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ORIGINAL RESEARCH

Biolimus-coated versus paclitaxel-coated balloons for coronary in-stent restenosis (BIO ASCEND ISR): a randomised, non-inferiority trial

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ABSTRACT

BACKGROUND: The treatment of in-stent restenosis (ISR) after drug-eluting stent (DES) implantation remains challenging in current clinical practice.

AIMS: The study was conducted to investigate a novel biolimus-coated balloon (BCB) for the treatment of coronary DES-ISR compared with the best-investigated paclitaxel-coated balloon (PCB).

METHODS: This was a prospective, multicentre, randomised, non-inferiority trial comparing a novel BCB with a clinically proven PCB for coronary DES-ISR. The primary endpoint was in-segment late lumen loss (LLL) at 9 months assessed by an independent core laboratory. Baseline and follow-up optical coherence tomography were performed in a prespecified subgroup of patients.

RESULTS: A total of 280 patients at 17 centres were randomised to treatment with a BCB (n=140) versus a PCB (n=140). At 9 months, LLL in the BCB group was 0.23±0.37 mm compared to 0.25±0.35 mm in the PCB group; the mean difference between the groups was –0.02 (95% confidence interval [CI]: –0.12 to 0.07) mm; p-value for non-inferiority<0.0001. Similar clinical outcomes were also observed for both groups at 12 months. In the optical coherence tomography substudy, the neointimal area at 9 months was 2.32±1.04 mm^2 in the BCB group compared to 2.37±0.93 mm^2 in the PCB group; the mean difference between the groups was –0.09 (95% CI: –0.94 to 0.76) mm^2; p=non-significant.

CONCLUSIONS: This head-to-head comparison of a novel BCB shows similar angiographic outcomes in the treatment of coronary DES-ISR compared with a clinically proven PCB. (ClinicalTrials.gov: NCT04733443)

KEYWORDS: biolimus; drug-coated balloon; drug-eluting stent; in-stent restenosis

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In-stent restenosis (ISR), particularly in patients with drug-eluting stents (DES), poses a significant clinical challenge, frequently necessitating repeat revascularisation interventions[1-3]. A meta-analysis published in 2020 indicates that, for DES-ISR, paclitaxel-coated balloons (PCB) are marginally less effective when compared to contemporary DES[4]. The distinct advantage of drug-coated balloons (DCBs) is their ability to deliver medication without requiring a new stent implantation. This underscores the crucial significance of the advancing DCB technology[5]. Different drug-coating formulations and coating-process technologies will result in different vascular responses due to variations in drug formulation, dosage, pharmacokinetics, and interactions with lesions[6]. Although previous research on DES has illuminated a range of benefits of -limus derivatives over paclitaxel[3], it remains unclear whether these benefits are transferable to DCB treatment.

Biolimus A9 (BA9 [Biosensor International]), a sirolimus derivative, has been modified to increase its lipophilicity 10-fold in comparison to sirolimus and other -limus compounds, while retaining its rapamycin inhibition properties. This enhancement makes biolimus particularly well suited for targeted, short-term delivery to vascular tissues. The biolimus-coated balloon (BCB), a semicompliant angioplasty balloon, is coated with 3 µg/mm^2 of biolimus, employing polyethylene oxide as the delivery matrix. Preclinical testing using a standard porcine coronary model (n=15) showed that, 1 hour after deployment, the maximum systemic blood concentration of biolimus was approximately 2.0 ng/ml per balloon. Of note, this concentration is 40 times less than the established safety threshold for biolimus[7]. Moreover, tissue analysis from the treated coronary arteries demonstrated that biolimus levels remained above 1 ng/mg 28 days after the procedure, exceeding the accepted therapeutic threshold for -limus-based drugs.

Recent studies have shed light on the efficacy of BCBs, yet they have not converged on a consensus. The BIO-RISE CHINA study confirmed the superior efficacy of a novel BCB over plain old balloon angioplasty in patients with small-vessel coronary disease undergoing percutaneous coronary intervention (PCI)[8]. On the other hand, the REFORM study portrayed a different picture, suggesting that a DCB coated with BA9 was less effective when compared to one coated with paclitaxel[9]. In contrast to the REFORM study, the crystallisation coating process employed in the BIO-RISE CHINA study for BA9 crystals yields a more consistent range of crystal size, which may have had a favourable impact on clinical outcomes. Given the ongoing uncertainty regarding the efficacy of BCBs for coronary artery disease, including ISR, there is an imperative need for additional research to elucidate their role in modern cardiovascular interventions.

Therefore, a prospective, multicentre, non-inferiority, randomised controlled clinical trial was initiated to compare the safety and efficacy of biolimus- versus paclitaxel-coated coronary balloon catheters in the treatment of DES-ISR.

Impact on daily practice

This clinical trial reveals that, for patients dealing with coronary drug-eluting stent in-stent restenosis, the use of a biolimus-coated balloon (BCB) was non-inferior in terms of angiographic outcomes at 9 months compared to a well-established paclitaxel-coated balloon. However, a higher number of revascularisation events were seen in the BCB group at 1 year. Due to the unique pharmacokinetic profile of -limus analogues, long-term follow-up is needed to establish the clinical efficacy of these technologies.

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Methods

STUDY DESIGN AND PATIENT POPULATION

The BIO ASCEND ISR study is a multicentre, randomised controlled (1:1), single-blinded, non-inferiority study conducted at 17 hospitals in China. The study was conducted in accordance with the Declaration of Helsinki and was registered on 29 January 2020 (ClinicalTrials.gov: NCT04733443). The main inclusion criteria were patients with Mehran type I, II, and III DES-ISR[10] with stable angina, acute coronary syndrome, or asymptomatic myocardial ischaemia. Main exclusion criteria included acute myocardial infarction within 1 week prior to intervention or without recovery of cardiac enzymes, previously treated ISR, left main lesions, and patients with total occlusion. The full list of inclusion and exclusion criteria is provided in **Supplementary Appendix 1**.

The study protocol received approval from independent ethics committees at each participating centre. All patients provided written informed consent before enrolment. All clinical events were adjudicated by an independent clinical events committee. Analysis of all angiograms was conducted by trained and blinded personnel at the central core laboratory, utilising standard methodologies **(Supplementary Appendix 2 and Supplementary Appendix 3)**.

Patients were randomly allocated (1:1) to treatment with either BCB or PCB. After successful lesion preparation, central randomisation was completed with a computed-generated allocation sequence, stratified by site. Patients and treating

Abbreviations

BCB	biolimus-coated balloon
CAD	coronary artery disease
CI	confidence interval
DCB	drug-coated balloon
DES	drug-eluting stents
ISR	in-stent restenosis
MACE	major adverse cardiac events
MI	myocardial infarction
OCT	optical coherence tomography
PCB	paclitaxel-coated balloon
PCI	percutaneous coronary intervention
TCFA	thin-cap fibroatheroma

physicians were aware of the group allocations, whereas outcome and core laboratory assessors were masked to this allocation.

STUDY DEVICES AND PROCEDURES

The control device is a commercially available PCB (SeQuent Please NEO [B. Braun Melsungen AG]) made in Germany. The PCB was coated with 3 µg of paclitaxel/mm² of balloon surface. The tested device, a BCB (BioAscend JWMS China), was coated with 3 µg biolimus per mm² using polyethylene oxide as an excipient[8]; this was the same BCB used in the BIO-RISE CHINA study. More detail is shown in **Supplementary Appendix 1**.

Based on clinical recommendations, all patients were administered aspirin, either in a daily dose of 100 mg for at least 3 days prior to PCI or a one-time loading dose of 300 mg before the procedure, along with clopidogrel (given as a loading dose of 300 or 600 mg, followed by 75 mg per day) or ticagrelor (administered as a loading dose of 180 mg, then continued with 90 mg twice daily). Following PCI, patients were advised to continue dual antiplatelet therapy for a minimum of 1 month, followed by lifelong aspirin use. In all cases, predilation with plain, scoring, or cutting balloons was required to reduce stenosis to less than 30%. Once adequate predilation of the lesion was achieved, patients were randomly assigned in a 1:1 ratio to be treated with either the PCB or the BCB, according to their group, while cases without proper predilation were not included in the randomisation. The selection of balloon sizes was left to the discretion of the interventional cardiologists. Inflation of the DCB lasted between 45 to 60 seconds at normal pressure, tailored to the specific morphological features of the lesion. Successful treatment was defined as achieving a postprocedural residual stenosis of less than 30% based on visual assessment. In a prespecified subgroup of 60 patients, optical coherence tomography (OCT) was performed at baseline, after the procedure, and at the 9-month follow-up to assess the outcomes.

