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Clinical Research

Safety and Efficacy of the Passeo-18 Lux Drug-Coated Balloon Catheter in Atherosclerotic Femoropopliteal Lesions: The Multicenter BIOLUX P-IV China Study

Jue Yang,[1] Jianing Yue,[1] Xueming Chen,[2] Haofu Wang,[3] Weiliang Jiang,[4] Xiaojin Huang,[5] Xinwu Lu,[6] Honglin Dong,[7] Xuan Li,[8] and Weiguo Fu,[1] Shanghai, Beijing, Qingdao, Harbin, Xiamen and Taiyuan, China

Background: The purpose of this trial was to assess the safety and effectiveness of a paclitaxel-coated balloon catheter in Chinese patients with *de novo* or nonstented restenotic femoropopliteal atherosclerotic lesions.

Methods: BIOLUX P-IV China is a prospective, independently adjudicated, multicenter, single-arm trial conducted in China. Patients with Rutherford class 2−4 were eligible, excluded were patients in which predilation resulted in severe ($\geq$ grade D) flow-limiting dissection or residual stenosis $>$ 70%. Follow-up assessments were conducted at 1, 6, and 12 months. The primary safety end point was 30-day major adverse event rate and the primary effectiveness end point was primary patency at 12 months.

Results: We enrolled 158 patients with 158 lesions. Mean age was 67.6 ± 9.6 years, diabetes was present in 53.8% ($n = 85$), and previous peripheral intervention/surgeries in 17.1% ($n = 27$). Lesions were 4.1 ± 0.9 mm in diameter and 74 ± 50 mm long with a mean diameter stenosis of 91 ± 13%; 58.2% ($n = 92$) were occluded (core laboratory analysis). Device success was achieved in all patients. The rate of major adverse events was 0.6% (95% confidence interval: 0.0; 3.5) at 30 days, consisting of 1 target lesion revascularization. At 12 months, binary restenosis was present in 18.7% ($n = 26$) and target lesion revascularization was performed in 1.4% ($n = 2$, all clinically driven), resulting in a primary patency of 80.0% (95% confidence interval:

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Declaration of interest: The authors declare that they have no competing interests.

[1]*Department of Vascular Surgery, Zhongshan Hospital of Fudan University, Shanghai, China.*

[2]*Department of Vascular Surgery, Beijing Friendship Hospital, Capital Medical University, Beijing, China.*

[3]*Department of Vascular Surgery, Affiliated Hospital of Qingdao University, Qingdao, China.*

[4]*Department of Vascular Surgery, The Second Affiliated Hospital of Harbin Medical University, Harbin, China.*

[5]*Department of Vascular Surgery, Zhongshan Hospital Xiamen University, Xiamen, China.*

[6]*Department of Vascular Surgery, Shanghai Nineth People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.*

[7]*Department of Vascular Surgery, Second Hospital of Shanxi Medical University, Taiyuan, China.*

[8]*Department of Interventional Vascular Surgery, Peking University Third Hospital, Beijing, China.*

Correspondence to: Fu Weiguo, Zhongshan Hospital of Fudan University, 180 Fenglin Road, Xuhui District, 200032 Shanghai, China; E-mail: Fuweiguo6288@126.com

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72.4, 85.8); no major target limb amputation occurred. Clinical improvement at 12 months, defined as improvement of at least 1 Rutherford class, was 95.3% ($n = 130$). The median walking distance per 6-minute walk test was 279 m at baseline and improved by 50 m at 30 days and by 60 m at 12 months; the visual analogue scale changed from 76.6 ± 15.6 at baseline to 80.0 ± 15.0 at 30 days and 78.6 ± 14.6 at 12 months.

Conclusions: Our results confirmed the clinical effectiveness and safety of a paclitaxel-coated peripheral balloon dilatation catheter for the treatment of *de novo* and nonstented restenotic lesion of the superficial femoral and proximal popliteal artery in Chinese patients (NCT02912715).

