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Durability of Treatment Effect Using a Drug-Coated Balloon for Femoropopliteal Lesions

24-Month Results of IN.PACT SFA

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ABSTRACT

BACKGROUND Evidence from large, randomized, controlled peripheral artery disease trials reporting long-term outcomes using drug-coated balloons (DCBs) is limited. Previously, the DCB showed favorable 1-year outcomes compared with conventional percutaneous transluminal angioplasty (PTA), yet durability of the treatment effect with DCBs remains unknown.

OBJECTIVES This study sought to investigate the longer-term outcomes of a paclitaxel-eluting DCB compared to PTA for femoropopliteal lesions.

METHODS We enrolled 331 patients with symptomatic (Rutherford 2 to 4) femoropopliteal lesions up to 18 cm in length. Patients were randomly assigned in a 2:1 ratio to treatment with DCB or PTA. The 24-month assessments included primary patency, freedom from clinically driven target lesion revascularization (CD-TLR), major adverse events, and quality of life and functional outcomes as assessed by the EuroQOL-5D quality-of-life questionnaire, walking impairment questionnaire, and 6-min walk test.

RESULTS At 24 months, patients treated with DCB showed significantly higher primary patency when compared with PTA (78.9% vs. 50.1%; $p < 0.001$). The rates of CD-TLR were 9.1% and 28.3% ($p < 0.001$) for the DCB and PTA groups, respectively. The overall mortality rate in the DCB group was 8.1% versus 0.9% in the PTA group ($p = 0.008$). There were no device- or procedure-related deaths and no major amputations in either group through 24-month follow-up. The rate of vessel thrombosis was low (1.5% DCB vs. 3.8% PTA; $p = 0.243$), with no new events reported between 1 and 2 years. Both groups showed similar functional improvement at 2 years, although DCB patients achieved this level of function with 58% fewer reinterventions.

CONCLUSIONS The 24-month outcomes from the trial demonstrate a durable and superior treatment effect of DCB versus PTA with significantly higher primary patency, lower CD-TLR, and similar functional status improvement with fewer repeat interventions. (Randomized Trial of IN.PACT Admiral Drug Eluting Balloon vs Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease [INPACT SFA I]; NCT01175850; and IN.PACT Admiral Drug-Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Superficial Femoral Artery [SFA] and Proximal Popliteal Artery [PPA] [INPACT SFA II]; NCT01566461) (J Am Coll Cardiol 2015;66:2329–38) © 2015 by the American College of Cardiology Foundation. Published by Elsevier. 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

ABI = ankle-brachial index

CD-TLR = clinically driven target lesion revascularization

CD-TVR = clinically driven target vessel revascularization

CEC = Clinical Events Committee

DCB = drug-coated balloon

PAD = peripheral artery disease

PTA = percutaneous transluminal angioplasty

SFA = superficial femoral artery

Endovascular procedures have become the predominant method for revascularization of patients with symptomatic peripheral artery disease (PAD), largely due to their less invasive nature and low complication rates (1). Although well established, percutaneous transluminal angioplasty (PTA) of the superficial femoral (SFA) and popliteal arteries is associated with a high incidence of restenosis when used for anything but the most focal, noncomplex lesions (2). Self-expanding nitinol stents have improved the durability of endovascular interventions in the femoropopliteal segment. Recent studies have reported superior results of stents over PTA for short to intermediate-length lesions in the SFA, with 1-year patency rates ranging from 63% to 83% (3–6) and longer-term patency rates of 60% to 75% (7,8). Despite the benefits of stents, concerns exist regarding the effect of in-stent restenosis, stent fractures, and other stent-related complications that negatively affect the patient's clinical progress over the long term (9–11). The search, therefore, continues for an effective and durable treatment strategy that minimizes the need for permanent metal implants and preserves future therapeutic options.

