

Drug-Coated Balloon Angioplasty of the Side Branch During Provisional Stenting

The Multicenter Randomized DCB-BIF Trial

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ABSTRACT

BACKGROUND Side branch stenting is often required during provisional stenting, leading to suboptimal results. Drug-coated balloons (DCB) for the compromised side branch have emerged as an attractive strategy. However, the benefit of DCB for coronary bifurcations remains unclear.

OBJECTIVES This study aimed to investigate whether DCB, compared with a noncompliant balloon (NCB), for the pinched side branch improves the outcomes of provisional stenting in patients with simple, true coronary bifurcations.

METHODS In this multicenter, randomized controlled trial, patients with true coronary bifurcations who had side branch diameter stenosis of $\geq 70\%$ after main vessel stenting at 22 centers in China, Indonesia, Italy, and Korea were randomly assigned to either DCB or NCB intervention. The primary endpoint was major adverse cardiac events, a composite of cardiac death, target vessel myocardial infarction, or clinically driven target-lesion revascularization at the 1-year follow-up.

RESULTS Between September 8, 2020, and June 2, 2023, 784 patients with true coronary bifurcation lesions undergoing main vessel stenting and having a severely compromised side branch were randomly assigned to the DCB (n = 391) or NCB (n = 393) group. One-year follow-up was completed in all patients. The primary endpoint occurred in 28 patients in the DCB group and 49 patients in the NCB group (Kaplan-Meier rate: 7.2% vs 12.5%; HR: 0.56; 95% CI: 0.35-0.88; $P = 0.013$), driven by a reduction in myocardial infarction. There were no significant differences between groups in procedural success, crossover to a 2-stent approach, all-cause death, revascularization, or stent thrombosis.

CONCLUSIONS In patients with simple and true coronary bifurcation lesions undergoing provisional stenting, main vessel stenting with a DCB for the compromised side branch resulted in a lower 1-year rate of the composite outcome compared with an NCB intervention for the side branch. The high rates of periprocedural myocardial infarction, which occurred early and did not lead to revascularization, are of unclear clinical significance. (JACC. 2024;■:■-■) © 2024 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

Manuscript received June 28, 2024; revised manuscript received August 22, 2024, accepted August 26, 2024.

**ABBREVIATIONS
AND ACRONYMS****DCB** = drug-coated balloon**KBI** = kissing balloon inflation**MI** = myocardial infarction**MV** = main vessel**NCB** = noncompliant balloon**PCI** = percutaneous coronary
intervention**PMI** = periprocedural
myocardial infarction**POT** = proximal optimization
technique**SB** = side branch**TLR** = target lesion
revascularization**TVMI** = target vessel
myocardial infarction

Coronary bifurcation lesions represent 15% to 20% of all percutaneous coronary interventions (PCIs). Stenting bifurcation lesions is technically challenging and is associated with suboptimal clinical events.¹ The upfront 2-stent approach,² particularly the double kissing crushing technique,³⁻⁵ has fewer clinical events for DEFINITION (Definitions and Impact of Complex Bifurcation Lesions on Clinical Outcomes After Percutaneous Coronary Intervention Using Drug-Eluting Stents) criteria-defined complex bifurcations⁵⁻⁷ and is recommended for distal left main bifurcation lesions.⁸ However, for those considered simpler, with a side branch (SB) lesion length of <10 mm, the provisional stenting approach of stenting the main vessel (MV) first and potentially performing SB rescue stenting if necessary is the preferred strategy.⁵⁻⁹

For the provisional stenting approach, SB predilation before MV stenting is not recommended to minimize the need for stenting the SB.^{1,3-5} Unfortunately, carina and plaque shift often lead to compression of the ostial SB with severe stenosis.^{1,7-9} Consequently, using a noncompliant balloon (NCB) to dilate the SB is effective to address the pinched SB. However, balloon angioplasty can easily result in SB dissection or abrupt occlusion, necessitating a second stent in the SB.^{1,4-9} In cases of in-stent restenosis, it tends to localize at the ostial SB following SB stenting, leading to stent thrombosis and repeat revascularization.^{1,3-7} Therefore, the concept of “nothing left” after SB intervention using a drug-coated balloon (DCB) is appealing to most interventional cardiologists.^{10,11}

The most commonly used drug coated on the balloon is paclitaxel, which can exert an anti-intimal hyperplasia effect, prevent restenosis, and reduce cell differentiation by blocking the formation of microtubules.¹⁰⁻¹² Previous studies have demonstrated the advantages of DCB in treating in-stent restenosis¹³ and small coronary artery lesions.^{14,15} However, the clinical benefits of DCB have not been thoroughly examined in powered randomized clinical trials for coronary artery bifurcation lesions. Therefore, we conducted this randomized trial to assess the efficacy of DCB compared to NCB angioplasty for the SB following stenting of the MV in true coronary artery bifurcation lesions.

METHODS

STUDY DESIGN AND PARTICIPANTS. DCB-BIF (Comparison of Noncompliant Balloon With Drug-Coated Balloon Angioplasties for Side Branch After Provisional Stenting for Patients With True Coronary Bifurcation Lesions) was a randomized, masked, multicenter trial conducted at 22 centers in China (n = 18), Italy (n = 1), Indonesia (n = 2), and Republic of Korea (n = 1) ([Supplemental Appendix](#)). The trial included patients with simple⁷ and true coronary bifurcation lesions (Medina 1,1,1; 0,1,1; or 1,0,1),¹⁶ and each operator was required to have more than 100 PCI procedures for bifurcation lesions annually, either at their centers or at other visiting centers.

The background and study design of the trial have been previously reported elsewhere.¹⁷ The trial was conducted in compliance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board or Ethics Committee at each participating center. A Data and Safety Monitoring Board monitored the trial, and an independent adjudication committee, masked to treatment allocation, assessed all clinical events.

Patients aged 18 years or older with silent ischemia, stable or unstable angina, or acute myocardial infarction (MI) older than 1 week from the onset of chest pain to admission were eligible for inclusion in the trial. Target lesions had to meet all the following specific criteria by visual estimation, including a reference vessel diameter (both MV and SB) of ≥ 2.5 mm, baseline diameter stenosis of $\geq 50\%$, SB lesion length of <10 mm, successful recanalization of a chronic total occlusion in either the MV or SB before enrollment, and ostial SB diameter stenosis of $\geq 70\%$ after stenting the MV ([Supplemental Table 2](#)). Exclusion criteria included allergy to the study balloon, stent, or protocol-required concomitant medications; intolerance to dual-antiplatelet therapy; life expectancy of <12 months; pregnancy or breastfeeding; participating in another clinical trial; restenotic lesion; severe calcification requiring rotational atherectomy; and hemodynamic instability (including cardiogenic shock). Written informed consent was obtained from all patients or their family members before random assignment, and sex data were collected through physical examination.

RANDOMIZATION AND MASKING. Patients with residual stenosis $\geq 70\%$ in the SB after stenting the MV were eligible for SB angioplasty and underwent

randomization using an interactive web-based system with 6 permuted block numbers. They were assigned to receive either DCB angioplasty or NCB angioplasty in a 1:1 ratio, stratified by diabetes, initial presentations, and sites.

Because of the nature of the procedure, random assignment was not blinded for the physicians and staff in the cardiac catheterization laboratory. However, patients and all personnel interacting with the patient postcatheterization, including researchers, treating physicians, and health outcomes assessors, were blinded to the random assignment.

PROCEDURES. Provisional stenting was performed for all bifurcation lesions in accordance with the European Bifurcation Club (EBC) recommendations ([Supplemental Figure 1](#)).^{1,6} Briefly, following wire placement in both the MV and SB, predilation of the MV was left at the operator's discretion, and predilation of the SB was not recommended. Stenting of the MV (at a 1:1 ratio of diameter) was followed by a proximal optimization technique (POT) using an NCB (balloon/stent ratio of 1:1). In cases where the ostial SB diameter stenosis was $\geq 70\%$ after POT, subsequent steps were performed based on randomization results.

