Drug-Coated Balloon Treatment of Femoropopliteal Lesions Typically Excluded From Clinical Trials: 12-Month Findings From the IN.PACT Global Study

Gary M. Ansel, MD[1] [ID], Marianne Brodmann, MD[2], Koen Keirse, MD[3], Antonio Micari, MD, PhD[4], Michael R. Jaff, DO[5], Krishna Rocha-Singh, MD[6], Eric J. Fernandez, MD[7], Hong Wang, MD, MPH[7], and Thomas Zeller, MD[8], for the IN.PACT Global Study Investigators

Abstract

Purpose: To report a post hoc analysis comparing outcomes between subjects who would have been included in the IN.PACT SFA randomized controlled trial vs those who would have been excluded. **Methods**: The 1406 subjects enrolled in the IN.PACT Global Study (*ClinicalTrials.gov* identifier NCT01609296) were retrospectively assigned to a standard-use group (n=281) based on the inclusion and exclusion criteria from the randomized IN.PACT SFA trial; the remaining 1125 patients were assigned to the broader-use group. Freedom from clinically-driven target lesion revascularization (CD-TLR) was evaluated at 12 months. The composite primary safety endpoint was freedom from 30-day device- and procedure-related death plus freedom from 12-month target limb major amputation and clinically-driven target vessel revascularization (CD-TVR). Functional outcomes were evaluated with dedicated questionnaires. **Results:** Compared with the standard-use cohort, the broader-use lesions were longer, more calcified, and had more popliteal involvement, bilateral disease, and in-stent restenosis (p<0.001 for all). Freedom from 12-month CD-TLR by Kaplan-Meier analysis was 96.6% for the standard-use group and 91.6% for the broader-use group (p=0.005). The safety endpoint was 96.2% in the standard-use group and 91.0% in the broader-use group (p=0.003). The 12-month CD-TLR (3.4% standard-use vs 8.5% broader-use, p=0.004) and CD-TVR (4.2% standard-use vs 9.1% broader-use, p=0.008) were increased in the broader-use group. Twelve-month all-cause mortality was not increased (3.8% standard-use vs 3.4% broader-use, p=0.852). **Conclusion:** Post hoc analysis of the IN.PACT Global Study of real-world patients demonstrated consistent outcomes with significant clinical improvement to 12 months in subjects with complex lesions typically excluded from a randomized controlled trial.

Keywords

angioplasty, drug-coated balloon, femoropopliteal segment, peripheral artery disease, popliteal artery, superficial femoral artery, target lesion revascularization, stenting

Introduction

Atherosclerotic peripheral artery disease (PAD) involving the superficial femoral artery (SFA) and/or popliteal arteries plays a central role in lifestyle-limiting claudication and critical limb ischemia (CLI). Drug-coated balloons (DCBs) were developed to overcome the challenges of traditional implantable drug-eluting and non-drug-based endovascular interventions. Currently, DCBs are coated with the antiproliferative agent paclitaxel, which transfers to the inner arterial wall on inflation and may persist in the vessel tissue for up to 180 days.[1–3]

Numerous randomized controlled trials (RCTs) have demonstrated that DCBs are safe and more effective for the treatment of patients with femoropopliteal lesions than uncoated balloon angioplasty (IN.PACT SFA,

[1]Department of Medicine, Ohio Health/Riverside Methodist Hospital, Columbus, OH, USA
[2]Department of Internal Medicine, Division of Angiology, Medical University, Graz, Austria
[3]Department of Vascular Surgery, Regional Hospital Heilig Hart, Tienen, Belgium
[4]GVM Care and Research, Maria Cecilia Hospital, Cotignola, Italy
[5]Newton-Wellesley Hospital, Newton, MA, USA
[6]Prairie Heart Institute, Springfield, IL, USA
[7]Medtronic, Santa Rosa, CA, USA
[8]Universitäts-Herzzentrum Freiburg–Bad Krozingen, Bad Krozingen, Germany

Corresponding Author:
Gary M. Ansel, Department of Medicine, Ohio Health/Riverside Methodist Hospital, 3705 Olentangy River Road Suite 100, Columbus, OH 43214 USA.
Email: gary.ansel@ohiohealth.com

LEVANT 2, BIOLUX P-1, THUNDER, ILLUMENATE EU, ILLUMENATE Pivotal).[4–10] Meta-analyses of clinical trials have also shown that DCBs are a cost-effective option that provides clinically meaningful benefit compared with traditional non-drug-based treatments, such as bare metal stents or angioplasty with an uncoated balloon.[11,12] However, randomized investigational device exemption (IDE) trials in the United States are characterized by strict enrollment criteria guided by discussions with the Food and Drug Administration (FDA) to ensure uniform patient populations. These criteria typically exclude complex but frequently encountered pathologies, such as long lesions [typically described as TransAtlantic Inter-Society Consensus II (TASC) C and D], de novo in-stent restenosis (ISR), long chronic total occlusions (CTO), and severe calcification in the most common classification schemes.

RCTs conducted elsewhere (THUNDER, FEMPAC, PACIFIER, CONSEQUENT, AcoArt I) typically include more complex patient cohorts but also fewer patients.[13–17] Different from trials in the United States, they report a primary outcome of late lumen loss using core laboratory–adjudicated angiography at 6 months and site-reported target lesion revascularization (TLR). Importantly, all demonstrated the clinical benefit of treatment with a DCB. However, there continues to be a need for larger controlled and adjudicated datasets on the use of DCBs in patients with complex lesions that are seen in everyday practice.