ENDPOINTS

Patients were scheduled for follow-up visits at 1, 6, 9 and 12 months, with an angiographic assessment planned within a period of 9±1 months. Data collection was conducted using electronic clinical report forms throughout the treatment process at all participating centres. The collection of data was prospectively finalised during the hospital stay and continued during subsequent follow-up visits.

The primary endpoint was in-segment late lumen loss (LLL) at 9 months after the procedure (defined as the postprocedural minimal lumen diameter minus the minimal lumen diameter at 9 months).

The major secondary endpoint was neointima area at 9 months (for the OCT subgroup only). Secondary endpoints included the following: (1) device success (defined as successful delivery, expansion and withdrawal), lesion success (defined as residual stenosis ≤30% and Thrombolysis in Myocardial Infarction [TIMI] flow 3 without type C [or above] dissection[11]) and clinical success (defined as lesion success with absence of death, myocardial infarction and target lesion revascularisation prior to discharge); (2) binary restenosis (≥50% diameter stenosis); (3) target lesion failure (TLF) as a device-oriented composite of cardiac death, target vessel myocardial infarction, and clinically driven target lesion revascularisation; and (4) a patient-oriented composite of all-cause mortality, myocardial infarction and any revascularisation, and definite or probable stent thrombosis[12]. All clinical events were evaluated by an independent clinical events committee unaware of the group assignment of the subjects.

QUANTITATIVE CORONARY ANGIOGRAPHY AND OCT ASSESSMENT

Trained and blinded personnel at the central core laboratory used standard methodologies to analyse all the angiograms. Quantitative coronary angiographic analysis was conducted using QAngio XA software, version 7.3 (Medis Medical Imaging Systems), in a blinded manner. The neointimal area was analysed using OCT 9 months after the procedure (OCT subgroup). Accordingly, OCT measurement indices contain lesion length, lumen diameter, lumen area, minimal lumen area, stent diameter, stent area, neointimal hyperplasia thickness, average intimal thickness, uncovered struts and their proportions, lipid-rich neointima, calcified neointima, mixed neointima, thin-cap fibroatheroma (TCFA), and thrombus. The neointima area was then calculated based on the above parameters.

STATISTICAL ANALYSIS

The study's sample size was determined to evaluate the non-inferiority of the investigational device concerning the primary endpoint, based on the following assumptions: a comparable LLL at 9 months of 0.46 mm in both groups, a common LLL standard error of 0.5, and a non-inferiority margin of 0.195 mm[13,14]. To ensure 80% power at a 2.5% alpha level for detecting non-inferiority, 105 patients per group were initially deemed necessary. Considering a potential 25% dropout rate for angiographic follow-up, the sample size was increased to 140 patients per group. This adjustment led to a total sample size of 280 patients. The sample size of the OCT substudy was based on neointimal area at 9 months. Assuming the comparable difference between groups as 0.5 mm², the standard error as 1.18 mm², and the alpha level as 5%, 204 OCT sections would be enough to guarantee 80% power[15]. Considering the cluster effect of multiple cross-sections of a patient, the intragroup correlation coefficient was conservatively estimated to be 0.05, and the corresponding design effect was approximately equal to 2, which translates into 408 OCT sections in 21 patients. With a maximum of a 25% rate of loss to angiographic follow-up, the OCT subgroup randomised 60 patients equally into 2 groups.

The full analysis set (FAS) and per-protocol set (PPS) were used to evaluate the endpoint. The FAS population comprised patients meeting the inclusion criteria, without fulfilling any exclusion criteria, who could provide informed consent. They were randomly allocated to either the BCB or PCB group, and their assessment data were collected after the procedure. The FAS is the main population in clinical events reporting. Patients were excluded from the PPS if they violated the protocol, were lost to follow-up, or had missing primary endpoint data. The PPS was specifically designated for reporting angiographic data.

For continuous variables, the mean±standard deviation was calculated in each group. For in-segment LLL as the primary outcome measure, a covariance analysis of adjusted centre and baseline (the minimal lumen diameter within the lesion segment immediately after intervention) effects was used to compare groups at the beginning of the study. The paired t-test was used to compare the secondary efficacy indices with normal distribution. The measurement data of non-normal distribution were tested by the Wilcoxon signed-rank test. McNemar's paired χ^2 test was used for intragroup comparison of qualitative indicators. Binary variables were presented as counts and percentages. Differences between the two groups were evaluated using the χ^2 or Fisher's exact tests, as deemed appropriate. The two 1-sided tests were employed to test non-inferiority. For lesion-level analysis, generalised estimating equations were used to account for the cluster effect. The Kaplan-Meier method was applied for the estimation of cumulative event rates, with the log-rank test used to assess differences between the groups. Analyses were conducted according to the intention-to-treat principle. A p-value of <0.05 was considered statistically significant. Additionally, SAS 9.4 (SAS Institute) was used for the analysis.

Results

PATIENTS AND PROCEDURAL RESULTS

From December 2020 to January 2022, we screened 290 patients with coronary DES-ISR, and finally, 280 of them were included, leaving 10 cases excluded before randomisation, as no significant in-stent stenosis was observed. There were no patients excluded on account of predilation failure. Five patients withdrew consent before receiving any study treatment **(Figure 1)**. The average age of the patients was 64 years, with 204 (74.2%) males. The FAS population involved 138 patients with 152 lesions in the BCB group and 137 patients with 153 lesions in the PCB group. No significant differences were observed between the BCB and PCB groups regarding demographic, clinical, or lesion characteristics (all p-values>0.05) **(Table 1)**.

Different balloon types were comparably utilised across the groups, with uniform measurements of DCB diameter, length, and inflation parameters, presenting no significant differences (all p-values>0.05). One DCB per lesion was utilised in all cases. Bailout procedures (stent or non-compliant balloon) performed because of edge dissection and obvious residual stenosis were similar in both groups (2.6% vs 1.3%, p=0.448). Following the intervention, TIMI flow grade 3 was observed in all vessels. Device and lesion success were achieved in all cases. Clinical success was observed in all patients in the BCB group and in 99.3% of patients in the PCB group, with only one case of periprocedural myocardial infarction noted **(Table 2)**.

The comparison between the BCB group and the PCB group showed no significant differences in most preprocedural and postprocedural angiographic outcomes. Both groups had similar reference vessel diameters (2.79±0.40 mm vs 2.80±0.39 mm; p=0.779) and minimal lumen diameters (0.84±0.35 mm vs 0.87±0.36 mm; p=0.544) before the procedure. No significant differences in diameter stenosis (69.91±11.05% vs 69.11±11.56%; p=0.540) or lesion length (16.26±7.21 mm vs 15.97±6.85 mm; p=0.718) were observed. The BCB group showed greater in-device diameter stenosis after the procedure than the PCB group (21.94±7.52% vs 20.15±7.06%; p=0.034). The minimal lumen diameter and acute lumen gain for both the in-device and in-segment measurements were also comparable after the procedure (all p-values>0.05) **(Table 3, Figure 2)**.

ANGIOGRAPHIC OUTCOMES

A total of 230 patients (83.6%) underwent the 9-month angiographic follow-up: 114 (82.6%) in the BCB group and 116 (84.7%) in the PCB group. In the per-patient analysis, the in-segment LLL at 9 months was 0.23±0.37 mm in the BCB group compared to 0.25±0.35 mm in the PCB group (p=0.632). The mean difference between the groups was –0.02 (95% CI: –0.12 to 0.07) mm; p<0.0001 for non-inferiority **(Central illustration, Supplementary Table 1)**. The per-lesion analysis revealed an in-segment LLL of 0.25±0.40 mm and

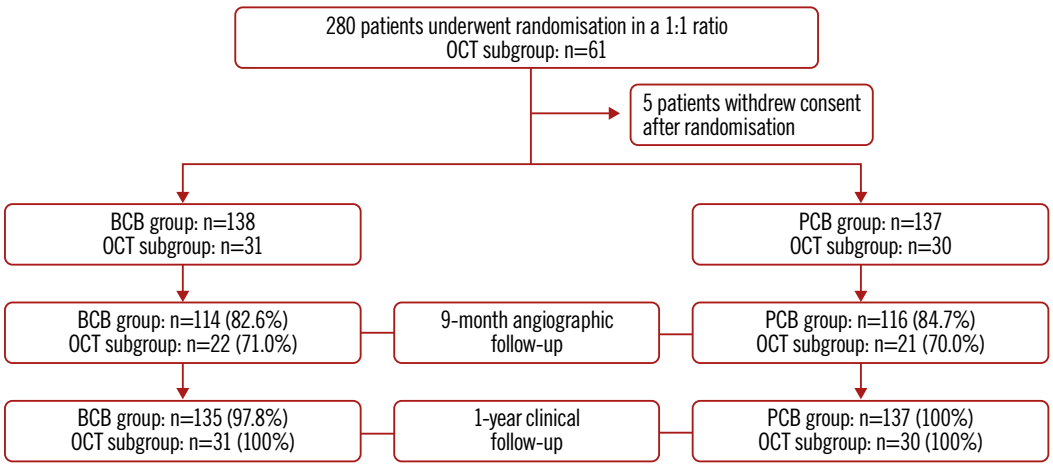


Figure 1. *Patient flow and follow-up. BCB: biolimus-coated balloon; OCT: optical coherence tomography; PCB: paclitaxel-coated balloon*

Table 1. Baseline patient and lesion characteristics (full analysis set population).

