Original Article



# Efficacy and safety of drug-coated balloons in the treatment of *de novo* coronary lesions in very small vessels: a prospective, multicenter, single-arm trial

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**Background:** Evidence of the use of drug-coated balloons (DCB) in *de novo* large or small coronary lesions and in-stent restenosis has accumulated over the past years. Due to their anatomical peculiarity, the treatment of very small vessels (VSV) (lumen diameter <2 mm) is still a controversial issue. Studies that examine the use of DCB in VSV are limited. We investigated the efficacy and safety of using DCBs for the *de novo* coronary lesions in VSV undergoing percutaneous coronary intervention (PCI).

**Methods:** In this prospective, single-arm study, we enrolled adult patients with coronary artery disease from six centers in China. A total of 29 patients had VSV with a target lesion stenosis ≥70% were included. All patients were treated with DCB. The primary endpoint was late lumen loss (LLL) at 9 months of follow-up. The secondary endpoints were major adverse cardiac events including target lesion revascularization, death, or myocardial infarction at 9 months of follow-up.

**Results:** Twenty-nine eligible patients with VSV were enrolled between November 2019 to May 2020. Angiographic and clinical follow-up were completed at 9 months in 18 (56.25%) patients (7 patients refused to final angiography; 2 failed to finish DCB angioplasty; 1 patient request; 1 other causes of death). The mean diameter of the reference vessel of the target lesion was 1.71±0.27 mm, the minimum lumen diameter (MLD) of the target lesion before operation was 0.31±0.24 mm, the average LLL of the target lesion was 0.13±0.28 mm, and the MLD of the target vessel immediately after operation was (1.19±0.20 mm) and at the 9-month follow-up (1.06±0.31 mm) were significantly higher than those before operation (P=0.043). One patient (5.56%) underwent revascularization. No myocardial infarction or death occurred during follow-up after treatment with DCBs.

**Conclusions:** DCB can be a safe and effective alternative in the treatment of *de novo* coronary lesions in VSV.

**Keywords:** Drug-coated balloons (DCB); percutaneous coronary intervention (PCI); small vascular lesions; coronary artery disease

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## Introduction

Percutaneous coronary intervention (PCI) is the current standard treatment strategy for coronary artery disease (1). PCI techniques have evolved rapidly, from the early plain old balloon angioplasty (POBA) to the later bare-metal stents (BMS), then second- and next-generation drug eluting stents (DES). The problems of elastic retraction, acute occlusion, and restenosis have been greatly reduced with DES (2-5), but late and very late stent thrombosis present new concerns (6,7).

Drug-coated balloons (DCBs) emerged as a therapeutic alternative in recent years (8). DCBs provide antiproliferative drugs that can be rapidly transferred to the vessel wall during DCBs dilation. Intimal proliferative response is avoided without the use of a durable polymer o r metal scaffold. The rate of late lumen loss (LLL) and in-stent restenosis (ISR) is reduced. Substantial evidence has accumulated over the past years in ISR and *de novo* large or small coronary lesions (8-10). Very small vessels (VSV; lumen diameter <2 mm) lesions are common in coronary arteries especially in the Asia-Pacific region. However, evidence of the use of DCB in VSV is limited. Due to the anatomical peculiarity and, especially, the lack of devices, the treatment of VSV is still a controversial issue. The aim of this study was to investigate the efficacy and safety of DCB in VSV of the coronary arteries. We present the following article in accordance with the TREND reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1266/rc).

## Methods

### *Study design and patients*

This study was a prospective, open-label, single-arm, multi-center trial conducted between November 2019 to May 2020. The sample size was set as 30. The trial registration number is ChiCTR2200056430 (Chictr.org.cn).

Adult patients with coronary artery disease were recruited from 6 centers (Beijing Anzhen Hospital, Beijing Fuwai Hospital, Beijing Chaoyang Hospital, The First Hospital of Jilin University, West China Hospital, The Affiliated Hospital of Zunyi Medical College) in China. DCB was provided by Hangzhou Revita medical technology company. Patients were included if they had VSV defined as lesion reference vessels ≤2.0 mm in diameter with a target lesion stenosis ≥70%. Major exclusion criteria were life expectancy of less than 1 year of the study, acute myocardial infarction within 7 days of the study, stroke within 6 months of the study, high risk of bleeding or contraindication to antiplatelet agents, severe congestive heart failure or NYHA(New York Heart Association) cardiac function class III or IV, creatinine clearance <30 mL/min, or total occlusion.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University of China (No. 2018-0311) and other participating hospitals also informed and approved this study. All subjects provided written informed consent.

