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Efficacy and safety of a novel paclitaxel-nano-coated balloon for femoropopliteal angioplasty: one-year results of the EffPac trial

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A list of the study collaborators can be found in the Appendix paragraph.

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KEYWORDS

- balloon
- claudication
- clinical trials
- drug-eluting balloon
- femoropopliteal disease

Abstract

Aims: Although paclitaxel drug-coated balloon (DCB) angioplasty is an established endovascular treatment for peripheral artery disease, restenosis remains a major concern. Thus, we compared a novel paclitaxel-coated DCB with nano-coating technology with uncoated plain old balloon angioplasty (POBA).

Methods and results: This multicentre trial randomly assigned 171 patients with stenotic and occlusive lesions of the femoropopliteal artery to angioplasty with a novel DCB or uncoated POBA. The primary endpoint, late lumen loss at six months, was 0.92 mm lower in the DCB group (95% CI: –1.36 to –0.49 mm, p<0.001). Patients showed improved walking after DCB treatment at six months (p=0.021). In the DCB group, 44.6% and 50% of the patients improved by three Rutherford-Becker classification stages after six to 12 months, respectively (POBA: 27.8% and 36.8%, respectively). Only one patient needed TLR (1.3%) in the DCB group, compared to 14 patients (18.7%) in the POBA group after 12 months (relative risk [RR]=0.08, 95% CI: 0.01-0.53, p<0.001). Primary patency was 90.3% (DCB group) versus 65.3% (POBA group) after 12 months (RR=1.38, 95% CI: 1.14-1.67, p<0.001).

Conclusions: The novel DCB was effective and safe for inhibiting restenosis. Moreover, it demonstrated a better improvement in walking than POBA and showed no mortality concerns due to paclitaxel application after 12 months. Clinical Trials Identifier: NCT02540018

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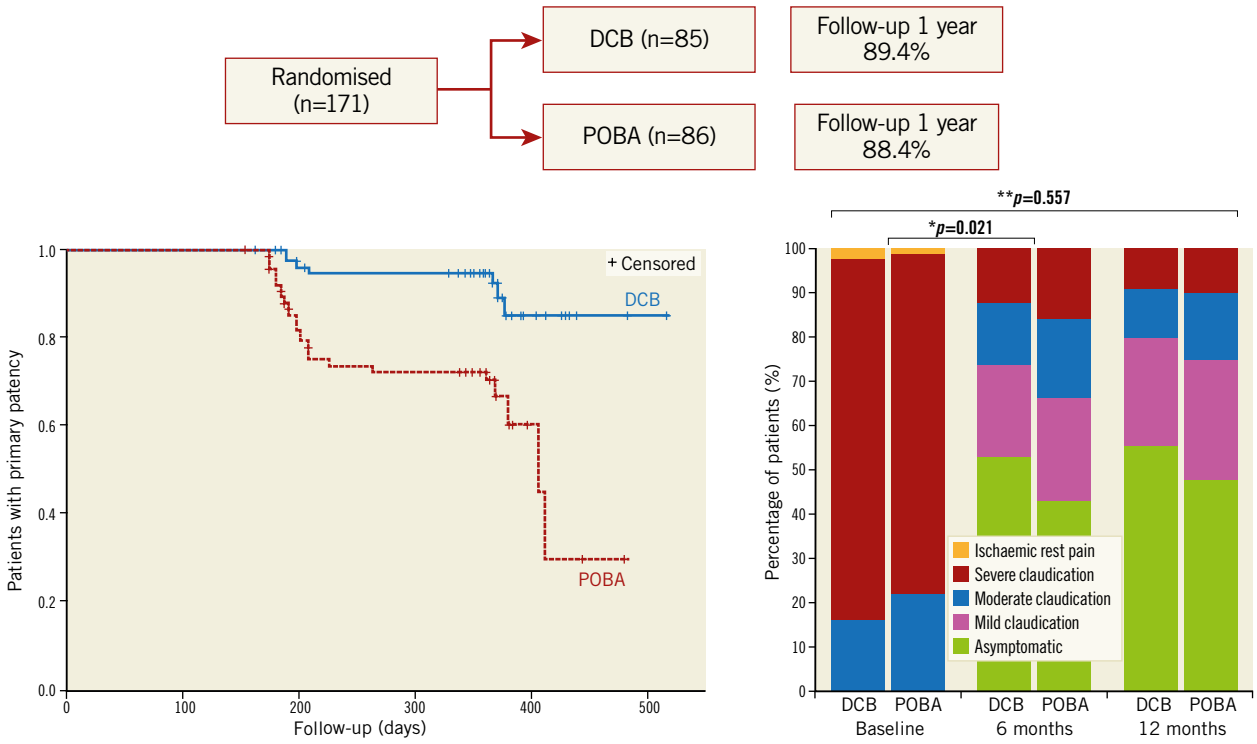

Visual summary. *Patient flow, Kaplan-Meier survival curves for primary patency, and change in Rutherford-Becker category over 12 months.*

Abbreviations

ABI	ankle-brachial index
CI	confidence interval
DCB	drug-coated balloon
DUS	duplex ultrasonography
EQ-5D	EuroQol Group's five-dimension index
LLL	late lumen loss
NNT	number needed to treat
POBA	plain old balloon angioplasty
RR	risk ratio
SAE	serious adverse events
SFA	superficial femoral artery
TLR	target lesion revascularisation
TVR	target vessel revascularisation
WIQ	Walking Impairment Questionnaire

Introduction

Intermittent claudication in the lower extremities is the most common symptom of peripheral artery disease and is often caused by stenosis or occlusion of the femoropopliteal artery segment[1]. Treatment in intermittent claudication aims to improve the pain-free walking distance and, ultimately, quality of life[2]. Uncoated plain old balloon angioplasty (POBA) followed by paclitaxel drug-coated balloons (DCBs) is increasingly considered as the treatment of choice for revascularisation in shorter lesions[3,4]. Early onset of neointimal proliferation is an important limitation that often leads to restenosis. Local drug delivery with paclitaxel DCBs is a promising method for inhibiting neointimal proliferation[5,6]. Different DCBs have already been tested; however, there is considerable heterogeneity (regarding efficacy) among such studies and a high risk of performance bias existed in earlier studies[7,8]. The current report outlines the 12-month outcomes of the EffPac trial, which compared a novel paclitaxel-coated DCB with nano-coating technology to uncoated POBA with regard to clinical benefit and safety.

Methods

STUDY CONCEPT

This investigator-initiated multicentre randomised controlled parallel-group trial was performed at 11 vascular centres across Germany. The trial was approved by the independent ethics review board at each of the participating institutions and all patients provided written informed consent. An independent clinical research organisation was appointed for the trial monitoring activities and a blinded independent core laboratory reviewed the primary endpoint measurements and duplex ultrasound measurements. The study protocol was published in the journal Trials[9]. The trial was reported according to the CONSORT statement[10].