	BCB group (n=138 patients; n=152 lesions)	PCB group (n=137 patients; n=153 lesions)	*p*-value
Age, years	63.64±8.90	64.24±8.84	0.576
Male	103 (74.6)	101 (73.7)	0.862
Body mass index, kg/m^2	25.96±3.59	25.91±3.31	0.887
Diabetes mellitus	51 (37.0)	59 (43.1)	0.301
Insulin-treated diabetes	23 (46.0)	29 (50.9)	0.614
Hypertension	86 (62.3)	98 (71.5)	0.104
Hyperlipidaemia	61 (44.2)	53 (38.7)	0.353
Previous MI	22 (15.9)	33 (24.1)	0.091
Previous CABG	0 (0)	0 (0)	-
Unstable angina	111 (94.1)	108 (93.1)	0.763
Left ventricular ejection fraction, %	61.02±8.01	60.87±8.96	0.883
Multivessel disease	0.30±0.49	0.29±0.50	0.837
Target vessel location	152 (100)	153 (100)	0.346
Left anterior descending artery	71 (46.7)	78 (51.0)	
Left circumflex artery	23 (15.1)	13 (8.5)	
Right coronary artery	54 (35.5)	58 (37.9)	
Other	4 (2.6)	4 (2.6)	
Number of non-target lesions	138 (100)	137 (100)	0.799
0	98 (71.0)	100 (73.0)	
1	38 (27.5)	34 (24.8)	
2	2 (1.4)	3 (2.2)	
Mehran type	152 (100)	153 (100)	0.617
I	25 (16.4)	31 (20.3)	
II	88 (57.9)	81 (52.9)	
III	39 (25.7)	41 (26.8)	
IV	0 (0)	0 (0)	

Values are mean±SD or n (%). The p-value is the difference in the biolimus DCB group compared with the SeQuent Please NEO DCB group.
BCB: biolimus-coated balloon; CABG: coronary artery bypass grafting; DCB: drug-coated balloon; MI: myocardial infarction; PCB: paclitaxel-coated balloon; SD: standard deviation

Table 2. Procedural characteristics and results (full analysis set population).

	BCB group (n=138 patients; n=152 lesions)	PCB group (n=137 patients; n=153 lesions)	*p*-value
Transradial approach	146 (96.1)	141 (92.2)	0.372
Predilation	152 (100)	153 (100)	0.728
Plain old balloon	217 (63.6)	218 (66.7)	
Scoring balloon	54 (15.8)	49 (14.9)	
Cutting balloon	52 (15.3)	42 (12.8)	
Number of DCBs	152 (100)	153 (100)	-
1	152 (100)	153 (100)	
2	0 (0)	0 (0)	
Mean diameter of DCB, mm	3.04±0.41	3.01±0.35	0.525
Total length of DCB, mm	25.13±6.63	24.38±6.82	0.328
Maximum inflation pressure with DCB, atm	9.20±2.33	9.27±2.52	0.782
Duration of inflation with DCB, sec	59.38±8.16	60.56±11.49	0.302
Bailout strategy	4 (2.6)	2 (1.3)	0.448
Postprocedural TIMI flow	152 (100)	153 (100)	-
1	0 (0)	0 (0)	
2	0 (0)	0 (0)	
3	152 (100)	153 (100)	
Successful outcomes*			
Device success	152 (100)	153 (100)	-
Lesion success	152 (100)	153 (100)	-
Procedural success	138 (100)	136 (99.3)	0.498

Values are n (%) or mean±SD. *Definitions for device, lesion, and procedural success are provided for the prespecified endpoints in the definitions section of **Supplementary Appendix 1**. BCB: biolimus-coated balloon; DCB: drug-coated balloon; PCB: paclitaxel-coated balloon; SD: standard deviation; TIMI: Thrombolysis in Myocardial Infarction

Table 3. Quantitative coronary angiography results (full analysis set population).

	BCB group	PCB group	*p*-value
Preprocedure	n=150	n=151	
Reference vessel diameter, mm	2.79±0.40	2.80±0.39	0.779
Minimal lumen diameter, mm	0.84±0.35	0.87±0.36	0.544
Diameter stenosis, %	69.91±11.05	69.11±11.56	0.540
Lesion length, mm	16.26±7.21	15.97±6.85	0.718
Post-procedure	n=150	n=151	
Minimal lumen diameter, mm			
In-device	2.24±0.37	2.27±0.35	0.375
In-segment	2.14±0.37	2.17±0.34	0.557
Diameter stenosis, %			
In-device	21.94±7.52	20.15±7.06	0.034
In-segment	23.24±7.34	21.69±6.84	0.059
Acute lumen gain, mm			
In-device	1.39±0.41	1.40±0.39	0.803
In-segment	1.30±0.40	1.30±0.40	0.988
9-month follow-up	n=125	n=130	
Minimal lumen diameter, mm			
In-device	1.96±0.62	1.98±0.56	0.832
In-segment	1.87±0.60	1.88±0.54	0.868
Diameter stenosis, %			
In-device	31.25±19.31	29.54±17.30	0.456
In-segment	32.59±18.78	31.61±16.99	0.662
Late lumen loss, mm			
In-device	0.26±0.42	0.29±0.40	0.579
In-segment	0.25±0.40	0.27±0.39	0.670
Net lumen gain†, mm			
In-device	1.13±0.62	1.11±0.55	0.772
In-segment	1.04±0.59	1.02±0.54	0.720
Binary restenosis, %			
In-device	17 (11.3)	20 (13.1)	0.806
In-segment	17 (11.3)	20 (13.1)	0.806

Values are n (%) or mean±SD. †Net lumen gain was defined as the difference between the minimal lumen diameter at follow-up and baseline.
BCB: biolimus-coated balloon; PCB: paclitaxel-coated balloon; SD: standard deviation

0.27±0.39 mm in the two groups, respectively, with a mean difference of −0.03 (95% CI: −0.13 to 0.07); p<0.001 for non-inferiority. This aligns with the comparison of in-segment LLL per patient. Furthermore, follow-up showed no significant distinctions between the BCB and PCB groups concerning other critical metrics, such as maintenance of lumen diameter, stenosis rates, and the occurrence of binary restenosis **(Table 3)**.

CLINICAL OUTCOMES

At 1-month follow-up, the analysis between the BCB and PCB groups showed no significant differences in major clinical outcomes. The incidence of the patient-oriented composite endpoint was equivalent for both groups at 0.7% (p=1.000). Target lesion failure rates were similarly low, with 0% in the BCB group and 0.7% in the PCB group (p=0.498). Rates of myocardial infarction, all-cause death, cardiac death, stent thrombosis, target vessel revascularisation (TVR), and target lesion revascularisation (TLR) were comparable in both groups, suggesting similar safety profiles in the early stage.

At 1-year follow-up, there were no significant differences in the incidence of target lesion failure between the BCB and PCB groups, with rates of 13.3% and 9.5%, respectively (p=0.318). The patient-oriented composite endpoint, with a rate of 23.4% in the BCB group and 14.6% in the PCB group, also indicated no statistically significant difference (p=0.064). Revascularisation rates, including any revascularisation (22.2% for the BCB group vs 13.2% for the PCB group) and TVR (17.0% for the BCB group vs 9.6% for the PCB group), showed no significant differences (p=0.052 for any revascularisation; p=0.068 for TVR). Similarly, there were no statistically significant differences in the rates of all-cause death, cardiac death, or myocardial infarction between the groups, confirming the comparative safety of the treatments during the first year **(Table 4, Figure 3)**.