### *Intervention*

All PCI procedures complied with the management principles of the Chinese guidelines of PCI and the DCB management consensus.

Initial and long-term antithrombotic strategies in this study were as follows: aspirin (100 mg) once daily combined with clopidogrel (75 mg) once daily or ticagrelor (90 mg) twice daily for 1–3 months (for patients with stable angina) or 12 months (for patients with acute coronary syndrome). Angiographic follow-up was performed at 9 months postoperatively.

Semi-compliant balloons with a balloon/vessel diameter ratio of 0.8–1.0 were dilated with moderate pressure (8–14 atm). We performed DCB dilation after adequate pre-dilatation and when the lesions satisfied with the following conditions: no or type A or B dissection; Thrombolysis in Myocardial Infarction (TIMI) flow class III; and residual stenosis ≤30%.The diameter ratio between DCB and vessel is 0.8–1.0. Balloon inflation time is 30–60 seconds. The DCB worked as drug delivery vehicles and should not be used to relieve stenosis of the lesions. To avoid geographic deficit between the DCB and the target lesion, the length of DCB was 2 mm beyond the diseased segment. The DCB should be delivered to the lesion within 2 minutes.

Baseline information was collected from participants, including demographic information (gender, age), risk factors (angina pectoris, diabetes, hypertension, hyperlipidemia, smoking, alcohol consumption), medical history information (family history of coronary artery disease, history of myocardial infarction, history of PCI, history of coronary artery bypass grafting, and vital organ functions [left ventricular ejection fraction (LVEF), glomerular filtration creatinine].

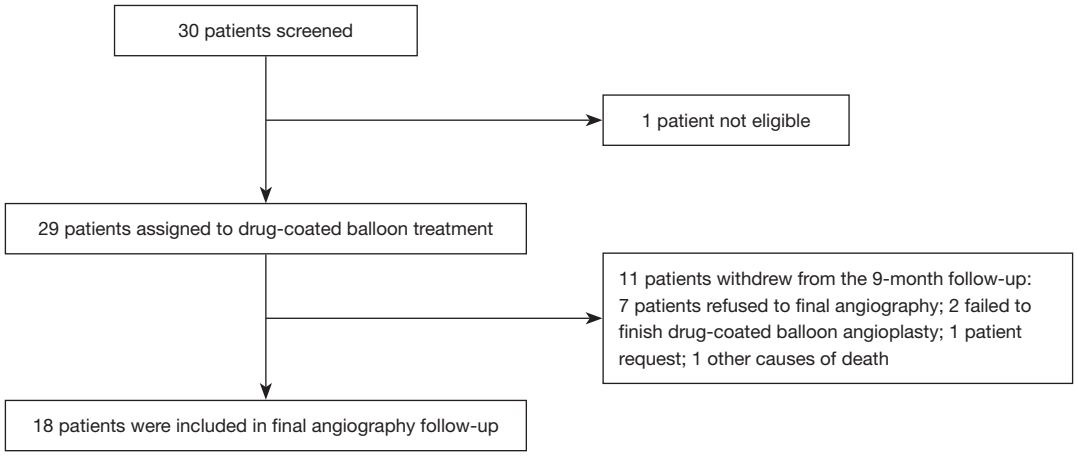


**Figure 1** Patients selection flowchart.

### *Endpoint*

LLL of the target lesion at the 9-month follow-up was the major clinical effectiveness endpoint. LLL was defined as the difference between the minimum lumen diameter (MLD) after the procedure and at follow-up. Baseline and follow-up quantitative coronary angiography (QCA) data were analyzed at the central laboratory. Procedural success included angiographic and clinical success. Angiographic success represented visual measurement of residual stenosis of the target lesion vessel ≤30% after the procedure. Clinical success meant the absence of target lesion failure (TLF) within 7 days after the procedure. Lumen restenosis meant ≥50% restenosis at the target lesion at follow-up. Other endpoints were major adverse cardiovascular events (MACE) including target lesion revascularization, death (cardiac death and all-cause death), or myocardial infarction at the 9-month follow-up.

