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Treatment Effect of Drug-Coated Balloons Is Durable to 3 Years in the Femoropopliteal Arteries

Long-Term Results of the IN.PACT SFA Randomized Trial

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Background—Randomized controlled trials have reported favorable 1-year outcomes with drug-coated balloons (DCBs) for the treatment of symptomatic peripheral arterial disease when compared with standard percutaneous transluminal angioplasty (PTA). Evidence remains limited on the durability of the treatment effect with DCBs in the longer term.

Methods and Results—IN.PACT SFA is a single-blind, randomized trial (Randomized Trial of IN.PACT Admiral Paclitaxel-Coated Percutaneous Transluminal Angioplasty [PTA] Balloon Catheter vs Standard PTA for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery [SFA] and/or Proximal Popliteal Artery [PPA]) that enrolled 331 patients with symptomatic (Rutherford 2–4) femoropopliteal lesions up to 18 cm in length. Patients were randomized 2:1 to receive treatment with DCB or PTA. The 36-month assessments included primary patency, freedom from clinically driven target lesion revascularization, major adverse events, and functional outcomes. At 36 months, primary patency remained significantly higher among patients treated with DCB compared with PTA (69.5% versus 45.1%; log rank $P<0.001$). The rates of clinically driven target lesion revascularization were 15.2% and 31.1% ($P=0.002$) for the DCB and PTA groups, respectively. Functional outcomes were similarly improved between treatment groups even though subjects in the DCB group required significantly fewer reinterventions versus those in the PTA group ($P<0.001$ for target lesion revascularization, $P=0.001$ for target vessel revascularization). There were no device- or procedure-related deaths as adjudicated by an independent Clinical Events Committee.

Conclusions—Three-year results demonstrate a durable and superior treatment effect among patients treated with DCB versus standard PTA, with significantly higher primary patency and lower clinically driven target lesion revascularization, resulting in similar functional improvements with reduced need for repeat interventions.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT01175850 for IN.PACT SFA phase I in the European Union and NCT01566461 for IN.PACT SFA phase II in the United States.

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Key Words: angioplasty ■ peripheral arterial disease ■ target lesion revascularization

Endovascular intervention has become the primary mode of revascularization for patients with symptomatic femoropopliteal peripheral artery disease. Multiple modalities of treatment exist; however, the mainstay is percutaneous transluminal angioplasty (PTA) and implantation of a bare metal stent (BMS).[1] Angioplasty, though effective in luminal gain, has been associated with restenosis rate of up to 60% at 12 months.[2,3] Although implantation of a BMS has been shown to reduce this restenosis rate by nearly half,[2–7] BMSs are associated with inherent problems, including in-stent restenosis, thrombosis, and stent fracture.[8–10]

See Editorial by Sethi and Parikh

To overcome the limitations of standard interventions such as PTA or BMSs, drug-coated balloons (DCBs) were developed in hopes of improved patency over the long term,

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WHAT IS KNOWN

- There are limited long-term data on the durability of drug-coated balloon treatment effect in patients with symptomatic femoropopliteal peripheral artery disease.

WHAT THE STUDY ADDS

- Three-year results from the IN.PACT Global Study (Randomized Trial of IN.PACT Admiral Paclitaxel-Coated Percutaneous Transluminal Angioplasty [PTA] Balloon Catheter vs Standard PTA for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery [SFA] and/or Proximal Popliteal Artery [PPA]) show that the effectiveness of paclitaxel drug-coated balloon treatment is durable up to 3 years and is associated with significantly higher primary patency and a lower rate of repeat interventions compared with percutaneous transluminal angioplasty.

without the disadvantages of a major metal implant such as a stent. DCBs are covered with an antiproliferative agent, paclitaxel, using urea as an excipient to facilitate the transfer of paclitaxel to the inner vessel surface on balloon inflation. After angioplasty, paclitaxel can persist in the vessel wall for up to 180 days in experimental models.[11] The sustained presence of paclitaxel provides continuous antiproliferative activity that inhibits neointimal hyperplasia, which is a major contributing factor to restenosis after angioplasty.

Clinical studies have demonstrated the short-term safety and effectiveness of paclitaxel-coated DCBs for the treatment of femoropopliteal peripheral artery lesions,[12–19] but there are limited long-term data beyond 2 years on the durability of treatment effect. This is the first report of a large randomized clinical trial to evaluate the long-term safety and effectiveness of treatment with a paclitaxel DCB in femoropopliteal lesions.

Methods

The data, analytic methods, and study materials may be made available to other researchers on request from the sponsor.

