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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

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ABSTRACT

OBJECTIVES The IN.PACT Global Study is the largest prospective, multicenter, independently adjudicated trial to evaluate a paclitaxel drug-coated balloon in patients with lifestyle-limiting claudication and/or ischemic rest pain due to atherosclerotic disease of the femoropopliteal artery and includes complex lesions beyond what are typically included in randomized controlled trials.

BACKGROUND Randomized controlled trials have demonstrated the safety and efficacy of drug-coated balloons for the treatment of Trans-Atlantic Inter-Society Consensus Document II A and B lesions, but there is a need for large-scale prospective studies to evaluate a broader range of lesions.

METHODS The IN.PACT Global Study enrolled 1,535 subjects, and 1,406 (1,773 lesions) were included in the pre-defined clinical cohort analysis. Freedom from clinically driven target lesion revascularization was evaluated at 24 months. The safety composite endpoint was freedom from device- and procedure-related death through 30 days and freedom from target limb major amputation and clinically driven target vessel revascularization within 24 months.

RESULTS Mean lesion length was 12.1 cm, 35.5% were total occlusions, and 18.0% had in-stent restenosis. Freedom from clinically driven target lesion revascularization at 24 months was 83.3%, the composite safety endpoint was met in 81.7%, the 2-year all-cause mortality rate was 7.0%, and the major target limb amputation rate was 0.7%. Increased lesion length and the presence of de novo in-stent restenosis or coronary artery disease were associated with increased risk for clinically driven target lesion revascularization by 24 months.

CONCLUSIONS This real-world study of femoropopliteal artery disease treatment with drug-coated balloons confirmed positive findings reported from more strictly designed randomized controlled trials and showed that outcomes are durable in this population up to 2 years after treatment. (IN.PACT Global Clinical Study; NCT01609296) (J Am Coll Cardiol Intv 2018;11:945–53) © 2018 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/).

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ABBREVIATIONS AND ACRONYMS

CD = clinically driven

CEC = clinical events committee

DCB = drug-coated balloon

RCT = randomized controlled trial

SFA = superficial femoral artery

TASC = Trans-Atlantic Inter-Society Consensus Document

TLR = target lesion revascularization

TVR = target vessel revascularization

Femoropopliteal artery disease is a major cause of lifestyle-limiting claudication and ischemic rest pain. Drug-coated balloons (DCBs) were developed to overcome the limitations of standard endovascular interventions, including angioplasty with an uncoated percutaneous transluminal angioplasty balloon. DCBs release the antiproliferative agent paclitaxel onto the inner vessel wall upon inflation. Both drug concentration and excipient determine levels of persistence in the tissue, with studies to the 180-day mark demonstrating the long-term residence of paclitaxel (1–3). Paclitaxel inhibits neointimal hyperplasia, which is a major contributor to restenosis after angioplasty. First-in-human and single-center studies using DCBs yielded promising results (4–9). Randomized controlled trials (RCTs) have demonstrated the safety and efficacy of DCBs for the treatment of Trans-Atlantic Inter-Society Consensus Document (TASC) II A and B lesions (10–16). However, data continue to be limited on DCBs for more complex lesions that can affect real-world patients seen in everyday practice (17–21). These include longer TASC II C and D lesions, restenotic lesions, calcified lesions, and other lesion types that are often excluded from RCTs with selective enrollment criteria. Although these studies were similar for evaluating lesions that are typically excluded from RCTs, the types and levels of evidence vary between each study.

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There is a need for large-scale studies to examine DCBs in patients with a broad range of femoropopliteal lesions, and the IN.PACT Global Study is the largest prospective, multicenter trial to evaluate the safety and efficacy of a paclitaxel DCB (IN.PACT Admiral, Medtronic, Dublin, Ireland) for the treatment of patients with lifestyle-limiting claudication and/or ischemic rest pain due to atherosclerotic disease of the femoropopliteal artery, including the entire native superficial femoral artery (SFA) and/or popliteal artery (P1 to P3) starting from the SFA origin. Previously reported results demonstrated consistent efficacy and safety through 1 year (22). Safety and efficacy outcomes are reported through 2 years.