SEE PAGE 2339

Paclitaxel-eluting drug-coated balloons (DCBs) have shown promise for the treatment of PAD (12–17). Paclitaxel is a proven antiproliferative agent that is well suited for this application due to its lipophilic nature. When combined with an excipient (carrier) molecule, paclitaxel is delivered into the vessel wall during DCB angioplasty, and therapeutic levels of paclitaxel remain at the treatment site for up to 180 days with certain excipients (18). Single-center experiences and small randomized trials have demonstrated a reduction in restenosis rates and the need for repeat procedures with DCB compared with standard PTA (12–15). More recently, larger prospective multicenter trials comparing DCB and PTA have been reported (17,19). The IN.PACT SFA randomized trial evaluated the safety and effectiveness of the DCB (IN.PACT Admiral, Medtronic, Santa Rosa, California) compared with standard PTA for the treatment of patients with symptomatic femoropopliteal artery disease. The 1-year results from the IN.PACT SFA trial demonstrated superior primary patency and a reduction in clinically driven target lesion revascularization (CD-TLR) with DCB compared with PTA (19). More recently, a second paclitaxel-eluting DCB has shown superior 1-year results in comparison to PTA (17). Despite these favorable short-term results, there are limited data regarding the longer-term effectiveness of this novel approach for the treatment of femoropopliteal disease. In the current report, we describe the 2-year outcomes from the IN.PACT SFA randomized trial.

METHODS

STUDY DESIGN. A detailed description of the IN.PACT SFA trial design, inclusion and exclusion criteria, and outcomes through 1 year have been previously reported (19). The IN.PACT SFA trial is a multicenter, randomized, single-blinded trial to assess the safety and efficacy of the DCB versus standard PTA balloons in patients with symptomatic SFA and/or proximal popliteal artery disease. Patients were randomly assigned in a 2:1 ratio to treatment

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with DCB (n = 220) or PTA (n = 111). Patients were eligible for enrollment if they had moderate to severe intermittent claudication or ischemic rest pain (Rutherford 2 to 4), stenosis of 70% to 99% with lesion lengths between 4 and 18 cm or occlusion with lengths of ≤10 cm involving the superficial femoral and proximal popliteal arteries, and met all other eligibility criteria, including successful pre-dilation. Before enrollment, written informed consent was obtained from all patients according to the protocols approved by the institutional review board or ethics committee at each investigational 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 authorities.

The trial included independent oversight by a Data Safety Monitoring Board and Clinical Events Committee (CEC) that reviewed and adjudicated all major adverse events through 24 months post-intervention. Independent duplex ultrasonography (VasCore, Massachusetts General Hospital, Boston, Massachusetts) and angiography (SynvaCor, Springfield, Illinois) core laboratories analyzed procedural and follow-up images. The independent core laboratories and CEC will remain blinded to the treatment assignments through the 60-month follow-up duration.

ENDPOINT DEFINITIONS

Assessments through 24 months included: primary patency, defined as freedom from CD-TLR or freedom from restenosis as determined by duplex ultrasonography-derived peak systolic velocity ratio ≤2.4; and CD-TLR, defined as reintervention at the target lesion due to symptoms or decrease in ankle-brachial index (ABI) ≥20% or >0.15 when compared with post-procedure baseline ABI. In addition, primary patency at 24 months plus the 30-day follow-up window was analyzed. The primary composite safety 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 (CD-TVR) through 24 months.

The major adverse event rate (death from any cause, CD-TVR, major target limb amputation, and thrombosis at target lesion site) was also evaluated at 24 months. Thrombosis was defined as a total occlusion due to thrombus formation, which is rapidly evolving as confirmed by sudden onset of symptoms and documented by Duplex ultrasonography and/or angiography. Additional endpoints evaluated through 24 months included cumulative binary restenosis (defined as core laboratory-assessed restenosis by Doppler ultrasound peak systolic velocity ratio >2.4 or angiographic diameter stenosis ≥50% at 24 months or before any revascularization), the individual components of the major adverse event composite, and primary sustained clinical improvement (defined as freedom from target limb amputation, freedom from target vessel revascularization, and increase in Rutherford class at 24 months). Functional assessments included general appraisal through administration of the EuroQOL (EQ)-5D, a 5-dimension generic health status questionnaire (20), and specific evaluation of walking capacity using the Walking Impairment Questionnaire (21). A 6-min walk test (22) was additionally conducted in the IN.PACT SFA II (U.S. patient cohort).

STATISTICAL ANALYSIS. All analyses were on the basis of the intent-to-treat principle. 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. The Kaplan-Meier method was used to evaluate time-to-event data for primary patency and CD-TLR over the 24-month follow-up period. The difference in the survival curves between groups was assessed using the log-rank test. For other outcomes, in addition to the descriptive statistics, the Fisher exact test was used for binary outcomes and Student *t* test for continuous outcomes. For all endpoints, the level of statistical significance was set at $p < 0.05$ with no correction for multiple comparisons. Statistical analyses were performed using SAS (SAS Institute, Cary, North Carolina) version 9.2 or higher.

