JACC: CARDIOVASCULAR INTERVENTIONS VOL. ■, NO. ■, 2020

Real-World Experience With a Paclitaxel-Coated Balloon in Critical Limb Ischemia

24-Month Subgroup Outcomes of BIOLUX P-III

Marianne Brodmann, MD,[a] Matej Moscovic, MD,[b] John Chaw Chian Wang, MD,[c] Giovanni Nano, MD,[d] Johannes Dahm, MD,[e] Thomas Zeller, MD,[f] Johnny Kent Christensen, MD,[g] Koen Keirse, MD,[h] Reza Ghotbi, MD,[i] Jean-Marc Corpataux, MD,[j] Gunnar Tepe, MD[k]

ABSTRACT

OBJECTIVES The aim of the BIOLUX P-III (A Prospective, International, Multi-Centre, Post-Market All-Comers Registry to Assess the Clinical Performance of the Passeo-18 Lux Paclitaxel Releasing Balloon Catheter in Infrainguinal Arteries – III) registry was to collect real-world data on the Passeo-18 Lux paclitaxel-coated balloon.

BACKGROUND Critical limb ischemia (CLI) is a severe condition associated with high morbidity and mortality. Prospective data are needed to provide further insights on drug-eluting devices.

METHODS BIOLUX P-III is a prospective, post-market, all-comers registry assessing the safety and performance of the Passeo-18 Lux. Clinical information was collected at 6, 12, and 24 months. The authors report 24-month outcomes of the CLI subgroup with patients in Rutherford classes 4 to 6.

RESULTS The CLI subgroup included 328 patients with 422 lesions. Patients were 71.1 ± 10.5 years of age, and 61.0% had diabetes. Femoropopliteal lesions were present in 53.8% (n = 227), below-the-knee lesions were present in 27.0% (n = 114), and lesions were moderate or heavily calcified in 45.0% (n = 190). Major adverse events, defined as 30-day device- or procedure-related mortality, major target limb amputation, and clinically driven target lesion revascularization, occurred in 9.8% of patients through 6 months, in 14.9% through 12 months, and in 19.4% through 24 months. Clinically driven target lesion revascularization occurred in 4.4%, 8.5%, and 12.1%, major amputation in 4.9%, 5.2%, and 6.1%, and mortality in 8.1%, 11.1%, and 20.1%, respectively. Predictors of mortality were age ≥75 years and higher Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease class, and higher Rutherford class was associated with increased mortality and amputation rates.

CONCLUSIONS In a large, multimorbid patient population with complex lesions and CLI, the safety and performance of the Passeo-18 Lux paclitaxel-coated balloon has been confirmed, with low rates of major amputation and target lesion revascularization. (J Am Coll Cardiol Intv 2020;■:■–■) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Division of Angiology, Medical University Graz, Graz, Austria; [b]Angiology Clinic, Institute of Cardiovascular Diseases, Kosice, Slovakia; [c]Department of Vascular Surgery, Singapore General Hospital, Singapore; [d]1st Vascular Surgery Department, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy; [e]Department of Angiology and Cardiology, Herz- und Gefäßzentrum Neu-Bethlehem, Göttingen, Germany; [f]Clinic Cardiology and Angiology II, Universitäts-Herzzentrum Freiburg - Bad Krozingen, Bad Krozingen, Germany; [g]Department of Radiology, Kolding Hospital, Kolding, Denmark; [h]Department of Vascular Surgery, Regional Hospital Heilig Hart, Tienen, Belgium; [i]Klinik für Gefäßchirurgie, Helios Klinikum München West, Munich, Germany; [j]Department of Thoracic and Vascular Surgery, Lausanne University Hospital, Lausanne, Switzerland; and the [k]Department of Interventional Radiology, Klinikum Rosenheim, Rosenheim, Germany. This study was sponsored by Biotronik. The sponsor was involved in the study design, conduct of the study, and statistical analysis. Furthermore, the sponsor reimbursed the medical writer who worked under the guidance of the coordinating author. The sponsor was not involved in the decision to submit the manuscript. Dr. Brodmann has received honoraria from Abbott Vascular, Biotronik, Philips-Spectranetics, Medtronic, Daiichi Sankyo, Bayer Healthcare, and BD Bard; is a consultant for Boston Scientific, Medtronic, Spectranetics, Intact Vascular,

ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2020.06.059

ABBREVIATIONS AND ACRONYMS

BTK = below-the-knee

CI = confidence interval

CLI = critical limb ischemia

CLTI = chronic limb-threatening ischemia

DCB = drug-coated balloon

MAE = major adverse event(s)

TASC = Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease

TLR = target lesion revascularization

WIfI = wound, ischemia, and foot infection

The BIOLUX P-III (A Prospective, International, Multi-Centre, Post-Market All-Comers Registry to Assess the Clinical Performance of the Passeo-18 Lux Paclitaxel Releasing Balloon Catheter in Infrainguinal Arteries - III) registry was initiated to gain information on the safety and effectiveness of the Passeo-18 Lux drug-coated balloon (DCB) (Biotronik, Buelach, Switzerland) when treating peripheral artery disease of the lower extremities in a large patient population under real-world conditions (1).

In addition, the registry was intended to assess outcomes in specific risk groups, such as patients with critical limb ischemia (CLI). CLI is a severe condition; if left untreated, nearly one-quarter of patients experience major amputation and nearly one-quarter die within 1 year (2,3). Notably, the term "critical limb ischemia" was replaced by the term "chronic limb-threatening ischemia" (CLTI) recently (4), defined as rest pain, gangrene, or lower limb ulceration with a duration of more than 2 weeks and associated with a growing prevalence and increased health care costs (2).

So far, the CLI population is understudied. The current European guidelines provide only rough guidance and recommend an endovascular-first strategy in short lesions or in long occlusions with no great saphenous vein graft material or in patients with increased risk for open surgery (4). The more recently published global vascular guidelines on the management of CLTI provide a more differentiated scheme that takes classifications such as the wound, ischemia, and foot infection (WIfI) scheme and the Global Limb Anatomic Staging System into consideration (2).

These global vascular guidelines on the management of CLTI also highlight the lack of comparative data to guide the choice of a specific endovascular approach in femoropopliteal lesions and define prospective studies to assess the safety and efficacy of drug-eluting devices such as DCBs with at least 2 years of follow-up as a research priority (2). We therefore additionally assessed the safety and effectiveness in femoropopliteal and below-the-knee (BTK) lesions.

