



# Comparison of Drug-Eluting Balloon Followed by Bare Metal Stent with Drug-Eluting Stent for Treatment of de Novo Lesions: Randomized, Controlled, Single-Center Clinical Trial

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The combined use of a drug-eluting balloon (DEB) and a bare metal stent (BMS) for the treatment of de novo non-small vessel coronary artery diseases (CAD) remains to be evaluated. We investigated the efficacy of a sequential treatment using a DEB together with a BMS implantation in comparison to a zotarolimus-eluting stent (ZES). This study was a prospective, randomized, open-label study. We designed it to demonstrate the non-inferiority of a sequential treatment using a DEB first followed by a BMS (DEB + BMS) compared with the use of a ZES. The primary endpoint was in-segment late loss (LL) at 9 months measured by quantitative coronary angiography (QCA). A total of 180 patients were enrolled in the study. The 9-month follow-up angiography was performed in 72 patients with DEB + BMS and 74 patients with ZES. When comparing the DEB + BMS results with the ZES ones, LL was  $0.50 \pm 0.46$  mm in DEB + BMS patients vs.  $0.21 \pm 0.44$  mm in ZES patients ( $P < 0.001$ ). The mean difference of the LL was 0.31 mm, which was larger than the prespecified non-inferiority margin of 0.19 mm, and the 2-sided 95% confidence interval was 0.15–0.48. The clinical outcomes were not significantly different. In conclusion, the DEB + BMS strategy is inferior to the ZES one in terms of the LL result at 9 months. The DEB strategy for de novo coronary artery lesions needs to be improved for it to become an alternative treatment option. This was a clinical trial study and was registered at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) (Identifier: NCT01539603; <http://www.clinicaltrials.gov/ct2/show/NCT01539603>).

**Keywords:** Drug-eluting Balloon; Bare Metal Stent; Drug-eluting Stent; In-segment Late Loss; Coronary Artery Disease

## INTRODUCTION

Percutaneous coronary interventions (PCIs) using bare metal stents (BMS) have raised concerns of restenosis of the lesion treated percutaneously (1,2). Although the use of drug-eluting stents (DES) has reduced the occurrence rate of restenosis and the subsequent need for repeat revascularization (3), the delayed vascular healing due to incomplete re-endothelialization, persistence of polymer, and the ongoing vascular inflammation after DES implantation represent challenges (4,5). The persistent presence of polymer in the vessel wall and a late catch-up phenomenon or accelerated neoatherosclerosis over time have all raised concerns about the extensive use of DES (6-8).

In contrast to DES, the drug-eluting balloon (DEB), a non-stent-based local antiproliferative drug-delivery system, works by locally releasing a controlled dose of drug, which is homogeneously distributed to the entire injured vessel wall and is not limited to the surface area adjacent to a stent strut (9). Compared to a standard uncoated balloon, a paclitaxel-coated balloon sig-

nificantly reduced neointimal proliferation and the need for target vessel revascularization in an in-stent restenosis (ISR) setting (10). Furthermore, the DEB was superior to DES with late lumen loss, and was associated with fewer adverse clinical events during the treatment of coronary ISR (11). Moreover, promising clinical data are available for the stand-alone use of the DEB in small vessel coronary disease (12) and bifurcation lesions (13). In a trial of de novo coronary artery lesions, a BMS mounted on a DEB was compared to a sirolimus-eluting stent in patients with stable and unstable angina. However, the per protocol analysis of this trial revealed that the BMS pre-mounted on DEB strategy did not meet the non-inferiority criteria when compared with the sirolimus-eluting stent (14). In the trial, drugs might be inappropriately delivered and unevenly distributed to the diseased vessel wall because of the pre-mounted stent strut. This might diminish the efficacy of the DEB that had been shown in the previous studies. Therefore, we investigated a different protocol in which a DEB is treated first followed by the BMS implantation (DEB + BMS) as opposed to the DES implantation alone.

## MATERIALS AND METHODS

### Study design

This is a prospective, randomized, open-label trial to demonstrate the non-inferiority of using a paclitaxel-coated balloon (Sequent® Please; B. Braun, Melsungen, Germany) first followed by BMS implantation (Coroflex® Blue; B. Braun) compared with a zotarolimus-eluting stent (ZES, Resolute Integrity™; Medtronic, Brooklyn Park, MN, USA) in de novo coronary lesions.

The protocol of the trial has been registered at <http://www.clinicaltrials.gov> (NCT01539603), and a brief flowchart of the study is summarized in Fig. 1. We designed this trial in 2010. We enrolled the first patient in April, 2011 and the final patient in September, 2013.

### Endpoints

The primary endpoint of the study is the in-segment late loss (LL) at 9 months measured by quantitative coronary angiography (QCA). The secondary endpoints include angiographic findings such as angiographic success, device success, binary angiographic restenosis, and clinical outcomes such as procedural success, death of all causes, myocardial infarction, target vessel revascularization, target lesion revascularization, and stent thrombosis.