The IN.PACT Global Study is a prospective, independently adjudicated trial that evaluated the use of DCBs for patients with a broad range of lesion types in the native SFA and/or popliteal artery.[18] The study design included 3 pre-specified cohorts for the prospective analysis of DCB safety and effectiveness in patients with distinct complex lesion types: long lesions ≥15 cm, de novo ISR, and CTO ≥5 cm. Twelve-month results from each of these analyses have been reported and support the safety and effectiveness of DCB use for each of these complex lesion types.[19–21]

This report details a post hoc analysis comparing 12-month clinical outcomes between subjects in the IN.PACT Global Study clinical cohort with clinical and lesion characteristics that are routinely included in RCTs (standard-use group) vs those typically excluded from RCTs owing to increased complexity (broader-use group).

Methods

Study Design

The IN.PACT Global Study is a prospective, multicenter, international, single-arm clinical study assessing the safety and effectiveness of the paclitaxel-coated IN.PACT Admiral DCB (Medtronic Inc., Dublin, Ireland) for the treatment of real-world patients with intermittent claudication and/or ischemic rest pain due to atherosclerotic disease of the femoropopliteal segment, including the entire native SFA and/or popliteal artery. The trial was registered on the National Institutes of Health website (*ClinicalTrials.gov*; identifier NCT01609296). The institutional review board or ethics committee at each study site approved the study protocol. Informed consent was obtained from all subjects before enrollment. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable laws as specified by all relevant governmental bodies. An independent Clinical Events Committee (CEC; Syntactx, New York, NY, USA) composed of interventional and noninvasive clinicians was established to assess the primary and certain secondary endpoints and to determine whether each met protocol-specified criteria.

The IN.PACT Global Study enrolled subjects with symptoms of intermittent claudication and/or ischemic rest pain (Rutherford categories 2–4) and angiographic evidence of ≥2-cm long stenosis or occlusion [de novo or restenosis (in-stent or native vessel)] in the SFA and/or popliteal artery (including P1–P3 segments). Details of the DCB device, study design, and treatment parameters have been previously described.[18] Pre- and postdilation were permitted at the discretion of the investigator. Vessel preparation by other devices was not permitted, and postdilation could be performed using an uncoated balloon only.

The current post hoc analysis compared 12-month clinical outcomes between subjects who would have been included in the IN.PACT SFA RCT vs those patients who would have been excluded. The flow of patients is shown in Figure 1. Of the 1535 subjects enrolled in IN.PACT Global, 119 were included in the 150-mm DCB cohort and used for regulatory purposes. These subjects were not included in the full cohort as they were not consecutively enrolled, introducing a potential treatment bias. In addition, 10 patients were not treated with a DCB, resulting in a full clinical cohort of 1406 subjects treated with a DCB (intention-to-treat population). The 1- and 2-year results of this cohort have been presented, and the imaging cohorts have been presented (CTO, long lesion)[20,21] and published (ISR).[19]

For this analysis, it was necessary to create a cohort typically enrolled in an RCT, so subjects from the 1406 clinical cohort patients were retrospectively assigned to a standard-use group based on the inclusion/exclusion criteria employed in the randomized IN.PACT SFA trial.[9] The 281 assigned patients had single 70% to 99% stenotic de novo or native artery restenotic lesions ≤18 cm long or CTOs ≤10 cm long. Lesions could have mild calcification but ISR was not allowed. The remaining 1125 clinical cohort patients were assigned to a broader-use group that included subjects who would have been excluded from the trial, namely, those with multiple lesions, single de novo lesions >18 cm, CTOs >10 cm, any ISR, moderate or severe calcification, or bilateral
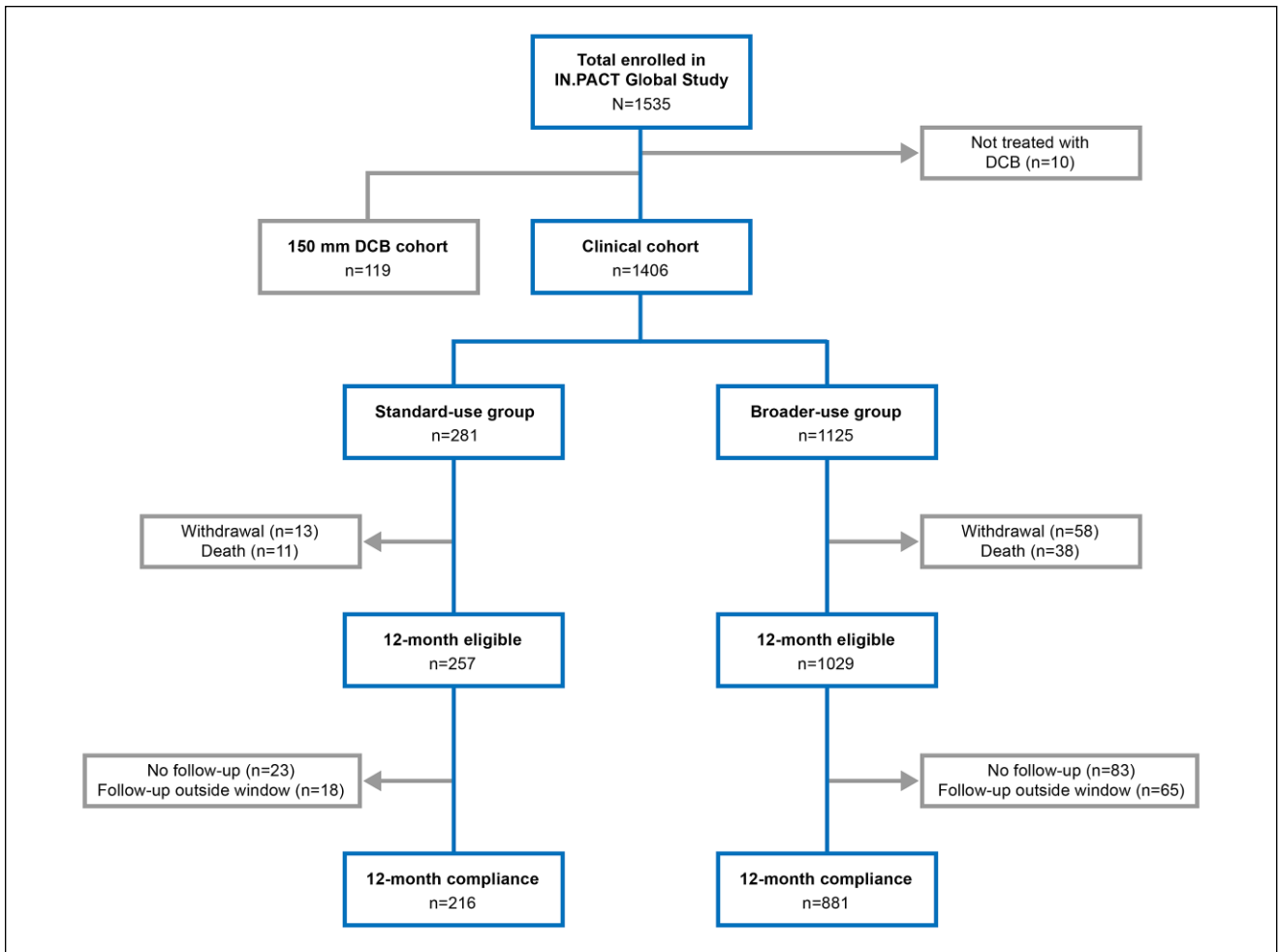
Figure 1. Patient flow in the standard-use and broader-use groups in the IN.PACT Global Study clinical cohort through 12 months. DCB, drug-coated balloon.