STUDY POPULATION AND ELIGIBILITY CRITERIA

Patients with symptomatic peripheral artery disease, with moderate to severe intermittent claudication or ischaemic rest pain

(Rutherford-Becker classes 2-4), were eligible for enrolment. *De novo* stenotic or non-stented restenotic or occlusive lesions with a lesion length ≤15 cm were considered. Only lesions in the superficial femoral artery (SFA) and the proximal popliteal artery up to the P1 segment were included. Bail-out stenting in flow-limiting dissection was also considered. The inclusion and exclusion criteria are outlined in **Supplementary Appendix 1**.

INVESTIGATIONAL PRODUCT

In the experimental arm, patients were treated with the paclitaxel-coated Luminor® DCB (iVascular S.L.U., Life Vascular Devices Biotech, Barcelona, Spain). A description of the investigational product with its TransferTech® nano-technology coating is provided in **Supplementary Appendix 2**.

RANDOMISATION AND THE INDEX PROCEDURE

Patients were randomly assigned after predilatation in a 1:1 allocation ratio using a computer-generated randomisation list with random block sizes and stratification by vascular centre (stratified block randomisation). For non-flow-limiting or flow-limiting dissections, prolonged percutaneous transluminal angioplasty (PTA) with the same PTA balloon was performed. For persistent flow-limiting dissections, bail-out stenting with a bare metal stent was permitted **(Figure 1)**. In case two or multiple PTA balloon catheters were used, a minimised overlap of 5 to 10 mm was required. A total of 93 drug-eluting Luminor 35 balloons were used.

ENDPOINTS AND FOLLOW-UP

The primary efficacy endpoint of our study was late lumen loss (LLL) after six months (defined as the difference between the angiographic minimum lumen diameter immediately after PTA and that at follow-up). Safety endpoints included freedom from target lesion revascularisation (TLR), investigation- and procedure-related serious adverse events (SAE)/AE, all-cause mortality, and minor and major target limb amputations. The secondary outcomes were primary patency, regarded as TLR + freedom from binary restenosis assessed by duplex ultrasound peak systolic velocity ratio <2.5, or angiography (core laboratory adjudicated); freedom from target vessel revascularisation (TVR); change in walking impairment assessed by the Walking Impairment Questionnaire (WIQ) and Rutherford-Becker classification (RBC) at follow-up; change in ankle-brachial index (ABI) after the intervention and at follow-up; change in "quality of life" as assessed by European quality of life with five dimensions of severity (EQ-5D) scale at follow-up; number of bail-out stents.

STATISTICAL ANALYSIS

The sample size calculation was based on the results of a previous trial[11]. All analyses were performed according to the intention-to-treat principle. Multiple imputation of missing values was conducted for the primary endpoint using the fully conditional specification method to evaluate the robustness of the conclusions. Continuous data are presented as means and standard deviations or medians and interquartile ranges according to the data distribution. Absolute and relative frequencies are given for categorical data. Data were analysed with SAS 9.4 (SAS Institute, Cary, NC, USA). A two-sided p-value of <0.05 was considered to indicate statistical significance. The statistical analyses for each endpoint are described in **Supplementary Appendix 3**.

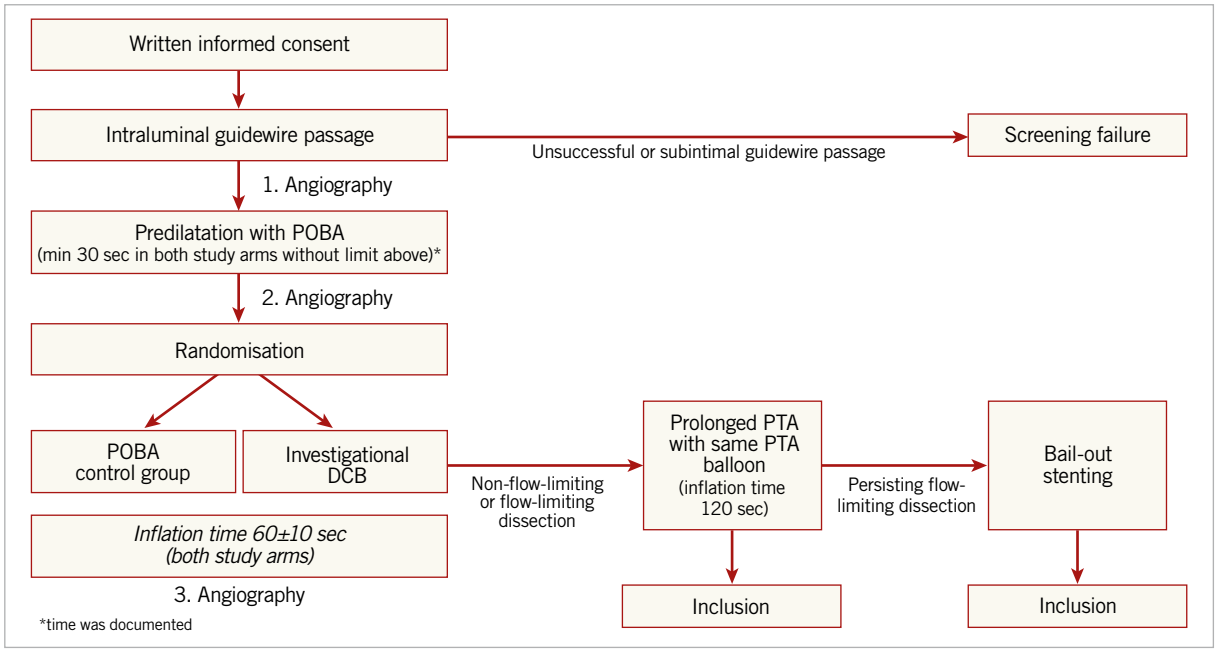

Figure 1. *Flow chart of the index procedure.*

Results

STUDY POPULATION AND TREATMENT

A total of 171 patients were enrolled between September 2015 and December 2016. Only one drop-out due to small-vessel diameter occurred in the DCB group after randomisation. Eighty-six patients were treated with POBA and 85 with the investigational DCB. The patient flow diagram according to CONSORT 2010 is shown in **Supplementary Figure 1**. The groups were well matched in baseline demographics and comorbidities **(Supplementary Table 1)**; 38.6% (66/171) of the patients were diabetics and 41.8% (71/171) were current smokers. Regarding the DCB versus POBA groups, the mean lesion length was 59±43 mm versus 56±39 mm, the total treated length was 89.8±48.6 mm versus 84.9±45.1 mm, and total occlusions comprised 20.2% (17/84) versus 25.6% (22/86) of the total lesions.