### Patient population

Patients of at least 18 years of age, who had stable angina or acute coronary syndrome (unstable angina or non-ST segment elevation myocardial infarction [NSTEMI]) of documented ischemia due to a significant lesion in a native coronary artery, were included in this study. Patients were eligible for inclusion if the native coronary lesion was greater than 50% diameter stenosis by visual estimation of the coronary angiogram with reference diameter between 2.5 mm and 4.0 mm and lesion length less than 28.0 mm. The following conditions were excluded from the study: ST-segment elevation myocardial infarction, unprotected left main lesion, ISR, intended bifurcation stenting, cardiogenic shock, chronic total occlusions, history of cerebrovascular accident or myocardial infarction within 1 year, and pregnancy. If all the inclusion criteria were met and none of the exclusion criteria applied, the patients were asked for their written informed consent, as required by the Institutional Review Board in accordance with the Declaration of Helsinki.

### Randomization and interventions

After enrollment, randomization was performed based on a single sequence of random assignments. Computer-generated random numbers were used for the sequence. The random table was concealed and independently managed at the Seoul National University Bundang Hospital Cardiovascular Research Center.

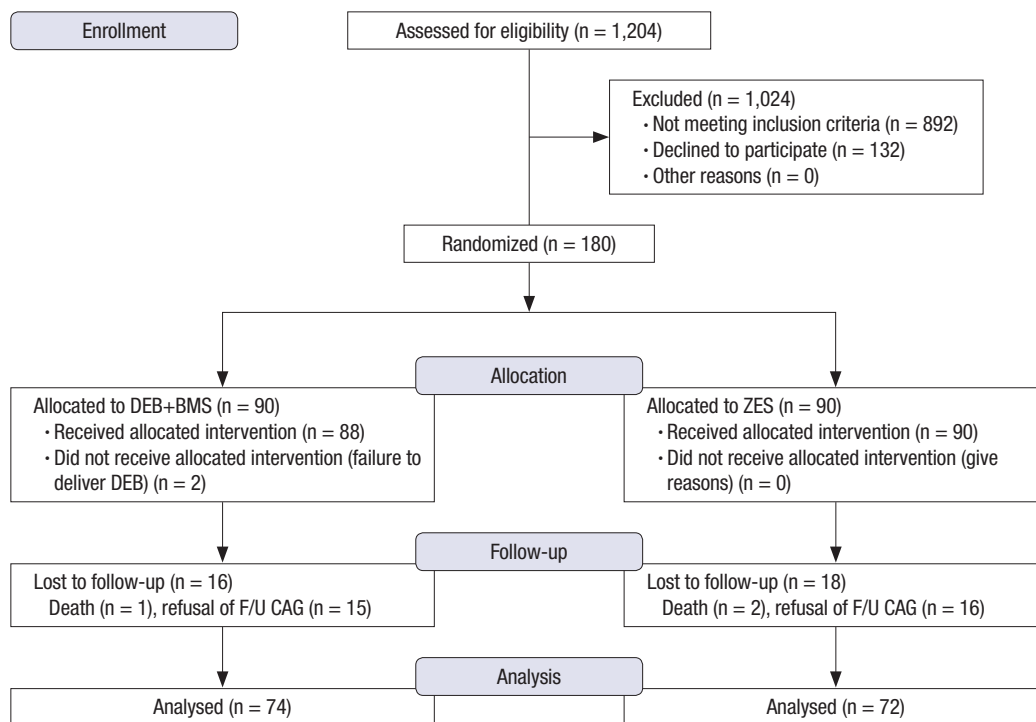


Fig. 1. The flowchart of the trial.

DEB = drug-eluting balloon, BMS = bare metal stent, ZES = zotarolimus-eluting stent, F/U CAG = follow-up coronary angiography.

### Index PCI

All patients received 300 mg aspirin and a loading dose of 300–600 mg clopidogrel before the procedure, unless the patient had been taking these medications for at least 1 week prior to the procedure. Heparin was administered intravenously in boluses to maintain an activated clotting time of > 250 seconds during the procedure. Administration of glycoprotein IIb/IIIa inhibitors was left to the physician's discretion. PCI was performed according to the current international guidelines (15). After obtaining the coronary angiograms, we underwent adequate predilatation of the target lesion with a plain balloon over nominal pressure. After we obtained appropriate results by the plain balloon angioplasty, we treated the full length of the lesion using a DEB over nominal pressure (mean  $\pm$  standard deviation [SD]:  $8.7 \pm 3.2$  atm) at least for 30 seconds (mean  $\pm$  SD:  $46.3 \pm 14.2$  seconds). Type A–D dissections occasionally occurred after the plain balloon angioplasty or DEB within the lesion but they were never extended over the DEB-treated segment. Further, we implanted a BMS (shorter by 5 mm compared with the DEB) within the treated lesion in the DEB + BMS group. We implanted a ZES to encompass the full length of the lesion in the ZES group. Therefore, the length of DEB and ZES was intended to match the lesion length, whereas the length of BMS was shorter than that of DEB to minimize geographic mismatch, and potentially optimize drug delivery to the edge of the BMS. After we implant any type of stent, we applied an adjunctive balloon at high pressure to minimize residual stenosis.