INTRODUCTION

Endovascular therapy for femoropopliteal revascularizations has become an established therapeutic strategy given the lower risk of procedural complications.[1] Initially treated with plain balloon angioplasty, drug-coated balloons (DCBs) have been developed to improve clinical outcomes through addition of highly lipophilic antiproliferative drugs.[2] Another treatment option are conventional stents that have the advantage of scaffolding the vessel to restore blood flow but are associated with the drawbacks of permanent implants such as stent fractures that may occur with an incidence of up to 65% in femoropopliteal lesions, potentially leading to restenosis, thrombosis, pseudoaneurysm, or embolization.[1]

DCBs have been successful in improving long-term patency compared to plain balloon angioplasty, leading to a Class IIb level A recommendation for their use in short (< 25 cm) femoropopliteal lesions.[2] However, there is a current debate about a possible excessive risk of mortality after paclitaxel-coated device use when compared to the use of uncoated devices. A meta-analysis that included more than 4,000 patients found elevated mortality in patients with femoropopliteal artery disease.[3] Yet, this meta-analysis was critiqued to be limited by the quality of included studies, for example, small sample sizes and incomplete follow-up.[4] Another meta-analysis including 5-year outcomes, and a real-world safety analysis with data over 11 years past application in more than 60,000 patients did not reveal an increased mortality after use of paclitaxel-coated balloons though.[4,5]

The Passeo-18 Lux paclitaxel-coated balloon is a DCB that showed superior outcomes compared to the uncoated Passeo-18 balloon (both BIOTRONIK AG, Buelach, Switzerland) in femoropopliteal lesions in a small randomized controlled trial.[6] Subsequently, Passeo-18 Lux was tested in BIOLUX-P-III, a large international all-comers registry with initially 700 patients that was extended to 1,084 patients. In this registry, multivariate Cox regression analysis revealed that the paclitaxel dose was not a predictor for mortality.[7]

To confirm the safety and effectiveness of the Passeo-18 Lux in *de novo* and nonstented restenotic lesion in femoropopliteal arteries in a Chinese patient population, the BIOLUX P-IV trial was initiated. Aside of assessing safety and effectiveness, BIOLUX P-IV assessed quality of life and walking impairment, relevant information that is rarely reported in studies using DCBs.

MATERIALS AND METHODS

Study Design and Patient Population

BIOLUX P-IV China is a prospective, multicenter, nonrandomized clinical trial with follow-up investigations at 1, 6, and 12 months that includes ankle brachial index assessment, Rutherford classification, EQ5-D and Walking Impairment questionnaires, 6-Minute Walk test, and Doppler ultrasound. It aimed to assess the safety and effectiveness of the paclitaxel-coated Passeo-18 Lux balloon in *de novo* and nonstented restenotic femoropopliteal lesions.

Main inclusion criteria were lesion in the superficial femoral or proximal popliteal artery, Rutherford class (RC) 2–4, ≥ 70% diameter stenosis of the target lesion, lesion length ≤ 200 mm, and reference vessel diameter ≥ 2 mm and ≤ 7 mm by visual estimate. Main exclusion criteria were contralateral femoropopliteal disease requiring treatment during the index procedure, additional lesions in the target vessel requiring treatment during index procedure that do not meet the inclusion criteria, complete occlusion of the lesion > 100 mm, in-stent restenosis or bypass, severe calcification, or predilatation that results in a major flow-limiting dissection or residual stenosis > 70%. The full list of inclusion and exclusion criteria can be accessed at ClinicalTrials.gov NCT02912715.

The trial was conducted as per local regulations, the Declaration of Helsinki, ISO14155: 2011, ICH-GCP and applicable National Medical Products

Table I. Demographic data and baseline characteristics

Outcomes	$N = 158$ patients
Age, years	67.6 ± 9.6
	27.1−89.7
Male gender	121 (76.6%)
Body mass index	24.3 ± 3.3
	15.0−32.1
Hypertension	122 (77.2%)
Hyperlipidemia	50 (31.6%)
Smoking habits	
Used to smoke	24 (15.2%)
Currently smoking	67 (42.4%)
Diabetes mellitus	85 (53.8%)
Renal disease	11 (7.0%)
Cancer	11 (7.0%)
Cerebrovascular disease	34 (21.5%)
Coronary artery disease	48 (30.4%)
History of peripheral artery disease	68 (43.0%)
Previous peripheral interventions/surgeries	27 (17.1%)
	$N = 158$ lesions (core laboratory analysis)
Reference diameter, mm, $N = 151$	4.1 ± 0.9
	2.1−6.9
Target lesion length, mm	74 ± 50
	5−200
Diameter stenosis, %	91 ± 13
	40−100
Occlusion	92 (58.2%)

Data are displayed as mean ± standard deviation, Min−Max, or *n* (%).