disease. Calcification was categorized as mild (on one side of the artery only and over less than half the total lesion length), moderate (one side of the artery only and over greater than or equal to half the total lesion length), moderately severe (both sides of the artery at the same location over less than half the total lesion length), and severe (both sides of the artery at the same location over greater than or equal to half the total lesion length).[22]

Site-reported baseline demographics and lesion characteristics are reported in Tables 1 and 2. Nineteen of the 116 subjects with bilateral disease had only standard lesions but were classified in the broader-use group because both legs were affected (1.7% of the 1125 patients).

Study Endpoints

The composite primary safety endpoint was freedom from device- and procedure-related mortality through 30 days and freedom from 12-month major target limb amputation and clinically-driven target vessel revascularization (CD-TVR).

The latter was assessed at the subject level and defined as the first event that required revascularization in the subject. The primary effectiveness endpoint was clinically-driven target lesion revascularization (CD-TLR) within 12 months. The CEC reviewed all CD-TLR and CD-TVR events to determine which were clinically driven, that is, due to symptoms or an ankle-brachial index (ABI) decrease $\geq 20\%$ or >0.15 when compared with the baseline value. Clinically-driven TLRs or TVRs did not include procedures that were performed on asymptomatic subjects or that were based only on diagnostic imaging procedures.

Secondary endpoints included CD-TLR, the incidence of major adverse events (all-cause mortality, CD-TVR, major target limb amputation, thrombosis at the target lesion site), any TLR, and any TVR at 12 months. Other secondary outcomes were the change in Rutherford category and primary sustained clinical improvement (defined as freedom from major target limb amputation, freedom from TVR, and improvement in Rutherford category). The CEC adjudicated all major adverse events.

Table 1. Baseline Demographics and Clinical Characteristics of Subjects in the Standard-Use and Broader-Use Groups.[a]

Variable (Site-Reported)	Standard-Use (n=281)[b]	Broader-Use (n=1125)[b]	p
Age, y	67.2±10.4 (280)	68.9±10.0 (1116)	0.012
Men	178/281 (63.3)	775/1125 (68.9)	0.087
Body mass index, kg/m^2	26.5±4.5 (279)	26.8±4.5 (1112)	0.354
Obesity (body mass index ≥30 kg/m^2)	52/279 (18.6)	233/1112 (21.0)	0.408
Diabetes mellitus	102/279 (36.6)	458/1123 (40.8)	0.219
Insulin-dependent	50/279 (17.9)	199/1123 (17.7)	0.930
Hypertension	214/279 (76.7)	955/1122 (85.1)	0.001
Hyperlipidemia	185/269 (68.8)	775/1093 (70.9)	0.502
Current smoker	107/281 (38.1)	340/1125 (30.2)	0.012
Coronary heart disease	87/263 (33.1)	453/1069 (42.4)	0.006
Carotid artery disease	41/238 (17.2)	200/958 (20.9)	0.240
Renal insufficiency[c]	21/245 (8.6)	115/972 (11.8)	0.173
Previous peripheral revascularization	106/281 (37.7)	631/1125 (56.1)	<0.001
Below-the-knee disease in target leg	108/255 (42.4)	486/1055 (46.1)	0.294
Rutherford category			0.002
1	0/281 (0.0)	1/1122 (0.1)[d]	
2	107/281 (38.1)	329/1122 (29.3)	
3	152/281 (54.1)	658/1122 (58.6)	
4	22/281 (7.8)	98/1122 (8.7)	
5	0/281 (0.0)	36/1122 (3.2)[d]	
Ankle-brachial index	0.70±0.23 (254)	0.67±0.22 (1139)	0.132
Bilateral disease	0/281 (0.0)	116/1125 (10.3)	<0.001

[a]Continuous data are presented as the means ± standard deviation (sample); categorical data are given as the number/sample (percentage).
[b]In some cases, baseline demographic or clinical data were not available.
[c]Defined as baseline creatinine ≥1.5 mg/dL.
[d]Owing to protocol violations, 1 Rutherford category 1 subject (broader-use group) and 36 Rutherford category 5 subjects (all broader-use group) were enrolled and included in the analysis.