Study Design

The IN.PACT SFA trial (Randomized Trial of IN.PACT Admiral Paclitaxel-Coated Percutaneous Transluminal Angioplasty [PTA] Balloon Catheter vs Standard PTA for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery [SFA] and/or Proximal Popliteal Artery [PPA]) was a prospective, multicenter, multinational, randomized, single-blind trial that was designed to evaluate the safety and effectiveness of a paclitaxel DCB (IN.PACT Admiral, Medtronic Inc, Dublin, Ireland) versus standard PTA balloons in the treatment of subjects with symptomatic superficial femoral artery and proximal popliteal artery disease. The IN.PACT SFA trial was conducted in 2 consecutive phases (IN.PACT SFA phase I in the European Union and IN.PACT SFA phase II in the United States). A list of investigators and clinical sites is given in Table I in the Data Supplement. The details of IN.PACT SFA trial design have been previously reported, as have outcomes through 2 years.[18,19]

Table 1. Baseline Subject and Procedural Characteristics*

Characteristic	DCB (Subjects=220/ Lesions=221)	PTA (Subjects=111/ Lesions=113)	*P* Value
Age, y	67.5±9.5	68.0±9.2	0.612
Male	65.0 (143/220)	67.6 (75/111)	0.713
Diabetes mellitus	40.5 (89/220)	48.6 (54/111)	0.161
Hypertension	91.4 (201/220)	88.3 (98/111)	0.431
Hyperlipidemia	84.5 (186/220)	82.0 (91/111)	0.637
Current smoker	38.6 (85/220)	36.0 (40/111)	0.719
ABI/TBI†	0.769±0.228	0.744±0.189	0.308
Rutherford Clinical Category			0.898
2	37.7 (83/220)	37.8 (42/111)	
3	57.3 (126/220)	55.9 (62/111)	
4	5.0 (11/220)	5.4 (6/111)	
5	0.0 (0/220)	0.9 (1/111)‡	
Lesion length, cm	8.94±4.89	8.81±5.12	0.815
Total occlusions	25.8 (57/221)	19.5% (22/113)	0.222
Calcification	59.3 (131/221)	58.4 (66/113)	0.907
Severe calcification	8.1 (18/1221)	6.2 (7/113)	0.662
Dissections			0.360
0	36.2 (80/221)	38.9 (44/113)	
A–C	63.8 (141/221)	60.2 (68/113)	
D–F	0.0 (0/221)	0.9 (1/113)	
Provisional stenting	7.3 (16/220)	12.6 (14/111)	0.110

ABI indicates ankle-brachial index; DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty; and TBI, toe-brachial index.

*Values are mean±SD or % (n/N).

†TBI allowed in cases of incompressible vessels in IN.PACT SFA phase II.

‡One subject in the PTA group was Rutherford Clinical Category 5 despite application of Rutherford Category 2 to 4 as inclusion criteria for enrollment.

Subjects were randomized in a 2:1 fashion into a DCB or PTA group. Eligible subjects had moderate to severe intermittent claudication or ischemic rest pain (Rutherford Clinical Category 2–4); stenosis of 70% to 99% with lesion lengths between 4 and 18 cm, or a complete occlusion with lengths of ≤10 cm involving the superficial femoral and proximal popliteal arteries and were required to have successful predilatation of the lesion before enrollment. Details on the use of preprocedure and periprocedure anticoagulant and antiplatelet medications are given in Table II in the Data Supplement.

Informed consent was obtained from all subjects before enrollment. An institutional review board or ethics committee approved all protocols at each trial site. The trial was conducted in accordance with the Declaration of Helsinki, good clinical practice guidelines, and applicable laws as specified by all relevant governmental bodies.

A Clinical Events Committee reviewed and adjudicated all major adverse events through the 36-month follow-up period. The Clinical Events Committee included interventional and noninterventional clinicians with pertinent expertise who were not participants in the study and did not have conflicts of interest. The Clinical Events Committee used a set of criteria that was specifically designed to classify major adverse events in the study. Independent core laboratories (duplex ultrasonography: VasCore, Boston, MA; angiography: SynvaCor, Springfield, IL) analyzed all procedural and follow-up images through 36 months. The independent core laboratories and Clinical Events Committee were blinded to treatment assignments.

