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Safety and Efficacy of All Comers Treated with a Paclitaxel Coated Balloon for Below Knee Intervention

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WHAT THIS PAPER ADDS

In this retrospective single centre cohort study comprising 552 consecutive patients predominantly suffering from critical limb threatening ischaemia, the use of paclitaxel coated balloons (PCBs) was found to be safe for infrapopliteal interventions with similar mortality and a signal towards lower amputation rates than standard balloon angioplasty in unadjusted and propensity score matched analysis. No benefit was seen for repeat revascularisation up to two years of follow up. Because PCBs have rarely been used for infrapopliteal procedures outside of clinical trials, these data show outcomes in a complex all comer cohort without the strict inclusion and exclusion criteria of randomised trials.

Objective: Data on paclitaxel coated balloons (PCBs) for below knee (BTK) angioplasty exhibited conflicting efficacy results, and previous meta-analyses suggested an increased mortality and amputation risk highlighting the need for further research. The aim of this study was to investigate safety and efficacy of PCBs for BTK interventions in a real world cohort.

Methods: Within a single centre cohort study, 552 consecutive patients were included undergoing BTK interventions with and without PCB use. Two year safety and efficacy results were compared in unadjusted and propensity score matched (PSM) analysis.

Results: BTK interventions were performed in 157 patients with PCB angioplasty (100% Lutonix 0.014 inch drug coated balloon; Bard Lutonix, New Hope, MN, USA) and 395 patients with plain old balloon angioplasty (POBA). The majority of interventions (> 70%) were performed for chronic limb threatening ischaemia. Mean lesion length was 20.8 ± 12.6 cm; 61.2% in the PCB and 66.7% in the POBA group were occlusions. In the PCB group, more procedures were performed for re-stenotic lesions than POBA (28.5 *vs.* 17.2%). In PSM analysis (128 matched pairs), the primary efficacy endpoint was freedom from clinically driven target lesion revascularisation (CD TLR), which occurred in 70.1% in the PCB and 73.1% in the POBA group at one year ($p = .85$; McNemar test). Survival analysis suggested lower rates of major amputations in the PCB group in unadjusted (94.4% ± 2.1 *vs.* 89.2% ± 1.9 in the POBA group) and PSM analyses (97.2% ± 1.6 *vs.* 89.3% ± 3.5) through two years, while no differences were seen for CD TLR and all cause mortality between the groups.

Conclusion: In this all comer analysis, PCBs were found to be safe for BTK interventions with a signal towards lower amputation rates but no benefit was seen for repeat revascularisation.

Keywords: Angioplasty, Below the knee, Mortality, Paclitaxel coated balloon
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INTRODUCTION

Peripheral arterial disease (PAD) of the lower extremities is a common disease that affects an estimated 27 million adults in Europe and North America and over 200 million people worldwide.[1] Owing to the ageing of the population and increasing number of patients with diabetes, more and more patients present with chronic limb threatening ischaemia (CLTI) and often complex, multivessel disease involving the arteries below the knee, requiring timely revascularisation.[2] Over the past decade, advances in endovascular therapy have led to the widespread use of interventional techniques to restore blood flow in these cases, avoiding open bypass

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surgery.[3] While the immediate success rate of below knee (BTK) interventions has improved substantially with new technologies and devices,[4] re-stenosis remains the most important limitation to long term success.[5] The adoption of drug eluting technologies has significantly improved primary patency after femoropopliteal procedures,[6–8] but no such substantial and distinct progress has been made in addressing re-stenosis after BTK interventions. While balloon expandable stents coated with sirolimus analogues have shown promising results in BTK lesions compared with bare metal stents and plain old balloon angioplasty (POBA) in reducing the risk of re-intervention and amputation,[9] these devices are mainly suitable for proximal, relatively short lesions and not for long, complex occlusions commonly seen in patients undergoing BTK interventions. Results from randomised controlled trials (RCTs) evaluating different paclitaxel coated balloons (PCBs) for endovascular BTK interventions showed mixed results. Two early multicentre trials clearly failed to show a benefit,[10,11] while a recently published large, multicentre RCT indicated a signal of improved patency with PCB use at six months after the procedure.[12] Importantly, two single centre studies also reported a clear advantage of PCBs over POBA for BTK interventions.[13,14] To date, it is unclear whether different interventional strategies or unique coating technologies and antire-stenotic properties of the various PCBs are responsible for the observed disagreements in outcomes.

In addition, a prior meta-analysis of RCTs identified an increased risk of death and amputation associated with the use of PCBs for CLTI treatment below the knee at one year follow up[15] and a similar mortality signal beyond two years follow up was previously postulated by the same researchers following femoropopliteal interventions.[16] Another recent meta-analysis postulated an increased amputation risk of PCB for both femoropopliteal and infrapopliteal interventions in patients presenting with CLTI as well as claudication.[17] While numerous subsequent studies including individual patient level meta-analyses, large cohort studies, and emerging RCT data have investigated the late mortality signal after femoropopliteal procedures,[18–23] only limited data have been published for patients undergoing BTK interventions. Thus, a recent cohort study refuted an increased mortality risk of drug eluting technologies when comparing different BTK treatment strategies based on health insurance claims data.[24] Against this background, the aim of the study was to evaluate the safety and efficacy of all consecutive BTK interventions with and without PCB use in the real world, in an all comer patient cohort at a large tertiary vascular centre to address safety and efficacy beyond the highly selected study population of RCTs with their stringent inclusion and exclusion criteria.

