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The Mid-Term Clinical Follow-Up Using Drug-Eluting Balloons on Tibial Artery "De Novo" Lesions in Patients With Critical Limb Ischemia: A Cohort Study

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Abstract

Rationale: Restenosis due to intimal hyperplasia (IH) is a major clinical issue that affects the success of lower limb endovascular surgery. After 1 year, restenosis occurs in 40% to 60% of the treated vessels. The possibility to reduce IH using local antiproliferative drugs, such as taxols, has been the rationale for the clinical applications of drug-eluting stents and drug-eluting balloons (DEBs). The purpose of this study was to evaluate the clinical and instrumental efficacy of DEBs versus simple percutaneous transluminal angioplasty (PTA) in patients affected by chronic limb ischemia (CLI) with tibial artery "de novo" lesions. **Methods:** A retrospective analysis was performed and included all consecutive patients who underwent endovascular treatment for CLI in our centers between January 2011 and March 2013. Inclusion criteria were (1) "de novo" tibial artery stenosis and (2) Rutherford class >4. Lesions were further divided by TransAtlantic Inter-Societal Consensus (TASC) classification into groups A, B, C, and D. **Results:** Between January 2010 and March 2013, a total of 138 patients underwent simple PTA or DEB for CLI, and the groups were clinically and demographically homogenous. We decided to use DEBs in 70 cases. An improvement in the Rutherford Scale in cumulative and single TASC lesions classification was better in the DEB group (74% vs 51%; $P = .024$) at 24 months than in the PTA group. In the DEB group, the increase in ankle–brachial index was significantly higher than in the PTA group ($P = .039$). **Conclusions:** Our experience in addition to the existing literature supports the use of DEB in patients with CLI Rutherford class >3.

Keywords
intimal hyperplasia, drug-eluting balloon, restenosis

Introduction

Restenosis due to intimal hyperplasia (IH) is a major clinical issue that affects the success of lower limb endovascular surgery. After 1 year, restenosis occurs in 40% to 60% of the treated vessels. The possibility to reduce IH using local antiproliferative drugs, such as taxols, has been the rationale for the clinical applications of drug-eluting stents and drug-eluting balloons (DEBs). TransAtlantic Inter-Societal Consensus (TASC) II classification has been recently updated.[1] The intent of this new revision is to provide a complete anatomic lower limb TASC lesion classification, including the infrapopliteal segment, and an updated literature review of new endovascular techniques and practice patterns employed by vascular specialists today.[4] The new infrapopliteal lesion classification incorporates several features that attempt to address the multivessel nature of possible infrapopliteal anatomies.[6,7,12] Occlusive disease in a single tibial artery rarely leads to clinical signs or symptoms. Thus, a clinically significant reduction in distal arterial perfusion requires multivessel disease that can occur from multiple anatomic patterns of arterial occlusions. According to the new TASC II classification,[1] the purpose of this study

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Table 1. Demographic and Clinical Data.

Variables Data	DEB	PTA	*P* Value
Patients (138)	70	68	
Age, years	65.4 ± 9.0	66.1 ± 9.6	.125
Male	37 (75.5%)	35 (71.4%)	.234
CAD	18 (36.7%)	20 (40.8%)	.389
Smoking	36 (73.4%)	38 (77.5%)	.202
Diabetes	12 (24.4%)	11 (22.4%)	.371
Hyperlipidemia	18 (36.7.7%)	16 (32.6%)	.442
Obesity	4 (8.1%)	6 (12.2%)	.312
Reactive C-protein, mg/dL, >9.8 mg/dL	8 (16.3%)	7 (14.2%)	.256
Plasmatic homocysteine >15 μmol/L	11 (22.4%)	12 (24.4%)	.371
Ankle–brachial index (ABI)	0.35 ± 0.18	0.36 ± 0.21	.231
Rutherford classification			Cumulative
4	45	43	.291
5	17	14	
6	8	11	
TASC classification			Cumulative
A	2	2	.451
B	13	14	
C	26	22	
D	8	11	

Abbreviations: CAD, coronary artery disease; DEB, drug-eluting balloon; PTA, percutaneous transluminal angioplasty; TASC, TransAtlantic Inter-Societal Consensus.

was to evaluate the clinical and instrumental efficacy of DEBs versus simple percutaneous transluminal angioplasty (PTA) in patients affected by chronic limb ischemia (CLI) with tibial artery "de novo" lesions.

Methods

Patients

A retrospective analysis was performed, including all consecutive patients who underwent an endovascular treatment for CLI in our centers between January 2011 and March 2013. Inclusion criteria were (1) "de novo" tibial arteries stenosis and (2) Rutherford class >4. Exclusion criteria were as follows: (1) recurrent stenosis; (2) inability to undergo aortography before the procedure; and (3) inability to give informed consent. Lesions were further divided by TASC II classification[1,2] into groups A, B, C, and D. A comparison was made between patients who were treated with paclitaxel DEB and simple balloon angioplasty (PTA). Patient selection was reviewed retrospectively to select patients with similar clinical and demographic data, but with different types of treatment (DEB or PTA), to reduce the bias of a nonrandomized cohort study (Table 1). All patients underwent aortography before the procedure to exclude iliac and femoral "in-flow" lesions and to study all of the tibial and plantar vessels. A written consent was obtained before the intervention for all patients. All bailout stenting and technical failures were considered a bias and were excluded from the analysis.[3] Study medication regimens and schedules were according to local clinical practice with aspirin (100-325 mg/d indefinitely) and clopidogrel or prasugrel loading dose (75 or 300 mg) with maintenance for 1 month. Clinical follow-up and instrumental follow-up were performed 24 months after the procedure.

Table 2. Type of Device.

Device	DEB	PTA
Elutax Aachen resonance	32	
Lutonix Bard	25	
Armada Abbott		38
FoxPlus Abbott		28
ClearPac Clearstream		36

Abbreviations: DEB, drug-eluting balloon; PTA, percutaneous transluminal angioplasty.

Techniques and Devices

An antegrade approach was used in the majority of the interventions. Procedures were performed with a portable imaging fluoroscopic C-arm (OEC 9900 elite; GE Medical Siemens, Milwaukee, Wisconsin) or in a hybrid operating room using an Artis Zeego system (Artis Zeego; Siemens AG, Forchheim, Germany). Iodinated or gadolinium contrast was used, respectively, in patients with normal creatinine or with creatinine level >1.5 mg/dL. Intraoperative anticoagulation was achieved using 100 U/kg heparin, and the activating clotting time was maintained above 250 seconds. A 4F (for Elutax Aachen, FoxPlus Abbott, ClearPAc Clearstream) or 6F (for Lutonix Bard, Armada Abbott) introducer sheath was used with a 0.14-inch guidewire. Catheters for PTA or DEB were selected from a dedicated vascular shelf (Table 2). Predilatation was performed in 100% of the DEB cases. A 1-mm oversizing, after PTA, was considered for DEB diameter. Hence, all patients were primarily treated with PTA after, according to the operator's choice, they did or did not undergo DEB. The interventionist's decision was based on clinical and angiogram findings, his or her experience, cost-effectiveness of the procedure, and final results after POBA.

End Points

All patients were clinically and instrumentally evaluated 24 months after the procedure in a dedicated outpatient study. The primary end point of our study was a significant improvement in Rutherford Scale (IRS). Secondary end points were ankle–brachial index (ABI), the rate of restenosis (RR) measured by color-duplex scanning, mortality, and amputation rate. Finally, we considered the single endovascular tool in terms of clinical and instrumental efficacy. The RR was defined as a peak systolic velocity >2.4 m/s and a circumferential IH with a lumen loss more than 70% detected on ultrasound.[8]

Table 3. Type of Lesions and IRS.

IRS	DEB	PTA	*P* Value
Cumulative	74%	51%	.024
TASC II A lesions	76%	69%	.047
TASC II B lesions	86%	59%	.012
TASC II C lesions	65%	41%	.042
TASC II D lesions	55%	31%	.044

Abbreviations: DEB, drug-eluting balloon; IRS, Rutherford Scale; PTA, percutaneous transluminal angioplasty; TASC, TransAtlantic Inter-Societal Consensus.

Statistical Analysis

Data were collected in a dedicated Office Xcel (Microsoft, Redmond, Washington) file and analyzed using SPSS 21.0 software (IBM, Armonk, New York). Continuous variables with a normal distribution are expressed as the mean ± standard deviation, and categorical variables as frequency and percentage. The study required at least 110 patients to provide ≥80% power to detect an improvement in the Rutherford classification, expressed as the change in the class number between baseline and the 24-month control (calculated for individual patients). Significance between the treatment groups was tested by Cochran-Mantel-Haenszel statistics. Categorical variables (given as number and percentage) were compared by the use of Fisher exact test. Survival and amputation are presented as Kaplan-Meier analysis with Mantel-Cox log-rank test. Differences were considered statistically significant at $P < .05$.

Results

Between January 2010 and March 2013, we treated 138 patients with CLI using simple PTA or DEB; the groups were clinically and demographically homogenous. We decided to perform DEB in 70 cases. Preoperative Rutherford classification showed an equal distribution for both the groups, and the same results were obtained when considering the anatomy of the lesions with TASC II classification[1] (lesion types A, B, C, and D). An antegrade and retrograde approach was used in 83.3% (110 cases) and 16.7% (28 cases), respectively.

Primary End Point

Rutherford Scale in cumulative and single TASC lesion classification was superior in the DEB group (74% vs 51%; $P = .024$) at 24 months than in the PTA group. The TASC II B lesions showed further superior results with a significant improvement in IRS with respect to the PTA group (Table 3). When matching the IRS in both groups, a longer lesion was associated with worst long-term results, even if the DEB group had a superior significant improvement in IRS. Irrespective of the type of treatment, TASC II type C and D lesions showed the worst results when compared to types A and B.

Table 4. ABI and RR in the Two Groups.

	DEB	PTA	*P* Value
ABI cumulative	0.64 ± 0.35	0.52 ± 0.22	.039
ABI TASC II A	0.65 ± 0.19	0.58 ± 0.15	.078
ABI TASC II B	0.71 ± 0.23	0.48 ± 0.12	.025
ABI TASC II C	0.49 ± 0.15	0.43 ± 0.21	.041
ABI TASC II D	0.40 ± 0.15	0.39 ± 0.21	.044
RR cumulative (psv >2.4 m/s + stenosis >70%)	19%	32%	.028
RR TASC II A	16%	19%	.068
RR TASC II B	15%	24%	.043
RR TASC II C	21%	38%	.034
RR TASC II D	38%	62%	.012

Abbreviations: ABI, ankle–brachial index; DEB, drug-eluting balloon; PTA, percutaneous transluminal angioplasty; RR, rate of restenosis; TASC, TransAtlantic Inter-Societal Consensus; psv, peak of systolic velocity.

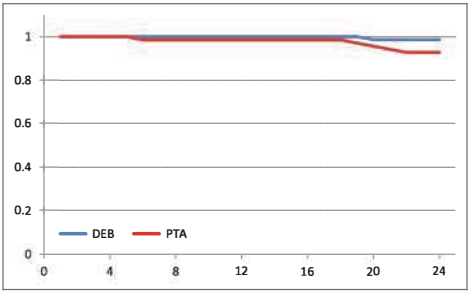

Figure 1. Cumulative Survival Rate.

Secondary End Point

In the DEB group, the increase in ABI was significantly higher than in the PTA group ($P = .039$; Table 4). For patients with TASC B lesions, DEB was most beneficial, resulting in a significant ABI increase and a lower RR (TASC B with DEB: from 0.35 ± 018 to 0.71 ± 0.23; TASC B with PTA: from 0.36 ± 0.21 to 0.48 ± 0.12; $P = .025$). In patients with TASC C and D lesions, the ABI improved less and the RRs were higher compared to the patients with TASC A and B lesions. Both the cumulative survival rate and the amputation rate showed significantly superior results for the DEB group (Figures 1 and 2). Major amputations were only performed in patients who were IRS 5 and 6. All analyzed variables were similar between the PTA and the DEB groups.

Discussion

In practical terms, although the level of evidence is low, the initial revascularization strategy for femoropopliteal disease is commonly an endovascular approach.[5,12,15] This is supported by a recent meta-analysis of the published literature regarding

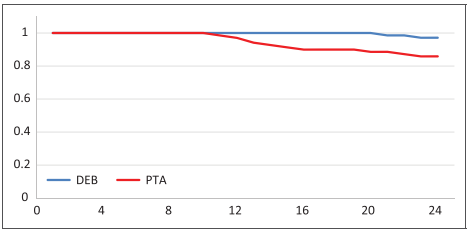

Figure 2. Amputation Rate.

endovascular versus surgical revascularization for femoropopliteal disease.[9] We investigated the long-term clinical results in patients with critical limb ischemia treated with PTA or DEB. Demographic data (Table 1) showed a homogenous distribution of the patients in the 2 groups, which reduced the bias resulting from a lack of randomization. Chronic limb ischemia remains a remarkable risk factor for cardiovascular events and amputation 1 year after the onset of symptoms. This aggressive pathology has been deeply investigated,[2,10] and there is a common agreement that CLI requires urgent and complete treatment. As reported by the TASC II and American Heart Association guidelines, endovascular therapy is the preferred treatment for type A and B lesions, whereas surgery is the preferred treatment for low-risk patients with type C and D lesions.[2,10] The patient's comorbidities, fully informed patient preference, and the local operator's long-term success rate must be considered when making treatment recommendations for type C and D lesions. According to this recommendation, we treated 98 patients with "de novo" lesions for CLI. Type C and D lesions were considered for endovascular therapy according to our endovascular experience, and all patients in the type C and D group were successfully treated with angioplasty. There has been an evolution of newer technologies, specifically patency-enhancing drug coating for balloons and stents. There is growing evidence from randomized trials that supports the use of DEB.[11,13,16,17] These trials underline the long-term benefit of lowering restenosis both for quality of life[18,19] and for life expentancy.[20] In our experience, we focused on clinical improvement using the IRS. Restoring an effective blood flow in the pedal and tibial vessels permits lesions to heal, relieves pain, and reduces the release of inflammatory cytokines.[21-23] The efficacy of endovascular therapy is correlated with vessel outflow, meaning there is a strict correlation between the number of patent vessels and the final outcome.[24] In our experience, we have used Lutonix Bard and Elutax Aachen as DEB. Lutonix has been supported by clinical trials,[10] and a second trial of Levant 2 is still ongoing to validate this DEB. No randomized trial has been considered for Elutax, and the literature lacks data[25] concerning the use of this DEB for tibial vessels. Nonetheless, we decided to use this device based on the good results in other experiences.[1,25] The 6-month results of Elutax SV showed this DEB to be comparable to and as effective as other DEBs that have undergone clinical trials. Our preliminary experiences reported that the ABI improved from 0.49 to 0.89, and the Rutherford stage decreased from 3 to 1. Another "pro" for the use of this DEB is the low-profile catheter, which always permits the use of a 4F introducer sheath with all of the diameters in peripheral vessels. Patients with reduced tibial outflow (3-vessel runoff) showed a significantly reduced patency relative to patients with 3-vessel runoff.[17,24] In our experience, we noted that reduced tibial outflow, such as in C type lesions, might be a causative factor in the reduced primary patency of percutaneous interventions; it is also possible that it is simply a marker for increased disease severity. Those with more severe or extensive disease might be more likely to represent with recurrent symptoms, thus leading to more frequent documentation of failure in this group relative to those with type A and B lesions. Drug-eluting balloons were shown to be more effective in controlling the worsening of IRS with significant cumulative results. Restenosis was significantly controlled in the DEB group, and an increased ABI was noted. The ABI provides key information on long-term prognosis, with an ABI $\leq$0.90 associated with a 3- to 6-fold increased risk of cardiovascular mortality. The benefits of a long-term improvement in ABI are evidenced by the better results in the free-from-amputation and survival rates as shown by Kaplan-Meier analysis (Figures 1 and 2).[7,14,15] The rationale of DEB has been already described,[11,13,18] but it is important to underline that the coated balloon releases most of the drug immediately during the first inflation when there is short contact with the vessel wall for 60 seconds. The duration of inhibition of cell proliferation exceeds the time that cells are actually exposed to the drug. In some studies,[11,18] only approximately 6.4% $\pm$ 2.9% of the original paclitaxel dose was found to be extractable from the surface of the balloons used in our trial. Although animal studies indicate that as much as 70% to 80% of the drug dose might be lost in the bloodstream,[25] the remaining dose and duration of drug exposure seem to be sufficient to prevent neointimal proliferation.

Conclusion

Although this study has a limitation due to the lack of randomization, we observed superior results with DEB. The cumulative free-from-amputation rate shows the benefit of using DEB. All patients who required an amputation belonged to Rutherford class 5 and 6. We showed that the DEB group obtained a better IRS, leading to a lower risk of amputation for these patients. Further research is needed before we can consider the DEB as the gold standard therapy for CLI. However, our experience, in addition to the existing literature, supports the use of DEB in patients with CLI Rutherford class >4. With the reduced need for a stent and considering the statement "leaving nothing behind", DEB can be considered a safe treatment of choice in CLI.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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CIRSE

Drug-Coated Balloon Angioplasty of Infrapopliteal Lesions in Patients with Critical Limb Ischaemia: 1-Year Results of the APOLLO Trial

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Abstract

Purpose This study intended to assess effectiveness and safety of the drug-coated balloon (DCB) angioplasty of infrapopliteal atherosclerotic lesions in patients with critical limb ischaemia (CLI) in a real-world setting.