In the DCB group, an NCB with a ratio of 1:1 balloon-to-vessel diameter was only allowed to dilate the ostial SB after rewiring. Sufficient predilation was defined as residual stenosis of $\leq 50\%$. Subsequently, a DCB, which had to be 2 to 3 mm longer on the proximal and distal sides than the predilation balloon length, was inflated at nominal pressure for 60 s. If patients experienced chest pain with ST-segment changes during inflation, the duration of DCB inflation had to be divided into 2 30-second intervals with 10 to 15 seconds of deflation between each inflation. The recommended ratio of the DCB diameter to the SB vessel diameter was between 0.8 and 1.0. The DCB had to be delivered to the lesion within 2 minutes after entering the guiding catheter. Following DCB angioplasty, kissing balloon inflation (KBI) using 2 NCBs (at a ratio of 1:1 to vessel diameter) and re-POT using another large NCB (with a balloon-to-proximal stent ratio of 1:1) were performed subsequently. Indications for SB rescue stent placement included type C dissection or TIMI flow grade of < 3 ([Supplemental Table 9](#)). Repeat KBI and POT had to be performed again after stenting the SB.

In the NCB group, all steps and indications for SB stenting were the same as those described in the DCB group, with the only exception being that a DCB was not used. To avoid the stent strut injury, a cutting

balloon or scoring balloon was not allowed to dilate the SB after stenting the MV.

Intravascular imaging assessments before and after procedures were left at the operator's discretion. Biomarker measurements (including high-sensitivity troponin) were performed before the procedure, every 6 to 9 hours within the first 24 hours and every 24 hours thereafter until 48 hours post-PCI. P2Y₁₂ receptor inhibitor and aspirin were to be prescribed for 12 months (unless patients were at high risk of bleeding) to reduce the risk of thrombosis. The choice of P2Y₁₂ receptor inhibitors was also left to the physician's discretion. A core laboratory used software from Beijing Crealife Technology Co, Ltd, Beijing, China, to measure the quantitative fractional reserve or quantitative coronary artery analysis. The mean of the distal and proximal reference vessel diameter was reported as the value for both MV and SB.

OUTCOMES. All primary and secondary clinical events were required to be adjudicated by an independent clinical events committee comprising physicians who were blinded to treatment allocation and used source documentation ([Supplemental Appendix](#)).

The primary endpoint was defined as the occurrence of major adverse cardiac events at 12 months following the procedures, encompassing cardiac death, target vessel MI (TVMI), or clinically driven target-lesion revascularization. Secondary endpoints included all-cause death or cardiac death, major adverse cardiac event without periprocedural MI (PMI), periprocedural and spontaneous MI, TVMI, clinically driven target lesion revascularization (TLR) or target vessel revascularization, angiographic and clinical/procedural success, and crossover from 1 stent to 2 stents. The safety endpoint included definite or probable stent thrombosis. To elaborate, cardiac death was delineated as any death resulting from a proximate cardiac cause (such as MI, heart failure, or fatal arrhythmia); unwitnessed death; death of unknown cause; and all procedure-related deaths, including those associated with concomitant treatment. TVMI encompassed PMI and spontaneous MI. PMI was defined as MI occurring within 48 hours of the index procedure, in accordance with the Society of Cardiac Angiography and Interventions Definition.¹⁸ Spontaneous MI, occurring beyond 48 hours after the index procedure, was defined following the Fourth Universal Definition of Myocardial Infarction.¹⁹ In cases of postprocedural MI in which no follow-up angiogram was performed, it was assumed to be target vessel related. Clinically driven revascularization included repeat PCI or coronary artery

bypass graft surgery and was defined based on its association with the target vessels and target lesions treated during the index PCI. Regarding stent thrombosis, Academic Research Consortium definite stent thrombosis was defined as angiographic or pathologic confirmation of stent thrombosis in or within 5 mm of the stent, alongside at least one of the following criteria with a 48-hour timeframe: acute ischemic symptoms at rest, new ischemic changes on electrocardiogram, and a typical rise and fall in troponin or creatine kinase-myocardial band. Academic Research Consortium probable stent thrombosis was defined as any unexplained death within the first 30 days after PCI or any MI at any time after PCI that was linked to documented acute ischemia in the territory of the implanted stent, without angiographic or pathologic confirmation of stent thrombosis and in the absence of any other apparent cause. Angiographic success was defined as residual diameter stenosis of <30% (stented lesion, or <50% in nonstented lesion) by visual estimation with TIMI flow grade 3 in the absence of SB (diameter of ≥ 2 mm by visual estimation) occlusion. Procedural success was defined as having no in-hospital major adverse cardiovascular events in the presence of angiographic success.

STATISTICAL ANALYSIS. Based on previous studies,²⁰⁻²⁵ we estimated a 1-year rate of the primary endpoint in the NCB group to be 17.0% ([Supplemental Table 4](#)). Randomization of 784 patients was conducted to provide 80% power to demonstrate a 41% risk reduction in the primary endpoint with the DCB, assuming a 2-sided *P* value of 0.05 and a dropout rate of 5%.

Categorical variables are presented as numbers and percentages and were compared using the chi-square test or Fisher exact test. Continuous variables are reported as mean $\pm$ SD, or median (Q1-Q3) if not normally distributed and were compared using the Student's *t*-test or the Mann-Whitney *U* test, respectively. Event rates were estimated using the Kaplan-Meier method and compared using the log-rank test. Treatment effects were estimated using Cox proportional hazards regression, with results presented as HR (95% CI). The primary outcome, with and without periprocedural MI, was analyzed using the subdistribution method of Fine and Gray to account for the competing risk of noncardiac death. Treatment effects for the primary analyses were adjusted for initial presentations (ie, stable angina,

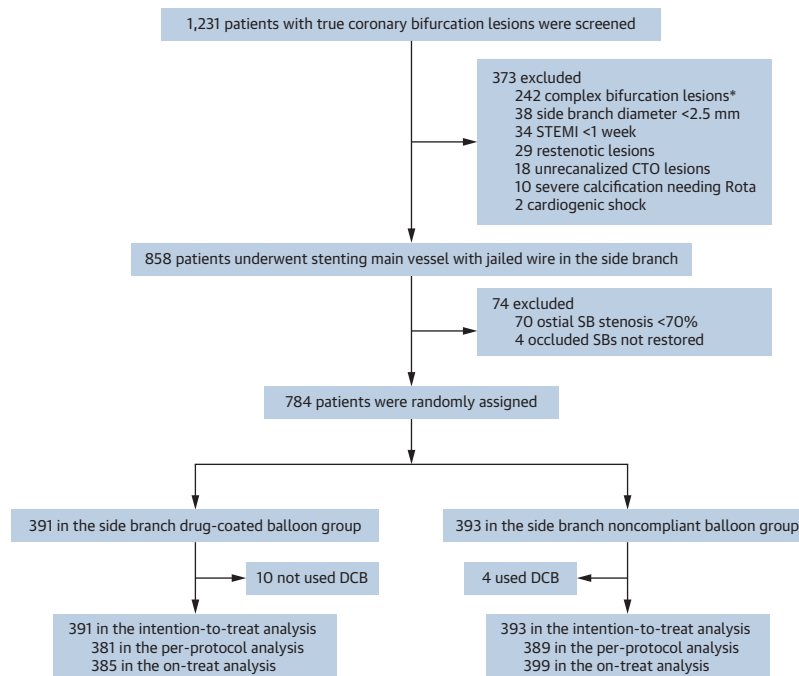
non-ST-segment elevation acute coronary syndrome vs ST-segment elevation MI), diabetes, and sites (non-Chinese, western China, eastern China, southern China, or northern China). No adjustment for multiplicity was performed for any secondary endpoints, and these should therefore be considered hypothesis-generating only. The relative treatment effects of the primary endpoint in prespecified subgroups were assessed using interaction terms in the Cox proportional hazards model. Missing data were not imputed or replaced.