MATERIALS AND METHODS

Patient population

Consecutive patients with symptomatic PAD (Rutherford clinical stage 2 – 6) undergoing BTK endovascular percutaneous interventions between 1 September 2014 and 31 December 2017 with or without PCB use were included in this single centre, retrospective, non-interventional cohort study. No formal inclusion or exclusion criteria were applied, and all patients included were uniquely assigned to one of the treatment arms. Thus, both limbs treated at separate time points could be included for analysis if the same treatment strategy was used. As part of clinical routine, patient demographics were obtained on admission including medical history and physical examination focusing on PAD with classification according to Rutherford and measurement of ankle brachial index (ABI). Patients with CLTI were classified according to the Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) system including the following characteristics: wound extent (e.g., size, depth, presence of gangrene), degree of ischaemia, and extent of foot infection. All three factors were individually graded on a scale of 0 to 3 and the grades were combined to create a WIfI clinical stage as a means to predict the risk of limb amputation at one year.[2] The study was performed in line with the requirements of the local ethics committee and ethical approval was obtained.

Procedural data and follow up

Detailed procedural data including prior revascularisation procedures, lesion location, type (*de novo*, re-stenotic, in stent) and segment (proximal, middle, distal; all tibioperoneal trunk lesions were considered proximal), lesion characteristics (degree of calcification; stenotic or occluded) and lengths (based on the maximum distance treated with balloon angioplasty), number and diameter of balloon angioplasty catheters used (both uncoated and paclitaxel coated), use of adjunctive devices as well as information on concomitant in- and outflow interventions were collected through review of angiograms and clinical charts. At the vascular centre, during the study period the only available CE certified 0.014 inch PCB catheter dedicated for infrapopliteal interventions was the Lutonix 0.014 inch drug coated balloon (DCB) (Bard Lutonix, New Hope, MN, USA). The device is an over the wire drug coated percutaneous transluminal angioplasty (PTA) dilatation catheter with a semicompliant balloon that is coated with paclitaxel at a concentration of 2 μg/mm^2 and the excipients polysorbate and sorbitol to facilitate drug release and tissue deposition. As local standard of care pre-dilatation with an undersized (diameter at least 0.5 mm smaller) uncoated balloon was performed before PCB use avoiding geographic miss by exceeding the proximal and distal margins of the pre-dilated segment. When using multiple PCBs for full lesion coverage, an overlap of at least five mm had to be ensured. The decision to use PCBs was made solely by the operator based on clinical judgement and anatomical features considered to be associated with increased subsequent re-stenosis risk, including lesion length, chronic occlusion, re-stenotic lesions, small vessel diameter, and poor outflow below the ankle. The institution gave no guidance other than that they should be reserved for patients at high risk of re-stenosis.

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During hospital admission patients presenting with Rutherford stage 5 (non-healing ulcer, focal gangrene) or 6 (major tissue loss extending above transmetatarsal level) were referred to a vascular surgeon to assess the need for amputation. For these patients access to specialised wound care teams was ensured at discharge.

In all patients, clinical follow up visits at the centre were identified up to two years after the index procedure. Patients were either routinely scheduled for follow up visits at the institution after six months and yearly thereafter or were monitored by a local vascular specialist/centre. The standardised institutional follow up protocol included physical examination, assessment of medical history and symptoms related to PAD, documentation of adverse events and pharmacotherapy, as well as ABI measurements and duplex ultrasound.

For clinical deterioration, patients were typically referred to the centre for re-intervention. Information on subsequent revascularisation procedures of the target vessel as well as other territories were captured including the use of further paclitaxel containing devices. Information on living status was obtained by chart review as well as a census register query up to two years after the index intervention.

Study endpoints

Based on a pre-defined statistical analysis plan, the primary effectiveness endpoint was defined as the rate of limbs not needing clinically driven target lesion revascularisation (CD TLR) 12 months after the index procedure. CD TLR was defined as any re-intervention to the target lesion for $\geq$ 50% re-stenosis as determined by angiography and clinical worsening (i.e., increase of one Rutherford class or more, delayed or worsening wound healing, new or recurrent wound, or recurrence of ischaemic rest pain). The primary safety endpoint was defined as the rate of patients without a major adverse event comprising all cause death, major (above the ankle) target limb amputation, or CD TLR through to 12 months post-procedure. Other secondary endpoints comprised procedural success defined as achievement of a final residual diameter stenosis of $<$ 50% without flow limiting arterial dissection at the end of the index procedure, all and CD TLR, major amputations, change in Rutherford clinical category, and all cause mortality through to two years.

Statistical analysis

Descriptive statistics were defined as counts and percentages for categorical data, and as mean and standard deviation or median (interquartile range) for continuous data. Differences between PCBs and POBA were analysed using Fisher's exact test for categorical variables. For comparison of continuous variables between groups, the robust Student *t* test or Mann—Whitney U test were used.

To account for potential confounders, a propensity score (PS) 1:1 matching was performed in order to yield comparable pairs of PCB and POBA patients. All endpoints and variables used for PS matching had to be unique values per patient. PS matching was performed using greedy algorithm and a calliper of 0.2 standard deviations with the subsequent covariables: age (years), body mass index (kg/m^2), prior target limb revascularisation (yes/no), concomitant inflow intervention (yes/no), concomitant pedal intervention (yes/no), lesion length (mm), calcification (none—mild or moderate—severe), tibioperoneal trunk (yes/no), anterior tibial artery (yes/no), posterior tibial artery (yes/no), peroneal artery (yes/no). Fixed categories comprised clinical status (claudicants/CLTI), lesion type (*de novo*/re-stenotic/in stent), proximal vessel segment treated (yes/no), and lesion severity (stenotic/occluded). The balance of the matched sample was checked using standardised differences and should not exceed 10% ($<$ 0.1) after matching. Differences in rates between the matched samples were analysed via McNemar's test. Differences in time to event data were assessed via Kaplan—Meier (KM) analyses and compared using the log rank test for unmatched and the stratified log rank test for matched data sets.