### QCA

The coronary angiograms recorded at baseline and at the 9-month follow-up were analyzed by an independent person who was blinded to the treatment group using an automated edge detection system (CASS 5.7.1; Pie Medical Imaging Systems, Maastricht, Netherlands). In each patient, QCA measures within the stent or the segments (including the stented region and the 5 mm edge regions) were analyzed and reported separately. LL was defined as the difference between the minimum lumen diameter immediately post-procedure and at 9-month follow-up, respectively. Binary restenosis was defined as > 50% diameter stenosis.

### Intravascular ultrasound (IVUS)

An IVUS was recommended to all patients enrolled in the study. We performed an IVUS before DEB or ZES deployment to assess the optimal size of the balloon or stent at index procedure. IVUS imaging was performed with a 20 MHz 2.9 F, phased-array IVUS catheter (Eagle Eye; Volcano Therapeutics, Rancho Cordova, CA, USA) after administering intracoronary nitroglycerin (200 mg). IVUS was also performed after obtaining angiographically optimal results of the index procedure. If the IVUS indicated that the procedural results were not optimal, it was

left to the operator's discretion whether to perform further post-dilatation or bailout stenting.

### Post PCI medication

All the patients included in this trial were treated according to the current American College of Cardiology/American Heart Association (ACC/AHA) guidelines regarding post-stenting management, which specify treatment with at least 100 mg of aspirin daily and 75 mg clopidogrel daily for at least 12 months after PCI (15).

### Follow-up

Clinical follow-up was conducted at 1, 3, 9, and 12 months after index PCI. Routine angiographic follow-up at 9 months (permitted window period:  $\pm$  3 months) was performed. Copies of angiograms were submitted to the angiographic laboratory of the Cardiovascular Research Center, Seoul National University Bundang Hospital.

### Sample size

We designed a trial to show that the DEB + BMS strategy would be non-inferior to the ZES one in terms of luminal LL at the 9-month follow-up. To test the hypothesis that the DEB + BMS is non-inferior to ZES and according to previous studies, we have used the SDs for the luminal LL with 0.51 mm in the DEB + BMS group and 0.26 mm in the ZES group (14,16). The non-inferiority margin was defined as a luminal LL of 0.19 mm. Assuming a 2-sided alpha-level of 0.05 and a statistical power of 80%, and an estimated attrition rate of 20% (for the 9-month angiographic follow-up), we would need a total of 180 patients, 90 patients in the DEB + BMS arm and 90 patients in the ZES arm. This number of patients would also have 85% power to detect superiority with difference luminal LL of 0.2 mm between the groups at a 2-sided alpha-level of 0.05.

### Statistical analysis

All the primary and secondary endpoints were analyzed on an intention-to-treat basis (the patients were analyzed as part of their assigned treatment group) and on per protocol basis (the patients were analyzed as part of their assigned treatment group only if they received their assigned treatment).

The baseline characteristics of the studied patients were summarized in terms of frequencies and percentages for categorical variables and in terms of means with SDs for continuous variables. The categorical variables were compared using the Fisher's exact test. The continuous variables were compared using the independent 2-sample t-test. A *P* value of 0.05 was considered as the level of statistical significance for all the tests.