Methods Consecutive patients with critical limb ischaemia who underwent infrapopliteal drug-coated balloon angioplasty with the ELUTAX SV DCB were enrolled into the prospective, multicentre, single-arm observational registry. Primary outcome was clinical improvement at 6 and 12 months. Secondary outcomes were change in quality of life, primary patency, freedom from repeat revascularisation, and amputation-free survival at 6 and 12 months.

Results A total of 164 patients (74.7 ± 9.2 years) with CLI were included at nine German sites between November 2015 and September 2017. The majority (79.9%) of patients had diabetes mellitus, 57.3% had renal insufficiency, and 35.3% had coronary artery disease. Mean lesion length was 71.2 ± 76.5 mm. The Rutherford category improved by 3.0 ± 2.0 ($p < 0.0001$) within 12 months, resulting in a clinical improvement by at least one Rutherford category in 80.2% of the patients. Walking impairment questionnaire score, European Quality of Life index, and patient-reported pain improved significantly from baseline to 6 and 12 months. Primary patency was 68.5%, freedom from target lesion revascularisation 90.6%, and amputation-free survival 83.5% at 12 months.

Conclusion Infrapopliteal drug-coated balloon angioplasty with the ELUTAX SV DCB in patients with critical limb ischaemia was efficacious and safe over the medium term. The study is registered with Clinical.Trials.gov (Identifier: NCT02539940).

Keywords Below the knee · Critical limb ischaemia · Drug-coated balloon angioplasty · Drug-eluting balloon · Infrapopliteal · Paclitaxel · Peripheral artery disease

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Introduction

Patients with critical limb ischaemia (CLI) have a risk of about 50% of major amputation or death within the first year from presentation [1, 2]. Even after major amputation, almost half of those aged 70 and older probably will die in the following year [3].

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CLI is usually a multilevel artery disease, mostly involving the infrapopliteal arteries. The majority of CLI patients concomitantly suffer from diabetes and other cardiovascular diseases, unfavourably reinforcing each other. Guidelines require infrapopliteal revascularisation for limb salvage whenever possible, and endovascular therapy should be considered in patients with stenosis, short occlusions, or at high risk for open surgery [4]. However, infrapopliteal artery disease is characterised by small vessels, particularly prone to elastic recoil [5], low flow, and a diffuse pattern of lesions, frequently accompanied by medial calcification. The incidence of restenosis of about 40–60% at 1 year after standard balloon angioplasty (POBA) is disappointing [6, 7]. Even bare-metal stent implantation does not make a substantial improvement [8]. In short lesions, drug-eluting stents were found to be superior to POBA or bare-metal stents, but did not decrease mortality.

In medium-length lesions, drug-coated balloons (DCBs) tended to prevent restenosis and target lesion revascularisation but did not improve the amputation-free survival [9]. However, advanced technology of DCBs could have improved efficacy and safety. This study aimed to assess the effectiveness of the ELUTAX SV paclitaxel-coated balloon in a real-world setting over a period of 12 months.

Methods

Study Design and Setting

The APOLLO study is a prospective, multicentre, observational, investigator-initiated trial. Recruitment took place over a period of 23 months at nine German sites. Clinical evaluation, duplex ultrasonography (DUS), assessment of quality of life (QoL) measures including Walking Impairment Questionnaire (WIQ) score [10], European Quality of Life-5 Dimensions (EQ-5D) index [11, 12], and patient-reported pain, as well as determination of the ankle–brachial index (ABI) were conducted at baseline and at 6 and 12 months after revascularisation. All target limb-related adverse events, device-related adverse events, adverse cardiovascular events, and all severe adverse events had to be reported by the investigators. The study is registered with ClinicalTrials.gov (Identifier: NCT02539940).

Patients

Patients who were at least 18 years of age and were scheduled for DCB angioplasty with the ELUTAX SV DCB for the treatment of below-the-knee artery stenosis of $\geq$ 70% or occlusion and suffered from critical limb ischaemia (Rutherford category 4–6 or CLI confirmed by photoplethysmography) were eligible. Inclusion was independent of a successful guide wire passage and lesion preparation. All patients provided written informed consent. The inflow artery had to be patent; however, its treatment prior to the index procedure was permitted. Per definition, a target vessel reconstitutes at or above the ankle. Key exclusion criteria were planned major target limb amputation, acute limb ischaemia, or application of DCB other than ELUTAX SV in a target limb artery.

Study Device and Procedure

The semi-compliant ELUTAX SV drug-coated balloon (Aachen Resonance, Aachen, Germany) is coated with a matrix, consisting of two layers of paclitaxel and a seal layer of dextran. Paclitaxel is supposed to inhibit neointimal proliferation and thus to prevent restenosis. The inner paclitaxel layer has an amorphous and the outer layer a crystalline structure. Paclitaxel dose density is 2.2 $\mu g/mm^2$. Dextran protects the paclitaxel layers from abrasion during introduction of the catheter, minimises the paclitaxel wash off by providing a continuous drug transfer to the vessel wall, and supports platelet inhibition. The DCB had to be used according to the manufacturer's instruction and the standard clinical practice of the participating centres. Inflation time recommended by manufacturer is 30 s. Predilation was not mandatory. However, pre-dilation as well as prolonged inflation, bailout stenting, or post-dilation in case of significant residual stenosis or flow-limiting dissection were left to investigator's discretion.

Concomitant study medication had to comply with current guidelines. To prevent systematic vascular events and limb events, long-term treatment with aspirin and, in case of bailout stenting, dual antiplatelet therapy with aspirin and clopidogrel for at least one month was recommended.

Study Outcome Measurements

Primary effectiveness outcome was clinical improvement based on the change in Rutherford category from baseline to 6 and 12 months. Secondary effectiveness outcome was change in QoL, incidence of primary patency, freedom from target lesion revascularisation (TLR), and freedom from target vessel revascularisation (TVR) at 6 and 12 months. QoL was determined by means of WIQ score, EQ-5D index, and patient-reported pain on a scale from zero to ten. Primary patency was given if DUS examination showed sufficient flow upon investigator's assessment without the need of prior TLR. Safety endpoints were freedom from minor amputation, freedom from major amputation, amputation-free survival, and all-cause mortality at 6 and 12 months. Minor amputation was defined as

transmetatarsal or distal amputation and major amputation as above transmetatarsal amputation.

Statistical Analysis

Continuous variables are reported as mean ± standard deviation (SD) and categorical variables as counts and percentages. Differences between variables were assessed with the two-sided sign test or the Wilcoxon sign-rank test. Kaplan–Meier analysis was performed to estimate freedom from TLR, TVR, amputation, or death, as well as primary patency. Results are presented as parameter estimates and their corresponding 95% confidence intervals (CIs). Logistic regression was used to assess predictors of clinical improvement without the need of TLR at 6 months and the composite of death and any amputation at 12 months. Established candidate variables were pre-screened based on univariable analysis with a P value cut-off of 0.25 based on Wald test from logistic regression. Subsequently, variable selection for multivariable modelling was continued by stepwise backward regression with an entry and removal threshold P value of 0.1. A two-sided value of $p < 0.05$ indicated statistical significance. Statistical analysis was performed using SPSS Statistics (version 25.0. IBM, Armonk, NY, USA).

Results

Study Population and Treatment

From November 2015 to September 2017, 164 consecutive CLI patients with 248 infrapopliteal artery lesions were enrolled at nine German centres. All but one underwent DCB angioplasty with the ELUTAX SV DCB. About 80% of the patients had diabetes mellitus and 44% were obese. Fifty-seven per cent of patients had renal insufficiency (Table 1). Mean lesion length was 71.2 ± 76.5 mm. Chronic occlusion and severe calcification were present in 43% and 27% of patients, respectively (Table 2). Inflow intervention was conducted in 31% and pre-dilation in 68% of patients (Table 3). Completion of DUS follow-up was 55.5% (91 of 164 patients) at 6 months and 47.0% (77 of 164 patients) at 12 months.

Table 1 Patient demographics and clinical characteristics (n = 164[a])

Age, years	74.7 ± 9.2
Sex	
Female	55 (33.5)
Male	109 (66.5)
Diabetes mellitus	131 (79.9)
Insulin dependent	82/130 (63.1)
Hyperlipidemia	88/159 (55.3)
Body mass index	29.2 ± 5.4
> 30	71/162 (43.8)
Hypertension	148 (90.2)
Smoking	66/146 (45.2)
Current	17/146 (11.6)
Coronary artery disease	55/156 (35.3)
Heart failure	41/160 (25.6)
Renal insufficiency	94 (57.3)
Cerebrovascular disease	29/154 (18.8)
Stroke	24/154 (15.6)
ABI (n = 83)	0.91 ± 0.46
< 0.5	13/83 (15.7)
≥ 1.3	22/83 (26.5)
Rutherford category	
3—severe claudication	7[b] (4.3)
4—ischaemic rest pain	29 (17.7)
5—minor tissue loss	109 (66.5)
6—major tissue loss	19 (11.6)
Previous amputation	42 (25.6)
Major amputation[c]	7/164 (4.3)
Medication	
Statin	100/162 (61.7)
Platelet inhibitor	64/163 (39.3)

Categorical values are presented as counts (percentages); continuous values are presented as mean ± standard deviation

[a]One patient did not receive the study device. No information about the kind of treatment is available

[b]Photoplethysmography indicated critical limb ischaemia

[c]Above transmetatarsal

Primary Effectiveness Outcome

Rutherford category improved by 2.5 ± 2.0 at 6 months ($p < 0.0001$) and 3.0 ± 2.0 at 12 months ($p < 0.0001$) (Fig. 1A). Clinical improvement by at least one Rutherford category was observed in 74.0% (94 of 127 patients) at 6 months (Fig. 1B) and in 80.2% (85 of 106 patients) at 12 months (Fig. 1C). Excluding patients who did not receive the study device or had peripheral artery diseases (PAD) of Rutherford category 3 at baseline, the 12-month incidence of clinical improvement was 79.0%.

Secondary Effectiveness Outcomes

The WIQ score improved by 7.1 ± 27.9% ($p = 0.0119$) of the maximum score within 6 months and by 10.7 ± 32.4% ($p = 0.0035$) from baseline to 12 months (Fig. 2A). The EQ-5D index improved by 0.08 ± 0.30 ($p = 0.0013$) within 6 months and by 0.07 ± 0.33 ($p = 0.0003$) over a period of 12 months (Fig. 2B). Patient-reported pain

Table 2 Lesion characteristics[a] (n = 248)

Lesion length, mm	71.2 ± 76.5
Total lesion length, mm	107.2 ± 92.6
Diameter stenosis, %	89.4 ± 10.5
Chronic total occlusion	
Artery based	105/273 (38.5)
Patient based	70/164 (42.7)
Severe calcification[b]	22/83 (26.5)
TASC classification[c]	
TASC A	48/162 (29.6)
TASC B	68/162 (42.0)
TASC C	39/162 (24.1)
TASC D	7/162 (4.3)
Affected arteries	273
Popliteal artery	29 (10.6)
Tibioperoneal trunk	42 (15.4)
Anterior tibial artery	100 (36.6)
Peroneal artery	55 (20.1)
Posterior tibial artery	47 (17.2)
Number of crural arteries with runoff to the foot	
0	27/155 (17.4)
1	73/155 (47.1)
2	43/155 (27.7)
3	12/155 (7.7)

Categorical values are presented as counts (percentages); continuous data are presented as mean ± standard deviation

[a]Adjacent lesions without angiographic evidence of healthy segments 20 mm or greater were considered as single lesion

[b]Assessed by visual estimate or medial calcification indicated by ABI ≥ 1.3

[c]Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC) classification of infrapopliteal lesions

Table 3 Procedure characteristics

Inflow intervention	51/164 (31.1)
SFA	25/51 (49.0)
P1	10/51 (19.6)
P2	11/51 (21.6)
P3	5/51 (9.8)
Pre-dilation (patient-based)	110/163 (67.5)
Pre-dilation (DCB-based)	159/286 (55.6)
Balloon length, mm	88.5 ± 46.6
Nominal diameter, mm	2.7 ± 3.3
Maximum pressure, atm	10.6 ± 3.3
Pre-dilation time, sec	48.5 ± 41.8
Drug-coated balloon[a]	286
DCB/lesion	1.15
Balloon length, mm	86.4 ± 43.8
Nominal diameter, mm	2.9 ± 2.2
Maximum pressure, atm	8.5 ± 2.0
Inflation time, sec	114.4 ± 34.7
Post-dilation	18/163 (11.0)
Scoring balloon	2 (1.2)
Balloon length, mm	63.1 ± 47.1
Nominal diameter, mm	5.0 ± 8.8
Maximum pressure, atm	10.0 ± 3.3
Inflation time, sec	82.8 ± 59.7
Bailout stenting[b]	5/163 (3.1)
Medication at 6 months	
Statin	98/137 (71.5)
Platelet inhibitor	50/136 (36.8)
Medication at 12 months	
Statin	89/119 (74.8)
Platelet inhibitor	33/116 (28.4)

Categorical values are presented as counts (percentages); continuous values are presented as mean ± standard deviation

DCB drug-coated balloon; *SFA* superficial femoral artery; *P1* proximal popliteal artery segment; *P2* mid-popliteal artery segment; *P3* distal popliteal artery segment

[a]One of 164 patients did not receive a drug-coated balloon

[b]Four lesions were stented due to dissection and one lesion due to residual stenosis > 30%

decreased by 1.2 ± 2.1 pain scale units ($p < 0.0001$) within 6 months and by 1.0 ± 2.8 units ($p = 0.003$) within 12 months (Fig. 2C). ABI increased significantly from baseline to 6 months (1.1 ± 0.4, $p = 0.0009$) and from baseline to 12 months (1.2 ± 0.4, $p = 0.0047$).

Freedom from TLR was achieved in 97.1% (standard error [SE] 1.4%) and 90.6% (SE 2.6%) of patients at 6 and 12 months, respectively (Fig. 3A). Freedom from TVR (including TLR) was achieved in 94.9% (SE 1.9%) and 88.4% (SE 2.8%) at 6 and 12 months, respectively (Fig. 3B). Patency at discharge was achieved in 97.8% (176 of 180 lesions). Cumulative incidence of patient-based primary patency was 91.6% (SE 3.0%) and 68.5% (SE 5.2%) at 6 and 12 months, respectively (Fig. 3C). Post hoc multivariable analysis revealed male sex as independent risk factor for worse clinical response at 6 months (odds ratio [OR] 0.17, $p = 0.010$). Inversely, statin medication at 6 months tended to be associated with clinical improvement (OR 3.08, $p = 0.053$) (Fig. 4).

Safety Outcomes

Freedom from minor amputation was 82.5% (95% CI: 75.1–87.9) at 6 months and 77.8% (95% CI: 69.4–84.1) at 12 months. Limb salvage was 97.1% (SE 1.4%) and 95.4% (SE 1.9%) at 6 and 12 months, respectively (Fig. 5A). Survival was 94.5% (SE 1.8%) and 87.8% (SE 2.7%) at 6

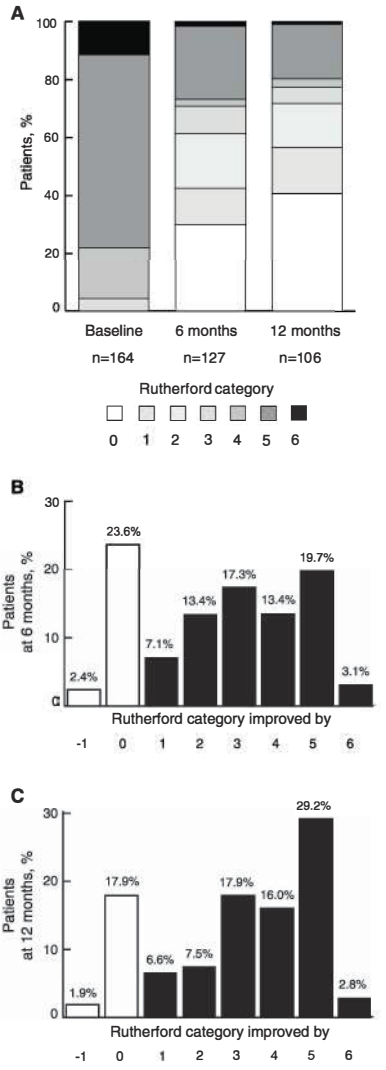

Fig. 1 Distribution of Rutherford categories at baseline and follow-ups (**A**), and clinical improvement from baseline to 6 months (**B**) and to 12 months (**C**)

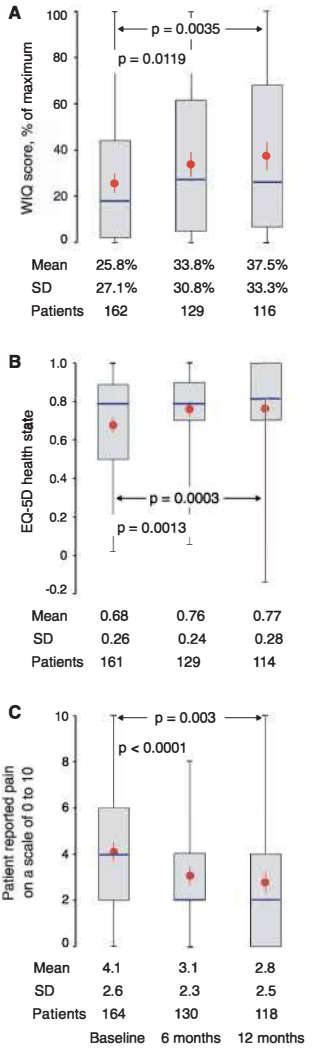

Fig. 2 Quality of life at baseline and at 6- and 12-month follow-ups expressed in Walking Impairment Questionnaire score (**A**), European Quality of Life-5 Dimensions score (**B**), and patient-reported pain (**C**). Box plots indicate median and interquartile range. Whiskers end with the lowest and highest data point. Red dots represent means with their corresponding 95% confidence interval. *SD* standard deviation, *WIQ* Walking Impairment Questionnaire, *EQ-5D* European Quality of Life-5 Dimensions score

and 12 months, respectively (Fig. 5B), and major amputation-free survival was 90.7% (SE 2.3%) and 83.8% (SE 3.0%) at 6 and 12 months, respectively (Fig. 5C).

