs. 95.7%, $p = 0.722$) with similar balloon diameter and pressure for both vessels. After the procedure, the maximum CK was similar between the two groups.

Angiographic analysis

The QCA results are shown in Table 3. Angiographic measurements of the proximal MV, bifurcation core, distal MV, and the SB at baseline and immediately after the procedure were similar in the two groups. Follow-up angiography was performed in 94 patients (84.7%) in the 2-link BES group and 100 patients (87.0%) in the 3-link EES group

Table 1 Patient clinical background

	2-link BES ($n=111$)	3-link EES ($n=115$)	p value
Age (years)	70 ± 10	69 ± 10	0.676
Male	87 (78.4)	83 (72.2)	0.286
Body mass index	24.6 ± 4.4	24.1 ± 3.3	0.373
Hypertension	88 (79.3)	71 (61.7)	0.005
Dyslipidemia	84 (75.7)	89 (77.4)	0.875
Diabetes mellitus	43 (38.7)	50 (43.5)	0.501
Diet	7 (6.3)	3 (2.6)	0.408
Oral hypoglycemic agent	27 (24.3)	39 (33.9)	
Insulin required	8 (7.2)	8 (7.0)	
Current smoking	18 (16.2)	14 (12.2)	0.310
Previous			
PCI	45 (40.5)	41 (35.7)	0.494
CABG	2 (1.8)	3 (2.6)	1.000
Ischemic stroke	14 (12.6)	12 (10.4)	0.679
Myocardial infarction	23 (20.7)	20 (17.4)	0.611
Peripheral artery disease	7 (6.3)	4 (3.5)	0.621
Family history of CAD	13 (11.7)	13 (11.3)	1.000
LV ejection fraction, %	61.7 ± 11.2	62.9 ± 10.0	0.413
Present status			
Stable angina pectoris	83 (74.8)	90 (78.3)	0.430
Unstable angina pectoris	8 (7.2)	11 (9.6)	
Silent myocardial ischemia	20 (18.0)	14 (12.2)	
Medication			
Statin	66 (59.5)	65 (56.5)	0.614
β blocker	37 (33.3)	28 (24.3)	0.124
ARB	51 (45.9)	39 (33.9)	0.066
ACE inhibitor	24 (21.6)	20 (17.4)	0.452
Warfarin	15 (13.5)	6 (5.2)	0.039

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *BES* biolimus-eluting stent, *CABG* coronary artery bypass graft surgery, *CAD* coronary artery disease, *EES* everolimus-eluting stent, *LV* left ventricle, *PCI* percutaneous coronary intervention

($p=0.729$). The median duration of the angiographic follow-up was 248 days (interquartile range, 244–271 days) in the 2-link BES and 253 days (range, 245–271 days) in the 3-link EES group ($p=0.314$). At 8 months, MLD at the SBO (the primary study endpoint) of the 2-link BES group was similar to that of the 3-link EES group (1.64 ± 0.50 mm vs. 1.63 ± 0.51 mm, $p=0.976$; Fig. 2). Other QCA results (MLD, DS, 8-month in-segment restenosis rate, and late lumen loss) were also similar between the 2 groups in the proximal MV, bifurcation core, distal MV, and SB. Restenosis at the SBO was 6.5% in the 2-link BES and 4.0% in the 3-link EES ($p=0.527$) (Table 3). Before the procedure, TIMI frame count in the 2-link BES group was significantly higher compared to that in the 3-link EES group (27.4 ± 12.5 vs. 24.3 ± 9.6, $p=0.043$) but similar after MV stenting and the post-procedure. The TIMI frame count in the SB was identical before the procedure, post-MV stenting, and immediately after the procedure.