All principal analyses were done in the intention-to-treat population, which included all subjects who were randomized (ie, when the subject number and allocated treatment were recorded in the Electronic Data Capture system). As a sensitivity analysis, the primary endpoint was evaluated in the per-protocol population, which comprised all randomized subjects without any significant deviations from the protocol. Subjects who did not receive the assigned treatment as recorded in the Electronic Data Capture system or received no treatment were excluded from the per-protocol population, for whom a further comparison based on the "on-treat" population (patients who really receive the DCB or NCB for the compromised SB after stenting the MV and POT) will be performed. All tests were 2-sided, and *P* < 0.05 was considered significant. Statistical analyses were done using SAS version 9.4 (SAS Institute, Inc).

RESULTS

Between September 8, 2020, and June 2, 2023, 1,231 patients with true coronary artery bifurcation lesions (Medina 1,0,1; 1,1,1; or 0,1,1) were screened ([Figure 1](#)). Of these, 858 patients with simple coronary artery bifurcation lesions underwent provisional stenting (stenting the MV with a jailed wire in the SB). The reasons for excluding 373 patients are shown in [Figure 1](#) and [Supplemental Table 5](#). Among those 858 patients who underwent provisional stenting, 784 were enrolled in the trial and randomly assigned to the DCB group (n = 391) or the NCB group (n = 393) ([Figure 1](#)). The reasons for excluding an additional 74 patients are also shown in [Figure 1](#) and [Supplemental Table 5](#).

Baseline characteristics were similar between the 2 groups ([Table 1](#), [Supplemental Table 6](#)). The median patient age was 65 years (Q1-Q3: 56-72 years). Among the participants, 601 (76.7%) were men, 183 (23.3%)

FIGURE 1 Study Flowchart of the DCB-BIF Trial

Of 858 patients with true coronary artery bifurcation lesions undergoing a provisional stenting approach (stenting the MV with a jailed wire in the side branch), 784 patients with a compromised side branch (ostial diameter stenosis $\geq 70\%$) after MV stenting and first proximal optimal technique were randomly assigned to either the DCB group ($n = 391$) or the NCB group ($n = 393$). Ten patients in the DCB group received NCB intervention for the side branch instead, and 4 patients in the NCB group received DCB intervention for the compromised side branch. These 14 patients were included in the intention-to-treat analysis but were excluded from the per-protocol population. Consequently, the on-treatment population consisted of 385 patients who received a DCB intervention for the side branch and 399 patients who received NCB angioplasty for the compromised side branch. Complex coronary bifurcation lesions were defined as side branch lesion length of ≥ 10 mm and diameter stenosis of $\geq 90\%$ (for non-left main bifurcation) or $\geq 70\%$ (for left main distal bifurcation). CTO = chronic total occlusion; DCB = drug-coated balloon; NCB = noncompliant balloon; SB = side branch; STEMI = ST-segment elevation myocardial infarction.

were women, and 287 (36.6%) had type 2 diabetes. The initial presentations were as follows: silent myocardial ischemia in 17 (2.2%) patients, stable angina in 53 (6.8%) patients, unstable angina in 479 (61.1%) patients, ST-segment elevation MI in 45 (5.7%) patients, and non-ST-segment elevation MI in 192 (24.5%).

Baseline angiographic and procedural characteristics were well matched between the groups (Table 2). Overall, 76.1% of patients had Medina 1,1,1 bifurcation lesions. Multiple vessel disease was present in 512 (65.3%) patients, bifurcation lesions in the left anterior descending artery were noted in 533 (67.9%) patients, and lesions localized at the distal left main were seen in 119 (15.2%) patients. The PCI was mostly performed via the transradial approach (764 of 784 patients; 97.4%) using a 6-F guiding catheter. Intravascular ultrasound guidance was used in 177 (22.6%) patients, and optical coherence guidance was used in

37 (4.7%) patients. After stenting the MV and ballooning the SB, KBI was performed in 760 (96.9%) patients, and re-POT was done in 658 (83.9%) patients. After stenting the MV, a DCB was used in 4 (1.0%) SBs in the NCB and 381 (97.4%) SBs in the DCB group (Table 2). The reasons for using or not using a DCB are described in Supplemental Table 8. Preparation using an NCB for SB after MV stenting was performed in all patients in the DCB group. The crossover from a 1-stent to 2-stent strategy occurred in 13 (3.3%) patients in the NCB group and 15 (3.8%) patients in the DCB group. The indications for SB stenting are shown in Supplemental Table 9. Quantitative coronary analysis after PCI showed that the mean minimal lumen diameter in the SB was 1.59 mm in the NCB group and 1.66 mm in the DCB group ($P = 0.045$). The mean acute gain in the SB was 0.55 mm in the NCB group and 0.63 mm in the DCB group ($P = 0.041$) (Table 3). The change of

TABLE 1 Baseline Characteristics and Medications at Admission

	Drug-Coated Balloon Group (n = 391)	Noncompliant Balloon Group (n = 393)	P Value
Age, y	63.8 ± 10.6	63.6 ± 10.5	0.71
Sex			0.45
Male	305 (78.0)	297 (75.6)	
Female	86 (22.0)	96 (24.4)	
Initial presentation			0.68
Silent ischemia	5 (1.3)	12 (3.1)	
Stable angina	29 (7.4)	24 (6.1)	
Unstable angina	238 (60.9)	239 (60.8)	
NSTEMI	97 (24.8)	95 (24.2)	
STEMI	22 (5.6)	23 (5.9)	
Medical history			
Hypertension	257 (65.7)	246 (62.6)	0.37
Diabetes	147 (37.6)	140 (35.6)	0.71
On insulin treatment	39 (26.5)	30 (21.4)	0.26
Dyslipidemia	251 (64.2)	236 (60.1)	0.24
Smoking ^a	164 (41.9)	153 (38.9)	0.11
Renal dysfunction ^b	10 (2.6)	17 (4.3)	0.24
Peripheral arterial disease	9 (2.3)	14 (3.6)	0.39
Previous stroke	40 (10.2)	31 (7.9)	0.27
Previous MI	44 (11.3)	39 (9.9)	0.56
Previous PCI	106 (27.1)	102 (26.0)	0.75
Previous CABG	3 (0.8)	1 (0.3)	0.37
Heart failure	25 (6.4)	23 (5.9)	0.77
Medications at admission			
Aspirin	354 (90.5)	362 (92.1)	0.45
Clopidogrel	168 (43.0)	162 (41.2)	0.66
Ticagrelor	226 (57.8)	232 (59.0)	0.77
ACEI or ARB	182 (46.5)	171 (43.5)	0.43
Calcium-channel blocker	92 (23.5)	92 (23.4)	1.00
Nitroglycerin	71 (18.2)	74 (18.8)	0.85
Statin	364 (93.1)	357 (90.8)	0.29

Values are mean ± SD or n (%). ^aDefined as ≥100 lifetime cigarettes and still smoking at the time of enrolment; other tobacco products were not included. ^bDefined as an estimated glomerular filtration rate of <60 mL/min/1.73 m².