METHODS

The study design has been described previously (1,5). In brief, BIOLUX P-III is a prospective, post-market, all-comers registry to assess the clinical performance of the Passeo-18 Lux paclitaxel-coated balloon catheter in infrainguinal arteries. We report the outcomes of the CLI subgroup. Included were adults who provided written informed consent with arteries suitable for the treatment with the Passeo-18 Lux DCB. Exclusion criteria were life expectancy <1 year, pregnancy, participation in another trial, and failure to cross the target lesion with a guidewire.

Lesions could be 1 focal lesion or a series of multiple, smaller lesions to be treated as 1 "treatment segment." After treatment with the Passeo-18 Lux DCB and inclusion in the BIOLUX P-III registry, patients were treated according to standard of care at the respective hospitals and initially followed from hospital discharge to 6, 12, and 24 months. According to the U.S. Food and Drug Administration's recommendations in response to the meta-analysis of Katsanos et al. (6), the follow-up period was extended to 5 years.

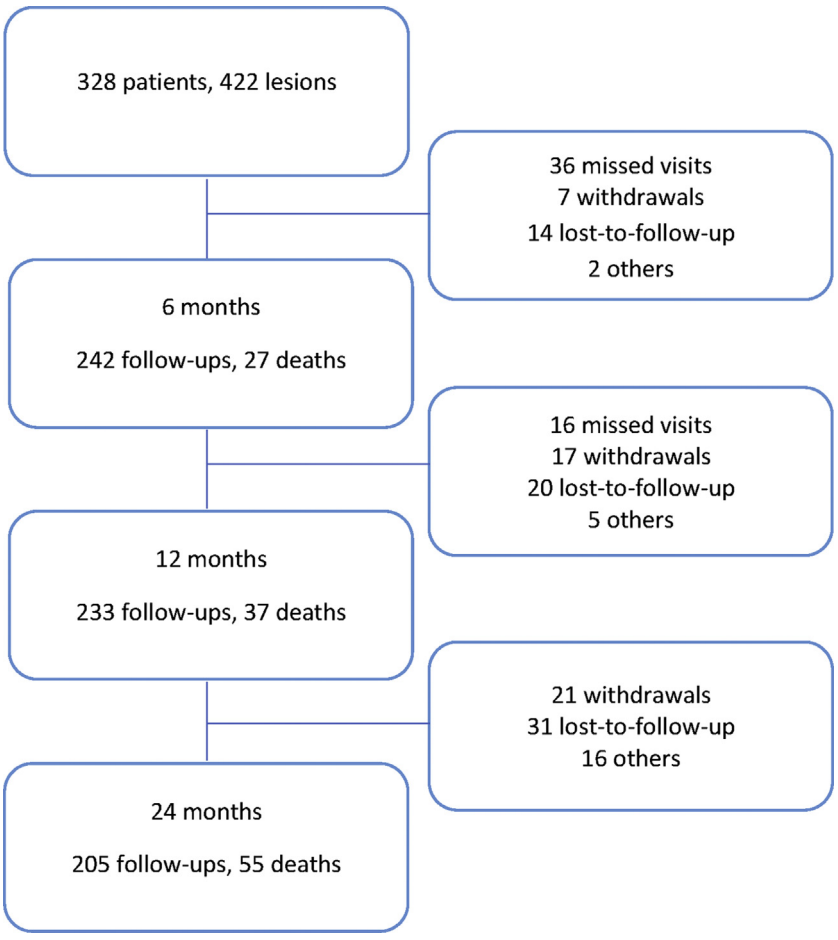
The registry was conducted according to the current version of the Declaration of Helsinki, applicable parts of ISO 14155:2011, and national and local requirements and was approved by the sites' ethics committees. Monitoring of endpoint-related data was performed using a risk-based strategy including at least 25% of patients; a clinical events committee adjudicated all major adverse events (MAE), target lesion revascularizations (TLRs), and deaths. The

Shockwave, Bayer, Vesper Medical, and BD Bard; and has received study support from 480 Biomedical, BD Bard, Biotronik, Medtronic, Philips, Shockwave, Med Alliance, Intact Vascular, and B. Braun. Dr. Dahm has received honoraria from AstraZeneca and Pfizer. Dr. Zeller has received honoraria from Abbott Vascular, Veryan, Biotronik, Boston Scientific, Cook Medical, Gore & Associates, Medtronic, Philips-Spectranetics, TriReme, Veryan, Shockwave, Biotronik, and B. Braun; is consultant for Boston Scientific, Cook Medical, Gore & Associates, Medtronic, Spectranetics, Veryan, Intact Vascular, and Veryan; and holds common stock in QT Medical. Dr. Ghotbi has cooperative research agreements with and performs consulting for Philips-Spectranetics, BD Bard, and Gore. Dr. Tepe has received study support from B. Braun, Bard, Bayer, Biotronik, Boston Scientific, Gore, Medtronic, Philips, and Veryan. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

Manuscript received May 18, 2020; revised manuscript received June 25, 2020, accepted June 30, 2020.

FIGURE 1 **Patient Disposition**



Follow-up compliance was 82.0% at 6 months, 82.3% at 12 months, and 79.3% at 24 months.

registry is registered at ClinicalTrials.gov (NCT02276313).

STUDY DEVICE. The Passeo-18 Lux DCB is a paclitaxel-coated balloon catheter that received the Conformité Européenne mark in January 2014. The balloon catheter is identical to the Passeo-18 plain balloon but coated with 3 μg paclitaxel per square millimeter of balloon surface, incorporated in the delivery matrix of n-butyryl tri-n-hexyl citrate. The drug load ranges between 0.9 mg paclitaxel for the smallest device (2 × 40 mm) and 9.1 mg for the largest device (7 × 120 mm). A sheath protects the balloon to keep its factory-made profile and drug coating and is used as an insertion aid during insertion of the catheter through the introducer sheath. The Passeo-18 Lux is indicated for the dilatation of lesions in infrainguinal arteries.