Clinical outcome

Major clinical events during follow-up are summarized in Table 4. All patients completed the 12-month clinical follow-up. At 12 months, the incidence of MACE did not significantly differ between the 2-link BES and 3-link EES groups (7.4% vs. 8.0%, $p=0.894$). Kaplan–Meier curves of MACE are shown in Fig. 3. No difference was identified between groups for MI, TVR, and TLR for target CBLs. During 12 months of follow-up, 1 BES- and 2 EES-treated patients experienced stent thrombosis (Table 5).

Sub-analysis of clinical outcome and QCA at the SBO in LMCA bifurcation

To examine the relationship between the SB RD and outcome of the 2-link and 3-link stents, we performed a subanalysis of LMCA CBLs (Table 6). The baseline RD of the SB was significantly higher in LMCA than in non-LMCA (2.54 ± 0.54 vs. 2.08 ± 0.41 mm, $p<0.001$). In LMCA CBLs, the 3.5-mm stent design was mainly deployed (2-link BES vs. 3-link EES; 73% vs. 80%, $p=0.666$); whereas in non-LMCA, the 2.5–3.0-mm stent design was implanted in 32% in 2-link BES groups and 21% in 3-link EES group ($p=0.073$). With respect to the clinical outcome and QCA at 8 months, no difference was observed between the 2 groups in either LMCA or non-LMCA subgroups.

Discussion

This prospective, randomized trial compared the efficacy of 2-link BES and 3-link EES deployment for the management of de novo true CBLs. Two-link BES and 3-link EES demonstrated similar MLD at the SBO at the 8-month angiographic follow-up. Both stent platforms exhibited similar outcomes for the clinical endpoint at the 12-month follow-up, suggesting that both devices were similarly effective in the treatment of true CBLs.

In a bench test using an LMCA bifurcation model, a 2-link cell design Nobori was superior to a 3-link Xience for reducing ISA at the SBO [7]. Another bench test reported that the likelihood of complete SBO dilation by the FKI was higher using a 2-link than a 3-link stent system, which incurred the risk of jailed struts remaining [6]. From the perspective of stent deformation in the proximal MV induced by overdilation of hugging FKI balloons, the 3-link design maintained its structure, whereas the 2-link system was widely opened and each strut were separated, which might cause DES efficacy loss due to polymer injury or decreased