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft surgery; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

quantitative fractional reserve is shown in [Table 3](#). KBI after dilating the SB was performed in 389 (98.9%) patients in the NCB group and 371 (94.9%) patients in the DCB group ($P = 0.001$). Complete revascularization by angiographic criteria was achieved in a similar proportion of patients in both groups. The rate of angiographic success was also comparable between the 2 groups. Procedural success was achieved in 299 (76.1%) patients in the NCB group and 332 (84.9%) patients in the DCB group ($P = 0.002$). Contrast use was similar in both groups (1.33 mL; 95% CI: -7.12 to 9.77), and procedure duration was nonsignificantly different (2.54 minutes; 95% CI: -2.29 to 7.39). There were 55 of 784 (7.0%)

patients who underwent a second PCI ([Table 2](#)). At 12 months since the procedures, 120 patients underwent repeat angiography, with 56 (14.2%) in the NCB group and 64 (16.4%) in the DCB group ($P = 0.41$).

A 1-year follow-up was completed in all patients. The primary endpoint at 1 year occurred in 49 patients in the NCB group and 28 patients in the DCB group (Kaplan-Meier rate: 12.5% vs 7.2%; HR: 0.56; 95% CI: 0.35-0.88; $P = 0.013$) ([Table 4](#), [Figure 2A](#)). The risk of spontaneous MI was also higher in the NCB group compared to the DCB group (Kaplan-Meier rate: 3.6% vs 1.0%; HR: 0.27; 95% CI: 0.09-0.81; $P = 0.029$), leading to a higher rate of TVMI in the NCB group (HR: 0.50; 95% CI: 0.30-0.84; $P = 0.009$) ([Figure 2C](#)). The numbers needed to treat were 18.9 (95% CI: 0.12-0.28) to prevent major adverse cardiac events and 38.5 (95% CI: 0.29-0.48) to prevent spontaneous MI.

We observed no significant differences in the secondary outcomes of all-cause death, cardiac death ([Supplemental Figure 2A](#)), PMI, major adverse cardiac events without PMI ([Supplemental Figure 2B](#)), clinically driven target-lesion revascularization ([Supplemental Figure 2C](#)), or stent thrombosis between the groups in the intention-to-treat population. Of 18 spontaneous MIs, 13 were diagnosed because of biomarkers increased and ST-T segment changes, 2 because of definite stent thrombosis, and the remaining 3 because of biomarkers increased and symptoms of ischemia. Of them, 13 underwent repeat angiograms, and TLR was done in 3 of 13 patients (2 in the DCB group and 1 in the NCB group). The median time interval from repeat angiography to PCI was 204 days (Q1-Q3: 119-290 days) in the DCB group and 252 days (Q1-Q3: 227-310 days) in the NCB group ($P = 0.104$). Two patients in the DCB group experienced definite stent thrombosis (at 111 days and 166 days, respectively) ([Supplemental Table 10](#)).

The relative risks of a major adverse cardiac events between the 2 groups were similar in analyses that were not covariate adjusted ([Supplemental Table 11](#), [Supplemental Figure 3](#)), in the per-protocol cohort ([Supplemental Table 12](#), [Supplemental Figure 4](#)), and in the on-treat population ([Supplemental Table 13](#), [Supplemental Figure 5](#)). The HRs for the primary endpoint were consistent across 10 prespecified subgroups in each trial group ([Figure 3](#)) with nonsignificant interaction P values. A lower rate of major adverse cardiac events without the inclusion of PMI was noted in the DCB group compared to the NCB group in both the per-protocol ([Supplemental Table 12](#)) and on-treat populations ([Supplemental Table 13](#)). The incidence of death, revascularization, and stent thrombosis was similar between patients

TABLE 2 Lesions and Procedural Characteristics

	Drug-Coated Balloon Group (n = 391)	Noncompliant Balloon Group (n = 393)	Difference, % (95% CI)	P Value
Medina classifications				
1,0,1	25 (6.4)	26 (6.6)	−0.2 (−3.8 to 3.3)	0.27
0,1,1	73 (18.7)	63 (16.0)	2.7 (−2.7 to 7.9)	0.70
1,1,1	293 (74.9)	304 (77.4)	−2.5 (−8.4 to 3.6)	0.44
Lesion characteristics				
Number of diseased vessels				
1-vessel disease	143 (36.6)	129 (32.8)	3.8 (−2.9 to 10.4)	0.29
2-vessel disease	153 (39.1)	159 (40.5)	−1.4 (−8.1 to 5.5)	0.72
3-vessel disease	95 (24.3)	105 (26.7)	−2.4 (−8.5 to 3.7)	0.46
Syntax score	21.1 ± 9.1	21.8 ± 8.9	−0.73 (−1.99 to 0.54)	0.10
≤22	235 (60.1)	218 (55.5)	4.6 (−2.3 to 11.5)	0.19
23–32	108 (27.6)	127 (32.3)	−4.7 (−11.1 to 1.7)	0.15
>32	48 (12.3)	48 (12.2)	0.1 (−4.6 to 4.7)	0.98
Lesion locations				
Distal left main	63 (16.1)	56 (14.2)	1.9 (3.2 to −6.9)	0.47
Left anterior descending artery	260 (66.5)	273 (69.5)	−3.0 (−9.5 to 3.6)	0.37
Left circumflex	43 (11.0)	46 (11.7)	−0.7 (−5.2 to 3.8)	0.76
Right coronary artery	25 (6.4)	18 (4.6)	1.8 (−1.4 to 5.1)	0.27
Lesions specificities				
Main vessel				
TIMI flow grade 3	336 (85.9)	330 (84.0)	1.9 (−3.1 to 6.9)	0.46
Chronic total occlusion	30 (7.7)	41 (10.4)	−2.7 (−6.9 to 1.3)	0.21
Thrombus containing	14 (3.6)	9 (2.3)	1.3 (−1.2 to 3.9)	0.29
≥Moderate calcification	80 (20.5)	84 (21.4)	−0.9 (−6.6 to 4.8)	0.79
Side branch				
TIMI flow grade 3	370 (94.6)	372 (94.7)	−0.1 (−3.3 to 3.2)	0.42
Chronic total occlusion	5 (1.3)	10 (2.5)	−1.2 (−3.5 to 0.8)	0.29
Thrombus containing	4 (1.0)	3 (0.8)	0.2 (−1.3 to 1.9)	0.73
≥Moderate calcification	13 (3.3)	12 (3.1)	0.2 (−2.3 to 2.9)	0.84

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with and without PMI (Supplemental Table 14). The details for 10 deaths are described in Supplemental Table 15. Through the 12-month follow-up, dual-antiplatelet therapy was used in 355 (90.8%) patients in the DCB group and 356 (90.6%) patients in the NCB group (Supplemental Table 16).

DISCUSSION

DCB-BIF, to our knowledge, is the first powered, multicenter, and randomized trial to demonstrate that stenting the MV with a drug-eluting stent combined with a DCB for the SB resulted in a lower incidence of major adverse cardiac events at the 1-year follow-up compared to the provisional approach with an NCB for the SB in patients with simple true coronary bifurcation lesions. This difference was driven by fewer TVMIs, especially spontaneous infarctions occurring more than 48 hours after the procedures, in the DCB group compared with the NCB group. The primary (intention-to-treat) analysis

results were consistent with those of the unadjusted, per-protocol, and on-treat analyses and across pre-specified subgroups. No significant differences in cardiac death, all-cause death, or stent thrombosis were observed between the NCB and DCB groups. Both groups had similar rates of angiographic success, crossover to a 2-stent strategy, and few procedural complications.

For true coronary artery bifurcation lesions treated by the provisional stenting approach, the use of a DCB to predilate an SB before or after stenting the MV is uncertain. Before designing this trial, we conducted a quantitative measurement, which showed that most scratched pharmaceutical particles were less than 4 to 5 μm in diameter, provided that sufficient dilation for the ostial SB was performed (Supplemental Figure 6). This formed the theoretic basis for our trial design, using a DCB for the SB following NCB dilation after the implantation of a drug-eluting stent in the MV.