METHODS

IN.PACT GLOBAL STUDY: DESIGN, SUBJECTS, AND TREATMENT. The IN.PACT Global Study is a prospective, multicenter, international, single-arm clinical study assessing the safety and effectiveness of a paclitaxel-coated DCB for the treatment of real-world patients with atherosclerotic disease of the femoropopliteal artery. The trial is registered as NCT01609296. Subjects with symptoms of intermittent claudication and/or ischemic rest pain (Rutherford class 2 to 4) and angiographic evidence of severe stenosis or occlusion (length ≥2 cm; de novo or restenosis, in-stent or not in-stent) in the entire femoropopliteal artery, including the entire native SFA and/or popliteal artery (P1 to P3), were eligible for enrollment. Details of study design and treatment have been described (22).

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.

CLINICAL COHORT STUDY ENDPOINTS. An independent clinical events committee (CEC) (Syntactx, New York, New York) was established to assess the primary and select secondary endpoints and to determine whether each met protocol-specified criteria. The CEC was composed of interventional and noninterventional clinicians with pertinent expertise who were not participants in the study and did not have any conflicts of interest.

The primary safety composite endpoint was freedom from device- and procedure-related mortality through 30 days and freedom from major target limb amputation and clinically driven (CD) target vessel revascularization (TVR) within 12 months after the index procedure. CD TVR was assessed at the subject level and defined as the first event that required CD TVR in the subject. The primary effectiveness endpoint

and Spectranetics; and his clinic has received study funds or funds for research or clinical trials from 480 Biomedical, Abbott Vascular, B. Braun, Bard Peripheral Vascular, Bayer Pharma, Biotronik, Caveo Med, Contego Medical, Cook Medical, Cardiovascular Systems, Inc., W.L. Gore & Associates, Innora, Intact Vascular, Medtronic, Mercator, Philips, Pluristem, Shockwave, Spectranetics, Terumo, TriReme, and Veryan. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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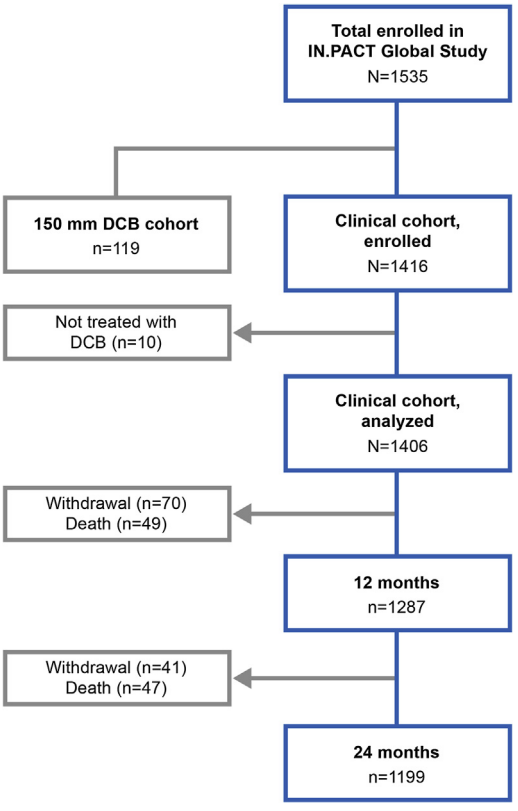
was freedom from CD target lesion revascularization (TLR) within 12 months. The safety and efficacy endpoints were assessed at 24 months and thereafter as co-secondary endpoints. The CEC reviewed all TLR and TVR events to determine which were CD, defined as any reintervention within the target lesion(s) because of symptoms or ankle-brachial index decrease of ≥20% or >0.15 compared with post-index procedure baseline ankle-brachial index. CD TLR and TVR did not include those procedures that were performed on asymptomatic subjects or were based only on diagnostic imaging procedures. Secondary endpoints included primary sustained clinical improvement (defined as freedom from major target limb amputation, freedom from TVR, and increase of at least 1 class in the Rutherford clinical category), CD TLR, CD TVR, any TLR, any TVR, and the incidence of major adverse events (all-cause mortality, CD TVR, major target limb amputation, and thrombosis at the target lesion site) at 24 months. The CEC adjudicated all major adverse events. Functional assessments included evaluation of walking capacity with the Walking Impairment Questionnaire and quality of life with the EuroQol-5D index.