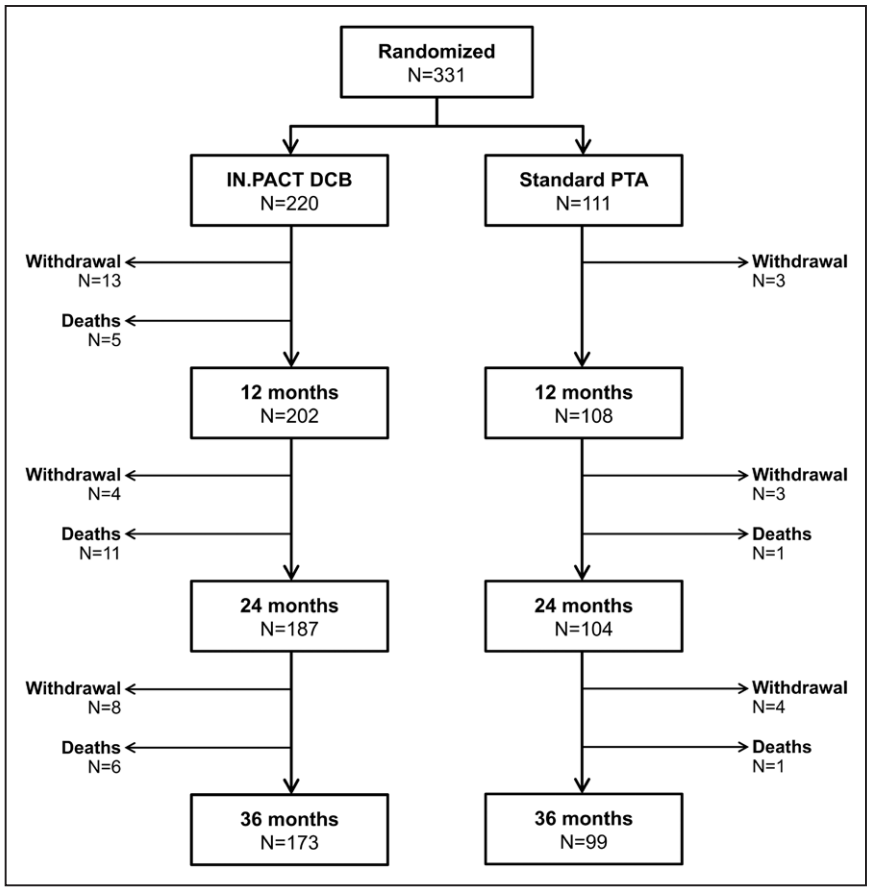

Figure 1. Subject flow in the IN.PACT SFA trial through 36 months. Three hundred thirty-one subjects were randomized 2:1 into groups that received percutaneous transluminal angioplasty (PTA) with a paclitaxel drug-coated balloon (DCB) or a standard uncoated balloon (PTA). Subjects are being followed for 5 years, and the results of intent-to-treat analyses have been previously reported for 12 months[18] and 24 months.[19]

End Point Definitions

Primary patency was defined as freedom from clinically driven target lesion revascularization (CD-TLR) and freedom from restenosis (duplex ultrasonography peak systolic velocity ratio ≤2.4) and was analyzed through 36 months. CD-TLR was defined as reintervention at the target lesion because of symptoms or a decrease in ankle-brachial index by ≥20% or >0.15 when compared with postprocedure baseline ankle-brachial index. The primary composite safety end point was freedom from device- and procedure-related death through 30 days and freedom from target limb major amputation and clinically driven (CD) target vessel revascularization through 36 months.

The rate of major adverse events (death from any cause, CD target vessel revascularization, target limb major amputation, and thrombosis) was evaluated at 36 months. Thrombosis was defined as occlusion because of thrombus formation, confirmed by sudden onset of symptoms and documented by duplex ultrasonography and angiography. Additional end points included the rate of each individual component of the major adverse event composite, primary sustained clinical improvement (defined as freedom from target limb major amputation, target vessel revascularization, and increase in Rutherford Clinical Category), all TLR, and ankle-brachial index (toe-brachial index allowed in cases of incompressible vessels in IN.PACT SFA phase II) at 36 months. Functional assessments included evaluation of walking capacity with the Walking Impairment Questionnaire (WIQ) and the 6-minute walk test (IN.PACT SFA phase II only).

Statistical Analysis

Analyses were based on the intent-to-treat principle. 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±SD and were compared by Student t tests; dichotomous and categorical variables were described as counts and proportions and were compared by the Fisher exact test or Cochran–Mantel–Haenszel modified ridit scores, respectively. Outcome analyses were performed at a subject level. The Kaplan–Meier method was used to evaluate time to event data for primary patency and CD-TLR over the 36-month follow-up period. The difference in the survival curves between treatment groups was assessed using the log-rank test. For other outcomes, the Fisher exact test was used for binary outcomes, and the Wilcoxon rank-sum test or Student *t* test was used for continuous outcomes. The level of statistical significance was set at $P<0.05$ with no correction for multiple comparisons. For event rates that were expressed as a proportion, the number of subjects with an event within 1080 days was the numerator and the number of subjects with an event or at least 1050 days of clinical follow-up was the denominator. For assessment of clinical characteristics at 36 months, subjects were required to have data at both baseline and 36 months to assess any changes from baseline. Statistical analyses were performed using SAS (SAS Institute, NC) version 9.4.

Results

Three hundred thirty-one subjects were randomized to receive treatment with DCB (n=220) or PTA (n=111). Demographic, clinical, and lesion characteristics were well matched between treatment groups at baseline (Table 1). The mean lesion length was 8.94±4.89 cm in the DCB group and 8.81±5.12 cm in the PTA group ($P=0.815$). Provisional stents were implanted in 7.3% of subjects in the DCB group and 12.6% of subjects in the PTA group ($P=0.110$; Table 1). Details on the reasons for provisional stenting are reported in Table III in the Data Supplement. Through 36 months of follow-up, 11.4% of DCB subjects and 9.0% of PTA subjects withdrew from the trial, and 10.7% of DCB subjects and 1.9% of PTA subjects died. Of the remaining 173 DCB subjects eligible for 36-month evaluation,

