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Drug-Coated Balloon Versus Drug-Eluting Stent for Small-Vessel Disease

The RESTORE SVD China Randomized Trial

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the angiographic efficacy and clinical outcomes of the Restore paclitaxel-coated balloon in a randomized trial designed to enable its approval with an indication for small-vessel disease (SVD).

BACKGROUND Higher rates of restenosis and stent thrombosis limit the effectiveness of drug-eluting stent (DES) treatment of SVD. Whether a drug-coated balloon (DCB)–only strategy is effective in de novo SVD is not yet established.

METHODS In the noninferiority RESTORE SVD China trial, eligible patients with reference vessel diameter ≥2.25 and ≤2.75 mm were randomized to the Restore DCB or the RESOLUTE Integrity DES in a 1:1 ratio stratified by diabetes and number of lesions treated. Patients with RVD ≥2.00 and <2.25 mm were enrolled in a nested very small vessel registry. Angiographic and clinical follow-up were planned at 9 months and 1 year, respectively, in all patients. The study was powered for the primary endpoint of 9-month in-segment percentage diameter stenosis.

RESULTS Between August 2016 and June 2017, a total of 230 subjects at 12 sites were randomized to the DCB group (n = 116) or DES group (n = 114); 32 patients were treated with the DCB in the very small vessel cohort. Nine-month in-segment percentage diameter stenosis was 29.6 ± 2.0% with the DCB versus 24.1 ± 2.0% with the DES; the 1-sided 97.5% upper confidence limit of the difference was 10.9%, achieving noninferiority of the DCB compared with the DES (p for noninferiority < 0.001). The DCB and DES had comparable 1-year rates of target lesion failure (4.4% vs. 2.6%, p = 0.72).

CONCLUSIONS In this multicenter randomized trial, the Restore DCB was noninferior to the RESOLUTE DES for 9-month in-segment percentage diameter stenosis. (Assess the Efficacy and Safety of RESTORE Paclitaxel Eluting Balloon Versus RESOLUTE Zotarolimus Eluting Stent for the Treatment of Small Coronary Vessel Disease; NCT02946307) (J Am Coll Cardiol Intv 2018;11:2381–92) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ATS = as-treated set

DAPT = dual antiplatelet therapy

DCB = drug-coated balloon

DES = drug-eluting stent(s)

DS = diameter stenosis

ITT = intention-to-treat

LL = late loss

MACE = major adverse cardiac event(s)

MI = myocardial infarction

MLD = minimal luminal diameter

PCI = percutaneous coronary intervention

%DS = percentage diameter stenosis

RVD = reference vessel diameter

SVD = small-vessel disease

TLF = target lesion failure

TLR = target lesion revascularization

VSV = very small vessel

Treatment of small vessel disease (SVD) is still challenging with drug-eluting stents (DES), mainly because of higher rates of restenosis and stent thrombosis. Drug-coated balloons (DCB) coated with paclitaxel, a potent cell inhibitor that irreversibly inhibits arterial smooth muscle cell proliferation, has emerged as an alternative therapeutic tool for coronary atherosclerotic disease (1). This non-stent-based device has the potential to have sustained antirestenotic efficacy without the limitations of permanent vascular implants. Such a device has shown promising results with high-concentration, rapid local delivery of paclitaxel without the use of drug reservoirs, thus reducing the inflammation caused by permanent metal implantation (2). The strategy of DCB therapy with bail-out stenting may have a clinical role, particularly in the setting of small vessels, in which the effect of neointimal hyperplasia is greater and DES perform poorly (3). Whether a DCB-only strategy is effective and safe in de novo SVD is controversial. In small randomized trials, the DIOR DCB failed to show equivalence to the Taxus DES regarding angiographic endpoints in percutaneous coronary intervention (PCI) of small coronary arteries (4), whereas in the BELLO (Balloon Elution and Late Loss Optimization) trial, use of DCBs yielded low major adverse cardiac event (MACE) rates (5). The Restore paclitaxel-coated balloon (Cardionovum, Bonn, Germany) is a new-generation DCB with innovative SAFEPAX shellac-ammonium salt excipient, which can avoid drug washing off and the potential risk for microembolization during catheter delivery to the target lesion site. The aim of the present study was to evaluate the angiographic efficacy and clinical safety and effectiveness of the Restore DCB in a randomized trial designed to enable approval of the new device (with an SVD indication) in China.

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METHODS

STUDY DESIGN AND PATIENT POPULATION. This prospective, randomized, open-label, multicenter trial was designed to assess the safety and efficacy of the Restore DCB in the treatment of de novo coronary lesions in small vessels or very small vessels (VSVs). The study was divided into a small vessel cohort and a VSV cohort. In the small vessel cohort, patients with visually estimated reference vessel diameters (RVDs) ≥2.25 and ≤2.75 mm were randomly assigned to the Restore DCB or the RESOLUTE Integrity DES in a 1:1 ratio. The study was powered to detect the noninferiority of the Restore DCB versus the RESOLUTE DES for a primary endpoint of in-segment percentage diameter stenosis (%DS) at 9 months. In the VSV cohort, patients with RVD ≥2.00 and <2.25 mm were treated with the Restore DCB of an appropriate size.

This study was approved by the Institutional Review Boards and complied with the Declaration of Helsinki. Adult patients (age ≥18 years) presenting with stable or unstable angina or with recently stabilized myocardial infarction (MI) were recruited from participating hospitals. Patients were eligible if they had: 1) only 1 lesion in the target small vessel with a visual stenosis of ≥70% or ≥50% complicated by evidence of ischemia before PCI; 2) lesion length limited to <26 mm; and 3) visual diameters of the target lesions limited to ≥2.25 and ≤2.75 mm in the small vessel cohort and ≥2.00 and <2.25 mm in the VSV cohort. Major exclusion criteria were acute MI within 1 week of the study, a left ventricular ejection fraction of <35%, total occlusion, bifurcation and left main lesions, or patients with more than 2 nontarget lesions requiring treatment. Full inclusion and exclusion criteria are shown in the Online Appendix. Subjects participated voluntarily in this study and signed informed consent forms.

ENDPOINTS AND DEFINITIONS. The trial was designed to examine whether the DCB was noninferior to the DES for the primary endpoint of 9-month angiographic in-segment %DS, defined as: (1 − minimal luminal diameter [MLD]/RVD) × 100%. In-segment was defined as stent/balloon length plus the proximal and distal 5-mm margins. If a patient underwent target lesion revascularization (TLR) >30 days post-procedure but before his or her scheduled angiographic follow-up, the event angiogram was used for the primary endpoint analysis. Secondary endpoints included acute success, in-device %DS, late loss (LL), binary restenosis rates, target lesion

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failure (TLF; a composite of cardiac death, target vessel MI, or ischemia-driven TLR), and definite or probable device thrombosis on the basis of the Academic Research Consortium definitions (6). Periprocedural MI, however, was defined as a rise in post-PCI creatine kinase-MB to >5-fold the upper reference limit (7). Detailed endpoint definitions are provided in the Online Appendix.

