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Efficacy and Safety of a Novel Paclitaxel-Nano-Coated Balloon for Femoro-Popliteal Angioplasty: 1-Year Results of EffPac Trial

Short Title: *EffPac Trial*

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A list of study collaborators can be found in the appendix*

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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 -

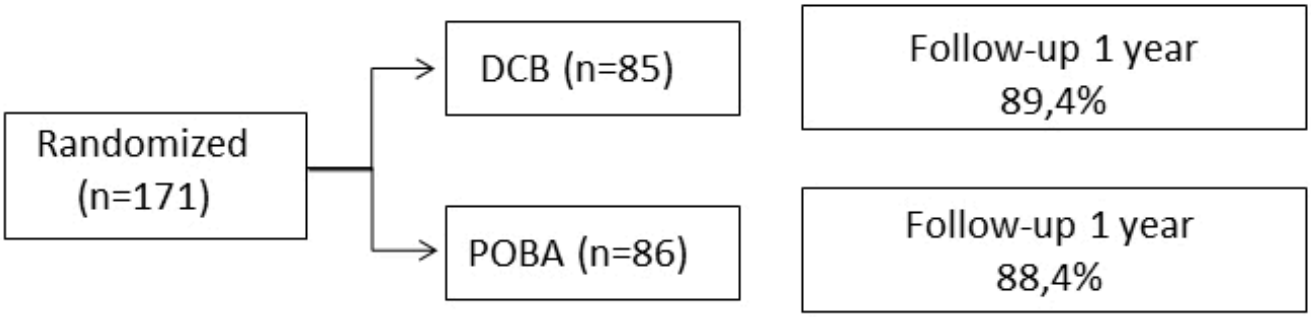
This multicenter trial randomly assigned 171 patients with stenotic and occlusive lesions of the femoropopliteal artery to angioplasty with the novel DCB or uncoated POBA. The primary endpoint late lumen loss at 6 months was 0.92 mm lower in the DCB group (95%CI: -1.36 mm; -0.49 mm, P<0.001). Patients showed improved walking after DCB treatment at 6 months (P=0.021). In the DCB group, 44.6%/50% of the patients improved by three Rutherford-Becker classification stages after 6/12 months (POBA: 27.8%/36.8%). Only one patient needed TLR (1.3%) in the DCB group, compared to 14 (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) vs. 65.3% (POBA group) after 12 months (RR=1.38, 95%CI: 1.14; 1.67, P<0.001).

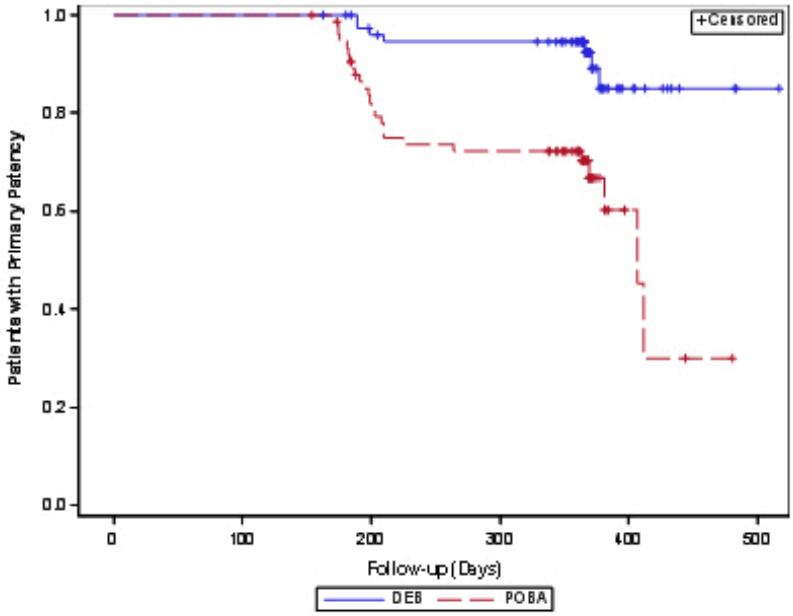
Conclusions **-** The novel DCB was effective and safe for inhibiting restenosis. Moreover, it demonstrated a better improvement in walking than POBA and showed no mortality concerns due to paclitaxel application after 12 months.

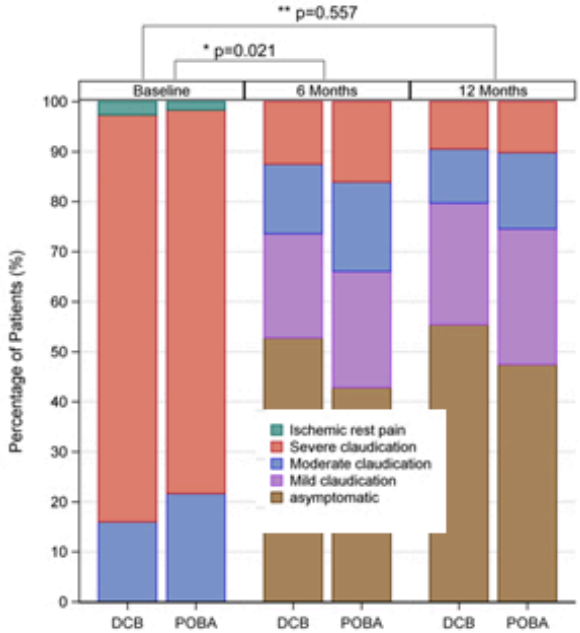
Clinical Trials Identifier: NCT02540018

CLASSIFICATION

Claudication, femoro-popliteal disease, drug-eluting balloon, clinical trials


Randomized
(n=171)
DCB (n=85)
POBA (n=86)
Follow-up 1 year
89,4%
Follow-up 1 year
88,4%


+Censored
Patients with Primary Patency
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
Follow-up (Days)
DEB
POBA


** p=0.557
* p=0.021
Baseline
6 Months
12 Months
Percentage of Patients (%)
100
90
80
70
60
50
40
30
20
10
0
Ischemic rest pain
Severe claudication
Moderate claudication
Mild claudication
asymptomatic
DCB
POBA
DCB
POBA
DCB
POBA

ABBREVIATIONS

ABI = ankle-brachial index

CI = confidence interval

DCB = drug-coated balloon

DUS = duplex ultrasonography

EQ-5D index = EuroQol-5 Dimensions index

LLL = late lumen loss

NNT = number needed to treat

POBA = plain old balloon angioplasty

RR = risk ratio

SAE = serious adverse event

SFA = superficial femoral artery

TLR = target lesion revascularization

TVR = target vessel revascularization

WIQ score = walking impairment questionnaire score

CONDENSED ABSTRACT

Multicenter RCT EffPac evaluates the safety and efficacy of the Luminor® paclitaxel-nano-coated balloon (DEB) vs. uncoated balloon catheter (POBA) in inhibiting restenosis and ensuring long-term patency. EffPac delivered good DCB outcomes in SFA TASC A&B lesions after 12 months and demonstrates that the investigational DCB catheter is highly effective and safe in inhibiting restenosis.