ENDPOINTS AND DEFINITIONS. The primary clinical endpoint was freedom from MAE, a composite of freedom from 30-day device- or procedure-related mortality and freedom from major target limb amputation and clinically driven TLR within 6 months post-procedure. The primary performance endpoint was freedom from clinically driven TLR within 12 months. Secondary endpoints included MAE and TLR at different time points; amputation-free survival; primary patency, defined as freedom from >50% restenosis in the target lesion as indicated by a duplex ultrasound peak systolic velocity ratio >2.5 or by visual assessment of an angiogram

TABLE 1 Baseline Demographics Characteristics

	Overall (N = 328)	BTK (n = 92)	FP (n = 176)	p Value
Age (yrs)	71.1 ± 10.5 (70.0-72.3)	70.8 ± 10.0 (69.7-72.9)	70.9 ± 10.6 (69.3-72.5)	0.926
Male	200 (61.0)	22 (23.9)	101 (57.4)	0.003
Body mass index (kg/m^2) (n = 290)	26.5 ± 4.3 (26.0-27.0)	27.1 ± 4.6 (26.0-28.1)	26.1 ± 4.3 (25.4-26.8)	0.122
Hypertension	284 (86.6)	79 (85.9)	147 (83.5)	0.616
Hyperlipidemia	201 (61.3)	54 (58.7)	106 (60.2)	0.736
Smoking (n = 325)	186 (57.2)	38 (41.3)	117 (66.5)	0.0002
Diabetes Insulin dependent	200 (61.0) 93 (28.4)	66 (71.7) 42 (45.6)	98 (55.7) 37 (21.0)	0.010 0.001
Renal disease (insufficiency) (n = 144 for GFR) GFR 30-60 ml/min/1.73 m^2 GFR <30 ml/min/1.73 m^2 Dialysis (n = 55)	144 (43.9) 62 (18.9) 41 (12.5) 29 (8.8)	40 (43.5) 18 (45.0) 14 (35.0) 12 (30.0)	71 (40.3) 31 (43.7) 20 (28.2) 13 (18.3)	0.621 0.584 0.157
Coronary artery disease	144 (43.9)	36 (39.1)	78 (44.3)	0.415
Cerebrovascular disease (n = 327)	71 (21.7)	20 (21.7)	40 (22.7)	0.753
History of peripheral arterial occlusive disease	173 (52.7)	45 (48.9)	101 (57.4)	0.186
Subjects with previous peripheral interventions	156 (47.6)	32 (34.8)	91 (51.7)	0.008
Cancer	38 (11.6)	5 (5.4)	30 (17.0)	0.007
Ankle brachial index (n = 122)	0.64 ± 0.26 (0.59-0.68)	0.84 ± 0.26 (0.73-0.96)	0.59 ± 0.25 (0.53-0.64)	0.0002
Rutherford class	4.9 ± 0.7 (4.8-4.9)	5.1 ± 0.7 (5.0-5.3)	4.7 ± 0.7 (4.6-4.8)	<0.0001
Pain scale score (n = 275)	5.6 ± 2.9 (5.2-5.9)	4.5 ± 2.9 (3.9-5.1)	6.2 ± 2.8 (5.7-6.6)	<0.0001

Values are mean ± SD (95% confidence interval) or n (%).
BTK = below-the-knee; FP = femoropopliteal; GFR = glomerular filtration rate.

with no clinically driven reintervention; change in ankle-brachial index; clinical success, defined as improvement in Rutherford classification compared with baseline; Wong-Baker pain scale and walking impairment questionnaire scores compared with baseline; device success, defined as successful delivery, inflation, deflation, and retrieval of the Passeo-18 Lux; technical success, defined as successful completion of the endovascular procedure and immediate morphological success with ≤50% residual diameter reduction of the treated lesion as determined by visual estimation; and procedure success, defined as technical or device success without reoccurrence of any MAE prior to discharge. Rutherford class was site reported without the use of objective criteria for ischemic rest pain (4).

STATISTICAL ANALYSIS. The primary endpoints were assessed using Kaplan-Meier analysis with 95% confidence intervals (CI) and standard errors according to the Greenwood formula. Descriptive statistics include the mean, SD, and median for quantitative variables as applicable. For categorical (qualitative) variables, the absolute and relative frequencies are displayed. Ninety-five percent CIs were calculated as applicable.

Functional outcomes such as ankle-brachial index measurements were compared with baseline using the signed rank test, and the log-rank test was used to compare Kaplan-Meier estimates. Cox regression analysis was used to determine predictors of mortality. In a post hoc analysis, patients with femoropopliteal lesions were compared with patients with BTK lesions using the chi-square and Wilcoxon tests. Patients with both femoropopliteal and BTK lesions were counted in the BTK group. Statistical calculations were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

The CLI subgroup of BIOLUX P-III included 328 patients with 422 lesions (Figure 1). Patients were 71.1 ± 10.5 years of age on average, 61.0% (n = 200) had diabetes mellitus, 43.9% (n = 144) had renal disease, and 43.9% (n = 144) had coronary disease. Cerebrovascular disease was present in 21.7% (n = 71) and cancer in 11.6% (n = 38), and 47.6% (n = 156) had undergone previous peripheral interventions (Table 1).

Target lesions were 81.5 ± 65.7 mm long; 42.7% (n = 180) were located in the superficial femoral