RANDOMIZATION AND ENROLLMENT. A total of 230 eligible patients enrolled in the small vessel cohort (visually estimated RVD ≥2.25 and ≤2.75 mm) who provided written informed consent were randomized in a 1:1 ratio to receive the DCB or DES at 12 sites in China. Randomization was stratified by site, complicated nontarget lesion, and diabetes status. Randomization was performed using an interactive Web response system with a block size of 4.

INTERVENTIONS. Aspirin 300 mg was administered at least 24 h before the intervention treatment, and clopidogrel 300 mg was administered at least 6 h before the intervention treatment and then maintained at 75 mg/day, or ticagrelor 180 mg was orally administered and then maintained at 90 mg twice daily. Unfractionated heparin (100 U/kg, intravenous) was administered before PCI, and activated clotting time was maintained at 250 to 350 s (HemoTec method). After discharge from the hospital, dual antiplatelet therapy (DAPT) was prescribed for at least 6 months.

Nontarget lesions, with fewer than 2 present, were treated before target lesions, and only subjects with nontarget lesions without complications after treatment were enrolled.

The balloon coating of the Restore DCB consists of a degradable, drug-eluting ammonium salt-paclitaxel composite that should have a potential impact on improving the procedure. Our protocol mandated careful lesion pre-dilation. The technique for pre-dilation was at the operator's discretion. Stenosis ≤30% after pre-dilation was regarded as successful pre-dilation. Post-dilation balloons could not be used for redilation after the application of a DCB.

In the control group treated with the DES, pre-dilation or post-dilation methods and procedures were at the discretion of investigators. The balloons were selected on the basis of the conditions set by the individual study sites.

The intervention treatment was considered successful if the visual post-procedural residual stenosis was ≤30% after PCI. If there was severe intra-operative dissection (in classes D, E, and F), or the visual residual stenosis was >30% immediately after DCB PCI, bare-metal stents were implanted for rescue treatment by investigators on the basis of clinical judgment.

FOLLOW-UP. Clinical follow-up (by telephone when necessary) was performed at post-procedural months 1, 6, and 12 and annually up to 5 years. The schedule for visits and evaluations of the subjects is shown in the Online Appendix. Clinical events were adjudicated by an independent and blinded clinical events committee (Online Appendix).

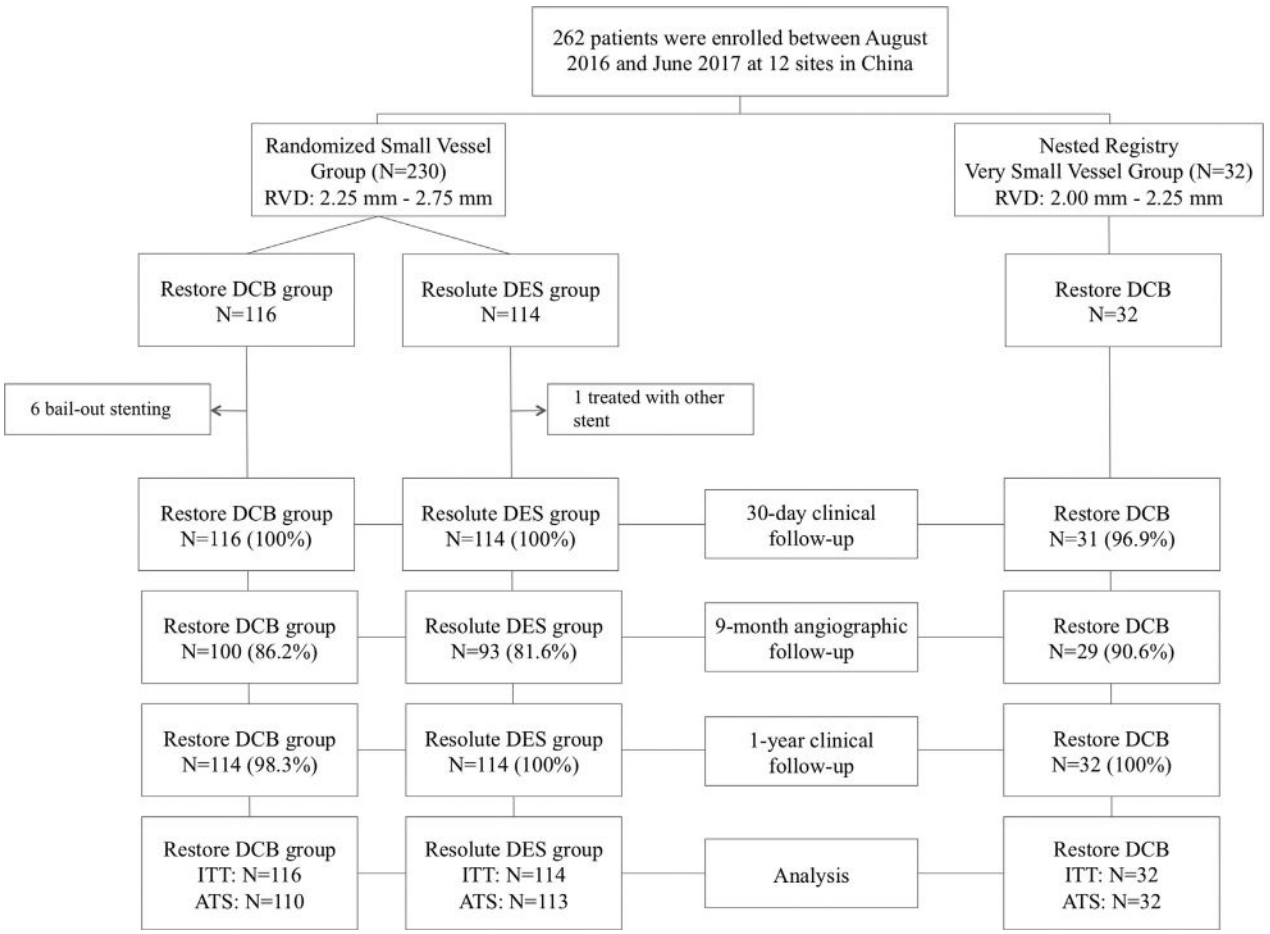
ANGIOGRAPHIC ANALYSIS. The coronary angiographic results were objectively evaluated by an independent core laboratory (JetMed, Beijing, China). All angiograms were carefully recorded in all critical periods. At least 2 orthographic views (reference views) were required in pre-procedural nidus angiograms, accurate DCB balloon location angiograms obtained before dilation, and 2 post-procedural angiograms with a similar projection angle as the pre-procedural angiograms. Follow-up angiograms were recorded with a similar projection angle as the post-procedural angiograms. All angiography was performed under the same standard conditions, and quantitative coronary artery analysis was performed using the QAngio XA system version 7.3 (Medis Medical Imaging Systems, Leiden, the Netherlands).