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, the quality of life (2). Uncoated plain-old balloon angioplasty (POBA) followed by paclitaxel drug-coated balloons (DCBs) is more and more considered as the treatment of choice for revascularization in shorter lesions (3,4). An 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 those 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 vs. uncoated POBA with regard to clinical benefit and safety.

METHODS

Study concept

This investigator-initiated multicenter randomized controlled parallel-group trial was performed at 11 vascular centers 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 Organization 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 Trials (9). The trial was reported according to CONSORT statement (10).

Study population and eligibility criteria

Patients with symptomatic peripheral artery disease, with moderate to severe intermittent claudication or ischemic rest pain (Rutherford-Becker classes 2-4), were eligible for enrollment. 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 and the proximal popliteal artery up to the P1 segment were included. Bailout stenting in flow-limiting dissection was also considered. The inclusion and exclusion criteria are outlined in Supplementary Text 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 shown in the **Supplementary Text 2**.

Randomization and the index procedure

Patients were randomly assigned after pre-dilatation in a 1:1 allocation ratio using a computer-generated randomization list with random block sizes and stratification by vascular center (stratified block randomization). For non-flow-limiting or flow-limiting dissections, prolonged PTA with the same PTA balloon was performed. For persistent flow-limiting dissections, bailout stenting with a bare metal stent was permitted (**Figure 1**).

In case two or multiple PTA balloon catheters were used, a minimized 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 6 months (defined

as the difference between the angiographic minimum lumen diameter immediately after PTA and at follow-up). Safety endpoints included freedom from target lesion revascularization (TLR), investigation- and procedure-related SAEs/AEs, 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 revascularization (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 records with 5 dimensions of severity (EQ5D) at follow-up; number of bailout 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 analyzed 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 the **Supplementary Text 3**.

RESULTS

Study population and treatment

A total of 171 patients were enrolled between September 1st, 2015, and December 31st, 2016. Only one drop-out due to small-vessel diameter occurred in the DCB group after randomization. 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**. Both 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 vs. POBA groups, the mean lesion length was 59±43 mm vs. 56±39 mm, the total treated length was 89.8±48.6 mm vs. 84.9±45.1 mm, and total occlusions comprised 20.2% (17/84) vs. 25.6% (22/86) of the total lesions.

Pre-dilation 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 bailout 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 embolization was unnoted.

Primary efficacy and safety outcomes

Regarding the DCB vs POBA groups, 62.4% (53/85) vs. 73.3% (63/86) of the patients underwent angiography after 6 months. LLL at 6 months was 0.14 mm (95%CI: -0.38; 0.67) for DCB vs. 1.06 mm (95%CI: 0.54; 1.59) for POBA. The difference between both groups was -0.92 mm (95%CI: -1.36; -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 6 months in the DCB and POBA groups, respectively (P<0.001). The relative risk reduction for TLR was 91.8% after 6 months according to the Cochran-Mantel-Haenszel estimation, and the number needed to treat (NNT) to prevent one additional TLR after 6 months was 7 (**Table 1**). After 12

months, the TLR rate was still significantly lower in the DCB group (1.3%, 1/76), with an NNT of 6, than in the POBA group (18.7%, 14/75) (P<0.001). The Kaplan Meier estimates for freedom from TLR are shown in the Supplementary Figure 2.

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

Secondary outcomes

Primary patency was 94.7% (72/76) and 75.0% (57/76) after 6 months in the DCB and POBA group, 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 remodeling is shown in **Table 1**. The Kaplan Meier estimates for patency are reported in the **Supplementary Figure 3**.Significantly more patients showed an improved RBC at 6 months after DCB angioplasty than after POBA (P=0.021). An improvement in 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 in 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; 12.0) higher after 6 months and 5.3 points (95%CI: -4.6; 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 uncompleted 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 former DCB trials (e.g. Pacifier, Fempac, and Thunder trials), with a similar surface dosage (11,13,14). "Negative remodeling" (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 remodeling can additionally indicate high DCB effectiveness. However, ectatic vessel changes were occasionally documented 6 months after DCB treatment (17). In our trial, no such inadvertent aneurysmal dilatations of the target lesion were observed. Only one revascularization was necessary after 6 and 12 months in the DCB group (TLR rate of 1.3%). Good TLR rates of 2–6% after one year were also noted with other DCBs (18,19).

Furthermore, EffPac showed a comparably low TLR rate in the control group, with an NNT of 7 (i.e. with every 7th 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 both study groups (especially regarding pre-dilatation and stenting rate), except for the applied catheter. This allows a more realistic assessment of the treatment effect and is consistent with newer trials that also performed pre-dilatation before randomization (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. NNT was 6 after 6 months and 4 after 12 months. This also suggests high anti-restenotic ability and is comparable to the performance of

other DCBs (e.g. 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 6 months' 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 revascularized in the POBA-group and only 1 in the DCB-group. Therefore, those patients obviously improved their walking capacity after secondary revascularization. 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). For note, the randomization was performed after pre-dilatation, therefore both study groups were pre-treated in the exact same way, minimizing 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, all subdomains of the questionnaire, higher mean scores were noted in the DCB group after 6 and 12 months as compared to POBA. The change of ABI to baseline was not significant between both study groups. Possible reasons could either be the lack of sufficient statistical power, the impairment of run-off vessels below-the-knee as well as microangiopathy, especially in patients with diabetes.

In the 2-year and 5-year long-term follow-ups, we will investigate if these clinical benefits will be preserved. According to 3-year data of the IN.PACT SFA trial and the 5-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 minimized by predefined treatment process (e.g. randomization after pre-dilatation, 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, since 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 comparative device to drug-eluting balloon catheters and LLL was imperative as primary endpoint to demonstrate technical efficacy. This was the only way to show that our investigated DCB is effective on one hand, and safe compared with a non-paclitaxel-coated balloon catheter on the other hand. The safety of DCB is best shown in an RCT with POBA as control group. At this timepoint, we are only able to proof that there are no mortality concerns due to paclitaxel application after 12 months in our EffPac trial. Katsanos et al. have recently shown in a meta-analysis comparing all kind of paclitaxel-coated devices for the SFA an increased risk of death following the application of paclitaxel-coated balloons and stents after 2 years and 5 years (29). The EffPac trial is a proof of principle study. Regarding the promising results of LLL as technical outcome, TLR, patency and

walking improvement as clinical outcomes after 1 year, we amended EffPac for additional 24-, 42- and 60-months follow-up. 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, so that the generalizability 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 and it is an important contribution to clinical practice.