### *Statistical analysis*

Continuous variables were reported as mean ± standard deviation. Categorical variables were reported as frequencies and percentages. The distribution of continuous parameters was tested for normality using the Kolmogorov-Smirnov test. The MLD of the target lesion before and after operation was compared using one-way analysis of variance (ANOVA), and Fisher's least significant difference (LSD) *t*-test was used for two-way comparisons. All statistical analyses were performed at a two-sided significance level of 0.05 with SPSS 19.0 software (SPSS Inc., Chicago, IL, USA).

## Results

### *Baseline characteristics*

A total of 29 patients with a mean age of (60.07±9.87) years were included in this study (*Figure 1*). Among them, 19 cases (65.52%) were male, 14 cases (48.28%) had diabetes, 19 cases (65.52%) had hypertension, 22 cases (75.86%) had hyperlipidemia, and 13 cases (44.83%) had a history of smoking. A history of alcohol consumption was present in 8 cases (27.58%), 2 cases (6.90%) had a family history of previous coronary artery disease, 9 cases (31.03%) had a history of myocardial infarction, 13 cases (44.83%) had a history of PCI, 1 case (3.45%) had a history of CABG, 26 cases (89.66%) had unstable angina, mean glomerular filtration rate (GFR) was (96.63±19.03)%, and mean LVEF was (63.25±8.81)% (*Table 1*).

### *Basic lesion and DCB treatment characteristics*

Of the 29 patients, 9 (31.03%) had lesions located in left anterior descending coronary artery (LAD), 15 (51.72%) in LCX, and 5 (17.24%) in right coronary artery (RCA). TIMI flow was ≥ grade II in all cases. The target vessels were all moderately or less calcified. None of the target vessels had stents and restenosis, none had thrombosis, and none had severe tortuosity. Most of the lesions were pre-treated with 1 balloon (89.66%), 2 cases with 2 balloons (6.90%), and 1 case with 3 balloons (3.45%). The mean pre-dilated balloon diameter was (1.67±0.35) mm, the length was (13.48±2.72) mm, and the dilation pressure was (11.21±3.43) atm. During DCB treatment, 1 DCB was used in 28 patients (96.55%), 2 DCB were used in 1 patient (3.45%), and the mean DCB

**Table 1** Basic characteristics of the study population

| Variables | DCB (n=29) |
|---|---|
| Male gender | 19 (65.52%) |
| Age, years (mean ± SD) | 60.07±9.87 |
| Diabetes mellitus | 14 (48.28%) |
| Hypertension | 19 (65.52%) |
| Hyperlipidemia | 22 (75.86%) |
| Smoking history | |
| Current smoker | 4 (13.79%) |
| Past smoker | 9 (31.03%) |
| History of alcohol consumption | |
| Alcohol consumption | 5 (17.24%) |
| Previous alcohol consumption | 3 (10.34%) |
| Family history of coronary artery disease | 2 (6.90%) |
| Previous MI | 9 (31.03%) |
| Previous PCI | 13 (44.83%) |
| Previous CABG | 1 (3.45%) |
| Unstable angina | 26 (89.66%) |
| GFR (%, mean ± SD) | 96.63±19.03 |
| LVEF (%, mean ± SD) | 63.25±8.81 |

Values are n (%). MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; DCB, drug coated balloon.

balloon diameter was (1.68±0.17) mm, the length was (18.50±4.38) mm, the dilation pressure was (10.17±2.65) atm, and the dilation time was (57.83±7.84) seconds. All patients achieved procedural success and were treated with dual antiplatelet therapy and statins (*Table 2*).

### *Clinical and angiographic follow-up and QCA analysis*

Eighteen of the enrolled patients completed the 9-month angiographic follow-up. The mean target lesion LLL was 0.13±0.28 mm, and the MLD of the target vessel immediately post-operation and at follow-up were both significantly larger than pre-operation (P<0.043). One patient (5.56%) underwent revascularization, and no MI or death was reported during follow-up after DCB treatment (*Table 3*).