Table 2 Lesion and procedure characteristics

	2-link BES ($n=111$)	3-link EES ($n=115$)	p value
Target vessel			0.843
Left main coronary artery	15 (13.5)	15 (13.0)	
Left descending anterior artery	70 (63.1)	69 (60.0)	
Left circumflex artery	14 (12.6)	14 (12.2)	
Right coronary artery	11 (9.9)	16 (13.9)	
Trans-radial approach	87 (78.4)	90 (78.3)	1.000
Trans-brachial approach	3 (2.7)	3 (2.6)	
Trans-femoral approach	21 (18.9)	22 (19.1)	
Medina classification			
(0.1.1)	22 (19.8)	27 (23.5)	0.813
(1.0.1)	11 (9.9)	11 (9.6)	
(1.1.1)	78 (70.3)	77 (67.0)	
TIMI flow grade in main vessel[a]			0.653
− 0	0 (0)	0 (0)	
− 1	1 (1.8)	2 (1.8)	
− 2	12 (10.9)	7 (6.3)	
− 3	94 (85.5)	101 (91)	
TIMI flow grade in side branch[a]			0.647
− 0	0 (0)	0 (0)	
− 1	0 (0)	2 (1.8)	
− 2	6 (5.5)	4 (3.6)	
− 3	102 (92.7)	104 (93.7)	
IVUS use (both pre- and post-procedure)	105 (94.6)	103 (89.6)	0.539
Pre-dilation for main vessel	106 (95.5)	109 (94.8)	1.000
Pre-dilation for side branch[a]	61 (55.5)	60 (54.1)	0.608
Proximal optimization technique[a]	5 (4.5)	11 (9.9)	0.112
Stent deployment technique			0.496
Single crossover stenting with FKI	74 (66.7)	84 (73.0)	
Single crossover stenting without FKI	2 (1.8)	5 (4.3)	
Provisional culottes stenting	21 (18.9)	16 (13.9)	
Provisional T-stenting	2 (1.8)	1 (0.9)	
Elective culottes stenting	9 (8.1)	9 (7.8)	
Elective T-stenting	2 (1.8)	0 (0)	
Stent diameter in main vessel, mm	3.1 ± 0.4	3.0 ± 0.4	0.544
Stent diameter in main vessel: 2.5 mm	25 (22.5)	23 (20.0)	0.643
2.75 mm	8 (7.2)	22 (19.1)	0.008
3.0 mm	36 (32.4)	35 (30.4)	0.746
3.5 mm	42 (37.8)	33 (28.7)	0.145
Stent inflation pressure in main vessel, atm	11.0 ± 3.4	12.0 ± 3.8	0.045
Additional stenting for main vessel	25 (22.5)	21 (18.3)	0.509
Proximal to first stent	9 (8.1)	11 (9.6)	0.371
Distal to first stent	16 (14.4)	10 (8.7)	
Final kissing balloon inflation	108 (97.3)	110 (95.7)	0.722
Balloon diameter in main vessel, mm	3.0 ± 0.4	3.0 ± 0.4	0.358
Balloon pressure in main vessel, atm	10.0 ± 3.6	10.7 ± 4.3	0.254
Balloon diameter in side branch, mm	2.4 ± 0.3	2.4 ± 0.4	0.809
Balloon pressure in side branch, atm	9.5 ± 3.4	10.0 ± 3.7	0.248
Dissection in side branch ostium[a]	5 (4.5)	8 (7.2)	0.284
Max CPK-MB, ng/Ml	16.5 ± 21.8	16.0 ± 25.2	0.582

BES biolimus-eluting stent, *CPK-MB* creatine phosphokinase-MB isozyme, *EES* everolimus-eluting stent, *FKI* final kissing balloon inflation, *IVUS* intravascular ultrasonography, *TIMI* Thrombolysis in Myocardial Infarction Trial