IMPACT ON DAILY PRACTICE

EffPac could show, for the first time, the statistically significant improvement assessing the walking capacity as "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.

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APPENDIX: STUDY COLLABORATORS

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Conflict of interest statement

UT is a consultant for iVascular and Endoscout GmbH. The other authors have no interest of conflict to declare

Figure / Table legends

Figure 1 Flowchart index procedure.

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

Table 1 Primary and secondary endpoints.

References

1. Meru AV, Mittra S, Thyagarajan B, Chugh A. Intermittent claudication: an overview. Atherosclerosis 2006;187:221-37.
2. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg 2007;33 Suppl 1:S1-75.
3. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Röther J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;39:763-816.
4. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FGR, Hamburg NM, Kinlay S, Lookstein R, Misra S, Mureebe L, Olin JW, Patel RAG, Regensteiner JG, Schanzer A, Shishehbor MH, Stewart KJ, Treat-Jacobson D, Walsh ME. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e726-e779.
5. Byrne RA, Joner M, Alfonso F, Kastrati A. Drug-coated balloon therapy in coronary and peripheral artery disease. Nat Rev Cardiol 2014;11:13-23.
6. Speck U, Cremers B, Kelsch B, Biedermann M, Clever YP, Schaffner S, Mahnkopf D, Hanisch U, Böhm M, Scheller B. Do pharmacokinetics explain persistent restenosis inhibition by a single dose of paclitaxel? Circ Cardiovasc Interv 2012;5:392-400.
7. Giacoppo D, Cassese S, Harada Y, Colleran R, Michel J, Fusaro M, Kastrati A, Byrne RA. Drug-Coated Balloon Versus Plain Balloon Angioplasty for the Treatment of Femoropopliteal Artery Disease: An Updated Systematic Review and Meta-Analysis of Randomized Clinical Trials. JACC Cardiovasc Interv 2016;9:1731-42.
8. Teichgraber UK, Klumb C. [Drug-coated Balloon Angioplasty in Femoropopliteal Arteries - Is There a Class Effect?]. Zentralbl Chir 2017;142:470-480.
9. Teichgraber U, Aschenbach R, Scheinert D, Zeller T, Brechtel K, Thieme M, Blessing E, Treitl M, Lichtenberg M, von Flotow P, Vogel B, Werk M, Riambau V, Wienke A, Lehmann T, Sixt S.. The effectiveness of the paclitaxel-coated Luminor(R) balloon catheter versus an uncoated balloon catheter in superficial femoral and popliteal arteries in preventing vessel restenosis or reocclusion: study protocol for a randomized controlled trial. Trials 2016;17:528.
10. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG.. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c869.

11. Werk M, Langner S, Reinkensmeier B, Boettcher HF, Tepe G, Dietz U, Hosten N, Hamm B, Speck U, Ricke J. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. Circulation 2008;118:1358-65.
12. Scheller B, Speck U, Abramjuk C, Bernhardt U, Bohm M, Nickenig G. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. Circulation 2004;110:810-4.
13. Tepe G, Zeller T, Albrecht T, Heller S, Schwarzwälder U, Beregi JP, Claussen CD, Oldenburg A, Scheller B, Speck U. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. New England Journal of Medicine 2008;358:689-699.
14. Werk M, Albrecht T, Meyer DR, Ahmed MN, Behne A, Dietz U, Eschenbach G, Hartmann H, Lange C, Schnorr B, Stiepani H, Zoccai GB, Hänninen EL. Paclitaxel-coated balloons reduce restenosis after femoro-popliteal angioplasty: evidence from the randomized PACIFIER trial. Circ Cardiovasc Interv 2012;5:831-40.
15. Bausback Y, Willfort-Ehringer A, Sievert H, Geist V, Lichtenberg M, Del Giudice C, Sauguet A, Diaz-Cartelle J, Marx C, Strobel A, Schult I, Scheinert D. Six-Month Results From the Initial Randomized Study of the Ranger Paclitaxel-Coated Balloon in the Femoropopliteal Segment. J Endovasc Ther 2017;24:459-467.
16. Jia X, Zhang J, Zhuang B, Fu W, Wu D, Wang F, Zhao Y, Guo P, Bi W, Wang S, Guo W. Acotec Drug-Coated Balloon Catheter: Randomized, Multicenter, Controlled Clinical Study in Femoropopliteal Arteries: Evidence From the AcoArt I Trial. JACC Cardiovasc Interv 2016;9:1941-9.
17. Diamantopoulos A, Gupta Y, Zayed H, Katsanos K. Paclitaxel-coated balloons and aneurysm formation in peripheral vessels. J Vasc Surg 2015;62:1320-2.
18. Schroeder H, Meyer DR, Lux B, Ruecker F, Martorana M, Duda S. Two-year results of a low-dose drug-coated balloon for revascularization of the femoropopliteal artery: Outcomes from the ILLUMENATE first-in-human study. Catheterization and Cardiovascular Interventions 2015;86:278-286.
19. Tepe G, Laird J, Schneider P, Brodmann M, Krishnan P, Micari A, Metzger C, Scheinert D, Zeller T, Cohen DJ, Snead DB1, Alexander B, Landini M, Jaff MR. Drug-Coated Balloon Versus Standard Percutaneous Transluminal Angioplasty for the Treatment of Superficial Femoral and Popliteal Peripheral Artery Disease 12-Month Results From the IN. PACT SFA Randomized Trial. Circulation 2015;131:495-+.
20. Krishnan P, Faries P, Niazi K, Jain A, Sachar R, Bachinsky WB, Cardenas J, Werner M, Brodmann M, Mustapha JA, Mena-Hurtado C, Jaff MR, Holden AH, Lyden SP. Stellarex Drug-Coated Balloon for Treatment of Femoropopliteal Disease: Twelve-Month Outcomes From the Randomized ILLUMENATE Pivotal and Pharmacokinetic Studies. Circulation 2017;136:1102-1113.
21. Steiner S, Willfort-Ehringer A, Sievert H, Geist V, Lichtenberg M, Del Giudice C, Sauguet A, Diaz-Cartelle J, Marx C, Ströbel A, Schult I, Scheinert D. 12-Month Results From the First-in-Human Randomized Study of the Ranger Paclitaxel-Coated Balloon for Femoropopliteal Treatment. JACC Cardiovasc Interv 2018;11:934-941.
22. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, Jones DN. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997;26:517-38.
23. Schneider PA, Laird JR, Tepe G, Brodmann M, Zeller T, Scheinert D, Metzger C, Micari A, Sachar R, Jaff MR, Wang H, Hasenbank MS,

Krishnan P. Treatment Effect of Drug-Coated Balloons Is Durable to 3 Years in the Femoropopliteal Arteries: Long-Term Results of the IN.PACT SFA Randomized Trial. Circ Cardiovasc Interv 2018;11:e005891.