## Discussion

PCI with DES remains the primary strategy for treatment of coronary artery disease (1). however, DCB has many advantages, such as uniform drug delivery to the vessel wall, drug release without a polymer, inhibition of negative remodeling, inhibition of proliferation of endothelial cells, reduction of the intensity and duration of antiplatelet therapy, decrease of the incidence of post-procedure bleeding, and that there is no foreign material left in the vessel lumen (8). DCB has the potential to treat ISR and small vessel lesions, but existing research is limited. Based on data from several RCTs and registry studies, Europe had made recommendations for DCB use in PCI (1,11). However, the demographics and disease characteristics of patients in the Asia-Pacific region, where coronary arteries are relatively small and diffuse lesions are more common, differ from those of European patients (12). These characteristics may reflect the high prevalence of diabetes mellitus in the Asia-Pacific region. Small vessels have a worse prognosis than large vessels in terms of ISR because there is less room for intimal hyperplasia after small vessel stenting (13). Long-term restenosis rates remain high in DES. The SPIRIT SV study (14) indicated a target vessel failure (TVF) rate of 10.8% at more than 1-year follow-up after small vessel PCI. Converging data analysis from the SPIRIT and COMPARE studies (15) showed a significantly higher MACE rate in small-vessels than that in large-vessels (10.4% *vs.* 5.6%; P<0.001). Another notable difference is the higher bleeding risk (especially gastrointestinal bleeding and hemorrhagic stroke) in patients from the Asia-Pacific region in the current antithrombotic therapy (16,17). Therefore, the use of DCB in the Asian population has a greater potential benefit.

As the field rapidly evolves, considerable evidence has been accumulated in the treatment of ISR and *de novo* coronary lesions with DCB. However, there is less evidence in VSV, and this study examined the efficacy and safety of DCB in VSV of the coronary arteries.

Our study showed that the mean target lesion LLL was 0.13±0.28 mm, and the MLD of the target vessel immediately postoperative and at the 9-month follow-up was significantly larger than the pre-procedure MLD. One patient underwent revascularization, and no MI or death was reported during the follow-up. These results confirmed the safety profile and 9-month efficacy of DCB in VSV. These findings can expand the scope of DCB application,

**Table 2** Basic lesion characteristics

| Variables | N=29 |
|---|---|
| Target lesion | |
| LAD | 31.03 (9/29) |
| LCX | 51.72 (15/29) |
| RCA | 17.24 (5/29) |
| TIMI flow | |
| Class 0 | 0.00 (0/29) |
| Class I | 0.00 (0/29) |
| Class II | 13.79 (4/29) |
| Class III | 86.21 (25/29) |
| Degree of calcification | |
| None | 79.31 (23/29) |
| Mild | 13.79 (4/29) |
| Moderate | 6.90 (2/29) |
| Severe | 0.00 (0/29) |
| Previous stented | 0.00 (0/29) |
| ISR | 0.00 (0/29) |
| Thrombus | 0.00 (0/29) |
| Severely tortuous | 0.00 (0/29) |
| Bifurcation | 3.45 (1/29) |
| Number of pre-dilated balloons used | |
| 1 | 89.66 (26/29) |
| 2 | 6.90 (2/29) |
| 3 | 3.45 (1/29) |
| Pre-dilated balloon information | |
| Balloon diameter, mm | 1.67±0.35 |
| Balloon length, mm | 13.48±2.72 |
| Dilation pressure, atm | 11.21±3.43 |
| Duration of inflation, s | 13.73±18.38 |
| Number of DCB used | |
| 1 | 96.55 (28/29) |
| 2 | 3.45 (1/29) |
| DCB information ($\bar{x}$±s) | |
| DCB diameter, mm | 1.68±0.17 |
| DCB length, mm | 18.50±4.38 |
| Duration of inflation, s | 57.83±7.84 |
| DCB dilation pressure, atm | 10.17±2.65 |
| Angiographic success | 100.00 (29/29) |
| Clinical success | 100.00 (29/29) |
| Procedural success | 100.00 (29/29) |
| Perioperative drug use | |
| Dual antiplatelet therapy | 100.00 (29/29) |
| Statins | 100.00 (29/29) |

Values are % (n/N) or mean ± SD. LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction; ISR, in stent restenosis; DCB, drug coated balloon.

especially in the Asia-Pacific population and those patients with relatively small coronary arteries and more diffuse lesions.