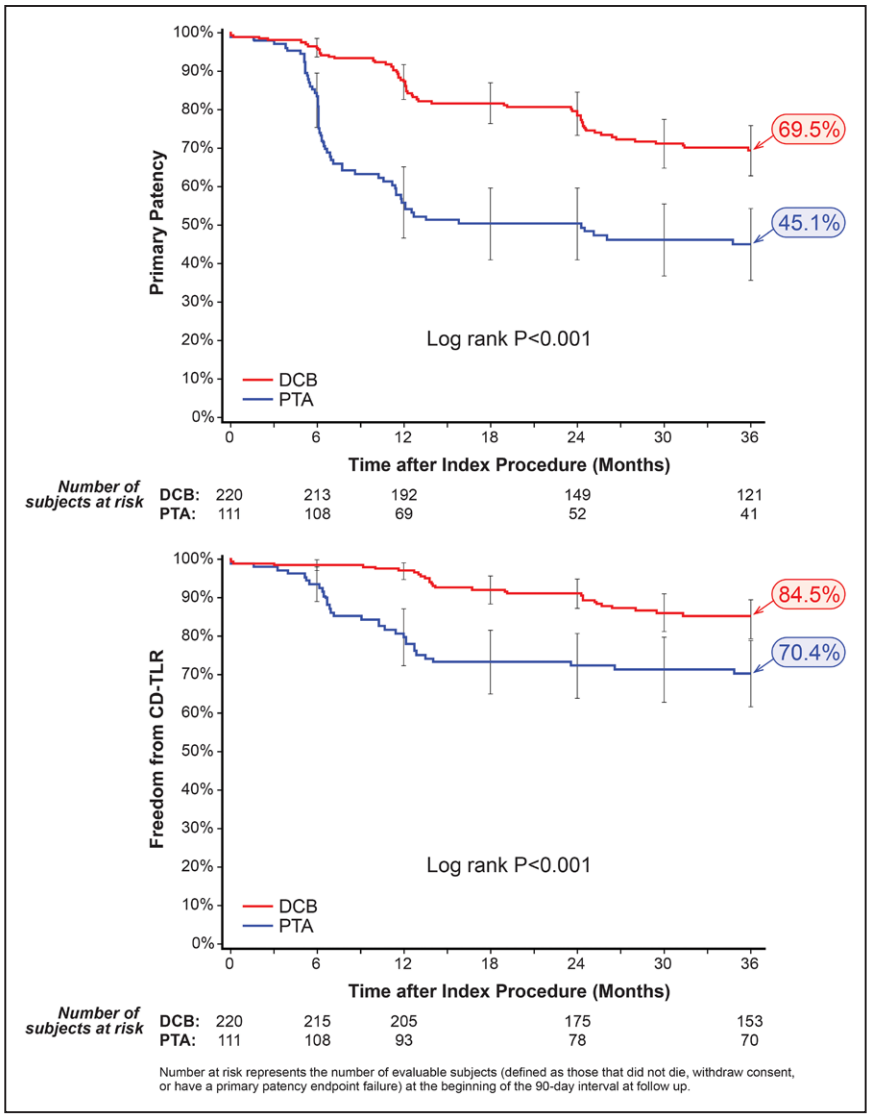

Figure 2. Durability of effect after treatment with a paclitaxel drug-coated balloon (DCB) for femoropopliteal lesions: primary patency and freedom from clinically driven target lesion revascularization (CD-TLR) at 36 months. **Top**, Primary patency by Kaplan–Meier estimate was significantly higher in the DCB group compared with the percutaneous transluminal angioplasty (PTA) group (log-rank test, *P*<0.001). **Bottom**, Freedom from CD-TLR by Kaplan–Meier estimate was significantly higher in the DCB group compared with the PTA group (log-rank test, *P*<0.001). **Top**, **Bottom**, Bars represent 95% confidence intervals. The number of subjects at risk represents the number of evaluable subjects at the beginning of each 90-day interval. An independent and blinded Clinical Events Committee adjudicated all target lesion revascularization events, and independent and blinded core laboratories reviewed all ultrasound and angiographic images.

93.1% had a completed 36-month follow-up visit (Figure 1). Of the remaining 99 PTA subjects eligible for 36-month evaluation, 92.9% had a completed 36-month follow-up visit.

Effectiveness Outcomes

Primary patency by Kaplan–Meier estimate was significantly higher in the DCB group compared with the PTA group at 36 months (Figure 2; 69.5% for DCB versus 45.1% for PTA; log rank *P*<0.001). Rates of CD-TLR were lower in the DCB group compared with the PTA group (15.2% for DCB versus 31.1% for PTA; *P*=0.002; Table 2). The time to first CD-TLR was longer in the DCB group compared with the PTA group (543±278 days for DCB versus 303±213 days for PTA; *P*<0.001). Freedom from CD-TLR by Kaplan–Meier estimate is shown in Figure 2. Primary sustained clinical improvement was achieved by a greater percentage of subjects in the DCB group compared with the PTA group (68.7% for DCB versus 52.6% for PTA; *P*=0.012).

A post hoc analysis was performed to evaluate the rates of CD-TLR among nonstented subjects at 36 months. The rate of CD-TLR was lower among nonstented subjects in the DCB group (14.4%) compared with those in the PTA group (32.2%; *P*=0.001). CD-TLR rates were not analyzed for stented subjects because of the small numbers of subjects that received stents in each group (16 subjects in DCB group and 14 in PTA group).