Table 2. Lesion Characteristics for 281 Subjects in the Standard-Use Group vs 1125 Subjects in the Broader-Use Group.[a]

Variable (Site-Reported)	Standard-Use (n=281)[b]	Broader-Use (n=1492)[b]	p
Lesion type			<0.001
De novo	260/281 (92.5)	1057/1492 (70.8)	
Restenotic (native artery)	21/281 (7.5)	115/1492 (7.7)	
In-stent restenosis	0/281 (0.0)	320/1492 (21.4)	
Lesion location[c]			
Superficial femoral artery	266/281 (94.7)	1287/1492 (86.3)	<0.001
Popliteal artery	46/281 (16.4)	438/1492 (29.4)	<0.001
P1	46/281 (16.4)	322/1492 (21.6)	0.054
P2	0/281 (0.0)	231/1492 (15.5)	<0.001
P3	0/281 (0.0)	84/1492 (5.6)	<0.001
Lesion length, cm	7.9±4.5 (281)	12.9±10.0 (1492)	<0.001
Occlusion	96/281 (34.2)	533/1492 (35.7)	0.635
Calcification present	154/281 (54.8)	1063/1490 (71.3)	<0.001
Severe calcification[d]	0/281 (0.0)	181/1490 (12.2)	<0.001
Reference vessel diameter, cm	5.2±0.7 (281)	5.2±0.7 (1492)	0.440
Diameter stenosis, %	89.1±11.2 (281)	88.7±12.5 (1492)	0.590

[a]Continuous data are presented as the means ± standard deviation (sample); categorical data are given as the number/sample (percentage).
[b]In some cases, lesion data were not available.
[c]A lesion could span more than 1 vessel.
[d]Severe calcification was defined as circumferential calcification and length greater than or equal to half the total lesion length.

Functional assessments included the ABI, EuroQol 5-Dimension Quality of Life Index (EQ-5D), the Walking Impairment Questionnaire (WIQ), and the nights in hospital (a cumulative measure over the 12-month follow-up that included any time a subject returned to the hospital for any issue related to the study lesion). Acute periprocedural outcomes (device success, procedure success, and clinical success) and categories of provisional stenting (spot stenting and partial lesion coverage) were previously defined.[18]

Statistical Analysis

All data used in the analysis were provided by the investigational sites and all summaries were based on nonmissing assessments. Unless otherwise specified, all baseline demographics and clinical characteristics were summarized on a subject basis; lesion characteristics were summarized on a lesion basis. For baseline characteristics, continuous variables were described as mean $\pm$ standard deviation and were compared using a 2-sample t test. Dichotomous and categorical variables were described as numbers (proportions) and were compared with the Fisher exact test or Cochran-Mantel-Haenszel modified ridit scores, respectively. For functional outcomes, change from baseline within each group was compared with Wilcoxon signed rank test, and differences between groups were compared with the Wilcoxon rank sum test.

The Kaplan-Meier method was used to evaluate time-to-event data for per-patient freedom from CD-TLR over the 12-month follow-up; the log-rank test was used for the group comparisons. For event rates that were expressed as a proportion, the number of subjects with an event within 360 days was the numerator and the total number of subjects with an event or at least 300 days of clinical follow-up was the denominator. Assessment of clinical characteristics from baseline to 12 months involved subjects who had data at both time points. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA)

Results

Group Comparison

Compared with the standard-use (SU) patients, the broader-use (BU) patients were older (p=0.012) and had more hypertension (p=0.001), coronary heart disease (p=0.006), previous peripheral interventions (p<0.001), and more severe ischemia (Rutherford categories 3–5; p=0.002) but fewer current smokers (p=0.012; Table 1). The BU group also had longer lesions (p<0.001), a higher percentage of calcified lesions (p<0.001), more popliteal involvement (p<0.001; Table 2) and included patients with bilateral disease (Table 1) and ISR (excluded from the SU group; Table 2).

Predilation was performed more frequently in subjects from the BU group (902/1125, 80.2%) compared with the SU group (195/281, 69.4%; p<0.001). Postdilation was performed in 36.4% (407/1117) of subjects in the BU group vs 30.0% (84/280) of SU patients (p=0.050; Table 3). Provisional stents were implanted more frequently in the BU group (328/1481, 22.1%) compared with the SU patients (45/280, 16.1%; p=0.025). The mean stent length was also longer in the BU (12.3$\pm$8.8 cm) compared with the SU patients (8.4$\pm$4.6 cm, p<0.001). Lesion coverage and reasons for stenting are reported in Table 3.

Safety Outcomes

The 12-month primary safety composite endpoint was met by proportionally fewer subjects in the BU group [91.0% (952/1046)] than in the SU cohort [96.2% (255/265), p=0.003] and was mainly driven by a higher incidence of CD-TVR in the BU patients [9.1% (95/1046)] vs the SU patients [4.2% (11/265), p=0.008; Table 4]. The rate of all-cause death at 12 months was not significantly different between groups [3.4% (36/1046) BU vs 3.8% (10/265) SU; p=0.852]. Independent adjudication by the CEC determined that none of the deaths was related to the study device. Two of the deaths in the BU group and 1 in the SU group occurred within 30 days of the index procedure, so the CEC adjudicated them as possibly or potentially procedure-related. Details of these events have been previously reported.[18]

There were no statistically significant differences between groups in the rates of major target limb amputation (p>0.999) or thrombosis (p=0.063; Table 4). Though the rate of thrombosis was low in both groups, there was a slight trend to more thrombosis in the BU group, which may not be unexpected given the complexity of the disease.