24. Tepe G, Schnorr B, Albrecht T, Brodmann M, Zeller T, Scheinert D, Metzger C, Micari A Sachar R, Jaff MR, Wang H, Hasenbank MS, Krishnan P. Angioplasty of Femoral-Popliteal Arteries With Drug-Coated Balloons 5-Year Follow-Up of the THUNDER Trial. Jacc-Cardiovascular Interventions 2015;8:102-108.
25. Albrecht T, Waliszewski M, Roca C, Redlich U, Tautenhahn J, Pech M, Halloul Z, Gögebakan Ö, Meyer DR, Gemeinhardt I, Zeller T, Müller-Hülsbeck S, Ott I, Tepe G. Two-Year Clinical Outcomes of the CONSEQUENT Trial: Can Femoropopliteal Lesions be Treated with Sustainable Clinical Results that are Economically Sound? Cardiovasc Intervent Radiol 2018;41:1008-1014.
26. Scheinert D, Duda S, Zeller T, Krankenberg H, Ricke J, Bosiers M, Tepe G, Naisbitt S, Rosenfield K. The LEVANT I (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) Trial for Femoropopliteal Revascularization First-in-Human Randomized Trial of Low-Dose Drug-Coated Balloon Versus Uncoated Balloon Angioplasty. Jacc-Cardiovascular Interventions 2014;7:11-19.
27. Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC, Brodmann M, Pilger E, Zeller T, Krishnan P, Gammon R, Müller-Hülsbeck S, Nehler MR, Benenati JF, Scheinert D. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. New England Journal of Medicine 2015;373:145-153.
28. Scheinert D, Schulte KL, Zeller T, Lammer J, Tepe G. Paclitaxel-Releasing Balloon in Femoropopliteal Lesions Using a BTHC Excipient: Twelve-Month Results From the BIOLUX P-I Randomized Trial. Journal of Endovascular Therapy 2015;22:14-21.
29. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc 2018;7.

Table 1. Primary and secondary endpoints

	DCB		POBA			
	n		n		Mean difference/ Relative risk [95% CI]	P-value
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 – no. (%)¶	76	10 (13.2)	76	24 (31.6)	0.40 [0.20; 0.79]	0.011
Target-lesion revascularization – no. (%)	76	1 (1.3)	76	13 (17.1)	0.08 [0.01; 0.56]	<0.001
Target-vessel revascularization – no. (%)	76	3 (3.9)	76	16 (21.1)	0.17 [0.05; 0.61]	0.001
Primary patency – no. (%)[]	76	72 (94.7)	76	57 (75.0)	1.26 [1.10; 1.45]	<0.001

Change in Rutherford-Becker stage – no. (%)	74		72		-	0.021
Deterioration of 1 stage		1 (1.4)		0		
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 EQ5D 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 – no. (%)¶	76	15 (19.7)	76	30 (39.5)	0.49 [0.28; 0.83]	0.005
Target lesion revascularization – no. (%)†	76	1 (1.3)	75	14 (18.7)	0.08 [0.01; 0.53]	<0.001
Target vessel revascularization – no. (%)	76	4 (5.3)	75	17 (22.7)	0.22 [0.07; 0.66]	0.002
Primary patency – no. (%)[]	72	65 (90.3)	72	47 (65.3)	1.38 [1.14; 1.67]	<0.001
Change in Rutherford-Becker stage	74		68		-	0.740

compared to baseline – no. (%)*f*						
Deterioration of 1 stage		1 (1.4)		1 (1.5)		
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 EQ5D VAS	74	3.2±16.4	70	8.0±18.8	-4.8 [-10.7; 1.0]	0.101
Additional analysis						
Negative remodeling (LLL<0 mm) after 6 months – no. (%)	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 6 months' follow-up.