[a]Core laboratory analysis

Table 3 Quantitative coronary angiography analysis

	2-link BES ($n=111$)	3-link EES ($n=115$)	p value
Proximal main vessel			
Reference diameter (mm)	3.1 ± 0.5	3.0 ± 0.5	0.767
Lesion length (mm)	6.7 ± 4.4	6.8 ± 4.9	0.807
Minimum lumen diameter, mm			
Before procedure	2.0 ± 0.8	2.1 ± 0.8	0.266
Immediately after procedure	3.0 ± 0.6	3.0 ± 0.6	0.877
8-month follow-up	2.9 ± 0.6	2.8 ± 0.6	0.764
Diameter stenosis (%)			
Before procedure	34.7 ± 21.0	31.0 ± 21.1	0.196
Immediately after procedure	11.3 ± 8.8	11.4 ± 8.6	0.983
8-month follow-up	13.4 ± 11.1	13.0 ± 9.8	0.802
Restenosis, *n/N* (%)	0/93 (0)	1/99 (1.0)	1.000
Late lumen loss, mm	0.127 ± 0.344	0.092 ± 0.330	0.486
Bifurcation core			
Reference diameter (mm)	2.9 ± 0.5	2.9 ± 0.5	0.965
Lesion length, mm	3.8 ± 1.1	3.7 ± 1.0	0.394
Minimum lumen diameter (mm)			
Before procedure	1.2 ± 0.5	1.3 ± 0.6	0.103
Immediately after procedure	2.8 ± 0.5	2.8 ± 0.5	0.505
8-month follow-up	2.7 ± 0.5	2.7 ± 0.4	0.452
Diameter stenosis (%)			
Before procedure	57.3 ± 17.9	53.7 ± 18.0	0.133
Immediately after procedure	16.1 ± 9.4	16.1 ± 9.4	0.947
8-month follow-up	17.3 ± 9.5	18.8 ± 9.5	0.291
Restenosis, *n/N* (%)	0/93 (0)	0/99 (0)	–
Late lumen loss (mm)	0.111 ± 0.349	0.096 ± 0.297	0.749
Distal main vessel			
Reference diameter (mm)	2.5 ± 0.4	2.6 ± 0.4	0.566
Lesion length (mm)	9.8 ± 8.9	10.1 ± 9.4	0.867
Minimum lumen diameter (mm)			
Before procedure	1.2 ± 0.4	1.2 ± 0.5	0.741
Immediately after procedure	2.1 ± 0.4	2.1 ± 0.4	0.399
8-month follow-up	2.1 ± 0.4	2.1 ± 0.4	0.799
Diameter stenosis (%)			
Before procedure	52.5 ± 16.4	52.8 ± 17.0	0.874
Immediately after procedure	22.2 ± 11.2	20.9 ± 11.3	0.375
8-month follow-up	21.4 ± 11.0	20.8 ± 9.3	0.694
Restenosis, *n/N* (%)	3/93 (3.2)	0/98 (0)	0.112
Late lumen loss, mm	−0.011 ± 0.298	0.018 ± 0.269	0.749
Side branch			
Reference diameter (mm)	2.1 ± 0.4	2.1 ± 0.5	0.904
Lesion length (mm)	7.6 ± 5.7	7.1 ± 5.4	0.598
Minimum lumen diameter (mm)			
Before procedure	1.1 ± 0.5	1.1 ± 0.4	0.843
Immediately after procedure	1.6 ± 0.5	1.6 ± 0.6	0.946
8-month follow-up	1.5 ± 0.5	1.5 ± 0.4	0.810
Diameter stenosis (%)			
Before procedure	49.3 ± 19.0	48.4 ± 17.0	0.703
Immediately after procedure	27.8 ± 15.3	27.1 ± 13.1	0.736
8-month follow-up	28.4 ± 15.8	26.6 ± 14.3	0.421
Restenosis, *n/N* (%)	9/93 (9.7)	4/99 (4.0)	0.154
Restenosis at the ostium (< 5 mm), *n/N* (%)	6/93 (6.5)	4/99 (4.0)	0.527
Late lumen loss, mm	−0.005 ± 0.298	0.004 ± 0.329	0.834
TIMI frame count			
Main vessel			
Before procedure	27.4 ± 12.5	24.3 ± 9.6	0.043
Post-stenting in main vessel	20.2 ± 8.6	20.5 ± 12.3	0.880
Immediately after procedure	20.2 ± 6.0	21.8 ± 10.1	0.164
Side branch			
Before procedure	23.6 ± 8.7	22.6 ± 8.5	0.387
Post-stenting in main vessel	19.7 ± 8.2	19.1 ± 6.4	0.652
Immediately after procedure	18.8 ± 5.4	19.0 ± 6.6	0.779

Restenosis is defined as a lesion with stenosis > 50% diameter in a segment at the 8-month angiography follow-up

BES biolimus A9-eluting stent, *EES* everolimus-eluting stent, *TIMI* thrombolysis in myocardial infarction

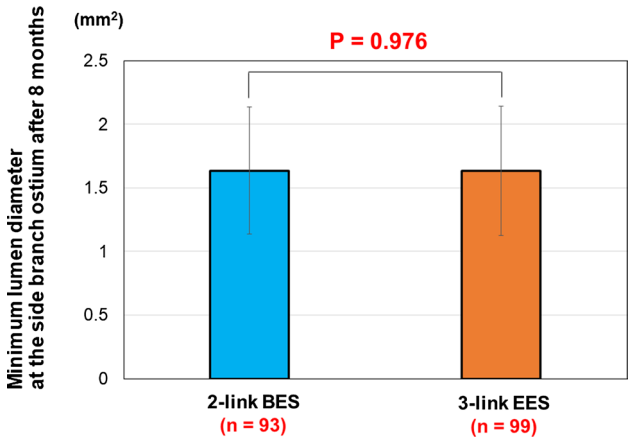

Fig. 2 Primary endpoint, minimum lumen diameter at the side branch ostium at 8 months, comparing 2-link BES (blue) and 3-link EES (orange). *BES* biolimus A9-eluting stent, *EES* everolimus-eluting stent