STATISTICAL ANALYSIS. The assumed mean in-segment %DS at 9 months was 25% for the RESOLUTE DES and 32.5% for the Restore DCB, with a conservative SD of 18% for both groups. The noninferiority margin was 15% according to results reported previously (5). With a 1-sided 0.025 alpha level and maximum 20% loss to angiographic follow-up rate, randomizing 230 patients would provide 80% power to demonstrate noninferiority of the Restore DCB to the RESOLUTE DES.

All our statistical analyses followed intention-to-treat (ITT) principles. The as-treated set (ATS) was also used for sensitivity analysis. Continuous variables are presented as mean ± SD and categorical variables as counts and percentages. We used the Student's *t*-test to compare normally distributed continuous variables. Chi-square or Fisher exact tests were used to compare categorical variables. We calculated the 95% confidence intervals of the difference between 2 treatment arms using the normal approximation for continuous variables and the Wald asymptotic method for binary variables.

We conducted both lesion- and patient-level analyses for 9-month in-segment %DS. When the primary endpoint was analyzed on a per subject basis, the comparison between 2 groups was presented by using analysis of covariance with adjusting center.

FIGURE 1 Patient Flow and Follow-Up



The as-treated set consisted of subjects who received only study devices at target lesions. ATS = as-treated set; DCB = drug-coated balloon; DES = drug-eluting stent(s); ITT = intention-to-treat; RVD = reference vessel diameter.

One-year clinical follow-up was performed at 360 ± 30 days. We plotted time-to-first event curves using Kaplan-Meier estimates and compared them using the log-rank test. Cox regression was used to determine hazard ratios and corresponding 95% confidence intervals. All statistical analyses were performed at a 2-sided significance level of 0.05 using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENTS AND PROCEDURAL RESULTS. Between August 2016 and June 2017, a total of 230 subjects at 12 Chinese sites were randomized to the DCB group (n = 116) or the DES group (n = 114). Thirty-two patients were treated with the DCB in the VSV cohort. Of the 230 patients in the ITT population, 7 did not meet ATS criteria: 6 subjects who underwent bail-out stenting in the DCB group and 1 subject treated with another stent in the DES group. The ATS population thus consisted of 223 patients (110 DCB and 113 DES) (**Figure 1**).

In the SVD cohort, baseline clinical characteristics of the patients and treated lesions were well matched between the 2 groups, except for significant differences in family history of CAD (p = 0.01 in the ITT population, p = 0.02 in the ATS population) and insulin-treated diabetes (p = 0.04 in the ITT population, p = 0.05 in the ATS population) in the DCB group (**Table 1**, Online Table S1). Procedural characteristics are shown in **Table 2** and Online Table S2. In the ITT population, pre-dilation was performed routinely in both groups. Bail-out stenting was required in 5.2% of lesions in the DCB group and 1.8% of lesions in the

TABLE 1 Baseline Patient and Lesion Characteristics (Intention-to-Treat Population)

	Small Vessel Group				Very Small Vessel Group (n = 32, 32 Lesions)
	Restore DCB Group (n = 116, 116 Lesions)	Resolute DES Group (n = 114, 114 Lesions)	Difference (95% CI)*	p Value	
Age, yrs	60.1 ± 10.5	60.5 ± 10.8	−0.4 (−3.2 to 2.4)	0.78	58.0 ± 9.9
Male	66.4 (77)	77.2 (88)	−10.8 (−22.4 to 0.7)	0.07	75.0 (24)
Body mass index, kg/m^2	25.6 ± 3.2	25.4 ± 3.1	0.2 (−0.7 to 1.0)	0.73	26.9 ± 3.6
Diabetes mellitus	39.7 (46)	42.1 (48)	−2.5 (−15.2 to 10.3)	0.71	40.6 (13)
Insulin-treated diabetes	10.3 (12)	20.2 (23)	−9.8 (−19.1 to 0.6)	0.04	15.6 (5)
Hypertension	67.2 (78)	75.4 (86)	−8.2 (−19.8 to 3.4)	0.17	81.3 (26)
Hyperlipidemia	52.6 (61)	48.2 (55)	4.3 (−8.6 to 17.3)	0.51	65.6 (21)
Current smoker	29.3 (34)	31.6 (36)	−2.3 (−14.2 to 9.6)	0.71	28.1 (9)
Previous MI	22.4 (26)	24.6 (28)	−2.2 (−13.1 to 8.8)	0.70	21.9 (7)
Previous PCI	38.8 (45)	33.3 (38)	5.5 (−6.9 to 17.9)	0.39	18.8 (6)
Previous CABG	0 (0)	0.9 (1)	−0.9 (−2.6 to 0.8)	0.50	0 (0)
Family history of CAD	24.1 (28)	11.4 (13)	12.7 (3.0 to 22.5)	0.01	15.6 (5)
Previous stroke	6.9 (8)	12.3 (14)	−5.4 (−13.0 to 2.2)	0.16	18.8 (6)
Chronic obstructive pulmonary disease	1.7 (2)	0 (0)	1.7 (−0.6 to 4.1)	0.50	0 (0)
Unstable angina	69.0 (80)	71.1 (81)	−2.1 (−13.9 to 9.8)	0.73	71.9 (23)
Left ventricular ejection fraction	60.6 ± 7.3 (116†)	59.9 ± 6.9 (113†)	0.7 (−1.2 to 2.5)	0.48	59.7 ± 5.4
Number of nontarget lesions	1.22 ± 0.42	1.29 ± 0.54	−0.1 (−0.3 to 0.1)	0.45	1.25 ± 0.45
0	52.6 (61)	54.4 (62)	−1.8 (−14.7 to 11.1)	0.78	62.5 (20)
1	37.1 (43)	34.2 (39)	2.9 (−9.5 to 15.2)	0.65	28.1 (9)
2	10.3 (12)	9.6 (11)	0.7 (−7.1 to 8.5)	0.86	9.4 (3)
3	0 (0)	1.8 (2)	−1.8 (−4.2 to 0.7)	0.24	0 (0)
Multivessel disease	41.4 (48)	39.5 (45)	1.9 (−10.8 to 14.6)	0.77	25.0 (8)
Target vessel location					
Left anterior descending coronary artery	8.6 (10)	8.8 (10)	−0.2 (−7.4 to 7.1)	0.97	9.4 (3)
Diagonal branch	12.1 (14)	13.2 (15)	−1.1 (−9.7 to 7.5)	0.80	21.9 (7)
Left circumflex coronary artery	50.9 (59)	41.2 (47)	9.6 (−3.2 to 22.5)	0.14	40.6 (13)
Obtuse marginal branch/ramus	3.4 (4)	5.3 (6)	−1.8 (−7.1 to 3.5)	0.54	6.3 (2)
Right coronary artery	7.8 (9)	8.8 (10)	−1.0 (−8.1 to 6.1)	0.78	0 (0)
PDA/PL	17.2 (20)	22.8 (26)	−5.6 (−15.9 to 4.8)	0.29	21.9 (7)
Reference vessel diameter by visual estimation	2.42 ± 0.15	2.42 ± 0.18	−0.01 (−0.1 to 0.04)	0.74	2.00 ± 0.02
Moderate or severe calcification	0 (0)	1.8 (2)	−1.8 (−4.2 to 0.7)	0.24	3.1 (1)
ACC/AHA type B2/C lesions	37.9 (44)	40.4 (46)	−2.4 (−15.0 to 10.2)	0.71	62.5 (20)

Values are mean ± SD or % (n). *The value is the difference in the Restore DCB group compared with the Resolute DES group. †Number of patients for whom continuous variables were calculated.

ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CI = confidence interval; DCB = drug-coated balloon; DES = drug-eluting stent(s); MI = myocardial infarction; PCI = percutaneous coronary intervention; PDA = posterior descending artery; PL = posterolateral.

DES group (p = 0.28). There was no significant difference in the prevalence of dissection after predilation between the DCB group and the DES group (29.3% vs. 28.1%; p = 0.84). Similar rates of type C dissection after DCB and DES treatment were observed (0.9% in both groups; p = 1.00).

Baseline angiographic analyses indicated that lesion length, MLD, and %DS were well matched in the 2 groups (**Table 3**, Online Table S3). However, the lesions treated in the DCB group occurred in significantly smaller vessels than those in the DES group (2.11 ± 0.27 mm vs. 2.21 ± 0.29 mm; p = 0.01). On the basis of the quantitative coronary analyses, all lesions had RVDs <2.75 mm, as stipulated by the inclusion criteria of the study. The acute post-procedural result was better after stenting compared with balloon angioplasty, with a larger final in-segment MLD (1.65 ± 0.26 mm with the DCB and 1.98 ± 0.25 mm with the DES, p < 0.001) and less residual in-segment %DS (19.8 ± 8.8% vs. 12.6 ± 6.4%; p < 0.001) in the DES group.

In the VSV cohort, the mean patient age was 58.0 ± 9.9 years, and 75.0% of subjects were male. Diabetes was present in 40.6% of patients, and 15.6% had

TABLE 2 Procedural Characteristics and Results (Intention-to-Treat Population)

	Small Vessel Group				Very Small Vessel Group (n = 32, 32 Lesions)
	Restore DCB Group (n = 116, 116 Lesions)	Resolute DES Group (n = 114, 114 Lesions)	Difference (95% CI)	p Value	
Transradial approach	98.3 (114)	99.1 (113)	−0.9 (−3.8 to 2.1)	1.00	96.9 (31)
Balloon pre-dilation	100 (116)	100 (114)	0.9 (−2.1 to 3.8)	NA	100 (32)
Maximal diameter of pre-dilation balloon, mm	2.11 ± 0.27	2.12 ± 0.33	−0.01 (−0.1 to 0.1)	0.80	1.87 ± 0.29
Maximal inflation pressure with pre-dilation balloon, atm	11.1 ± 3.0	11.1 ± 3.3	−0.02 (−0.8 to 0.7)	0.95	11.5 ± 3.4
Duration of inflation with pre-dilation balloon, s	12.9 ± 12.2	11.4 ± 10.4	1.5 (−1.2 to 4.3)	0.27	12.6 ± 13.2
Dissection after pre-dilation	29.3 (34)	28.1 (32)	1.2 (−10.5 to 12.9)	0.84	34.4 (11)
A	22.4 (26)	22.8 (26)	−0.4 (−11.2 to 10.4)	0.94	28.1 (9)
B	6.0 (7)	4.4 (5)	1.7 (−4.1 to 7.4)	0.57	6.3 (2)
C	0.9 (1)	0.9 (1)	−0.02 (−2.4 to 2.4)	1.00	0 (0)
Mean diameter of DCB or DES, mm	2.41 ± 0.16	2.41 ± 0.18	0 (−0.04 to 0.1)	0.95	2.01 ± 0.04
Total length of DCB or DES, mm	21.0 ± 4.9	20.4 ± 5.8	0.6 (−0.8 to 2.0)	0.37	21.9 ± 5.0
Maximal inflation pressure with DCB or DES, atm	9.11 ± 2.89	10.7 ± 2.33	−1.6 (−2.3 to −1.0)	<0.001	9.25 ± 3.15
Duration of inflation with DCB or DES, s	56.0 ± 11.2	9.88 ± 6.14	46.1 (43.8 to 48.5)	<0.001	54.8 ± 18.0
Dissection after balloon/stent treatment	26.7 (31)	10.5 (12)	16.2 (6.4 to 26.0)	0.001	34.4 (11)
A	21.6 (25)	7.0 (8)	14.5 (5.7 to 23.4)	0.001	28.1 (9)
B	4.3 (5)	2.6 (3)	1.7 (−3.0 to 6.4)	0.72	6.3 (2)
C	0.9 (1)	0.9 (1)	−0.02 (−2.4 to 2.4)	1.00	0 (0)
Bail-out stenting	5.2 (6)	1.8 (2)	3.4 (−1.3 to 8.1)	0.28	3.1 (1)
Procedural complications	8.6 (10)	4.4 (5)	4.2 (−2.1 to 10.6)	0.19	3.1 (1)
Residual dissection	24.1 (28)	7.9 (9)	16.2 (7.0 to 25.5)	<0.001	37.5 (12)
A	20.7 (24)	6.1 (7)	14.6 (6.0 to 23.1)	<0.001	28.1 (9)
B	3.4 (4)	0.9 (1)	2.6 (−1.2 to 6.3)	0.37	9.4 (3)
C	0 (0)	0.9 (1)	−0.9 (−2.6 to 0.8)	0.50	0 (0)
Device success	94.8 (110)	96.5 (110)	−1.7 (−6.9 to 3.6)	0.75	96.9 (31)
Lesion success	100 (116)	99.1 (113)	0.9 (−0.8 to 2.6)	0.50	100 (32)
Procedure success	99.1 (115)	99.1 (113)	0.02 (−2.4 to 2.4)	1.00	100 (32)

Values are % (n) or mean ± SD.
NA = not applicable; other abbreviations as in Table 1.

family histories of cardiovascular disease. Unstable angina was present in 71.9% of the subjects. In the VSV cohort, 96.9% of lesions achieved device success, and only 1 lesion required bail-out stenting.