Administration regulations, and approved by the ethic committees of the participating centers. All patients provided an informed consent. Monitoring encompassed 100% source document verification, an independent core laboratory (Hangzhou Yingfang Biotechnology Co., Ltd Jing Hu) assessed the angiographic and duplex ultrasound images, and a clinical events committee adjudicated all major adverse events, target lesion revascularizations (TLRs), adverse device effects, and serious adverse events. Data management and statistical analysis were performed by the Medical Research and Biometrics Center, National Center for Cardiovascular Diseases.

Study Device and Procedure

Passeo-18 Lux has been previously described.[6,7] It is a paclitaxel-coated balloon (3 μg paclitaxel/mm^2) using Butyryl-tri-hexyl-citrate as excipient that degrades to citric acid and alcohol.[8] The SafeGuard insertion aid is premounted on the balloon, protects the balloon coating from drug loss, and can be retracted and peeled away after insertion. Balloon diameters up to 4.0 mm are 4F compatible; diameters $\geq$ 5.0 mm are 5F compatible. The device gained CE-mark in January 2014 but was not approved for the Chinese market during trial enrollment.

Predilatation with a standard balloon was required. The Passeo-18 Lux ought to closely match the reference diameter of the target vessel and the balloon length should extend 0.5 to 1 cm beyond the ends reached by the predilatation balloon. The balloon should be inflated for at least 30 sec. In case of major ($\geq$ grade D) dissection or residual stenosis of $>$ 50%, prolonged ($<$ 3 min) balloon inflation with a plain balloon ought to be performed and bail-out stenting if this proved to be unsuccessful. Dual antiplatelet therapy (using Clopidogrel 75 mg daily) was recommended for at least 1 month.

Study End Points

The primary outcome effectiveness end point was primary patency at 12 months postprocedure, defined as freedom from clinically driven target lesion revascularization (cd-TLR) and freedom from binary restenosis (either by peak systolic velocity ratio $>$ 2.4 or $>$ 50% stenosis by quantitative

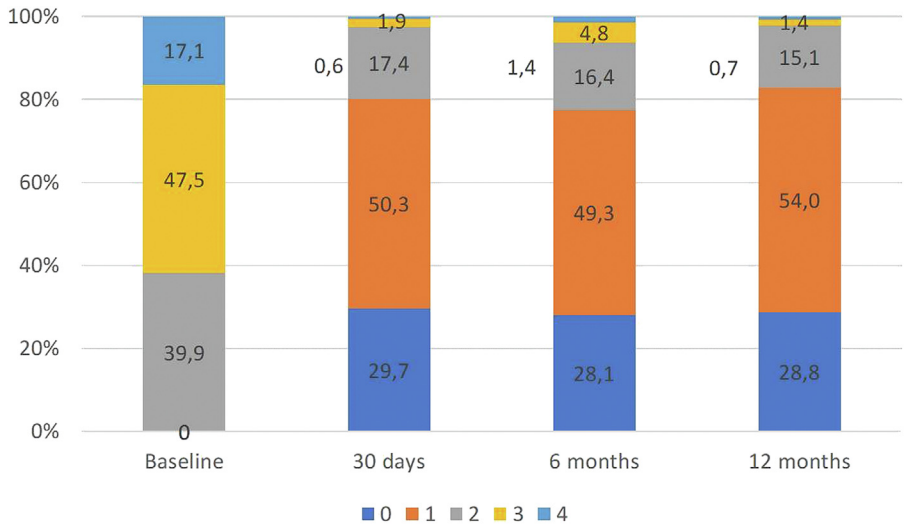


Fig. 1. Rutherford class at baseline and follow-up data were available for 157 patients at baseline, 155 patients at 30 days, 146 at 6 months, and 139 at 12 months. Mean Rutherford class improved from 2.73 ± 0.67 at baseline to 0.94 ± 0.78 at 30 days, 1.02 ± 0.87 at 6 months, and 0.91 ± 0.75 at 12 months.