### Ethics statement

This study has been approved and monitored by the Institution-

**Table 1.** Baseline patient characteristics

Characteristics	Total patients (n = 180)	DEB + BMS (n = 90)	ZES (n = 90)	P value	Patients with F/U angiography (n = 146)	DEB + BMS (n = 74)	ZES (n = 72)	P value
Age, yr	61.8 ± 11.5	61.2 ± 11.1	62.4 ± 11.9	0.457	61.4 ± 11.3	61.3 ± 10.8	61.5 ± 11.9	0.920
Man	131 (72.8)	68 (75.6)	63 (70.0)	0.503	106 (72.6)	57 (77.0)	49 (68.1)	0.267
BMI, kg/m <sup>2</sup>	25.6 ± 3.1	25.6 ± 3.1	25.7 ± 3.2	0.805	25.6 ± 3.1	25.7 ± 3.1	25.6 ± 3.2	0.773
Diabetes	54 (30.0)	28 (31.1)	26 (28.9)	0.871	40 (27.4)	21 (28.4)	19 (26.4)	0.854
Hypertension	65 (36.1)	25 (27.8)	40 (44.4)	0.029	92 (63.0)	54 (73.0)	38 (52.8)	0.016
Dyslipidemia	33 (18.3)	15 (16.7)	18 (20.0)	0.700	28 (19.2)	15 (20.3)	13 (18.1)	0.834
Current smoker	46 (25.6)	27 (30.0)	19 (21.1)	0.211	38 (26.0)	25 (33.8)	13 (18.1)	0.044
Family history of CAD	8 (5.6)	3 (3.3)	5 (5.6)	0.720	6 (4.1)	3 (4.1)	3 (4.2)	1.000
Previous MI	7 (3.9)	3 (3.3)	4 (4.4)	1.000	5 (3.4)	3 (4.1)	2 (2.8)	1.000
Previous PCI	14 (7.8)	5 (5.6)	9 (10.0)	0.405	9 (6.2)	5 (6.8)	4 (5.6)	1.000
Previous CVD	5 (2.8)	4 (4.4)	1 (1.1)	0.368	4 (2.7)	3 (4.1)	1 (1.4)	0.620
Multivessel disease	100 (55.6)	45 (50)	55 (61.1)	0.324	39 (26.7)	38 (51.4)	42 (58.3)	0.498
Clinical indication				0.216				0.362
Stable angina	85 (47.2)	42 (46.7)	43 (47.8)		66 (45.2)	32 (43.2)	34 (47.2)	
Unstable angina	48 (26.7)	20 (22.2)	28 (31.1)		40 (27.4)	18 (24.3)	22 (30.6)	
NSTEMI	47 (26.1)	28 (31.1)	19 (21.1)		40 (27.4)	24 (32.4)	16 (22.2)	
Medication at discharge								
Aspirin	179 (99.4)	89 (98.9)	90 (100.0)	1.000	146 (100.0)	74 (100.0)	72 (100.0)	NA
Clopidogrel	178 (98.9)	88 (97.8)	90 (100.0)	0.497	144 (98.6)	72 (97.3)	72 (100.0)	0.497
Other antiplatelet agent	9 (5.0)	7 (7.8)	2 (2.2)	0.169	8 (5.5)	6 (8.1)	2 (2.8)	0.276
Statin	152 (84.4)	72 (80.0)	80 (88.9)	0.149	124 (84.9)	60 (81.1)	64 (88.9)	0.248
ACE inhibitor	66 (36.7)	34 (37.8)	32 (35.6)	0.877	56 (38.4)	29 (39.2)	27 (37.5)	0.866
ARB	58 (32.2)	34 (37.8)	24 (26.7)	0.151	42 (28.8)	26 (35.1)	16 (22.2)	0.101
Beta-blocker	121 (67.2)	64 (71.1)	57 (63.3)	0.341	94 (64.4)	50 (67.6)	44 (61.1)	0.490
Calcium channel blocker	55 (30.6)	26 (28.9)	29 (32.2)	0.746	43 (29.5)	23 (31.1)	20 (27.8)	0.718

Values are mean ± SD or number (%). P value was calculated using Pearson  $\chi^2$  for categorical variables and Student t-test for continuous variables.

DEB = drug-eluting balloon, BMS = bare metal stent, ZES = zotarolimus-eluting stent, F/U = follow-up, BMI = body mass index, CAD = coronary artery diseases, MI = myocardial infarction, PCI = percutaneous coronary intervention, CVD = cerebrovascular disease, NSTEMI = non-ST segment elevation myocardial infarction, NA = not available, ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blocker, SD = standard deviation.

al Review Board of Seoul National University Bundang Hospital (IRB No. E-1104/061-001). The written informed consent was obtained for all the subjects (Clinical trials registry, Clinical Trials.gov; Identifier, NCT01539603).

## RESULTS

### Patients

Ninety patients were randomized to treatment with DEB + BMS and 90 patients to the ZES implantation alone. The baseline clinical characteristics of all patients were similar in the 2 groups except the presence of hypertension, which was higher in the ZES group (Table 1). There was relatively higher drop-out rate for the 9-month follow-up angiography. However, baseline characteristics of the patients with follow-up angiography were also similar in the 2 groups except the presence of hypertension and current smoker.

### Baseline lesion and procedural characteristics

Before the index procedure, the minimal lumen diameter, reference diameter, percentage diameter stenosis, and lesion length did not differ between the 2 groups (Table 2). Furthermore, fol-

lowing the index PCI, the size and length of DEB and ZES were not different between the 2 groups. In the patients randomized to treatment with DEB + BMS, the length of the BMS was 17.1 mm, on average 5.4 mm shorter than the length of deployed DEB (22.3 mm). We failed to deliver a DEB in 2 patients due to calcification and severe tortuosity of the lesion. In those cases, we inserted a ZES. Moreover, in all the cases the length of the segments treated with paclitaxel-coated balloon catheters exceeded the proximal and distal end of the BMS. The results evidenced a significant decrease in the minimal luminal diameter and less acute gain in the patients treated with DEB + BMS compared with those treated with ZES. The maximal pressure at stent deployment was significantly higher in the DEB + BMS group, because the nominal pressure was 10 atm for the Coroflex<sup>®</sup> Blue stent (B. Braun), compared with 9 atm for the Resolute Integrity<sup>™</sup> stent (Medtronic). Further, the maximal pressure at the adjunctive balloon was not different between the 2 groups.