Pre- and post-dilatation were permitted at the discretion of the investigator. Provisional stenting was allowed if 1 of the criteria was not met despite repeated and prolonged balloon inflations: flow-limiting dissection, visually estimated residual stenosis ≥50%, or translesional gradient >10 mm Hg. For categories of provisional stenting, spot stenting was defined as use 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, and partial lesion coverage was use of a stent length longer than the residual stenosis but shorter than the original length of the target lesion.

CLINICAL COHORT STATISTICAL ANALYSIS. All analyses were based on the intent-to-treat principle. 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 are described as mean ± SD; dichotomous and categorical variables are described as counts and proportions. The Kaplan-Meier method was used to evaluate time-to-event data for freedom from CD TLR over the 24-month follow-up period. The outcome analysis was performed at a subject level. For event rates that were expressed as a proportion, the number of subjects with events within 720 days was the numerator, and the total number of subjects with events or at least 660 days of clinical follow-up was the denominator. For assessment of clinical characteristics at 24 months, subjects were required to have data at baseline and 24 months. A Cox proportional hazards model with potential baseline predictors was fitted on CD TLR through 720 days, and a stepwise selection process with an entry criterion of 0.20 and a stay criterion of 0.10 was used (see the Online Appendix for baseline predictors tested). Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

FIGURE 1 Patient Flow Diagram Through 24 Months



Patient follow-up is displayed through 24 months. A total of 1,406 intent-to-treat patients were included in this analysis.

RESULTS

BASELINE SUBJECT AND LESION CHARACTERISTICS. The IN.PACT Global Study enrolled a total of 1,535 subjects. The full clinical cohort within the IN.PACT

TABLE 1 Baseline Demographics and Clinical Characteristics of Subjects in the Clinical Cohort (n = 1,406)*

Age, yrs	68.6 ± 10.1 (1,396)
Male	67.8 (953/1,406)
Body mass index, kg/m^2	26.7 ± 4.5 (1,391)
Obesity (body mass index ≥30 kg/m^2)	20.5 (285/1,391)
Diabetes mellitus	39.9 (560/1,402)
Insulin dependent diabetes mellitus	17.8 (249/1,402)
Hypertension	83.4 (1169/1,401)
Hyperlipidemia	70.5 (960/1,362)
Current smoker	31.8 (447/1,406)
Coronary heart disease	40.5 (540/1,332)
Carotid artery disease	20.2 (241/1,196)
Renal insufficiency†	11.2 (136/1,217)
Previous peripheral revascularization	52.4 (737/1,406)
Below-the-knee disease of target leg	45.3 (594/1,310)
Rutherford class	
0	0.0 (0/1,403)
1	0.1 (1/1,403)‡
2	31.1 (436/1,403)
3	57.7 (810/1,403)
4	8.6 (120/1,403)
5	2.6 (36/1,403)‡
6	0.0 (0/1,403)
ABI§, mm Hg, per target limb	0.678 ± 0.218 (1,395)
Bilateral disease	8.4 (118/1,406)

Values are mean ± SD (N) or % (n/N). *Summaries are based on nonmissing assessments. In some cases, baseline demographic or clinical data were not available, and therefore the total number of subjects for that variable is <1,406. †Defined as baseline creatinine ≥1.5 mg/dl. ‡Because of protocol violations, one Rutherford class 1 subject and 36 Rutherford class 5 subjects were enrolled and included in the analysis. §For subjects with bilateral disease, ABI is included for each target limb.

ABI = ankle-brachial index.

TABLE 2 Lesion Characteristics From Subjects in the Clinical Cohort (n = 1,406, 1,773 Lesions)*

Pre-procedure	
Lesion type	
De novo	74.3 (1,317/1,773)
Restenotic (nonstented)	7.7 (136/1,773)
In-stent restenosis	18.0 (320/1,773)
Vessel	
Superficial femoral artery	87.6 (1,553/1,773)
Proximal popliteal artery	27.3 (484/1,773)
Lesion length, cm	12.09 ± 9.54 (1,773)
Occluded	35.5 (629/1,773)
With calcification	68.7 (1,217/1,771)
With severe calcification†	10.2 (181/1,771)
Reference vessel diameter, mm	5.186 ± 0.681 (1,773)
Diameter stenosis, %	88.8 ± 12.3 (1,773)
Procedure	
DCBs per lesion	1.7 ± 1.0 (1,766)
Pre-dilatation	78.0 (1,097/1,406)
Post-dilatation	35.1 (491/1,397)
Provisional stenting	21.2 (373/1,761)
Provisional stents per lesion	1.3 ± 0.6 (373)
Post-procedure	
Device success‡	99.4 (2,984/3,002)
Procedural success§	99.3 (1,386/1,396)
Clinical success¶	98.8 (1,379/1,396)
Dissections	
0	56.8 (1,006/1,772)
A–C	35.4 (627/1,772)
D–F	7.8 (139/1,772)