vascular angiography, assessed by an independent core laboratory). The primary safety end point was 30-day major adverse event rate (MAE, defined as composite of device and procedure mortality, major target limb amputation, and cd-TLR). Secondary outcomes were individual components of MAE, death, TLR, target vessel revascularization (TVR), clinically driven TVR, thrombosis at the target lesion site, sustained clinical improvement (defined as improvement of at least 1 Rutherford category compared to baseline), duplex-defined binary restenosis (PSVR $>$ 2.4), Walking Impairment Questionnaire, 6-Minute-Walk-Test, EQ-5D questionnaire, device success (successfully delivery, balloon inflation, deflation, and retrieval of the study device without burst below the rated burst pressure), procedural success (residual stenosis of $\leq$ 50% (non-stented subjects) or $\leq$ 30% (stented subjects) by core laboratory assessment, and clinical success (procedure success without procedural complications such as death, major target limb amputation, thrombosis of the target lesion, or TVR).

Statistical Analysis

Data management and biostatistical analysis were performed by Medical Research & Biometrics Center, National Center for Cardiovascular Diseases. Data are presented for the intention-to-treat population. Details of the sample size calculation are provided in the Supplementary Tables 1 and 2. In brief, the sample size was calculated based on the published results of the In.PACT SFA, LEVANT 2, PACIFIER, THUNDER, and FEMPAC trials.[8–14] H0 was 12-month patency $<$ 55%, considering a DCB patency of 70%, 80% power, unilateral significance level $\alpha = 0.025$, an expected drop-out rate of 25%, and post-DCB stenting of 30%. A sample size of 158 patients was calculated to be required (83 patients + lost to follow-up + post-DCB stenting). This sample size is also adequate to evaluate the MAE-safety end point, assuming a 5% MAE-rate at 30 days at a confidence level of 95% confidence interval (CI) that the MAE incidence will be in the range of ± 3.4% from 5%.

Continuous variables are displayed as mean ± standard deviation and median with interquartile ranges as applicable. Categorical variables are presented as frequencies and percentages of the total. Adverse event rates refer to the respective time intervals (e.g., 365 ± 30 days). To test the study-specific objective performance goal of primary patency, the one-sample normal approximation for the binomial test is applied. Primary patency was calculated using Kaplan–Meier methods and standard errors were calculated using the Greenwood's formula. Clinical outcomes were calculated as frequencies, considering the patient numbers at follow-up (including died patients for determining mortality rates and excluding died patients for calculating complication rates). CIs were calculated as appropriate. All statistical analyses were carried out using SAS 9.4 (SAS Institute Inc. Cary, North Carolina).

Table II. Procedural characteristics

Outcomes	$N = 158$
Puncture	
Femoral artery	157 (99.4%)
Popliteal artery	1 (0.6%)
Introducer sheath size	
4F	4 (2.5%)
5F	45 (28.5%)
6F	95 (60.1%)
7F	10 (6.3%)
8F	4 (2.5%)
Access	
Antegrade	35 (22.2%)
Overlapping	4 (2.5%)
Retrograde	119 (75.3%)
Passeo-18 Lux, $N = 222$	
Diameter, mm	5.0 ± 0.5 3.0−6.0
Length, mm	96.0 ± 28.4 40.0−120.0
Number of balloon dilatations	1.02 ± 0.18 1−3
Max pressure applied, atm	8.0 ± 1.7 5.0−12.0
Cumulative inflation time, sec	91.4 ± 47.2 30.0−300.0
Device success, $N = 222$	222 (100.0%)
Procedural success[a]	155 (98.1%)
Clinical success[a]	155 (98.1%)

Data are displayed as mean ± standard deviation, Min−Max, or *n* (%).

[a]Including 2 patients who received bailout-stenting for post-treatment diameter stenoses of 41.8% and 41.6% and 1 patient had a post-treatment diameter stenosis of 57.4%.

RESULTS

From November 2016 to July 2018, 204 patients were screened in 16 centers in China, thereof 158 were enrolled; no patient failed to receive DCB treatment. Thirty-day follow-up data are available for 155 patients and 12-month data for 145 patients (13 patients were lost to follow-up).