Effectiveness Outcomes

The Kaplan-Meier estimate of freedom from CD-TLR at 12 months was 91.6% in the BU group vs 96.6% in the SU patients (log-rank p=0.005; Figure 2). Freedom from CD-TLR at 13 months was 89.7% vs 95.4%, respectively (log-rank p=0.004). Twelve-month CD-TLR occurred more frequently in the BU group [8.5% (89/1046)] compared with the SU group [3.4% (9/265), p=0.004]. There was no difference in mean time to first CD-TLR between groups (5.3$\pm$3.6 months BU vs 7.4$\pm$3.6 months SU, p=0.096; Table 4).

Functional Outcomes

Both groups had significant improvements in Rutherford class from baseline to 12 months (p<0.001; Table 5). There was no significant difference between the changes in each group (p=0.087). The rate of primary sustained clinical improvement was lower in the BU group [78.7% (747/949)

Table 3. Procedure Details for 281 Subjects in the Standard-Use Group vs 1125 Subjects in the Broader-Use Group.[a]

Variable (Site-Reported)	Standard-Use (n=281)[b]	Broader-Use (n=1492)[b]	p
Lesion access			
Ipsilateral antegrade	130/281 (46.3)	626/1492 (42.0)	0.189
Contralateral retrograde	149/281 (53.0)	850/1492 (57.0)	0.238
DCBs per lesion [median]	1.3±0.5 (281) [1.0]	1.8±1.0 (1485) [1.0]	<0.001
Predilation	195/281 (69.4)	902/1125 (80.2)	<0.001
Postdilation	84/280 (30.0)	407/1117 (36.4)	0.050
Provisional stenting	45/280 (16.1)	328/1481 (22.1)	0.025
Stents used [median]	1.1±0.4 [1.0]	1.3±0.6 [1.0]	
Stent length, cm	8.4±4.6	12.3±8.8	<0.001
Lesion coverage			
Spot stenting[c]	6/45 (13.3)	85/328 (25.9)	0.067
Partial[d]	13/45 (28.9)	128/328 (39.0)	0.251
Entire	26/45 (57.8)	115/328 (35.1)	0.005
Reason for stenting			
Residual stenosis ≥50%	26/45 (57.8)	195/328 (59.5)	0.872
Gradient >10 mm Hg	0/45 (0.0)	2/328 (0.6)	1.000
Flow-limiting dissection	26/45 (57.8)	174/328 (53.0)	0.633
Other	2/45 (4.4)	17/328 (5.2)	1.000
Postprocedure outcomes			
Device success[e]	353/353 (100.0)	2631/2649 (99.3)	0.257
Procedure success[f]	279/279 (100.0)	1107/1117 (99.1)	0.227
Clinical success[g]	278/279 (99.6)	1101/1117 (98.6)	0.221
Dissections[h]			0.035
None	138/281 (49.1)	868/1491 (58.2)	
A–C	117/281 (41.6)	510/1491 (34.2)	
D–F	26/281 (9.3)	113/1491 (7.6)	

Abbreviation: DCB, drug-coated balloon.

[a]Continuous data are presented as the means ± standard deviation (sample) unless otherwise stated; categorical data are given as the number/sample (percentage).
[b]In some cases, lesion data were not available. Also, some analyses are not based on lesions but as noted in the footnote for that variable.
[c]Spot stenting was defined as utilization of the single shortest stent in which minimal length was sufficient to cover the residual stenosis but did not cover the entire original length of the target lesion.
[d]Partial lesion coverage was defined as utilization of a stent no longer than the residual stenosis but shorter than the original length of the target lesion.
[e]Device success was defined as successful delivery, inflation, deflation, and retrieval of the intact study balloon without burst below the rated burst pressure. This analysis is balloon based.
[f]Procedure success was defined as residual stenosis ≤50% for nonstented subjects or ≤30% for stented subjects by core laboratory assessment (site-reported estimate was used if core laboratory assessment was not available). This analysis is lesion based.
[g]Clinical success was defined as procedure success without complications (death, major target limb amputation, thrombosis of the target lesion, or target vessel revascularization) prior to discharge. This analysis is subject based.
[h]Dissections were classified as A, luminal haziness; B, linear dissection; C, extraluminal contrast; D, spiral dissection; E, reduced flow; and F, total occlusion.

vs the SU patients [88.0% (206/234), p=0.001] at 12 months (Table 6). Mean EQ-5D scores were significantly improved from baseline to 12 months in both groups (p<0.001). Mean change from baseline in EQ-5D score at 12 months was significantly higher for the SU group compared with the BU patients (p<0.001; Table 6).

Mean WIQ scores and ABI were also significantly improved from baseline to 12 months in both groups (all p<0.001). For both measures, the mean change from baseline to 12 months was similar between groups (WIQ, p=0.069; ABI, p=0.448). There was no difference in the median ABI at baseline between groups, whether the cutoff of 1.3 or 1.4 was used to define noncompressible arteries.

Mean nights in hospital were 0.55±4.39 for the BU group and 0.24±1.57 for the SU patients (p=0.325; Table 6).