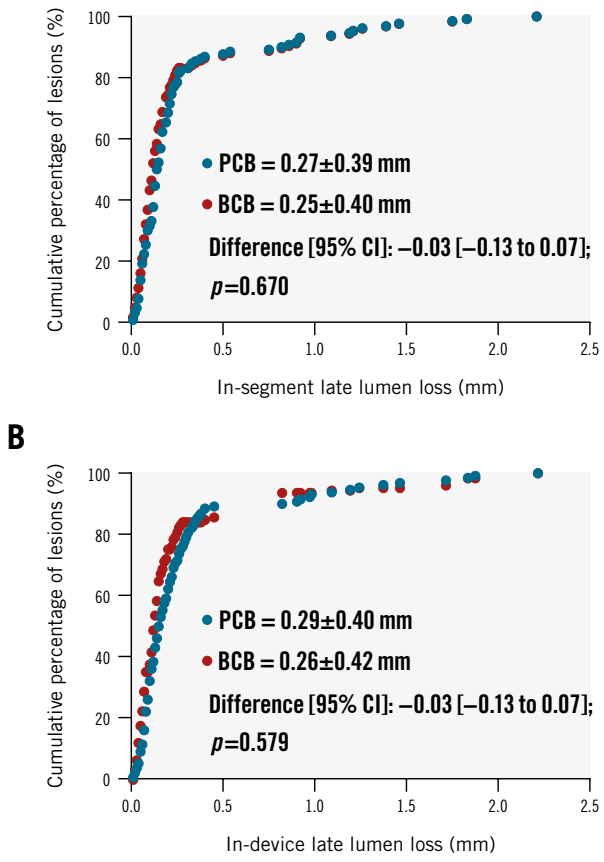


Figure 2. *Nine-month in-segment and in-device late lumen loss distribution. Cumulative frequency distribution curves of in-segment (A) and in-device (B) late lumen loss at 9-month angiographic follow-up. BCB: biolimus-coated balloon; CI: confidence interval; PCB: paclitaxel-coated balloon*

OCT SUBSTUDY RESULTS

In the 9-month OCT follow-up of patients treated with either BCB or PCB, data revealed no significant difference in the average neointimal cross-sectional area between the two groups, with values of 2.32±1.04 mm² for the BCB group and 2.37±0.93 mm² for the PCB group (p=0.882). Other parameters, including mean and minimal luminal areas, stent areas, neointimal volume, the number of analysed struts, and uncovered struts, also showed no significant differences between the groups, indicating comparable outcomes for both treatments **(Supplementary Table 2)**.

Discussion

This is a head-to-head randomised controlled trial directly comparing a novel Chinese BCB, utilising optimised biolimus drug crystallisation technology, against a commercially accessible PCB. In patients with coronary DES-ISR, the study demonstrated that (1) a novel BCB (BioAscend biolimus drug-coated balloon) was non-inferior to the PCB (SeQuent Please NEO paclitaxel-coated balloon) in terms of in-segment LLL when treating coronary DES-ISR; (2) the rates of adverse clinical events were similar between both treatment groups with 1-year clinical follow-up, except the rates of TLF and any revascularisation, which were numerically increased in the BCB group; (3) no significant difference in the major secondary endpoint of neointima area at 9 months was observed between the two devices.

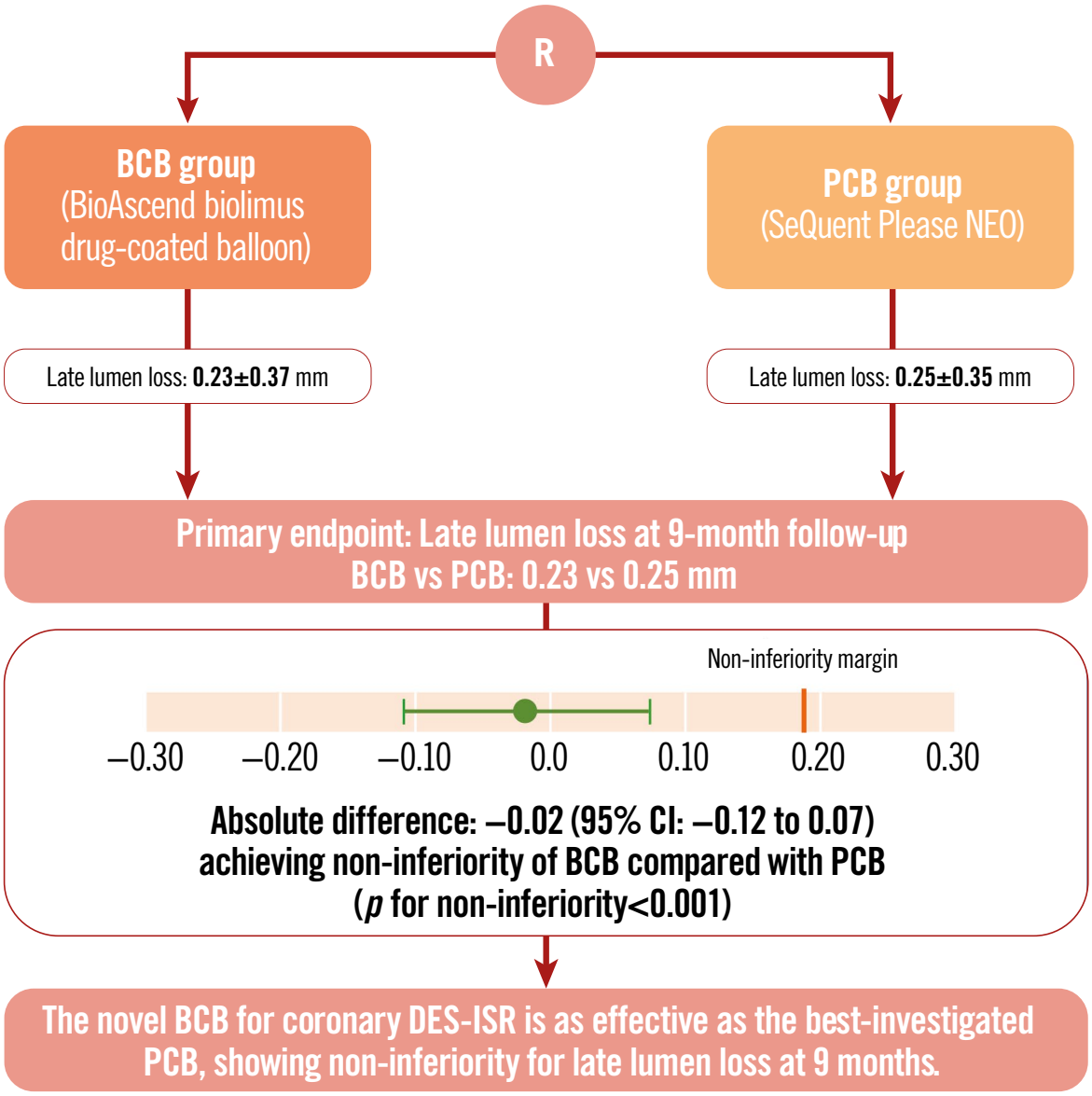
DCBs integrate angioplasty with drug-coating techniques to affix antiproliferative drugs onto the surface of the balloon. As a lipophilic drug, paclitaxel rapidly traverses the cell membrane, irreversibly binds to microtubules, and continuously inhibits cell division and proliferative inflammation. It stands as the main clinical DCB coating drug[16]. In recent years, drugs with a better antiproliferation effect and higher safety (such as rapamycin) have not been applied to DCBs, as they cannot quickly pass through the cell membrane to achieve an effective residence time. Apart from the drug itself, excipients, pharmacokinetics, and interactions with the lesion can also cause different vascular responses[6]. With advancements in drug formulation and coating technology, rapamycin and its derivatives have emerged as potential candidates for DCBs[17]. BA9, a modified sirolimus analogue with increased lipophilicity, aims to optimise local drug delivery from stents and balloons. Unlike sirolimus, BA9 is a crystallised drug with less drug loss during delivery and has 10 times more lipophilic solubility than sirolimus. This allows rapid absorption by tissues while minimising exposure loss, resulting in more efficiency in inhibiting endovascular hyperplasia and reduction of late lumen loss.

A prospective trial conducted at 10 centres in China, known as the BIO-RISE CHINA study[8], demonstrated that a novel biolimus-coated balloon exhibited superior efficacy to plain old balloon angioplasty in patients with small-vessel coronary disease in terms of LLL. The present study demonstrated no significant difference at 9 months in neointimal formation after treatment of DES-ISR between the BCB investigated here and the PCB counterpart. The specific BCB (biolimus in a dose of 3 μg/mm² using polyethylene oxide as an excipient) analysed in this study was equivalent to the best-investigated PCB with regard to the angiographic endpoint of DES-ISR.

The in-segment LLL of 0.25±0.40 mm observed at 9 months with the BCB in this trial is consistent with findings from other -limus-coated balloon trials in DES-ISR. The first clinical experiment was reported on 50 patients with ISR treated with sirolimus in a liquid formulation delivered by a porous balloon (SABRE [Sirolimus-eluting Angioplasty Balloon for In-Stent REstenosis] Trial)[18]. In this patient population, in-segment LLL at 6 months was 0.31±0.52 mm. Scheller et al conducted a joint analysis of two parallel randomised trials comparing sirolimus-coated (SCB) and paclitaxel-coated balloons in coronary in-stent restenosis lesions[19]. After 6 months, in-segment LLL was 0.25±0.57 mm in the PCB group versus 0.26±0.60 mm in the SCB group. Clinical events up to 12 months did not differ between the groups. It is worth mentioning that the preliminary findings of the randomised REFORM trial (A Prospective, Randomized, Non-Inferiority Trial to Determine the Safety and Efficacy of the BA9™ Drug Coated Balloon for the Treatment of In-Stent Restenosis: First-in-Man Trial), involving 201 patients, were showcased at EuroPCR 2023[20]. This trial revealed that the biolimus A9-coated balloon did

EuroIntervention — Central **Illustration**

BIO ASCEND ISR study: a prospective, multicentre, non-inferiority trial in patients with coronary in-stent restenosis*.