RESULTS

The IN.PACT SFA trial included 331 patients randomized to treatment with DCB (n = 220) and PTA (n = 111). Through 24 months of follow-up, 17 DCB subjects and 6 PTA subjects withdrew from the trial, and 16 DCB subjects and 1 PTA subject died. Of the remaining 187 DCB subjects eligible for the 24-month evaluations, 170 (90.9%) had a completed 24-month follow-up visit. Similarly, of the 104 PTA subjects eligible for the 24-month evaluations, 94 (90.4%) had a completed 24-month follow-up visit. As previously reported, the treatment groups were well matched at baseline with similar demographics, comorbidities, and lesion characteristics (**Table 1**) (19). The mean lesion length was 8.94 ± 4.89 cm in the DCB group versus 8.81 ± 5.12 cm in the PTA group (p = 0.815).

TABLE 1 Baseline Patient and Procedural Characteristics

	IN.PACT (n = 220)	PTA (n = 111)	p Value
Age, yrs	67.5 ± 9.5	68.0 ± 9.2	0.612
Male	65.0 (143/220)	67.6 (75/111)	0.713
Diabetes	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
Severe calcification	8.1 (18/221)	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

Values are mean ± SD or % (n/N). *TBI allowed/used in cases of incompressible vessels in phase II.
ABI = ankle-brachial index; PTA = percutaneous transluminal angioplasty; TBI = toe-brachial index.

EFFECTIVENESS OUTCOMES THROUGH 24 MONTHS. The primary patency rate through 24 months was significantly higher with DCB than PTA (78.9% vs. 50.1%; log rank $p < 0.001$) (Central Illustration). At the end of the 30-day follow-up window for 2 years, the primary patency rate was 73.5% for DCB versus 47.4% for PTA. DCB-treated patients maintained significantly lower CD-TLR rates at 24 months compared with patients treated with PTA (9.1% vs. 28.3%; $p < 0.001$) (Table 2). Kaplan-Meier estimates of freedom from CD-TLR are demonstrated in the Central Illustration. Core laboratory-assessed cumulative binary restenosis rates by Kaplan-Meier estimate at 24 months were 19.8% for DCB versus 46.9% for PTA (log rank $p < 0.001$). Significantly higher primary sustained clinical improvement was observed in the DCB group compared with PTA (76.9% vs. 59.2%; $p = 0.003$) (Table 2). A post-hoc subgroup analysis showed a beneficial treatment effect of DCB across numerous clinical and anatomic subgroups (Figure 1). Importantly, primary patency was significantly better for diabetic patients treated with DCB compared with PTA (73.3% vs. 45.8%; $p < 0.001$). Female patients in the DCB group outperformed their PTA-treated counterparts (Figure 1). Primary patency for female patients treated with DCB was 76.7% compared with 42.3% for those treated with PTA ($p < 0.001$).