Safety Outcomes

Safety outcomes through 36 months are reported in Table 3. The primary composite safety end point was achieved in 81.2% of subjects in the DCB group and 64.1% in the PTA group (*P*=0.002). Rates of CD target vessel revascularization were significantly lower in the DCB group compared with the PTA group (18.8% for DCB versus 35.9% for PTA; *P*=0.002). Six deaths occurred between the 24- and 36-month follow-up periods: 5 in the DCB group (septic shock at 756 days, hemorrhagic stroke at 788 days, cardiac arrest at 907 days, acute respiratory failure at 1051 days, and gastric perforation at 1055 days) and 1 in the PTA group (worsening preexisting carcinoma at 877 days). Independent adjudication by the Clinical Events Committee determined that none of the deaths were related to the study device or procedure. The median time to death was 610 days in the DCB group and 637 days in the PTA group.

Table 2. Effectiveness Outcomes at 36 Months*

Characteristic	DCB (Subjects=220)	PTA (Subjects=111)	*P* Value†
Primary patency‡	69.5 (59)	45.1 (59)	<0.001§
CD-TLR‖	15.2 (30/197)	31.1 (32/103)	0.002
Time to first CD-TLR, d			
Mean±SD	542.9±278.2	302.9±213.0	<0.001¶
Median	464.0	243.5	
Interquartile range (Q3–Q1)	370.0	186.0	
Min, Max	1, 1080	1, 1045	
All TLR#	16.2 (32/197)	34.0 (35/103)	<0.001
Primary sustained clinical improvement**	68.7 (114/166)	52.6 (51/97)	0.012
ABI/TBI††	0.917±0.231	0.894±0.194	0.429

ABI indicates ankle-brachial index; CD-TLR, clinically driven target lesion revascularization; DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty; and TBI, toe-brachial index.

*Values are % (n), % (n/N), or mean±SD.

†Unless otherwise specified, all tests were for superiority using the Fisher exact test for binary variables and Student *t* test for continuous variables.

‡Defined as freedom from CD-TLR or freedom from restenosis as determined by duplex ultrasonography peak systolic velocity ratio ≤2.4 within 36 months. The 36-month primary patency was calculated based on Kaplan–Meier estimate, and the number of primary patency failure subjects is displayed in the parentheses.

§Log rank *P* value.

‖Defined as any reintervention at the target lesion because of symptoms or drop of ABI of ≥20% or >0.15 when compared with postprocedure baseline ABI/TBI.

¶Wilcoxon rank-sum test *P* value.

#Includes clinically-driven and incidental or duplex-driven TLR.

**Defined as freedom from target limb major amputation, target vessel revascularization, and increase in Rutherford class.

††TBI allowed in cases of incompressible vessels in IN.PACT SFA phase II.

Table 3. Safety Outcomes at 36 Months*

Characteristic	DCB (Subjects=220)	PTA (Subjects=111)	*P* Value†
Primary composite safety‡	81.2 (160/197)	64.1 (66/103)	0.002
Major adverse events§	27.9 (55/197)	37.9 (39/103)	0.089
All-cause deaths‖	10.7 (21/197)	1.9 (2/103)	0.006
Device- or procedure-related deaths	0.0 (0/197)	0.0 (0/103)	N/A
Clinically driven TVR	18.8 (37/197)	35.9 (37/103)	0.002
Target limb major amputation	0.0 (0/197)	0.0 (0/103)	N/A
Thrombosis	2.0 (4/197)	4.9 (5/103)	0.283

DCB indicates drug-coated balloon; PTA, percutaneous transluminal angioplasty; and TVR, target vessel revascularization.

*Values are % (n/N).

†*P* values are based on Fisher exact test for superiority with significance level of 0.05.

‡Defined as 30-day freedom from device- and procedure-related death and target limb major amputation and 36-month freedom from clinically driven TVR.

§Composite of death, clinically driven TVR, target limb major amputation, and thrombosis.

‖No deaths were adjudicated as device- or procedure-related by the Clinical Events Committee. Median postindex days to death was 610 days (DCB) and 637 days (PTA).

Functional Outcomes

There was sustained improvement in functional outcomes in both treatment groups (Table 4) through 3 years. Subjects in the DCB group achieved the same level of functional improvement despite 48% fewer reinterventions than those required in the PTA group. Six-minute walk test distance was similar between groups at 36 months (283±130 m for DCB versus 293±124 m for PTA; *P*=0.583). Total WIQ score was also similar between groups at 36 months (72±34 for DCB versus 75±29 for PTA; *P*=0.785).

Discussion

The prospective, multicenter, multinational, randomized IN.PACT SFA trial demonstrated that treatment with a paclitaxel-coated balloon is superior to standard PTA through 3 years in subjects with symptomatic femoropopliteal artery disease. The study design included adjudication of all major adverse events by an independent and blinded Clinical Events Committee and all angiography and duplex ultrasonography by independent and blinded core laboratories.