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BCB: biolimus-coated balloon; CI: confidence interval; DES-ISR: drug-eluting stent in-stent restenosis; PCB: paclitaxel-coated balloon; R: randomisation

*This is a corrected version of the original illustration that was published ahead of print in May 2024.

not exhibit non-inferiority compared to the paclitaxel-iopromide device. Both the REFORM study and the current study used biolimus DCBs to treat coronary ISR lesions, but their results varied because of several factors. Firstly, the REFORM study included both bare metal stent ISR and DES-ISR patients, while our study only included DES-ISR patients. The varying pathophysiological processes between the two types of lesions may impact the efficacy of DCB treatment. Secondly, the REFORM study had a smaller sample size and a shorter angiographic follow-up period of 6 months, significantly limiting its statistical power. Furthermore, the BA9 drug-coated balloons in the two studies were from different manufacturers, which resulted in differences between the systems' production quality and manufacturing processes. The excipient on the balloon of both DCBs was exactly the same, but the crystallisation coating process of the two pellets

Table 4. Clinical outcomes in the full analysis set.

	BCB group	PCB group	*p*-value
At 1 month*	n=138	n=137	
Target lesion failure†	0 (0)	1 (0.7)	0.498
Patient-oriented composite endpoint‡	1 (0.7)	1 (0.7)	1.000
All-cause death	0 (0)	0 (0)	-
Cardiac death	0 (0)	0 (0)	-
Myocardial infarction	0 (0)	1 (0.7)	0.498
Target vessel MI	0 (0)	1 (0.7)	0.498
Periprocedural MI	0 (0)	1 (0.7)	0.498
Any revascularisation	1 (0.7)	0 (0)	1.000
TVR	0 (0)	0 (0)	-
TLR	0 (0)	0 (0)	-
Stent thrombosis	0 (0)	0 (0)	-
At 1 year**	n=135	n=137	
Target lesion failure†	18 (13.3)	13 (9.5)	0.318
Patient-oriented composite endpoint‡	32 (23.4)	20 (14.6)	0.064
All-cause death	2 (1.5)	1 (0.7)	1.000
Cardiac death	0 (0)	1 (0.7)	1.000
Myocardial infarction	0 (0)	1 (0.7)	1.000
Target vessel MI	0 (0)	1 (0.7)	1.000
Periprocedural MI	0 (0)	1 (0.7)	1.000
Any revascularisation	30 (22.2)	18 (13.2)	0.052
TVR	23 (17.0)	13 (9.6)	0.068
TLR	18 (13.3)	11 (8.1)	0.161
Stent thrombosis	0 (0)	1 (0.7)	1.000
Definite	0 (0)	0 (0)	
Probable	0 (0)	0 (0)	
Acute (0-24 h)	0 (0)	0 (0)	
Subacute (>24 h to 30 days)	0 (0)	0 (0)	
Late (>30 days to 1 year)	0 (0)	1 (0.7)	

Values are n (%). *1-month follow-up includes a window of ±7 days; **1-year follow-up includes a window of ±30 days. †Target lesion failure was defined as a composite of cardiac death, target vessel MI, or TLR. ‡Patient-oriented composite endpoint was defined as a composite of all-cause death, all MI, or any revascularisation. BCB: biolimus-coated balloon; MI: myocardial infarction; PCB: paclitaxel-coated balloon; TLR: target lesion revascularisation; TVR: target vessel revascularisation

was different. The crystallisation process of BA9 used in this study can obtain more uniform BA9 crystals, which may considerably influence the outcomes.

In the subgroup analysis using OCT, no notable disparity was found in the 9-month neointimal area between the two groups. This finding further supports the conclusion that there was no inferiority in in-segment late lumen loss between the two DCBs. Nevertheless, quantitative coronary angiography analysis revealed that the BCB group exhibited a higher level of percentage stenosis after the procedure. This could potentially be attributed to the higher compliance of the PCB group compared to the BCB group. Consequently, under the same dilation pressure, it is plausible that the PCB group would experience a larger lumen diameter, resulting in a lower degree of postprocedural stenosis.

Although there were no significant differences in the rates of all clinical events, the BCB group exhibited numerically higher rates of the patient-oriented composite endpoint and any revascularisation compared to the PCB group. The observed differences may stem from various factors. The limited sample size undermines robust statistical comparisons of clinical event rates, and the possibility of random occurrences cannot be entirely excluded. Moreover, the potential shorter duration of biological activity associated with -limus compared to paclitaxel may contribute to a late catch-up phenomenon in clinical event rates at the 12-month follow-up[21]. Therefore, due to the moderate sample size of this study, further research with larger participant cohorts and extended follow-up durations should be conducted to provide a more comprehensive understanding of this matter.

Limitations

Firstly, the study had an insufficient number of patients to detect differences in clinical endpoints, and the completion rate for the 9-month angiographic follow-up fell slightly

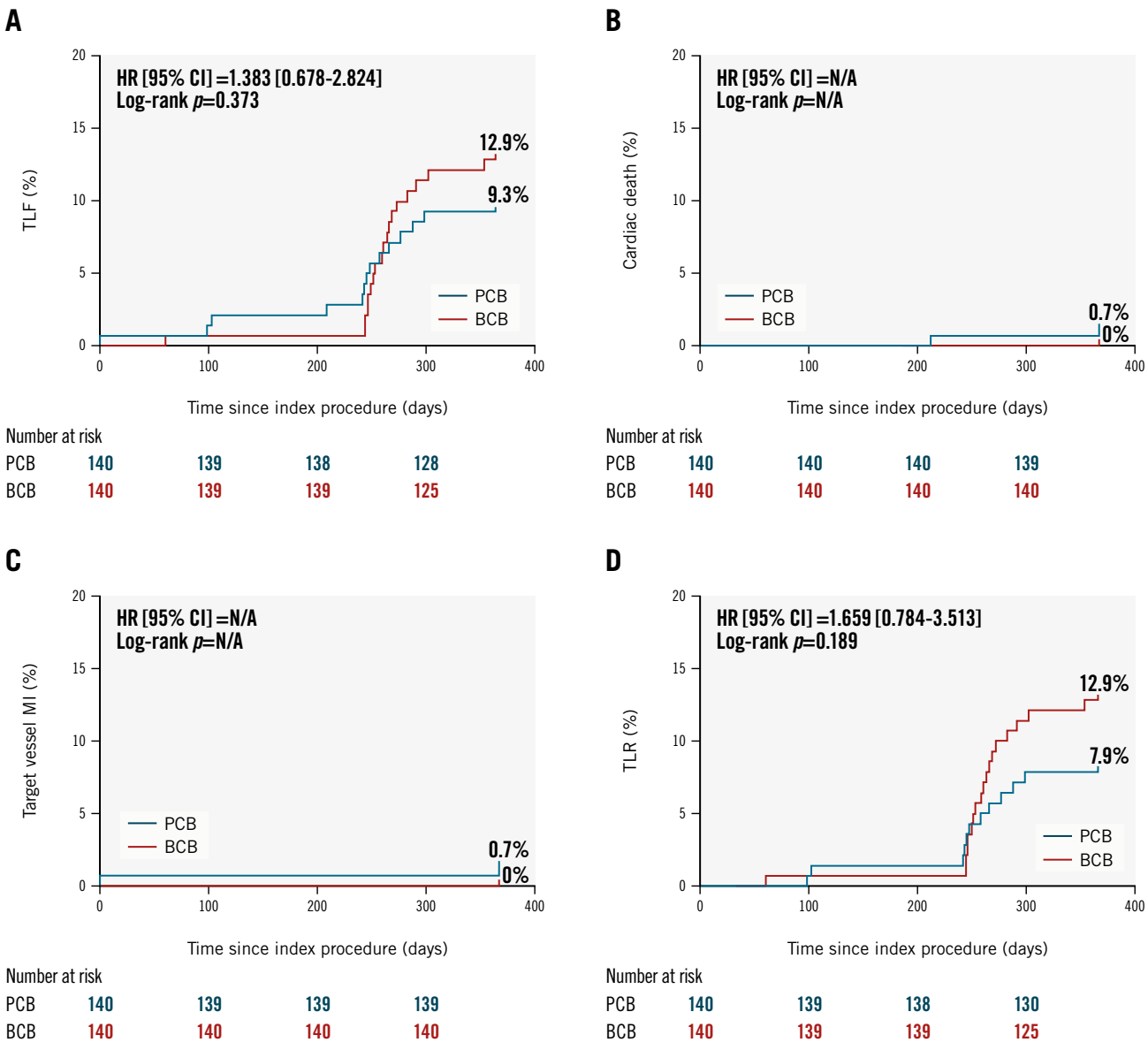

Figure 3. *Time-to-event curves for selected clinical endpoints up to 1 year. Kaplan-Meier curves show the cumulative incidence of (A) target lesion failure; (B) cardiac death; (C) target vessel MI; and (D) TLR. BCB: biolimus-coated balloon; CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; N/A: not applicable; PCB: paclitaxel-coated balloon; TLF: target lesion failure; TLR: target lesion revascularisation*