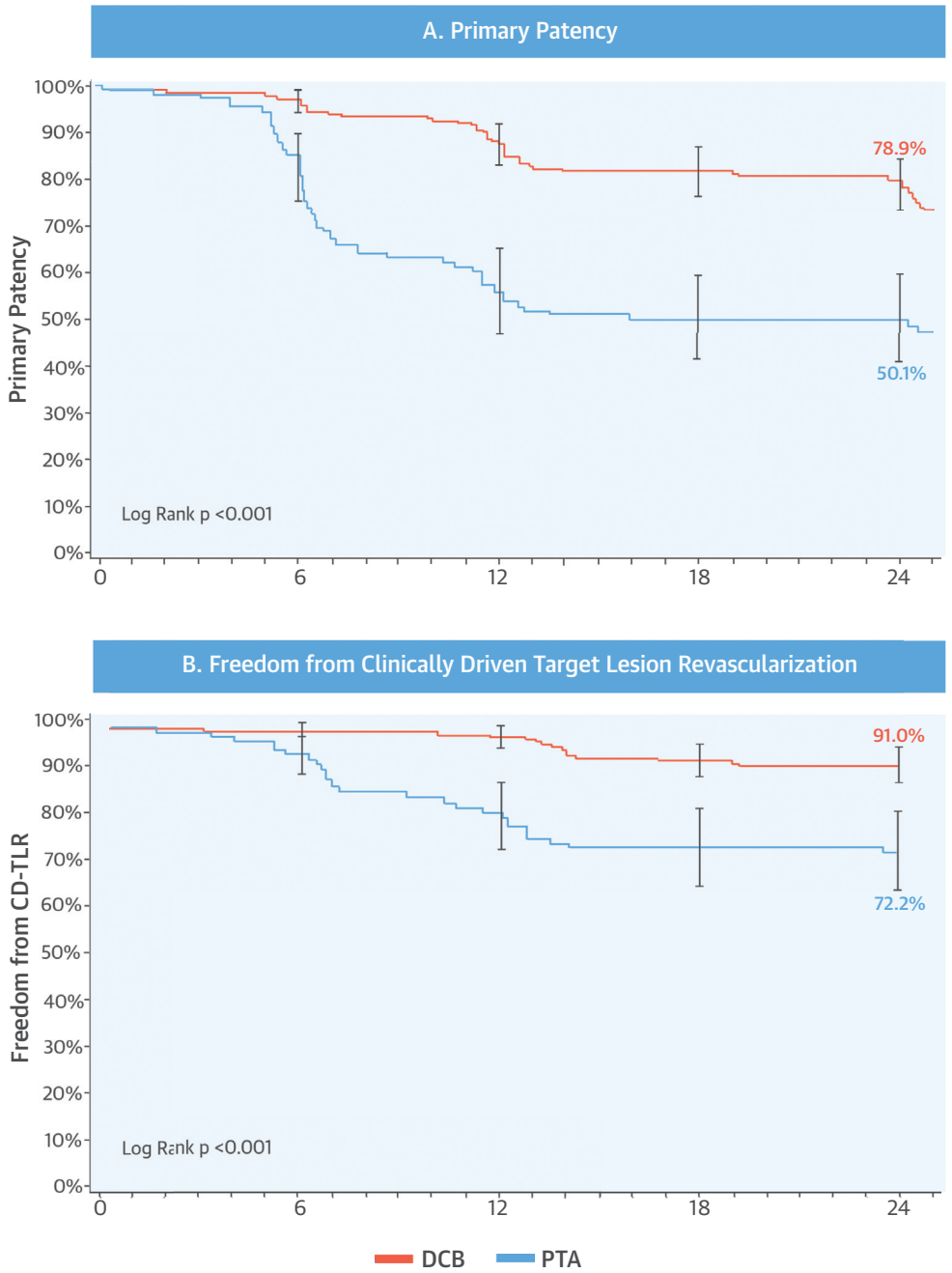
SAFETY OUTCOMES THROUGH 24 MONTHS. Table 3 summarizes the safety outcomes through the 24-month follow-up. The primary safety composite endpoint of freedom from 30-day device- and procedure-related death and target limb major amputation and CD-TVR within 24 months was 87.4% in the DCB group versus 69.8% in the PTA group ($p < 0.001$). Rates of CD-TVR remained significantly lower for patients treated with DCB versus PTA (12.6% vs. 30.2%; $p < 0.001$). Although there were no device- or procedure-related deaths in either group, the rate of all-cause mortality was higher for patients treated with DCB compared with PTA (8.1% vs. 0.9%; $p = 0.008$). The causes of death as adjudicated by the blinded, independent CEC are listed in Table 4. The deaths occurred relatively late in the study follow-up, with a median time to death of 564.5 days in the DCB group and 397 days in the PTA group.

FUNCTIONAL OUTCOMES. At 24 months, both treatment groups showed improvement from baseline in all functional outcomes assessed, including the quality-of-life assessment by the EQ-5D index, 6-min walk test, and Walking Impairment Questionnaire (Table 5). In the quality-of-life assessment using the EQ-5D index, results trended in favor of patients treated with DCB (Table 5). Using the 6-min walk test, the distance covered at baseline was comparable between groups (253.2 ± 123 m for DCB vs. 256.0 ± 114.7 m for PTA; $p = 0.883$). At 24 months, there was similar improvement in walking distance for the DCB and PTA groups (30.9 ± 87.7 m vs. 60.5 ± 97.6 m; $p = 0.117$). Patients treated with DCB achieved these similar levels of quality-of-life improvement despite 58% fewer reinterventions than with PTA.