The PICCOLETO study comparing DCB with DES in small vessels showed that the trial did not bring better results due to the use of first generation DCB (18). The subsequently improved BELLO study showed no statistical difference between DCB and DES in terms of TLR, MACE, and restenosis, but the DEB group was superior to the DES group in terms of LLL (19). The PICCOLETO II study included 232 patients from multiple centers, all subjects were randomized to the DCB group (n=118) or DES group (n=114) (20). The results demonstrated that LLL was significantly lower in the DCB group than in the DES group (0.04 *vs.* 0.17 mm; P<0.03), and there was no statistical difference between the two groups in MACE, MI, and intravascular thrombosis at the 12-month follow-up. The BASKET-SMALL2 study included the largest population, 758 patients, who were randomized into the DCB group (n=382) or the DES group (n=376) and showed there was no statistical difference between the two groups in MACE, death, MI, TVR, ISR, or major bleeding at a 3-year follow-up (21,22). The results verified the long-term effectiveness and safety of DCB in the small vessels. The RESTORE SVD study was a multicenter study from China in which a total of 230 patients were randomized to the DCB group (n=116) or the DES group (n=114), and the results at the 9-month follow-up showed a significantly lower diameter stenosis rate in the DCB group than in the DES group (24.1 *vs.* 29.6%; P<0.001), with no statistically significant difference in TVF between the two groups (23). The RESTORE SVD study divided a group of 32 patients

**Table 3** Outcomes at the 9-month angiographic follow-up

| Variables | N=18 |
|---|---|
| Pre-procedure QCA | |
| Reference vessel diameter, mm | 1.71±0.27 |
| Minimum lumen diameter, mm | 0.31±0.24 |
| Diameter stenosis, % | 88.60±6.93 |
| Lesion length, mm | 15.52±4.66 |
| Post-procedure QCA | |
| Minimum lumen diameter, mm | 1.19±0.20 |
| Diameter stenosis, % | 19.68±9.36 |
| 9-month follow-up QCA | |
| Minimum lumen diameter, mm | 1.06±0.31 |
| Late lumen loss, mm | 0.13±0.28 |
| Restenosis rate, % | 22.22 (4/18) |
| Clinical outcomes | |
| Target lesion revascularization | 5.56 (1/18) |
| Myocardial infarction | 0.00 (0/18) |
| Death | 0.00 (0/18) |
| Cardiac death | 0.00 (0/18) |
| All-cause death | 0.00 (0/18) |
| composite endpoint | 5.56 (1/18) |

Values are % (n/N) or mean ± SD. QCA, quantitative coronary angiography.

in the VSV group (2.0 mm ≤ vessel diameter <2.25 mm), with a mean target lesion LLL of 0.27±0.38 mm; 2 target lesions underwent revascularization, and no death or MI occurred. LLL in this group was higher than that in our study (0.13±0.28 mm). One patient (5.56%) underwent revascularization and no death or MI occurred at the 9-month follow-up in our study.

There are some limitations in this study. First, the sample size was small, and the angiographic follow-up rate was low, therefore an effort should be made to enlarge the sample size in the future. Second, DES could not be set as a control group because of stent size and other factors, and a head-to-head comparison needs to be performed in subsequent studies between DCBs. Third, the combination of intracoronary imaging and physiological testing is more promising to verify the effectiveness and safety of treatment with DCBs.

## Conclusions

The VSV was special, there is no DES of this size, and when severe stenosis occurs, conservative treatment or POBA treatment is preferred. The advent of DCB provides a new idea for such lesions. The effectiveness of DCB compared with POBA or DES has been well documented, but it has been less studied in the VSV lesions included in this study. Findings show that DCB may be a safe and effective treatment for patients with small vessels, especially in Asian populations with a high proportion of diabetes.

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## Footnote

*Reporting Checklist*: The authors have completed the TREND reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1266/rc

*Data Sharing Statement*: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1266/dss

*Conflicts of Interest*: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1266/coif). The authors have no conflicts of interest to declare.

*Ethical Statement*: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethical Review Committee of Beijing Anzhen Hospital, Capital Medical University of China (No. 2018-0311) and other participating hospitals also informed and approved this study. All patients were enrolled after receiving detailed explanation of the study protocol, they or their family members had provided written informed consent.



 

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