Values are % (n/N) or mean ± SD (N). *Summaries are based on nonmissing assessments. In some cases, baseline or clinical data were not available, and therefore the total number of lesions for that variable is <1,773. †Severe calcification defined as calcification with circumference ≥180° (both sides of vessel at the same location) and length greater than or equal to one-half of the total lesion length. ‡Device success defined as successful delivery, inflation, deflation, and retrieval of the intact study balloon device without burst below the rated burst pressure. This analysis is device (balloon) based. §Procedural success defined as residual stenosis of ≤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. ¶Clinical success defined as procedural success without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or target vessel revascularization) before discharge. This analysis is subject based.

DCB = drug-coated balloon.

Global Study included 1,416 subjects, of whom 1,406 were treated with the paclitaxel DCB and included in the intent-to-treat group. Clinical follow-up is shown in Figure 1. The rate of compliance for follow-up within the pre-specified window was 77.6% (n = 930 of 1,199). Baseline demographics and characteristics are reported in Tables 1 and 2.

Provisional stents were implanted in 353 patients (25.3%) and 373 lesions (21.2%) (Table 2). Of these, 24.4% (n = 91 of 373) were spot stented, 37.8% (n = 141 of 373) were partial lesion coverage, and 37.8% (n = 141 of 373) were whole lesion coverage.

EFFECTIVENESS OUTCOMES. The Kaplan-Meier estimate of freedom from CD TLR was 83.3% at 24 months (Figure 2). The rate of CD TLR at 24 months was 16.9% (n = 214 of 1,269). Of these, 13 events occurred in the first 30 days after the index procedure, and the Kaplan-Meier estimate of freedom from CD TLR was 99.1%. The mean time to first CD TLR was 342.7 ± 197.3 days. Primary sustained clinical improvement was achieved by 68.6% of subjects (n = 737 of 1,075).

A post hoc analysis was performed to compare effectiveness outcomes in subgroups defined by the presence of baseline clinical or procedural characteristics (Figure 3, Table 3).

Lesions ≥15 cm and lesions with popliteal involvement had significantly higher rates of CD TLR through 24 months ($p < 0.001$). The mean lesion length was 13.4 ± 9.1 cm for subjects with SFA-alone lesions and 17.4 ± 10.6 cm for subjects with lesions that had popliteal artery involvement ($p < 0.001$).

SAFETY OUTCOMES. Safety outcomes are reported in Table 4. Major target limb amputation was required in 0.7% of subjects (n = 9 of 1,269). The average time to amputation was 310.2 ± 174.1 days. Three subjects had major target limb amputations at 12 months, and an additional 6 subjects had amputation by 24 months. The 3 subjects with amputation at 12 months were in Rutherford classes 3, 4, and 5 at baseline (the Rutherford class 5 patient was enrolled as a protocol deviation). The average age of the 6 subjects who required major target limb amputation between the first and second years after the index procedure was 68 ± 10.5 years, 4 were male, 3 had diabetes mellitus, and 4 had previous peripheral vascular disease. Two of the subjects were in Rutherford class 2, 3 were in class 3, and 1 was in class 4. Mean lesion length was 17.4 ± 8.9 cm.