TABLE 2 Baseline Lesion Characteristics

	Overall (N = 422)	BTK (n = 114)	FP (n = 227)	p Value
Mean target lesion length (visual estimate) (mm)	81.5 ± 65.7 (75.2-87.8)	80.8 ± 69.4 (67.9-93.7)	92.2 ± 68.7 (83.2-101.2)	0.036
Reference vessel diameter (visual estimate) (mm)	4.3 ± 1.2 (4.2-4.4)	2.9 ± 0.6 (2.8-3.0)	5.0 ± 0.8 (4.9-5.1)	<0.0001
Diameter stenosis (visual estimate) (%)	87.5 ± 13.0 (86.2-88.7)	87.9 ± 12.5 (85.6-90.2)	87.2 ± 13.2 (85.5-88.9)	0.745
Indication				0.0008
De novo lesion	220 (52.1)	69 (60.5)	107 (47.1)	
Occlusion	114 (27.2)	27 (23.7)	65 (28.6)	
Restenosis	46 (10.9)	16 (14.0)	22 (9.7)	
In-stent restenosis	42 (10.0)	2 (1.8)	33 (14.5)	
Calcification*				0.521
None	88 (20.9)	24 (21.1)	44 (19.4)	
Mild	144 (34.1)	43 (37.7)	76 (33.5)	
Moderate	130 (30.8)	35 (30.7)	70 (30.8)	
Heavy	60 (14.2)	12 (10.5)	37 (16.3)	
TASC classification (n = 419)				<0.0001
A	144 (34.4)	35 (31.5)	70 (30.8)	
B	118 (28.2)	16 (14.4)	80 (35.2)	
C	79 (18.9)	23 (20.7)	44 (19.4)	
D	78 (18.6)	37 (33.3)	33 (14.5)	
Target lesion location				NA
Common femoral	3 (0.7)	0 (0.0)	0 (0.0)	
Superficial femoral artery	180 (42.7)	0 (0.0)	180 (79.3)	
Popliteal artery	109 (25.8)	0 (0.0)	47 (20.7)	
Anterior tibial artery	49 (11.6)	49 (43.0)	0 (0.0)	
Posterior tibial artery	28 (6.6)	28 (24.6)	0 (0.0)	
Tibioperoneal trunk	15 (3.6)	15 (13.2)	0 (0.0)	
Peroneal artery	22 (5.2)	22 (19.3	0 (0.0)	
Other	16 (3.8)†	0 (0.0)	5 (2.1)	
Thrombus present (n = 421)	35 (8.3)	6 (5.3)	21 (9.3)	0.335
Lesion morphology				0.970
Focal lesion	223 (52.8)	59 (51.8)	117 (51.5)	
Diffuse lesion	199 (47.2)	55 (48.2)	110 (48.5)	
Number of lesions per subjects (n = 328)	1.3 ± 0.6 (1.2-1.3)	1.4 ± 0.6 (1.3-15)	1.3 ± 0.6 (1.2-1.4)	0.331
Amputation status target limb (n = 332)				0.003
None	287 (86.4)	73 (77.7)	163 (91.6)	
Minor	43 (13.0)	21 (22.3)	14 (7.9)	
Major	2 (0.6)	0 (0.0)	1 (0.6)	
Ulceration type target limb (n = 332)				0.0009
None	128 (38.6)	21 (22.3)	81 (45.5)	
Arterial	174 (52.4)	59 (62.8)	84 (47.2)	
Venous	1 (0.3)	0 (0.0)	1 (0.6)	
Diabetic/pressure	29 (8.7)	14 (14.9)	12 (6.7)	

Values are mean ± SD (95% confidence interval) or n (%). *Per site assessment without specific definition. †More than 1 vessel affected (n = 12), bypass (n = 3), common iliac (n = 1).

NA = not applicable; TASC = Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease; other abbreviations as in Table 1.

artery, 12.8% (n = 109) were located in the popliteal artery, and 27.0% (n = 114) were BTK. In-stent restenosis was present in 10.8% (n = 38), moderate or heavy calcification in 45.0% (n = 190), and Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC) C or D lesions in 37.4% (n = 158). Ulcerations and gangrene were present in 61.4% of the target limbs (Table 2).

Treatment of more than 1 lesion was performed in 78 patients (23.8%). Device success was observed in all but 1 device (99.8%) and technical success in all but 4 lesions (99.1%), and procedure success was obtained in 95.7% of patients (n = 314); 11.8% of lesions (n = 50) required bailout stenting (Table 3).

The ankle-brachial index improved significantly from 0.64 ± 0.26 at baseline to 0.87 ± 0.22 at 6 months ($p < 0.0001$), 0.88 ± 0.19 at 12 months ($p < 0.0001$), and 0.83 ± 0.26 at 24 months ($p = 0.0001$) (Supplemental Table 1, Supplemental Figure 1). Likewise, Rutherford class improved significantly at follow-up. At baseline, mean Rutherford class was 4.9 ± 0.7, with 31.4% in Rutherford class 4 (ischemic rest pain), 51.2% in class 5 (minor tissue loss), and 17.4% in class 6 (major tissue loss).

TABLE 3 Procedural Characteristics

	Overall (N = 422)	BTK (n = 114)	FP (n = 227)	p Value
Target lesion preparation	314 (74.4)	89 (78.1)	161 (70.9)	0.159
Uncoated balloon	272 (84.2)	98 (92.5)	149 (82.8)	0.022
Atherectomy	14 (4.3)	5 (4.7)	5 (2.8)	
Cutting balloon	13 (4.0)	0 (0.0)	10 (5.8)	
Rotational thrombectomy	12 (3.7)	0 (0.0)	8 (4.4)	
Scoring balloon	7 (2.2)	1 (0.9)	5 (2.8)	
Other	5 (1.5)	2 (1.9)	3 (1.7)	
Device diameter (mm) (n = 326)	3.7 ± 1.2 (3.6-3.9)	2.5 ± 0.6 (2.4-2.6)	4.4 ± 0.9 (4.3-4.5)	<0.0001
Device length (mm) (n = 328)	83.4 ± 51.3 (77.8-88.9)	94.2 ± 60.3 (82.2-106.3)	82.0 ± 46.6 (74.8-89.2)	0.172
Number of devices per lesion	1.2 ± 0.6 (1.2-1.3)	1.3 ± 0.6 (1.2-1.4)	1.2 ± 0.5 (1.2-1.3)	0.330
Paclitaxel dose per subject (mg) (n = 328)	6.6 ± 4.9 (6.1-7.2)	5.7 ± 4.4 (4.7-6.6)	8.0 ± 5.2 (7.2-8.8)	<0.0001
Passeo-18 Lux diameter (mm^2) (n = 524)	4.3 ± 1.2 (4.2-4.4)	2.9 ± 0.5 (2.8-2.9)	5.0 ± 0.8 (4.9-5.1)	<0.0001
Passeo-18 Lux length (mm) (n = 524)	89.0 ± 32.4 (86.2-91.8)	89.4 ± 32.7 (84.1-94.7)	93.7 ± 31.0 (90.0-97.3)	0.204
Maximum pressure applied (atm) (n = 504)	9.2 ± 2.9 (8.9-9.4)	9.4 ± 3.2 (8.9-9.9)	8. 9 ± 2.7 (8.6-9.2)	0.205
Cumulative inflation time (s) (n = 524)	142.4 ± 67.1 (136.6-148.1)	123.2 ± 52.2 (114.8-131.75)	155.0 ± 74.5 (146.3-163.7)	<0.0001
Bailout stenting	50 (11.8)	1 (0.9)	44 (19.4)	<0.0001
Device success (n = 524 devices)*	523 (99.8)	149 (100.0)	300 (100.0)	–
Technical success (n = 422 lesions)*	418 (99.1)	112 (98.2)	226 (99.6)	0.220
Procedure success (n = 328 patients)*	314 (95.7)	84 (91.3)	171 (97.2)	0.034

Values are n (%) or mean ± SD (95% confidence interval). *Device success was defined as successful delivery, inflation, deflation, and retrieval of Passeo-18 Lux. Technical success was defined as residual diameter reduction of the treated lesion as determined by visual estimation ≤50%. Procedural success was defined as technical and device success without the occurrence of any major adverse events.