NINE-MONTH ANGIOGRAPHIC OUTCOMES IN THE SVD COHORT. Nine-month angiographic follow-up data were available in 86.2% of DCB patients (100 of 116) and 81.6% of DES patients (93 of 114) per ITT. The primary endpoint of 9-month in-segment %DS in the ITT population analysis was 29.6 ± 2.0% with the DCB versus 24.1 ± 2.0% with the DES. The upper 1-sided 97.5% confidence limit of the difference was 10.9%, which was below the pre-specified noninferiority margin of 15% (p for noninferiority < 0.001). In the ATS population, the DCB was also noninferior to the DES for 9-month in-segment %DS (Table 4). The 9-month angiographic results are reported in Table 3 and Online Table S3, and %DS cumulative frequency distribution curves are shown in the Figure 2 and Online Figure S1. At 9 months, the DCB group had a smaller MLD (1.40 ± 0.42 mm vs. 1.71 ± 0.39 mm; p < 0.001) but similar LL (0.25 ± 0.42 mm vs. 0.27 ± 0.36 mm; p = 0.73) and angiographic binary restenosis rates (11.0% vs. 8.6%; p = 0.58) compared with the DES within the segment.

ONE-YEAR CLINICAL OUTCOMES IN SVD COHORT. All patients, except for 2 in the DCB group, completed 1-year follow-up. In the DCB group, there was only 1 peri-procedural MI. Similar rates of 1-year TLF occurred in both groups (4.4% in the DCB group and 2.6% in the DES group, p = 0.72). There were no significant differences between DCB and DES in the rates of TLF, cardiac death, target vessel MI, and TLR (Table 5, Online Table S4, Figure 3, Online Figure S2).

The peri-procedural MI rates were low and similar between the DCB and DES by the protocol definition

TABLE 3 Quantitative Coronary Angiographic Results (Intention-to-Treat Population)

	Small Vessel Group				
	Restore DCB Group	Resolute DES Group	Difference (95% CI)	p Value	Very Small Vessel Group
Pre-procedure QCA	n = 116	n = 114			n = 32
Reference vessel diameter, mm	2.11 ± 0.27	2.21 ± 0.29	−0.1 (−0.2 to −0.03)	0.01	1.86 ± 0.28
Minimal luminal diameter, mm	0.64 ± 0.22	0.65 ± 0.26	0 (−0.1 to 0.1)	0.92	0.48 ± 0.22
Diameter stenosis, %	69.6 ± 9.3	71.0 ± 10.5	−1.4 (−4.0 to 1.2)	0.30	74.3 ± 10.7
Lesion length, mm	10.5 ± 4.8	10.8 ± 5.2	−0.3 (−1.6 to 1.0)	0.63	12.2 ± 5.6
Post-procedure QCA	n = 116	n = 114			n = 32
Minimal luminal diameter, mm					
In-device	1.66 ± 0.26	2.04 ± 0.26	−0.4 (−0.5 to −0.3)	<0.001	1.40 ± 0.24
In-segment	1.65 ± 0.26	1.98 ± 0.25	−0.3 (−0.4 to −0.3)	<0.001	1.38 ± 0.22
Diameter stenosis, %					
In-device	19.9 ± 8.8	11.9 ± 6.0	8.0 (6.1 to 10.0)	<0.001	23.4 ± 10.2
In-segment	19.8 ± 8.8	12.6 ± 6.4	7.2 (5.2 to 9.2)	<0.001	23.7 ± 10.1
9-month follow-up QCA	n = 100	n = 93			n = 29
Minimal luminal diameter, mm					
In-device	1.40 ± 0.43	1.75 ± 0.39	−0.4 (−0.5 to −0.2)	<0.001	1.14 ± 0.46
In-segment	1.40 ± 0.42	1.71 ± 0.39	−0.3 (−0.4 to −0.2)	<0.001	1.12 ± 0.44
Diameter stenosis, %					
In-device	29.3 ± 20.2	22.8 ± 15.3	6.5 (1.5 to 11.6)	0.01	37.3 ± 22.5
In-segment	29.3 ± 20.2	23.9 ± 15.9	5.5 (0.3 to 10.6)	0.04	38.4 ± 21.5
Late lumen loss, mm					
In-device	0.26 ± 0.42	0.30 ± 0.35	−0.1 (−0.2 to 0.1)	0.41	0.28 ± 0.40
In-segment	0.25 ± 0.42	0.27 ± 0.36	−0.02 (−0.1 to 0.1)	0.73	0.27 ± 0.38
Net luminal gain,* mm					
In-device	0.78 ± 0.45	1.11 ± 0.43	−0.3 (−0.5 to −0.2)	<0.001	0.66 ± 0.47
In-segment	0.77 ± 0.45	1.08 ± 0.42	−0.3 (−0.4 to −0.2)	<0.001	0.65 ± 0.46
Binary restenosis, %					
In-device	11.0 (11)	7.5 (7)	3.5 (−4.7 to 11.6)	0.40	17.2 (5)
In-segment	11.0 (11)	8.6 (8)	2.4 (−6.0 to 10.8)	0.58	17.2 (5)

Values are mean ± SD or % (n). *Net luminal gain was defined as the difference between the minimal luminal diameters at follow-up and baseline.
QCA = quantitative coronary angiography; other abbreviations as in Table 1.

of the Society for Cardiovascular Angiography and Interventions (8) (0.9% vs. 0%; p = 1.00) or the Academic Research Consortium-2 definition (9) (3.4% vs. 4.4%; p = 0.75), the World Health Organization definition (10) (6.9% vs. 3.5; p = 0.37), or the third universal definition (11) (21.6% vs. 24.6%; p = 0.59) (Online Table S5).

ANGIOGRAPHIC AND CLINICAL OUTCOMES IN THE VSV COHORT. Nine-month angiographic follow-up data were available in 90.6% of VSV patients (29 of 32). The primary endpoint of 9-month in-segment % DS was 38.4 ± 21.5%. TLF occurred in 2 patients because of TLR, without death, MI, or thrombosis events in the VSV population.