### QCA

Seventeen DEB + BMS and 16 ZES clinically asymptomatic patients refused the angiographic follow-up. One patient in the DEB + BMS group and 2 patients in the ZES group died before

**Table 2.** Baseline lesion and procedural characteristics

Characteristics	Total (n = 180)	DEB + BMS (n = 90)	ZES (n = 90)	P value
<b>Before index procedure</b>				
Lesion location				0.720
LAD	79 (43.9)	37 (41.1)	42 (46.7)	
LCX	51 (28.3)	26 (28.9)	25 (27.8)	
RCA	50 (27.8)	27 (30.0)	23 (25.6)	
Multivessel intervention	48 (26.7)	23 (25.6)	25 (27.8)	0.866
ACC/AHA B2 or C type	142 (78.8)	69 (76.7)	73 (81.1)	0.884
Minimal luminal diameter, mm	0.89 ± 0.39	0.89 ± 0.45	0.89 ± 0.32	0.926
Reference vessel diameter, mm	2.96 ± 0.52	2.97 ± 0.59	2.96 ± 0.45	0.943
Diameter stenosis, mm	73.0 ± 14.6	72.9 ± 15.1	73.1 ± 14.1	0.951
Lesion length, mm	18.9 ± 5.5	18.9 ± 3.7	18.8 ± 6.9	0.948
<b>After index procedure</b>				
No. of stents per patient	1.32	1.31	1.34	0.934
Stent length per lesion, mm	19.7 ± 6.0	17.1 ± 4.3	22.2 ± 6.4	< 0.001
Stent diameter, mm	3.06 ± 0.41	3.06 ± 0.43	3.06 ± 0.38	0.891
Maximal pressure at stent deployment, atm	10.4 ± 1.9	11.3 ± 1.7	9.7 ± 1.8	< 0.001
Maximal pressure at adjunctive balloon, atm	14.0 ± 4.0	13.9 ± 4.7	14.3 ± 3.3	0.600
DEB diameter, mm	-	3.00 ± 0.38	-	-
DEB length, mm	-	22.3 ± 4.7	-	-
Procedural time, min	56.9 ± 20.1	58.7 ± 23.1	55.2 ± 18.5	0.263
Contrast dye	175.0 ± 62.1	176.2 ± 65.7	173.8 ± 58.6	0.797
Minimal luminal diameter (In-stent), mm	2.55 ± 0.40	2.48 ± 0.42	2.61 ± 0.37	0.022
Minimal luminal diameter (In-segment), mm	2.51 ± 0.41	2.45 ± 0.41	2.57 ± 0.40	0.063
Diameter stenosis (In-stent), mm	12.70 ± 6.00	13.00 ± 5.99	12.40 ± 6.00	0.467
Diameter stenosis (In-segment), mm	12.8 ± 7.1	13.4 ± 7.2	12.1 ± 6.9	0.247
Lesion success	180 (100.0)	90 (100.0)	90 (100.0)	-
Device success	178 (98.9)	88 (97.8)	90 (100.0)	0.497
Procedural success	180 (100.0)	89 (100.0)	90 (100.0)	1.000

Values are mean ± SD or number (%).

DEB = drug-eluting balloon, BMS = bare metal stent, ZES = zotarolimus-eluting stent, LAD = left anterior descending, LCX = left circumflex, RCA = right coronary, ACC/AHA = American College of Cardiology/American Heart Association, SD = standard deviation.

the angiographic follow-up. The angiographic follow-up rate was 81.1%, and was obtained at 298 days after PCI.

Before the index procedure, the minimal lumen diameter, reference diameter, percentage diameter stenosis, and lesion length did not differ between the 2 groups (Table 3, Fig. 2A). After the index PCI, there was significantly decreased minimal luminal diameter and less acute gain in the patients treated with DEB + BMS compared with those treated with ZES. The LL, thus the primary endpoint, was significantly higher in the lesions treated with DEB + BMS than in those treated with ZES ( $0.50 \pm 0.46$  mm vs.  $0.21 \pm 0.44$  mm;  $P < 0.001$ ) (Fig. 2B). The mean difference of the LL was 0.31 mm and 2-sided 95% confidence interval, 0.15–0.48 (Fig. 3), which was higher than the prespecified non-inferiority margin ( $P$  for non-inferiority = 0.138). The binary restenosis rate was also higher in the DEB + BMS group although the result was not statistically significant.

### Subgroup analysis

There was only one patient with chronic kidney disease (CKD) defined by serum creatinine over 1.5 mg/dL. Therefore, we did not perform any subgroup analysis of CKD. Instead, we analyzed the effect of hypertension because the proportion of hyperten-

sion was significantly different between the 2 groups. The subgroup analysis of old age, diabetes mellitus, hypertension, and multivessel stenting demonstrated that the inferiority observed when comparing the DEB + BMS groups with the ZES group was evidenced in all the subgroups as well (Fig. 3, Table 4).