Table 4 Clinical outcomes at 1 year

	2-link BES ($n=111$)	3-link EES ($n=115$)	p value
Major adverse cardiovascular events	8 (7.4)	9 (8)	0.894
Cardiac death	0 (0)	1 (0.9)	0.339
Non-cardiac death	0 (0)	0 (0)	–
Myocardial infarction	4 (3.6)	3 (2.6)	0.654
Target vessel revascularization	8 (7.6)	7 (6.2)	0.573
Target lesion revascularization	5 (4.8)	3 (2.7)	0.280
TLR for target bifurcation	4 (3.8)	2 (1.8)	0.378
Stent thrombosis	1 (0.9)	2 (1.7)	1.000

BES biolimusA9-eluting stent, *EES* everolimus-eluting stent, *TLR* target lesion revascularization. Data were analyzed by the log-rank test

drug penetration [6]. For 2.5–3.0-mm stents, both of the 2-link Nobori and 3-link Xience have 6 crowns. However, for the 3.5-mm stent, the 2-link Japanese version Nobori has 10 crowns, whereas the 3-link Xience has 9 crowns. A higher number of crowns (i.e., 10 crowns in the Nobori) has the merit to attenuate widely separated each strut by overexpansion of hugging balloon by FKI in proximal MV. Furthermore, the 3.5-mm stents with 10 crowns in the 2-link Nobori system were better equipped to widely open the SB strut than those with 9 crowns in the 3-links Xience system (4.2 mm Nobori vs. 3.6 mm Xience). In a previous bench test, MV overdilation by FKI has been reported to induce polymer injury as shown by electron microscopy analysis [14]. In this regard, it is unknown whether abluminal biodegradable polymer of Nobori or the fully coated durable polymer of Xience after overdilation by FKI is associated