DISCUSSION

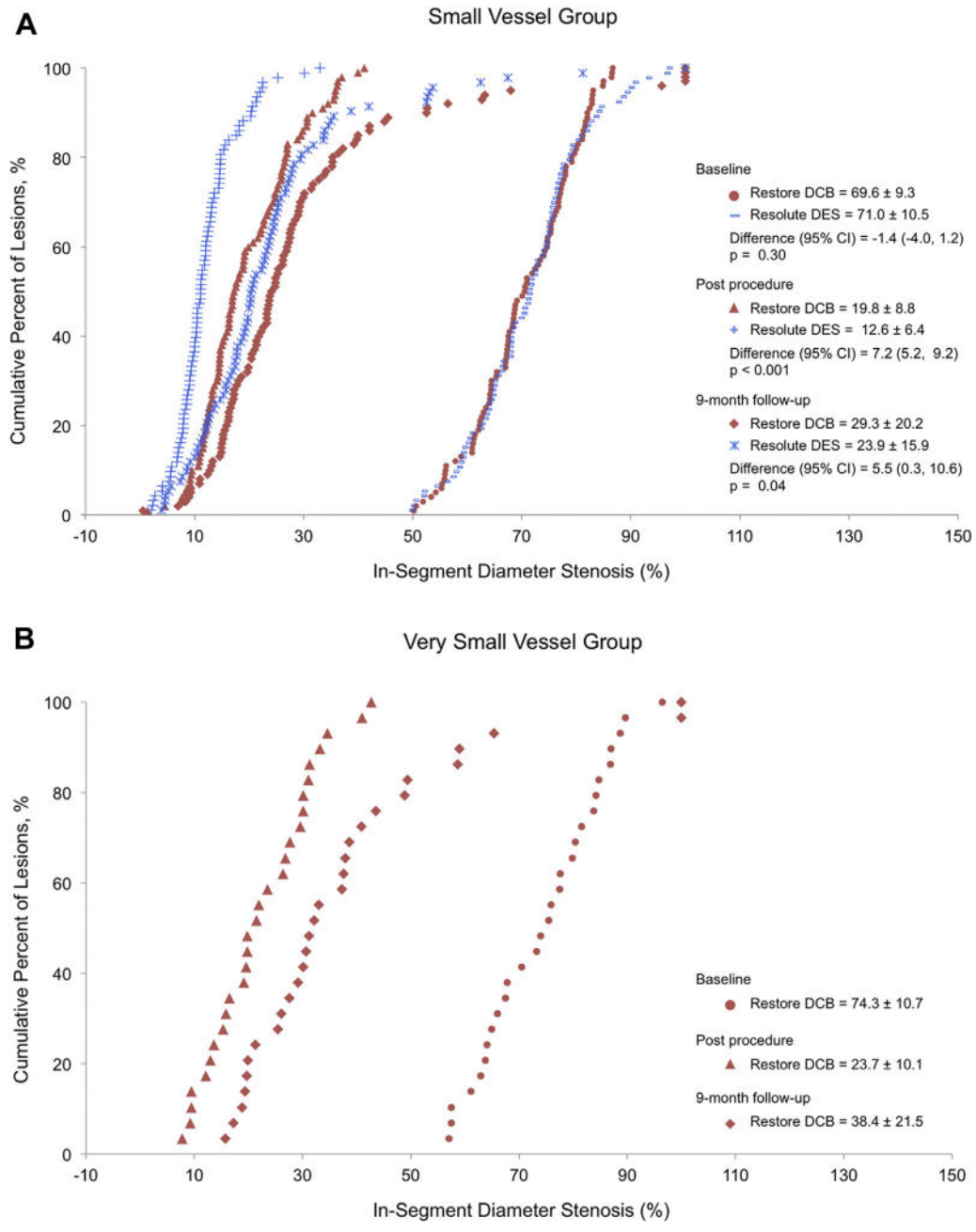
The RESTORE SVD China randomized trial is the first randomized clinical trial comparing the angiographic endpoints of a DCB with those of a

TABLE 4 Nine-Month In-Segment Percentage Diameter Stenosis in the Intention-to-Treat and As-Treated Populations

	Restore DCB Group	Resolute DES Group	Difference (95% CI)	Noninferiority p Value
Intention-to-treat population	(n = 100, 100 lesions)	(n = 93, 93 lesions)		
In-segment diameter stenosis, % (per subject)	29.6 ± 2.0	24.1 ± 2.0	5.5 (0.2-10.9)	<0.001
In-segment diameter stenosis, % (per lesion)	29.6 ± 2.0	24.1 ± 2.0	5.5 (0.2-10.9)	<0.001
As-treated set	(n = 96, 96 lesions)	(n = 93, 93 lesions)		
In-segment diameter stenosis, % (per subject)	30.1 ± 2.1	24.1 ± 2.0	6.0 (0.5-11.4)	0.04
In-segment diameter stenosis, % (per lesion)	30.1 ± 2.1	24.1 ± 2.0	6.0 (0.5-11.4)	0.04

Values are mean ± SE. Analysis of covariance with center adjustment was used for the comparison between 2 groups.
Abbreviations as in Table 1.

FIGURE 2 Nine-Month In-Segment Diameter Stenosis Distribution



Cumulative frequency distribution curves of in-segment percentage diameter stenosis at baseline, post-procedure, and 9-month angiographic follow-up. CI = confidence interval; DCB = drug-coated balloon; DES = drug-eluting stent(s).

second-generation DES in patients presenting with de novo SVD. In this study, the DCB was non-inferior to the new-generation DES for the primary endpoint of angiographic in-segment %DS at 9 months. Furthermore, the DCB and DES were associated with similar rates of angiographic restenosis, MACE, and repeat revascularization in small vessels. These results were obtained with the need for bail-out stenting in 5.2% of patients randomized to the DCB.

RESTORE SVD China was designed with in-segment %DS as the primary endpoint, a well-accepted surrogate of the clinical endpoint of ischemia-driven TLR. Follow-up %DS was equally effective as luminal loss in predicting TLR, whereas the impact of LL on the likelihood of TLR varies with vessel size, whereas the %DS-TLR relationship is vessel size independent (12). Restenosis is the result of the interaction of a variety of mechanical and biological processes that begin immediately after balloon injury, including early vessel recoil (13,14), negative vascular remodeling (15), and excessive neointimal proliferation (16,17). The most important limitation of balloon angioplasty is abrupt vessel closure, resulting from elastic recoil and occlusive plaque dissection. An endpoint such as LL, which is commonly used in stent trials, is not suitable, because modalities with fairly high acute gain tend to incur increased LL. For these reasons, %DS at follow-up is preferred as the primary endpoint for such comparative efficacy analyses. The mean 9-month in-segment %DS for the DES in this trial (24.1%) is similar to that reported for the RESOLUTE stent in the RESOLUTE Japan SVS trial (18) at 9 months (23.1%) and the RESOLUTE ZEUS trial (19) at 10 months (21.5%). Compared with the Taxus DES used in the BELLO study, the new-generation RESOLUTE DES is superior in terms of both in-segment %DS (24.1% with the RESOLUTE DES and 33.3% with the Taxus DES) and MACE (9.6% with the RESOLUTE DES and 16.3% with the Taxus DES). The mean 9-month in-segment %DS for the DCB in the SVD cohort (29.6%) is less than the mean in-segment %DS with the IN-PACT DCB (35.0%) at 6 months in the BELLO trial (5) and the DIOR I DCB (43.6%) at 6 months in the PICCOLETO trial (4). The poor performance of the DIOR I DCB might have been related to inadequate lesion preparation with standard balloon pre-dilation as well as the limited efficacy of this DCB. Compared with the BELLO trial and the PICCOLETO trial, the superiority of angiographic endpoints with the DCB in this study was explained mainly by appropriate vessel preparation, which resulted in a low prevalence of bail-out stenting. The unique characteristics of the Restore DCB may have a potential impact on improving outcome, which requires further study to prove.