DISCUSSION

The IN.PACT SFA randomized trial demonstrated that, for lesions in the SFA and proximal popliteal artery (mean length 8.9 cm), the DCB provided superior outcomes at 1 year compared with standard PTA (19). Primary patency and CD-TLR rates were significantly better in the DCB group. The 12-month CD-TLR rate of 2.4% was the lowest reported in the published medical data for a femoropopliteal endovascular therapy. The current analysis of the longer-term results from this trial demonstrates a sustained benefit of DCB over PTA at 24 months. The 24-month DCB outcomes were excellent, with a primary patency rate of 78.9% and a CD-TLR rate of only 9.1%. The Kaplan-Meier curves for primary patency and CD-TLR remain parallel after 1 year for the 2 treatment groups, demonstrating no "catch up" phenomenon with regard to late target lesion failure and the need for

CENTRAL ILLUSTRATION **Durability of Treatment Effect Using a DCB for Femoropopliteal Lesions at 24 Months: Primary Patency and Target Lesion Revascularization**



Laird, J.R. et al. J Am Coll Cardiol. 2015; 66(21):2329–38.

(A) Primary patency by Kaplan-Meier estimate was significantly higher in the drug-coated balloon (DCB) group than in the percutaneous transluminal angioplasty (PTA) group ($p < 0.001$). The primary patency rate was 78.9% for DCB versus 50.1% for PTA at 24 months. **Bars** represent 95% confidence interval. All target lesion revascularization events were adjudicated by the independent and blinded clinical events committee, and all ultrasound and angiographic images were analyzed by independent and blinded core laboratories. **(B)** Freedom from clinically driven target lesion revascularization (CD-TLR) by Kaplan-Meier estimate was significantly higher in the DCB group than in the PTA group ($p < 0.001$). The CD-TLR rate was 91.0% for DCB versus 72.2% for PTA at 24 months. **Bars** represent 95% confidence interval. All target lesion revascularization events were adjudicated by the independent and blinded clinical events committee.

TABLE 2 Effectiveness Outcomes at 24 Months

	IN.PACT (n = 220)	PTA (n = 111)	p Value*
Primary patency†	78.9 (42)	50.1 (54)	<0.001‡
CD-TLR§	9.1 (18/198)	28.3 (30/106)	<0.001
Time to first CD-TLR, days	351.9 ± 165.9	261.7 ± 139.0	0.049
All TLR‖	10.1 (20/198)	29.2 (31/106)	<0.001
Primary sustained clinical improvement¶	76.9 (133/173)	59.2 (61/103)	0.003
ABI/TBI#	0.924 ± 0.261	0.938 ± 0.184	0.611

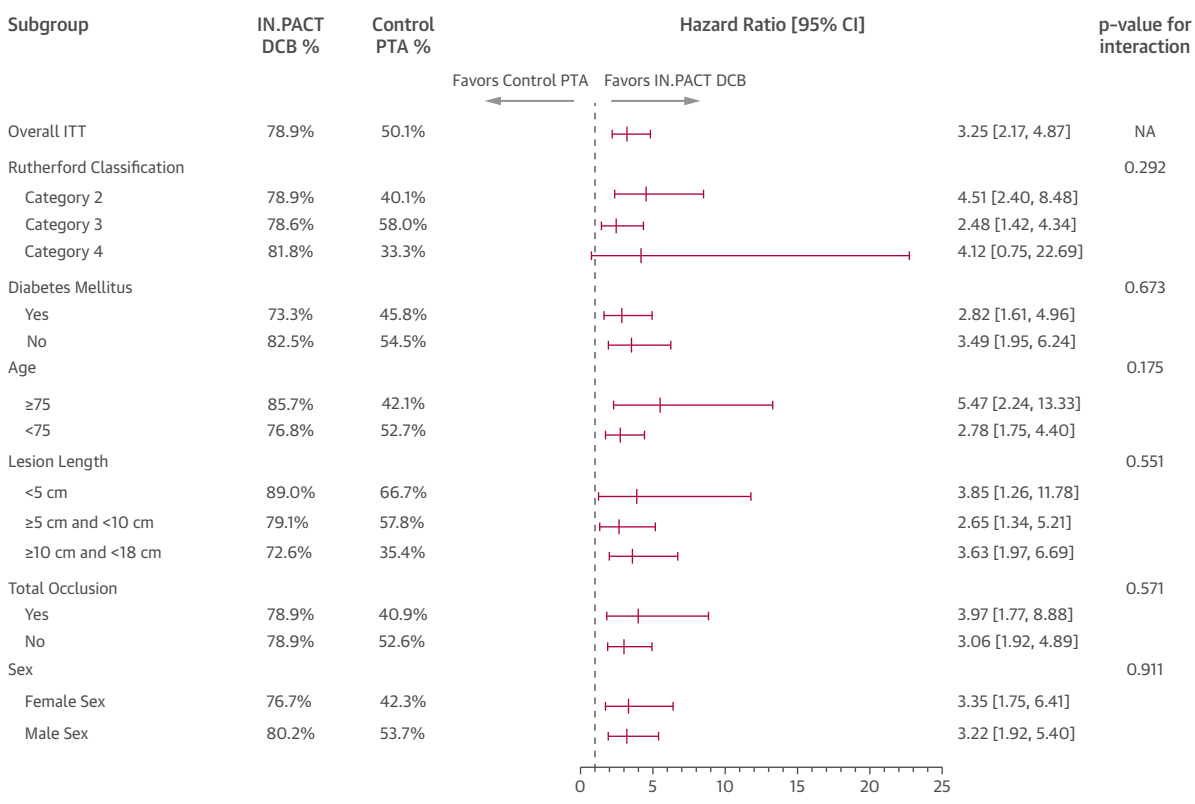
Values are % (n), % (n/N), or mean ± SD. *Unless otherwise indicated, all tests were for superiority using the Fisher exact test for binary variables and Student *t* test for continuous variables. †Freedom from clinically driven TLR or freedom from restenosis as determined by Duplex ultrasound peak systolic velocity ratio ≤2.4 within 24 months. The 24-month primary patency was calculated based on Kaplan-Meier estimate, and the number of primary patency failure subjects are displayed in the parentheses. ‡Log rank p value. §Any reintervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared with post-procedure baseline ABI/TBI. ‖Includes clinically driven and incidental or duplex-driven TLR. ¶Freedom from target limb amputation, TVR, and increase in Rutherford class. #TBI allowed/used in case of incompressible vessels in phase II.