Since the first-in-man PEPCAD-V (Paclitaxel Eluting PTCA Balloon in Coronary Artery Disease)²⁰

TABLE 2 Continued

	Drug-Coated Balloon Group (n = 391)	Noncompliant Balloon Group (n = 393)	Difference, % (95% CI)	P Value
Procedure characteristics				
Transradial approach	379 (96.9)	385 (98.0)	−1.1 (−3.5 to 1.3)	0.38
6-F guiding catheter	328 (83.9)	339 (86.3)	−2.4 (−7.4 to 2.6)	0.37
Predilation				
Main vessel	381 (97.4)	375 (95.4)	2.0 (−0.7 to 4.8)	0.18
Side branch	80 (20.5)	68 (17.3)	3.2 (−2.3 to 8.6)	0.27
Main vessel stent				
Number of stents	1.62 ± 0.71	1.65 ± 0.74	−0.03 (−0.13 to 0.72)	0.56
Diameter, mm	3.05 ± 0.39	3.00 ± 0.35	−0.05 (−0.01 to 0.09)	0.08
Length, mm	41.97 ± 19.99	42.13 ± 21.38	−0.16 (−3.06 to 2.75)	0.92
Maximal inflation pressure, atm	10.63 ± 3.30	10.27 ± 3.65	0.36 (−0.13 to 0.85)	0.15
POT	337 (86.2)	351 (89.3)	−3.1 (−7.8 to 1.5)	0.18
SB ballooning after MV stenting				
Using noncompliant balloon	391 (100.0)	393 (100.0)	0.0 (−0.9 to 0.9)	1.00
Using drug-coating balloon	381 (97.4)	4 (1.0)	96.4 (−93.8 to 97.7)	<0.0001
KBI after SB ballooning	371 (94.9)	389 (98.9)	−4.0 (−6.8 to 1.7)	0.0008
Re-POT after the first KBI	325 (83.1)	333 (84.7)	−1.6 (−6.8 to 3.6)	0.56
Side branch stent				
Crossover to 2 stents	15 (3.8)	13 (3.3)	0.5 (−2.2 to 3.3)	0.69
Number of stents	1.33 ± 0.48	1.15 ± 0.38	0.18 (−0.16 to 0.52)	0.29
Diameter	2.43 ± 0.17	2.56 ± 0.27	−0.13 (−0.31 to 0.04)	0.13
Length	24.87 ± 10.26	24.23 ± 13.06	0.64 (−8.43 to 9.69)	0.89
Maximal inflation pressure	10.47 ± 2.99	10.10 ± 2.60	0.37 (−2.04 to 2.77)	0.76
Final KBI after SB stenting	14 (93.3)	12 (92.3)	1.0 (−22.9 to 27.2)	0.98
Final POT after final KBI	13 (92.9)	12 (100.0)	−7.1 (−31.5 to 17.8)	0.12
Final TIMI flow grade 3				
Main vessel	388 (99.2)	391 (99.5)	−0.3 (−1.8 to 1.2)	0.50
Side branch	389 (99.5)	389 (99.0)	0.5 (−0.9 to 2.1)	0.34
Intravascular imaging guidance				
Intravascular ultrasound	101 (25.8)	111 (28.2)	−2.4 (−8.6 to 3.8)	0.45
Optical coherence tomography	84 (21.5)	93 (23.7)	−2.2 (−8.0 to 3.7)	0.47
Optical coherence tomography	18 (4.6)	19 (4.8)	−0.2 (−3.3 to 2.9)	0.89
Procedural time, min	57.84 ± 30.23	55.30 ± 35.07	2.54 (−2.29 to 7.39)	0.30
Contrast volume, mL	188.29 ± 55.45	186.96 ± 60.37	1.33 (−7.12 to 9.77)	0.76
Complete revascularization	248 (63.4)	235 (59.8)	3.6 (−3.20 to 10.4)	0.31
Staged coronary intervention	25 (6.4)	30 (7.6)	−1.2 (−4.9 to 2.4)	0.58

Values are n (%) or mean ± SD, unless otherwise indicated.

KBI = kissing balloon inflation; MV = main vessel; POT = proximal optimization technique; SB = side branch.

study used a DCB alone for both the MV and SB, several subsequent studies^{21–25} have used a drug-eluting stent in the MV and a DCB in the SB. These studies showed improvements in angiographic and clinical outcomes with the DCB compared to the NCB. However, features such as nonrandomization, small sample size, varying follow-up duration, and wide discrepancy in defining clinical outcomes in these studies led to neutral clinical results in meta-analyses comparing the DCB and NCB approaches.^{25–27}

Our results were consistent with those of the first randomized study,²⁰ which included only 40 patients and also demonstrated a reduction in 1-year major adverse cardiac events. Another multicenter

randomized study, BEYOND (A drug-coated Balloon for the trEatment of coronary bifurcation lesions in the side branch: a prospective multicenter randomized clinical trial),²⁵ enrolled 222 patients with coronary bifurcation lesions and reported that angiographic improvement at the 9-month follow-up did not translate into a reduction in clinical events. The key differences between our trial and the BEYOND study, such as the unblinded design, reference vessel minimal lumen diameter of ≥ 1.25 mm, and the exclusion of distal left main bifurcations, might explain the negative results observed in BEYOND when comparing the DCB and NCB groups. The low rate of 1-year major adverse cardiac events in