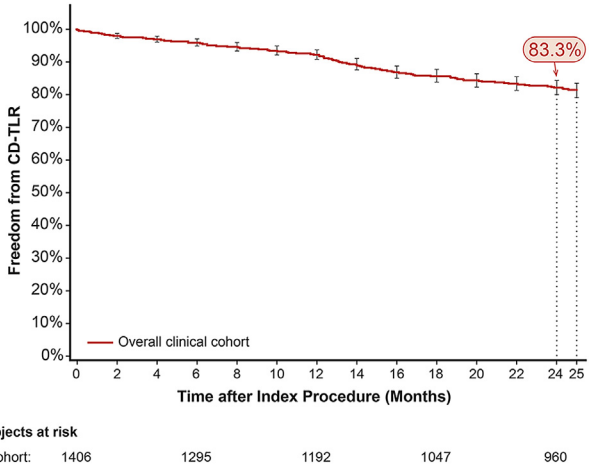
The rate of all-cause death was 7.0% (n = 89 of 1,269) at 24 months (which does not include deaths that occurred during the 2-month extension follow-up). Independent adjudication by the CEC determined that none of the deaths were related to the study device, and 3 of the deaths were possibly or potentially related to the study procedure, as any death within 30 days of the index was adjudicated by the CEC as procedure related. Details of the possibly procedure-related events have been previously reported (22).

FUNCTIONAL OUTCOMES. Mean score on the EuroQol-5D index was 0.6089 ± 0.2994 at baseline (n = 1,382) and 0.7744 ± 0.2551 (n = 964) at 24 months. The mean change from baseline in EuroQol-5D index score at 24 months was 0.1495 ± 0.3346 (n = 951). The mean ankle-brachial index at 24 months was 0.896 ± 0.226, and the change from baseline was 0.220 ± 0.263 ($p < 0.001$). Changes in Rutherford values are shown in Table 5.

Mean overall walking impairment score by the Walking Impairment Questionnaire was 33.8 ± 26.9 at baseline (n = 1,356) and 75.1 ± 30.9 (n = 952) at 24 months.

MULTIVARIATE ANALYSIS. A multivariate Cox proportional hazards regression analysis was performed to identify potential baseline predictors of CD TLR in the clinical cohort through 24 months. Increasing lesion length, presence of de novo in-stent restenosis, and presence of coronary artery disease were associated with increased risk for CD TLR by 24 months. Unilateral disease, SFA-alone lesions, increasing reference vessel diameter, increasing age, and absence of target limb posterior tibial artery pulse were associated with reduced risk for CD TLR (Table 6).

FIGURE 2 Kaplan-Meier Curve of Freedom From Clinically Driven Target Lesion Revascularization in the Clinical Cohort Through 24 Months