Discussion

The IN.PACT Global Study evaluated real-world patients with adjudication of subgroups based on complex, often difficult to treat lesion types, including long lesions (≥15 cm), de novo ISR, and CTOs (≥5 cm); the effectiveness of DCB treatment was reflected in the 92.6% freedom from CD-TLR in a heterogeneous population.[18]

The current post hoc analysis was performed to compare 12-month outcomes between subjects with clinical and

Table 4. 12-Month Safety Outcomes in the Standard-Use and Broader-Use Groups.[a]

Safety Outcome[b]	Standard-Use (n=265)[c]	Broader-Use (n=1046)[c]	p
CD-TLR[d]	9 (3.4)	89 (8.5)	0.004
Time to first CD-TLR, mo	7.4±3.6 (9)	5.3±3.6 (89)	0.096
Primary safety endpoint[e]	255 (96.2)	952 (91.0)	0.003
Major adverse events[f]	21 (7.9)	136 (13.0)	0.026
Death (all-cause)	10 (3.8)	36 (3.4)	0.852
Major target limb amputation	0 (0.0)	3 (0.3)	>0.999
Thrombosis	3 (1.1)	35 (3.3)	0.063
CD-TVR	11 (4.2)	95 (9.1)	0.008
Any TLR	10 (3.8)	92 (8.8)	0.009
Any TVR	12 (4.5)	98 (9.4)	0.005

Abbreviations: CD-TLR, clinically driven target lesion revascularization; CD-TVR, clinically driven target vessel revascularization; TLR, target lesion revascularization; TVR, target vessel revascularization.
[a]Continuous data are presented as the means ± standard deviation (sample); categorical data are given as the number (percentage).
[b]An independent Clinical Events Committee adjudicated all major adverse events (MAEs).
[c]Event rates were based on the number of evaluable subjects with an MAE within 360 days or without any MAE but had at least 300 days of clinical follow-up.
[d]CD-TLR was defined as any reintervention within the target lesion(s) due to symptoms or a drop in the ankle-brachial index ≥20% or >0.15 when comparing postprocedure with baseline index values.
[e]The primary safety composite endpoint was freedom from device- and procedure-related mortality through 30 days and freedom from major target limb amputation and CD-TVR within 12 months after the index procedure.
[f]Major adverse event was defined as all-cause mortality, CD-TVR, major target limb amputation, or thrombosis at the target lesion site.
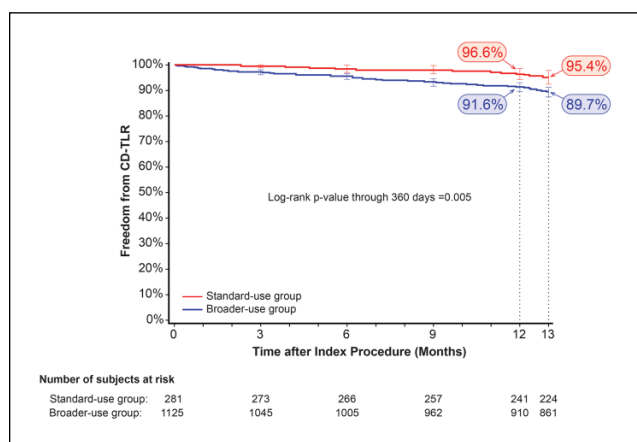
Figure 2. Kaplan-Meier curve of freedom from clinically driven target lesion revascularization (CD-TLR) through 12 months in the standard-use and broader-use groups. Numbers at risk represent the patients at the beginning of the 30-day window prior to each follow-up interval.

Table 5. Changes in Rutherford Category at 12 Months in the Standard-Use and Broader-Use Groups.[a]

Change	Standard-Use (n=231)	Broader-Use (n=930)	p
−5	0 (0.0)	9 (1.0)	
−4	10 (4.3)	44 (4.7)	
−3	83 (35.9)	316 (34.0)	
−2	89 (38.5)	292 (31.4)	
−1	32 (13.9)	154 (16.6)	
0	16 (6.9)	87 (9.4)	
+1	1 (0.4)	21 (2.3)	
+2	0 (0.0)	7 (0.8)	
+3	0 (0.0)	0 (0.0)	
+4	0 (0.0)	0 (0.0)	
p	<0.001[b]	<0.001[c]	0.087[d]

[a]Data are given as the number (percentage).
[b]Baseline to 12 months in standard-use group.
[c]Baseline to 12 months in broader-use group.
[d]Between groups from baseline to 12 months.

lesion characteristics that are usually included in RCTs and those that are typically excluded but commonly seen in daily practice. The results demonstrate DCB performance that is parallel with not only strictly controlled RCTs but also trials of DCBs that have been specifically designed to evaluate performance in patients with complex femoropopliteal lesions. For example, the 96.6% estimated freedom from CD-TLR in the SU group was similar to the 97.5% estimate from the IN.PACT SFA RCT of TASC II A/B lesions.[9] Similarly, the 91.6% estimate for CD-TLR in the

BU group (22% stented) was comparable to data for different types of complex lesions from the IN.PACT Global imaging cohorts (94.2% for long lesions with 40.4% stenting,[20] 92.9% for de novo ISR with 14.5% stenting,[19] and 89.1% for CTO with 46.8% stenting[21]).

The IN.PACT Global Study was designed to enroll a real-world patient population, and when subjects in the full clinical cohort were retrospectively dichotomized based on the selection criteria used in the IN.PACT SFA RCT, only 20% of subjects were assigned to the SU group.