A total of twenty patients (15.9%) died within one year of the intervention. Five patients died from heart failure, four from sepsis, two each from stroke, renal failure, pneumonia, or haemorrhage, and one each from myocardial infarction or arrhythmia. One death remained unexplained (Table 4). Without consideration of patients who did not receive the study device or had PAD of Rutherford category 3 at baseline, 12-month incidence of restenosis was 25.7%, of repeat revascularisation 11.3%, of minor or major amputations 26.5% and 5.3%, respectively, and of mortality 15.8%.

Post hoc logistic regression revealed a higher BMI and inflow vessel intervention as independent predictors for a reduced risk of death or amputation at 12 months (OR 0.88 [$p = 0.007$] and OR 0.37 [$p = 0.040$], respectively). Renal insufficiency tended to increase the risk of death or amputation (OR 2.2, $p = 0.078$) (Fig. 6).

Discussion

After angioplasty with the ELUT AXSV DCB, the majority of patients improved clinically. A significant share reported on an improved quality of life that maintained throughout the following year. Repeat revascularisation was needed in about one of eight patients, and minor amputation in one of four. Eighty-four per cent of the patients survived the first year after revascularisation without major amputation.

Clinical Improvement

Clinical improvement and quality of life (QoL) are rarely reported in trials on CLI because limb salvage is paramount. Although QoL is highly subjective, it is a useful complement of clinical effectiveness outcomes. This study found a sustained improvement of QoL in a population with advanced disease and multiple comorbidities. Increased walking ability and activity might have contributed to patency and collateralisation. The favourable impact of statin on clinical improvement is supported by previous results from the CRITISCH registry [13] and a large-scale Swedish registry [14]. Therefore, preventive pharmacological treatment pursuant to guidelines [4] should be strongly recommended. The former registry additionally confirms the worse treatment response in men.

Patency and Repeat Revascularisation

Meta-analysis on three randomised trials that compared infrapopliteal DCB angioplasty with POBA in CLI patients (DEBATE-BTK [15], IN.PACT DEEP [16], BIOLUX P-II [17]) reported on a non-significant trend in favour of DCB angioplasty regarding restenosis [7, 9]. However, heterogeneity was significant. One-year incidence of restenosis after POBA varied between 47 and 74% [6, 9, 15]. In contrast, incidence of restenosis after DCB is reported with 30% and thus is in line with the findings from this study. This advantage is probably due to inhibition of neointimal proliferation by paclitaxel.

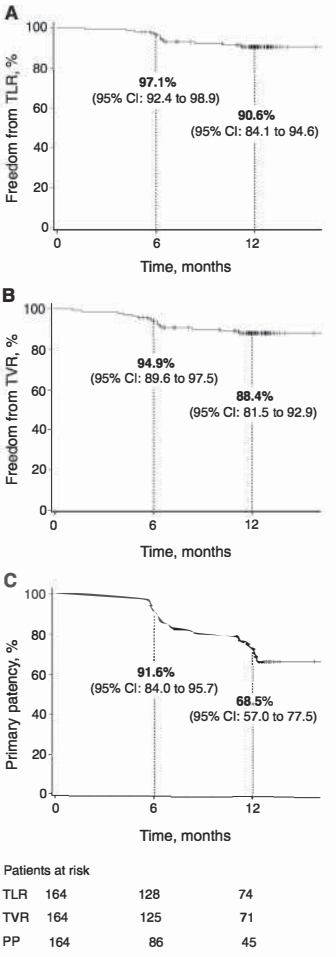

Fig. 3 Kaplan–Meier survival estimates for freedom from target lesion revascularisation (**A**), freedom from target vessel revascularisation (**B**), and primary patency (**C**). *CI* confidence interval, *PP* primary patency, *TLR* target lesion revascularisation, *TVR* target vessel revascularisation

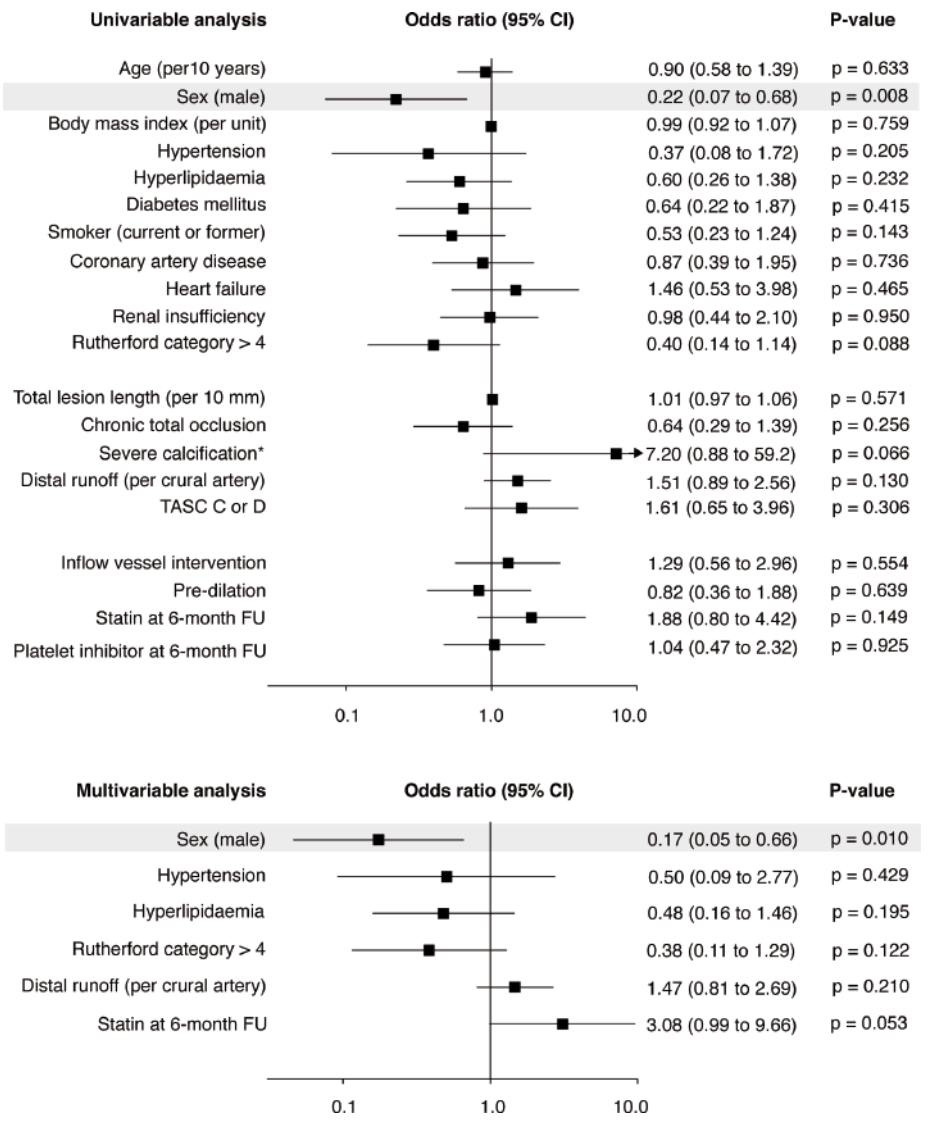

Fig. 4 Probability of improvement by at least one Rutherford category at 6 months without the need of target lesion revascularisation. *Not included into multivariable regression due to numerous missing data. *CI* confidence interval, *FU* follow-up, *TASC* inter-society consensus for the management of peripheral arterial disease classification of infrapopliteal lesions

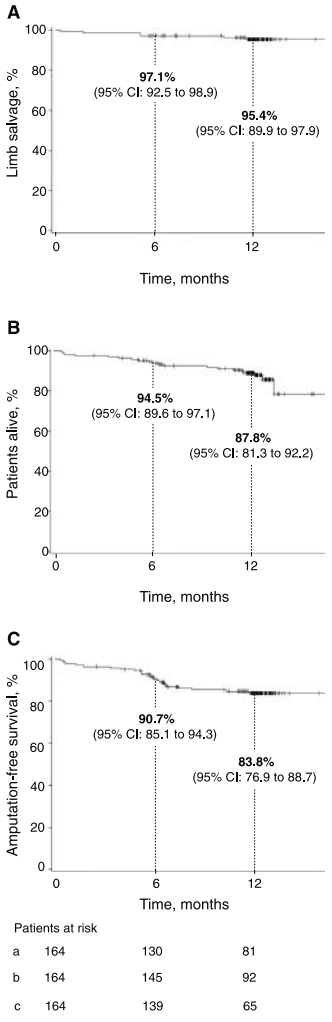

Fig. 5 Kaplan–Meier estimates for limb salvage (**A**), survival (**B**), and major amputation-free survival (**C**). *CI* confidence interval

In this study, TLR was less frequently conducted than in previous DCB studies. It might be assumed that in shorter, less complex lesions, restenosis more rarely needs to be revascularised. The above-mentioned meta-analysis revealed a difference to POBA that was just below statistical significance [9]. From this, one could conclude that with new-generation DCB, there might be a significant advantage over POBA. However, a meta-analysis of 27 trials on infrapopliteal POBA revealed a somewhat lower incidence of TLR with significant heterogeneity [6]. Thus, superiority of DCB angioplasty over POBA remains to be proven by future randomised trials.

Table 4 Incidence of safety outcomes

	At 6 months	At 12 months
All-cause mortality[a]	10/141 (7.1)	20/126 (15.9)
Major target limb amputation[b]	4/137 (2.9)	6/119 (5.0)
Minor target limb amputation[c]	26/137 (19.0)	30/119 (25.2)
Repeat revascularisation[d]	9/137 (6.6)	13/119 (10.9)
Restenosis[e]	10/91 (11.0)	18/77 (23.4)
Thrombectomy	1/163 (0.6)	1/163 (0.6)
Atherectomy	0/162 (0.0)	0/162 (0.0)

Values are given as counts (percentages)

[a]Five patients died from heart failure, four patients from sepsis, two patients each from stroke, renal failure, pneumonia, or haemorrhage, and one patient each from myocardial infarction, or arrhythmia. On death remained unexplained

[b]Above transmetatarsal

[c]Transmetatarsal or distal

[d]Target vessel revascularisation including target lesion revascularisation

[e]No sufficient flow through the target lesion by duplex ultrasonography

Amputation and All-Cause Mortality

Limb salvage is the primary objective of revascularisation in CLI patients. In this study, considerable fewer patients underwent major amputation than during previous studies on infrapopliteal POBA [6] and DCB angioplasty [9].

Incidence of all-cause mortality in this study was slightly higher compared to previous meta-analysis on DCB [9, 18], similar to POBA [6], and lower compared to any kind of CLI revascularisation [19]. Except for renal insufficiency, every single comorbidity statistically was not associated with death or amputation. However, CLI patients frequently suffer from multiple comorbidities which may adversely affect one another and may enhance disease progression. Advanced age, physical constitution, and cardiovascular medication probably carry weight. Finally, mortality and causes of death of patients who withdrew or were lost to follow-up remain unknown.

Shammas et al. [20] reported on a threefold increased risk of major amputation and a 14-fold increased risk of death in diabetic compared to non-diabetic CLI patients. In addition, the above-mentioned Swedish registry supports the finding on an increased risk of death or amputation in

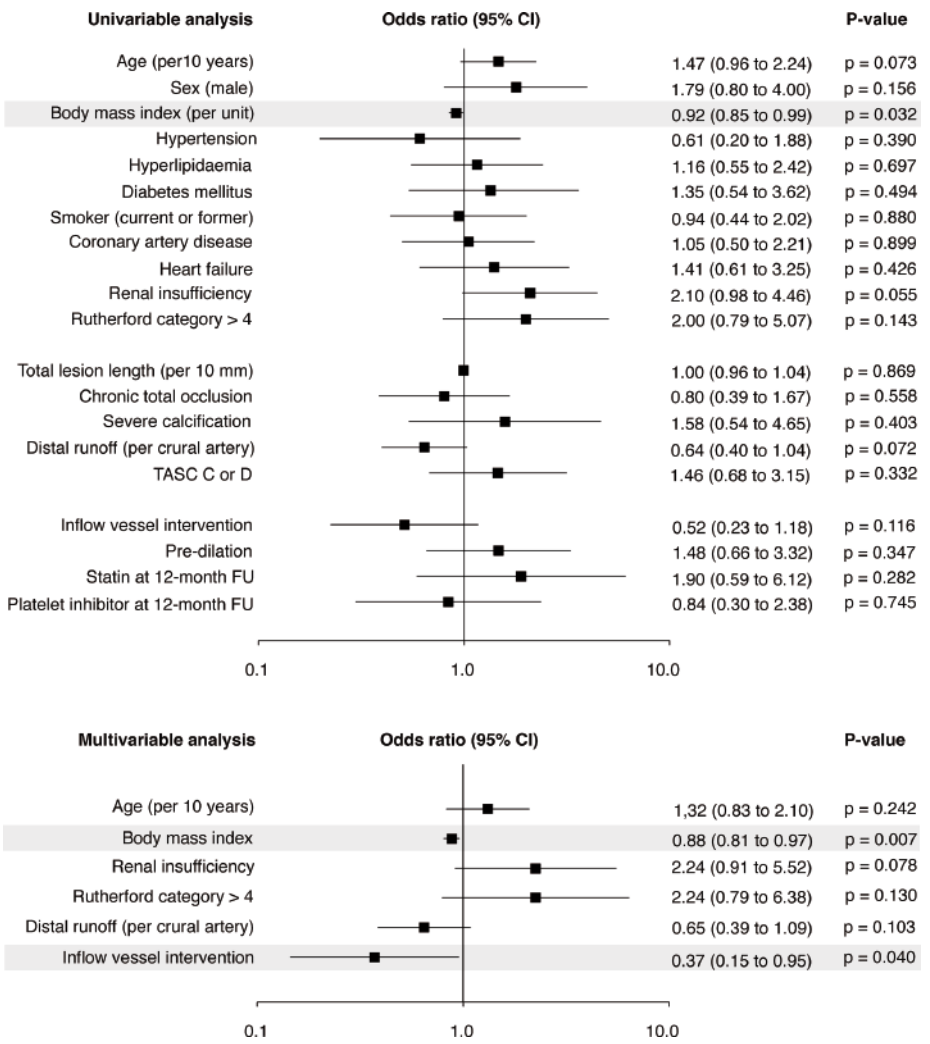

Fig. 6 Probability of death or any amputation at 12 months. *CI* confidence interval, *FU* follow-up, *TASC* inter-society consensus for the management of peripheral arterial disease classification of infrapopliteal lesions

patients with renal insufficiency [14]. In the light of this, mortality in this study was consistent.

A higher BMI was associated with less mortality or amputation. Accordingly, Moussa et al. [21] found a worse in-hospital mortality of underweight compared to normal-BMI patients with severe peripheral artery disease. This might suggest that in CLI patients, downward deviations from the normal BMI may be indicative for poor health. Inflow intervention did not considerably increase clinical improvement but significantly reduced the risk of death or

amputation. This might be attributed to patients who underwent minor amputation and subsequently improved clinically. A previously suggested interaction between diameter stenosis and major adverse events [18] could not be confirmed by this study. Total occlusions at baseline were not associated with death or amputation. Finally, with regard to recent concerns about adverse long-term effects of paclitaxel-coated devices, data from trials that prioritise safety endpoints are needed [22].

Strength and Limitations

The strength of this study is that it provides detailed results on clinical improvement and change in quality of life. Moreover, post hoc analysis identified predictive variables for clinical improvement and risk factors for death and amputation. The study has some limitations. First, return of patients for DUS follow-up was low. Standard errors of primary patency at 6 and 12 months, however, were reasonable. Second, patency was given if flow was clearly demonstrated by DUS. To simplify study-related follow-up evaluations, quantitative measurement was not mandatory. Third, ABI data were obtained by only about half of the patients. In addition, due to medial calcification, a high proportion of ABIs were not suitable to determine the hemodynamic condition. Fourth, severity of calcification was not rated based on an established calcium scoring system but only by investigator's estimate or ABI $\geq$ 1.3. Fifth, classification of wounds and quality of wound care management were not inquired. Sixth, seven patients with PAD of Rutherford category 3 were included. Exclusion of these patients from the analysis led to slightly worse results.