Patients were 67.6 ± 9.6 years in average and 76.6% were males. The analysis of the risk factors revealed 77.2% hypertension, 53.8% diabetes, and 43.0% previous peripheral artery disease. Furthermore, 21.5% of patients had cerebrovascular disease and 30.4% concomitant coronary artery disease (Table I).

As per the angiographic core laboratory analysis, the target lesion length was 74 ± 50 mm, occlusive lesions accounted for 58.2%, the average length of occlusive lesions was 24 ± 30 mm, and the diameter stenosis was 91 ± 13%. Postprocedure, the mean diameter stenosis improved to 27 ± 9%. Dissections occurred in 26.6% ($n = 42$), thereof $n = 27$ Grade B, $n = 14$ grade C, and $n = 1$ Grade D.

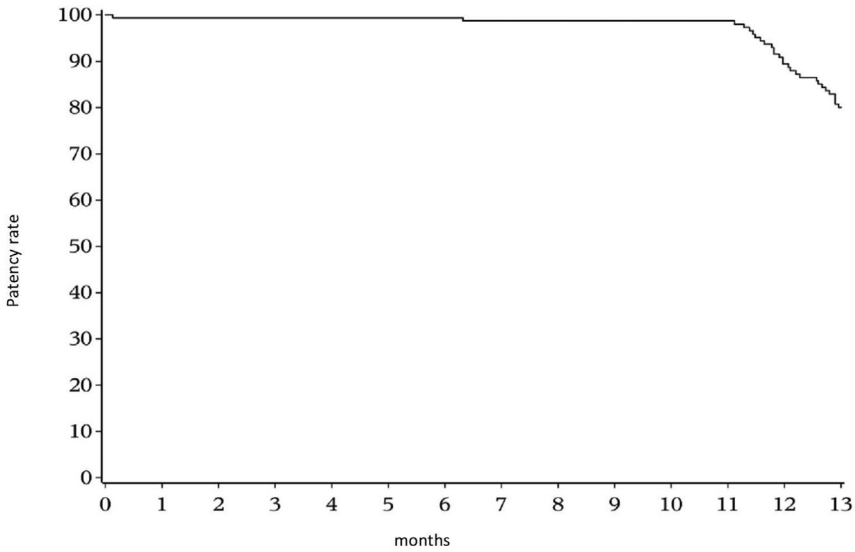
Table II lists the index procedure characteristics. Only 1 lesion per patient was treated. A total of 222 Passeo-18 Lux DCB were used, including 62.7% of patients treated with 1 balloon, 34.2% treated with 2 balloons, and 3.2% with 3 balloons. Bail-out stenting was performed in 5.1% ($n = 8$, 6 for dissection and 2 for residual stenosis). Rutherford classification at baseline and follow-up is displayed in Figure 1. Mean RC improved by 1.7 ± 0.9 at 6 months and by 1.8 ± 0.9 at 12 months. Improvement of at least 1 RC in patients without TLR (primary clinical improvement) was 89.7% (131/146) at 6 months and 93.5% (130/139) at 12 months. Secondary improvement, including patients with TLR, was 90.4% (132/146) at 6 months and 95.0% (132/139) at 12 months.

The walking impairment questionnaire (WIQ) score improved by 26.8 ± 34.9 at 30 days ($N = 154$), by 21.6 ± 32.8 at 6 months ($N = 145$) and by 26.6 ± 32.6 at 12 months ($N = 139$). Thereby the walking distance average score increased by 31.7 ± 34.7 at 30 days ($N = 152$), 26.4 ± 35.4 at 6 months ($N = 145$), and 26.7 ± 37.3 at 12 months ($N = 139$). Per 6-minute walking test, the average walking distance was 262 ± 96 m at baseline ($N = 153$, median 279 m, Q1−Q3: 211−330); it improved by 72 ± 102 m at 30 days ($N = 147$, median 50 m, Q1−Q3: 15−121), by 59 ± 92 m at 6 months ($N = 140$, median 58 m, Q1−Q3: 6−125), and by 63 ± 98 m at 12 months ($N = 136$, median 60 m, Q1−Q3: 2−122) (Supplemental Fig. 1). Notably, patients with missing WIQ values at 12 months had lower 6-month values than those who had 12-month follow-up WIQ performed (Supplemental Table 3).