Predilation was performed in all but one POBA patient (DCB: 100% [84/84]; POBA: 98.8% [85/86]). The rate of dissections (DCB: 37.6% [32/85]; POBA: 40.7% [35/86]) and the bail-out stenting rate (DCB: 15.3% [13/85]; POBA: 18.8% [16/85]) were similar in both groups. Moreover, no significant differences existed in the other angiographic parameters at baseline **(Supplementary Table 2)**. Periprocedural distal thrombotic embolisation was not recorded.

PRIMARY EFFICACY AND SAFETY OUTCOMES

Regarding the DCB versus POBA groups, 62.4% (53/85) versus 73.3% (63/86) of the patients underwent angiography after six months. LLL at six months was 0.14 mm (95% CI: –0.38 to 0.67) for DCB versus 1.06 mm (95% CI: 0.54-1.59) for POBA. The difference between the groups was –0.92 mm (95% CI: –1.36 to –0.49, p<0.001). We found no evidence that the results of the primary endpoint were biased due to dropouts. The TLR rate was 1.3% (1/76) and 17.1% (13/76) after six months in the DCB and POBA groups, respectively (p<0.001). The relative risk reduction for TLR was 91.8% after six months according to the Cochran-Mantel-Haenszel estimation, and the number needed to treat (NNT) to prevent one additional TLR after six months was seven **(Table 1)**. After 12 months, the TLR rate was still significantly lower in the DCB group (1.3%, 1/76), with an NNT of six, than in the POBA group (18.7%, 14/75) (p<0.001). The Kaplan-Meier estimates for freedom from TLR are shown in **Supplementary Figure 2**.

Other safety endpoints did not differ significantly between the groups. There was one minor amputation (1.2%) and there were two deaths (2.3%) in the POBA group after 12 months versus one death in the DCB group (1.2%). All deaths were considered unrelated to the device, procedure, or index limb.

SECONDARY OUTCOMES

Primary patency was 94.7% (72/76) and 75.0% (57/76) after six months in the DCB and POBA groups, respectively, (p<0.001). After 12 months, primary patency remained significantly higher in the DCB group (90.3%, 65/72 vs 65.3%, 47/72; p<0.001). The additional analysis for negative remodelling is shown in **Table 1**. The Kaplan-Meier estimates for patency are reported in **Supplementary Figure 3**. Significantly more patients showed an improved RBC at six months after DCB angioplasty than after POBA (p=0.021). An improvement of three stages was noted in 44.6% (33/74) and 27.8% (20/72) of patients for DCB and POBA, respectively **(Figure 2)**. The DCB group also showed better RBC improvement after 12 months: 50% of the patients (37/74) in the DCB group showed an improvement of three stages of RBC compared to only 39.7% in the POBA group (27/68), although the difference was non-significant (p=0.740). Further, compared to the POBA group values, the average WIQ score in the DCB group was 2.6 points (95% CI: –6.9 to 12.0) higher after six months and 5.3 points (95% CI: –4.6 to 15.2) higher after 12 months. Further results are shown in **Table 1**.

Discussion

Angioplasty with paclitaxel DCBs can effectively reduce neointimal proliferation[12]. Decisive factors for the effectiveness of DCB catheters are the loss of the coating layer during catheter transfer and incomplete drug delivery to the vessel wall. The DCB catheter in our trial is based on a new proprietary nano-coating technology, with very low drug loss during catheter insertion and advancement, as well as a high paclitaxel delivery to the vessel wall during inflation.

In the DCB group, LLL was lower than in previous DCB trials (e.g., PACIFIER, FemPac, and THUNDER trials), with a similar surface dosage[11,13,14]. "Negative remodelling" (negative LLL defined as lumen gain during follow-up) occurred in 30.2% of the DCB patients, i.e., twice as frequently as in POBA patients. Similar observations were shown in recent DCB trials with low TLR rates[15,16]. Negative remodelling can additionally indicate high DCB effectiveness. However, ectatic vessel changes were

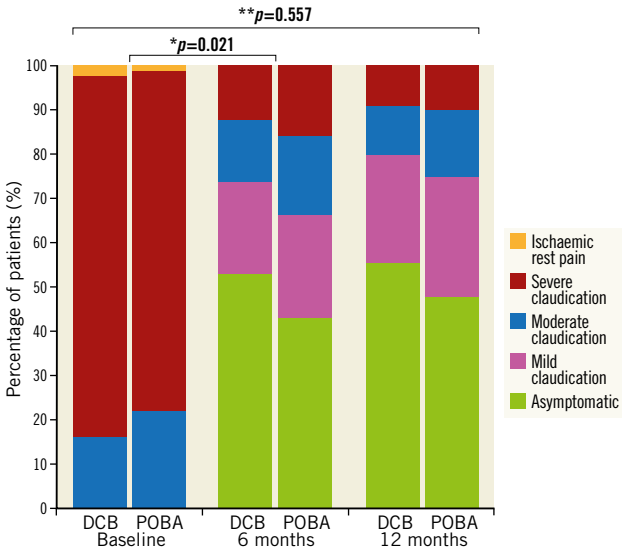

Figure 2. *Percentage of patients with different Rutherford-Becker classifications at baseline, 6 months, and after 12 months.*

Table 1. Primary and secondary endpoints.

		DCB		POBA		Mean difference/ relative risk [95% CI]	*p*-value
		n		n			
Primary endpoint							
Late lumen loss (LLL) after 6 months, mm*		53	0.32±1.07	60	1.26±1.29	–0.92 [–1.36; –0.49]	<0.001
Secondary endpoints after 6 months							
Restenosis, n (%)¶		76	10 (13.2)	76	24 (31.6)	0.40 [0.20; 0.79]	0.011
Target lesion revascularisation, n (%)		76	1 (1.3)	76	13 (17.1)	0.08 [0.01; 0.56]	<0.001
Target vessel revascularisation, n (%)		76	3 (3.9)	76	16 (21.1)	0.17 [0.05; 0.61]	0.001
Primary patency, n (%)¶		76	72 (94.7)	76	57 (75.0)	1.26 [1.10; 1.45]	<0.001
Change in Rutherford-Becker stage, n (%)	Deterioration of 1 stage	74	1 (1.4)	72	0	–	0.02
	No improvement		10 (13.5)		18 (25.0)		
	Improvement of 1 stage		9 (12.2)		15 (20.8)		
	Improvement of 2 stages		21 (28.4)		19 (26.4)		
	Improvement of 3 stages		33 (44.6)		20 (27.8)		
Change in ABI to baseline		60	0.24±0.28	57	0.22±0.31	0.03 [–0.09; 0.14]	0.625
Change in WIQ score		64	27.0±29.3	60	24.3±27.6	2.3 [–7.6; 12.3]	0.640
Change in EQ-5D VAS		75	4.5±16.2	74	7.4±16.6	–2.9 [–8.2; 2.4]	0.281
Secondary endpoints after 12 months							
Restenosis, n (%)¶		76	15 (19.7)	76	30 (39.5)	0.49 [0.28; 0.83]	0.005
Target lesion revascularisation, n (%)◊		76	1 (1.3)	75	14 (18.7)	0.08 [0.01; 0.53]	<0.001
Target vessel revascularisation, n (%)		76	4 (5.3)	75	17 (22.7)	0.22 [0.07; 0.66]	0.002
Primary patency, n (%)¶		72	65 (90.3)	72	47 (65.3)	1.38 [1.14; 1.67]	<0.001
Change in Rutherford-Becker stage compared to baseline, n (%)ƒ	Deterioration of 1 stage	74	1 (1.4)	68	1 (1.5)	–	0.740
	No improvement		6 (8.1)		7 (10.3)		
	Improvement of 1 stage		13 (17.6)		12 (17.6)		
	Improvement of 2 stages		17 (23.0)		21 (30.9)		
	Improvement of 3 stages		37 (50.0)		27 (39.7)		
Change in ABI		61	0.28±0.27	55	0.29±0.27	–0.02 [–0.12; 0.09]	0.745
Change in WIQ score		74	26.7±30.7	70	21.9±29.4	4.5 [–5.1; 14.0]	0.356
Change in EQ-5D VAS		74	3.2±16.4	70	8.0±18.8	–4.8 [–10.7; 1.0]	0.101
Additional analysis							
Negative remodelling (LLL <0 mm) after 6 months, n (%)		53	16 (30.2)	60	9 (15.0)	1.91 [0.87; 4.16]	0.093