Using the full data set, multivariable Cox proportional hazards regression analysis was conducted including the following covariables: sex (female/male), age (years), clinical status (claudicants/CLTI), body mass index (kg/m^2), diabetes (yes/no), hypertension (yes/no), hyperlipidaemia (yes/no), smoking status (current/previous/never), coronary artery disease (yes/no), lipid lowering drug (yes/no), chronic renal disease (renal failure/chronic renal insufficiency/none), PCB use (yes/no), prior target limb revascularisation (yes/no), concomitant inflow intervention (yes/no), concomitant pedal intervention (yes/no), lesion length, (mm), calcification (none—mild or moderate—severe), lesion type (*de novo*/re-stenotic/in stent), lesion severity (stenotic/occluded), and stent use (yes/no). Due to the comparatively small sample size, variable selection was implemented via a stepwise procedure with a chosen significance level for entry of 0.15 and a chosen significance level for stay of 0.2.

All analyses were intentionally calculated to a full significance level of 5%, that is, they were not corrected in respect to multiple tests. For all analyses SAS 9.4 (SAS Institute Inc, Cary, NC, USA) for Windows was used.

RESULTS

Baseline characteristics and acute outcomes in the full cohort

Over the study period, 552 patients were identified undergoing 573 interventions comprising 157 patients (165 limbs) treated with PCBs and 395 patients (408 limbs) with POBA. Detailed patient, lesion, and procedural characteristics for both groups are given in Table 1 and Table 2. Over 70% of patients suffered from CLTI, as 15.5% of patients presented with ischaemic rest pain and 57.8% with skin ulcerations. The high WIfI score (58.6% with WIfI 3 or 4, Table 1), which has been associated with a high risk of amputation in previous studies of patients with CLTI, underscores the advanced disease.[2] In claudicants, infrapopliteal interventions were only performed when patients

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Table 1. Baseline characteristics of 552 patients undergoing below the knee intervention for symptomatic peripheral artery disease treated with paclitaxel coated balloon (PCB) or plain old balloon angioplasty (POBA)

	PCB group (n = 157 patients; 165 limbs)	POBA group (n = 395 patients; 408 limbs)	p value
Demographics			
Age − y	72.6 ± 11.1	72.9 ± 10.9	.71
Male gender	117 (74.5)	286 (72.4)	.67
BMI − kg/m^2	27.0 ± 4.6	27.5 ± 5.6	.26
BMI ≥ 30 kg/m^2	35 (22.3)	105 (26.6)	.33
Medical history			
Hypertension	153 (97.5)	374 (94.7)	.18
Hyperlipidaemia	138 (87.9)	292 (73.9)	<.001
Diabetes	86 (54.8)	243 (61.5)	.15
Smoking			.16
Current	46 (29.3)	88 (22.3)	
Prior	35 (22.3)	111 (28.1)	
Never	76 (48.4)	196 (49.6)	
Renal function			
Chronic renal insufficiency*	53 (33.8)	145 (36.7)	.64
Kidney failure†	9 (5.7)	30 (7.6)	.58
Coronary artery disease	64 (40.8)	174 (44.1)	.51
Prior MI	26 (16.6)	63 (15.9)	.90
Cerebrovascular disease	35 (22.3)	85 (21.5)	.91
Medication			
Aspirin	118 (75.2)	276 (69.9)	.25
Clopidogrel	53 (33.8)	100 (25.3)	.058
Other anticoagulants	43 (27.4)	121 (30.6)	.47
Statins	108 (68.8)	252 (63.8)	.28
ACE inhibitor/ARB	115 (73.2)	278 (70.4)	.53
Beta blocker	94 (59.9)	238 (60.3)	1.0
Other antihypertensive drug	98 (62.4)	250 (63.3)	.85
Target limb characteristics			
Prior target limb intervention	115 (69.7)	258 (63.2)	.15
Surgical	34 (20.6)	108 (26.5)	.17
Endovascular	110 (66.7)	224 (54.9)	.011
Rutherford class			.006
2	15 (9.1)	28 (6.9)	
3	36 (21.8)	74 (18.1)	
4	16 (9.7)	73 (17.9)	
5	75 (45.5)	206 (50.5)	
6	23 (13.9)	27 (6.6)	
Clinical status			.18
Claudicant	51 (30.9)	102(25.0)	
CLTI	114 (69.1)	306 (75.0)	
WIfI stage in patients with CLTI			
2	25 (21.9)	59 (19.3)	.45
3	44 (38.6)	105 (34.3)	
4	45 (39.5)	142 (46.4)	

Data are presented as n (%) or mean ± standard deviation. PCB = paclitaxel coated balloon; POBA = plain old balloon angioplasty; MI = myocardial infarction; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; WIfI = WIfI Classification System (Wound, Ischemia, and foot Infection); CLTI = chronic limb threatening ischaemia.

* Defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2 and ≥ 15 mL/min/1.73 m^2.