TABLE 3 Quantitative Coronary Artery Analysis by Core Laboratory

	Drug-Coated Balloon Group (n = 391)	Noncompliant Balloon Group (n = 393)	Difference (95% CI)	P Value
Lesion length, mm				
Main vessel	29.41 ± 13.16	28.84 ± 12.99	0.57 (–1.34 to 2.49)	0.56
Side branch	5.92 ± 4.55	6.55 ± 5.03	–0.63 (–1.32 to 0.07)	0.08
Before procedures				
Main vessel				
Reference vessel diameter, mm	2.97 ± 0.65	3.00 ± 0.64	–0.03 (–0.13 to 0.06)	0.52
Minimal lumen diameter, mm	1.27 ± 0.48	1.28 ± 0.49	–0.01 (–0.08 to 0.06)	0.70
Diameter stenosis, %	55.39 ± 10.87	55.73 ± 10.79	–0.34 (–2.01 to 1.32)	0.69
Quantitative fractional reserve	0.64 ± 0.21	0.63 ± 0.20	0.01 (–0.30 to 0.27)	0.87
Patients	360	358	–	–
<0.8	273 (75.8)	284 (79.3)	3.5 (–2.6 to 9.6)	0.28
Side branch				
Reference vessel diameter, mm ^a	2.24 ± 0.53	2.25 ± 0.50	–0.03 (–0.10 to 0.05)	0.58
Minimal lumen diameter, mm	1.03 ± 0.26	1.04 ± 0.25	–0.01 (–0.11 to 0.03)	0.30
Diameter stenosis, %	54.02 ± 10.44	53.78 ± 10.02	–0.03 (–1.65 to 0.07)	0.52
Quantitative fractional reserve	0.69 ± 0.23	0.69 ± 0.22	–0.01 (–0.40 to 0.03)	0.65
Patients	364	358	–	–
<0.8	223 (61.3)	222 (62.0)	–0.7 (–7.8 to 6.3)	0.88
After main vessel stenting				
Main vessel				
Reference vessel diameter, mm	3.18 ± 0.65	3.19 ± 0.62	–0.01 (–0.05 to 0.09)	0.57
Minimal lumen diameter, mm	2.51 ± 0.59	2.47 ± 0.53	0.04 (–0.03 to 0.11)	0.30
Diameter stenosis, %	21.16 ± 10.02	22.24 ± 9.62	–1.08 (–0.49 to 0.35)	0.14
Quantitative fractional reserve	0.95 ± 0.06	0.95 ± 0.05	0.00 (–0.01 to 0.01)	0.95
Patients	371	364	–	–
<0.8	11 (3.0)	5 (1.4)	1.6 (–0.6 to 3.9)	0.21
Side branch				
Reference vessel diameter, mm	2.19 ± 0.53	2.14 ± 0.51	0.05 (–0.13 to 0.02)	0.19
Minimal lumen diameter, mm	0.79 ± 0.39	0.78 ± 0.40	0.01 (–0.02 to 0.12)	0.17
Diameter stenosis, %	63.9 ± 11.21	63.6 ± 12.07	0.30 (–3.94 to 1.39)	0.35
Quantitative fractional reserve	0.59 ± 0.20	0.58 ± 0.21	0.01 (–0.02 to 0.03)	0.56
Patients	368	361	–	–
<0.8	285 (78.9)	298 (80.9)	–1.1 (–3.8 to 7.8)	0.14
Immediately after procedures				
Main vessel				
Reference vessel diameter, mm	3.27 ± 0.63	3.27 ± 0.61	0.01 (–0.09 to 0.08)	0.87
Minimal lumen diameter, mm	2.72 ± 0.57	2.72 ± 0.55	0.00 (–0.08 to 0.08)	0.98
Acute gain, mm	1.45 ± 0.67	1.44 ± 0.64	0.01 (–0.08 to 0.08)	0.98
Diameter stenosis, %	16.8 ± 7.07	16.9 ± 7.36	–0.10 (–1.39 to 0.69)	0.51
Quantitative fractional reserve	0.97 ± 0.03	0.97 ± 0.03	0.00 (–0.01 to 0.01)	0.87
Patients	376	371	–	–
<0.8	0 (0.0)	1 (0.3)	0.3 (–0.8 to 1.5)	0.50
Side branch				
Reference vessel diameter, mm	2.23 ± 0.51	2.21 ± 0.48	0.02 (–0.05 to 0.09)	0.51
Minimal lumen diameter, mm	1.66 ± 0.43	1.59 ± 0.42	0.07 (0.01–0.12)	0.045
Acute gain, mm	0.63 ± 0.45	0.55 ± 0.48	0.08 (0.02–0.13)	0.041
Diameter stenosis, %	25.12 ± 13.16	27.18 ± 13.25	–2.06 (3.96 to –0.17)	0.033
Quantitative fractional reserve	0.94 ± 0.07	0.93 ± 0.07	0.01 (–0.001 to 0.01)	0.11
Patients	376	371	–	–
<0.8	14 (3.7)	14 (3.8)	0.1 (–2.8 to 2.9)	0.56

Continued on the next page

TABLE 3 Continued

	Drug-Coated Balloon Group (n = 391)	Noncompliant Balloon Group (n = 393)	Difference (95% CI)	P Value
At 12 months				
Patients	64 (16.4)	56 (14.2)	−2.2 (−7.2 to 2.9)	0.41
TIMI flow grade 3				
Main vessel	64 (100.0)	54 (96.4)	3.6 (−12.1 to 2.7)	0.78
Side branch	63 (94.4)	56 (100.0)	−1.6 (−4.9 to 8.3)	0.67
Total occlusion				
Main vessel	0 (0)	2 (3.6)	3.6 (−2.7 to 8.1)	0.557
Side branch	1 (1.6)	0 (0)	−1.6 (−8.3 to 4.9)	0.302

Values are mean ± SD, n, or n (%), unless otherwise indicated. *Reference vessel diameter was the mean of distal and proximal diameter.

this trial also reflected the development of the provisional stenting approach.¹⁻⁸

The recent AGENT IDE²⁷ reported a lower incidence of TVMI with the DCB for in-stent restenosis.

Furthermore, a meta-analysis²⁸ reported that DCB intervention was not inferior to drug-eluting stent in patients with acute MI. This evidence aligns with our findings and addresses the urgent need to explore the

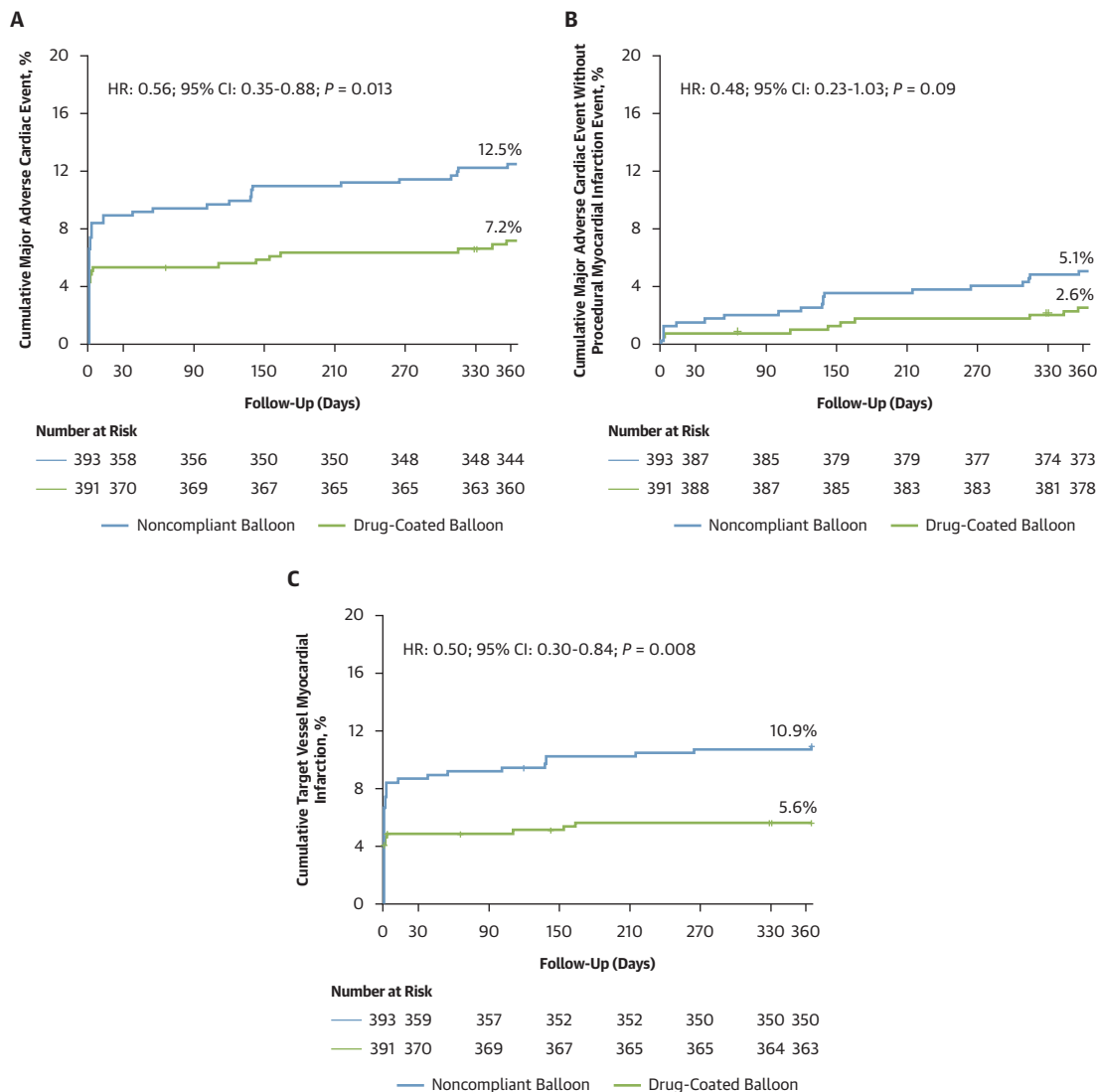
TABLE 4 Primary, Secondary, and Safety Endpoints on Intention-to-Treat Population^a