below expectations (83%). Secondly, there lacked the necessary scale for conducting subgroup analyses, and a significant number of high-risk patients and complex lesions were excluded from participation. Additional research should be carried out to ascertain the efficacy of BCBs in these specific patient populations and lesion types. Thirdly, due to the limited availability of fully mature conditions for conducting OCT examinations across all participating centres, only a small subset of patients completed the OCT assessments, limiting the statistical power of the OCT subgroup data analysis. Finally, the current follow-up period only spanned one year. As per the study protocol, a 3-year clinical follow-up should be conducted to evaluate the long-term prognosis of BCBs in treating DES-ISR. Moreover, it would have been intriguing to consider the emerging paradigm that ISR treatment should be tailored based on its underlying causative mechanism. It should be noted that there was no class effect among DCBs. Therefore, our findings cannot be widely generalised to other -limus-coated DCBs.

Conclusions

This randomised trial has confirmed that the novel BCB for coronary DES-ISR is as effective and safe as the established PCB, showing non-inferiority for 9-month LLL and neointimal area, with no stent thrombosis or myocardial infarction up to 12 months. These results suggest the potential of BCBs to improve clinical outcomes in coronary ISR treatment.

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Conflict of interest statement

The authors have no conflicts of interest to declare in regard to this manuscript.

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Supplementary data

Supplementary Appendix 1. BIO ASCEND ISR China study protocol.

Supplementary Appendix 2. CONSORT 2010 checklist of information to include when reporting a randomised trial.

Supplementary Appendix 3. BIO ASCEND ISR study organisation and participating centres.

Supplementary Table 1. Nine-month in-segment late lumen loss in the full analysis set and per protocol set.

Supplementary Table 2. Optical coherence tomography substudy results.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00295

Supplementary data

Supplementary Appendix 1. BIO ASCEND ISR China study protocol.

Inclusion and Exclusion Criteria

General selection criteria:

1．18 years old ≤ The age of the subject ≤80 years old;

2. Stable angina pectoris, acute coronary syndrome, old myocardial infarction (MI) or confirmed asymptomatic myocardial ischemia;

3. The subjects had no contraindications to coronary revascularization (PCI or CABG);

4. The subjects agreed to receive clinical follow-up at discharge, 1 month after operation, 6 months after operation, 9 months after operation, 1 year, 2 years and 3 years after operation, and angiographic follow-up 9 months after operation.

5．Subjects can understand the purpose of the study and have sufficient compliance with the research plan. And willing to sign the informed consent and accept the risks and benefits stated in the informed consent.

Lesion-related:

1. First stent restenosis (including bare stent, inert coating stent and active drug coating stent): Mehran type I, type II and type III stenosis;

2. At most, there are 2 ISRs that need interventional therapy confirmed by angiography (diameter stenosis ≥70% or ≥50% with ischemia evidence) or functional examination (such as FFR<0.8), and the lesion segments include new lesions within 5mm outside the edge of the stent;

3. In the study, at most 2 drug balloons were used (Biolimus released coronary balloon catheter or paclitaxel-released coronary balloon catheter), and only one drug balloon could be used for each lesion;

4. The distance between other primary lesions requiring interventional therapy and target lesions must be > 10 mm.

Exclusion Criteria:

Any subject meeting any of the below clinical exclusion criteria will not be eligible for enrollment in the study:MI

General exclusion criteria:

1. Patients with any MI within 1 week, or patients with for more than one week, but the myocardial enzyme CK or CK-MB has not returned to normal;

2. Patients with severe congestive heart failure (NYHA IV) or severe valvular heart disease;

3. Female patients who are planning or are pregnant (or breastfeeding);
4. Patients with severe renal failure with creatinine > 2.0 mg/dL(177μmol/L);
5. Left ventricular ejection fraction < 30%;
6. Coagulation disorder, platelet count < 100×10^{9} / L;
7. Patients with cardiogenic shock;
8. Patients who need to receive cytostatics or radiotherapy for accompanying diseases;
9. Patients who are known to be allergic to aspirin, clopidogrel, graceful mousse, tigrello, heparin, contrast agent and paclitaxel, or who have contraindications for the use of aspirin or clopidogrel or tigrello;
10. Patients with hemorrhagic constitution, or with a history of cerebral hemorrhage, active peptic ulcer or gastrointestinal bleeding in the past 6 months, will restrict or prohibit the use of anticoagulant therapy or anticoagulant drugs;
11. Patients with life expectancy less than 1 year or potential factors of clinical follow-up difficulties;
12. Patients who are participating in any other clinical trials;
13. For other reasons, the researchers think that patients are not suitable for selection.

Lesion-related:

1. The total number of lesions expected to be treated is more than 3 (including non-target lesions that need to be treated), and the number of lesions expected to be treated on each coronary artery is more than 2;
2. ISR lesions that have been treated before;
3. The target lesion is tortuous, severely calcified and angulated, and it is expected that the drug balloon will not pass;
4. Left main trunk and opening lesions within 5mm from root aorta;
5. Patients who have undergone CABG before;
6. Patients with three-vessel disease requiring treatment;
7. The target lesion involves branches, and the diameter of branch vessels is > 2.5mm;
8. Evidence of extensive thrombosis in the target vessel before intervention;
9. Total occlusion of TIMI 0 blood flow in the target lesion (Mehran IV stenosis).

The rationale and preclinical evidence of Biosimus A9

Biosimus A9 (BA9) is a derivative of sirolimus, which is a patented product exclusively invented by the parent company of JW Medical Systems, Singapore Biosensor International Group. BA9 retains the basic skeleton of sirolimus, and carries out derivative modification at its 40th position. It can effectively prevent the proliferation of smooth muscle cells and inhibit the inflammatory reaction of intimal hyperplasia by arresting the cell cycle in G1 phase. So as to prevent the occurrence of vascular restenosis. At the same time, BA9 is ten times more fat-soluble than sirolimus, and can be quickly absorbed by tissues, thus minimizing exposure and quickly entering the blood circulation, effectively inhibiting intimal hyperplasia and reducing late lumen loss.

In the animal experiment, 15 miniature pigs were used, with naked balloons as control, and one balloon was used in RCA, LAD and LCX of each pig. The safety and effectiveness were evaluated at 28 days, and the detailed evaluation of internal histology, safety and pharmacokinetics (PK), drug release characteristics of BA9 at different time points and target tissue uptake were compared. These BCB was produced by JWMS which was the same product as used in BIO-RISE China study. The results show that:

- **28-day histopathological evaluation**

– There was no significant difference in the main reference data such as lumen area, intima area, intima thickness, percentage of area stenosis and injury score between the test group and the control group.

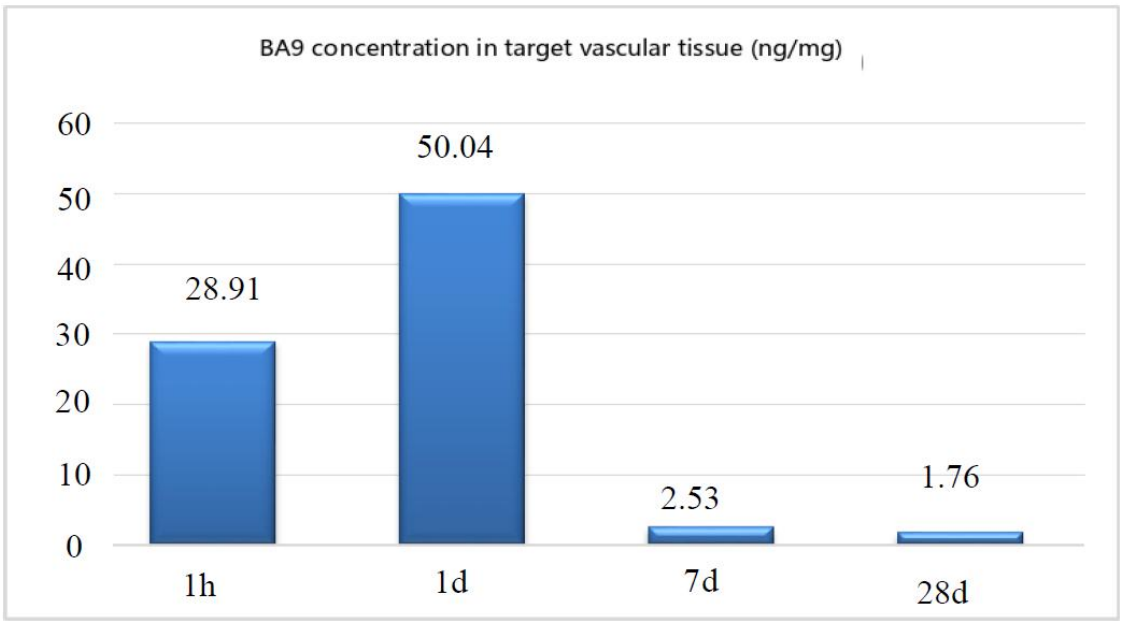
– Compared with bare balloon, DCB-BA9 drug balloon has higher fibrin and inflammation score, which is the result of biological reaction caused by drugs existing in tissues and cells.