† Defined as estimated glomerular filtration rate < 15 mL/min/1.73 m^2 or requirement of renal replacement therapy.

had an unacceptably high, lifestyle limiting disease burden. All of these patients were initially classified as Fontaine stage IIb and then reclassified for this data analysis according to Rutherford clinical category, limiting the validity of this classification. More patients in the PCB group had had a prior endovascular target limb revascularisation, and in parallel more re-stenotic lesions were treated with PCBs. Median lesion length was around 20 cm and two thirds of lesions were chronic occlusions without differences between the groups. Procedural characteristics differed between the groups as the tibioperoneal trunk and proximal lesions were treated more commonly and maximum balloon diameter was on average higher in the PCB group. In both groups, procedural success — defined as a final in lesion residual stenosis ≤ 50% — was high, around 95% based on the operator's assessment of the final angiogram.

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Table 2. Lesion and procedural characteristics in 552 patients undergoing below knee intervention for symptomatic peripheral artery disease treated with paclitaxel coated balloon (PCB) or plain old balloon angioplasty (POBA)

	PCB group (n = 157 patients; 165 limbs)	POBA group (n = 395 patients; 408 limbs)	p value
Target lesion characteristics			
Lesion type			<.001
De novo lesion	103 (62.4)	327 (80.1)	
Re-stenotic lesion	47 (28.5)	70 (17.2)	
In stent re-stenosis	15 (9.1)	11 (2.7)	
Chronic occlusions	101 (61.2)	272 (66.7)	.25
Calcification			.018
None/mild	115 (69.7)	241 (59.1)	
Moderate/severe	50 (30.3)	167 (40.9)	
Lesion location[*]			
Anterior tibial	86 (52.1)	215 (52.7)	.93
Tibioperoneal trunk	61 (37)	104 (25.5)	.008
Posterior tibial	36 (21.8)	110 (27.0)	.24
Peroneal	50 (30.3)	101 (24.8)	.18
Lesion length (IQR) − cm	16.1 (20.0)	21.0 (14.5)	.44
Procedural characteristics			
Treated vessels − *n*			.070
1 vessel intervention	108 (65.5)	300 (73.5)	
2 vessels intervention	46 (27.8)	95 (23.3)	
3 vessels intervention	11 (6.7)	12 (2.9)	
4 vessels intervention	0 (0)	1 (0.2)	
Proximal vessel segment treated	155 (93.9)	359 (88.0)	.034
Retrograde recanalisation	24 (14.5)	59 (14.5)	1.0
Atherectomy	15 (9.1)	12 (2.9)	.004
Directional atherectomy	12 (7.3)	6 (1.5)	
Laser atherectomy	3 (1.8)	6 (1.5)	
Pre-dilatation performed	111 (67.3)	−	
Maximum balloon diameter − mm	2.9 ± 0.5	2.7 ± 0.6	<.001
BTK stent implantation	26 (15.8)	95 (23.3)	.054
Type of BTK stent			1.0
Drug eluting stent	24 (92.3)	88 (92.6)	
Bare metal stent	2 (7.7)	7 (7.4)	
Cumulative length of BTK stents − mm	69.3 ± 33.1	57.7 ± 37.4	.13
No. of PCBs used	2 ± 1	−	
Concomitant inflow intervention	61 (37)	177 (43.4)	.16
Concomitant outflow intervention, below the ankle	12 (7.3)	48 (11.8)	.13
Intraprocedural use of thrombolysis	8 (4.8)	26 (6.4)	.56
Procedural success[†]	158 (95.8)	385 (94.4)	.68
Ankle–brachial index[‡]			
Pre-intervention	0.68 ± 0.40	0.54 ± 0.41	.002
Post-intervention	0.96 ± 0.35	0.91 ± 0.39	.24
Vascular access closure			
Manual compression	72 (43.6)	131 (32.1)	.012
Proglide	38 (23.0)	133 (32.6)	.026
Femoseal	4 (2.4)	5 (1.2)	.29
Other	51 (30.9)	139 (34.1)	.44
Bleeding complications at the access site	4 (2.4)	18 (4.4)	.34
Post-interventional death within 24 h	0 (0.0)	3 (0.7)	.56
Length of stay − d	6.98 ± 8.22	9.75 ± 11.46	.014

Data are presented as *n* (%) or mean ± standard deviation unless otherwise stated. BTK = below knee; IQR = interquartile range.

[*] Lesion could be located in multiple segments.

[†] Procedural success defined as final in lesion residual diameter stenosis ≤ 50% as assessed in the final angiogram.

[‡] Valid ABI measurements were available in 129 and 119 patients in the PCB and in 301 and 292 patients in the POBA group before and after the index intervention, respectively.

Acute target lesion re-occlusion before discharge was observed in seven patients (4.2%) in the PCB and 25 patients (6.1%) in the POBA group ($p = .43$).

The majority of patients received a vascular closure device (64.6%), and when this was not possible, manual compression. Overall, complications at the puncture site of the common femoral artery were rare. In three patients haemorrhagic shock necessitating intensive care unit stay and blood transfusion occurred due to either active bleeding from the puncture side (one case) or puncture

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related retroperitoneal haematoma (two cases). Other interventions included surgical repair of a large pseudoaneurysm and implantation of a covered stent in two cases either due to active groin bleeding despite manual compression or for treatment of an arteriovenous fistula. No other puncture related events requiring surgical or endovascular interventions were reported.

Two patients (one from each group) developed compartment syndrome after the procedure requiring surgical decompression therapy. In two patients with prolonged post-procedural local lysis, major bleeding events were reported. One patient suffered from massive acute epistaxis requiring intubation for airway protection and necessitating blood transfusion. Another patient suffered duodenal haemorrhage requiring blood transfusion.