	Drug-Coated Balloon Group (n = 391)	Noncompliant Balloon Group (n = 393)	HR or Difference (95% CI)	P Value
Primary endpoint				
Major adverse cardiac event	28 (7.2)	49 (12.5)	0.56 (0.35-0.88)	0.013
Secondary endpoint				
Cardiac death	4 (1.0)	2 (0.5)	2.46 (0.38-11.31)	0.45
Major adverse cardiac event without periprocedural MI	10 (2.6)	20 (5.1)	0.48 (0.23-1.03)	0.09
Target vessel MI	22 (5.6)	43 (10.9)	0.50 (0.30-0.84)	0.009
Periprocedural MI	18 (4.6)	29 (7.4)	−2.8 (−6.23 to 0.59) ^b	0.13
Spontaneous MI	4 (1.0)	14 (3.6)	0.27 (0.09-0.81)	0.029
Clinically driven TLR	5 (1.3)	6 (1.5)	0.81 (0.25-2.66)	1.00
Main vessel	5 (1.3)	6 (1.5)	0.81 (0.25-2.66)	0.75
Side branch	3 (0.8)	1 (0.3)	3.45 (0.36-32.99)	0.28
Clinically driven TVR	6 (1.5)	7 (1.8)	0.83 (0.28-2.47)	1.000
Main vessel	6 (1.5)	7 (1.8)	0.83 (0.28-2.47)	0.73
Side branch	3 (0.8)	1 (0.3)	3.44 (0.36-33.00)	0.28
Angiographic success				
Main vessel	375 (95.9)	371 (94.4)	1.5 (−1.65 to 4.71) ^b	0.33
Side branch	367 (93.9)	360 (91.6)	2.3 (−1.40 to 6.0) ^b	0.22
Procedural success	332 (84.9)	299 (76.1)	8.8 (3.3-14.3) ^b	0.002
Crossover to 2 stents	15 (3.8)	12 (3.1%)	0.7 (−1.90 to 3.50) ^b	0.55
Safety endpoint				
Stent thrombosis	4 (1.0)	0 (0)	1.0 (−0.13 to 2.60) ^b	0.06
Definite stent thrombosis	2 (0.5)	0 (0)	0.5 (−0.53 to 1.85) ^b	0.25
Probable stent thrombosis	2 (0.5)	0 (0)	0.5 (−0.53 to 1.85) ^b	0.25
All-cause death	7 (1.8)	3 (0.8)	2.35 (0.61-9.08)	0.22

Values are n (%) of events (Kaplan-Meier estimated percentage at 1 year), unless otherwise indicated. ^aAll comparisons are adjusted by sex, diabetes, and initial presentations.

^bData are difference (95% CI).

MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization.

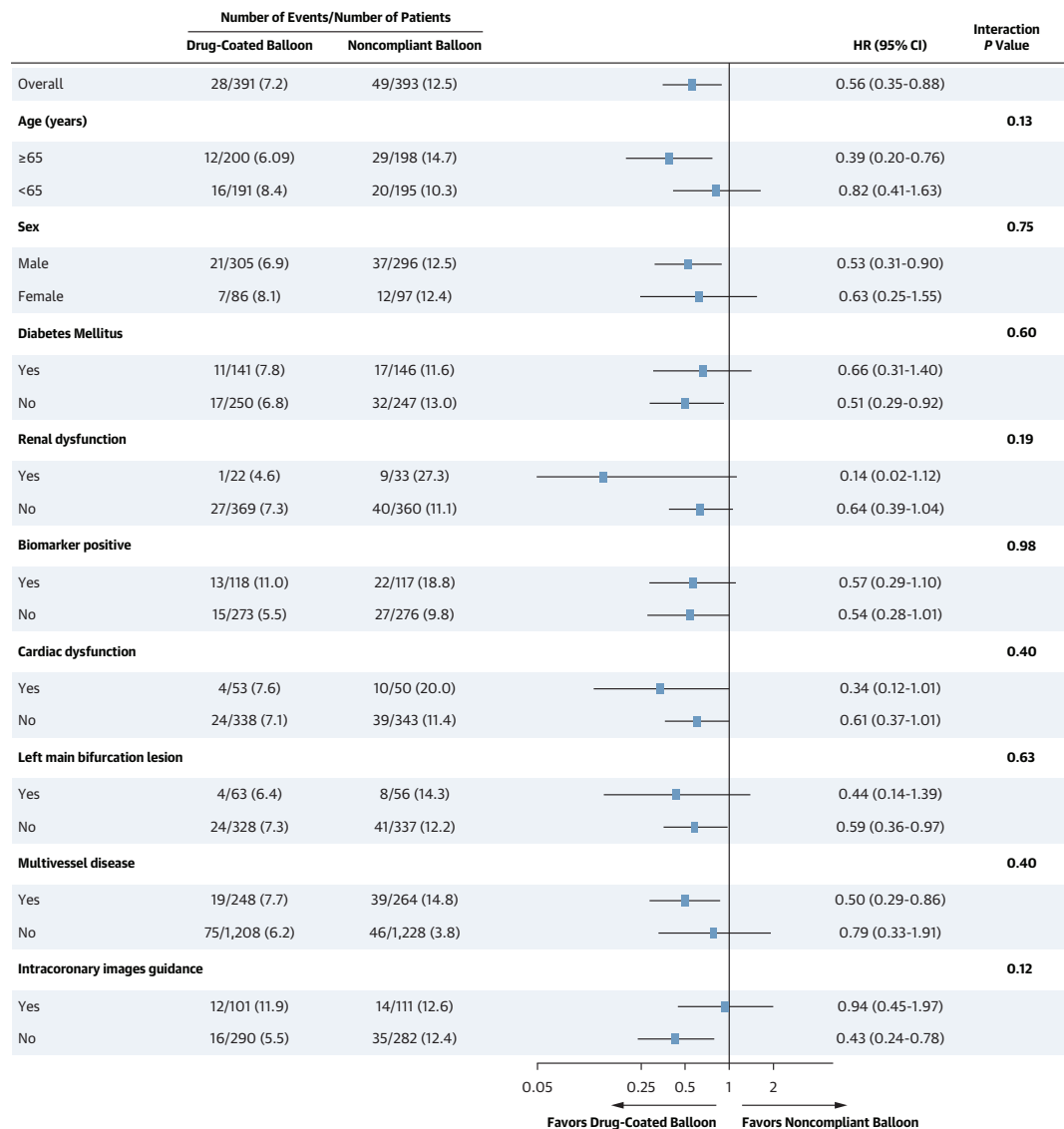
FIGURE 2 Cumulative Incidence of Major Adverse Cardiac Events

(A) The primary endpoint was major adverse cardiac events, defined as the composite of death from cardiac causes, target vessel myocardial infarction, or clinically driven target lesion revascularization in the intention-to-treat population through 1 year of follow-up. (B) The secondary endpoint of major adverse cardiac events excluding procedural myocardial infarction. (C) Target vessel myocardial infarction.

mechanisms attributable to the reduction of MI by DCB intervention. The longer duration of inflation at lower pressure may be one reason for reduced TVMI by DCB. The occurrence of 2 definite stent thromboses in the DCB group could be attributable to chance.