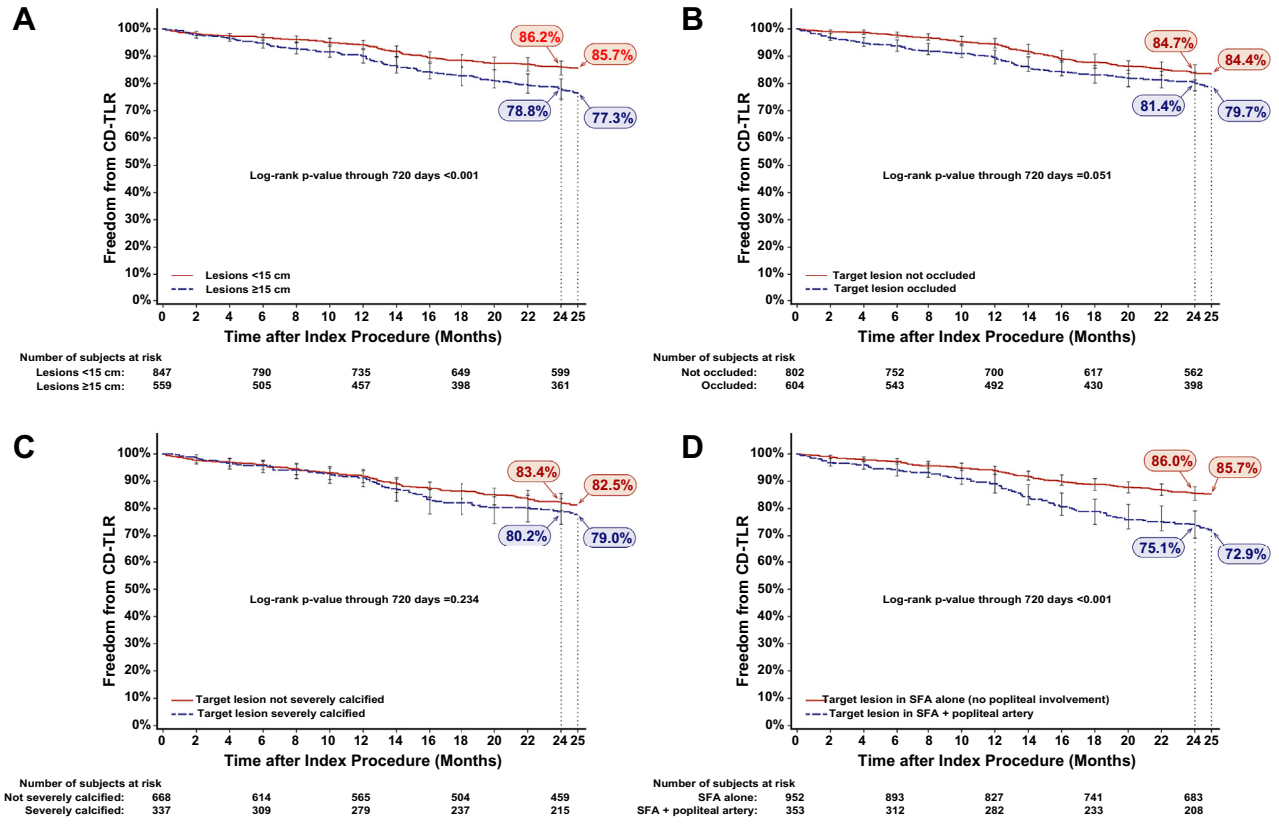


Number at risk represents the number at the beginning of the 60-day window before each follow-up interval.

DISCUSSION

One-year outcomes from the IN.PACT Global Study showed that treatment with a paclitaxel DCB was safe and effective in the full clinical cohort, consistent with the results of RCTs of patients with TASC II A and B lesions that are less challenging to treat (15,22). Two-year outcomes show that the safety and effectiveness of a paclitaxel DCB is durable in this same patient cohort. The DCB had a good safety profile, and Kaplan-Meier estimate of freedom from CD TLR at 24 months was 83.3%. This is consistent with 2-year outcomes reported from the randomized IN.PACT SFA trial of the same paclitaxel DCB (IN.PACT Admiral), with the Kaplan-Meier estimate of freedom from CD TLR being 91.0% at 24 months and a mean time to first CD TLR of 351.9 ± 165.9 days (11). Notably, the IN.PACT SFA trial evaluated subjects and/or lesions that were less challenging to treat than in the IN.PACT Global Study. In the IN.PACT SFA trial, mean lesion length was 8.94 cm, 25.8% of lesions were total occlusions, and 8.1% were severely calcified (11). In the IN.PACT Global Study, mean lesion length was 12.1 cm, 35.5% of

FIGURE 3 Kaplan-Meier Curves of Freedom From Clinically Driven Target Lesion Revascularization in the Clinical Cohort Through 24 Months by Baseline Characteristic Subgroups



(A) Subjects with lesions <15 cm compared with subjects with lesions ≥15 cm. **(B)** Subjects with total occlusions compared with subjects without total occlusions. **(C)** Subjects with severely calcified lesions compared with subjects without severely calcified lesions. **(D)** Subjects with lesions in the superficial femoral artery (SFA) alone (no popliteal involvement) compared with subjects with lesions in the SFA and popliteal artery. Number at risk represents the number at the beginning of the 60-day window before each follow-up interval.

lesions were total occlusions, and 10.2% were severely calcified. Importantly, calcium definitions between these trials were different.

The 2-year results of the IN.PACT Global full clinical cohort are similar to what has been reported from the Lutonix Global SFA registry study of the Lutonix 035 DCB (Bard Lutonix, New Hope, Minnesota) in a heterogeneous population of real-world patients (20). The Kaplan-Meier estimate of TLR-free survival at 24 months was similar but slightly higher in the overall population and several of the same subgroups compared with those that were analyzed in the IN.PACT Global clinical cohort (overall cohort, 90.3% Lutonix vs. 83.3% IN.PACT Admiral; occluded lesions, 90.6% Lutonix vs. 81.4% IN.PACT Admiral; long lesions, 89.4% Lutonix [≥14 cm] vs. 78.8% IN.PACT Admiral [≥15 cm]), though the performance of individual DCBs cannot be compared in the absence of a direct head-to-head comparison (20). The subject populations were generally similar between the 2 studies, though a higher percentage of subjects in the IN.PACT Global Study had calcified lesions at baseline (68.7% IN.PACT Global vs. 50.2% Lutonix Global) (20). Another important difference between the studies was the use of a CEC in the IN.PACT Global Study to adjudicate all major adverse events and determine which TLR events were CD.