Three early deaths within 24 hours after the procedure were reported in the POBA group, none in the PCB group. Two patients presenting in Rutherford category 6 died due to septicaemia and multi-organ failure; one patient died due to acute heart failure.

Efficacy and safety results through two year follow up

Unadjusted analyses. Figure 1 shows the patient flow diagram. In unadjusted analysis, the primary effectiveness endpoint freedom from CD TLR at 12 months was reported in 70.6% (96/136 limbs) in the PCB and 75.9% (205/270 limbs) in the POBA group ($p = .25$). The primary safety endpoint major adverse events at 12 months was reported in 41.1% (58/141 patients) in the PCB and 44.4% (142/320 patients) in the POBA group ($p = .52$). Distribution of Rutherford clinical categories at baseline, 12, and 24 months is shown in Figure 2. Survival curves and KM estimates for all cause mortality and CD TLR were similar between the groups through to 24 months (Figs 3A and 4A), while fewer major amputations were reported in the PCB group (Fig. 5A). Lesion and procedural characteristics of re-interventions are presented in Supplementary Table S1. After two years, one in four patients had died: freedom from all cause mortality was 76.8 ± 3.6% in the PCB group and 75.2 ± 2.3% in the POBA group based on KM analysis (log rank $p = .22$), while freedom from major amputations was higher in the PCB group (94.4% ± 2.1%) than in the POBA group (89.2% ± 1.9%) after two years (log rank $p = .050$). Around 90% of all 37 major amputations were performed in patients presenting with CLTI at baseline (four in the PCB group, 29 in the POBA group), while only four major amputations were performed in claudicants (three in the PCB group, one in the POBA group) through to two years. Subgroup analyses by clinical presentation (patients with CLTI and claudicants) are shown in Supplementary Figures S1A–S3B. As expected, event rates were higher in patients with CLTI, but the results comparing POBA and PCBs in the subgroup analyses were consistent with the overall results. KM estimates for freedom from all cause death were 69.6% ± 2.4% in patients with CLTI and 90.7% ± 2.5% in claudicants at two years (log rank $p < .001$). With regard to other relevant covariables, additional subgroup analyses were performed for re-stenotic *vs. de novo* lesions in patients with CLTI and claudicants (Supplementary Figures S4A–B) and for patients in Rutherford clinical category 4 *vs.* patients in Rutherford clinical categories 5 and 6 (Supplementary Figures S7A–C).

Cox regression analysis was performed to identify risk factors for all cause death and CD TLR. Significant predictors of death were age (hazard ratio [HR] per 10 years 1.6, 95% confidence interval [CI] 1.4 – 2.0), CLTI (HR 2.1, 95% CI 1.4 – 3.1), diabetes (HR 1.4, 95% CI 1.0 – 2.0), history of coronary artery disease (HR 1.5, 95% CI 1.1 – 2.1), and renal dysfunction, with the highest risk for renal failure (renal failure *vs.* non-impaired renal function; HR 2.5, 95% CI 1.4 – 4.8). For CD TLR, significant predictors were CLTI (HR 1.6, 95% CI 1.1 – 2.4), prior target limb revascularisation (HR 1.7, 95% CI 1.1 – 2.5), treatment of vessel occlusion (HR 2.1, 95% CI 1.4 – 3.2), and renal failure *vs.* chronic renal insufficiency (HR 2.1, 95% CI 1.1 – 4.0). Full results of

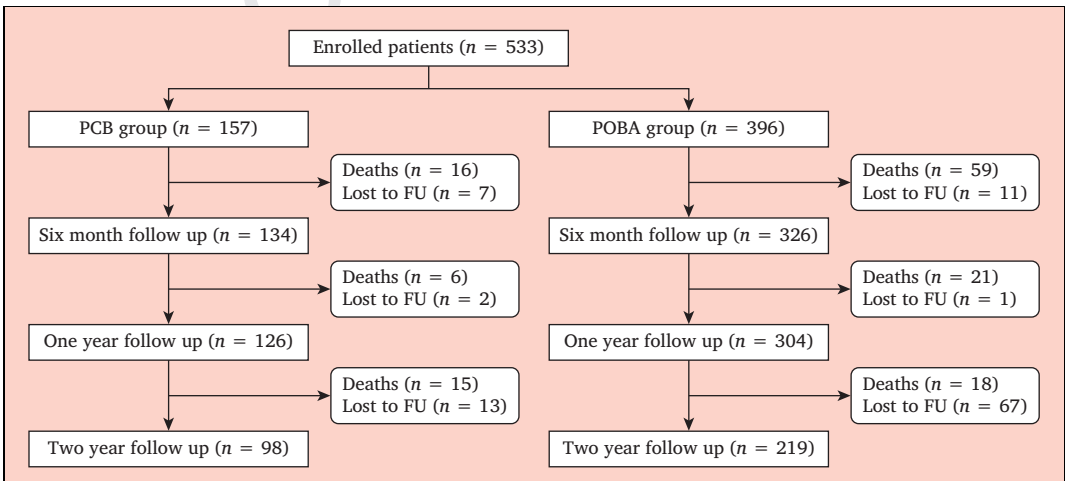

Figure 1. Flow diagram of patients undergoing below knee endovascular intervention for symptomatic peripheral artery disease with paclitaxel coated balloon (PCB) or with plain old balloon angioplasty (POBA) and their two year follow up (FU).