CD-TLR = clinically driven target lesion revascularization; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

repeat interventions (Central Illustration). These results support the notion that a short duration of paclitaxel uptake into the vessel wall after balloon angioplasty can result in effective inhibition of neointimal proliferation and sustained clinical benefit. At 2 years, these data continue to support an excellent safety profile with no major amputations in the DCB group and no new thrombosis events reported between 1 and 2 years.

Although no large randomized trials have been published comparing DCB with bare-metal stents, drug-eluting stents, or atherectomy, the IN.PACT Admiral DCB results compare favorably with results from other randomized clinical trials in this patient population. Despite inclusion of longer lesion lengths that are at a higher risk of treatment failure, the 2-year primary patency rate of 78.9% is in line with results from bare-metal and drug-eluting stent trials (8,23-25). The 2-year CD-TLR rate of 9.1% remains 1 of

FIGURE 1 Subgroup Analysis of Primary Patency at 24 Months



Forest plots show primary patency based on Kaplan-Meier estimate in key subgroups at 24 months. Comparisons between drug-coated balloon (DCB) and percutaneous transluminal angioplasty (PTA) for all subgroup analyses were statistically significant at a significance level of 0.05, except the Rutherford Classification 4 subgroup. Treatment-by-subgroup interactions were tested using a Cox proportional hazards model containing the main effects of treatment (DCB and PTA), subgroup, and the treatment-by-subgroup interaction. CI = confidence interval; ITT = intent-to-treat.

the lowest ever reported for an SFA device trial. These results were achieved despite a low rate of bailout stenting (7.3%) in the DCB arm of the trial (19). This low bailout stenting rate highlights the fact that careful attention to technique and long-duration balloon inflations can achieve satisfactory angiographic results and obviate the need for stenting in the majority of cases. The potential benefits of avoiding implantation of a permanent metallic endoprosthesis in the femoropopliteal vascular bed have been well described and include prevention of complications associated with stent fracture and in-stent restenosis (9). Once diffuse in-stent restenosis or in-stent occlusion occurs, additional interventions are associated with a high rate of recurrent restenosis or reocclusion (26,27).

A post-hoc subgroup analysis demonstrated outcomes in favor of DCB across a variety of clinical and anatomic subgroups. With the exception of patients having ischemic rest pain (Rutherford Category 4), all subgroups showed better results with DCB. Longer and more complex lesions, including total occlusions, had significantly better primary patency following treatment with DCB. A strong treatment effect was also observed for diabetic patients and women. These findings are of great importance given the historically poorer outcomes for diabetic patients following lower extremity interventions (28,29).