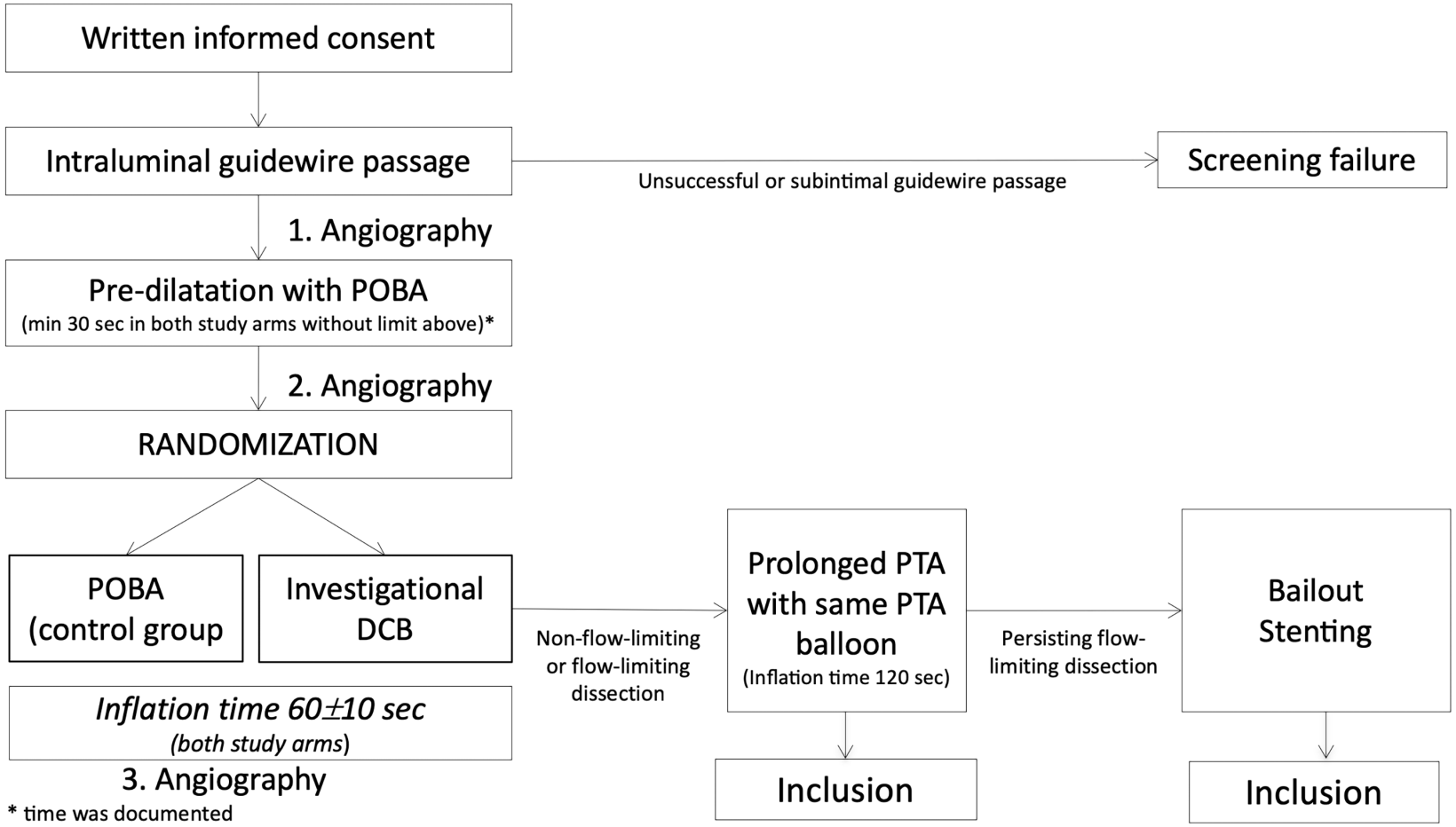
¶ Restenosis = presence of >50% stenosis in the target lesion assessed by duplex ultrasonography (peak systolic velocity ratio ≥2.5) or by angiography.

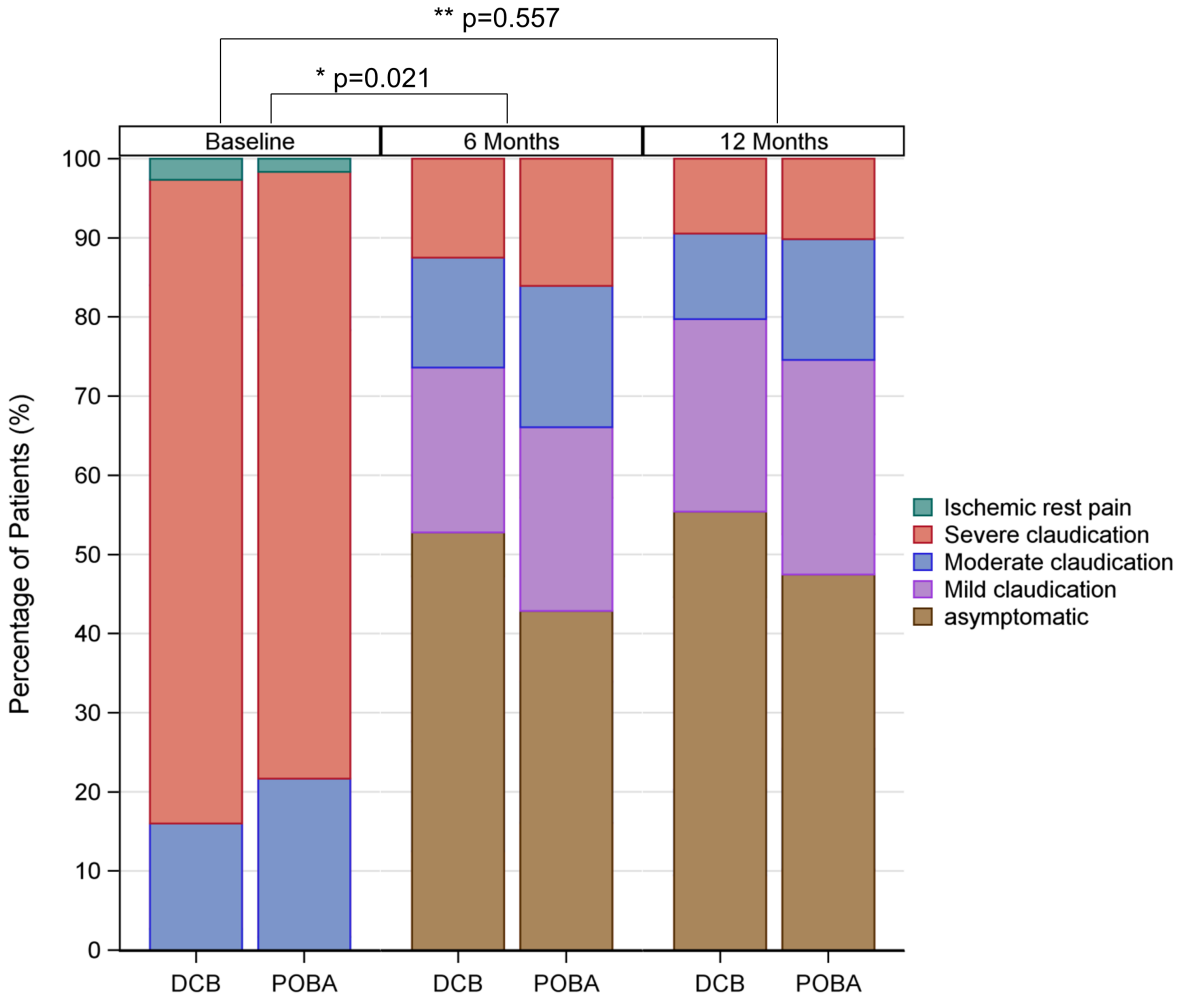
† Target lesion revascularization = reintervention for >50% diameter stenosis or reocclusion within the target lesion determined by duplex ultrasonography or angiography.

∏ Primary patency =absence from target lesion restenosis (adjudicated by the core laboratory) and freedom from target lesion revascularization.

f Patients with target lesion revascularization at 6 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 revascularization.