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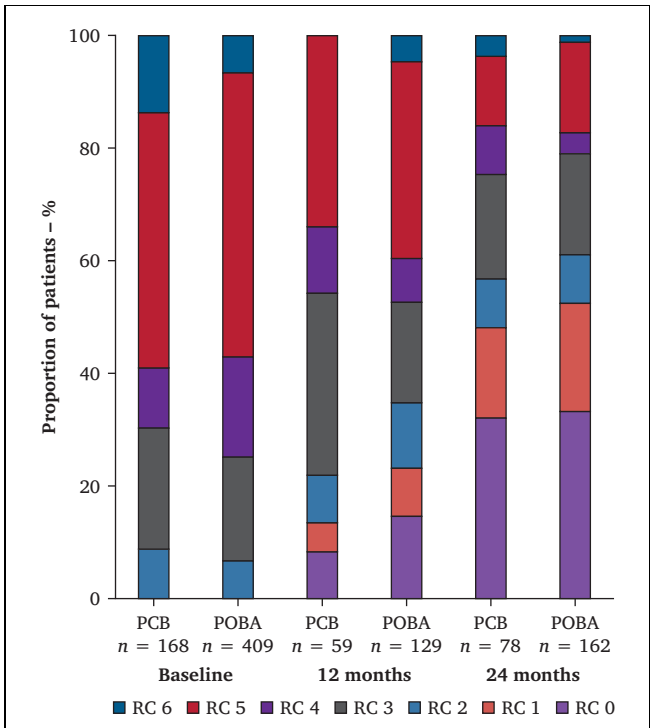

Figure 2. Distribution of Rutherford clinical categories (RC) at baseline, 12, and 24 months amongst patients with peripheral artery disease treated by endovascular below knee intervention with paclitaxel coated balloon (PCB) or plain old balloon angioplasty (POBA).

stepwise multiple Cox regression analysis are presented in Supplementary Table S2.

Propensity score matched analysis. After PS matching 128, well balanced pairs were derived as presented in Supplementary Table S3. Covariables were evenly distributed after matching since standardised differences did not indicate relevant imbalance after matching. In the matched cohort, the primary effectiveness endpoint freedom from CD TLR at 12 months was reported in 70.1% in the PCB group and 73.1% in the POBA group (including 52.2% concordant cases; $p = .85$; McNemar Test). The primary safety endpoint at 12 months was reported in 44.5% in the PCB group and 46.7% in the POBA group (including 21.7% concordant cases; $p = .88$; McNemar Test). Results from KM analysis through to 24 months were in line with unadjusted analyses of the full cohort. Survival curves for all cause mortality (Fig. 3B) and CD TLR (Fig. 4B) were almost overlapping, while fewer amputations were observed in the PCB group (Fig. 5B).

DISCUSSION

In this all comer analysis of a large, single centre cohort, no safety signal with respect to all cause mortality was identified for BTK interventions with PCBs over two years of follow up in unmatched and propensity score matched (PSM) analysis. While major amputations were reduced in the PCB cohort, no benefit was seen for PCB use over POBA in terms of the need for revascularisation of target lesions.

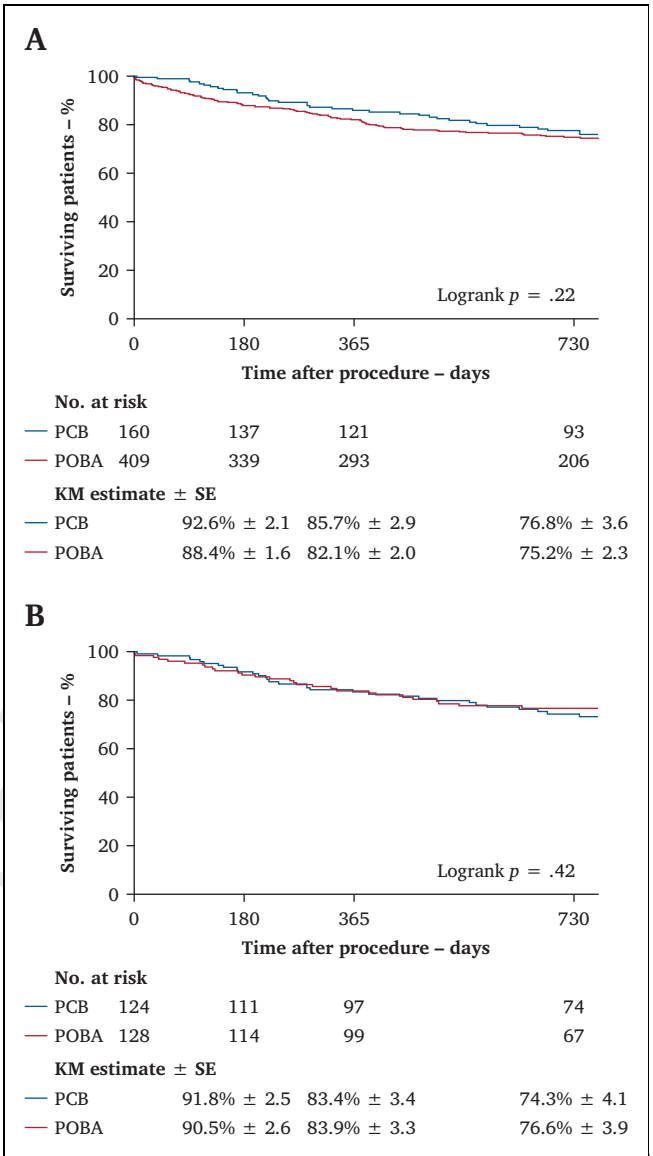

Figure 3. Cumulative Kaplan–Meier (KM) estimates of freedom from all cause death for plain old balloon angioplasty (POBA) and Paclitaxel coated balloon (PCB) in the (A) entire and (B) propensity score matched cohorts of patients with symptomatic peripheral artery disease. SE = standard error.