One unexpected finding of the trial was a higher mortality rate at 24 months in the DCB group. Following evaluation by the independent, blinded clinical events committee, however, none of the deaths were deemed related to the study device or the procedure. When compared with other published series in a similar patient population, the 24-month mortality rate in the PTA group in IN.PACT SFA (0.9%) was unusually low. Typical mortality rates in these trials range from 3.5% to 11% (7,15). However, the mortality rate of 8.1% for DCB at 2 years is consistent with results from contemporary PAD trials (ranging from 7.6% to 9.0% [7,17]) and is in line with a recent publication by Mueller et al. (30) in which they observed higher mortality rates in PAD patients compared with non-PAD control subjects. The higher mortality rate in the DCB arm bears watching, however, and longer-term follow-up from the IN.PACT SFA trial and results from other trials will provide additional insights regarding this observation.

The ultimate goal of any lower extremity revascularization procedure for patients with intermittent claudication is to improve functional status, reduce disability, and improve overall quality of life. In the IN.PACT SFA trial, quality of life and walking improvement, as assessed by the EQ-5D and walking impairment questionnaire at 2-year follow-up, was similarly improved from baseline for patients undergoing PTA and DCB, despite 58% fewer re-interventions for the DCB group. A similar result was observed in the 2-year ABI/toe-brachial index endpoint. This is the first prospective, multicenter randomized trial of peripheral artery devices in which a subset of patients underwent serial 6-min walk tests. There was similar improvement in walking distance for both treatment groups. The maintenance of this important patient-centered metric over 2 years is encouraging and reinforces a role of this

TABLE 3 Safety Outcomes at 24 Months

	IN.PACT (n = 220)	PTA (n = 111)	p Value*
Primary safety composite†	87.4% (173/198)	69.8% (74/106)	<0.001
Major adverse events‡	19.2% (38/198)	31.1% (33/106)	0.023
All-cause death§	8.1% (16/198)	0.9% (1/106)	0.008
Device- and procedure-related death	0.0% (0/198)	0.0% (0/106)	>0.999
Clinically driven TVR	12.6% (25/198)	30.2% (32/106)	<0.001
Target limb major amputation	0.0% (0/198)	0.0% (0/106)	>0.999
Thrombosis	1.5% (3/198)	3.8% (4/106)	0.243

Values are % (n/N). *p values are based on Fisher exact test for superiority with significance level of 0.05. †Freedom from 30-day device- and procedure-related death and target limb major amputation and clinically driven TVR within 24 months. ‡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 post-index days to death: 564.5 days in DCB versus 397 days in PTA.

PTA = percutaneous transluminal angioplasty; other abbreviations as in Tables 1 and 2.

TABLE 4 Causes of Death* Through 24 Months

	Treatment Assignment	Days to Death	Procedure-Related (Y/N)	Device-Related (Y/N)
Infarction of the right cerebral hemisphere in the anterior and medial flow region	DCB	127	No	No
Biliary sepsis	DCB	168	No	No
Sudden death	DCB	287	No	No
Perforated transverse colon secondary to cecal volvulus	DCB	314	No	No
Sepsis	DCB	374	No	No
Acute diastolic congestive heart failure	DCB	540	No	No
Metastatic colon cancer	PTA	397	No	No
Unknown	DCB	541	No	No
GI cancer	DCB	561	No	No
Cardiac arrest	DCB	568	No	No
Deterioration of general condition	DCB	603	No	No
Cardiac arrest	DCB	610	No	No
CAD	DCB	615	No	No
Acute respiratory failure	DCB	657	No	No
Dementia	DCB	679	No	No
Hypoxic respiratory failure	DCB	681	No	No
Ischemic cardiomyopathy	DCB	699	No	No

*Causes of death as reported by sites. Adjudicated by the blinded clinical events committee for relatedness to device or procedure.

CAD = coronary artery disease; GI = gastrointestinal; other abbreviations as in Table 1.