### Clinical follow-up

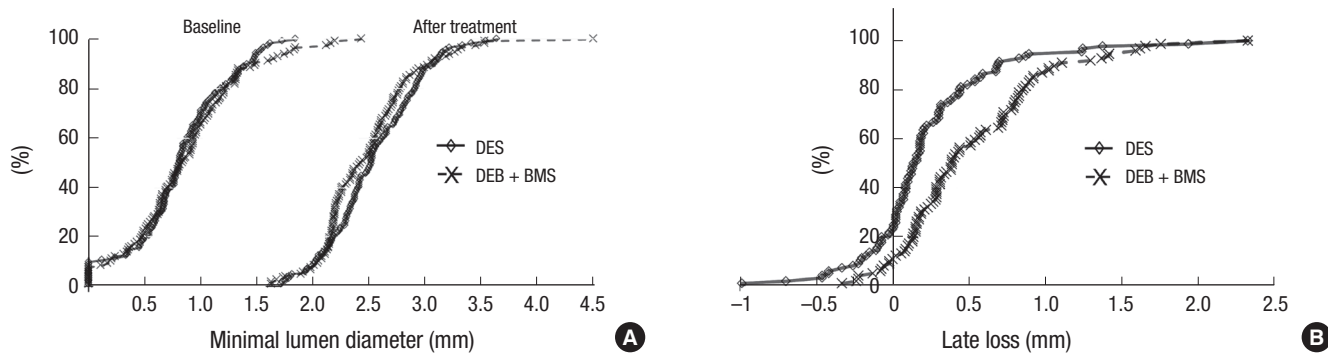
There was no clinical follow-up loss at 12 months (Table 5). Death occurred in one patient (1.1%, non-cardiac; traffic accident) from the DEB + BMS group and in 2 (2.2%, cardiac; both unexplained) from the ZES group. There were 2 myocardial infarctions in the DEB + BMS group. Both cases occurred at admission for the non-cardiac surgery department, and were associated with definite stent thrombosis during cessation of antiplatelet agents. Repeat revascularizations were performed as follows: 1) target lesion revascularization, 5/90 patients (5.6%, DEB + BMS group) and 3/90 patients (3.3%, ZES group); and 2) target vessel revascularization, 5/90 patients (5.6%, DEB + BMS group) and 5/90 patients (5.6%, ZES group). The major adverse cardiac event was defined by the target lesion revascularization, myocardial infarction was attributed to the target vessel, and cardiac death rate was not different when comparing the 2 groups. This study

**Table 3.** QCA analysis (per-patient analysis, index lesion)

Parameters	Total (n = 146)	DEB + BMS (n = 74)	ZES (n = 72)	P value
Before index procedure				
Minimal luminal diameter, mm	0.89 ± 0.40	0.92 ± 0.46	0.86 ± 0.32	0.419
Reference vessel diameter, mm	2.96 ± 0.55	2.98 ± 0.62	2.95 ± 0.46	0.787
Diameter stenosis, mm	72.6 ± 14.8	71.4 ± 14.9	73.8 ± 14.6	0.323
Lesion length, mm	18.7 ± 5.1	18.8 ± 3.8	18.6 ± 6.2	0.819
After index procedure				
Minimal luminal diameter, mm				
In-stent	2.54 ± 0.41	2.48 ± 0.43	2.61 ± 0.37	0.042
In-segment	2.49 ± 0.41	2.43 ± 0.40	2.55 ± 0.41	0.113
Diameter stenosis, mm				
In-stent	12.5 ± 5.87	12.9 ± 5.90	12.0 ± 5.84	0.326
In-segment	12.6 ± 7.12	13.3 ± 7.48	11.8 ± 6.70	0.215
Acute gain, mm				
In-stent	1.66 ± 0.43	1.56 ± 0.45	1.76 ± 0.39	0.010
In-segment	1.60 ± 0.46	1.52 ± 0.46	1.70 ± 0.45	0.033
Follow-up at 9 mon				
Minimal luminal diameter, mm				
In-stent	2.12 ± 0.61	1.93 ± 0.63	2.32 ± 0.53	< 0.001
In-segment	2.10 ± 0.63	1.93 ± 0.59	2.34 ± 0.47	< 0.001
Diameter stenosis, mm				
In-stent	24.5 ± 17.1	30.6 ± 17.8	18.2 ± 13.9	< 0.001
In-segment	24.3 ± 17.7	29.5 ± 16.1	16.5 ± 10.6	< 0.001
Late luminal loss, mm				
In-stent	0.41 ± 0.47	0.54 ± 0.48	0.28 ± 0.43	0.001
In-segment	0.36 ± 0.47	0.50 ± 0.46	0.21 ± 0.44	< 0.001
Binary restenosis				
In-stent	10 (6.8)	8 (10.8)	2 (2.8)	0.098
In-segment	11 (7.5)	9 (12.2)	2 (2.8)	0.056

Values are mean ± SD or number (%).

QCA = quantitative coronary angiography, DEB = drug-eluting balloon, BMS = bare metal stent, ZES = zotarolimus-eluting stent, SD = standard deviation.



**Fig. 2.** Cumulative frequency plot for minimal LL and late lumen loss. (A) Cumulative frequency plot for minimal lumen diameter before and after index procedure. (B) Cumulative frequency plot for late lumen loss before and after index procedure.

LL = late loss, DES = drug-eluting stent, DEB = drug-eluting balloon, BMS = bare metal stent.

was not powered to detect differences in clinical endpoints.