The included study population and procedural characteristics provide a good representation of the type of patients typically treated for infrapopliteal disease of the peripheral arteries. More than two thirds of patients were treated for CLTI, predominantly presenting in WIfI stage 3 and 4 with a high risk of major amputation. As commonly seen in BTK procedures, long vessel segments had to be treated, and over 60% (61.2% PCB; 66.7% POBA) of the procedures involved occlusions. In approximately 10% of all procedures, treatment also involved the pedal arch of the foot, which has been identified previously as a predictor of limb loss. Relevant differences were identified when comparing patients with PCB *vs.* POBA treatment. Patients undergoing BTK angioplasty with PCB were more often treated for re-stenotic and in stent re-stenotic lesions, while

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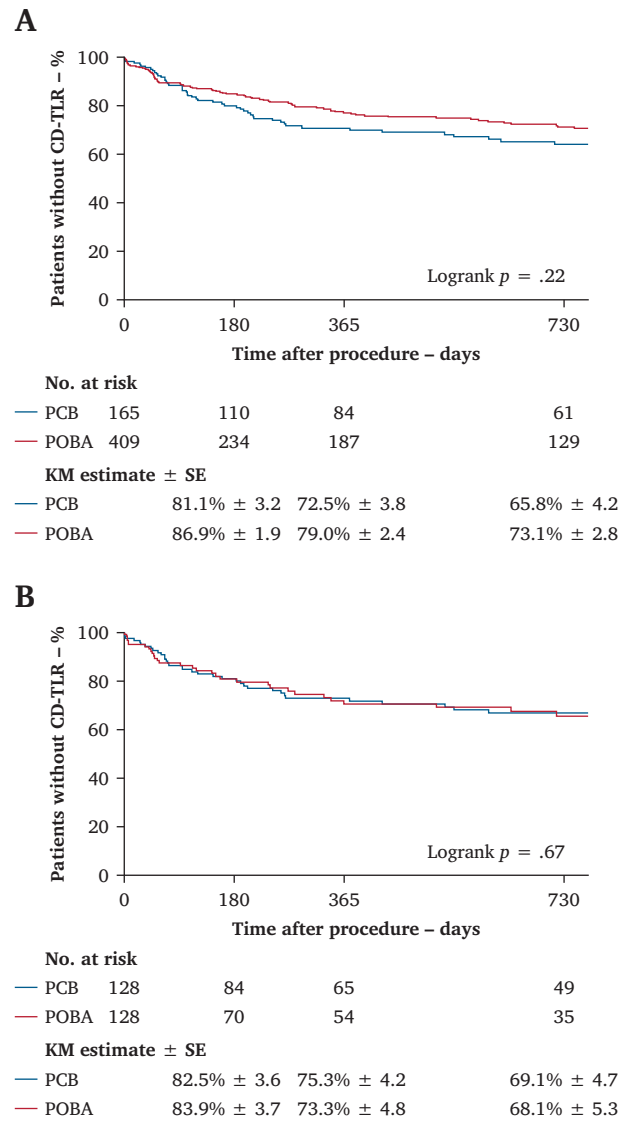

Figure 4. Cumulative Kaplan–Meier (KM) estimates of freedom from clinically driven target lesions revascularisation (CD-TLR) for plain old balloon angioplasty (POBA) and Paclitaxel coated balloon (PCB) in the (A) entire and (B) propensity score matched cohorts of patients with symptomatic peripheral artery disease. SE = standard error.

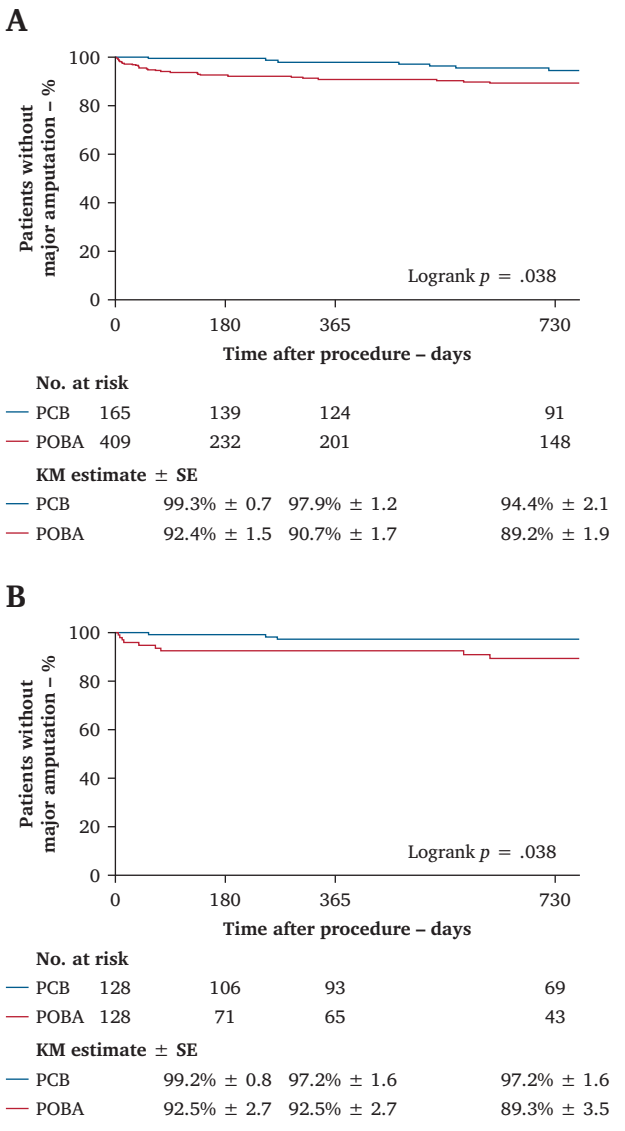

Figure 5. Cumulative Kaplan–Meier (KM) estimates of freedom from major amputations for plain old balloon angioplasty (POBA) and plain old balloon angioplasty (PCB) in the (A) entire and (B) propensity score matched cohorts of patients with symptomatic peripheral artery disease. SE = standard error. Q3