DCB angioplasty is intended to be a durable stand-alone therapy that, especially in cases of noncomplex lesions, obviates the need for permanent implants such as BMSs, stent grafts, and drug-eluting stents (DES). There are inherent difficulties with comparing outcomes across trials with 3-year findings, given differences in end point definitions and study populations. Nevertheless, the primary patency and CD-TLR rates were significantly better in the DCB group compared with the PTA group over this longer-term follow-up period and compare favorably to outcomes reported for other endovascular interventions in the same vascular bed at 3 years. Primary patency was 69.5% at 36 months for DCBs in this study, compared with 60.0% to 71.5% for BMS, DES, and stent grafts.[7,20,21] Freedom from CD-TLR was 84.5% at 36 months for DCBs in this study, compared with previous reports of 69.7% to 75.5% freedom from TLR at 36 months for BMS[5,7] and 83.6% freedom from TLR for a DES.[20] The 36-month CD-TLR rate of 15.2% for DCBs is less than half of what has been reported for BMS (31.1% CD-TLR at 3 years)[7] and stent grafts (34.7% TLR at 3 years).[21] We observed these results despite the fact that the mean lesion length in the DCB arm of the IN.PACT SFA trial was at the upper margin of lesion length reported in other studies. The mean lesion length in the DCB arm of the IN.PACT SFA trial was 8.94 cm compared with 6.64 cm in a randomized controlled trial of a DES[20] and 7.00 to 8.91 cm in the major BMS trials.[5,7] The mean lesion length in the stent graft trial was longer (19 cm).[21] These data suggest that treatment with DCBs is associated with results at least as favorable as those obtained with stenting but without the risks associated with an endoprosthesis.

This long-term treatment effect is supported by the persistence of paclitaxel in the vessel up to 180 days after application in experimental models.[11] The mechanical force of balloon angioplasty triggers inflammatory pathways that stimulate neointimal hyperplasia and restenosis.[22] The sustained presence of paclitaxel is thought to provide antiproliferative activity over an extended period of time that is sufficient to inhibit the neointimal hyperplasia that causes restenosis.

Table 4. Functional Outcomes at 36 Months*

Outcomes	DCB		PTA		*P* Value
	Baseline	36 mo	Baseline	36 mo	
6MWT†					
Mean distance, m					0.988‡
					0.583§
N	119	55	60	29	
Mean±SD	253.2±123.0	282.9±129.7	256.0±114.7	292.6±124.0	
Median [IQR]	274.3 [208.8]	289.6 [219.5]	278.6 [159.9]	304.8 [156.4]	
Change from baseline, m					0.117§
N	…	54	…	29	
Mean±SD	…	9.0±119.1	…	56.0±101.4	
Median [IQR]	…	25.1 [149.5]	…	61.0 [83.2]	
WIQ, %					
Walking impairment					0.799‡
					0.785§
N	214	158	109	91	
Mean±SD	42.1±28.9	71.8±34.2	41.3±29.9	74.7±29.2	
Median [IQR]	50.0 [25.0]	100.0 [50.0]	50.0 [25.0]	75.0 [50.0]	
Walking distance					0.861‡
					0.680§
N	177	95	83	46	
Mean±SD	32.3±27.7	67.4±37.8	30.4±24.2	65.0±37.9	
Median [IQR]	26.5 [41.2]	89.3 [65.5]	27.6 [36.2]	79.8 [72.4]	
Walking speed					0.847‡
					0.351§
N	177	96	82	46	
Mean±SD	31.8±23.5	52.4±31.6	29.3±17.1	47.1±28.4	
Median [IQR]	26.1 [29.3]	56.5 [51.1]	27.2 [26.1]	46.7 [38.0]	
Stair climbing					0.802‡
					0.786§
N	175	96	83	46	
Mean±SD	42.5±31.3	66.4±36.8	40.7±29.0	68.2±35.9	
Median [IQR]	41.7 [50.0]	75.0 [62.5]	37.5 [50.0]	83.3 [67.7]	

6MWT indicates 6-minute walk test; DCB, drug-coated balloon; IQR, interquartile range; PTA, percutaneous transluminal angioplasty; and WIQ, Walking Impairment Questionnaire.

*Values are mean±SD (n). The number of subjects evaluated at each interval is reported in parentheses. Based on number of subjects with available data. Site-reported data.

†Data collected in IN.PACT SFA phase II only.

‡Wilcoxon test for comparison of treatment groups at baseline.

§Wilcoxon test for comparison of treatment groups at 36 months.

The rate of all-cause death was significantly higher in the DCB group compared with the PTA group. However, the site investigator and blinded Clinical Events Committee reviewed each event, and none of the deaths were determined related to the balloon treatment (DCB or PTA group). All events occurred late after therapy. The death rate in the DCB group (10.7%) was consistent with reported death rates in other similar peripheral artery disease studies,[5,7,21,23] whereas the death rate in the PTA group (1.9%) was significantly lower than in previous trials.

The WIQ is the most commonly used self-report tool to evaluate patient's walking ability.[24] Previous studies have reported moderate to strong correlations between scores on the WIQ and walking performance as measured by treadmill tests in patients with intermittent claudication.[25–27] The WIQ contains 14 items that contribute to 3 subscales (walking distance,

walking speed, and stair-climbing ability) and an overall score. Each score ranges from 0 to 100 with a lower score indicating greater walking impairment (low performance). Validation studies have identified a WIQ overall score of <42.5 as an indicator of low performance.[28] The combined walking distance and stair-climbing score has been shown to provide the best indication of high performance with a cutoff of 75.5.[28] In the current study, subjects in the DCB and PTA treatment groups had evidence of significant walking impairment at baseline (overall score 42.1 versus 41.3). At 36 months, there was evidence of sustained improvement in walking ability (combined walking distance and stair-climbing score 133.8 versus 133.2) that was similar for both groups. This same level of functional improvement in the DCB group was achieved with 48% fewer reinterventions. The time to first CD-TLR was nearly twice as long in the DCB group (543 days) compared with the PTA group (303 days), and the rate of reintervention over the 3-year follow-up period was relatively low and without evidence of any significant late surge in TLRs or catch-up effect.