Conclusions

In conclusion, infrapopliteal angioplasty with the ELUTAX SV DCB improved the clinical status and quality of life of CLI patients over a period of 12 months. Restenosis, TLR, and all-cause death were comparable to previous data from infrapopliteal DCB angioplasty in CLI patients and less frequent than known from POBA. Considerably fewer major amputations were necessary than previously reported from any other strategy of revascularisation.

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Compliance with Ethical Standards

Conflict of interest All other authors declare that they have no conflict of interest, except of Prof. Teichgräber who received a funding for the APOLLO study by Aachen Resonance.

Ethical Approval All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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ESC European Society of Cardiology

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FASTTRACK CLINICAL RESEARCH
Vascular medicine

Mortality after use of paclitaxel-based devices in peripheral arteries: a real-world safety analysis

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Aims Drug-eluting devices (DED) represent a well-established therapy being widely used for endovascular revascularization (EVR) of peripheral vessels. Recent data indicate a two-fold increased long-term mortality in patients treated with paclitaxel-based DED. The subsequent safety concerns affected international regulatory authorities to enunciate several alerts for further application of DED.

Methods and results In 9.2 million insurants of the German BARMER Health Insurance, data on the application of paclitaxel-based drug-eluting stents (DES) and drug-coated balloons (DCB) were retrieved from their introduction on the market in 2007 until present. All patients with first EVR between 2007 and 2015 were indexed and followed until 31 December 2017. Each subsequently applied DES, DCB, bare-metal stent, and uncoated balloon was included in further analyses. Multivariable Cox regression analysis considered potential non-linear time-dependent hazard ratios (HRs) of DES and DCB over 11 years. We identified 64 771 patients who underwent 107 112 EVR procedures using 23 137 DED. Multivariable Cox regression analysis showed paclitaxel-based DES not to be associated with increased long-term mortality for over 11 years past application (all $P > 0.057$). DCB was associated with decreased long-term mortality for the first year past application (HR 0.92; $P < 0.001$), and indifferent correlation in the years thereafter (all $P > 0.202$).

Conclusion Our real-world analysis showed no evidence for increased mortality associated with paclitaxel-based DED for over 11 years.

Keywords Drug-eluting stent • Drug-coated balloon • Paclitaxel device • Endovascular revascularization • Lower extremity artery disease • Patient safety

Introduction

In the last decade, the technology of drug-eluting devices (DED) for endovascular therapy of patients with lower extremity artery disease (LEAD) rapidly developed. Since its introduction on the US market in 2012,[1–3] the anti-proliferative drug paclitaxel became widely accepted as a coating substance of drug-eluting stents (DES) and drug-coated balloons (DCB).[1,4–7] Randomized clinical trials (RCTs) showed promising results for DES on small-sized selected cohorts to improve late-lumen loss and restenosis rates compared to conventional angioplasty (plain old balloon angioplasty, POBA) or nitinol stents (bare-metal stent, BMS).[1,6,8,9] Unlike DES that release their drug coating over a period of 2–4 weeks to the intimal endothelial layer, DCB-mediated paclitaxel application is a one-off procedure leaving nothing behind. Despite critical voices mainly in the face of weak clinical efficacy and cost-effectiveness,[10,11] DED of various designs expand on the international market.[7,12] Today, DED have become a recommended and commonly used tool for peripheral endovascular revascularization (EVR)[13] exceeding annually 55 000 implanted DCB and over 6600 DES (thereof 97% paclitaxel-eluting) alone in Germany (Federal Statistical Offices DESTATIS, 2016).[14]

Lately, a serious debate on the sensitive issue of patient safety in the use of DED was brought up by unexpected results of a meta-analysis on 28 RCTs ($n = 4663$ patients, thereof 2552 treated with

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DED).[15] The authors stated an increased risk of all-cause death at two [odds ratio (OR) 1.68; 95% confidence interval (CI) 1.15–2.47] and 4–5 years follow-up (FU; OR 1.93; 95% CI 1.27–2.93) by use of paclitaxel-coated compared to uncoated devices in femoro-popliteal LEAD.

As a consequence, two ongoing major RCTs investigating DED technology (BASIL-3 ISRCTN14469736; SWEDEPAD NCT02051088) halted recruitment.[16] Companies of the vascular device sector endeavour to provide preliminary patient-level data in order to address safety concerns of their products.[17] From official site, the US Food and Drug Administration (FDA) released a recommendation appealing for critical indication and informed patient consent in the use of DED,[18] to which international regulatory authorities were further referring.[19] In a recent update, the FDA again tightened its recommendations as a result of preliminary long-term analyses of the three critical RCTs, showing a 'potentially concerning signal of increased long-term mortality in study subjects treated with paclitaxel-coated products'.[20] According to the revalidation of the original trial data, the 5-year mortality risk of DED was 20.1% vs. 13.4% in non-DED treated patients ($n = 975$). However, the FDA stated persistent doubts in the interpretation of these results due to relevant limitations, most notably the small number of long-term cohorts.

These precautions in the use of state-of-the-art technology reflect the current high uncertainty in the face of the pre-eminent importance of patient safety. The ongoing debate points out the need for continuing critical surveillance of new technologies beyond its establishment in clinical routine. Administrative data related to national and health insurance claims may provide an effective approach to answer these demands.

Herewith, we present a real-world safety analysis on 64 771 patients that covers the entire period from the market introduction of DED until today. Our analysis evaluates if the use of paclitaxel-based DES and DCB represent a potential hazard for the actual non-idealised patients in which these devices were applied during the past decade. Exemplified on DED, our work shows the prospects of health services research to assess patient safety without undue delay.

Methods

The German reimbursement system governs the remuneration of healthcare services subject to encoded diagnoses (International Statistical Classification of Diseases, German Modification; ICD-10 GM) and procedures (German procedure classification; OPS) by means of the 'German Diagnosis Related Groups' taxonomy (G-DRG). This obligatory documentation and accounting system is specified and regulated in detail by mandatory coding instructions. Big data derived from national and health insurance claims such as the BARMER are characterized by high transsectoral integrity and validity.[21,22]

Patient selection

We were provided access to the anonymized insurance claims of ~9.2 million patients of the German BARMER Health Insurance. All patients who were encoded in-hospital balloon- or stent-assisted EVR of the lower limbs (OPS 8-836.0*, 8-836.f,g,t,s,h,j*, 8-840.0-5*, 8-841.0-5*, 8-848.0-5*; *codes 9,b,c,q,s) between 1 January 2007 and 31 December 2015 were indexed for further analyses. Patients aged <18 years at index ($n = 32$), with incomplete basic information ($n = 15$), pre-index period <12 months ($n = 456$), implausible exit of database ($n = 11$), or encoded DES of non-paclitaxel or unspecified drug-coating ($n = 519$) were omitted.

Patients were assigned to one of the four sub-groups in hierarchical order according to their first EVR procedure within the index period:

(1) Drug-eluting stents: if ≥1 DES procedure code (OPS 8-836.h*, 8-836.j*, 8-841.0-5*, 8-848.0-5*) combined with paclitaxel material code (OPS 8-83b.03-06) was used.
(2) Drug-coated balloon: if among the remaining patients a balloon angioplasty code (OPS 8-836.0*) combined with ≥1 DCB material code (OPS 8-83b.b2-5, 8-83b.ba-d) was used.
(3) Bare-metal stent: if among the remaining patients ≥1 stent procedure code (OPS 8-840.0-5*, 8-836.f,g,t,s*) was used.
(4) Plain old balloon angioplasty: if among the remaining patients a balloon angioplasty code (OPS 8-836.0*) without any DES, DCB, or BMS codes used.

The selection process including applied ICD-10-GM and OPS codes is presented in detail in the Supplementary material online, *Appendix Figure S1* and *Table S1*.

Cohort characterization

Baseline characteristics were determined for each subgroup according to primary and secondary diagnoses, and procedures during index-hospitalization and within the previous 24 months (*Supplementary Appendix Table S2*). Diagnoses include LEAD, chronic ischaemic heart disease, previous acute myocardial infarction, chronic heart failure, cerebrovascular disease, and ischaemic stroke, chronic kidney disease, hypertension, diabetes, dyslipidaemia, obesity, smoking, and cancer (Supplementary material online, *Appendix Table S2*). These were complemented by previous peripheral and coronary vascular procedures and previous amputation of the lower limbs. Notably, all patients were naive related to paclitaxel-coated peripheral devices, since these were not yet available previous to the index-period (before 2007).

Short-term outcome in the four treatment groups at index (DES, DCB, BMS, and POBA) was assessed based on 30-day mortality, amputations, and other complications (for detailed definitions by coding see Supplementary material online, *Appendix Table S2*).

Follow-up

All patients were continuously followed until death or end of follow-up (FU). All subsequent EVR procedures (inpatient and ambulatory) of individual patients were precisely recorded. For each EVR, the number of applied devices was determined by evaluation of the OPS matrix: the use of up to six BMS (OPS 8-840.0-5), up to six DES (OPS 8-841.0-5, OPS 8-848.0-5), and up to four DCB (OPS 8-83b.ba-bd) per EVR were separately encoded as described in Supplementary material online, *Appendix Table S1*. The cumulative number of applied DES and DCB served as estimate for patients' paclitaxel exposure. Data ascertainment reached until 31 December 2017, providing a median FU of 92 months (2760 days). FU time was 98.8% complete.

Statistical methods

Statistical methods are described in detail in the Supplementary material online, *Appendix*. In brief, logistic regression analyses of 30-day all-cause mortality tested each type of index EVR in hierarchical order (DES, DCB, BMS, and POBA) to evaluate the association between DED and short-

term mortality. The model adjusted for the possible confounders age, sex, pre-existing cardiovascular risk factors, and comorbidities as described above.

To evaluate the association between DED and long-term mortality for up to 11 years FU, a multivariable time-dependent Cox regression analysis was performed that adjusted for patients' risk profile at index and during FU. Per definition, the outcome was the time from index EVR to all-cause death if not censored previously for reaching the end of FU, previous exit of the database ($n = 1020$), exceeding >10 EVR during FU ($n = 345$), or for being treated with a device coated with a drug other than paclitaxel ($n = 456$).

The multivariable Cox regression analysis included all devices that were applied during FU. For each individual device, the analysis accounted for its specific type (DES, DCB, BMS, and POBA) and application date. Particularly, the model allowed for a hazard of DED that is non-constant over time and may alter its effect on long-term mortality past device application. Thereby, also a potentially detrimental effect of DED in the later course of time would become verifiable despite a potentially beneficial effect in the early years or potential aggregation of subsequently applied devices. The hazard ratios (HRs) of individual devices of the same type showed no relevant differences in the time course so that in the final model devices of the same type were cumulated in yearly time intervals to serve as estimates of the patients' paclitaxel exposure. Elementary mortality HRs for each type of device is presented in annual intervals. Combined HRs for any scenario including multiple devices that were applied various years ago can be determined as the product of elementary HRs. Further details of the established Cox model are given in the statistical analysis plan (Supplementary material online, *Appendix*). All analyses were explorative and *P*-values are regarded as noticeable if $P \leq 0.05$. All statistical analyses were performed using SAS (version 9.4 for Windows, SAS Institute Inc., Cary, NC, USA).

Results

We identified 64 771 patients with an index procedure, defined as first EVR of the iliac and lower limb arteries between 2007 until 2015. DED applied in 5.1% of index EVRs with 2648 DCB (4.1%) and 676 DES (1.0%) procedures (*Table 1*, Supplementary material online, *Figure S1*).

Table 1 Patient characteristics at baseline according to index procedure

Characteristics	DES procedure (*N* = 676)	DCB procedure (*N* = 2648)	BMS procedure (*N* = 28 290)	POBA procedure (*N* = 33 157)	All (*N* = 64 771)	*P*
Mean age (year)	73	73	70	74	72	<0.001
Female sex, *n* (%)	293 (43.34)	1249 (47.17)	12 438 (43.97)	15 385 (46.40)	29 365 (45.34)	<0.001
Lower extremity artery disease, *n* (%)						
Lower extremity artery disease (any)	622 (92.01)	2603 (98.30)	26 830 (94.84)	31 416 (94.75)	61 471 (94.91)	<0.001
Lower extremity artery disease (Rutherford Stage 1–3)	364 (53.85)	1517 (57.29)	17 952 (63.46)	15 391 (46.42)	35 224 (54.38)	
Lower extremity artery disease (Rutherford Stage 4)	83 (12.28)	268 (10.12)	3161 (11.17)	3527 (10.64)	7039 (10.87)	
Lower extremity artery disease (Rutherford Stage 5)	88 (13.02)	409 (15.45)	2627 (9.29)	5688 (17.15)	8812 (13.60)	
Lower extremity artery disease (Rutherford Stage 6)	86 (12.72)	407 (15.37)	3059 (10.81)	6763 (20.40)	10 315 (15.93)	
Previous procedures of lower limb arteries, *n* (%)						
Endovascular revascularization	16 (2.37)	76 (2.87)	666 (2.35)	1256 (3.79)	2014 (3.11)	<0.001
Vascular surgery	42 (6.21)	187 (7.06)	1740 (6.15)	2643 (7.97)	4612 (7.12)	<0.001
Amputation	19 (2.81)	71 (2.68)	467 (1.65)	1278 (3.85)	1835 (2.83)	<0.001
Arteriosclerotic co-diagnoses, *n* (%)						
Coronary heart disease	346 (51.18)	1250 (47.21)	13 235 (46.78)	17 222 (51.94)	32 035 (49.49)	<0.001
Previous myocardial infarction	90 (13.31)	318 (12.01)	3560 (12.58)	4405 (13.29)	8373 (12.93)	0.032
Previous coronary revascularization	65 (9.62)	218 (8.23)	2157 (7.62)	2562 (7.73)	5002 (7.72)	0.191
Cerebrovascular disease	239 (35.36)	906 (34.21)	9147 (32.33)	11 332 (34.18)	21 624 (33.39)	<0.001
Previous stroke	109 (16.12)	398 (15.03)	3684 (13.02)	5479 (16.52)	9670 (14.93)	<0.001
Cardiovascular risk factors, *n* (%)						
Atrial fibrillation or flutter	160 (23.67)	588 (22.21)	4548 (16.08)	8217 (24.78)	13 513 (20.86)	<0.001
Chronic kidney disease	207 (30.62)	801 (30.25)	6587 (23.28)	10 604 (31.98)	18 199 (28.10)	<0.001
Chronic heart failure	221 (32.69)	842 (31.80)	7295 (25.79)	11 656 (35.15)	20 014 (30.90)	<0.001
Diabetes mellitus	329 (48.67)	1306 (49.32)	11 589 (40.97)	17 409 (52.50)	30 633 (47.29)	<0.001
Diabetes mellitus (on insulin)	149 (22.04)	595 (22.74)	4337 (15.33)	8257 (24.90)	13 338 (20.59)	<0.001
Dyslipidaemia	512 (75.74)	1975 (74.58)	20 567 (72.70)	23 706 (71.50)	46 760 (72.19)	<0.001
Hypertension	614 (90.83)	2439 (92.11)	24 850 (87.84)	30 393 (91.66)	58 296 (90.00)	<0.001
Nicotine abuse	190 (28.11)	807 (30.48)	10 844 (38.33)	8062 (24.31)	19 903 (30.73)	<0.001
Obesity	158 (23.37)	646 (24.40)	6370 (22.52)	8619 (25.99)	15 793 (24.38)	<0.001
Cancer, *n* (%)	168 (24.85)	607 (22.92)	6197 (21.91)	7734 (23.33)	14 706 (22.70)	<0.001

BMS, bare-metal stent; DCB, drug-coated balloon; DES, drug-eluting stent; POBA, plain old balloon angioplasty.

Of those who had no DED at index ($n = 61\,447$), 5184 (8.4%) received at least one DED during FU, and 2064 patients had repeated DED exposure. Baseline characteristics of the four index cohorts are shown in *Table 1*. These illustrate relatively homogeneous subgroups in terms of age (average 71.5 years), sex (45.3% female), and cardiovascular comorbidity. LEAD was encoded in 94.9% of patients as the underlying reason for EVR, thereof 42.7% at critical stages of disease. Every second patient had coronary heart disease at baseline, one-third had cerebrovascular disease. Common comorbidities comprised arterial hypertension (90.0%), dyslipidaemia (72.2%), diabetes (47.3%), chronic heart failure (30.9%), and chronic kidney disease (28.1%). Within two years afore index, amputation of the lower limbs was performed in 2.8% of patients, and vascular surgery was performed in 7.1%. EVR previous to the index-procedure applied in 3.1% of patients, notably none of these with DED.

During the study, in total, 107 112 inpatient and ambulatory EVR procedures were identified, thereof 9401 DCB and 1395 DES procedures (10 796 DED procedures, 10.1%). These correspond to the use of 1973 DES and 21 164 DCB devices (in total ≥ 23 137 DED), accounting for 11.5% of all 200 681 devices being applied (Supplementary material online, *Appendix Figure S2*).

Acute outcomes

Observed 30-day mortality was 1.6% in DED vs. 2.0% in non-DED procedures (2.1% DES, 1.5% DCB, 1.6% BMS, 2.4% POBA; $P < 0.001$; *Table 2*). Multivariable logistic regression was established and detailed model performance is shown in the Supplementary material online, *Appendix Figure S3*). The logistic regression analysis allowing for co-prevalent risk factors showed adjusted 30-day mortality to be independent from the use of DED, both for DES (vs. BMS: OR 0.93, $P = 0.790$) and DCB (vs. POBA: OR 0.79, $P = 0.131$) (*Figure 1*).