TABLE 5 24-Month Functional Outcomes

Outcomes	IN.PACT DCB		PTA		p Value
	Baseline	24 Months	Baseline	24 Months	
Quality-of-life assessment by EQ-5D index	0.7431 ± 0.1652 (216)	0.8436 ± 0.1862 (170)	0.7450 ± 0.1627 (108)	0.7939 ± 0.2107 (94)	
Change from baseline by EQ-5D index	–	0.0957 ± 0.2159 (167)	–	0.0545 ± 0.2286 (92)	0.151
6-min walking test, m*	253.2 ± 123.0 (119)	298.0 ± 124.3 (73)	256.0 ± 114.7 (60)	311.6 ± 137.0 (35)	
Change in walking distance from baseline by 6MWT, m*	–	30.9 ± 87.7 (72)	–	60.5 ± 97.6 (35)	0.117
Walking Impairment Questionnaire scores, %					
Walking impairment	42.1 ± 28.9 (214)	72.5 ± 34.1 (170)	41.3 ± 29.9 (109)	67.2 ± 33.6 (93)	0.228†
Walking distance	32.3 ± 27.7 (177)	68.1 ± 38.8 (106)	30.4 ± 24.2 (83)	58.6 ± 41.7 (53)	0.156†
Walking speed	31.8 ± 23.5 (177)	54.6 ± 34.6 (106)	29.3 ± 17.1 (82)	47.7 ± 31.6 (52)	0.231†
Stair climbing	42.5 ± 31.3 (175)	67.5 ± 36.4 (106)	40.7 ± 29.0 (83)	56.6 ± 38.3 (52)	0.082†

Values are mean ± SD (n). The number of subjects evaluated at each interval is displayed in the parentheses. *Data collected in phase II only. †p values for 24-month assessments.
6MWT = 6-min walk test; EQ = EuroQOL; other abbreviations as in Table 1.

treatment strategy in patients with life-style-limiting claudication. The IN.PACT SFA trial and previous interventional trials have not been designed to truly prove the benefit of newer endovascular therapies over standard therapies with regard to walking distance and quality of life. Any trial that evaluates walking impairment or quality of life at a prescribed time, while allowing reintervention for target lesion failure in the interval time period (and failing to quantify the decrement in quality of life associated with additional procedures), might be expected to fail to capture the full clinical benefit of a therapy that results in improved vessel patency. In the future, innovative trial designs should address this shortcoming.

Although the DCB was shown to be superior to PTA in this trial, these results may not be generalizable to other DCBs. Each DCB is unique with respect to the paclitaxel dose (varying from 2 to 3.5 μg/mm^2), the excipient molecule, the balloon material, and the balloon and coating technology used. Each of these features can influence the dose of paclitaxel delivered into the vessel wall and the ultimate effectiveness of the DCB for the prevention of neointimal proliferation (31,32). Although the results of the IN.PACT SFA trial and other randomized trials demonstrate superiority of DCB over PTA for short to intermediate-length lesions, the benefit of DCB has not been proven for longer lesions (>18 cm) and more complex lesion subsets, including severely calcified lesions and thrombus-containing lesions. Ongoing, prospective, multicenter registries, including the IN.PACT Global Study, are evaluating the effectiveness of DCB for these challenging lesions.

STUDY LIMITATIONS. As previously reported, the IN.PACT SFA trial was deliberately and prospectively conducted in 2 sequential phases, and the results of phase I were not released until the completion of phase II. When the data were analyzed, there were no statistical differences between the 2 phases. Although the patient, study sponsor, and independent angiographic and ultrasound laboratories were blinded to the treatment received, significant differences in the appearance of the DCB compared with a standard angioplasty balloon prevented blinding of the treating physician. In addition, the physician responsible for clinical follow-up of the research subjects was also not blinded to the treatment received and was aware of the ultrasound and/or angiographic results at the follow-up visits to ensure appropriate clinical decision making. All repeat revascularization procedures in both arms of the trial were reviewed by the blinded CEC as to their appropriateness.

CONCLUSIONS

The 2-year outcomes from this prospective, multicenter, multinational, randomized trial demonstrate durability and continued superiority of the IN.PACT Admiral DCB over PTA. DCB use resulted in significantly higher primary patency and a marked reduction in the need for repeat interventions compared with PTA. These results demonstrate sustained clinical benefit of local delivery of paclitaxel and have the potential to change the treatment paradigm for patients with symptomatic femoropopliteal artery disease.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Endovascular procedures have become an accepted method of revascularization for patients with intermittent claudication that have failed medical therapy and a walking program.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients with complex femoropopliteal lesions should be made aware that restenosis rates following balloon angioplasty are high, and alternative therapies such as DCBs may provide better patency and reduce the need for repeat procedures.

TRANSLATIONAL OUTLOOK 1: The 24-month results from the IN.PACT SFA trial demonstrate a sustained treatment effect from the local delivery of the antiproliferative agent paclitaxel at the time of balloon angioplasty.

TRANSLATIONAL OUTLOOK 2: Although DCBs provide better outcomes than standard balloon angioplasty, randomized comparisons of DCB angioplasty with other treatment modalities such as atherectomy and bare-metal or drug-eluting stents are needed.

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