Abbreviations: ABI, ankle-brachial index; WIQ, Walking Impairment Questionnaire; EQ5D, European quality of life records with 5 dimensions of severity; VAS, visual analog scale; TLR, target lesion revascularization; TVR, target vessel r e vascularization


Written informed consent
Intraluminal guidewire passage
Unsuccessful or subintimal guidewire passage
Screening failure
1. Angiography
Pre-dilatation with POBA
(min 30 sec in both study arms without limit above)*
2. Angiography
RANDOMIZATION
POBA
(control group
Investigational
DCB
Inflation time 60±10 sec
(both study arms)
3. Angiography
* time was documented
Non-flow-limiting
or flow-limiting
dissection
Prolonged PTA
with same PTA
balloon
(Inflation time 120 sec)
Persisting flow-
limiting dissection
Bailout
Stenting
Inclusion
Inclusion


** p=0.557
* p=0.021
Baseline
6 Months
12 Months
Percentage of Patients (%)
100
90
80
70
60
50
40
30
20
10
0
DCB
POBA
DCB
POBA
DCB
POBA
Ischemic rest pain
Severe claudication
Moderate claudication
Mild claudication
asymptomatic

Supplementary Text 1. Eligibility Criteria

A. Inclusion criteria

1. Age ≥ 18 years
2. Subject must agree to undergo the 6-month angiographic and clinical follow-up (at 12 and 24 month 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 (see definition chapter 6.5)
9. ≥ one patent intrapopliteal run-off artery to the foot of the index limb
10. Successful endoluminal guidewire passage through the target lesion
11. Pre-dilatation prior to randomization
12. Life expectancy, in the investigators opinion of at least one year
13. Subject is able to verbally 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 greater 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 concern 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 6 month amenorrhea with serum FSH > 40mlU/ml)
    b. sterilization-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 2 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 against 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 3 months) in another interventional study.

Supplementary Text 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 minimize friction. The balloon is coated with a homogeneous mixture of paclitaxel and a physiologically innocuous matrix, the excipient. Drug's dose is 3 $\mu g/mm^2$ of balloon surface and it is intended to avoid cellular proliferation, consequently decreasing re-intervention 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 increase drug transit loss before the balloon reaches the target location, and coating integrity can also be more easily compromised during storage.

Ultrasonic spray coating of iVascular 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 can be 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 favors the obtaining of amorphous coatings and smooth textures. On the other hand, increasing the size of the drop, 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 assure a sufficient dosage of paclitaxel onto the arterial wall, inflation process must last from 30 seconds to 1 minute. Using longer inflation times at discretion of the interventionlist can optimize dilatation of the lesion. The balloon is designed to reach different diameters at different pressures, as predicted by the compliance curve included in the instruction 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 used anatomic model 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 Text 3. Statistical Methods

The primary endpoint was analyzed by fitting a linear mixed model with treatment as fixed effect and vascular centers 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 centers was applied. Change in ABI and "Quality of Life" according to patient's self-rated EQ5D and WIQ were analyzed by applying linear mixed models including treatment as fixed effect and vascular center as random effect. The frequencies of restenosis, number of bailouts, TLR, and TVR (at 6 and 12 months) were compared by Cochran-Mantel-Haenszel test, with vascular center 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 and, 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 6 months was on average 0.5mm (SD 1.1mm) in the DCB group and 1.0mm (SD 1.1mm) 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 done with use of nQuery Advisor 7.0). Given a dropout rate for primary endpoint data of 10% a total of 172 patients were planned to be included in the trial.

As generally recommended in multi-center trials, we performed in EffPac a stratified randomization with centers as strata to get a balanced distribution of the treatments in each center. 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 will be applied. Therefore, we fitted a linear mixed model with treatment as fixed effect and clinical centers as random effect for the primary endpoint LLL. For the same reason Cochran-Mantel-Haenszel test with centers as strata was used to analyze 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 m=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 DCB- and POBA-group of -0.92 mm [95% CI: -1.36; -0.48], confirming the results of the main analysis without imputation.

Supplementary Table 1. Baseline demographic and clinical characteristics

Patient characteristics	Paclitaxel-coated balloon (n=85)	Standard angioplasty balloon (n=86)	p value
Age – yr	68.0±7.5	68.1±8.8	0.956
Male – no. (%)	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 – no. (%)	22 (26.5)	20 (23.3)	0.722
Smoking status – no. (%)			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 – no. (%)	31 (36.5)	35 (40.7)	0.638
Hypertension – no. (%)	74 (87.1)	73 (84.9)	0.826
Hyperlipidemia – no. (%)	60 (70.6)	59 (68.6)	1.000
Renal insufficiency – no. (%)	15 (17.6)	13 (15.1)	0.684
Angina pectoris – no. (%)	1 (1.2)	4 (4.7)	0.368
Arrhythmia – no. (%)	13 (15.3)	10 (11.6)	0.509
Congestive heart failure – no.(%)	6 (7.1)	6 (7.0)	1.000
Coronary arterial disease – no.(%)	26 (30.6)	21 (24.4)	0.493
Myocardial infarction – no. (%)	9 (10.6)	11 (12.8)	0.813
Stroke – no. (%)	6 (7.1)	3 (3.5)	0.329
Transient ischemic attack – no. (%)	3 (3.5)	2 (2.3)	0.682
Rutherford-Becker stage – no.(%)			0.531
2	13 (15.3)	18 (21.2)	
3	69 (81.2)	66 (67.6)	
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 Fishers exact test / chi-square test.

Supplementary Table 2. Baseline lesion characteristics and procedure outcomes

Lesion characteristics and procedure 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 – no. (%)	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 – no. (%)			0.879
Right	46 (54.1)	45 (52.3)	
Left	39 (45.9)	41 (47.7)	
Total treated length	89.8±48.6	84.9±45.1	0.515
Target lesion location – no. (%)			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 – no. (%)			0.748
A	55 (64.7)	58 (67.4)	
B	30 (35.3)	28 (32.6)	
Calcification – no. (%)			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 vessel – no. (%)			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)	
Pre-dilatation – no. (%)	84 (100)	85 (98.8)	1.000
Pre-dilatation: 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 – no. (%)	32 (37.6)	35 (40.7)	0.755
Bailout stenting – no. (%)	13 (15.3)	16 (18.8)	0.684
Inflation pressure (ATM)	8.4±2.3	8.8±2.0	0.234

Index procedure			
Post pre-dilatation diameter stenosis (%) according to visual estimate	7.6±9.3	8.3±10.1	0.700
Postprocedural 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)	

Supplementary data

Supplementary Text 1. Eligibility Criteria

Supplementary Text 2. Investigational Product

Supplementary Text 3. Statistical Methods

Supplementary Table 1. Baseline demographic and clinical characteristics.