Long-term outcomes

Over the entire study period, 41.9% of patients died. A time-dependent Cox regression analysis was performed that adjusted long-term mortality for DED application and cardiovascular risk indicators at baseline and during FU (*Figure 2*). The performance of any stent EVR was associated with increased mortality risk within the first two years (first and second year: HR 1.03; $P = 0.004$ and $P = 0.013$), which was not verifiable in the following years. For the use of paclitaxel-based DES, a tendency towards increased hazards became apparent beyond the fourth year past application. However, these associations with increased long-term mortality could not be statistically confirmed for up to 11 years after DES application (HR between 0.64 and 1.10; all $P > 0.057$). Balloon angioplasty was associated with increased mortality for the first year past balloon EVR (HR 1.10; $P < 0.001$). Paclitaxel coating was not associated with increased long-term mortality for up to 11 years past DCB application. On the contrary, DCB use was associated with decreased mortality for the first year (HR 0.92; $P < 0.001$), which however became irrelevant in the subsequent years. The mortality hazard for the use of multiple devices, e.g. repeated DED exposure, is the product of elementary hazards as illustrated in the example in *Figure 2*. Since none of the elementary hazards for DES or DCB reached statistical noticeability, also multiple DED exposure within the same time period will not result in a statistically noticeable increase of long-term mortality.

Discussion

Based on our analysis, from introduction to the market until present, the use of DED was not associated with exceeding death rates compared to non-DED. Therefore, our study debilitates current safety concerns resulting from previous findings.[15]

Our analysis on 64 771 patients and 107 112 peripheral interventions over a median time period of 92 months (7.6 years) implies high data validity and informational value of the presented results. Compared to the meta-analysis by Katsanos *et al.*[15] that resulted from small-sized selected cohorts of the underlying RCTs, our data reflect the unselected real-world patient collective to which the devices actually apply to. Our cohort is representative compared to

Table 2 In-hospital outcome according to index procedure

In-hospital outcome	DES procedure ($N = 676$)	DCB procedure ($N = 2648$)	BMS procedure ($N = 28\,290$)	POBA procedure ($N = 33\,157$)	All ($N = 64\,771$)	*P*
Cardiovascular events, *n* (%)						
Acute myocardial infarction	6 (0.89)	16 (0.60)	294 (1.04)	375 (1.13)	691 (1.07)	0.070
Acute stroke	<5 (<0.70)	8 (0.30)	140 (0.49)	228 (0.69)	378 (0.58)	<0.001
Lower limb complications, *n* (%)						
Amputation, any	46 (6.80)	183 (6.91)	1199 (4.24)	3282 (9.90)	4710 (7.27)	<0.001
Minor amputation	36 (5.33)	159 (6.00)	917 (3.24)	2605 (7.86)	3717 (5.74)	<0.001
Major amputation	10 (1.48)	24 (0.91)	282 (1.00)	677 (2.04)	993 (1.53)	<0.001
Other complications, *n* (%)						
Acute renal failure	18 (2.66)	40 (1.51)	394 (1.39)	591 (1.78)	1043 (1.61)	<0.001
Bleeding event	73 (10.80)	196 (7.40)	2257 (7.98)	3643 (10.99)	6169 (9.52)	<0.001
Infection including sepsis	15 (2.22)	32 (1.21)	288 (1.02)	595 (1.79)	930 (1.44)	<0.001
Death from any cause, *n* (%)	14 (2.07)	39 (1.47)	440 (1.56)	787 (2.37)	1280 (1.98)	<0.001

BMS, bare-metal stent; DCB, drug-coated balloon; DES, drug-eluting stent; POBA, plain old balloon angioplasty.

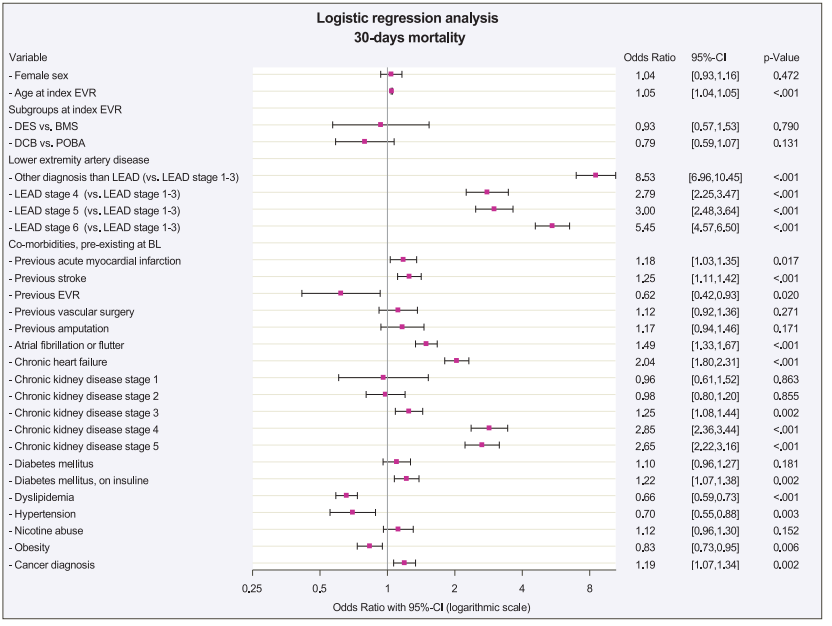


Figure 1 Thirty-day mortality adjusted for baseline risk. Thirty-day mortality after multivariable adjustment for baseline characteristics as assessed within 24 months previous to index EVR. Logistic regression model included co-prevalent cardiovascular risk factors, previous vascular procedures, as well as in-hospital complications and adverse events. Death (from any cause) at 30 days did not differ significantly between stent nor balloon angioplasty with vs. without paclitaxel (DES vs. BMS: OR 0.93, 95% confidence interval 0.57–1.53; $P = 0.790$; drug-coated balloon vs. POBA: OR 0.79, 95% confidence interval 0.59–1.07; $P = 0.131$). BL, baseline; BMS, bare-metal stent; CI, confidence interval; DCB, drug-coated balloon; DES, drug-eluting stent; EVR, endovascular revascularization; LEAD, lower extremity artery disease; OR, odds ratio; POBA, plain balloon angioplasty.

other large epidemiological studies in terms of age, sex, cardiovascular risk burden, and LEAD severity.[23,24]

Long-term mortality

Our database included a high percentage of patients with chronic limb-threatening ischaemia (CLTI 42.7%) which corresponds well with the 43.5% reported for German nationwide inpatient LEAD cases.[25] Since CLTI is associated with dramatically increased death rates ranging between 40% and 50% within 5 years,[21,24] this explains the observed 41.9% overall mortality during 7.6 years FU in our real-world cohort.

In contrast, Katsanos *et al.*[15] reported markedly lower mortality rates with 14.7% in DED and to 8.1% in non-DED at 4–5 years. The three underlying RCTs, ZILVER-PTX,[1] IN.PACT SFA,[3] and THUNDER[6] included in total $n = 268$ DCB, $n = 214$ DES, and $n = 403$ unspecified non-DED procedures. All procedures were performed on femoropopliteal lesions in patients at moderate LEAD Rutherford stages (ZILVER-PTX: 9% CLTI; IN.PACT SFA: 5.4% CLTI only Rutherford stage, RF 4; THUNDER: mean RF at index 3.1–3.4, no RF 6). Study protocols further limited risk and complexity of the vascular status, as for example, patients with low life expectancy, poor inflow or absence of at least one patent crural artery were excluded upfront from the trials. Importantly, analyses did not include potential subsequent EVR procedures involving paclitaxel exposure outside the frame of the studies.

The hereupon applied meta-analysis resulted in an almost two-fold increased mortality risk for DED (RR 1.93, 95% CI 1.27–2.93) and indicated an increasing risk per paclitaxel dosage. However, reasonable doubts on these results involve methodical issues such as lack of information on the original patient data and a relevant loss of FU in the RCTs. Moreover, a missing discrimination between stent and balloon EVR as well as statistical simplification of bail-out changeovers between treatment arms in ZILVER-PTX were discussed.[26]

Value of health claims data for safety concerns

Large-sized administrative data related to national reimbursement and/or health insurance claims may provide an advantageous approach for surveillance after regulatory approval to address patient

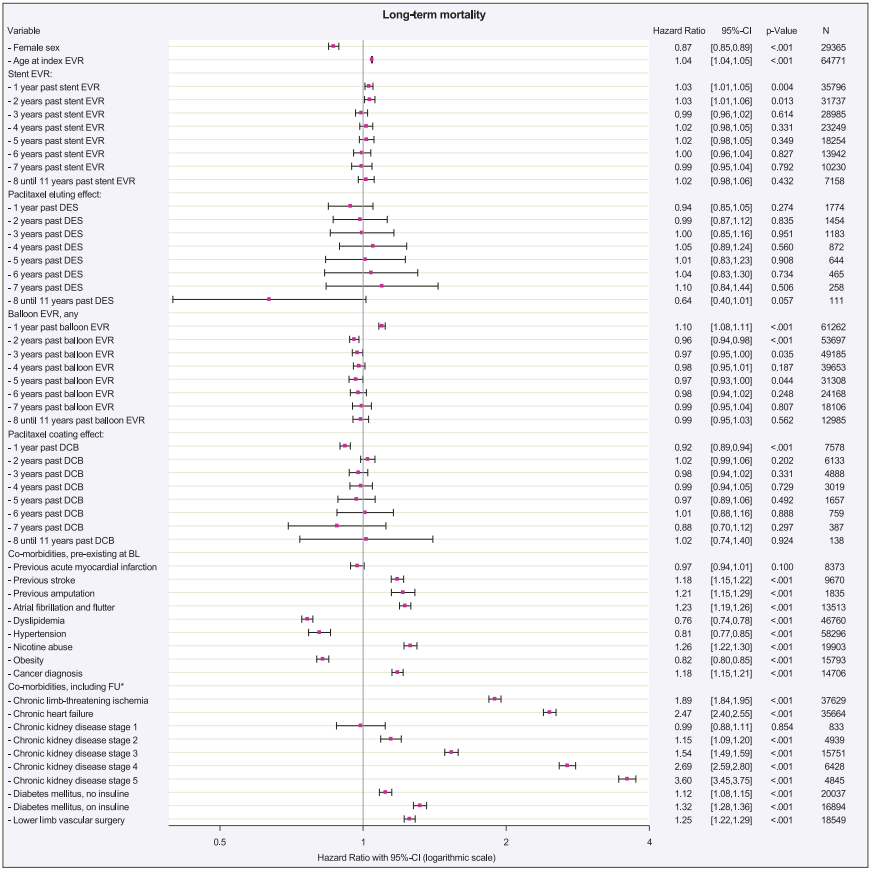
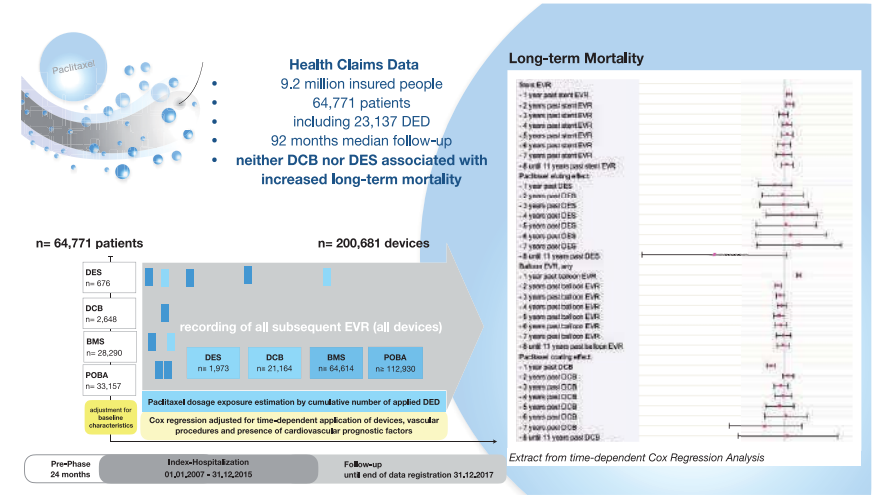


Figure 2 Time-dependent Cox-regression allowing for non-linear and time-dependent hazard ratio of the respective devices. All devices applied between 1 January 2007 and 31 December 2017 were included in the model. HRs for each type of device are given per application of one distinct device over annual time intervals. HR for stent EVR (any device) was increased for the first 2 years (both HR 1.03; $P = 0.004$ and $P = 0.013$), reflecting the procedural risk and general hazard being involved with the need for stent implantation. The additional effect by use of paclitaxel-based DES was not associated with increased mortality in up to 11 years past application. Likewise, balloon EVR (any device) was associated with evident increased mortality in the first year of application (HR 1.10; $P < 0.001$). Paclitaxel coating effect in DCB was associated with a protective effect in the first year of DCB application (HR 0.92; $P < 0.001$), which became irrelevant in the years thereafter. The HR of any combination of applied devices including use of multiple devices in different years and concomitant risk factors can be calculated by multiplying elementary HRs: e.g. a patient with previous stroke, diabetes without insulin and one DES 1 year ago plus two POBA 3 years ago compared to a patient without stroke, without diabetes, only one POBA 3 years ago and identical baseline characteristics (e.g. age and gender) has a HR = [1.18 (previous stroke) * 1.12 (diabetes w/o insulin) * 1.03 (1 stent one year ago) * 0.94 (DES) * 0.97^2 (two POBAs 3 years ago)]/[0.97 (1 POBA three years ago)] = 1.20/0.97 = 1.24. BL, baseline; CI, confidence interval; DCB, drug-coated balloon; DES, drug-eluting stent; EVR, endovascular revascularization; FU, follow-up period; N, number of patients at end of FU. *Time-dependent adjustment of covariates.



Take home figure Safety analysis of paclitaxel based drug eluting devices for application in peripheral arteries.

safety in the long-term. Based on 9.2 million insurants, respectively over 10% of the German population, our data represent the current practice in endovascular treatment of LEAD.

As expected from other trials,[27,28] acute complications and deaths during the first 30 days occurred at relatively low levels irrespective of the devices applied. In the long-term, the categorical risk being involved with medical indication for a repeated EVR was reflected in the slightly increased HR for stent and balloon application in the first year. However, thereafter the EVR the procedure itself had no negative impact on overall mortality anymore. Adjusting for an additional effect by the use of paclitaxel-based DED did not result in increased mortality risks.

DES analysis, based on 1973 encoded devices, indicated slightly decreased mortality in the first year past application. Thereafter, DES indeed trended towards hazardous risks although all of these missed statistical conspicuities. Given the relatively high share of DES (44% of DED cases) in the designated low-risk cohorts, the previous meta-analysis[15] fits in the greater picture drawn by our analysis. However, the reported hazardous effects were likely overweighted due to the afore-mentioned limitations.[26]

DCB, based on 21 164 encoded devices, were associated with an 8% decreased mortality hazard per applied DCB within the first year. Up to 8 years past application, a protective or hazardous association was not verifiable. Beyond the eighth year past DED application, the model faces the limitations of decreasing sample sizes for DES and DCB due to the timeliness of the index period.

Strengths and limitations

Strengths of our analysis are its large and comprehensive database of unselected real-world patients, covering the entire period of DED usage from its introduction on the market until today. Pursuant to the structure of the German health care system and legal framework the study contains no missing values. Since exact coding of each device of DES, BMS, and DCB trigger a markedly increase in reimbursement in the G-DRG-System, completeness of the applicable codes could be expected to be very high. The methodical approach of our analysis overcomes changeover between EVR treatment strategies during FU and further considered any aggregation of subsequently applied devices. To detect any possible detrimental effect of DED in the later course of time against a potential early benefit, the chosen model was also able to consider a non-linear time-dependent effect of DED changing its mortality HR over the time course.

Our study is limited by the general constraints in the use of secondary health care data as previously described in detail.[21] Specifically, real-world administrative data do not provide information on the underlying reason for DED treatment, representing a potential selection bias. Further, the restricted level of detail in some of the codes affected the present study: paclitaxel exposure was estimated by means of the cumulative number of each device. Up to six DES and a maximum of four DCB can be encoded per procedure. However, the collected numbers for DED as estimates for paclitaxel exposure are correct in all probability since the use of more than four DCB or six DES within the same procedure is certainly a rare exception. Further, the OPS coding system does not register the exact product and manufacturer; individual paclitaxel load or length of device are missing.

Our time-dependent Cox regression analysis cumulated devices of each type within annual time intervals. Preliminary working models showed that this methodological simplification was justified as the temporal course of the HR of each device proved to be independent

from the chronological order of its application. Finally, our explorative model needs to be validated externally. We will provide this confirmation in a timely manner in a subsequent publication.