Table 6. Twelve-Month Functional Outcomes in the Standard-Use and Broader-Use Groups.[a]

Functional Outcome (Site-Reported, per Patient)	Standard-Use (n=281)	Broader-Use (n=1125)	p
Primary sustained clinical improvement[b]	206/234 (88.0)	747/949 (78.7)	0.001
EQ-5D			
Baseline	0.60± 0.30 (278)	0.61±0.30 (1104)	0.555
12 months	0.84±0.21 (224)	0.79±0.25 (890)	<0.001
Change from baseline	0.23±0.32 (222)	0.16±0.33 (879)	<0.001
p (baseline vs 12 months)	<0.001	<0.001	
WIQ			
Baseline	34.8±26.4 (272)	33.5±27.0 (1084)	0.329
12 months	80.9±29.3 (223)	75.0±30.9 (886)	0.004
Change from baseline	46.5±37.3 (215)	41.8±36.9 (861)	0.069
p (baseline vs 12 months)	<0.001	<0.001	
ABI[c]			
Baseline	0.70±0.23 (254)	0.67±0.22 (1139)	0.132
12 months	0.92±0.22 (216)	0.91±0.21 (932)	0.451
Change from baseline	0.23±0.27 (196)	0.23±0.25 (873)	0.448
p (baseline vs 12 months)	<0.001	<0.001	
Nights in hospital[d]	0.24±1.57 (143)	0.55±4.39 (527)	0.325

Abbreviations: ABI, ankle-brachial index; EQ-5D, EuroQol 5-Dimension Quality of Life Index; WIQ, Walking Impairment Questionnaire.
[a]Continuous data are presented as the means ± standard deviation (sample); categorical data are given as the number/sample (percentage).
[b]Primary sustained clinical improvement was defined as freedom from major target limb amputation, freedom from target vessel revascularization, and an improvement in Rutherford category.
[c]Cutoff value for noncompressible arteries was 1.3.
[d]Nights in hospital was a cumulative measurement over the 12-month follow-up that included any time a subject returned to the hospital for any issue related to the study lesion.

There are multiple implications to this observation. First, strict enrollment criteria for randomized IDE trials mandated by the FDA severely limit the number of patients who will be eligible for participation in an RCT. Perhaps more importantly, the results of an RCT may be generalizable only to the small fraction of patients meeting the enrollment criteria. Notably, those RCTs conducted outside the United States have different enrollment criteria, often allowing more severe patients to participate. This is commendable and allows for a more diverse patient type to be studied in a randomized fashion. However, the number of patients in these trials is usually smaller, and endpoints are not uniformly reported.

Second, it is necessary to adopt a comprehensive approach that includes more than RCTs, including post hoc analyses and global registries, to provide evidence of safety and effectiveness in the other 80% of patients who would typically be excluded from an RCT. Finally, 12-month clinical outcomes from the RCT-simulated SU group (96.6% freedom from CD-TLR) were parallel to data from the IN.PACT SFA RCT of the Admiral DCB (97.5% freedom from CD-TLR), substantiating the current post hoc approach for evaluating treatments in SU vs BU groups.[9]

Bilateral disease, regardless of lesion type, was a criterion for automatic assignment to the BU group; 1.7% of subjects in the BU group had lesions that would have assigned them to the SU group, but because lesions were present in both legs, the subjects were assigned to BU. Although these lesions are more easily treated and could be argued to have increased the rates of success in the BU group, this small fraction of patients was not likely to have a significant impact on the results. Nearly 9% of the bilateral disease subjects in the BU group had at least 1 lesion that would have disqualified them from assignment to the SU group.

DCB treatment appears safe among patients in the BU group. Although the safety composite endpoint was met by a significantly smaller percentage of BU patients (driven by a higher rate of CD-TVR), the endpoint was still met by >90% of patients in the BU group. Of significance for the practicing clinician, there were no differences in the incidence of most individual major adverse events (all-cause death, major target limb amputation, and thrombosis).

Treatment with a DCB led to clinically meaningful improvements in all functional and quality-of-life measures between baseline and 12 months in each group. The difference in outcomes between the groups was the result of a higher TVR rate in the BU patients. Improved function and quality of life in SU patients is consistent with RCTs that have demonstrated the clinical value and cost-effectiveness of DCBs in patients with femoropopliteal disease.[11,12,23] The added value of the current analysis is

that DCB treatment is now associated with functional and quality-of-life improvements in an additional population of patients typically excluded from RCTs but common in everyday practice.

The decrease in quality of life from claudication is severe and of similar magnitude to that of other significant chronic diseases.[24] Functional and quality-of-life outcomes are used across multiple therapeutic areas to evaluate the clinical value of various treatment options, often in the larger context of cost effectiveness. Though few question the clinical benefit of total knee arthroplasty procedures for patients with osteoarthritis of the knee, a recent analysis revealed that knee replacement surgery had minimal effect on overall quality of life or cost savings in an overall cohort of patients spanning a range of arthritis severity.[25] A deeper analysis revealed that quality of life and cost savings could improve if knee replacement surgery were limited to patients with severe knee osteoarthritis.[25] In this way, the current IN.PACT Global Study post hoc analysis demonstrated that treatment with a DCB is safe and effective and leads to clinically meaningful improvements not only in patients with characteristics that are typical of RCTs but also in those with more complex disease usually excluded from RCTs.

Limitations

As a single-arm study that includes all-comers, this study does not have a control or active comparator group, unlike RCTs. As such, the results do not allow direct comparison to other DCBs or endovascular modalities. In addition, the prospective evaluation of anatomic outcomes by duplex ultrasonography and/or angiography was limited to subjects who were assigned to predefined cohorts (long lesion, de novo ISR, and CTO), which means that data from the current post hoc analysis were obtained from the investigational sites. Thus, analyses that were performed on the entire clinical cohort (imaging and nonimaging components) were limited to clinical outcomes, and an independent CEC reviewed and adjudicated all events that were reported as part of these outcomes (CD-TLR, CD-TVR, and major adverse events).

Conclusion

Patients with PAD present with a broad range of clinical and lesion characteristics, but RCTs, especially those in the US, typically exclude most patients with complex lesions that are commonly seen in everyday practice. This post hoc analysis demonstrated that the paclitaxel IN.PACT Admiral DCB appears safe, with clinically important effectiveness at 12 months in the treatment of patients with lesions that are typically excluded from an RCT, although there were increased incidences of CD-TLR and CD-TVR. Moving forward, there is a need for a comprehensive approach that includes RCTs, post hoc analyses, and global registries that can provide information about the safety and effectiveness of endovascular treatment options in patients with lesions of any type or complexity.