*Late lumen loss: difference between the angiographic minimum lumen diameter immediately after angioplasty and at six-month follow-up. ¶Restenosis: presence of >50% stenosis in the target lesion assessed by duplex ultrasonography (peak systolic velocity ratio ≥2.5) or by angiography. ◊Target lesion revascularisation: reintervention for >50% diameter stenosis or reocclusion within the target lesion determined by duplex ultrasonography or angiography. ¶Primary patency: absence of target lesion restenosis (adjudicated by the core laboratory) and freedom from target lesion revascularisation. ƒPatients with target lesion revascularisation at six and 12 months were excluded in this analysis for the change in Rutherford-Becker classification in order to reflect the purged results in both study groups, eliminating any false improvement eventually caused by secondary revascularisation. ABI: ankle-brachial index; EQ-5D: European quality of life with five dimensions of severity scale; TLR: target lesion revascularisation; TVR: target vessel revascularisation; VAS: visual analogue scale; WIQ: Walking Impairment Questionnaire

occasionally documented six months after DCB treatment[17]. In our trial, no such inadvertent aneurysmal dilatations of the target lesion were observed. Only one revascularisation was necessary after six and 12 months in the DCB group (TLR rate of 1.3%). Good TLR rates of 2-6% after one year have also been noted with other DCBs[18,19].

Furthermore, EffPac showed a comparably low TLR rate in the control group, with an NNT of seven (i.e., with every seventh DCB treatment, one additional reintervention is prevented). Unlike in earlier trials, which partly suggested lower NNTs, EffPac did not show any significant treatment differences between the study groups (especially regarding predilatation and stenting rates), except for the applied catheter. This allows a more realistic assessment of the treatment effect and is consistent with newer trials that also performed predilatation before randomisation[20,21].

Along with a lower reintervention rate, EffPac showed a higher primary patency rate after DCB treatment and thus fewer restenoses that did not require treatment (≥50%) defined by peak systolic velocity ratio by Doppler ultrasound ≥2.5. The NNT was six

after six months and four after 12 months. This also suggests high antirestenotic ability and is comparable to the performance of other DCBs (e.g., in the AcoArt I, IN.PACT SFA, and ILLUMENATE EU trials)[16,18,19]. RBC is an easily applicable yet established clinical staging system for peripheral arterial disease and seems reliable for indicating the necessity of a possible reintervention[22]. Our trial demonstrates a significant improvement in RBC after DCB treatment at six-month follow-up. This is the most important outcome compared to the other endpoints, which may be considered surrogates. Also, after 12 months an improvement is notable, even though it loses its statistical significance. As a matter of fact, the results at 12-month follow-up are biased to walking improvement by the fact that 12 patients were revascularised in the POBA group and only one in the DCB group. Therefore, those patients obviously improved their walking capacity after secondary revascularisation. This represents a performance bias, which leads to the loss of statistical significance at 12 months.

A significant clinical improvement was also reported by the AcoArt I trial, but EffPac additionally demonstrated, for the first time, the clinical improvement for blinded follow-up visits under the same treatment conditions in both groups[16]. Of note, the randomisation was performed after predilatation; therefore, both study groups were pre-treated in the exact same way, minimising performance bias early in the study design **(Figure 1)**. An improvement in walking capacity was also affirmed by the patient-blinded WIQ results. Although not significant, in all subdomains of the questionnaire, higher mean scores were noted in the DCB group after six and 12 months as compared to POBA. The change of ABI compared to baseline was not significant between the study groups. Possible reasons could be either the lack of sufficient statistical power, the impairment of run-off vessels below the knee or microangiopathy, especially in patients with diabetes.

In the two-year and five-year long-term follow-ups, we will investigate whether these clinical benefits will be preserved. According to the three-year data of the IN.PACT SFA trial and the five-year data of the THUNDER trial, the occurrence of a late catch-up seems unlikely[23,24].

Limitations

Several limitations of this study need to be discussed. Although the Data Safety and Monitoring Board and core laboratory personnel were blinded to treatment, physicians performing the index procedure were not blinded because of the visible coating on the DCB catheter.

The risk of performance bias was minimised by the predefined treatment process (e.g., randomisation after predilatation, stent implantation only after persistent flow-limiting dissection). No significant differences in the key parameters of treatment were found.

Another limitation might be the short lesion lengths (approximatively 5.7 cm) compared to some other recent trials (AcoArt I, CONSEQUENT trial)[16,25]. However, shorter lesions are more suitable for a balloon-only approach ("leaving nothing behind") and reflect clinical practice. Comparable trials that also focused on TASC II A and B lesions also investigated short lesions from 4.0-9.8 cm[11,18,19,26-28]. In longer lesions with more occlusions, the need for adjunctive treatment, e.g., atherectomy and stent implantation, increases.

When our trial was initiated in 2015, POBA was still the standard as the comparative device to drug-eluting balloon catheters and LLL was imperative as the primary endpoint to demonstrate technical efficacy. This was the only way to show that our investigated DCB was effective on the one hand, and safe compared with a non-paclitaxel-coated balloon catheter on the other hand. The safety of a DCB is best shown in an RCT with POBA as control group. At this time point, we are only able to prove that there are no mortality concerns due to paclitaxel application after 12 months in our EffPac trial. In a meta-analysis comparing all kinds of paclitaxel-coated devices for the SFA, Katsanos et al have recently shown an increased risk of death following the application of paclitaxel-coated balloons and stents after two years and five years[29]. The EffPac trial is a proof-of-principle study. Regarding the promising results of LLL as technical outcome, and TLR, patency and walking improvement as clinical outcomes after one year, we amended EffPac for additional 24-, 42- and 60-month follow-ups. Also, a head-to-head trial will be the next step allowing direct comparison to other DCB catheters. Finally, patients were recruited on the basis of strict inclusion and exclusion criteria; therefore, the generalisability and the clinical relevance of the data to real-world cases may be limited.