Abbreviations as in Table 1.

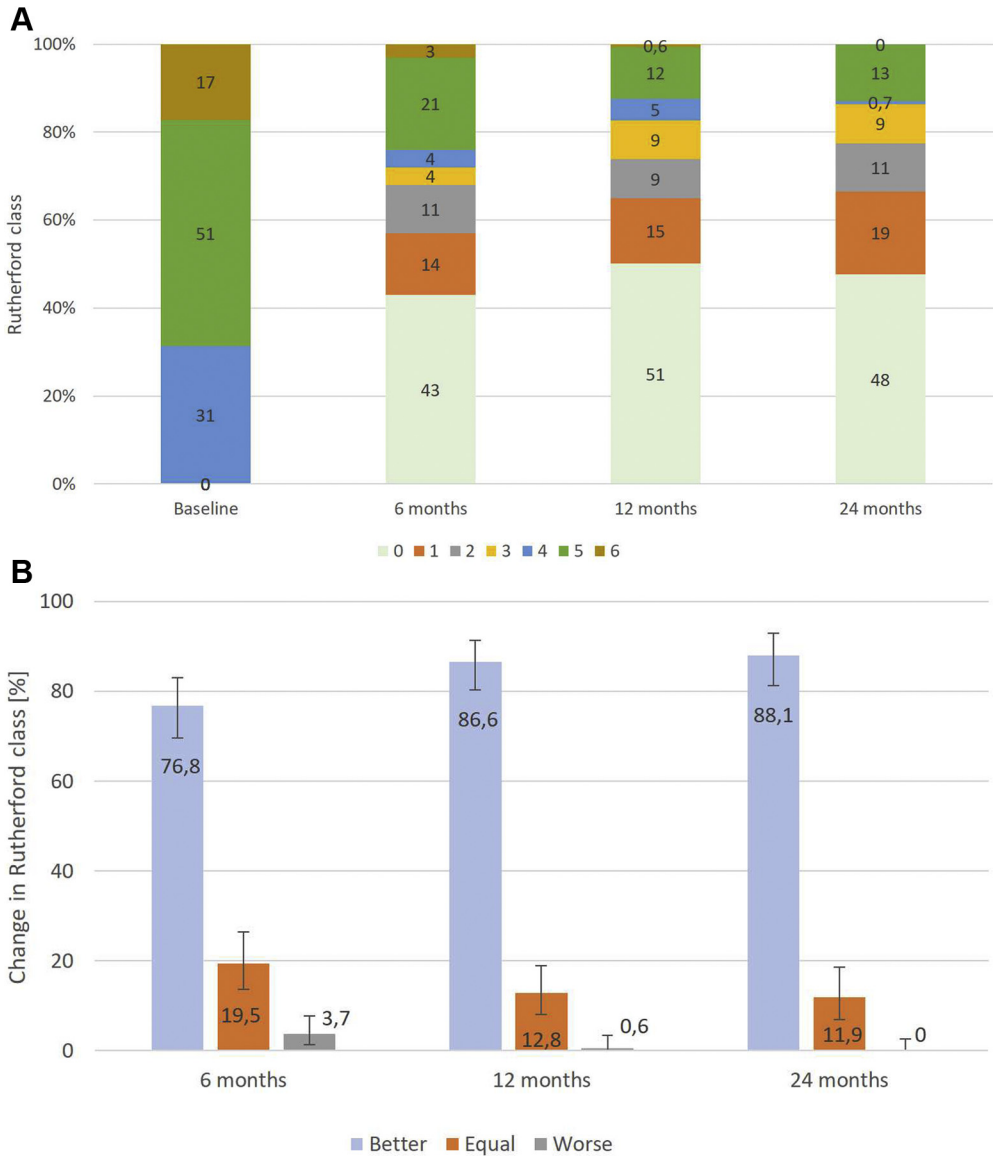
At 6-, 12-, and 24-month follow-up, Rutherford class improved in 76.8%, 86.6%, and 88.1% of patients, with mean values ranging from 1.9 ± 2.1 at 6 months to 1.3 ± 1.7 at 24 months (Supplemental Table 1, **Figure 2**). Furthermore, Wong-Baker pain scale scores improved in about 75% of patients, and walking impairment questionnaire scores showed significant improvement compared with baseline ($p < 0.0001$ at 6, 12, and 24 months) (Supplemental Table 1).

Median follow-up duration was 694 days (interquartile range: 371 to 740 days). At 24 months, the MAE rate was 19.4% (95% CI: 15.2% to 24.7%), the clinically driven TLR rate was 12.1% (95% CI: 9.0% to 16.2%), the rate of major target limb amputation was 6.1% (95% CI: 3.9% to 9.6%), and the mortality rate was 20.1% (95% CI: 15.7% to 25.6%) (**Table 4, Central Illustration**). Of the 55 deaths, 27.3% (n = 15) were cardiac, 5.5% (n = 2) were vascular, and 12.7% (n = 7) were caused by cancer, of which nearly one-half (n = 3) had pre-existing cancer at baseline. No deaths was device related. By Rutherford class, 24-month mortality was 9.4% (95% CI: 5.0% to 17.4%) for Rutherford class 4, 23.3% for class 5, and 30.4% for class 6 ($p = 0.012$). Furthermore, higher Rutherford class was associated with significantly higher 24-month overall and major amputation rates (5.2%, 15.6%, and 26.6% [$p = 0.0005$] and 1.1%, 6.9%, and 13.0% [$p = 0.006$] for Rutherford classes 4, 5, and 6, respectively). In addition, a post hoc Cox regression analysis showed that older age and higher TASC classification were predictors of mortality (Supplemental Table 2).

Comparing patients with CLI with those without CLI within the BIOLUX P-III registry, the CLI group had significantly higher MAE, target limb amputation, and mortality rates, but there was no significant difference in TLR and primary patency (Supplemental Figure 2).