The EQ5D quality-of-life questionnaire consists of 5 question and 1 visual analogue scale ranging from 0 (worst health 1 can imagine) to 100 (best health 1 can imagine). The visual analogue scale changed from 76.6 ± 15.6 at baseline ($N = 157$) to 80.0 ± 15.0 at 30 days ($N = 153$, change of 3.4 ± 17.7), to 76.2 ± 17.3 at 6 months ($N = 146$, change of −0.42 ± 18.48), and to 78.6 ± 14.6 at 12 months ($N = 145$, change of 1.7 ± 20.4). Further details are provided in Supplementary Tables 3 and 4.

The primary patency at 12 months was 80.0% (95% CI: 72.4; 85.8) (Fig. 2), standard error 0.338, thereby 1.4% ($n = 2$) of patients had TLR and 18.7% ($n = 26$) binary restenosis. Primary patency at 30 days and 6 months was both 99.4%.

The primary safety end point, MAE at 30 days, was 0.6% (95% CI: 0.0; 3.5), consisting of 1



Follow-up time	0	1	2	3	4	5	6	7	8	9	10	11	12	13
# at risk	158	154	152	150	150	150	148 PHS	142	141	140	139	138	125	111

Fig. 2. Kaplan-Meier analysis of the primary end point—primary patency at 12 months.

thrombosis with subsequent TLR. The patient suffered from severe pain 4 days postprocedure and the Doppler ultrasound showed a low echo reflex; a thrombolysis was successfully performed. The second TLR occurred on day 185. There was no additional TVR (Table III).

Five patients died during the cause of the study, 2 of cancer on postoperative day (POD) 279 and 319 (thereof 1 was pre-existing), 1 of aortic rupture on POD 40 (the patient had a medical history of thoracic and abdominal aortic stent implantation due to penetrating ulcers of the abdominal aorta which led to a massive bleeding 5 weeks after the index procedure), 1 of respiratory disease in combination of heart failure after revascularization of a nontarget lesion on POD 85, and 1 of hemorrhagic stroke on POD 271. All deaths were adjudicated as not being related to the device or procedure.

DISCUSSION

The BIOLUX P-IV trial confirmed the safe and effective use of the Passeo-18 Lux DCB in Chinese patients with femoropopliteal lesions with similar outcomes to international DCB trials in this indication.

BIOLUX P-IV reflects a common patient population in clinical trials. Similar to the IN.PACT SFA China trial,[15] only RC 2−4 was permitted, whereas ACO-ART I China enrolled 16% of patients with RC 5. This may impact outcomes as higher RC may result in higher TLR rates, as assessed in the In.Pact Global substudy, that reported 12-month TLR rates of 6.6% for RC 2 and 3 patients and 13.7% for RC 4 and 5 patients, $P = 0.007$.[16] This may also explain the lower TLR rates in our series as compared to outcomes in femoropopliteal lesions of BIOLUX P-III (12-month TLR rate of 1.4% vs. 6.1%), as BIOLUX P-III had less restrictive inclusion and exclusion criteria and also included patients in RC 5 and 6.[7] However, in the overall BIOLUX P-III population, surprisingly, there was no significant difference between RC class ≤ 3 and > 3,[17] yet this may be related to the fact that the overall BIOLUX P-III population encompassed infrainguinal lesions including below-the-knee lesions. Another possible explanation for the lower TLR rate might be that Chinese patients may have a higher tolerability of ischemic symptoms and that most patients would not accept a procedure until the ankle brachial index is < 0.5, as speculated by other authors.[18] This would also explain that despite the difference in TLR, the primary patency at 12 months was similar between BIOLUX P-IV and BIOLUX P-IIII (80.0% vs. 80.2% in the imaging cohort from the BIOLUX P-III femoropopliteal lesions subgroup analysis[7]), reflecting the possible difference in the revascularization threshold.