In the IN.PACT Global clinical cohort, the long mean time to first CD TLR (342.7 ± 197.3 days) and the absence of a spike in CD TLR events in the immediate post-procedural period (only 13 events in the first 30 days) suggest that most reinterventions were due to

TABLE 3 Clinically Driven Target Lesion Revascularization Outcomes by Subgroup

Subgroup	Kaplan-Meier Estimate of Freedom From CD TLR at 720 Days	Log-Rank p Value
Stented subjects	80.8% (n = 353)	0.206
Nonstented subjects	83.9% (n = 1,044)	
Subjects with pre-dilatation	82.8% (n = 1,097)	0.414
Subjects without pre-dilatation	84.9% (n = 309)	
Subjects with post-dilatation	83.7% (n = 491)	0.754
Subjects without post-dilatation	82.9% (n = 906)	
Lesions ≥15 cm	78.8% (n = 559)	<0.001
Lesions <15 cm	86.2% (n = 847)	
Occluded target lesion	81.4% (n = 604)	0.051
Stenosed target lesion	84.7% (n = 802)	
Severely calcified lesion	80.2% (n = 337)	0.234
Not severely calcified lesion	83.4% (n = 668)	
SFA alone	86.0% (n = 952)	<0.001
Popliteal involvement	75.1% (n = 353)	

CD = clinically driven; SFA = superficial femoral artery; TLR = target lesion revascularization.

TABLE 5 Rutherford Outcomes Through 24 Months

Change in Rutherford Class Through 24 Months	
−5	0.6% (6/1,013)
−4	5.3% (54/1,013)
−3	33.6% (340/1,013)
−2	33.0% (334/1,013)
−1	15.1% (153/1,013)
0	10.0% (101/1,013)
+1	1.5% (15/1,013)
+2	0.9% (9/1,013)
+3	0.1% (1/1,013)
+4	0.0% (0/1,013)
p value	<0.001

Values are % (n/N).

physiological failure (e.g., neointimal hyperplasia) and/or disease progression as opposed to mechanical failure (e.g., acute recoil).

A post hoc analysis showed that in most cases, DCB performance was similar between subgroups that were defined by the presence of a key clinical or procedural characteristic. Freedom from CD TLR by Kaplan-Meier estimate at 24 months was not statistically significantly different between subjects with or without pre-dilatation, post-dilatation, severe calcification, total occlusions, or provisional stenting. In each of these subgroup comparisons, the similarity in clinical outcomes supports the conclusion that DCBs are consistently effective across a broad range of lesion types.

A multivariate regression analysis identified baseline clinical and lesion characteristics that were significantly associated with outcomes in the clinical cohort. Increasing lesion length was positively associated with increased risk for reintervention within 24 months, which is consistent with other reports that have identified lesion length as a predictor of TLR or restenosis after endovascular interventions, such as standard angioplasty with stenting (23–25). Lesion location was also identified as a predictor of reintervention in the clinical

TABLE 4 24-Month Safety Outcomes* in the Clinical Cohort (n = 1,269)†

CD TLR‡	214 (16.9)
Time to first CD TLR, days	342.7 ± 197.3 (214)
Primary safety endpoint§	1,037 (81.7)
Major adverse events¶	314 (24.7)
Death (all-cause)	89 (7.0)
Major target limb amputation, n (%)	9 (0.7)
Thrombosis	57 (4.5)
CD TVR	224 (17.7)
Any TLR	218 (17.2)
Any TVR	229 (18.0)

Values are n (%) or mean ± SD (n). *An independent clinical events committee adjudicated all major adverse events. †Event rates expressed as a proportion: the number of subjects with events is the numerator, and the number of subjects with at least 660 days of clinical follow-up is the denominator. ‡CD TLR defined as any reintervention within the target lesion(s) due to symptoms or drop of ABI of ≥20% or >0.15 compared with post-index procedure baseline ABI. §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 post-index procedure. ¶Major adverse event defined as all-cause mortality, CD TVR, major target limb amputation, thrombosis at the target lesion site.