	Medial/Intimal Fibrin Score*	Adventitial Inflammation Score*
DCB-BA9 (n=10)	0.033±0.11	0.13±0.17
Bare balloon (n=10)	0.00±0.00	0.033±0.11
P-value	0.32	0.13

Values represent the overall means±SD for each cohort, which includes the mean of three sections per vessel.
* Injury to the vessel was graded 0 to 4 to determine if all the treatment groups had consistent or similar amounts of overstretch. A score of less than "1.0" is considered minimal injury according to the criteria as defined by Yazdani et al[22].

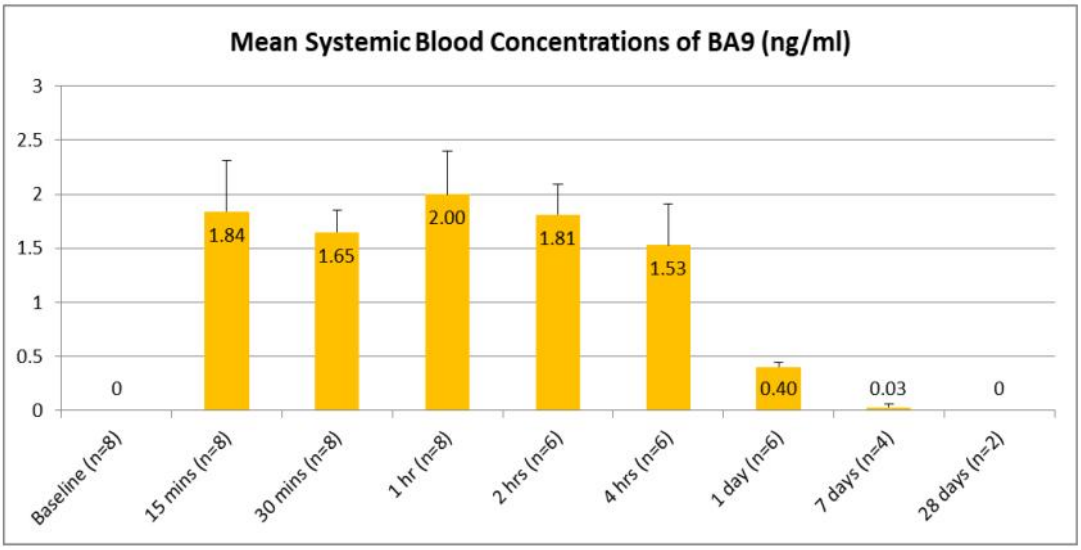
Conclusion: 1. There is no acute thrombus in the target vessel; 2. There are no serious adverse reactions caused by drugs or auxiliary drugs.

- **Drug concentration in target vascular tissue**



Conclusion: 1. BA9 can be quickly absorbed by the target vascular tissue; 2. BA9 can stay in the target blood vessel for more than 28 days.

- **Pharmacokinetic study in vivo**



	Baseline	15 mins	30 mins	1 hr	2 hrs	4 hrs	1 day	7 days	28 days
N	8	8	8	8	6	6	6	4	2
mean of BA9B*	0.00	1.84	1.65	2.00	1.81	1.53	0.40	0.03	0.00
SD	0.00	0.47	0.20	0.40	0.28	0.38	0.04	0.03	0.00

*BA9B = Systemic Blood Concentrations of BA9 (ng/ml)

BA9 correlation test	C_{max} (ng/ml)
DCB animal (porcine) experiment PK	2
Clinical PK of BA9 drugs[7]	79.4
BioFreedom stent clinical PK	7.23

C_{max} = Drug Maximum concentration.

Conclusion: The blood concentration of BA9 is lower than that of other clinical trials, and there is no drug toxicity.

Pre-specified Endpoints and Definitions

Primary Endpoint

In-segment late lumen loss (LLL) at 9 months after the procedure (defined as the postprocedural minimal lumen diameter minus the minimal lumen diameter at 9 months).

Major secondary endpoint:

Neointimal area 9 months after the procedure (OCT subgroup)

Secondary Endpoints

1. **The success rate of interventional therapy:**

    - **Device success:** The drug balloon catheter can reach the treatment lesion, expand successfully, without rupture (rated bursting pressure), and withdraw successfully.
    - **Lesion success:** defined as residual stenosis of target lesion ≤30% and TIMI blood flow 3, without obvious dissection of type C or above.
    - **Clinical success:** defined as the lesion was successful, and no major adverse cardiac events (including target lesion revascularization, MI and death) occurred before discharge.

2. **Clinical endpoints:**

    - **Restenosis rate in target lesion segment 9 months after the procedure:** refers to the proportion of patients with restenosis in the target lesion segment and the degree of diameter stenosis ≥50%.
    - **Target lesion failure (TLF)**, refers to a device-oriented composite of cardiac death, target vessel MI, and clinically-driven target lesion revascularisation.
    - **Patient-oriented composite endpoint (PoCE)**, including all-cause death, all MI, or any revascularization.
    - **Stent thrombosis,** Stent thrombosis was defined according to Academic Research Consortium (ARC) criteria.

Definitions

1. **Death:** Death was defined according to the Academic Research Consortium
    - **Cardiac death:** Any death due to a proximate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths including those related to concomitant treatment..

- **Non-cardiac death:** Any death with a definite non-cardiac cause, including infection, malignancy, sepsis, pulmonary disease, accident, suicide, trauma, or stroke.
- All deaths were considered to be cardiac death unless an alternate non-cardiac cause could be unequivocally identified, even in patients with coexisting serious non-cardiac disease (e.g., cancer, infection, or end-stage kidney disease).

2. **Procedural MI:** Procedural MI was defined according to the SCAI Definition of Myocardial Infarction. Procedural MI occurs within 48 hours of the index procedure:
   - In patients with normal baseline CK-MB: Elevation of CK-MB >10×99th percentile of the upper reference limit (URL), or CK-MB increase >5×99th percentile of the URL plus new pathological Q waves in >2 contiguous leads or new left bundle branch block (LBBB).
   - In patients with elevated baseline CK-MB in whom CK-MB levels are stable or falling: CK-MB rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
   - In patients with elevated CK-MB in whom CK-MB levels have not been shown to be stable or falling: CK-MB rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant Ml, such as new onset or worsening heart failure or sustained hypotension
3. **Clinically-driven revascularization:** Clinically-driven revascularization was defined according to the Academic Research Consortium:
   - **Target lesion:** A target lesion was defined as a lesion revascularized in the index procedure (or during a planned or provisional staged procedure).
   - **Target Vessel:** The target vessel was defined as the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself.
   - **Target Vessel Non-Target Lesion:** The target vessel non-target lesion was a lesion in the epicardial vessel or branch or graft that contains the target lesion; however, this lesion is outside of the target lesion by at least 5 mm distal or proximal to the target lesion determined by quantitative coronary angiography.
   - **Non-Target Vessel:** The non-target vessel was any vessel that was not attempted to be revascularized at the index procedure but was subsequently revascularized.
   - **Target Lesion Revascularization (TLR):** Target lesion revascularization was defined as any repeat PCI of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion.
   - **Target Vessel Revascularization:** Target vessel revascularization was defined

as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel.

- **Non-Target Lesion Revascularization:** Any revascularization in a lesion other than the target lesion was considered a non-target lesion revascularization.
- **Non-Target Vessel Revascularization:** Any revascularization in a vessel other than the target vessel was considered a non-target vessel revascularization.