The rapid absorption of paclitaxel into the SB vascular wall theoretically should lead to less negative remodeling and restenosis at the ostial SB,^{29,30} resulting in a subsequent reduction in revascularization. Unfortunately, we did not observe a reduction in

either clinically driven target vessel revascularization or cardiac death with a DCB. Because most MIs occurred early, whereas most TLRs occurred relatively late, it is possible that the observed MIs in this study did not have enough clinical significance to warrant intervention (Supplemental Figure 2). We have seen in prior studies that simple bifurcation lesions tend to have a lower rate of TLR in general.^{3,5} Taken together, this suggests the urgent need to further explore the mechanisms attributable to the

FIGURE 3 Subgroup Analysis for the Primary Endpoint at 1 Year

The HR for the primary endpoint of major adverse cardiac events at 1 year was consistent across prespecified subgroups, including initial clinical presentations. Renal dysfunction is defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m². Biomarker positive is defined as either troponin or creatine kinase-myocardial band of >1× increase.

reduction of MI by DCB intervention, including the evaluation of complex bifurcation lesions that may portend more clinical significance than the simple SBs in this trial.

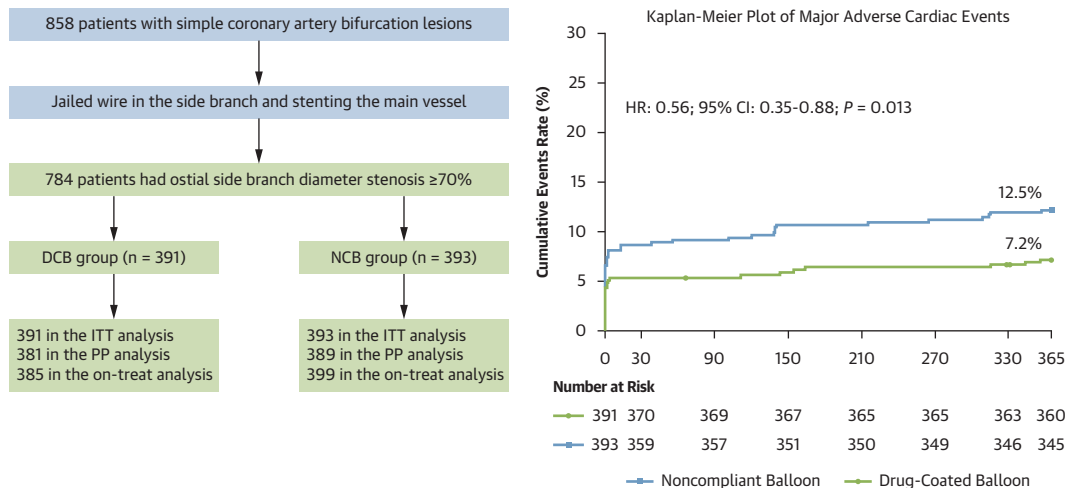
The incidence of major adverse cardiac events (or target lesion failure) in the NCB group in this trial was consistent with previous studies.^{3,5,7} The EBC MAIN (European Bifurcation Club Left Main Coronary Stent)⁹ study used the same definitions for defining MI as this trial and reported a 14.7% rate of 1-year

major adverse cardiac events in patients with simple distal left main bifurcation lesions undergoing provisional stenting. When this definition for MI was applied to DKCRUSH (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) II (including both distal left main and non-left main bifurcation lesions)³ and the simple distal left main bifurcations subgroup from the DKCRUSH V study,⁵ the 1-year rates of major adverse cardiac events were 11.6% and 13.8% (as

CENTRAL ILLUSTRATION Key Results From the DCB-BIF Trial

Key question: A second side branch stent is commonly required during provisional stenting procedures, which leads to high rates of restenosis, stent thrombosis, and revascularization.

Key finding: Stenting the main vessel using a drug-eluting stent and side branch intervention using a drug-coated balloon is associated with a significant reduction in major adverse cardiac event.



Gao X, et al. JACC. 2024;■(■):■-■.

A total of 784 patients with a compromised side branch (ostial diameter stenosis $\geq 70\%$) after main vessel stenting and first proximal optimal technique were randomly assigned to either the DCB group (n = 391) or the NCB group (n = 393). The 1-year rate of major adverse cardiac events was 12.5% in the NCB group and 7.2% in the DCB group. DCB = drug-coated balloon; ITT = intent-to-treat; NCB = noncompliant balloon; PP = per-protocol.

calculated from the study results), respectively. The alignment of the NCB group outcomes in our study with prior bifurcation trials suggests the representative nature of the control arm in this study.

STUDY LIMITATIONS. First, the random assignment to DCB and NCB angioplasty for the SB could not be masked to the operators, potentially introducing performance bias. However, we believe that masking patients and caregivers outside the catheterization laboratory, as well as the Clinical Events Committee, minimized the risk of ascertainment bias. Second, our results may not be applicable to sirolimus-coating balloons, which were not used in this trial. Third, 60.8% of patients included in this trial were classified as having unstable angina. Further studies enrolling more patients with MI and true coronary artery bifurcation lesions are warranted. Fourth, complex bifurcation lesions were excluded from this trial. Given that an upfront 2-stent approach has been shown to be superior to provisional stenting for patients with complex coronary artery bifurcation lesions,⁵⁻⁷ further studies are needed to evaluate the treatment difference between DCB and NCB

intervention after stenting the MV in patients with complex bifurcation lesions or patients with distal left main bifurcations. Fifth, predilation using a DCB for the MV was not recommended in this trial. Despite this, our results showed a lower rate of clinically driven target vessel revascularization in both groups. Lesion preparation in the MV using a DCB should be tested in future studies. Sixth, SB lesion preparation using a DCB before stenting the MV is another option. Fortunately, our results showed fewer and smaller pharmaceutical particles dislodged by MV stent struts, supporting the potential of this trial's design. Seventh, intravascular imaging guidance was not used for all patients; however, it was similarly used in the 2 groups, which may minimize the bias. Eighth, the interventional procedures were not guided by physiologic assessment. However, our results confirmed the significant improvement in quantitative fractional reserve in both the MV and SB in both groups after procedures. Ninth, our trial included fewer (only 23.2%) female participants, similar to a recent meta-analysis³¹ which reported an underrepresentation of female participants. We will encourage principal investigators to enroll more female patients.

Finally, SB predilation was performed in 148 patients, which is not consistent with the EBC recommendations. However, we did not find a significant impact of SB predilation on quantitative fractional reserve after the MV stenting.

CONCLUSIONS

DCB-BIF is the first powered, large, randomized controlled trial to compare the outcomes of a DCB vs NCB intervention for the SB in a large population with true coronary bifurcation lesions treated by a provisional stenting approach. The study demonstrated that stenting the MV with a DCB for a compromised SB results in a lower 1-year risk of major adverse cardiac events compared with stenting the MV and using NCB angioplasty for the SB (**Central Illustration**). The high rates of MI, which did not lead to revascularization, are of unclear clinical significance.

ACKNOWLEDGMENTS The authors appreciate all staff participating in data collection and remote

monitoring. The authors thank Professor Feng Chen for leading statistical team to perform statistical analysis.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This trial was funded by the National Key Research and Development Plan (2022YFC2503503), the Chinese Society of Cardiology (grant number CSCF 2019-A0003), the National Natural Scientific Foundation of China (grant numbers NSFC 91639303, 81770441, and 82121001), and the Jiangsu Provincial and Nanjing Municipal Clinical Trial Project (grant number BE 2019615) and jointly supplied by B Braun Medical (Melsungen, Germany), Shenqi Medical (Shanghai, China), Yinyi Medical (Dalian, China), Yingsheng Medical (Shanghai, China), and Kaidenuo Medical (Wuhan, China). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS coronary bifurcation lesions, drug-coated balloon, drug-eluting stent, major adverse cardiac events, provisional stenting

APPENDIX For supplemental figures and tables, please see the online version of this paper.