Supplementary Table 2. Baseline lesion characteristics and procedure outcomes.

Supplementary Figure 1. Patient Flow Diagram according to CONSORT 2010 Statement

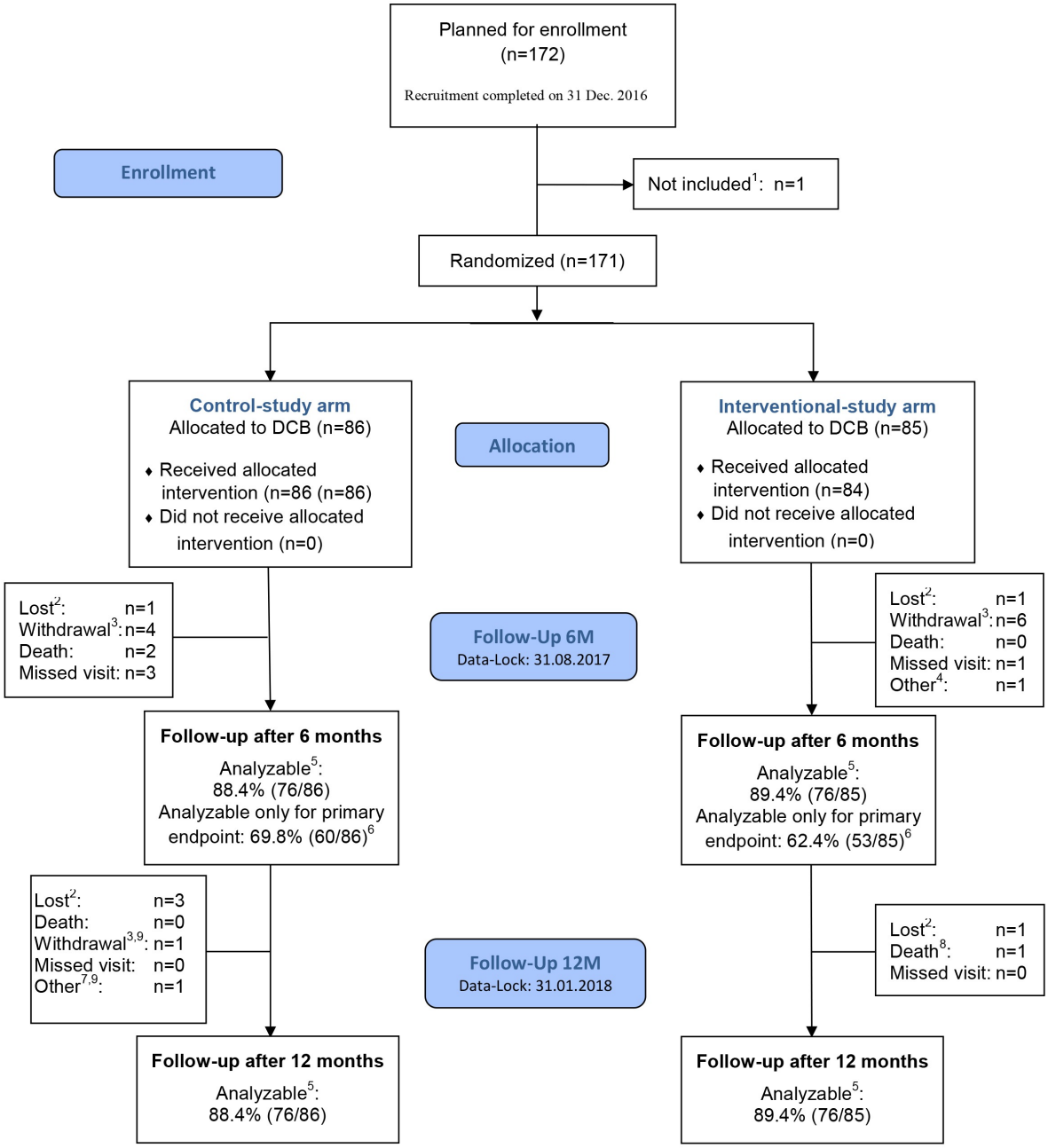
Description Figure 1:

[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 patients 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 analyzable for all secondary endpoints at 6 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 revascularization or restenosis before 12 months and was therefore analyzable for the secondary endpoint TLR / restenosis ≤12 months
[8] Patient had a revascularization and restenosis before 12 months and was therefore analyzable for the secondary endpoint TLR / restenosis ≤12 months
[9] Exclusion criteria met (PTA <4mm)

Supplementary Figure 2.1 and 2.2. Kaplan-Meier Analysis for Freedom from Target Lesion Revascularization (TLR) at 12 Months

Supplementary Figure 3.1 and 3.2. Kaplan-Meier Analysis for Primary Patency at 12 Months