BTK stent placement was more often performed in POBA patients. Importantly, only one type of a dedicated paclitaxel releasing balloon for BTK interventions was available for routine use during the study period, the Lutonix 0.014 inch DCB, and the observed results cannot be generalised to any other PCB. The Lutonix 0.014 inch DCB was compared recently against POBA in the prospective, multicentre, 2:1 randomised Lutonix BTK trial enrolling 507 vessels.[12] The primary effectiveness endpoint (composite of limb salvage and primary patency) at six months was reported in 74.7% in the Lutonix 0.014 inch DCB group and 64.2% in the PTA group, with no statistically significant difference. No safety concern was raised regarding the risk of major amputations. In contrast to the observed modest benefit for primary patency in the Pivotal RCT, need for repeat revascularisation did not differ between the groups in the cohort in both unadjusted and PSM analysis. While matching including a variety of covariables yielded a relatively balanced distribution of measured known predictors of re-stenosis, this method cannot account for all confounders and selection bias caused by the operators cannot be ruled out. Importantly, PCBs were approved but not reimbursed for BTK procedures in Germany during the study period, limiting their widespread use. Therefore, operators would use PCBs in situations where they perceived an extraordinarily high risk of re-stenosis, which is underscored by the fact that more re-stenotic lesions were treated in the PCB group. Importantly, the rate of major amputations in the PCB group was very low at approximately 2.2% at one year, much

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lower than in the Lutonix-BTK trial.[12] No signal for an increasing risk over time was seen in contrast to findings from a prior meta-analysis.[15] In the POBA group, more amputations were performed within the first weeks after the index intervention. A possible explanation could be the treatment of patients with very advanced disease and low chances of limb salvage, as endovascular revascularisation is also pursued as a last option in these patients. In this scenario, PCBs would be used rarely because any potential clinical benefit is even more doubtful.

Within two years, one in four patients in the cohort had died, and the mortality rate was substantially higher in patients with CLTI than in claudicants. The high mortality rate of approximately 30% at two years in patients with CLTI underscores the excessive risk profile of these patients resulting from their advanced age, severe multisite PAD, and multiple comorbidities including cardio- and cerebrovascular disease. However, there was no signal for different mortality rates between PCB and POBA treated patients as in PSM analysis KM curves were almost overlapping. Following the publication of several meta-analyses by Katsanos and co-workers since December 2018,[15–17] a controversy has arisen surrounding the late mortality signal with paclitaxel eluting devices for peripheral endovascular interventions. Since then, a multitude of studies , including novel RCT data and large observational studies[19–23], have been published supporting the safety of paclitaxel eluting devices for femoropopliteal interventions. In contrast, few data are available for BTK interventions because PCBs have rarely been used in cohorts outside of dedicated clinical trials. Previous findings based on insurance data postulated a mortality advantage for patients undergoing BTK procedures with paclitaxel releasing devices, although the reason for the observed benefit remains unclear.[24] This study also supports the safety of PCBs for BTK interventions for routine use. Importantly, a contemporary all comer cohort was included that goes beyond the highly selected patient populations of clinical trials. Randomised trials are particularly difficult to conduct in BTK disease and are usually hampered by slow recruitment.

Limitations

The retrospective nature and the reliance on patient records are major limitations of this study. However, the relatively large number of patients available for analysis without stringent inclusion or exclusion criteria allows a good reflection of real world outcomes in this patient population. Due to the limited power of the small sample, all results should be considered hypothesis generating only.

Assessment of imaging and outcome data was not performed by a core laboratory or clinical events committee, but all data entry was carried out by a well trained study team with many years of experience in the field of endovascular trials. Imaging follow up was not available in all patients, and the possibility of differential attrition of patients in the two groups cannot be excluded. Since only one type of PCB was used in this study, the results cannot be generalised to other devices.

Conclusions

In this all comer analysis, PCB was found to be safe for BTK interventions with a signal towards lower amputation rates but no benefit was seen for repeat revascularisation. Mortality rates did not differ at two years, but longer follow up would be needed to detect a possible late signal.

CONFLICT OF INTEREST

Tim Wittig: None. Andrej Schmidt: Consultant for Abbott, Boston Scientific, Cook Medical, Cordis, CR Bard, ReFlow Medical, Upstream Peripheral Technologies. Maria Kabelitz: None. Martin Hukauf: None. Toni Pflug: None. Dierk Scheinert: Consultant or advisory board member for Abbott, Biotronik, Boston Scientific, Cook Medical, Cordis, CR Bard, Gardia Medical, Medtronic/Covidien, TriReme Medical, Trivascular, and Upstream Peripheral Technologies. Sabine Steiner: Consultant for Bayer, Boston Scientific, Cook Medical. Research funding: C.R. Bard.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2022.08.004.

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