The primary patency at 12 months in IN.PACT SFA China was 90.9% and cd-TLR 2.9%.[15] The Aco-Art China had a higher TLR rate (7.2%) but similar primary patency (84.1%) but had lesions

Table III. Clinical outcomes

Outcomes	30 days	6 months	12 months
All-cause mortality	$N = 155$	$N = 148$	$N = 144$
	0 (0%)	2 (1.4%)	5 (3.5%)
Target lesion revascularization	$N = 155$	$N = 146$	$N = 140$
	1 (0.6%)	2 (1.4%)	2 (1.4%)
Clinically driven target lesion revascularization	$N = 155$	$N = 146$	$N = 140$
	1 (0.6%)	2 (1.4%)	2 (1.4%)
Target vessel revascularization	$N = 155$	$N = 146$	$N = 140$
	1 (0.6%)	2 (1.4%)	2 (1.4%)
Clinically driven target vessel revascularization	$N = 155$	$N = 146$	$N = 140$
	1 (0.6%)	2 (1.4%)	2 (1.4%)
Target limb major amputation	$N = 155$	$N = 146$	$N = 140$
	0 (0%)	0 (0%)	0 (0%)
Thrombosis at target lesion	$N = 155$	$N = 146$	$N = 140$
	1 (0.6%)	1 (0.7%)	1 (0.7%)

Data are displayed *n* (%). Data up to 37 days are considered for the 30-day interval, up to 210 days for the 6-month interval, and up to 395 days for the 12-month interval.

nearly twice as long (147 mm in average) and 16% RC 5 patients compared to BIOLUX P-IV and IN.PACT SFA. Another difference among the trials is the rate of provisional stenting that was 19% for Aco-Art China versus 4.2% for IN.PACT SFA China and 5.1% in our series.[15,18] The difference in outcomes thereby is likely related to the differences in baseline characteristics. Notably, in the femoropopliteal subgroup of BIOLUX P-III,[7] the rate of provisional stenting was 20.2%, thus 4 times higher than in our series. This may be due to difference in RC, with RC 5 and 6 patients enrolled in BIOLUX P-III or due to the difference in protocol recommendations but more likely reflect a tendency to avoid provisional stenting if possible. Our outcomes suggest that this is a feasible approach.

Aside of the better TLR and lower provisional stenting rates, outcomes of DCB-treated Chinese patients are similar to those of international series.[15,18,19] For instance, the MAE rate at 30 days was very low (0.6%) and comparable to other series in China such as IN.PACT SFA with 0.7%.[15] Major target limb amputation at 12 months was 0% in BIOLUX P-IV China versus 1.7% in the femoropopliteal BIOLUX P-III subgroup and all-cause mortality was 3.5% vs. 5.9%, respectively.[7] Notably, only 2 patients died of cancer, thereof 1 on day 12 was pre-existing.

Related to performance outcomes, there was a substantial clinical improvement with 93.5% of patients having improved by at least 1 RC. In contrast, quality of life increased only slightly but the patient population was not severely impacted in their daily life to start with, so there was not much room for improvement. Rather, an improvement in pain and walking capacity was observed, a similar pattern as seen in IN.PACT SFA China.[15]

Limitations

This trial has several limitations. It is not randomized and therefore comparison to other series is hampered. Thirteen patients were lost to follow-up and RC was only available in 88% of patients at follow-up. This circumstance might have biased outcomes and might be responsible for the drop in 6-month quality of life and walking scores that increased again at 12 months. In particular, patients with missing 12-month assessments had lower WIQ scores than those with 12-month assessment, potentially reflecting the fact that patients who did worse did not attend the 12-month follow-up. Data related to lesions treated outside the target vessel were not collected. Follow-up has only been scheduled for 12 months. In the light of the current discussion on potential paclitaxel-associated mortality, data beyond 12 months would have been interesting. However, BIOLUX P-III was extended to 5 years and further data can be expected from this series.[20]

CONCLUSION

In conclusion, the safety and efficacy of the Passeo-18 Lux paclitaxel-coated balloon catheter in treating superficial femoral and proximal popliteal artery lesions in Chinese patients have been confirmed. Low complication rates and high effectiveness were observed, comparable to outcomes of international series and Chinese trials performed with other types

of drug-coated balloons, resulting in the decision to apply for market authorization in China.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.avsg.2023.01.040.

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