Conclusions

In summary, our analysis found the use of DED to be safe for endovascular therapy of the lower limbs. Particularly with regard to long-term mortality, neither DCB nor DES was associated with increased risk compared to non-DED. Furthermore, our analysis exemplarily demonstrates the significance of health claims data for assessing urgent safety concerns without undue delay.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Mechanical rotational thrombectomy with Rotarex system augmented with drug-eluting balloon angioplasty versus stenting for the treatment of acute thrombotic and critical limb ischaemia in the femoropopliteal segment

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Abstract

Introduction: *Mechanical thrombectomy is an alternative to local thrombolysis for the treatment of severe ischaemia in the femoropopliteal segment, but stent implantation is usually required after this procedure. The use of drug-eluting balloons (DEBs) may overcome long-term problems associated with stents, but it remains unclear how often such a treatment is technically feasible and efficient.*
Aim: *This post hoc single-centre study was aimed at assessment of the feasibility, safety and efficacy of mechanical thrombectomy followed by application of DEBs.*
Material and methods: *Fifty-one patients, aged 69.1 ±11.6 years, were managed for acute thrombotic or chronic critical ischaemia in the femoropopliteal segment using the Rotarex device. Following mechanical thrombectomy, on condition that there was no significant residual stenosis or dissection, lesions were managed with paclitaxel-coated DEBs, which was a desired strategy (24 patients). The remaining 25 patients underwent stent implantations, which was regarded as bailout treatment. Final follow-up was scheduled 12 months after the procedure.*
Results: *The primary-assisted patency rate after mechanical rotational thrombectomy with additional balloon angioplasty and/or stenting was 97.1% (49 patients). The early mortality rate was 2.0% (1 patient) and the amputation rate was 4.1% (2 patients). There were no late mortalities or limb amputations at 12-month follow-up, but significant restenoses occurred in 13 (27.1%) patients. These restenoses were more frequent in patients who underwent stent implantation (45.5%) than those managed with DEBs (12.5%), and in patients managed for secondary lesions.*
Conclusions: *In selected patients mechanical rotational thrombectomy in the femoropopliteal segment followed by application of DEB is a safe, effective and long-lasting method of revascularisation.*

Key words: *critical ischaemia, stent, drug-eluting balloon, mechanical thrombectomy, acute limb ischaemia.*

Introduction

Both acute thrombotic and chronic critical lower limb ischaemia are associated with high morbidity and mortality, and also with a high risk of unsuccessful revascularisation of the limb, requiring its amputation. Routine management of both types of limb ischaemia consists of anticoagulation followed

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by open surgical repair of occluded arteries (usually bypass grafting) [1–4]. Yet, such a treatment in patients with acute thrombotic ischaemia is associated with an amputation rate at the level of 10–70% and in-hospital mortality even as high as 15% [5]. In patients with critical limb ischaemia the amputation rate after surgical revascularization is at the level of 20–25% and the 2-year mortality rate in these patients is about 50% [2, 5, 6]. Although local thrombolysis is associated with better clinical outcomes and currently it is preferred to surgical revascularization [7–10], not all occlusions can be opened by thrombolytic agents. Those primarily atherosclerotic poorly respond to thrombolysis. Moreover, even if thrombolysis is successful, these arteries usually re-occlude and stent implantation is often required, which carries another problem – in-stent stenosis or occlusion, primarily associated with intimal hyperplasia within the stent. Mechanical thrombectomy seems to be an alternative treatment modality [5, 11–14], but stent implantation with similar late problems is usually required after this endovascular procedure. The use of drug-eluting balloons (DEB) instead of stents may theoretically overcome clinical problems associated with stents, but it remains unclear how often such a treatment is technically feasible in these challenging patients and how efficient mechanical thrombectomy not augmented with stent implantations is in the long run.

Aim

This post hoc single-centre study was aimed at assessment of the feasibility, safety and efficacy of mechanical thrombectomy followed by application of DEBs for acute thrombotic or chronic critical ischaemia of the lower limbs in the femoropopliteal segment. We also analysed how often the use of rotational thrombectomy enabled an endovascular procedure not accompanied by stent implantation, and whether the utilisation of DEBs instead of stents was associated with a better clinical outcome.

Material and methods

We reviewed our register of endovascular interventions and identified patients with acute thrombotic ischaemia or chronic critical lower limb ischaemia due to occlusions in the femoropopliteal segment, who were managed using mechanical rotational thrombectomy (Rotarex®s device; Straub Medical AG, Wangs, Switzerland). Technical success of mechanical rotational thrombectomy was defined in terms of absence of relevant post-procedural residual stenosis, with cutoff at the level of 50%. Primary-assisted patency rate was defined as exempt from significant stenosis (cutoff at the level of 30%) in the target artery following rotational thrombectomy and additional endovascular interventions during the primary procedure, such as balloon angioplasty and stenting.

Potential risks and benefits associated with such a procedure were discussed with the patients, and all patients gave their written informed consent. Clinical indications for mechanical rotational thrombectomy in our centre included:

– occlusions and/or critical stenoses of the distal femoral artery (distally from the profunda femoris artery) or the popliteal artery (with or without involvement of its branches);
– atherosclerotic, atherothrombotic and atheroaneurysmatic lesions;
– primary lesions and secondary lesions after previous balloon angioplasty or stent implantations.

Exclusion criteria comprised: highly calcified lesions, no adequate vascular access, contraindications for antiplatelet therapy, and lack of the patient's consent.

In this study we did not include patients presenting with arterial emboli. From June 2014 to November 2016 there were 51 eligible patients, 26 men and 25 women, with a mean age of 69.1 ±11.6 years. Thirteen (25.5%) patients were managed for acute non-embolic occlusions of the distal femoral artery and/or popliteal artery and its branches. Out of these patients, 6 (46.2%) presented with an acutely occluded stent. Thirty-eight (74.5%) patients were admitted to the hospital because of critical limb ischaemia resulting from atherothrombotic lesions at the same level as patients with acute ischaemia. In this group there were 5 (13.2%) patients with thrombotic occlusions after balloon angioplasty and 18 (47.4%) patients with chronically occluded stents. A majority of patients presented with grade 4 and 5 (21 and 25 patients, accordingly) of the Rutherford classification, and 5 patients presented with severe ischaemic ulcers (grade 6 in this classification). The demographic profile of both groups of patients and their co-morbidities are presented in Table I, while localisations and characteristics of arterial lesions are described in Table II.

Table I. Clinical characteristics of patients

Parameter	All patients (*n* = 51)	Critical limb ischaemia (*n* = 38)	Acute non-embolic limb ischaemia (*n* = 13)
Male/female ratio	26/25 (51.0/49.0%)	17/21 (44.7/55.3%)	9/4 (69.2/30.8%)
Patients' age [years]	69.1 ±11.6	70.2 ±11.8	67.9 ±15.5
Diabetes mellitus type 2	20 (39.2%)	12 (31.6%)	8 (61.5%)
Cigarette smoking	17 (33.3%)	13 (34.2%)	6 (46.2%)
Hypercholesterolaemia	22 (43.1%)	16 (42.1%)	6 (46.2%)
Arterial hypertension	44 (86.3%)	34 (89.5%)	10 (76.9%)
Family history cardiovascular disease	9 (17.6%)	7 (18.4%)	2 (15.4%)
History of myocardial infarction	11 (21.6%)	7 (18.4%)	4 (30.8%)

Table II. Localisations and characteristics of arterial lesions

Variable	All patients (*n* = 51)	Critical limb ischaemia (*n* = 38)	Acute non-embolic limb ischaemia (*n* = 13)
Distal part of femoral artery	12 (23.5%)	10 (26.3%)	2 (15.4%)
Popliteal artery	14 (27.5%)	10 (26.3%)	4 (30.8%)
Distal part of femoral artery and popliteal artery	16 (31.4%)	13 (34.2%)	7 (53.8%)
Popliteal artery and its branches	7 (13.7%)	5 (13.2%)	2 (15.4%)
Popliteal artery with aneurysmatic dilatation	3 (5.9%)	1 (2.6%)	2 (15.4%)
Distal part of femoral artery and popliteal artery with aneurysmatic dilatation	2 (3.9%)	2 (5.3%)	0
Mean length of the lesion [mm]	247.0 ±135.8	253.2 ±129.9	303.8 ±140.0
Thrombosis in the area of lesion	34 (66.7%)	22 (57.9%)	12 (92.3%)
Total occlusion of the target artery	44 (86.3%)	31 (81.6%)	13 (100%)
Degree of stenosis (%)	93 ±3.1	92 ±2.2	100
Ankle/brachial index at baseline	0.2 ±0.1	0.4 ±0.15	0.2 ±0.15
Primary lesion	26 (51.0%)	19 (50.0%)	7 (53.8%)
Restenotic lesion	25 (49.0%)	19 (50.0%)	6 (46.2%)

Endovascular procedures were performed through ipsi- or contralateral femoral access. Before intervention all patients received 300 mg of clopidogrel and 75 mg of aspirin. During endovascular intervention patients were administered intravenously unfractionated heparin. Dosing of heparin depended on the duration of the procedure. We used 110 cm or 135 cm long 6 Fr Rotarex®s catheters. Firstly we navigated through the occluded segment with a 0.018" guidewire and then performed 2–6 passages of the Rotarex system. After at least 2 passages of the rotational catheter, control catheter angiography was performed. If there was still over 50% stenosis, balloon angioplasty was performed. Afterwards, if there was no major residual stenosis (over 40%) in the target artery and no significant dissection, this area was managed with paclitaxel-coated DEBs, such as Elutax SV (Aachen Resonance, Aachen,

Germany) or Luminor (iVascular, Barcelona, Spain). This was a desired strategy, which was possible in 24 patients (49.0%). In 25 (51.0%) patients arteries revealed significant stenoses despite balloon angioplasty, or there were severe (grade C or higher) dissections. These patients underwent stent implantations, which was regarded as a bailout treatment. In addition, 6 (11.8%) patients presenting with over 60% residual stenosis following balloon angioplasty and/or significant peripheral embolisation received alteplase intra-arterially (5 mg as a bolus, and then 15 mg during 12 h). Details regarding results of rotational mechanical thrombectomy with the Rotarex system are given in Tables III and IV.

All patients were assessed before discharge from the hospital. They were discharged with the recommendation of dual antiplatelet therapy with aspirin (75–150 mg daily) and clopidogrel (75 mg daily). Their follow-ups were scheduled 30 days, 6 and 12 months after the procedure. Since there was 1 death and 2 amputations during the hospital stay, only 48 patients were followed up (24 patients managed

Table III. Results of rotational mechanical thrombectomy with Rotarex system in patients with acute vs. critical leg ischaemia

Variables	All patients (n = 51)	Critical limb ischaemia (n = 38)	Acute non-embolic limb ischaemia (n = 13)
Number of passages of the Rotarex system	3 ±2	4 ±2	3 ±1
Degree of stenosis after mechanical thrombectomy (%)	54 ±15	55 ±15	45 ±13
Duration of mechanical thrombectomy [min]	5 ±2	7 ±2	5 ±2
Patients finally managed with drug-eluting balloons	24	19	5
Degree of residual stenosis after drug-eluting balloons (%)	13.5 ±4	10.5 ±6	12.5 ±9
Patients finally managed with stents	27	19	8
Degree of residual stenosis after stenting (%)	11.5 ±4	10.5 ±6	10.5 ±6
Ankle/brachial index at hospital discharge	0.73 ±0.10	0.75 ±0.12	0.75 ±0.14

Table IV. Results of rotational mechanical thrombectomy with Rotarex system in patients finally managed with drug-eluting balloons vs. those managed with stents.

Variable	All patients (n = 51)	Patients managed with drug-eluting balloons (n = 24)	Patients managed with stents (n = 27)
Patients presenting with critical limb ischaemia	38 (74.5%)	19 (79.2%)	19 (70.4%)
Patients presenting with acute non-embolic limb ischaemia	13 (25.5%)	5 (20.8%)	8 (29.6%)
Number of passages of the Rotarex system	4 ±2	3 ±1	4 ±1
Degree of stenosis after mechanical thrombectomy (%)	47 ±20	41 ±18	45 ±13
Degree of residual stenosis after balloon angioplasty and/or stenting (%)	14.3 ±6	21.5 ±12	10.5 ±6
Ankle/brachial index at hospital discharge	0.71 ±0.14	0.72 ±14	0.70 ±0.12

with DEBs and 22 patients who underwent stent implantation). At each visit patients underwent physical examination, evaluation of degree of limb ischaemia according to the Rutherford classification and duplex sonography of the recanalised arteries. Patients were also evaluated in a case of clinical worsening or delayed wound healing. Clinical worsening, restenosis revealed by sonographic examination and delayed healing of an arterial ulcer were the indications for control angiography and reintervention.

Statistical analysis

Multivariate stepwise backward conditional logistic regression analysis was used to determine independent predictors of restenosis/occlusion. The significance of this analysis was set at $p < 0.05$.

Results

Technical success of mechanical rotational thrombectomy alone was achieved in 20 (19.6%) patientsand there was a 97.1% primary-assisted patency rate (49 patients) after additional balloon angioplasty and stenting. In 2 (4.1%) patients despite recanalisation of the target artery and stenting this procedure clinically failed and in both of them amputations of ischaemic limbs were performed during the hospital stay. Such an unfavourable outcome occurred in 1 patient presenting with acute thrombotic limb ischaemia and in 1 with chronic critical ischaemia. In both patients, in addition to occlusions of the distal femoral artery and popliteal artery, there were occlusions of the branches of the popliteal artery. There was one in-hospital death (mortality rate: 2.0%). This patient died because of intracranial bleeding, which probably was associated with infusion of alteplase. There were local complications associated with mechanical thrombectomy in 5 (9.8%) patients – distal embolisation in 4 patients, which was successfully managed with aspiration and local infusion of alteplase, and perforation of the artery in 1 case, which required implantation of a covered stent. There were neither mortalities nor major adverse events, such as myocardial infarction, stroke or limb amputation in all 48 remaining patients during 12 months of follow-up. At 12 month follow-up the clinical status of the majority of ischaemic limbs had improved. Only 1 (2.1%) patient suffered from rest pain and 7 (14.6%) patients from severe claudication. There were no patients presenting with ischaemic ulcers. Details are given in Figure 1. In 13 patients (27.1%, excluding deceased and amputated patients) duplex sonography revealed occlusions or severe stenoses in the target arteries. These lesions primarily occurred in patients managed for secondary lesions (12 limbs). There was only 1 patient with restenosis after primary intervention. Also, restenoses and occlusions at follow-up were significantly more frequent in patients who underwent stent implantation (10 patients; 45.5%) than in those managed with DEBs (3 patients; 12.5%) – Figure 2. The risk of recurrent lesions was higher in patients with chronic critical lower limb ischaemia (11 patients; 30.6%) than those managed for acute thrombotic occlusions (2 patients; 16.7%). Details are described

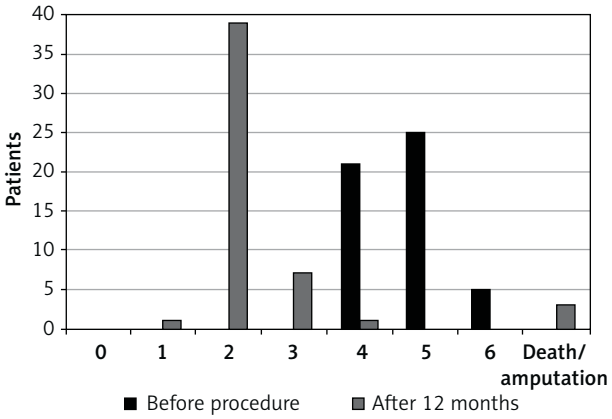

Figure 1. Degree of ischaemia according to the Rutherford classification before intervention and at 12-month follow-up

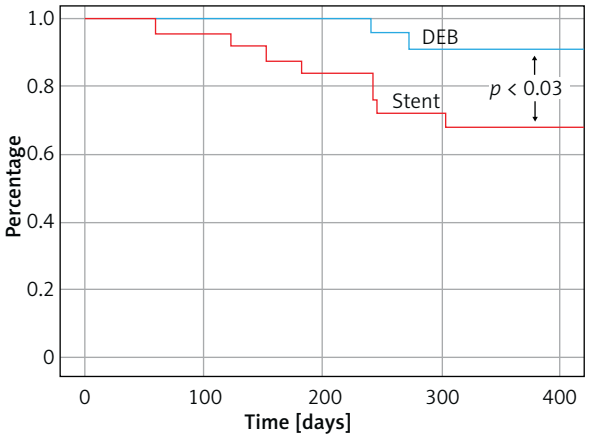

Figure 2. Kaplan-Meier event-free curves displaying the freedom from restenosis/reocclusion in patients managed with drug-eluting balloons (DEB) vs. those managed with stents

Table V. Number of patients presenting with severe restenoses and occlusions at 12-month follow-up (patients who died or had their limbs amputated during first hospitalization were excluded)

Parameter	All patients	Critical limb ischaemia (n = 36)	Acute non-embolic limb ischaemia (n = 12)
All patients (n = 48)	13 (27.1%)	11 (30.6%)	2 (16.7%)
Patients managed with drug-eluting balloons (n = 24)	3 (12.5%)	3 (15.8%)	0
Patients managed with stents (n = 24)	10 (41.7%)	8 (47.1%)	2 (28.6%)
Patients managed for primary lesions (n = 22)	1 (4.5%)	1 (6.7%)	0
Patients managed for secondary lesions (n = 26)	12 (46.2%)	10 (47.6%)	2 (40.0%)

in Table V. The logistic regression analysis revealed that peripheral embolisation during the procedure and more than 4 passages of the Rotarex system were significantly associated with a higher risk of restenosis/occlusion (hazard ratio: 5.6 and 5.0; p = 0.018 and 0.025 respectively).