4. **Stent thrombosis:** Stent thrombosis was defined according to Academic Research Consortium criteria.
    - **Definite stent thrombosis:** Definite stent thrombosis was considered to have occurred by either angiographic or pathologic confirmation. Angiographic confirmation of stent thrombosis was defined as the presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent, with at least 1 of the following criteria within a 48-hour time window: 1) acute onset of ischemic symptoms at rest; 2) new ischemic ECG changes that suggested acute ischemia; 3) typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI); 4) non-occlusive thrombosis (a spherical, ovoid, or irregular non-calcified filling defect or lucency surrounded by contrast material on 3 sides or within a coronary stenosis seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream); 5) occlusive thrombus (TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if it originates from the side branch). Pathological confirmation of stent thrombosis was defined as evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy. Note: The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms was not considered a confirmed stent thrombosis (silent occlusion).
    - **Probable stent thrombosis:** Probable stent thrombosis was considered to have occurred in the following cases: 1) any unexplained death within the first 30 days after intracoronary stent implantation (note: for patients presenting with STEMI, one might consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis); 2) irrespective of the time after the index procedure, any MI that was related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.
    - **Possible stent thrombosis:** Possible stent thrombosis was considered to have occurred with any unexplained death from 30 days after intracoronary stent

implantation until end of trial follow-up.

- **Acute stent thrombosis:** 0-24 hours post stent implantation (note: time 0 was defined as the time point after the guiding catheter had been removed and the subject had left the catheterization lab).
- **Subacute stent thrombosis:** >24 hours-30 days post stent implantation.
- **Early stent thrombosis:** 0-30 days post stent implantation including acute or subacute stent thrombosis.
- **Late stent thrombosis:** 31 days-1 year post stent implantation.
- **Very late stent thrombosis:** >1 year post stent implantation.

Supplementary Appendix 2. CONSORT 2010 checklist of information to include when reporting a randomised trial*.

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7

Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	7
	11b	If relevant, description of the similarity of interventions	N/A

Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	11
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	14
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12-14

Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	17
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	By request
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2

Citation: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8:18.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.

Supplementary Appendix 3. BIO ASCEND ISR study organisation and participating centres.

The BIO ASCEND ISR China study investigators, angiographic core lab, statistical analysis, data management, data monitoring and coordination, sponsor, and sites are listed as follows:

Principal Investigator: Yundai Chen, MD

Angiographic Core Lab: Cardiovascular Imaging Center, Beijing Health Promotion Association, Beijing, China

Data Management and Statistics: Medical Research and Biometrics Center, National Center for Cardiovascular Diseases, Beijing, China

Data Monitoring and Coordination: R&G, Beijing, China

Sponsor: Shandong JW Medical Systems Ltd.

Sites and Investigators:

[1]Department of Cardiology, the First Medical Center of Chinese PLA General Hospital, Beijing, China（Yundai Chen, Lian Chen, Zhijun Sun, Yu Wang）

[2]Senior Department of Cardiology, the Sixth Medical Center of Chinese PLA General Hospital, Beijing, China (Lei Gao)

[3]Beijing AnZhen Hospital Capital Medical University, Beijing, China. (Liu Jinghua, Peng Hongyu, Li Wenzheng, Wu Zheng)

[4]Beijing Friendship Hospital Capital Medical University, Beijing, China (Chen Hui, Li Dongbao, Wang Dongxing, Ding Xiaosong)

[5] The first hospital of Jilin university, Changchun, China (Tong Qian, Gao Xiaodong, Liu Quan, Zhao Xuezhong)

[6] Tianjin Chest Hospital, Tianjin, China (Qin Qin, Yang Ning, Yang Jingyu, Li Yang)

[7] Cangzhou Central Hospital, Cangzhou, China (Zhang Jun, Niu Heping, Fu Jinguo, Wan yanfang)

[8] First affiliated hospital of Zhengzhou university, Zhengzhou, China (Qiu Chunguang, Wang Xi, Wang Xule, Lu Wenjie)

[9] The Ninth People's Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China (Wang Changqian, Zhang Junfeng, Fan Yuqi)

[10]Sir Run Run Shaw Hospital, Zhejiang University School of Medicine，Hangzhou, China (Fu guosheng, Qiu Fuyu, Zhu Jun, Kong Xugang)

[11] Zhongda Hospital Southeast University, Nanjing, China (Magenshan, Wei Qin, Chen Lijuan, Tong Jiayi)

[12] Nanjing Drum Tower Hospital The Affiliated Hospital of Nanjing University Medical School, Nanjing, China (Xu Biao, Wang Kun, Wang Yi, Song Jie)

[13] Xiangya Hospital Central South University, Changsha, China (Yu zaixin, Xie Wei, Long Tianyi)

[14] The Third Xiangya Hospital of Central South University, Changsha, China (Cao Yu, Huang Wei, Sheng Zhe, Zhou Li)

[15]Xiangtan Central Hospital, Xiangtan, China (Wu mingxing, Wang Lei, Huang Haobo, Hu Hailong)

[16]Shanxi Provincial Cardiovascular Hospital, Taiyuan, China (An Jian, Dong Jin, Wang Zhongchao, Zhang Zhulin)

[17]General Hospital of Ningxia Medical University, Yinchuan, China (Jia Shaobin, Zhang Guoshan, Wei Ning, Chen Dapeng)

[18] West China Hospital of Sichuan University, Chengdu, China (He Yong, He Sen, Yang Xuemei, Huang Baotao)

Supplementary Table 1. Nine-month in-segment late lumen loss in the full analysis set and per protocol set.

	BCB group	PCB group	Difference (95% CI)	$p_{noninferiority}$ value
Full-Analysis-Set	Patients n=114; Lesions n=125	Patients n=116; Lesions n=130		
In-segment LL, mm (per patient)	0.23±0.37	0.25±0.35	-0.02 [-0.12 to 0.07]	<0.0001
In-segment LL, mm (per lesion, GEE)	0.25±0.40	0.27±0.39	-0.03 [-0.13 to 0.07]	<0.0001
Per-Protocol-Set	Patients n=113; Lesions n=123	Patients n=115; Lesions n=129		
ln-segment LL, mm (per patient)	0.22±0.34	0.25±0.35	-0.03 [-0.12 to 0.06]	<0.0001
ln-segment LL, mm (per lesion, GEE)	0.24±0.39	0.27±0.39	-0.04 [-0.14 to 0.06]	<0.0001

Values are n (%) or mean±SD. GEE model was used for lesion-level analysis to account for the cluster effect.
GEE=generalized estimating equation; LL=late loss; other abbreviations as shown in Table 1.

Supplementary Table 2. Optical coherence tomography substudy results

	Preoperative			Immediately after PCI			Follow-up		
	BCB group (n=21)	PCB group (n=21)	p value	BCB group (n=27)	PCB group (n=27)	p value	BCB group (n=23)	PCB group (n=20)	p value
Mean luminal area	5.02±1.46	4.88±1.89	0.849	6.23±1.57	5.58±1.82	0.163	5.71±1.44	5.13±1.64	0.226
Minimal luminal area	2.28±0.96	2.04±1.37	0.611	4.56±1.35	3.97±1.46	0.134	3.55±1.04	3.43±1.16	0.717
Mean stent area	7.45±2.26	7.64 ±2.37	0.850	8.16 ±2.17	7.63 ±2.17	0.371	8.03±2.15	7.50±2.26	0.436
Minimal stent area	5.70±1.76	6.15±2.17	0.578	6.49±1.73	6.08±2.02	0.429	6.25±1.76	5.98±2.02	0.635
Average neointimal cross-sectional area	2.44±1.40	2.75±1.16	0.562	1.93±1.01	2.05±0.88	0.640	2.32±1.04	2.37±0.93	0.882
Change of average neointimal cross-sectional area*	-	-	-	-	-	-	0.29±0.35	0.28±0.43	0.913
Average neointimal volume	65.87±47.41	69.30±30.68	0.839	49.20±30.37	51.7±27.3	0.751	57.89±36.96	58.35±24.84	0.962
Change of average neointimal volume†	-	-	-	-	-	-	7.58±9.98	7.90±10.83	0.921
Number of analyzed struts	249.85± 106.35	250.36±65.42	0.989	235.74±91.49	223.44±61.98	0.566	230.87±80.76	220.25±47.88	0.598
Number of uncovered struts	2.54 ±2.70	1.00±2.72	0.179	1.41±3.65	0.78±2.14	0.444	0.65±2.92	0.45±1.39	0.769
Ratio of uncovered struts	0.97±1.05	0.29±0.80	0.094	0.49 ±1.22	0.43±1.30	0.868	0.23±1.01	0.29±0.96	0.831

Values are mean±SD. *Defined as average neointimal cross-sectional area at follow-up minus the post-procedural average neointimal cross-sectional area. †Defined as average neointimal volume at follow-up minus the post-procedural average neointimal volume. PCI=percutaneous coronary intervention; other abbreviations as shown in Table 1.