TVR = target vessel revascularization; other abbreviations as in Tables 1 and 3.

TABLE 6 Baseline Predictors of Clinically Driven Target Lesion Revascularization in the Clinical Cohort Through 24 Months

	Coefficient	SE	Hazard Ratio (95% CI)	p Value
Total lesion length	0.037	0.007	1.037 (1.022–1.053)	<0.001
Target limb (unilateral vs. bilateral)	−0.747	0.226	0.474 (0.305–0.737)	<0.001
Target lesion location (SFA alone vs. SFA + popliteal)	−0.514	0.165	0.598 (0.433–0.827)	0.002
Age	−0.020	0.008	0.980 (0.965–0.994)	0.007
Reference vessel diameter	−0.314	0.121	0.730 (0.576–0.925)	0.009
Target lesion type (de novo ISR vs. not de novo ISR)	0.467	0.180	1.596 (1.122–2.269)	0.009
Target limb posterior tibial artery pulse (absent vs. present)	−0.489	0.209	0.613 (0.407–0.924)	0.019
Coronary artery disease (present vs. absent)	0.329	0.161	1.389 (1.013–1.905)	0.041

Multivariate predictors were chosen by a stepwise procedure using an entry criterion of 0.20 and a stay criterion of 0.10. Baseline characteristics were evaluated for potential predictive associations by multiple Cox proportional hazards regression analysis.

CI = confidence interval; ISR = in-stent restenosis; SFA = superficial femoral artery.

cohort, with SFA-alone lesions (no popliteal involvement) being associated with reduced risk for CD TLR within 24 months. This is consistent with the finding that Kaplan-Meier estimate of freedom from CD TLR within 24 months was significantly higher in the SFA-alone group compared with the popliteal-involvement group and, to our knowledge, is the first report of lesion location being identified as a predictor of CD TLR in femoropopliteal disease.

The rate of all-cause mortality was 7.0% at 24 months, up from 3.5% at 12 months (22). None of the deaths between 12 and 24 months were procedure or device related, on the basis of independent adjudication by the CEC. A similar all-cause death rate was reported in the Lutonix Global trial: 2.8% at 12 months and 5.9% at 24 months.

STUDY LIMITATIONS. The study was a single-arm trial. In the absence of a control or active comparator, the results cannot support direct comparison with other endovascular treatment modalities. Also, the evaluation of DCB effectiveness was limited to clinical outcomes in this full clinical cohort. Not all patients had data available for the analysis of anatomic outcomes, as only pre-defined cohorts (long lesion, de novo in-stent restenosis, and chronic total occlusion) were planned for prospective duplex ultrasound and imaging analyses.

CONCLUSIONS

Results of the IN.PACT Global Study clinical cohort analysis showed durable safety and efficacy of the paclitaxel IN.PACT Admiral DCB through 2 years in patients with a range of lesion types in the SFA and/or popliteal arteries, which is consistent with reports of positive outcomes from RCTs of paclitaxel DCBs in TASC II A and B lesions.

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PERSPECTIVES

WHAT IS KNOWN? Multiple RCTs have demonstrated the safety and efficacy of DCBs for TASC II A and B lesions, but there is a need for large-scale prospective studies on DCBs in complex lesions that are seen in everyday practice, including longer TASC II C and D lesions, restenotic lesions, and calcified lesions. IN.PACT Global, a study that included such complex lesions, reported 1-year safety and efficacy results consistent with the findings of RCTs in TASC II A and B lesions.

WHAT IS NEW? Two-year results from the IN.PACT Global Study show that the safety and efficacy of paclitaxel DCB treatment is durable up to 2 years in patients with complex femoropopliteal lesions.

WHAT IS NEXT? There is a need for prospective, randomized, double-blind, head-to-head studies of different DCBs and other endovascular treatments with economic analyses and assessments of how patients with different lesion characteristics may have different long-term outcomes.

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KEY WORDS angioplasty, drug-coated balloon, femoropopliteal artery, peripheral artery disease, target lesion revascularization

APPENDIX For a list of investigators who enrolled subjects in the IN.PACT Global Study, please see the online version of this paper.