Recent analysis of IN.PACT SFA phase II data showed that the cost of DCB or PTA treatment within 2 years of follow-up was nearly identical. The higher initial cost of the DCB was offset by improved clinical outcomes, including a reduced need for repeat reinterventions, supporting the ultimate conclusion that treatment with DCB is cost-effective, and an economically dominant option compared with standard PTA.[29] A similar study from the United Kingdom found that DCBs, especially paclitaxel-coated DCBs with a urea excipient, had the greatest economic value compared with PTA, BMSs, and DES.[30] These studies suggest that the sustained longer-term maintenance of patency and avoidance of TLR should produce additional cost benefits over time.

There are several minimally invasive options for revascularization in patients with symptomatic peripheral artery disease, and there is a need for level-one evidence on long-term outcomes after treatment with a DCB for femoropopliteal lesions. The IN.PACT SFA is the first large, randomized trial to show sustained effect of a DCB through 3 years after treatment, with significantly higher primary patency and a lower rate of repeat interventions compared with standard PTA.

Limitations

Physicians involved in follow-up evaluations were aware of ultrasound and angiographic results to ensure optimal decision-making in each case. However, the subject and study sponsor were blinded through the 12-month follow-up period, and the Clinical Events Committee and core laboratories were blinded throughout the entire 3-year follow-up period.

As in any clinical trial, the number of subjects that are available for evaluation is gradually reduced as the length of the follow-up period increases. Despite the >90% 36-month follow-up compliance rates, because of the 2:1 randomization, the number of subjects in the PTA arm at 3 years was relatively low.

Conclusions

The 3-year outcomes from the prospective, multicenter, multinational, randomized IN.PACT SFA trial demonstrate the durable effectiveness after treatment with a paclitaxel DCB compared with a standard PTA balloon. Treatment with a DCB was associated with significantly higher primary patency and a lower rate of repeat interventions compared with PTA. The results of this analysis show sustained clinical benefit up to 3 years after treatment with a DCB and support use of the paclitaxel-coated DCB as an intervention for patients with symptomatic femoropopliteal disease.

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Treatment Effect of Drug-Coated Balloons Is Durable to 3 Years in the Femoropopliteal Arteries: Long-Term Results of the IN.PACT SFA Randomized Trial

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for the IN.PACT SFA Trial Investigators

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. List of Investigators Who Enrolled Subjects in the IN.PACT SFA Trial.

EU Clinical Site	Location	Principal Investigator
Landeskrankenhaus – Universitätsklinikum Graz	Graz, Austria	Prof. Marianne Brodmann
Inselspital Universitätsspital Bern	Bern, Switzerland	Prof. Iris Baumgartner
Ospedale Regionale di Lugano	Lugano/TI, Switzerland	Dr. Jos Van den Berg
Imeldaziekenhuis	Bonheiden, Belgium	Dr. Patrick Peeters
AZ Sint-Blasius	Dendermonde, Belgium	Dr. Marc Bosiers
Universitair Ziekenhuis Gent	Gent, Belgium	Prof. Frank Vermassen
Universitäts-Herzzentrum Freiburg – Bad Krozingen GmbH	Bad Krozingen, Germany	Prof. Thomas Zeller
RoMed Klinikum Rosenheim	Rosenheim, Germany	Prof. Gunnar Tepe
MVZ Prof. Mathey, Prof. Schofer GmbH	Hamburg, Germany	Dr. Sebastian Sixt
Universitätsklinikum Leipzig AöR	Leipzig, Germany	Prof. Dierk Scheinert
Università Cattolica del Sacro Cuore Policlinico Gemelli	Roma, Italy	Dr. Carlo Trani
Clinical Montevergine	Mercogliano (AV), Italy	Dr. Giovanni Sorropago
Maria Eleanora Hospital	Palermo, Italy	Dr. Antonio Micari
US Clinical Site	**Location**	**Principal Investigator**
Cleveland Clinic	Cleveland, OH, USA	Dr. Mehdi Shishehbor
Saint Luke's Episcopal Hospital – Texas Medical Center	Houston, TX, USA	Dr. Neil Strickman
Hospital of the University of Pennsylvania	Philadelphia, PA, USA	Dr. Ronald Fairman
University of Virginia Medical Center	Charlottesville, VA, USA	Dr. John Angle
The Mount Sinai Medical Center	New York, NY, USA	Dr. Prakash Krishnan
EMH Elyria Medical Center	Elyria, OH, USA	Dr. Naim Farhat
Saint Luke's Hospital	Kansas City, MO, USA	Dr. Steven Laster
New York Presbyterian Hospital/Columbia University Medical	New York, NY, USA	Dr. William Gray
Sentara Norfolk General Hospital	Norfolk, VA, USA	Dr. Marc Glickman
Washington Hospital	Fremont, CA, USA	Dr. Ash Jain