Conclusions

The EffPac findings further validate the superiority of DCBs, showing a notable LLL, and TLR and patency rates as technical and clinical outcomes, respectively. What defines the new-generation paclitaxel DCB is its significant improvement of walking capacity, which is the most relevant clinical endpoint in patients with intermittent claudication. This is an important contribution to clinical practice.

Impact on daily practice

EffPac showed, for the first time, a statistically significant improvement assessing walking capacity as a "real" clinical endpoint and is therefore crucial for patients with peripheral artery disease. Our study uncovers the important role of additional measurement tools such as Rutherford-Becker classification and walking impairment tests.

Appendix. Study collaborators

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Conflict of interest statement

U. Teichgräber is a consultant for iVascular and endoscout GmbH. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Eligibility criteria

A. Inclusion criteria

1. Age ≥18 years.
2. Subject must agree to undergo the six-month angiographic and clinical follow-up (at 12 and 24 months post procedure).
3. Peripheral vascular disease Rutherford class 2-4.
4. De novo stenotic/re-stenotic lesion or occlusive lesions in the superficial femoral (SFA) and/or popliteal arteries (PA).
5. If the index lesion is re-stenotic, the prior PTA must have been >30 days prior to treatment in the current study.
6. ≥70% diameter stenosis or occlusion.
7. Target lesion length: ≤15 cm (TASC II A and B).
8. Only one lesion per limb and per patient can be treated.
9. ≥ one patent infrapopliteal run-off artery to the foot of the index limb.
10. Successful endoluminal guidewire passage through the target lesion.
11. Predilatation prior to randomisation.
12. Life expectancy, in the investigators' opinion, of at least one year.
13. Subject is able verbally to acknowledge and understand the aim of this trial and is willing and able to provide informed consent.

B. Exclusion criteria

1. Previous surgery in the target vessel.
2. Patients who require a PTA balloon catheter in diameter size ≤4 mm or in diameter size >7 mm.
3. Major amputation in the same limb as the target lesion.
4. Acute myocardial infarction within 30 days before intervention.
5. Severely calcified target lesions in the SFA/PA resistant to PTA.
6. Subjects requiring different treatment or raising serious safety concerns regarding the procedure or the required medication.
7. Women of childbearing potential except women with the following criteria:
    a. post-menopausal (12 months natural amenorrhea or six-month amenorrhea with serum FSH >40 mlU/ml)

b. sterilisation after bilateral ovariectomy with or without hysterectomy
c. using an effective method of birth control for the duration of the trial: implants, injectables, combined oral contraceptives, intrauterine device (in place for a period of at least two months prior to screening) and with negative serum pregnancy test
d. sexual abstinence
e. vasectomy partner

8. Pregnant and nursing women.
9. Acute thrombus aneurysm in the index limb or vessel.
10. In-stent restenosis in the target lesion.
11. Renal insufficiency with a serum creatinine >2.0 mg/dL at baseline.
12. Platelet count <50 G/l or >600 G/l at baseline.
13. Known hypersensitivity or contraindication to contrast agent that cannot be adequately pre-medicated.
14. Subjects with known allergies to paclitaxel.
15. Subjects with intolerance to antiplatelet, anticoagulant, or thrombolytic medications that would be administered during the trial.
16. Dialysis or long-term immunosuppressant therapy.
17. Current participation (or within the last three months) in another interventional study.

Supplementary Appendix 2. Investigational product

Luminor is based on iVascular's proprietary nanotechnology coating, TransferTech®. The drug formulation is spread on the balloon by ultrasound spray pulse. The balloon surface is covered with multiple and independent nanodrop layers. The shaft of the Luminor 35 is coated with a proprietary hydrophilic formula in order to minimise friction. The balloon is coated with a homogeneous mixture of paclitaxel and a physiologically innocuous matrix, the excipient. Drug dose is 3 µg/mm^2 of balloon surface and it is intended to avoid cellular proliferation, consequently decreasing the reintervention rate.

The nanotechnology controls the surface finishing of the drug coating, also known as texturing. Textures can range from amorphous to crystalline, or smooth to rough. What differentiates textures is cohesion. Cohesion is the strength of the bonds between the various molecules in the coating. Increasing the cohesive forces reduces the coating surface area which means less exposure. Lower exposure reduces compromise of coating integrity during storage or transit through the vessel. Amorphous coatings limit drug loss. In the same way, reducing the surface area also reduces drug delivery upon inflation at the lesion site. On the other hand, increasing the surface area of the coating promotes drug delivery upon balloon inflation. A rougher coating results in greater contact of the coating with the vessel wall, encouraging absorption. However, this coating texture also increases drug transit loss before the balloon reaches the target location, and coating integrity can also be more easily compromised during storage.

iVascular's ultrasonic spray coating provides improved process flexibility and reliability in creating and reproducing a range of textures. However, parameters such as flow rate, ultrasonic power and application distance are key to achieving the drug coating texture. Unlike conventional spray techniques which are used by other coating technologies, ultrasonic nozzles do not rely on pressure to shear the solution into droplets. Using high-frequency vibration, mathematically defined capillary waves on the nozzle tip create drops within a very narrow drop size distribution (only microns large). Using air shaping, the droplets are guided to the balloon to create a coating of the drug solution. The texture obtained is related to the size of the drops spread on the balloon. Reducing the size of the drop, the drying is faster and favours obtaining amorphous coatings and smooth textures. On the other hand, by increasing the size of the drop, the drying is slower, and provides crystalline and rough coatings. Other factors,

such as solvent, concentration, application separation, or rotation contribute to the texture of the coating.

Drug is released from the balloon by means of a rapid inflation at the target lesion of the femoropopliteal artery so that a high dose is released in a very short period of time. In order to ensure a sufficient dosage of paclitaxel onto the arterial wall, the inflation process must last from 30 seconds to one minute. Using longer inflation times at the discretion of the interventionalist can optimise dilatation of the lesion. The balloon is designed to reach different diameters at different pressures, as predicted by the compliance curve included in the instructions for use (device description).

The process of a coronary balloon angioplasty using an in vitro model was simulated in a bench test to quantify the drug loss during catheter navigation. The anatomic model used was equivalent to the model described in ASTM F2394. Furthermore, the nanotechnology coating (TransferTech) was assessed in a preclinical study on a porcine model to determine arterial drug deposition of paclitaxel, as well as efficacy and safety.