Comparing BTK with femoropopliteal lesions within the CLI group, patients with BTK lesions were more frequently men, more frequently had diabetes, underwent fewer previous peripheral interventions, had less pain, and had higher ankle-brachial index and Rutherford class. Furthermore, BTK lesions were more frequently de novo lesions, had smaller reference vessel diameters, and had higher TASC classifications, and the target limb had more prior amputations and ulcerations. Likewise, the device diameter was smaller, lesions were shorter, and the paclitaxel dose was lower in BTK lesions, and less bailout stenting was required. There was no difference in clinical outcomes, however, except for a nonsignificant trend toward more target lesion amputations and cardiac deaths in the BTK group

FIGURE 2 Rutherford Class at Baseline and Follow-Up



(A) Unpaired data; data were available for 328 patients at baseline, 164 patients at 6 and 12 months, and 134 at 24 months. **(B)** Comparison with baseline; paired data. **Whiskers** represent the 95% exact binomial confidence interval.

(**Tables 1 to 3 and 5**). Likewise, 24-month ankle-brachial index, Rutherford class, and pain scale score were not significantly different among the groups (Supplemental Table 3).

DISCUSSION

CLI (or CLTI) is associated with significant mortality, limb loss, TLR, pain, and diminished quality of life; a higher incidence of early post-operative complications; and higher therapeutic costs (2,7–9). The aim of therapy is pain relief, wound healing, and limb preservation (2). Our series showed that the Passeo-18 Lux DCB can be safely applied in real-world practice with significant and sustained functional improvement, pain relief, and low major amputation rates.

PATIENT POPULATION. The patient population is typical for CLI patients, with approximately 50% of

TABLE 4 Kaplan-Meier Estimates of Clinical Events in Patients With Critical Limb Ischemia

	6 Months	12 Months	24 Months
Major adverse events	30 (9.8)	44 (14.9)	54 (19.4)
Primary patency, lesion based*	25 (93.5)	50 (86.2)	69 (78.9)
Clinically driven TLR, lesion based	17 (4.4)	31 (8.5)	41 (12.1)
TVR, vessel based	18 (5.1)	33 (9.9)	46 (15.1)
Target limb amputation, limb based	33 (10.6)	35 (11.3)	428 (14.3)
Major	15 (4.9)	16 (5.2)	18 (6.1)
Minor	21 (6.8)	22 (7.1)	28 (9.7)
AFS, limb based†	45 (85.8)	53 (83.1)	75 (73.9)
Mortality	25 (8.1)	34 (11.1)	55 (20.1)
Cardiac death	9 (3.0)	11 (3.7)	15 (5.7)
Vascular death	0 (0.0)	0 (0.0)	3 (1.3)

Values are number of events (Kaplan-Meier estimate [%]). *Imaging follow-up was available for only 88 patients. Calculating primary patency only for patients with imaging follow-up, the 24-month primary patency rate was 61.5%. †Major amputations.

AFS = amputation-free survival; TLR = target lesion revascularization; TVR = target vessel revascularization.

patients with prior interventions and histories of peripheral artery disease and a high prevalence of diabetes and renal disease (2,8). The clinical presentation, with more than one-half of the patients with ulceration and about 20% of patients in Rutherford class 6, is similar to the Medicare population reported by Mustapha et al. (10), whereas other studies deliberately excluded Rutherford class 6 (8,11,12).

With the caveat that calcification was site assessed, it is surprising that nearly one-half of the lesions were moderate and heavily calcified, considering that DCBs might be less effective in these lesion settings, as calcium represents a barrier to optimal drug absorption (13). Furthermore, the rate of femoropopliteal lesions is higher than expected for patients with CLI, which might be attributed to the fact that the efficacy of DCBs over uncoated balloons has been proved in femoropopliteal lesions, but controversial outcomes have been reported for BTK lesions (2,14–16).

Comparing BTK with femoropopliteal lesions, as expected, patients with BTK lesions more frequently had diabetes and smaller vessel diameters (14,15), whereas the higher ankle-brachial index is most likely due to arterial stiffening, leading to artificially high values (4). Noteworthy is the low rate of bailout stenting in BTK lesions (0.9% vs. 19.4%; $p < 0.0001$).

CLINICAL OUTCOMES. BIOLUX P-III shows good outcomes in the CLI subgroup compared to current research, as depicted in Supplemental Table 4. However, comparisons outside of randomized trials are nearly impossible, as outcomes depend largely on baseline parameters such as age, Rutherford class, TASC classification, presence of in-stent restenosis, lesion location, WIfI class, and Global Limb Anatomic Staging System stage but also on concomitant therapy and wound care (2,4,7,9–11,17,18). Even the country can influence outcomes, as for instance the threshold for amputation or treatment practices may vary. There is also a substantial difference in life expectancy within Europe, ranging from 75.3 to 82.8 years in the VASCUNET report, which may be relevant considering the average age of 71.1 ± 10.1 years in this analysis (19).

Interestingly, there was no significant difference in clinical outcomes between BTK and femoropopliteal lesions. This might be attributed to the small numbers, with only 92 patients with BTK lesions, particularly as there was a trend toward increased target limb amputations and cardiac mortality in the BTK group.

MORTALITY. In BIOLUX P-III, patients with CLI had a higher mortality rate compared with those without CLI (20.1% vs. 6.2% at 24 months; $p < 0.0001$), as seen in other studies such as in IN.PACT Global (11). Only one-third were cardiovascular deaths.

