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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].

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 µg/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. Pre-dilation 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

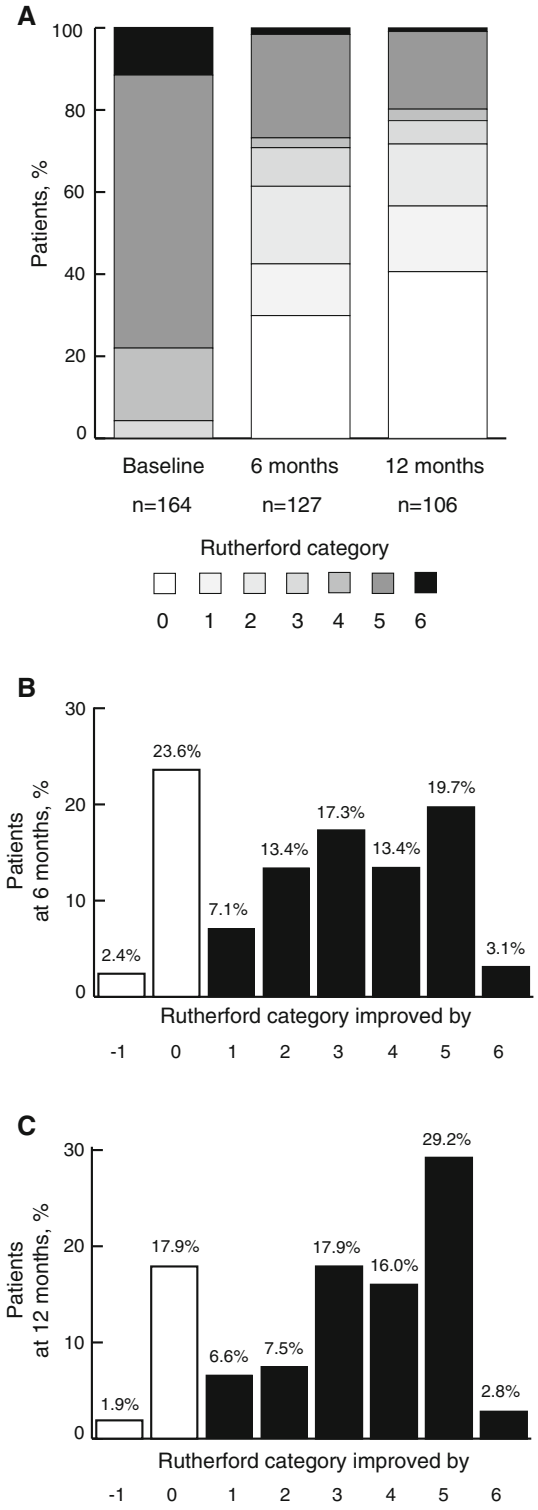

Fig. 1 Distribution of Rutherford categories at baseline and follow-ups (**A**), and clinical improvement from baseline to 6 months (**B**) and to 12 months (**C**)

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).