Discussion

In this post-hoc analysis we have demonstrated that the majority of severe atherothrombotic lesions in the femoropopliteal segment that result in acute or chronic critical limb ischaemia, and are not highly calcified, can be reopened using mechanical rotational thrombectomy. In our patient series the primary-assisted patency rate after thrombectomy augmented by balloon angioplasty and stenting was as high as 97.1%. in the in-hospital amputation rate was 4.1%. Such management was also safe. In-hospital mortality was 2.0%, which was significantly lower than after an open surgical revascularization. Moreover, in 49% of patients it was possible to avoid stent implantation and instead to manage the area of occlusion with DEB.

Analysis of the clinical outcome of our patients at 12-month follow-up demonstrated that mechanical rotational thrombectomy with the Rotarex system followed by DEB was not inferior to such a thrombectomy assisted by stent implantation. Actually, the results after DEB were better; there were fewer restenoses and no amputations. Yet, stents were implanted in patients with more advanced pathology and therefore these differences should be interpreted with caution. Similarly, although we identified peripheral embolisation during the procedure and more than 4 passages of the Rotarex system as risk factor of reocclusion, these events were probably predictors of more advanced arterial disease, and thus the risk of reocclusion in these patients was higher. Similarly worse late results in patients who required local fibrinolysis in addition to mechanical thrombectomy have already been reported by Kronlage [5].

Large epidemiological studies have revealed a significant risk of major amputation and/or mortality associated with open surgical revascularization for acute and critical leg ischaemia [1–3, 15]. Consequently, local fibrinolysis or endovascular thrombectomy is currently suggested to be a preferred treatment modality [16–20]. In the large study by Freitas *et al.*, who managed with Rotarex 525 patients presenting with acute and subacute ischaemia, with an average length of occluding lesions of 159 mm, there was 1.1% mortality and a 2.3% major amputation rate during 30-day follow-up. Adverse events associated with the treatment occurred in 6.9% of patients and mortality after 1 year was 8% [19]. Similar outcomes were reported by Kronlage *et al.* They managed 202 patients and in this group amputation-free survival was 94.3% [5].

Although mechanical thrombectomy with the Rotarex system has been demonstrated to be both relatively safe and efficient [5, 7–9, 14, 16–19], it remains to be established how to optimize such treatment. Even if short-term results are encouraging, long-term patency rates in the femoropopliteal segment after standard balloon angioplasty or stent implantation are relatively low. The 1-year reocclusion rate after balloon angioplasty is at the level of 60% [21–28]. Stents do not seem to be a proper solution either. When implanted in this part of the arterial system, especially in the distal part of the popliteal artery or in its branches, a significant proportion of currently available stents occlude in the long run, either because of a fracture, or due to thrombosis and intimal hyperplasia [21–29]. Although novel wire-in-

terwoven Nitinol or helically shaped stents, exhibiting a swirling flow, try to overcome these problems, they are not yet routinely used and their actual long-term advantage remain to be proven [30–35]. On the other hand, long-term patency rates in the femoropopliteal segment after DEBs are higher than after standard balloon angioplasty [36–47], while the problems associated with stents are avoided.

The results of our study suggest that the use of DEB after mechanical thrombectomy for thrombotic acute or critical leg ischaemia resulting from arterial occlusion in the femoropopliteal segment could be a desired treatment strategy. However, it should be emphasized that it was a retrospective analysis and the groups of patients were not fully comparable. A larger prospective study should be designed and performed in order to fully compare the clinical value of DEBs with stents in these challenging patients. Also, probably some novel area-dedicated stents (such as the aforementioned helically shaped ones) should be applied in such a trial.

Conclusions

The short and intermediate term results from this nonrandomised study indicate that the combination of mechanical thrombectomy with DEB is safe and feasible for the treatment of intermediate to long superficial femoral artery/popliteal artery lesions in selected patients with severe limb ischaemia. The DEB group had higher rates of primary patency and freedom from restenosis than the group of patients with stent implantation.

Conflict of interest

The authors declare no conflict of interest.

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Results of New Dual-Drug Coated Balloon Angioplasty versus POBA for Femoropopliteal Lesions

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Background: The study aimed to assess the 24-month safety and effectiveness of a new generation drug-coated balloon (DCB) (Elutax; AR Baltic Medical, Vilnius Lithuania—also marketed as Emperor in some European countries; Aachen Resonance, Germany, and AB Medica, Italy) for the treatment of patients with femoropopliteal lesions.

Methods: From January 2019 to January 2020, DCB angioplasties using Elutax were performed on 53 consecutive patients (53 limbs) with femoropopliteal lesions (group A) and compared with a noncontemporary control group (group B) consisting of 71 patients (71 limbs) treated with plain old balloon angioplasty (POBA) between January 2017 and January 2018. Before performing the angioplasty, both groups underwent clinical examination, ultrasound evaluation, and computed tomography angiography to delineate subject clinical and baseline lesion characteristics. Primary end point was primary patency rate at 24 months. Secondary end points included clinically driven target lesion revascularization (CD-TLR), overall survival and limb salvage rates.

Results: In both groups technical success rate was 100% with bailout stenting performed in 16.9% (9/53) of lesions in group A, while stenting was necessary in 22.5% of lesions (16/71) in group B. Patients treated with Elutax exhibited lower 24-month restenosis/reocclusion rate and improved primary patency compared to those treated with POBA (restenosis/reocclusion rate: 9.4% vs. 25.3%, CI 95% 0.01−0.30, $P = 0.034$; primary patency: 88.2% vs. 71.5%, log rank $P = 0.03$). Twenty-four-month CD-TLR rate was 7.5% for DCB versus 18.3% for POBA. No device or procedure-related deaths occurred, and no 30-day mortality was observed in either group. During the follow-up period, the limb salvage rate was 94.9% for A group and 92.1% for B group. All minor amputations occurred in limbs presented with chronic limb threatening ischemia (CLTI). Overall survival was 91.7% for group A and 89.4% for group B.

Conclusions: Paclitaxel + Dextran DCB angioplasty proved safe and effective in managing chronic lesions of femoropopliteal arteries. Our experience has shown superior primary patency rate for Elutax when compared to POBA.

Conflicts of interest: There are no financial conflicts of interest to disclose.

Authors contribution: All authors contributed to (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

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INTRODUCTION

European guidelines[1] recommend an endovascular strategy for lesions <25 cm in both artery symptomatic femoropopliteal disease and below knee artery disease as a first-line treatment. For chronic limb threatening ischemia (CLTI), the guidelines recommend a revascularization strategy in accordance with lesion complexity.

Surgical revascularization was once the only strategy available but in recent years endovascular approaches have gained popularity due to their faster recovery times and correspondingly lower morbidity and mortality rates, particularly in patients with multiple medical comorbidities.

That being said, higher restenosis rates and low long-term patency rates remain limiting factors for the endovascular approach. In order to improve the primary patency rate following plain old balloon angioplasty (POBA), bare-metal stents may be implanted, even if the presence of a permanent metallic scaffold seems to increase restenosis and occlusions.

Over the last years, Paclitaxel-based drug-coated balloons (DCB) and drug-eluting stents (DES) have been showing promise for the treatment of peripheral artery disease and have been introduced to help with lowering restenosis and improving patency rates.[2] Several meta-analyses have reported the superior performance of paclitaxel-based DCBs compared to standard POBA for femoropopliteal peripheral artery lesions,[3,4] causing some authors to consider DCB a first choice for treatment of de novo stenosis. Many commercial devices are available and a new generation of DCBs can combine two drugs to improve results.

A published meta-analysis of randomized controlled trials has shown an increased risk of mortality within 5 years following application of paclitaxel-coated DCB and DES in femoropopliteal lesions,[5,6] postulating a dose-dependent relationship between the death and paclitaxel administration. However, it remains unclear whether treatment of femoropopliteal lesions with a paclitaxel-coated DCB leads to an increase in all-cause mortality in a real-world setting.

The objective of this study is to analyze the safety and effectiveness of a new generation DCB (Elutax; AR Baltic Medical, Vilnius Lithuania—also marketed as Emperor in some European countries; Aachen Resonance, Germany, and AB Medica, Italy) for femoropopliteal lesions and to demonstrate a reduction in restenosis rates and need for reintervention compared to standard POBA, using a case-control study as a model.

MATERIALS AND METHODS

We retrospectively reviewed for a case-control study a prospectively maintained registry of all patients with symptomatic femoropopliteal artery lesions treated with Elutax between January 2019 and January 2020 and POBA between January 2017 and January 2018. Approval from the investigational review board of the Interuniversity Center of Phlebolymphology, International Research and Educational Program in Clinical and Experimental Biotechnology (approval number: ER.ALL.2018. 49 A) was obtained. Inclusion criteria were Rutherford class from 3 to 5, significant femoropopliteal stenosis or occlusion >40 mm in length with patency of at least 1 below-the-knee vessel, and life expectancy >1 year. Exclusion criteria were occlusion longer than 25 cm, occlusion of all below-the-knee vessel, multilevel atherosclerotic disease requiring additional procedures (i.e., iliac angioplasty/stenting, common femoral artery endarterectomy, and so on), and preplanned major amputation (Table I). Indications for intervention included the following: lifestyle-limiting intermittent claudication (Rutherford 3), ischemic rest pain (Rutherford 4), minor tissue loss-nonhealing ulcer, and focal gangrene with diffuse pedal ischemia (Rutherford 5). All patients had a computed tomography angiography to study the features of the arterial lesions and plan the intervention.

Prior to procedure, patient demographics, clinical presentation, and ankle-brachial index (ABI) assessment and comorbidities were identified and recorded (Table II).

Fifty-three consecutive patients (36 males) treated with Elutax were enrolled and defined as group A, and 71 consecutive patients (47 males) treated with POBA were defined as group B. Subjects were followed for a total of 24 months and underwent duplex ultrasonography evaluationat 30 days and 6, 12, and 24 months, thereafter. We performed additional ultrasonographic evaluation, for patients who clinically needed re-evaluation due to recurrent symptoms and/or worsening pain at rest in the limb treated, and nonhealing lesions. Ultrasound performance and interpretation was blinded. Assessments at 1, 6, 12, and 24 months included the occurrence of reintervention (target vessel recanalization, target lesion revascularization (TLR), and amputation), major adverse cardiovascular and cerebrovascular events (MACCE) and health status. Primary patency, defined as freedom from restenosis (duplex ultrasonography peak systolic velocity ratio ≤2.4) and/or reocclusion, was

Table I. Study enrollment criteria

Inclusion criteria	Exclusion criteria
Rutherford 3−4−5	Rutherford 0−1−2−6
Significant femoropopliteal stenosis or occlusion >40 mm in length	Occlusion longer than 25 cm
At least 1 below-the-knee vessel with distal runoff	Poor distal runoff (occlusion of all below-the-knee vessel)
Life expectancy >1 year	Multilevel atherosclerotic disease requiring additional procedures
	Preplanned major amputation

analyzed throughout 24 months per study protocol and considered as the primary end point. Secondary end points included the following: clinically driven target lesion revascularization (CD-TLR) rate, defined as rate of patients with restenosis/reocclusion of the target vessel with need for revascularization due to recurrence of symptoms; overall survival and limb salvage rate.

Statistical analysis was carried out with version April 1, 1106 2009−2021 RStudio, PBC. Continuous variables (age, body mass index, ABI, target lesion reference vessel diameter and length, sheath size, predilation balloon diameter, length and pressure, number of treatment balloons per subject) and outcomes (ABI, procedural time, follow-up time and hospital stay) were analyzed with a Welch two sample *t*-test, while categorical variables (males, current smoker, hypertension, diabetes, insulin-dependent diabetes, dyslipidemia, coronary artery disease, prior myocardial infarction, chronic kidney disease, previous amputation and stenting, Rutherford category, popliteal involvement, total occlusion, no. of patent runoff vessels, contralateral femoral access, type of lesion and need for stenting) with a two-sample test for equality of proportions with continuity correction. Categorical outcomes (restenosis/reocclusion, CD-TLR, target limb major amputation, all-cause death and MACCE-related death) were analyzed with Fisher's test.

The Kaplan−Meier method was used to evaluate time-to-event data. Difference in the survival curves between the treatment groups was assessed using the log-rank test.

The DCB used for our study was Elutax, a third-generation balloon that is the newest of its kind, which enables a long-term drug release over a period of months with only a single inflation. The balloon integrated two different drugs (Dextran + Paclitaxel) on its surface: Dextran, which provided an antithrombotic effect to reduce erythrocyte aggregation, platelet adhesiveness and function while activating plasminogen with a thrombolytic effect, and Paclitaxel which blocked progression of cellular mitosis inhibiting cell division and proliferation to reduce restenosis.[6−8]

Local anesthesia was administrated to all patients. An ipsilateral or contralateral femoral approach was used to perform procedure. After the introducer sheath was successfully inserted, 3500 UI heparin sodium was administrated. In all cases we used plain balloon with a diameter of 1 mm undersized to the reference vessel diameter (RVD) to predilate target lesion. After that, the lesions were dilated with Elutax balloon using a diameter 1:1 ratio to the RVD, which ranged from 4.0 to 6.0 mm. Elutax was inflated at 10 atmospheres for at least 180 sec according to manufacturer's instructions for use. As flow limiting dissection is a significant risk factor for restenosis/occlusion, in cases of a flow-limiting dissection or >50% residual stenosis after Elutax angioplasty, a bailout stent (Everflex Self-Expanding Peripheral Stent System; ev3 Inc. Plymouth, Minnesota, United States) was deployed. Following procedure, all patients were prescribed with a dual antiplatelet therapy, acetylsalicylic acid (aspirin, 100 mg/d) and clopidogrel (75 mg/d) for 24 months, and a single antiplatelet therapy was indefinitely prescribed thereafter. No significant difference about the adherence to anti-platelet therapy between the POBA and Elutax groups was observed. Standard and advanced wound care was continued after intervention until healing was achieved. Primary and secondary end points were assessed at 24 months and no patients were lost to follow up during this period.

RESULTS

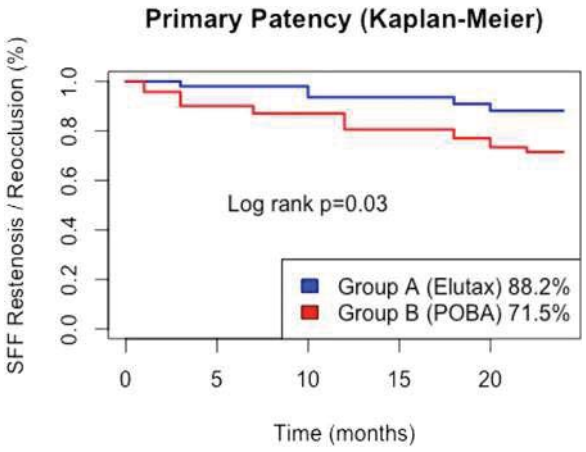
Both treatment groups had similar demographics, comorbidities, and lesion characteristics at baseline (Table II). Cardiovascular risk factors were prevalent in the patients included in the study (Table II), and 13.7% of patients suffered from chronic kidney disease. Half the patients presented with CLTI (Table II). Mean lesion length was 121.5 ± 58.1 mm in