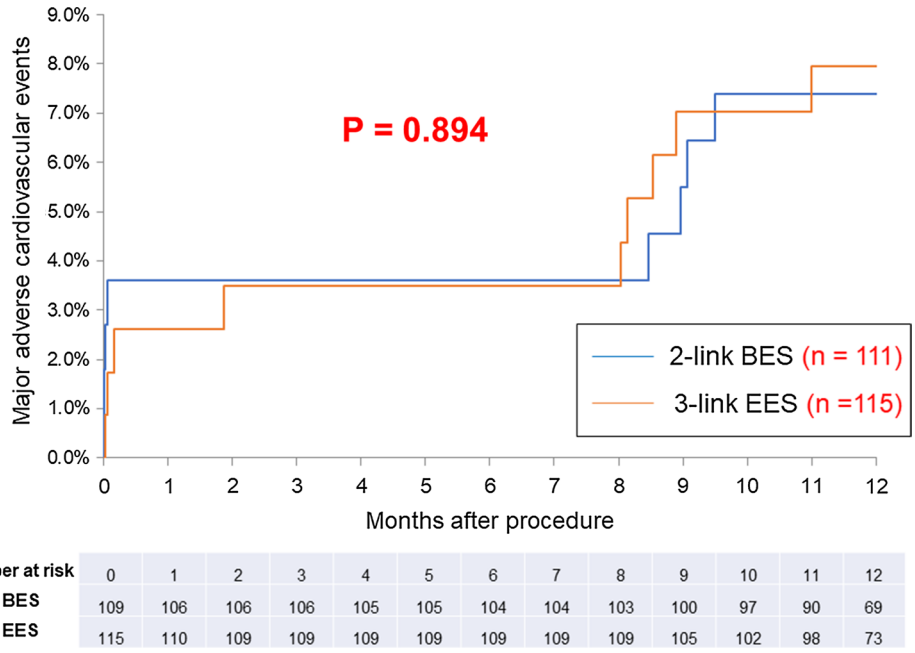

Fig. 3 Kaplan–Meier analysis of major adverse cardiovascular events over 12 months comparing patients with coronary bifurcation lesions treated with 2-link BES (blue line) and those treated with 3-link EES (orange line). Major adverse cardiovascular events are defined as a composite endpoint of cardiac death, Q-wave or non-Q-wave myocardial infarction, or target vessel revascularization. *BES* biolimus A9-eluting stent, *EES* everolimus-eluting stent

Table 5 Stent thrombosis

Patient	1	2	3
Stent	3-link EES	2-link BES	3-link EES
Technique	Single crossover stenting with FKI	Elective T stenting	Single crossover stenting with FKI
Staged PCI for another vessel	Yes	Yes	No
Day from procedure	2	2	5
DAPT at time of stent thrombosis	Yes	Yes	Yes
Number of stent in target vessel	2	2	1
Lesion location	LAD diagonal	LAD diagonal	LAD diagonal
Clinical consequence	MI and TLR	MI and TLR	MI and TLR

BES biolimus-eluting stent, *DAPT* dual antiplatelet therapy, *EES* everolimus-eluting stent, *FKI* final kissing balloon inflation, *LAD* left anterior descending artery, *MI* myocardial infarction, *TLR* target lesion revascularization

Table 6 Sub-analysis of left main coronary artery bifurcation. Quantitative coronary angiography for the side branch and 1-year clinical outcome

	Left main coronary artery bifurcation			Non-left main coronary artery bifurcation		
	2-link BES	3-link EES	*p* value	2-link BES	3-link EES	*p* value
3.5 mm stent, *n*/*N* (%)	11/15 (73)	12/15 (80)	0.666	31/96 (32)	21/100 (21)	0.073
Quantitative coronary angiography						
Minimum lumen diameter in the side branch						
Before procedure, mm	1.36 ± 0.52	1.45 ± 0.47	0.599	1.10 ± 0.48	1.11 ± 0.39	0.855
Immediately after procedure, mm	2.15 ± 0.63	2.19 ± 0.66	0.893	1.70 ± 0.57	1.65 ± 0.46	0.552
8-month follow-up, mm	2.04 ± 0.52	2.02 ± 0.77	0.934	1.58 ± 0.47	1.57 ± 0.42	0.935
Diameter stenosis in the side branch						
Before procedure, %	44.8 ± 20.2	41.2 ± 21.7	0.643	47.3 ± 20.5	46.4 ± 16.9	0.746
Immediately after procedure, %	22.0 ± 14.4	19.4 ± 16.3	0.640	22.0 ± 16.9	21.7 ± 14.8	0.894
8-month follow-up, %	20.1 ± 11.2	23.8 ± 20.7	0.507	24.8 ± 15.9	23.7 ± 14.5	0.636
Frequency of the side branch with DS > 50%						
Before procedure, *n*/*N* (%)	6/15 (40)	5/15 (33)	1.000	50/99 (52)	35/96 (35)	0.029
Immediately after procedure, *n*/*N* (%)	1/15 (7)	1/15 (7)	1.000	9/94 (9)	5/95 (5)	0.282
8-month follow-up, *n*/*N* (%)	0/12 (0)	2/14 (13)	0.483	6/81 (6)	2/85 (2)	0.161
Late lumen loss, mm	− 0.02 ± 0.32	0.14 ± 0.77	0.497	0.10 ± 0.30	0.06 ± 0.29	0.352
Clinical outcome at 1 year						
Major adverse cardiovascular event, *n*/*N* (%)	3/15 (20)	2/15 (13)	1.000	5/96 (5)	7/100 (7)	0.768
Target vessel revascularization, *n*/*N* (%)	0/15 (0)	1/15 (7)	1.000	9/96 (9)	6/100 (6)	0.429
Target lesion revascularization, *n*/*N* (%)	0/15 (0)	0/15 (0)	–	5/96 (5)	3/100 (3)	0.491
Stent thrombosis, *n*/*N* (%)	0/15 (0)	0/15 (0)	–	1/96 (1)	2/100 (2)	1.000