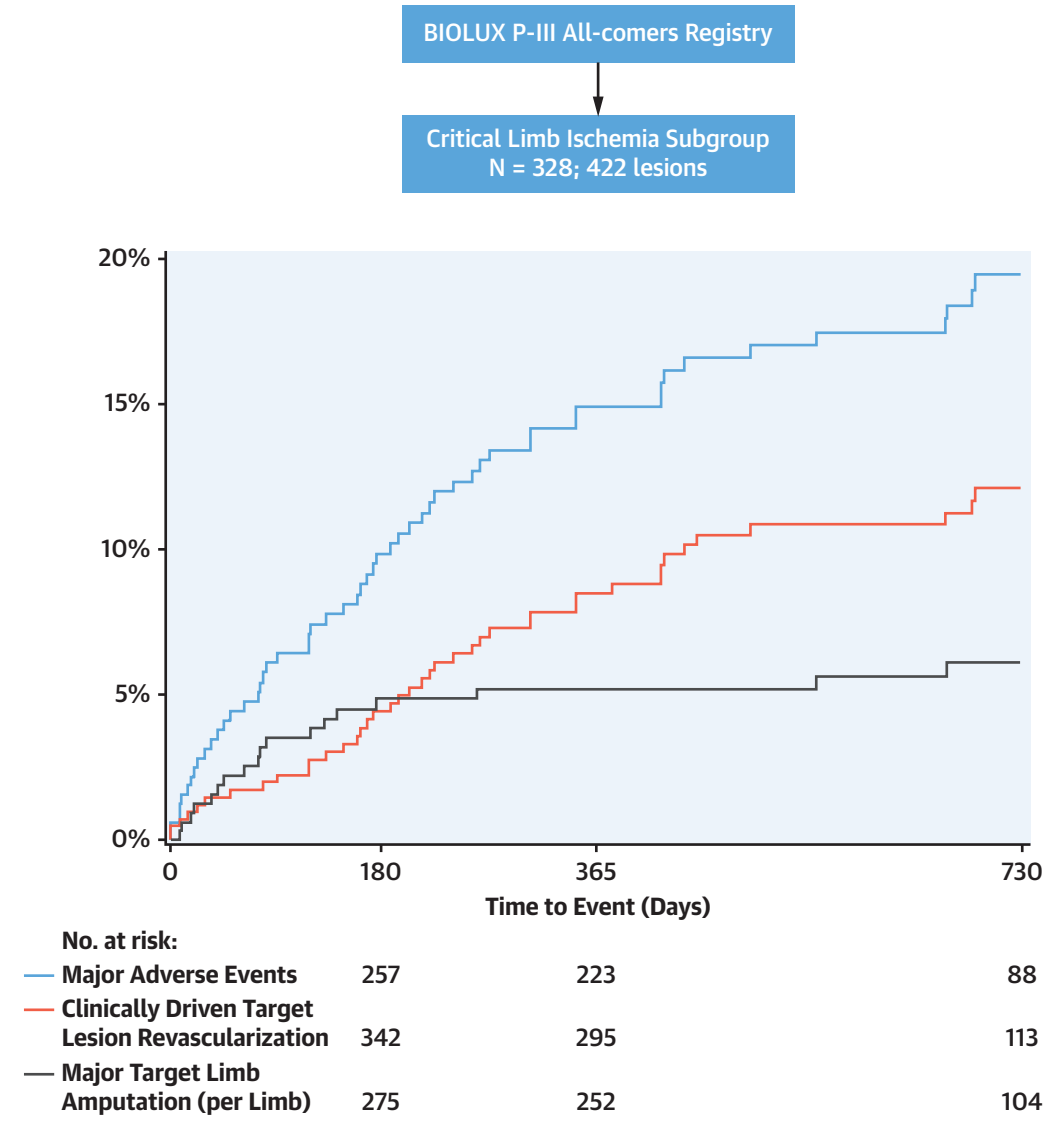
Predictors of mortality reported in published studies are older age, diabetes, coronary artery disease, chronic kidney disease, malignancies, and increased Rutherford class and tissue loss (9,10,17). With the limitation that our series was not powered for multivariate regression analysis, we found that age ≥75 years and higher TASC or Rutherford class was associated with a higher hazard for mortality, but not the paclitaxel dose.

AMPUTATIONS. In BIOLUX P-III, patients with CLI had a higher rate of major amputation compared with those without CLI (6.1% vs. 0.7% at 24 months; $p < 0.0001$), as seen in other studies such as IN.PACT Global (11).

We also found significantly elevated amputation rates with increased Rutherford class. Likewise, in published studies, an increased risk for major amputation has been reported for patients with chronic kidney disease, higher Rutherford class, diabetes, chronic heart failure, gangrene, higher ulcer classification, and higher WIfI score (9,10,18); for example, 1-year major amputation rate varied from 0% to 34% depending on WIfI score (18), and 4-year amputation rate varied from 37.7% to 63.5% depending on Rutherford class (9).

IMPROVEMENTS OF FUNCTIONAL OUTCOMES. Pain relief is the major goal in patients with CLI (2,17). This goal was achieved and sustained until the last follow-up visit at 24 months, when 71.9% had

CENTRAL ILLUSTRATION **Kaplan-Meier Analysis of Major Adverse Events and Their Components**



Brodmann, M. et al. J Am Coll Cardiol Intv. 2020;■(■):■-■.

No device- or procedure-related death occurred.

reductions in pain. In average, the pain scale score decreased by 3.2 points from 5.6 at baseline to 2.3 at 24-month follow-up (paired data). Furthermore, Rutherford class improved significantly at follow-up.

STUDY LIMITATIONS. First, BIOLUX P-III has the limitations inherent to a registry (e.g., a lack of randomization that hampers comparison with other devices or procedures). Second, the follow-up compliance rate was only 79.3% at 24 months, and only about one-half of patients had Rutherford class and pain score assessments.

Third, important parameters such as the presence of wounds and infection were not assessed, other parameters such as lesion calcification at baseline were not clearly defined, and ischemic rest pain was site reported without objective criteria. Furthermore, life expectancy of <1 year was an exclusion criterion. This is a subjective criterion, and it is unknown to what extent that criterion might have affected

TABLE 5 Kaplan-Meier Estimates of Clinical Events at 24 Months in Patients With Critical Limb Ischemia With BTK Versus FP Lesions

	BTK (n = 92)	FP (n = 176)	p Value
Major adverse events	17 (20.7)	27 (18.5)	0.378
Primary patency, lesion based	16 (81.4)	41 (78.3)	0.738
Clinically driven TLR, lesion based	11 (11.6)	21 (10.7)	0.577
TVR, vessel based	13 (13.1)	26 (16.1)	0.861
Target limb amputation, limb based	15 (20.9)	21 (12.3)	0.076
Major	4 (5.4)	12 (7.2)	0.697
Minor	11 (16.1)	13 (7.7)	0.055
AFS, limb based*	21 (69.5)	42 (75.3)	0.470
Mortality	20 (26.8)	31 (20.4)	0.346
Cardiac death	8 (11.6)	6 (3.9)	0.053
Vascular death	2 (3.1)	1 (0.8)	0.247

Values are number of events (Kaplan-Meier estimate [%]). *Major amputations.
Abbreviations as in Tables 1 and 4.

outcomes. However, as detailed in the discussion, the patient population reflects the common CLI population, and therefore we believe that the impact of the criterion is marginal. A positive aspect of this analysis is the relatively large patient cohort.