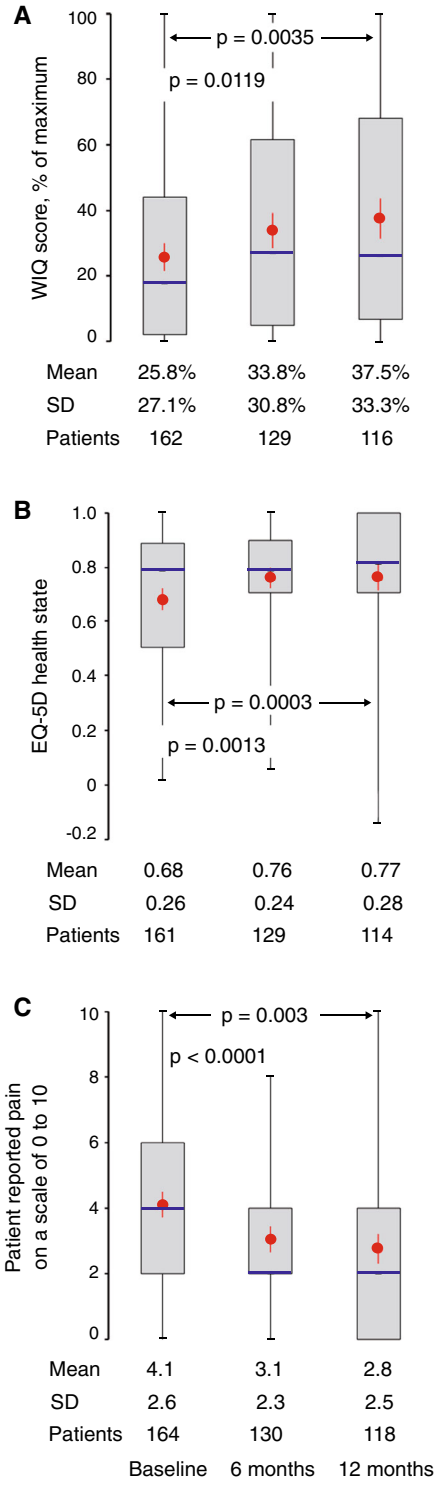

Fig. 2 Quality of life at baseline and at 6- and 12-month follow-ups expressed in Walking Impairment Questionnaire score (**A**), European Quality of Life-5 Dimensions score (**B**), and patient-reported pain (**C**). Box plots indicate median and interquartile range. Whiskers end with the lowest and 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

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 ELUTAX SV 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.

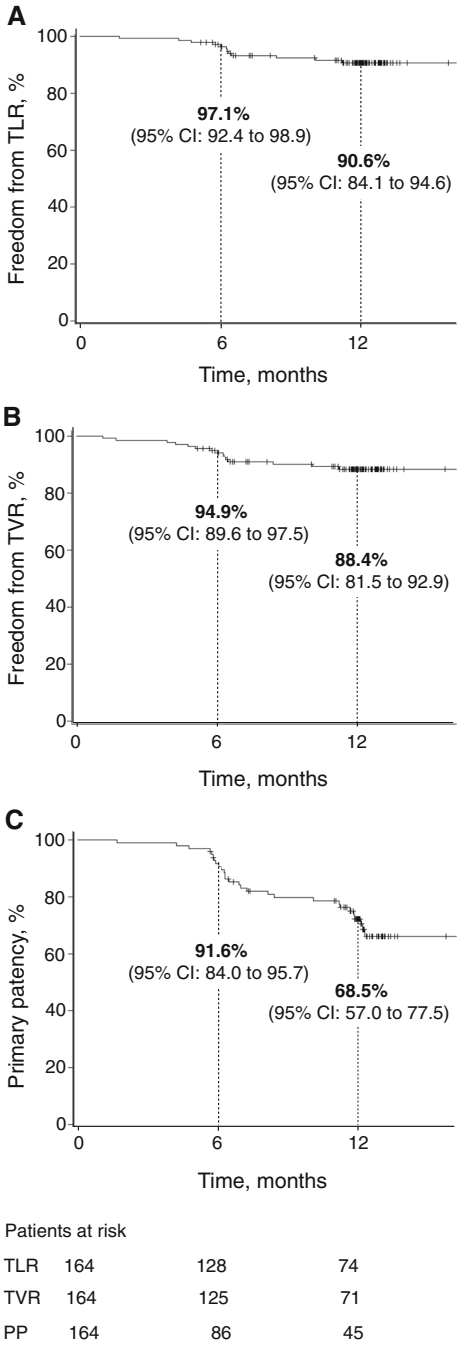

Fig. 3 Kaplan–Meier survival estimates for freedom from target lesion revascularisation (**A**), freedom from target vessel revascularisation (**B**), and primary patency (**C**). *CI* confidence interval, *PP* primary patency, *TLR* target lesion revascularisation, *TVR* target vessel revascularisation