DS diameter stenosis

with a better clinical outcome. Strut thickness is larger in Nobori than in Xience.

A previous large all-comer randomized trial demonstrated the non-inferiority of the Nobori system over the Xience system in terms of any TLR at 1-year and death or MI at 3 years [15, 16]. However, randomized studies of EES or BES with other second-generation DES for the treatment of CBLs are lacking. Only single-center retrospective analyses and sub-analyses of a large randomized trial are available [11–13]. To focus on SBO enlargement, we prospectively confirmed the technical consensus because bifurcation PCI requires multiple technical steps, which might influence the SB result. In our study, we adopted the strategy of aggressive treatment for SB. Participant operators were strongly recommended to: (1) cross the guide wire to the distal cell using a DLC and confirm placement under IVUS guidance; (2) perform FKI; (3) reach a consensus of angiographic SB endpoint < 50% immediately after the procedure; and (4) perform the culotte/TAP technique and omit the crush/mini-technique technique, which was reportedly associated with an inadequate SB expansion [3]. Our study is the first randomized CBL trial comparing 2-link and 3-link second-generation DES designs for the management of the SBO, which has been shown to be related to a higher likelihood of restenosis after PCI. Theoretically, 2-link systems are superior to 3-link systems in terms of open jailed SB struts; however, our randomized study could not demonstrate this hypothesis. In clinical outcomes, TVR was also comparable at 1 year (7.6% vs. 6.2%, $p = 0.573$, respectively). Although previous studies were not dedicated trials for CBLs but sub-analyses of large randomized trials without technical consensus of CBLs-PCI, a similar TVR rate was observed in the TWENTE (Xience vs. Resolute: 4.9% vs. 4.0%, $p = 0.66$ at 3 years) and CENTURY-II (Xience vs. Ultimaster: 10.1% vs. 6.3%, $p = 0.34$ at 2 years) studies and a single-center retrospective study (Xience vs. NOBORI; 7.8% vs. 5.8% at 1 year) with comparable other clinical outcomes [11–13]. Results from these previous studies support our data.

In our study, although statistical significance was not established, worse results were observed to be higher in the BES than in the EES regarding SB restenosis (9.7% vs. 4.0%), TLR (4.8% vs. 2.7%), and TLR for target bifurcation (3.8% vs. 1.8%), which were almost twice as those in the EES. Despite the randomized trial design of our study, the baseline SBO stenosis (DS > 50%) rate was higher in the 2-link BES group than in the 3-link EES group in non-LMCA CBLs (Table 6), which might be related to a higher rate of SB restenosis at 8 months in 2-link BES group. However, MLD (1.64 ± 0.50 mm vs. 1.63 ± 0.51 mm, $p = 0.976$; Fig. 2) and binary restenosis (6.5% vs. 4.0%,

$p = 0.527$) at the SBO (< 5 mm from carina) were similar at 8 months. With regard to TLR, a large-scale randomized control trial for CBLs is needed to elucidate the difference of outcomes because our study was statistically underpowered to demonstrate this.