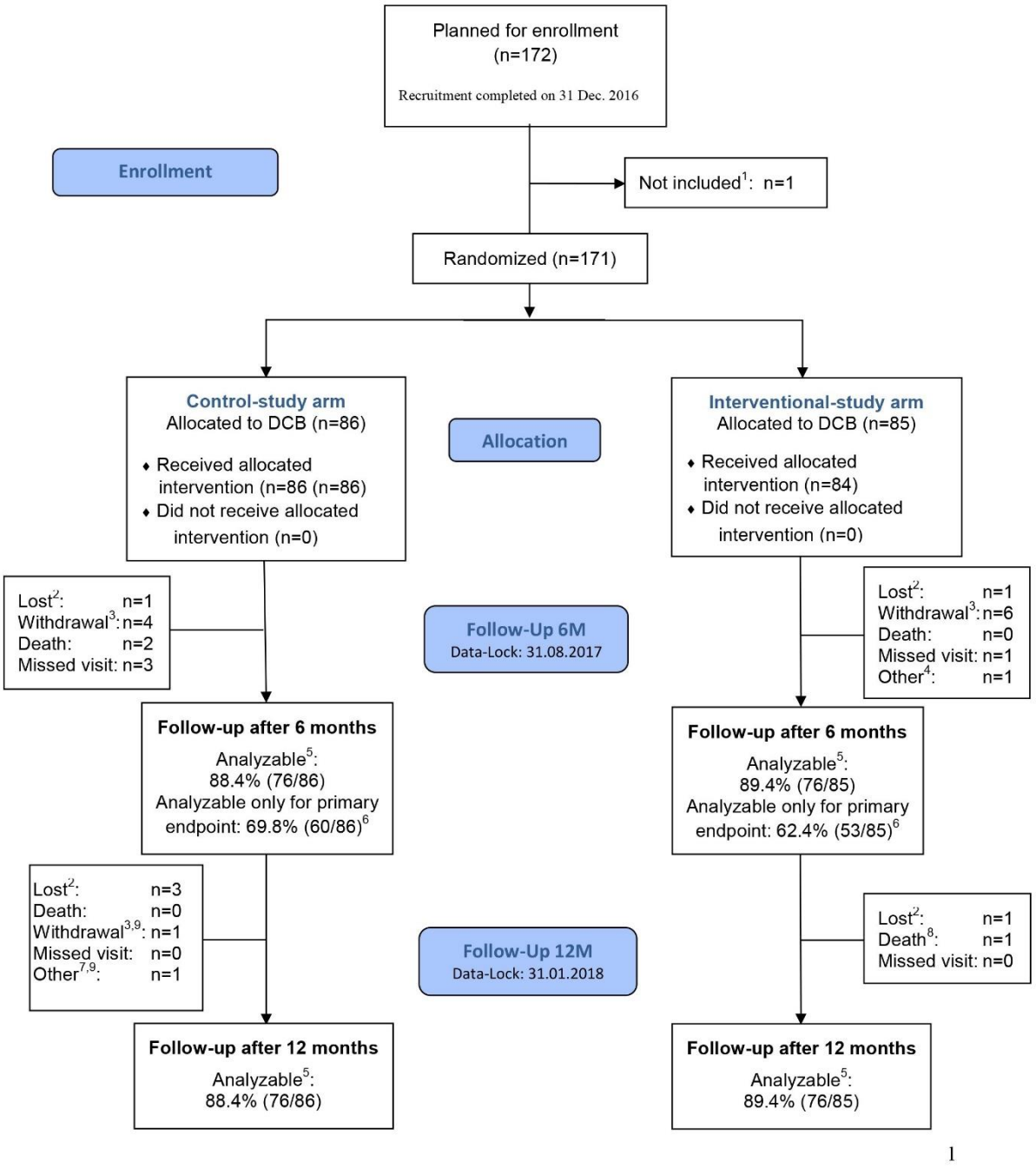
Supplementary Appendix 3. Statistical methods

The primary endpoint was analysed by fitting a linear mixed model with treatment as fixed effect and vascular centres as random effect. To compare both treatment groups regarding the change in the RBC criteria, the Cochran-Mantel-Haenszel mean score test (with ranks as scores) stratified for vascular centres was applied. Change in ABI and "quality of life" according to the patient's self-rated EQ-5D and WIQ were analysed by applying linear mixed models including treatment as fixed effect and vascular centre as random effect. The frequencies of restenosis, number of bail-outs, TLR, and TVR (at six and 12 months) were compared by Cochran-Mantel-Haenszel test, with vascular centres as strata. Kaplan-Meier analyses were performed for time-to-event data (TLR/TVR, patency, minor and major amputations, death), and the survival curves of the groups were compared by log-rank test. The tests for secondary endpoints were not adjusted for multiplicity; therefore, the results are not confirmatory for these endpoints.

The sample size calculation was based on the results of Werk et al (FemPac) [11]. In this trial, the LLL after six months was on average 0.5 mm (SD 1.1 mm) in the DCB group and 1.0 mm (SD 1.1 mm) in the POBA group [3]. At a 5% significance level, a two-sided independent samples t-test will have 80% power to detect this effect size of 0.45 when the sample size in each group is 77 patients (calculation was carried out with the use of nQuery Advisor 7.0). Given a dropout rate for primary endpoint data of 10%, it was planned to include a total of 172 patients in the trial.

As generally recommended in multicentre trials, in EffPac we performed a stratified randomisation with centres as strata to get a balanced distribution of the treatments in each centre. It is widely acknowledged in the statistical literature that the statistical analysis should reflect the design of the study, and any stratification variables should be adjusted for in the analysis. The reason is that, in an unstratified analysis (e.g., two-sample t-test, Mann-Whitney U test), standard errors for the treatment effect will be biased upwards compared to stratified analyses. This means that 95% confidence intervals are too wide, type I error rates are too low and the statistical power is reduced, if unstratified analyses are applied. Therefore, we fitted a linear mixed model with treatment as fixed effect and clinical centres as random effect for the primary endpoint LLL. For the same reason, the Cochran-Mantel-Haenszel test with centres as strata was used to analyse categorical secondary endpoints.

To assess the sensitivity of the main results due to missing values, multiple imputation of the primary endpoint was performed using the fully conditional specification approach (number of imputations n=20). Baseline characteristics of the patients (age, gender, BMI, smoking status) as well as bail-out stenting were included in the imputation model to impute the missing primary outcomes. The analysis of the imputed data reveals a difference between the DCB group and the POBA group of -0.92 mm [95% CI: -1.36; -0.48], confirming the results of the main analysis without imputation.



Supplementary Figure 1. Patient flow diagram according to the CONSORT 2010 statement.

Description of Supplementary Figure 1:

1. Reason: end of patient recruitment.

2. Lost to follow-up: patient refused to come to the visit or could not be reached by telephone or letter.

3. Withdrawal at patient's request or at the request of their legal representative.

4. DCB does not exist for specific reference vessel diameter (e.g., 4 mm).

5. Patients with data of at least one endpoint (primary or secondary).

6. Patients denied follow-up angiography but were analysable for all secondary endpoints at six and 12 months; especially if symptom free, 23 patients denied diagnostic study-related angiography in the POBA arm, and 13 patients in the DCB arm.