## DISCUSSION

The DEB + BMS strategy did not increase the procedure time or the amount of contrast dye, whereas 2/90 patients failed to obtain procedural success because of decreased crossability over tortuous lesions. As we intended, the DEB + BMS strategy re-

sulted in using DEB and ZES of same length and shorter BMS (BMS < ZES). Unexpectedly, the DEB + BMS strategy led to a decreased post-PCI minimal lesion diameter and less acute gain when compared with the ZES strategy, despite similar maximal pressure at adjunctive ballooning. The 9-month follow-up angiography revealed an inferior LL in the DEB + BMS group when compared with the ZES group. Moreover, the result of death, myocardial infarction, target lesion revascularization, target

vessel revascularization, or stent thrombosis were not different between the 2 groups.

The combination of a paclitaxel-coated balloon plus BMS addresses both issues: 1) a decrease of the neointimal proliferation due to homogenous administration of high concentration paclitaxel to the vessel wall, and 2) a decrease of the risk of stent thrombosis by facilitating a more rapid endothelialization due to the use of a BMS compared to the use of a DES (17). It could reduce the duration of dual antiplatelet therapy (DAPT) use in patients with high risks of bleeding. In the follow-up of the Paclitaxel-Eluting Percutaneous Transluminal Coronary Angioplasty (PTCA)-Balloon Catheter to Treat Small Vessel Coronary Artery Disease (PEPCAD) I study, all the patients received at least 100 mg aspirin daily. Clopidogrel (75 mg/day) was given for one month following stand-alone DEB angioplasty, and for 3 months after additional BMS implantation. In the PEPCAD II study, all the patients received at least 100 mg of aspirin daily lifelong. Clopidogrel (75 mg/day) was given for 3 months after

DEB angioplasty and for 6 months after DES implantation. There was no late thrombosis within the 6-month follow-up. The protocols of DEB studies suggest that the dual antiplatelet therapy with aspirin and clopidogrel of 4 weeks after DEB is safe and effective (18).

The DEB with BMS protocol also allows for a longer paclitaxel-coated balloon to be used instead of the stented segment one. This may be favorable since about one-third of restenosis after DES implantation occurs proximal or distal to the stent margin (17,19). To optimize the rate of drug delivery in the present study, we used a longer DEB (DEB > BMS), and estimated the diameter of DEB and ZES based on the IVUS findings. There were 11 binary restenoses (9 in DEB + BMS group and 2 in ZES group) as shown in Table 3. ISR pattern of DEB + BMS group included 2IB, 4IC, 1ID, 1II, and 1III (5 in-stent and 4 involving stent edge) according to Mehran ISR classification (20). ISR pattern of ZES group were 1IC and 1II (both, in-stent). Therefore, ZES showed no edge restenosis while longer DEB + short BMS did not prevent edge restenosis in the present study. However, the numbers of patients and ISR occurrence were too small to conclude this issue.

Opposed to our expectation, once more the DEB + BMS strat-

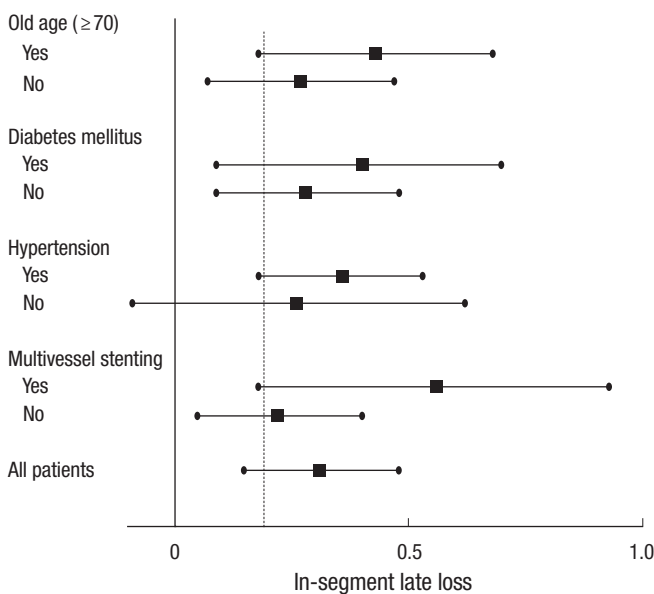


Fig. 3. The mean difference of in-stent LL and 95% CI and its subgroup analysis. The broken line denotes the prespecified non-inferiority margin (0.19 mm). LL = late loss, CI = confidence interval.

Table 4. Subgroup analysis of in-segment LL

Subgroups	DEB + BMS	ZES	P value	P for interaction
Old age (≥ 70)				0.411
Yes	0.54 ± 0.31	0.11 ± 0.39	0.001	
No	0.55 ± 0.55	0.27 ± 0.52	0.010	
Diabetes mellitus				0.543
Yes	0.57 ± 0.42	0.17 ± 0.55	0.013	
No	0.53 ± 0.55	0.25 ± 0.47	0.005	
Hypertension				0.600
Yes	0.54 ± 0.45	0.19 ± 0.37	< 0.001	
No	0.54 ± 0.66	0.28 ± 0.60	0.142	
Multivessel stenting				0.077
Yes	0.74 ± 0.58	0.18 ± 0.57	0.005	
No	0.47 ± 0.47	0.25 ± 0.47	0.014	

Values are mean ± SD or number (%). LL = late loss, DEB = drug-eluting balloon, BMS = bare metal stent, ZES = zotarolimus-eluting stent, SD = standard deviation.