Routine performance of FKI in the 1-stent strategy has been under debate [17, 18]. Nordic-Baltic III showed that FKI following single stenting was related to a lower rate of SB stenosis only in true bifurcation [17]. A recent large registry demonstrated the merits of FKI after 1 stent strategy in clinical outcomes [18]. In our study, the provisional SB approach was the main strategy. FKI was performed in > 95% of cases after single stenting because all bifurcations enrolled in this study were true CBLs with baseline stenosis at the SBO. The true CBLs rates of previous CBLs studies were lower than that in our study [17, 19].

Our results failed to demonstrate the theoretical advantage of 2-link over 3-link systems with respect to 8-month angiographic SB results. This finding might be explained by the following three mechanisms other than stent platform design. First, baseline plaque and calcium distributions might influence SB lumen enlargement immediately after PCI. Pre-/post-procedural volumetric IVUS analysis for MV and SB in the J-REVERSE trial demonstrated that carina shift, not plaque shift, was more frequently observed at the SBO after 1-stenting with FKI [20]. (1) Negative remodeling and a plaque burden at the carina in the distal MV and (2) accumulated plaque at the SBO were pre-procedural IVUS findings to predict residual stenosis at the SBO after FKI [20]. The second point involves the guide wire re-crossing point and stent link location at the SBO before FKI. The 3D optical coherence tomography (OCT) bifurcation registry demonstrated that (1) links connected to the carina and (2) with a higher bifurcation angle (perpendicular SBO observed by 3D-OCT in the MV) were related to an increased risk of ISA at the SBO after FKI, although the guide wire was successfully re-crossed to the distal cell [21]. A link-free configuration on the carina is favorable for SB dilation; however, it is not controllable by operators. In one report, fewer longitudinal links per crown might increase the incidence of the favorable link-free configuration on the carina (2-link Nobori vs. 3-link Xience, 56.3% vs. 40.0%, respectively) [21]. However, in our study, this advantage in 2-link design was not associated with procedure angiographic outcome. Nagoshi reported that distal re-wiring was achieved in approximately 91.7% under 3D-OCT guidance versus 75.6% under 2D-OCT guidance ($p = 0.004$) [22]. We used DLC under fluoroscopic and IVUS guidance. Although no data are available regarding the appropriate wire re-crossing point in our study, these technical issues might influence the SB results. The third issue is POT. POT may facilitate distal re-wiring and improve proximal apposition [21]. Thus, the relatively lower use of POT before FKI might affect the distal re-crossing rate in our study.

Conclusion

In this multicenter randomized trial of the treatment of complex true CBLs, 2-link BES did not appear superior to 3-link EES with respect to 8-month maintenance of SB ostial enlargement despite aggressive treatment for SB.

Limitation

Our study has several limitations. First, the major limitation is its sample size, which was smaller than the number established prior to commencement due to low recruitment as observed in a previous randomized trial [23]. With the final sample size, the power of the statistical test was 78.7% based on the initial assumption of a 0.2-mm difference in primary endpoint (MLD at the SBO). Thus, the study has substantial power to detect the assumed difference. Moreover, the post hoc power calculation elucidated that 2 million lesions are needed to achieve 80% power to detect a 0.002-mm difference in the primary endpoint, which was an estimated difference from the actual data. This consideration suggests the validity of our conclusion regardless of the sample size. Second, angiographic outcomes have potential limitations. There is a discrepancy between QCA and physiological ischemia at the SBO [24]. Physiological assessments for myocardial ischemia were not performed in this trial. Third, the actual pre-procedural SB diameter measured in the core laboratory was approximately 2.1 mm. In previous bench test, a significant difference of ISA at the SBO in favor of the Nobori over the Xience system was demonstrated in the model of 3.5-mm SB diameter [7]. Even in LMCA sub-analysis, SB diameter was 2.54 ± 0.54 in the present study, suggesting that CBLs with SB diameter 3.5 mm or more are less frequently treated in daily practice. Fourth, this trial was not based on an all-comer design; thus, selection bias was introduced. Fifth, the clinical follow-up period was short (only 12 months). A long follow-up period is required to confirm the continuing durability of these devices.

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