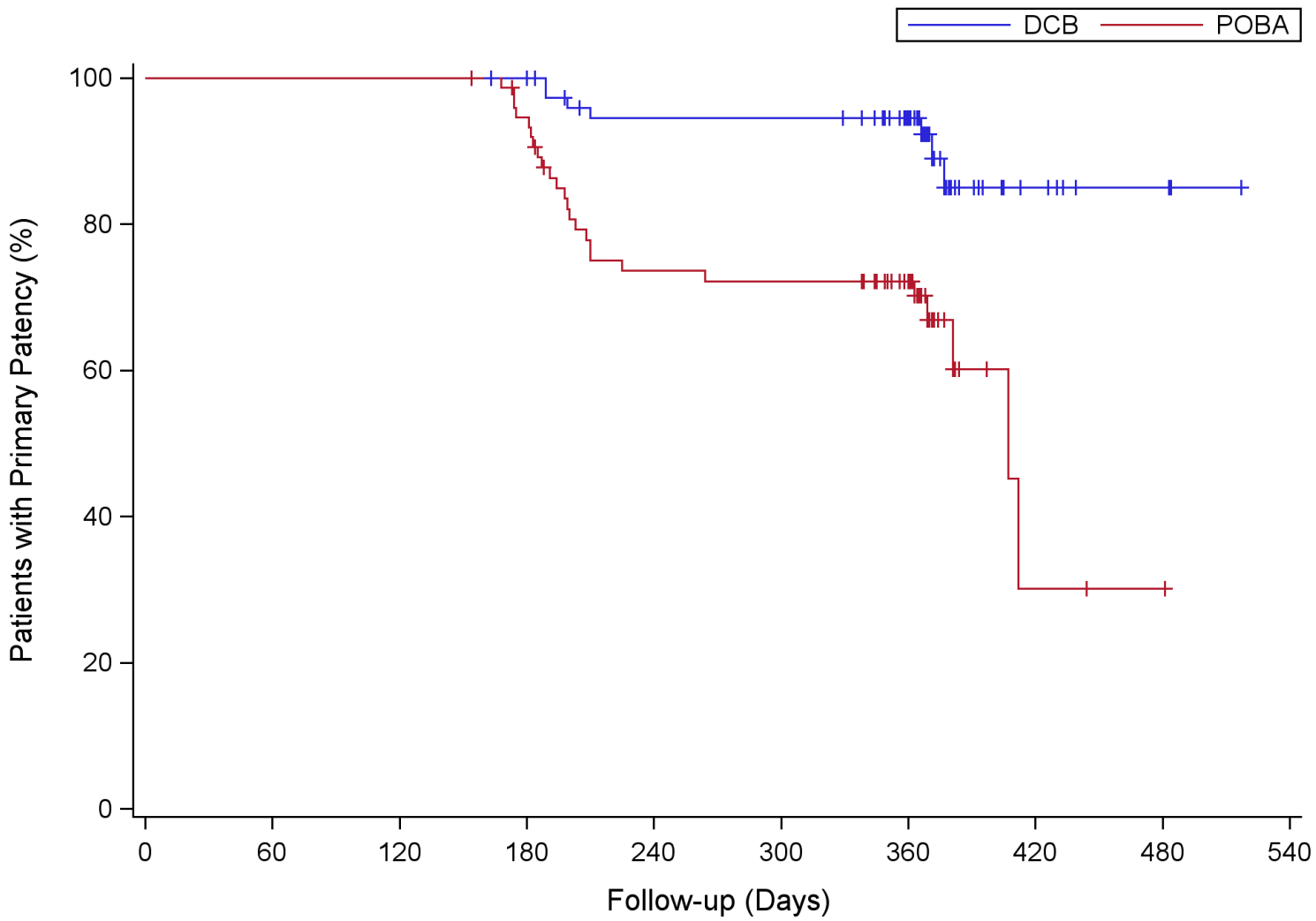
Supplementary Figure 1. Patient Flow Diagram according to CONSORT 2010 Statement



Supplementary Figure 2. Kaplan-Meier Analysis for Freedom from Target Lesion Revascularization (TLR) at 12 Months

	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: $p<0.001$).

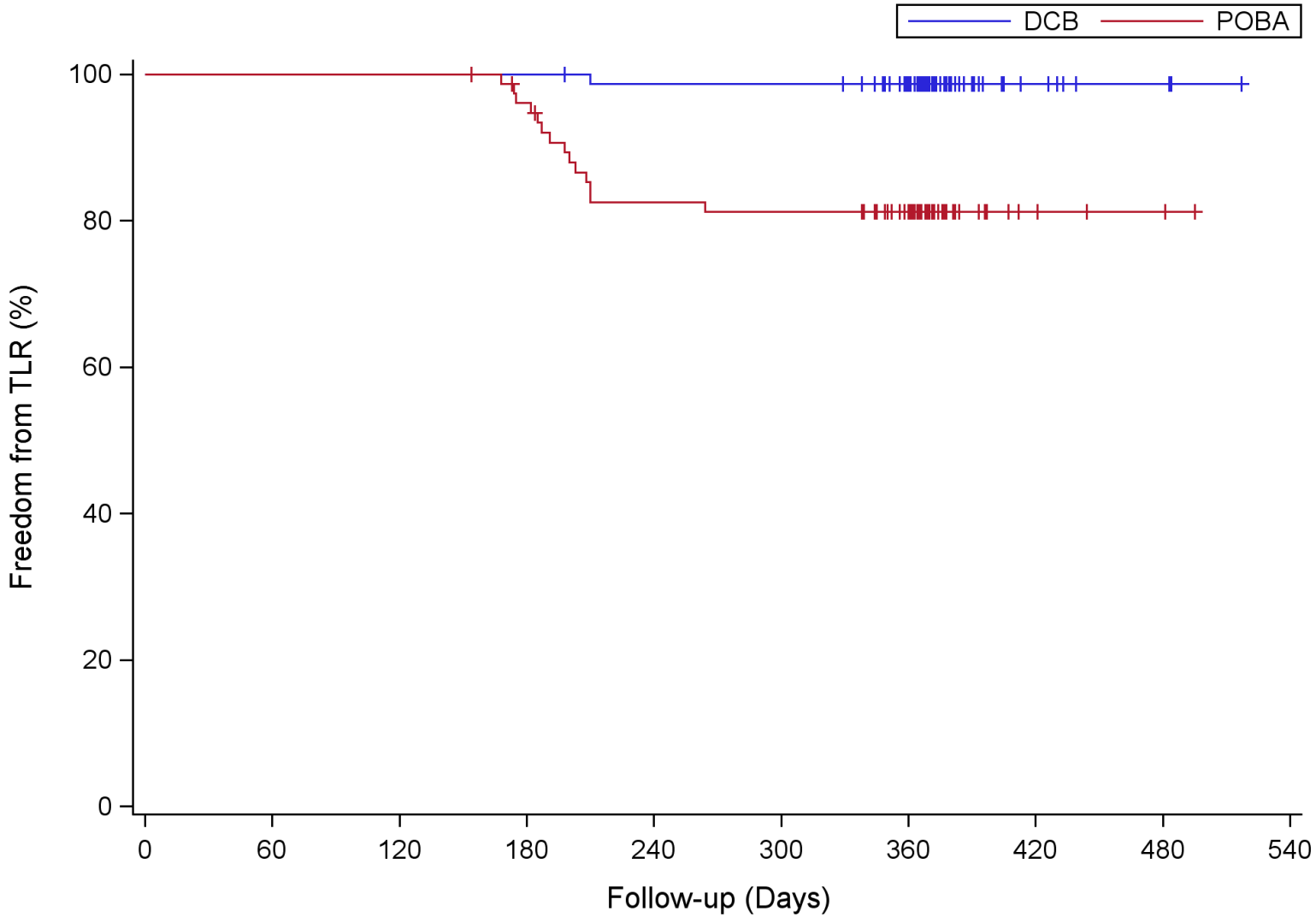


DCB	77	77	77	76	68	68	58	7	3	0
POBA	76	76	76	70	52	51	42	2	1	0

Supplementary Figure 3. Kaplan-Meier Analysis for Primary Patency at 12 Months

	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: $p<0.001$).



DCB	77	77	77	77	75	75	64	7	3	0
POBA	78	78	78	73	61	60	51	4	2	0