7. Patient had a revascularisation or restenosis before 12 months and was therefore analysable for the secondary endpoint TLR/restenosis ≤12 months.

8. Patient had a revascularisation and restenosis before 12 months and was therefore analysable for the secondary endpoint TLR/restenosis ≤12 months.

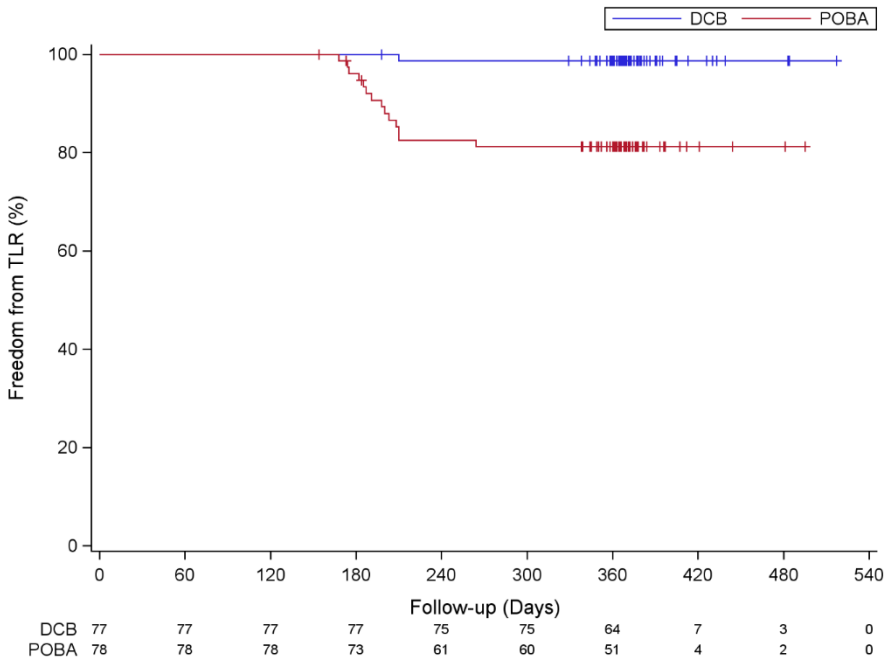
9. Exclusion criteria met (PTA <4 mm).

A

	Paclitaxel-Coated Balloon				Standard Angioplasty Balloon			
Time	**Survival % [95% CI]**	**Subjects with Event**	**Censored Subjects**	**Subjects at Risk**	**Survival % [95% CI]**	**Subjects with Event**	**Censored Subjects**	**Subjects at Risk**
210 days*	98.7% [91.0, 99.9]	1	1	76	82.6 [71.8, 89.5]	11	3	64
395 days*	98.7% [91.0, 99.9]	0	65	11	81.2 [70.3, 88.5]	14	40	10

* A time delay of up to 30 days was permitted for each visit. Therefore, timepoint at 210 days and 395 days were chosen to show the survival probabilities at the different visits. The survival curves of the DCB- and the POBA-group are significantly different (log rank test: p<0.001).

B



Supplementary Figure 2. Kaplan-Meier analysis for freedom from target lesion revascularisation (TLR) at 12 months.

A) Incidence of freedom from target lesion revascularisation at 210 and 395 days after DCB angioplasty or POBA.

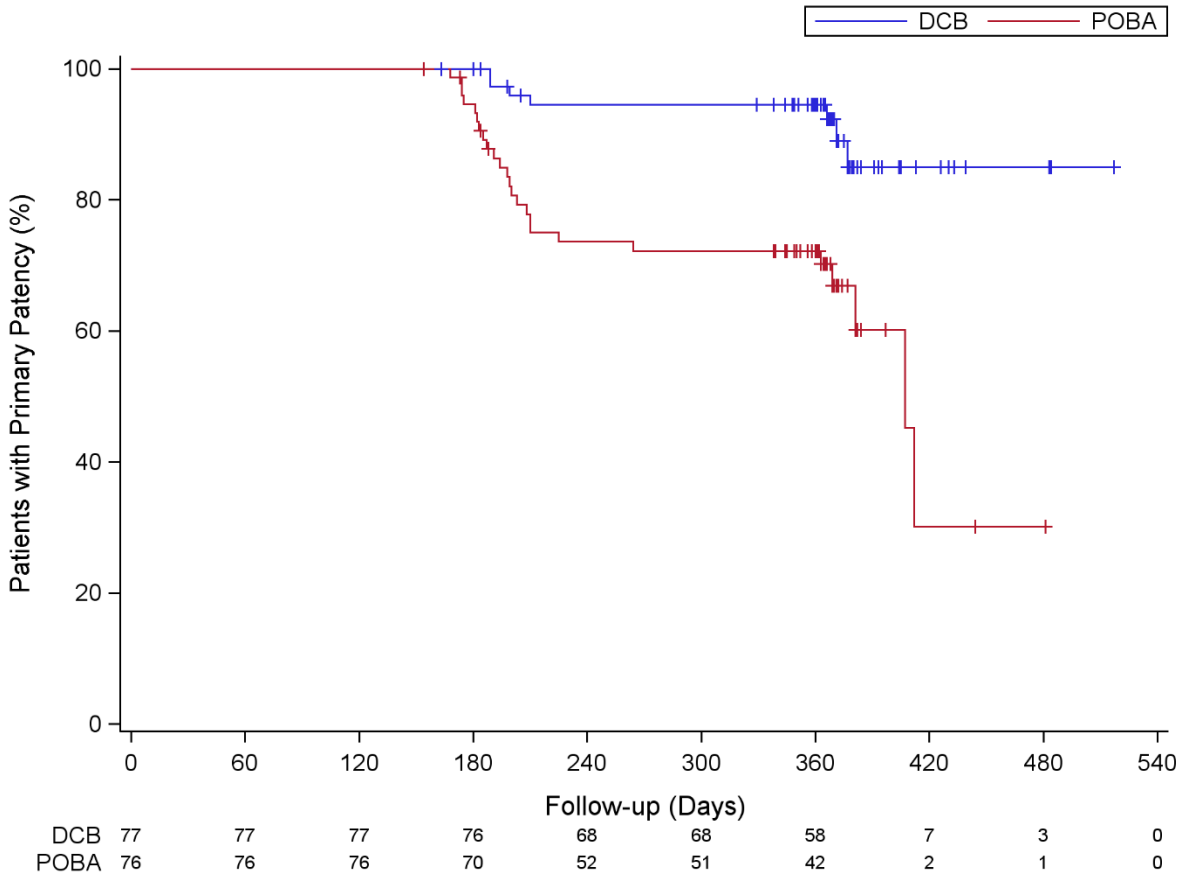
B) Kaplan-Meier survival curves for freedom from target lesion revascularisation (log-rank p <0.001). Censoring is indicated by tick marks.