The specified VSV cohort was a cohort assessing the effectiveness and safety of DCBs in treating coronary vessel with visual reference diameter between 2.0 and 2.25 mm. The 9-month in-segment stenosis rate in the VSV cohort (38.4%) was apparently higher than that in the SVD cohort, once again underscoring that smaller vessel size may result in worse outcomes. The Spanish Registry (20) published the results of the second-generation DIOR in 103 patients with disease in vessels with mean RVD of 1.95 ± 0.32 mm, angiographic diameter stenosis at 6 months (39.7%), and the rate of MACE at 1 year (4.8%) 2.25 mm showing similar efficacy as the DCB in this study. Nonetheless, the similar %DS (37.9%) with the RESOLUTE Onyx 2.0-mm zotarolimus-eluting stent (21) indicates that DCBs may be a choice in treating VSV disease.

Considering the absolute magnitude, the difference in 9-month in-segment %DS in the present study between the DCB and the DES is not likely to be clinically meaningful. Pocock et al. (12) demonstrated that when the follow-up in-segment %DS is <30%, TLR rates are very low, with further reductions in DS% unlikely to reduce clinical events. The low 9-month in-segment DS% in the DCB group from the present study (29.6%) was associated with low in-segment LL (0.25 mm) and 1-year ischemia-driven TLR (4.4%), comparable with the in-segment LL (0.27 mm) and ischemia-driven TLR (2.6%) observed with DES group.

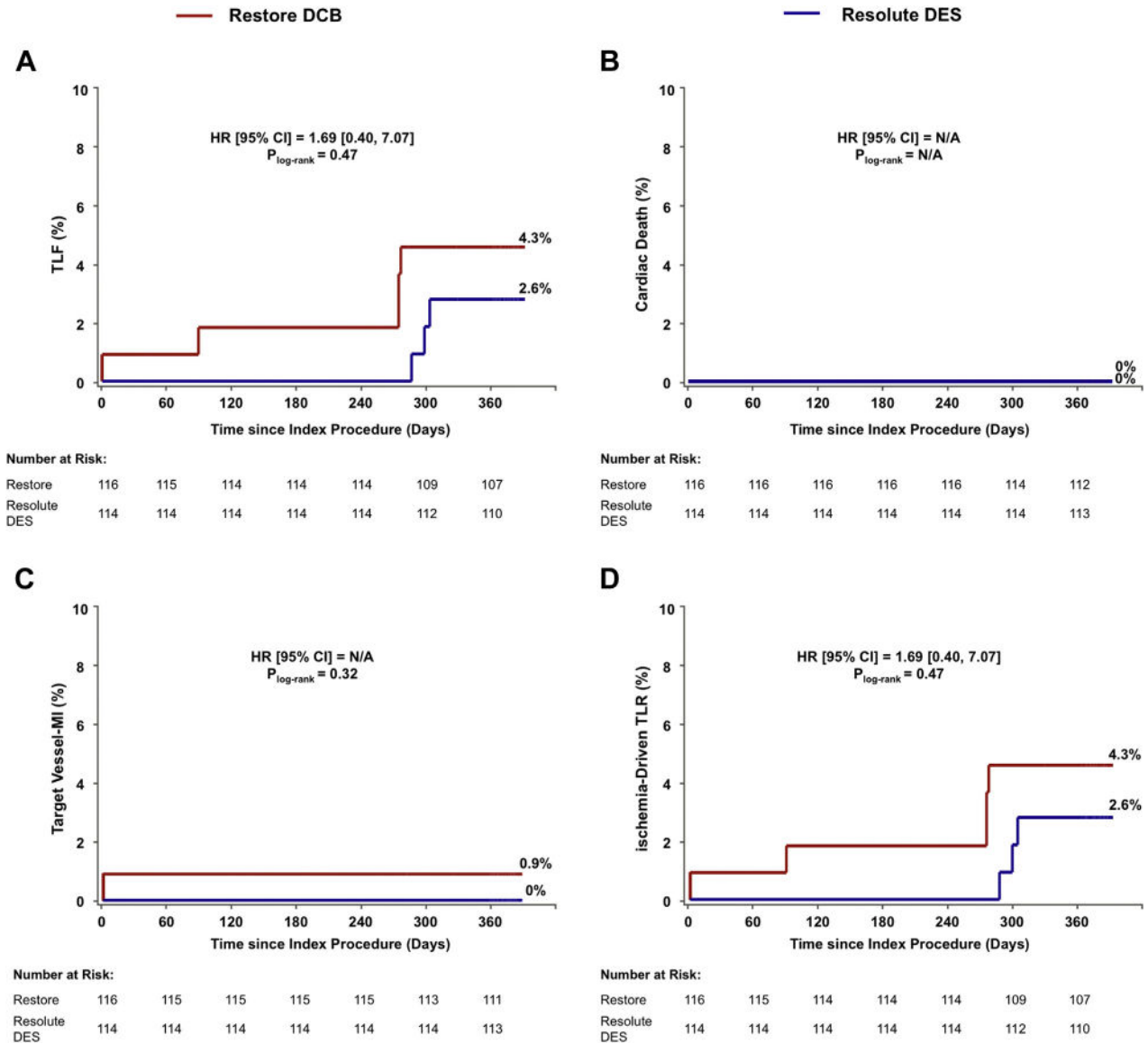
TABLE 5 Clinical Outcomes in the Intention-to-Treat Population

	Small Vessel Group				
	Restore DCB Group	Resolute DES Group	Difference (95% CI)	p Value	Very Small Vessel Group
1 month*	n = 116	n = 114			n = 31
Target lesion failure†	0.9 (1)	0 (0)	0.9 (−0.8 to 2.5)	1.00	0 (0)
Patient-oriented composite endpoint‡	1.7 (2)	0 (0)	1.7 (−0.6 to 4.1)	0.50	0 (0)
All-cause death	0 (0)	0 (0)	–	–	0 (0)
Cardiac death	0 (0)	0 (0)	–	–	0 (0)
MI	0.9 (1)	0 (0)	0.9 (−0.8 to 2.5)	1.00	0 (0)
Target vessel MI	0.9 (1)	0 (0)	0.9 (−0.8 to 2.5)	1.00	0 (0)
Periprocedural MI	0.9 (1)	0 (0)	0.9 (−0.8 to 2.5)	1.00	0 (0)
Any revascularization	1.7 (2)	0 (0)	1.7 (−0.6 to 4.1)	0.50	0 (0)
Ischemia-driven TVR	0.9 (1)	0 (0)	0.9 (−0.8 to 2.5)	1.00	0 (0)
Ischemia-driven TLR	0.9 (1)	0 (0)	0.9 (−0.8 to 2.5)	1.00	0 (0)
Definite/probable device thrombosis	0 (0)	0 (0)	–	–	0 (0)
1 yr*	n = 114	n = 114			n = 32
Target lesion failure	4.4 (5)	2.6 (3)	1.8 (−3.0 to 6.5)	0.72	6.3 (2)
Patient-oriented composite endpoint	9.6 (11)	9.6 (11)	0 (−7.7 to 7.7)	1.00	15.6 (5)
All-cause death	0 (0)	0 (0)	–	–	0 (0)
Cardiac death	0 (0)	0 (0)	–	–	0 (0)
MI	0.9 (1)	0 (0)	0.9 (−0.8 to 2.6)	1.00	0 (0)
Target vessel MI	0.9 (1)	0 (0)	0.9 (−0.8 to 2.6)	1.00	0 (0)
Periprocedural MI	0.9 (1)	0 (0)	0.9 (−0.8 to 2.6)	1.00	0 (0)
Any revascularization	9.6 (11)	9.6 (11)	0 (−7.7 to 7.7)	1.00	15.6 (5)
Ischemia-driven TVR	5.3 (6)	6.1 (7)	−0.9 (−6.9 to 5.1)	0.78	9.4 (3)
Ischemia-driven TLR	4.4 (5)	2.6 (3)	1.8 (−3.0 to 6.5)	0.72	6.3 (2)
Definite/probable device thrombosis	0 (0)	0 (0)	–	–	0 (0)