US Clinical Site	Location	Principal Investigator
Munroe Regional Medical Center	Ocala, FL, USA	Dr. Robert Feldman
Mercy Medical Center	Des Moines, IA, USA	Dr. David Chew
Arizona Heart Institute	Phoenix, AZ, USA	Dr. Venkatesh Ramaiah
Abbott Northwestern Hospital	Minneapolis, MI, USA	Dr. Peter Alden
Scripps Green Hospital/Scripps Clinic Torrey Pines	La Jolla, CA, USA	Dr. Curtiss Stinis
Banner Good Samaritan Medical Center	Phoenix, AZ, USA	Dr. Ashish Pershad
Holy Spirit Hospital	Camp Hill, PA, USA	Dr. Rajesh Dave
Washington Hospital Center	Washington, DC, USA	Dr. Robert Gallino
Wellmont Holston Valley Medical Center	Kingsport, TN, USA	Dr. Christopher Metzger
Riverside Methodist Hospital	Columbus, OH, USA	Dr. Gary Ansel
Deborah Heart & Lung Center	Browns Mills, NJ, USA	Dr. Richard Kovach
Saint Vincent Heart Center of Indiana	Indianapolis, IN, USA	Dr. Brian Bigelow
The University of Kansas Hospital	Kansas City, KS, USA	Dr. Kamal Gupta
Mercy Hospital and Medical Center	Chicago, IL, USA	Dr. Paul Jones
Beth Israel Deaconess Medical Center	Boston, MA, USA	Dr. Marc Schermerhorn
The Christ Hospital	Cincinnati, OH, USA	Dr. Monica Hunter
The Miriam Hospital	Providence, RI, USA	Dr. Peter Soukas
Stanford Hospital & Clinics	Stanford, CA, USA	Dr. Michael Dake
Saint Francis Hospital	Roslyn, NY, USA	Dr. George Petrossian
Saint Elizabeth's Medical Center	Boston, MA, USA	Dr. Lawrence Garcia
WakeMed Health and Hospitals	Raleigh, NC, USA	Dr. Ravish Sachar
Christiana Hospital	Newark, DE, USA	Dr. Mark Garcia
Baptist Hospital of Miami	Miami, FL, USA	Dr. James Benenati
Aurora Saint Luke's Medical Center	Milwaukee, WI, USA	Dr. Mark Mewissen
Providence Health Center	Waco, TX, USA	Dr. Rodney Brown
Arrowhead Hospital	Glendale, AZ, USA	Dr. Rahul Malhotra

US Clinical Site	Location	Principal Investigator
Rex Hospital	Raleigh, NC, USA	Dr. James Zidar
Edward Hospital	Naperville, IL, USA	Dr. Mark Goodwin
Terrebonne General Medical Center	Houma, LA, USA	Dr. Craig Walker
Kaiser Permanente – Moanalua Medical Center and Clinic	Honolulu, HI, USA	Dr. Peter Schneider
Pomerado Hospital	Poway, CA, USA	Dr. Rod Serry
Longview Regional Medical Center	Longview, TX, USA	Dr. Samir Germanwala
Advanced Vascular Associated	Morristown, NJ, USA	Dr. Amit Patel
University of Pittsburgh Medical Center Passavant	Pittsburgh, PA, USA	Dr. Luke Marone

Supplemental Table 2. Use of Anticoagulant and Antiplatelet Medications at Baseline in the IN.PACT SFA Trial.

	DCB (N=220)	**PTA** (N=111)	**P value**
Acetylsalicylic acid (ASA)	99.5% (219/220)	97.3% (108/111)	0.112
Clopidogrel	93.6% (206/220)	94.6% (105/111)	0.812
Prasugrel	0.9% (2/220)	0.9% (1/111)	1.000
Ticlopidine	3.2% (7/220)	2.7% (3/111)	1.000
ASA + Clopidogrel/Prasugrel/Ticlopidine	97.3% (214/220)	95.5% (106/111)	0.517
Procedural Anticoagulent/Antiplatelet			
Heparin	98.6% (217/220)	98.2% (109/111)	1.000
Glycoprotein IIb/IIIa Inhibitors	0.8% (1/121)	0.0% (0/60)	1.000
Activated Clotting Time (s)*			
N	119	58	
Mean ± SD	312.0 ± 107.1	330.9 ± 131.2	0.308
Median	283.0	285.5	
Min, Max	171, 999	229, 1000	

Numbers are % (counts/sample size) unless otherwise specified.
Site reported data.
* Not reported in IN.PACT SFA I phase.

Supplemental Table 3. Reasons for Provisional Stenting in the IN.PACT SFA Trial.

	DCB (N=16)	**PTA** (N=14)	**P value**
Major flow-limiting dissection	93.8% (15/16)	71.4% (10/14)	0.157
Persistent ≥50% residual stenosis	12.5% (2/16)	28.6% (4/14)	0.378
>10 mmHg peak trans-lesional gradient*	6.3% (1/16)	14.3% (2/14)	0.586

Numbers are % (counts/sample size) unless otherwise specified.
Site reported data.
* Required for IN.PACT SFA II phase; not required for IN.PACT SFA I phase.
* Major not specified in IN.PACT SFA I phase.