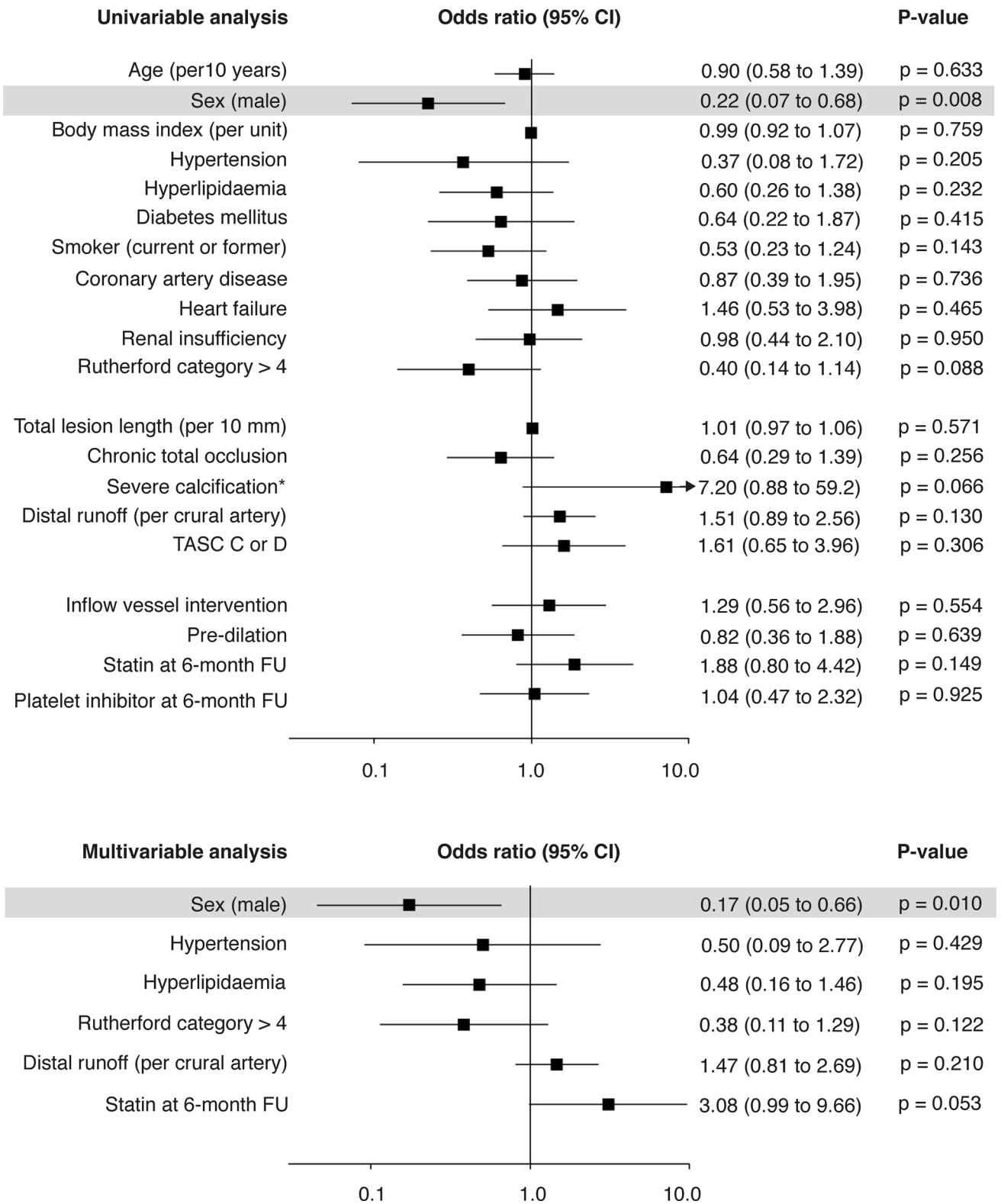

Fig. 4 Probability of improvement by at least one Rutherford category at 6 months without the need of target lesion revascularisation. *Not included into multivariable regression due to numerous missing data. *CI* confidence interval, *FU* follow-up, *TASC* inter-society consensus for the management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

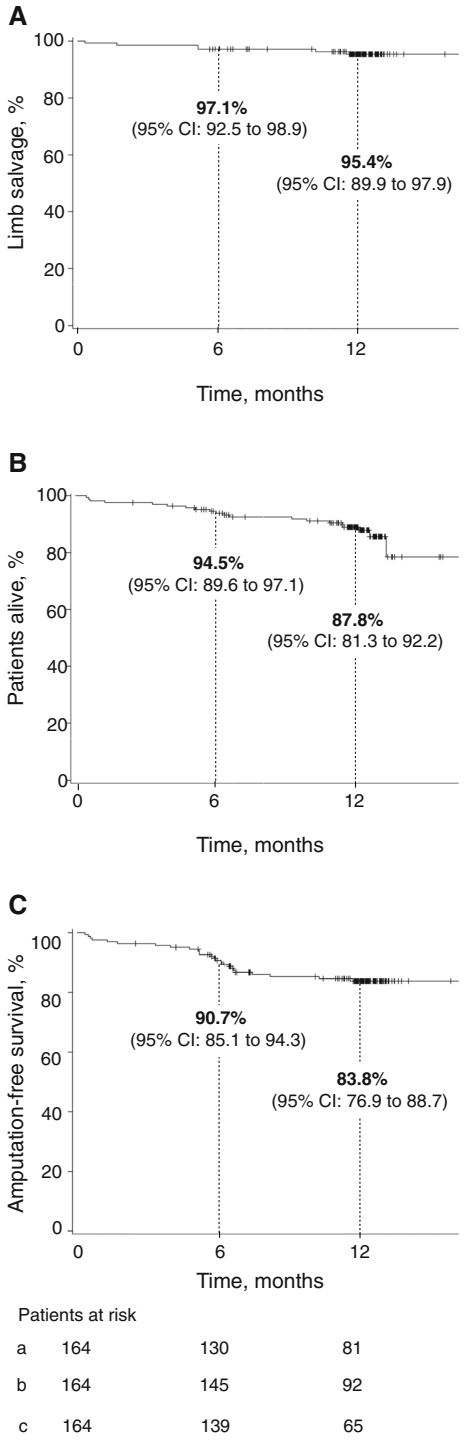

Fig. 5 Kaplan–Meier estimates for limb salvage (**A**), survival (**B**), and major amputation-free survival (**C**). *CI* confidence interval

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

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

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.