A

	Paclitaxel-Coated Balloon				Standard Angioplasty Balloon			
Time	**Survival % [95% CI]**	**Subjects with Event**	**Censored Subjects**	**Subjects at Risk**	**Survival % [95% CI]**	**Subjects with Event**	**Censored Subjects**	**Subjects at Risk**
210 days*	94.5% [86.0, 98.0]	4	5	69	75.0% [63.3, 83.5]	18	3	55
395 days*	85.0% [68.6, 93.3]	3	55	11	60.2% [41.8, 74.5]	5	43	7

* A time delay of up to 30 days was permitted for each visit. Therefore, timepoint at 210 days and 395 days were chosen to show the survival probabilities at the different visits. The survival curves of the DCB- and the POBA-group are significantly different (log rank test: p<0.001).

B



Supplementary Figure 3. Kaplan-Meier analysis for primary patency at 12 months.

A) Incidence of primary patency at 210 and 395 days after DCB angioplasty or POBA.

B) Kaplan-Meier survival curves for primary patency (log-rank p <0.001). Censoring is indicated by tick marks.

Supplementary Table 1. Baseline demographic and clinical characteristics.

Patient characteristics	Paclitaxel-coated balloon (n=85)	Standard angioplasty balloon (n=86)	*p*-value
Age, yrs	68.0±7.5	68.1±8.8	0.956
Male, n (%)	51 (60.0)	60 (69.8)	0.202
Height, cm	169.7±8.4	170.2±9.0	0.744
Weight, kg	78.9±14.6	80.2±15.1	0.569
Body mass index, kg/m^2			
Mean	27.4±4.8	27.7±4.7	0.689
≥30, n (%)	22 (26.5)	20 (23.3)	0.722
Smoking status, n (%)			0.943
Current smoker	34 (40.5)	37 (43.0)	
Former smoker	36 (42.9)	35 (40.7)	
Never smoked	14 (16.7)	14 (16.3)	
Diabetes mellitus, n (%)	31 (36.5)	35 (40.7)	0.638
Hypertension, n (%)	74 (87.1)	73 (84.9)	0.826
Hyperlipidaemia, n (%)	60 (70.6)	59 (68.6)	1.000
Renal insufficiency, n (%)	15 (17.6)	13 (15.1)	0.684
Angina pectoris, n (%)	1 (1.2)	4 (4.7)	0.368
Arrhythmia, n (%)	13 (15.3)	10 (11.6)	0.509
Congestive heart failure, n (%)	6 (7.1)	6 (7.0)	1.000
Coronary arterial disease, n (%)	26 (30.6)	21 (24.4)	0.493
Myocardial infarction, n (%)	9 (10.6)	11 (12.8)	0.813
Stroke, n (%)	6 (7.1)	3 (3.5)	0.329
Transient ischaemic attack, n (%)	3 (3.5)	2 (2.3)	0.682
Rutherford-Becker stage, n (%)			0.531
2	13 (15.3)	18 (21.2)	
3	69 (81.2)	66 (77.6)	
4	2 (2.4)	1 (1.2)	
5	1 (1.2)	0	
6	0	0	
Target limb ankle-brachial index	0.73±0.23	0.74±0.23	0.779

Values are presented as mean±standard deviation or as numbers and percentages.

Continuous baseline characteristics are compared by two-sided unpaired t-test, categorical characteristics by Fisher's exact test/chi-square test.

Supplementary Table 2. Baseline lesion characteristics and procedural outcomes.

Lesion characteristics and procedural outcomes	Paclitaxel-coated balloon (n=85)	Standard angioplasty balloon (n=86)	*p*-value
Lesion length, mm	59.1±43.4	55.8±39.1	0.600
Total occlusion, n (%)	17 (20.2)	22 (25.6)	0.468
Degree of stenosis, %	88.0±9.8	90.1±8.8	0.156
Reference vessel diameter, mm	5.4±0.6	5.4±0.7	0.603
Minimal lumen diameter, mm	0.9±0.7	0.8±0.7	0.375
Limb, n (%)			0.879
Right	46 (54.1)	45 (52.3)	
Left	39 (45.9)	41 (47.7)	
Total treated length, mm	89.8±48.6	84.9±45.1	0.515
Target lesion location, n (%)			0.904
Proximal SFA	14 (16.5)	10 (11.6)	
Mid SFA	26 (30.6)	27 (31.4)	
Distal SFA	35 (41.2)	37 (43.0)	
Proximal popliteal (POP 1)	12 (14.1)	14 (16.3)	
Mid popliteal (POP 2)	13 (15.3)	9 (10.5)	
Distal popliteal (POP 3)	3 (3.5)	3 (3.5)	
TASC II, n (%)			0.748
A	55 (64.7)	58 (67.4)	
B	30 (35.3)	28 (32.6)	
Calcification, n (%)			0.109
None/mild	45 (54.2)	38 (44.2)	
Moderate	35 (42.2)	38 (44.2)	
Severe	3 (3.6)	10 (11.6)	
Number of patent run-off vessels, n (%)			0.227
0	0	1 (1.2)	
1	19 (22.4)	19 (22.1)	
2	35 (41.2)	27 (31.4)	
3	31 (36.5)	39 (45.3)	
Predilatation, n (%)	84 (100)	85 (98.8)	1.000
Predilatation: **Balloons per lesion**			0.679
1	71 (84.5)	62 (72.9)	
2	6 (7.1)	18 (21.2)	
3	4 (4.8)	5 (5.9)	
4	2 (2.4)	0	
5	1 (1.2)	0	
Length, mm	54.6±34.2	57.4±33.4	0.594
Diameter, mm	4.8±0.6	5.0±0.6	0.149
Pressure, atm	9.8±3.0	9.4±2.6	0.376
Time, sec	41.3±33.2	35.8±25.5	0.230
Dissection, n (%)	32 (37.6)	35 (40.7)	0.755
Bail-out stenting, n (%)	13 (15.3)	16 (18.8)	0.684
Inflation pressure, atm	8.4±2.3	8.8±2.0	0.234
Index procedure			
Post predilatation diameter stenosis (%) according to visual estimate	7.6±9.3	8.3±10.1	0.700
Post-procedural diameter stenosis (%) according to visual estimate	15.5±16.7	14.9±16.2	0.808
Angioplasty			
Procedure time, min	48.8±19.2	48.1±21.7	0.823

Fluoroscopy time, min	7.9±4.0	8.2±4.6	0.604
Amount of contrast, cc (ml)	98.1±36.3	99.1±40.1	0.862
Access approach used			0.547
Contralateral femoral	69 (81.2)	73 (84.9)	
Ipsilateral femoral	16 (18.8)	13 (15.1)	