Table II. Subject clinical, baseline lesion, and procedural characteristics

Subject clinical characteristics	Overall ($N = 124$)	Group A (Elutax) $n = 53/124$	Group B (POBA) $n = 71/124$	CI 95%	*P*-value (<0.05)
Age (years)	67.3 ± 8.1	67.3 ± 9.0	67.2 ± 7.4	[−3.15; 2.88]	0.927
Males	83/124 (66.9%)	36/53 (67.9%)	47/71 (66.1%)	[−0.20; 0.16]	0.992
BMI (kg/m^2)	27.0 ± 3.3	26.8 ± 3.4	27.2 ± 3.2	[−0.81; 1.60]	0.515
Current smoker	51/124 (41.1%)	19/53 (35.8%)	32/71 (45%)	[−0.09; 0.28]	0.396
Hypertension(SAP>140 mm Hg and/or DAP>90 mm Hg)	102/124 (82.2%)	43/53 (81.1%)	59/71 (83%)	[−0.13; 0.17]	0.963
Diabetes (glycemia>125 mg/dL and/or use of HD/insulin)	76/124 (61.2%)	31/53 (58.4%)	45/71 (63.3%)	[−0.14; 0.23]	0.713
Insulin-dependent diabetes	30/76 (39.4%)	13/31 (41.9%)	17/45 (37.7%)	[−0.29; 0.20]	0.900
Dyslipidemia(Tot. Chol.>240 mg/dL and/or TGL>150 mg/dL and/or use of LLD)	84/124 (67.7%)	35/53 (66%)	49/71 (69%)	[−0.15; 0.21]	0.875
CAD	47/124 (37.9%)	19/53 (35.8%)	28/71 (39.4%)	[−0.15; 0.22]	0.825
Prior MI	16/124 (12.9%)	9/53 (16.9%)	7/71 (9.8%)	[−0.21; 0.06]	0.368
CKD (GFR<60 ml/min/1,73m^2)	17/124 (13.7%)	5/53 (9.4%)	12/53 (16.9%)	[−0.06; 0.20]	0.351
Previous amputation	4/124 (3.2%)	3/53 (5.6%)	1/71 (1.4%)	[−0.12; 0.04]	0.416
Previous stenting	12/124 (9.6%)	8/53 (15.1%)	4/71 (5.6%)	[−0.22; 0.03]	0.145
ABI	0.52 ± 0.09	0.51 ± 0.08	0.52 ± 0.09	[−0.02; 0.04]	0.527
Rutherford 3	57/124 (45.9%)	26/53 (49%)	31/71 (43.6%)	[−0.24; 0.13]	0.678
Rutherford 4	41/124 (33%)	16/53 (30.1%)	25/71 (35.2%)	[−0.13; 0.23]	0.692
Rutherford 5	26/124 (20.9%)	11/53 (20.7%)	15/71 (21.1%)	[−0.14; 0.15]	1.000
Baseline lesion and procedural characteristics					
Popliteal involvement	32/124 (25.8%)	13/53 (24.5%)	19/71 (26.7%)	[−0.14; 0.19]	0.941
Target lesion RVD (mm)	5.1 ± 0.6	5.1 ± 0.6	5.1 ± 0.6	[−0.21; 0.23]	0.938
Target lesion length (mm)	117 ± 55.2	121.5 ± 58.1	113.6 ± 53.2	[−28; 12.3]	0.441
Total occlusion	96/124 (77.4%)	42/53 (79.2%)	54/71 (76%)	[−0.19; 0.13]	0.839
No. of patent runoff vessels					
1	45/124 (36.2%)	18/53 (33.9%)	27/71 (38%)	[−0.14; 0.22]	0.781
2	36/124 (29%)	14/53 (26.4%)	22/71 (30.9%)	[−0.13; 0.22]	0.722
3	43/124 (34.6%)	21/53 (39.6%)	22/71 (30.9%)	[−0.27; 0.10]	0.418
Contralateral femoral access	107/124 (86.3%)	47/53 (88.6%)	60/71 (84.5%)	[−0.17; 0.09]	0.686
Type of lesion					
De novo	101/124 (81.4%)	41/53 (77.3%)	60/71 (84.5%)	[−0.08; 0.22]	0.435
Restenosis/reocclusion	19/124 (15.3%)	9/53 (16%)	10/71 (14%)	[−0.17; 0.11]	0.848
Intrastent restenosis/reocclusion	4/124 (3.2%)	3/53 (5.6%)	1/71 (1.4%)	[−0.12; 0.04]	0.416
Sheath size (French)	5.8 ± 0.7	5.8 ± 0.8	5.8 ± 0.7	[−0.31; 0.22]	0.735
Predilation balloon diameter (mm)	4.3 ± 0.7	4.3 ± 0.8	4.2 ± 0.7	[−0.31; 0.24]	0.806
Predilation balloon length (mm)	74.7 ± 27.3	75.8 ± 28	73.9 ± 26.9	[−11.8; 8.01]	0.704
Predilation balloon pressure (atm)	8.5 ± 2.7	8.5 ± 2.9	8.5 ± 2.6	[−1.07; 0.92]	0.885
No. of treatment balloons per subject	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.2	[−0.13; 0.08]	0.603
Need for stenting	25/124 (20.1%)	9/53 (16.9%)	16/71 (22.5%)	[−0.10; 0.21]	0.591

BMI, body mass index; SAP, systolic arterial blood pressure; DAP, diastolic arterial blood pressure; HD, hypoglycemic drugs; TGL, triglycerides; LLD,lipid-lowering-drugs; CAD, coronary artery disease; MI, myocardial infarction; CKD, chronic kidney disease; GFR, glomerular filtration rate; RVD, reference vessel diameter.

the Elutax group versus 113.6 ± 53.2 mm in the POBA group ($P = 0.441$). Forty-two (79.2%) of 53 Elutax-treated lesions and 54 (76%) of 71 POBA-treated lesions were occlusions. Thirty-three-point nine percent and 38% of the lesions in groups A and B respectively, had only 1 distal outflow vessel with the remainder having at least 2 distal outflow vessels. Owing to the >50% residual stenosis (CLTI limbs, 4) and flow-limiting dissections (CLTI limbs, 5), 9 superficial femoral lesions in group A and 16 in group B required stent placement, resulting in a stent-assisted technical success rate of



groups=Elutax

time	n.risk	n.event	survival	std.err
3	51	1	0.980	0.0194
10	44	2	0.936	0.0359
18	35	1	0.909	0.0437
20	33	1	0.882	0.0503

groups=POBA

time	n.risk	n.event	survival	std.err
1	71	3	0.958	0.0239
3	67	4	0.901	0.0357
7	60	2	0.871	0.0403
12	54	4	0.806	0.0485
18	45	2	0.770	0.0526
20	42	2	0.734	0.0561
22	39	1	0.715	0.0577

Fig. 1. The Kaplan-Meier estimate of primary patency.

100%. Technical success, defined as residual diameter stenosis ≤50% for non-stented patients or ≤30% for stented patients, was achieved in 100% of the subjects in both groups.

The restenosis/reocclusion rate at 24-months was significantly lower with Elutax than with POBA (restenosis/reocclusion rate: 9.4% vs. 25.3%, odds ratio [OR] 0.30, 95% confidence interval [CI]: 0.08−0.95, $P = 0.034$). The Kaplan−Meier estimate of primary patency was 88.2% for Elutax compared to 71.5% for POBA (log rank $P = 0.03$; Fig. 1). Elutax-treated patients showed no significant difference in CD-TLR rate at 24 months (7.5% vs. 18.3%, OR: 0.36, 95% CI: 0.08−1.28, $P = 0.114$) compared with patients treated with POBA (Table III, Fig. 2). The mortality rate at 24-months was similar in both groups (5.6% vs. 8.4%, OR 0.65, 95% CI: 0.10−3.23, $P = 0.731$). The Kaplan−Meier estimate of overall survival was 91.7 % for Elutax compared to 89.4% for POBA (log rank $P = 0.5$; Fig. 3). Four were MACCE-related deaths (1.8% vs. 4.2%, OR: 0.43, 95% CI: 0.008−5.64, $P = 0.635$) while 3/124 and 2/124 were respiratory insufficiency- and septic state-related deaths.

During the follow-up period of 24 months, 2 above-the-knee amputations in group A versus 5 amputations in group B were observed (3.7% vs. 7%, OR: 0.52, 95% CI: 0.04−3.33, $P = 0.697$). The Kaplan−Meier estimate of limb salvage was 94.9% for Elutax compared to 92.1% for POBA (log rank $P = 0.4$; Fig. 4).

No deaths or other major complications (i.e., rupture, perforation, embolization of distal arteries, and contrast nephropathy) were observed in any of the patients within 30 days after procedure in either group.

DISCUSSION

Several randomized trials report on the superior benefits/major advantages of employing DCB over POBA in patients with femoropopliteal disease,[7,9,10] denoting higher patency rates compared to uncoated balloons.

Our study demonstrates that performing endovascular DCB angioplasty with Elutax can be safe and effective in treating patients with atherosclerotic femoropopliteal lesions leading to high levels of technical success, limb salvage and patency rates as well as low prevalence of procedure-related complications, even in limbs presenting CLTI and long-segment occlusion lesions.

Elutax has been used in several trials to treat de novo coronary and intracranial artery stenosis resulting in a more favorable angiographic outcome of ''new generation'' DCBs versus other DCBs, thereby demonstrating their feasibility and safety in patients with symptomatic high-grade stenosis and is supported by significantly lower rates of ischemic re-events or restenosis.[11,12]

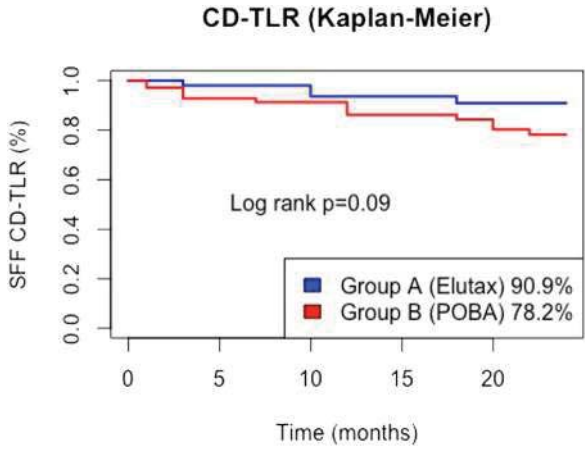
Treatment of long steno-occlusive femoropopliteal lesions is associated with a high risk of dissection to rechannel vessel increasing the impact of future restenosis, so it could be necessary stents implantation even if in short no flow limiting dissections it should be unnecessary.[13] Long-segment occlusions typically treated with subintimal recanalization using balloon cause tears and dissections. In such cases the use of DCB could improve angioplasty result and late vascular remodeling.[14]

Because flow-limiting dissection is a significant risk factor for restenosis/reocclusion,[14] 25 out of the 124 treated cases in our study required stent placement due to flow-limiting dissections. Moreover, it was found that, when compared to POBA, DCB was associated with decreased arterial wall fibrosis after

Table III. Safety and effectiveness outcomes (24-months)

Safety and effectiveness outcomes (24 months)	Overall	Group A (Elutax)	Group B (POBA)	Odds ratio	CI 95%	*P*-value (<0.05)
	N = 124	*n* = 53/124	*n* = 71/124			
Restenosis/reocclusion (No. of restenosis or reocclusions/total limb treated)	23/124 (18.5%)	5/53 (9.4%)	18/71 (25.3%)	0.30	[0.08; 0.95]	0.034
CD-TLR	17/124 (13.7%)	4/53 (7.5%)	13/71 (18.3%)	0.36	[0.08; 1.28]	0.114
Target limb major amputation	7/124 (5.6%)	2/53 (3.7%)	5/71 (7%)	0.52	[0.04; 3.33]	0.697
All-cause death	9/124 (7.2%)	3/53 (5.6%)	6/71 (8.4%)	0.65	[0.10; 3.23]	0.731
MACCE related death	4/124 (3.2%)	1/53 (1.8%)	3/71 (4.2%)	0.43	[0.008; 5.64]	0.635
ABI	0.8 ± 0.12	0.85 ± 0.12	0.77 ± 0.12	-	[−0.11; −0.03]	<0.001
Procedural time (min)	86.4 ± 34.5	85.1 ± 36.5	87.4 ± 33.2	-	[−10.2; 15.0]	0.711
Hospital stay (days)	2 ± 1.8	2 ± 2	2 ± 1.7	-	[−0.71; 0.65]	0.934
Follow-up time (months)	24 ± 0	24 ± 0	24 ± 0	-	NA	NA
Technical success	124/124 (100%)	53/53 (100%)	71/71 (100%)	NA	NA	NA

CD-TLR, clinically-driven target lesion revascularization; MACCE, major adverse cardiovascular and cerebrovascular events; NA, not applicable.



groups=Elutax

time	n.risk	n.event	survival	std.err
3	51	1	0.980	0.0194
10	44	2	0.936	0.0359
18	35	1	0.909	0.0437

groups=POBA

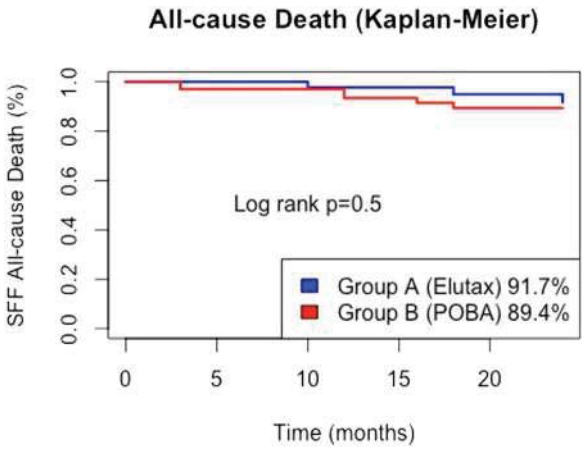
time	n.risk	n.event	survival	std.err
1	71	2	0.972	0.0196
3	67	3	0.928	0.0309
7	60	1	0.913	0.0340
12	54	3	0.862	0.0429
18	45	1	0.843	0.0461
20	42	2	0.803	0.0519
22	39	1	0.782	0.0545

Fig. 2. The Kaplan-Meier estimate of CD-TLR.

overstretch injuries by balloon angioplasty and reduced degrees of constrictive remodeling and neointimal hyperplasia.[11,15] Notwithstanding these findings, however, the effects of various DCBs or stents on the subintimal channel require further investigation.

Severe calcification reducing the antirestenotic effect of the drug is considered a risk factor for restenosis in the femoropopliteal segment[16] following DCB angioplasty,[17] and to support this 5 reocclusion episodes did occur in our Elutax group while in the POBA angioplasty group the reocclusion rate was even higher (18/71). These patients had been elected for surgical or hybrid procedures benefiting from the complementary role of endovascular and surgical treatments which compensated for unsatisfactory results of both approaches.[18,19]

Infrapopliteal outflow is considered a significant factor potentially affecting the primary patency rate of femoropopliteal occlusive diseases. Salapura et al.[20] reports that restenosis or reocclusion occurred in 23% of subjects with compromised outflow and 11% of patients with good runoff 1 month after femoropopliteal angioplasty, though restenosis or reocclusion incidence increased at approximately identical rates in both groups after 6 months (49% vs. 43%) and 12 months (57% vs. 52%) leading the authors to conclude that patients are predisposed to early restenosis or reocclusions if there is a compromised postprocedural infrapopliteal outflow. A retrospective review[21] of 86 patients treated with angioplasties for femoropopliteal occlusions found that a decreased primary patency and limb salvage rate was significantly associated with isolated popliteal artery outflow or one tibial vessel outflow during a mean follow-up time of 2.4 years (880 ± 68.84 days), suggesting that the impact of infrapopliteal outflow on long-term patency after



groups=Elutax

time	n.risk	n.event	survival	std.err
10	44	1	0.977	0.0225
18	35	1	0.949	0.0351
24	29	1	0.917	0.0467

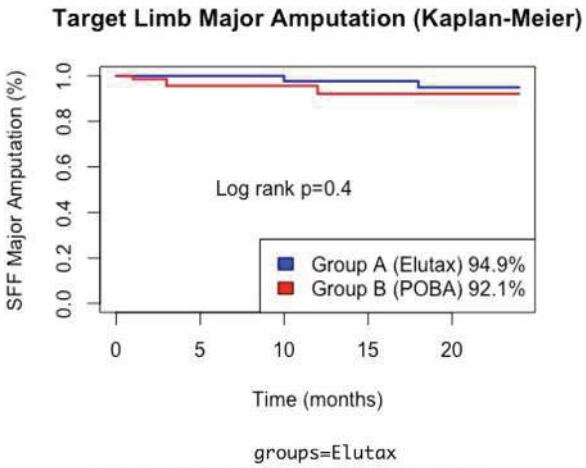
groups=POBA

time	n.risk	n.event	survival	std.err
3	67	2	0.970	0.0208
12	54	2	0.934	0.0320
16	47	1	0.914	0.0370
18	45	1	0.894	0.0413

Fig. 3. The Kaplan-Meier estimate of overall survival.

popliteal DCB angioplasty requires a longer follow-up period. A systematic review and meta-analysis by Katsanos et al. reported an increased risk of all-cause mortality following the application of paclitaxel-coated balloons and stents in the femoropopliteal artery.[6] In our study, no coating related adverse events were observed at 12- and 24-months follow-up with the Elutax approach. Moreover, overall survival at 24 months was higher in the Elutax group than in the POBA one (91.7% vs. 89.4%, log-rank $P = 0.5$; Fig. 1C). Due to the limited follow-up period, we were unable to evaluate the long-term safety of Elutax angioplasty in femoropopliteal artery lesions and further research with a longer follow-up duration is undoubtedly required for safety concerns. Several studies have proven that paclitaxel-DCB is also effective in treating limbs with CLTI caused by infrapopliteal lesions as evidenced by relief of rest pain and promotion of ulcer healing, citing that they give better results in outcomes when compared to POBA angioplasty.[3,4,9]

Due to the favorable results revealed by our analysis and reported herein, we can conclude that paclitaxel + dextran DCB is considered a safe and effective modality for treating femoropopliteal lesions, albeit a longer follow-up period is necessary to confirm its long-term efficacy.



groups=Elutax

time	n.risk	n.event	survival	std.err
10	44	1	0.977	0.0225
18	35	1	0.949	0.0351

groups=POBA

time	n.risk	n.event	survival	std.err
1	71	1	0.986	0.0140
3	67	2	0.956	0.0246
12	54	2	0.921	0.0341

Fig. 4. The Kaplan-Meier estimate of limb salvage.

CONCLUSIONS

New generation DCBs have firmly secured their propitious role in femoropopliteal disease proving excellent short-term patency and low TLR rates when compared to POBA alone. They have also been shown to be safe. Given the reduction in TLR and its ease of use, new generation DCBs can be considered an attractive alternative to conventional POBA. More randomized trials are necessary to optimize the drug dosage needed so as to ensure better long-term outcomes. This can be done by evaluating paclitaxel + dextran-based DCBs and establishing their safety in femoropopliteal disease.

The results of our study lead us to conclude that, when compared with POBA, treatment with Elutax provides superior clinical benefits throughout early and midterm follow-up bearing in mind, however, that longer-term outcomes are as yet uncertain and need to be studied further.

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