CONCLUSIONS

This analysis represents one of the largest prospective multicenter registries using DCBs in patients with CLI in a real-world scenario. In a multimorbid patient population with CLI and complex lesions, such as moderate or heavily calcified lesions, in about one-half of the patients, the Passeo-18 Lux DCB has been demonstrated to be safe and effective, with low major amputation rates and substantial clinical improvement, confirming the usefulness of the device for this indication.

ACKNOWLEDGMENT The authors thank Beatrix Doerr for her help in preparing the manuscript, reimbursed by Biotronik.

ADDRESS FOR CORRESPONDENCE: Prof. Dr. Marianne Brodmann, Department of Angiology, Medical University Graz, Auenbruggerplatz 15, 8036 Graz, Austria. E-mail: marianne.brodmann@medunigraz.at.

PERSPECTIVES

WHAT IS KNOWN? There is still a lack of knowledge as to which device performs best in specific peripheral artery disease subsets. In particular, for patients with CLI, clinical studies include only small patient numbers, often with <150 patients. The global vascular guidelines for patients with CLTI call for further prospective trials in this indication (2).

WHAT IS NEW? This is one of the largest prospective series of the use of DCBs in patients with CLI and the largest series of the Passeo-18 Lux DCB. It confirms the safety and efficacy of this device under real-world use and adds further knowledge to the field by determining risk factors for mortality and major amputations.

WHAT IS NEXT? To ultimately assess the usefulness of DCBs, randomized controlled trials powered for clinical endpoints would be needed. However, these trials are difficult to conduct, as they require a large patient number, and enrollment is usually slow, as seen in the BASIL-3 trial (20).

REFERENCES

1. Tepe G, Zeller T, Moscovic M, et al. Paclitaxel-coated balloon for the treatment of infrainguinal disease: 12-month outcomes in the all-comers cohort of BIOLUX P-III global registry. J Endovasc Ther 2020;27:304–15.

2. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. Eur J Vasc Endovasc Surg 2019;58:S1–109.e33.

3. Abu Dabrh AM, Steffen MW, Undavalli C, et al. The natural history of untreated severe or critical limb ischemia. J Vasc Surg 2015;62:1642–51.e3.

4. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries endorsed by: the European Stroke Organization (ESO) the Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;39:763–816.

5. Brodmann M, Zeller T, Christensen J, et al. Real-world experience with a paclitaxel-coated balloon for the treatment of atherosclerotic infrainguinal arteries: 12-month interim results of the BIOLUX P-III registry first year of enrolment. J Vasc Bras 2017;16:276–84.

6. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 2018;7:e011245.

7. Roh JW, Ko YG, Ahn CM, et al. Risk factors for restenosis after drug-coated balloon angioplasty for complex femoropopliteal arterial occlusive disease. Ann Vasc Surg 2019;55:45–54.

8. AbuRahma AF, AbuRahma ZT, Scott G, et al. Clinical outcome of drug-coated balloon angioplasty in patients with femoropopliteal disease: a real-world single-center experience. J Vasc Surg 2019;70:1950–9.

9. Reinecke H, Unrath M, Freisinger E, et al. Peripheral arterial disease and critical limb ischaemia: still poor outcomes and lack of guideline adherence. Eur Heart J 2015;36:932–8.

10. Mustapha JA, Katzen BT, Neville RF, et al. Disease burden and clinical outcomes following initial diagnosis of critical limb ischemia in the Medicare population. J Am Coll Cardiol Intv 2018; 11:1011–2.

11. Reijnen M, van Wijck I, Zeller T, et al. Outcomes after drug-coated balloon treatment of femoropopliteal lesions in patients with critical limb ischemia: a post hoc analysis from the IN.PACT Global study. J Endovasc Ther 2019;26:305–15.

12. Riambau V, Acin F, de Blas MJ, Alonso M, Gimenez-Gaibar A. Drug-coated balloon angioplasty in clinical practice for below-the-knee, popliteal, and crural artery lesions causing critical limb ischemia: 1-year results from the Spanish Luminor registry. Ann Vasc Surg 2020;62:387–96.

13. Fanelli F, Cannavale A, Gazzetti M, et al. Calcium burden assessment and impact on drug-eluting balloons in peripheral arterial disease. Cardiovasc Intervent Radiol 2014;37:898–907.

14. Scheinert D, Schulte KL, Zeller T, Lammer J, Tepe G. Paclitaxel-releasing balloon in femoropopliteal lesions using a BTHC excipient: twelve-month results from the BIOLUX P-I randomized trial. J Endovasc Ther 2015;22:14–21.

15. Zeller T, Beschorner U, Pilger E, et al. Paclitaxel-coated balloon in infrapopliteal arteries: 12-month results from the BIOLUX P-II randomized trial (BIOTRONIK's-First in Man Study of the Passeo-18 LUX Drug Releasing PTA Balloon Catheter vs. the Uncoated Passeo-18 PTA Balloon Catheter in Subjects Requiring Revascularization of Infrapopliteal Arteries). J Am Coll Cardiol Intv 2015;8:1614–22.

16. Kayssi A, Al-Atassi T, Oreopoulos G, Roche-Nagle G, Tan KT, Rajan DK. Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for peripheral arterial disease of the lower limbs. Cochrane Database Syst Rev 2016;8:CD011319.

17. Conte MS, Geraghty PJ, Bradbury AW, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. J Vasc Surg 2009;50:1462–73.e1–e3.

18. Ward R, Dunn J, Clavijo L, Shavelle D, Rowe V, Woo K. Outcomes of critical limb ischemia in an urban, safety net hospital population with high WIfI amputation scores. Ann Vasc Surg 2017;38: 84–9.

19. Behrendt CA, Sigvant B, Szeberin Z, et al. International variations in amputation practice: a VASCUNET report. Eur J Vasc Endovasc Surg 2018; 56:391–9.

20. Birmingham Clinical Trials Unit. Basil-3 trial recruitment. Available at: https://www.birmingham.ac.uk/research/bctu/trials/portfolio-v/Basil-3/Investigators/Recruitment.aspx. Accessed December 18, 2019.

KEY WORDS chronic limb-threatening ischemia, critical limb ischemia, drug-coated balloon, drug-eluting balloon, peripheral artery disease

APPENDIX For supplemental tables, supplemental figures and their legends, and supplemental references, please see the online version of this paper.