Values are % (n). *1-month follow-up includes a window of ±7 days, and 1-yr follow-up includes a window of ±30 days. †Target lesion failure was defined as a composite of cardiac death, target vessel MI, or ischemia-driven TLR. ‡Patient-oriented composite endpoint was defined as a composite of all-cause death, all MI, or any revascularization.

TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

FIGURE 3 Time-to-Event Curves for Selected Clinical Endpoints Through 1 Year



Analyses were performed in the intention-to-treat population. Kaplan-Meier curves show the cumulative incidence of **(A)** target lesion failure (TLF), **(B)** cardiac death, **(C)** target vessel myocardial infarction (MI), and **(D)** ischemia-driven target lesion revascularization (TLR). CI = confidence interval; DCB = drug-coated balloon; DES = drug-eluting stent(s); HR = hazard ratio; N/A = not applicable.

In the present study, the 1-year rates of clinical endpoints were comparable between the DCB and the DES. Similar results were reported in the BELLO trial. In both trials (182 and 230 randomized patients, respectively), DCBs and DES had comparable rates of TLF, cardiac death, target vessel MI, all MI, and ischemia-driven TLR. Moreover, despite the lower post-procedural %DS with the DCB compared with the DES, similar rates of periprocedural myonecrosis were noted with both devices in both trials, regardless of the definition of MI used. The BASKET-SMALL 2 study (22) was designed to test the noninferiority of a DCB (SeQuent Please) compared with DES (Taxus, XIENCE/Primus) in patients undergoing PCI in small coronary vessels (reference diameter <3 mm) using clinical endpoints in a large all-comers population of 758 subjects. Our study may provide the angiographic mechanism of the noninferior clinical endpoints

achieved and the experience in optimizing the procedure of DCB treatment in SVD.

Adequate pre-dilation is a necessary preparation for the vessel. A large inflation pressure with the pre-dilation balloon may lead to severe dissection, whereas insufficient inflation may result in worsening long-term outcomes. Tanaka et al. (23) indicated that an angiographically inadequate result before DCB treatment was an independent predictor of TLR, even after adjusting for RVD and lesion length (hazard ratio: 1.99; 95% confidence interval: 1.02 to 3.87; $p = 0.04$). Balance was required in resolving the protocol of pre-dilation. In the present study, the maximal diameter (2.11 ± 0.27 mm) and the maximal inflation pressure (11.1 ± 3.0 atm) of the pre-dilation balloon in the DCB group were comparable with those in the DES group, and similar rates of dissection after pre-dilation occurred in both groups (29.3% in the DCB group and 28.1% in the DES group, $p = 0.84$). In the DCB group, using relatively lower dilation pressures (9.11 ± 2.89 atm in the DCB group and 10.7 ± 2.33 atm in the DES group, $p < 0.001$, 9.6 ± 2.5 atm in the DCB group of the BELLO study), in-segment %DS ($19.8 \pm 8.8\%$ in the DCB group and $12.6 \pm 6.4\%$ in the DES group, $p < 0.001$) and in-segment MLD (1.65 ± 0.26 mm in the DCB group and 1.98 ± 0.25 mm in the DES group, $p < 0.001$) obtained immediately post-procedure were lower than those in the DES group, as anticipated. Meanwhile, low rates of residual dissection (greater than level C) (0%) and bail-out stenting in the DCB group (5.2% in RESTORE SVD China and 20.2% in BELLO) achieved, comparable with the RESOLUTE DES, proved the safety of DCB treatment for SVD.

In the comparison of DAPT duration between the DCB and DES groups, no significant difference was observed: 91.4% subjects in the DCB group and 94.7% subjects in the DES group received 12-month DAPT treatment (Online Figure S3), which was recommended by the investigators of the PEPCAD China ISR study (24). The prolonged DAPT duration was partly secondary to the high proportion of unstable angina in this study and the high incidence of MACE in small vessels. In patients treated with DCB, dedicated clinical trials investigating the optimal duration of DAPT are lacking. Additional studies assessing shortening of DAPT duration are required after regulatory approval of the Restore DCB in China.

STUDY LIMITATIONS. RESTORE SVD China was an open-label trial (like other studies comparing DCBs with DES), and some degree of bias cannot be excluded. However, the effect of potential bias on outcomes was minimized by use of an independent clinical events committee to adjudicate events on the basis of original source documents and an independent angiographic core laboratory using established algorithms and criteria.

This study was powered for an angiographic endpoint. Therefore, the number of patients was insufficient for the detection of differences in clinical endpoints.

Intravascular imaging was used in few patients in our study, and additional studies are required to determine if routine use of either intravascular ultrasound or optical coherence tomography would improve DCB outcomes.

The duration of DAPT in this study was assigned as at least 6 months, to enable approval of the new device (with SVD indication) in China.

CONCLUSIONS

In this multicenter randomized trial, the Restore DCB was noninferior to the second-generation RESOLUTE Integrity DES for the primary endpoint of in-segment %DS at 9 months.

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PERSPECTIVES

WHAT IS KNOWN? A previous randomized trial demonstrated that DCBs were superior to first-generation DES for 6-month LL in treating de novo SVD and might have longer term clinical benefit. However, whether a DCB-only strategy in SVD is as effective as the contemporary DES was undefined.

WHAT IS NEW? In patients undergoing small-vessel PCI, the 9-month angiographic efficacy and 1-year clinical results of Restore, a new DCB, were comparable with those of the RESOLUTE DES.

WHAT IS NEXT? An adequately powered clinical study is needed to evaluate real clinical advantage with this new device for treatment of SVD.

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KEY WORDS drug-coated balloon, drug-eluting stent(s), percentage diameter stenosis, small-vessel disease

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