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

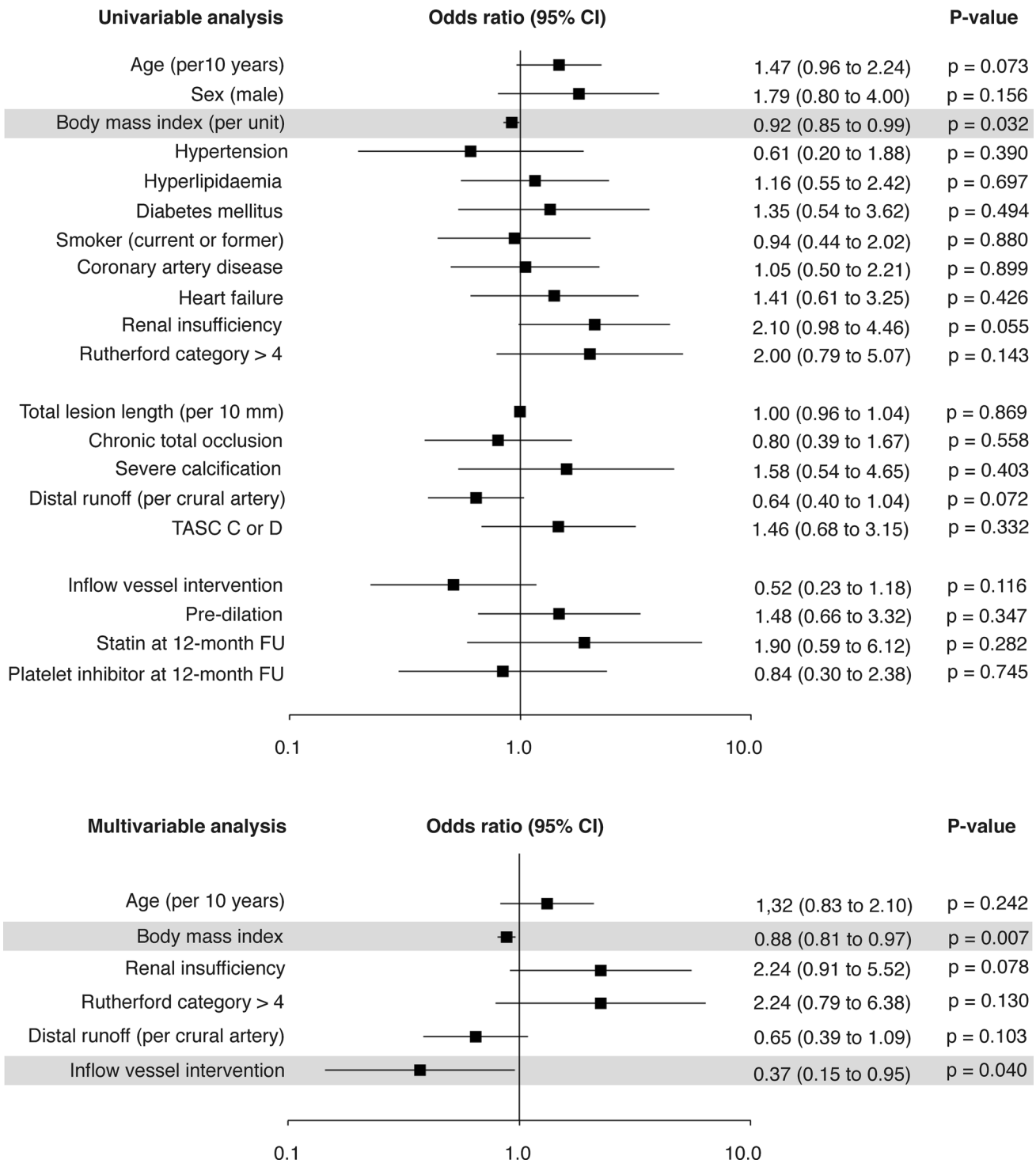

Fig. 6 Probability of death or any amputation at 12 months. *CI* confidence interval, *FU* follow-up, *TASC* inter-society consensus for the management of peripheral arterial disease classification of infrapopliteal lesions

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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