Table 5. Cumulative incidence of clinical events up to 1 year (intention-to-treat per patient)

Parameters	Total (n = 180)	DEB + BMS (n = 90)	ZES (n = 90)	P value
All-cause death	3 (1.7)	1 (1.1)	2 (2.2)	1.000
Cardiac death	2 (1.1)	0 (0.0)	2 (2.2)	0.497
Myocardial infarction	2 (1.1)	2 (2.2)	0 (0.0)	0.497
Target lesion revascularization	8 (4.4)	5 (5.6)	3 (3.3)	0.720
Target vessel revascularization	10 (5.6)	5 (5.6)	5 (5.6)	1.000
Non-target vessel revascularization	6 (3.3)	5 (5.6)	1 (1.1)	0.211
Stent thrombosis	2 (1.1)	2 (2.2)	0 (0.0)	0.497
Target lesion failure	10 (5.6)	5 (5.6)	5 (5.6)	1.000
Major advanced cardiac event	16 (8.9)	9 (10.0)	7 (7.8)	0.794

DEB = drug-eluting balloon, BMS = bare metal stent, ZES = zotarolimus-eluting stent.

egy failed to prove its non-inferiority to DES alone strategy. Moreover, DES alone therapy was superior to the DEB + BMS therapy. The design of the combination treatment (premounted vs. sequential) or the sequence of DEB and BMS application did not seem to affect the inhibition of restenosis (21,22).

The reasons why the DEB + BMS was inferior to DES alone can be explained by the following issues. First, the efficacy of paclitaxel in inhibiting restenosis may be inherently inferior to not only sirolimus but also to zotarolimus. The paclitaxel-eluting stent was inferior to sirolimus-eluting stent as well as to ZES (23,24). Therefore, in the present study the paclitaxel-coated balloon may not inhibit neointimal hyperplasia as efficient as the sustained released of the ZES.

Second, the difference between these 2 strategies may be the drug-release kinetics. As the DEB used in the present study is known to release the coated drug within 1 month, which is markedly shorter than the ZES, it would influence the performance of DEB + BMS implantation strategy. Third, the DEB + BMS therapy resulted in a significantly decreased post-PCI minimal luminal diameter and less acute gain compared with the ZES therapy. We cannot demonstrate the mechanism of the inferior acute gain in the DEB + BMS arm. We applied the predilation with similar diameter balloons at similar pressure. The diameter of the implanted stents and the maximal pressure of the adjunctive ballooning following stent implantation were not different when comparing the 2 arms. Although the procedure methods were similar, BMS and ZES have different stent platform, which provides different radial strength and conformability to the vessel wall. In the present study, the BMS had thinner strut compared with the ZES. It might result in less acute gain in DEB + BMS group. However, it was reported that the stent with thinner struts showed a comparable acute gain while it elicited less angiographic and clinical restenosis compared with the thicker-strut stent (14,25). Nevertheless, in the present study, the less acute gain may partly influence the negative outcome since it is known that the late lumen diameter, late percent stenosis, and binary restenosis depend on the immediate lumen diameter following the procedure and the immediate residual percent stenosis, but not on the specific intervention (26).

Finally, Shin et al. (27) presented the similar efficacy and safety of DEB vs. second generation DES in treatment of de novo coronary stenosis even without additional BMS implantation. They emphasized the perfect lesion preparation with predilation to obtain fractional flow reserve (FFR) > 0.85. In this regard, our strategy might not be sufficient to obtain a proper lesion preparation for the best efficacy of the following DEB because we used gentle predilation to minimize serious dissection.

We used simple randomization based on a single sequence of random number table. Because the present study is a relatively small sample size clinical trial, this randomization method could be problematic, resulting in an unequal number of

participants with hypertension and current smoking between the groups. The rate of drop-out was relatively high in the present study. This may be a critical methodological issue. Because we designed this study in 2010, we performed PCI to guidelines at that time. However, in more recent, e.g. focused update from 2014 or the European guidelines from 2014, the importance of physiologic assessment of coronary lesions is highlighted. Therefore, it is possible that we overestimated lesion severity on lesions in the present study. The study was not powered to detect differences in clinical endpoints.

In conclusion, the DEB + BMS strategy is inferior to the ZES one in terms of the LL at 9 months, although we do not confirm any increase in the death rate or MI when comparing the present results with those of the previous study.

## DISCLOSURE

The authors have no potential conflicts of interest to disclose.

## AUTHOR CONTRIBUTION

Conceptualization: Chae IH, Yoon CH. Data curation: Yoon CH. Formal analysis: Yoon CH, Park JJ, Oh IY. Investigation: Chae IH, Yoon CH, Oh IY, Suh JW, Cho YS, Youn TJ, Choi DJ. Writing - original draft: Yoon CH. Writing - review & editing: Chae IH, Park JJ.

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