ORCID iD

Gary M. Ansel [iD] https://orcid.org/0000-0003-0612-4269

References

 1. Peterson S, Hasenbank M, Silvestro C, et al. IN.PACT Admiral drug-coated balloon: Durable, consistent and safe treatment for femoropopliteal peripheral artery disease. *Adv Drug Deliv Rev*. 2017;112:69–77.
 2. Schorn I, Malinoff H, Anderson S, et al. The Lutonix® drug-coated balloon: A novel drug delivery technology for the treatment of vascular disease. *Adv Drug Deliv Rev*. 2017;112:78–87.
 3. Speck U, Cremers B, Kelsch B, et al. Do pharmacokinetics explain persistent restenosis inhibition by a single dose of paclitaxel? *Circ Cardiovasc Interv*. 2012;5:392–400.
 4. Krishnan P, Faries P, Niazi K, et al. Stellarex drug-coated balloon for treatment of femoropopliteal disease: 12-month outcomes from the randomized ILLUMENATE pivotal and pharmacokinetic studies. *Circulation*. 2017;36:1102–1113.
 5. Laird JR, Schneider PA, Tepe G, et al. Durability of treatment effect using a drug-coated balloon for femoropopliteal lesions: 24-month results of IN.PACT SFA. *J Am Coll Cardiol*. 2015;66:2329–2338.
 6. Rosenfield K, Jaff MR, White CJ, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. *N Engl J Med*. 2015;373:145–153.
 7. Scheinert D, Schulte KL, Zeller T, et al. 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.
 8. Schroeder H, Werner M, Meyer DR, et al. Low-dose paclitaxel-coated versus uncoated percutaneous transluminal balloon angioplasty for femoropopliteal peripheral artery disease: one-year results of the ILLUMENATE European randomized clinical trial (randomized trial of a novel paclitaxel-coated percutaneous angioplasty balloon). *Circulation*. 2017;135:2227–2236.
 9. Tepe G, Laird J, Schneider P, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. *Circulation*. 2015;131:495–502.
10. Tepe G, Schnorr B, Albrecht T, et al. Angioplasty of femoral-popliteal arteries with drug-coated balloons: 5-year follow-up of the THUNDER trial. *JACC Cardiovasc Interv*. 2015;8:102–108.
11. Katsanos K, Geisler BP, Garner AM, et al. Economic analysis of endovascular drug-eluting treatments for femoropopliteal artery disease in the UK. *BMJ Open*. 2016;6:e011245.
12. Pietzsch JB, Geisler BP, Garner AM, et al. Economic analysis of endovascular interventions for femoropopliteal arterial disease: a systematic review and budget impact model for the United States and Germany. *Catheter Cardiovasc Interv*. 2014;84:546–554.
13. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med*. 2008;358:689–699.
14. Werk M, Langner S, Reinkensmeier B, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. *Circulation*. 2008;118:1358–1365.
15. Werk M, Albrecht T, Meyer DR, et al. Paclitaxel-coated balloons reduce restenosis after femoro-popliteal angioplasty: evidence from the randomized PACIFIER trial. *Circ Cardiovasc Interv*. 2012;5:831–840.
16. Tepe G, Gogebakan O, Redlich U, et al. Angiographic and clinical outcomes after treatment of femoro-popliteal lesions with a novel paclitaxel-matrix-coated balloon catheter. *Cardiovasc Intervent Radiol*. 2017;40:1535–1544.
17. Jia X, Zhang J, Zhuang B, et al. Acotec drug-coated balloon catheter: randomized, multicenter, controlled clinical study in femoropopliteal arteries: evidence from the AcoArt I trial. *JACC Cardiovasc Interv*. 2016;9:1941–1949.
18. Micari A, Brodmann M, Keirse K, et al. Drug-coated balloon treatment of femoropopliteal lesions for patients with intermittent claudication and ischemic rest pain: 2-year results from the IN.PACT Global Study. *JACC Cardiovasc Interv*. 2018;11:945–953.
19. Brodmann M, Keirse K, Scheinert D, et al. Drug-coated balloon treatment for femoropopliteal artery disease: the IN.PACT Global Study de novo in-stent restenosis imaging cohort. *JACC Cardiovasc Interv*. 2017;23:2113–2123.
20. Tepe G. A real-world experience: 12-month outcomes from the IN.PACT Global long lesions imaging cohort. Paper presented at: LINC; January 26–29, 2016; Leipzig, Germany.
21. Tepe G. IN.PACT Global drug-coated balloon for treatment of chronic total occlusions in the SFA. Paper presented at: Charing Cross Symposium; April 25–28, 2016; London, UK.
22. Dattilo R, Himmelstein SI, Cuff RF. The COMPLIANCE 360° trial: a randomized, prospective, multicenter, pilot study comparing acute and long-term results of orbital atherectomy to balloon angioplasty for calcified femoropopliteal disease. *J Invasive Cardiol*. 2014;26:355–360.
23. Salisbury AC, Li H, Vilain KR, et al. Cost-effectiveness of endovascular femoropopliteal intervention using drug-coated balloons versus standard percutaneous transluminal angioplasty: results from the IN.PACT SFA II trial. *JACC Cardiovasc Interv*. 2016;9:2343–2352.
24. Regensteiner JG, Hiatt WR, Coll JR, et al. The impact of peripheral arterial disease on health-related quality of life in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) Program. *Vasc Med*. 2008;13:15–24.
25. Ferket BS, Feldman Z, Zhou J, et al. Impact of total knee replacement practice: cost effectiveness analysis of data from the osteoarthritis Initiative. *BMJ*. 2017;356:j1131.