

ORIGINAL ARTICLE



# Long-Term Clinical Effectiveness of a Drug-Coated Balloon for the Treatment of Femoropopliteal Lesions

## Five-Year Outcomes From the IN.PACT SFA Randomized Trial

See Editorial by Banerjee and Shishehbor

**BACKGROUND:** While randomized trials have demonstrated the superiority of drug-coated balloon (DCB) angioplasty versus standard percutaneous transluminal angioplasty (PTA) in patients with femoropopliteal peripheral artery disease, the long-term durability of DCB angioplasty remains uncertain.

**METHODS AND RESULTS:** IN.PACT SFA is a prospective, multicenter, randomized single-blinded 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 subjects with symptomatic (Rutherford 2–4) femoropopliteal lesions. Subjects were randomly assigned 2:1 to the IN.PACT Admiral DCB or PTA. Assessments through 5 years included freedom from clinically driven target lesion revascularization, the primary safety end point, and major adverse events. Through 5 years, patients treated with the IN.PACT Admiral DCB demonstrated a sustained treatment effect with superior freedom from clinically driven target lesion revascularization when compared with PTA (Kaplan-Meier estimate of 74.5% versus 65.3%; log-rank  $P=0.020$ ). The primary safety composite was achieved in 70.7% of subjects in the DCB and 59.6% in the PTA groups ( $P=0.068$ ). The major adverse event rate was 42.9% for DCB and 48.1% for PTA ( $P=0.459$ ). There were no device- or procedure-related deaths in either group as adjudicated by an independent and blinded Clinical Events Committee.

**CONCLUSIONS:** The IN.PACT SFA randomized trial demonstrates that the IN.PACT Admiral DCB continues to perform better than PTA through 5 years with higher freedom from clinically driven target lesion revascularization. The sustained safety and effectiveness profile of this DCB supports its use as a preferred treatment choice compared with PTA for femoropopliteal lesions.

**VISUAL OVERVIEW:** A [visual overview](#) is available for this article.

**CLINICAL TRIAL REGISTRATION:** URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT01175850 (IN.PACT SFA phase I) and NCT01566461 (IN.PACT SFA phase II).

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**Key Words:** angioplasty ■ drug-coated balloons ■ paclitaxel ■ peripheral artery disease

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### WHAT IS KNOWN

- Compared with percutaneous transluminal angioplasty, treatment with a drug-coated balloon provides superior clinical benefit through early and mid-term follow-up. However, long-term outcomes remain uncertain.

### WHAT THE STUDY ADDS

- Outcomes from this large randomized trial are the first statistically powered 5-year follow-up data after angioplasty with a drug-coated balloon in patients with femoropopliteal atherosclerotic lesions and demonstrate a lower rate of repeat interventions when compared with percutaneous transluminal angioplasty.
- These results provide evidence about the 5-year safety profile of the IN.PACT Admiral drug-coated balloon compared with percutaneous transluminal angioplasty for patients with peripheral artery disease.

**P**aclitaxel-based drug-coated balloons (DCB) have shown promise for the treatment of peripheral artery disease (PAD). Several randomized clinical trials have demonstrated superior performance of paclitaxel-based DCBs compared with standard percutaneous transluminal angioplasty (PTA) for femoropopliteal peripheral artery lesions.<sup>1-6</sup> A large prospective nonrandomized study has also shown DCB angioplasty to be effective for complex femoropopliteal lesions, including long lesions, chronic total occlusions, and in-stent restenosis.<sup>7-10</sup> DCB angioplasty offers the advantage of ease of use, simplicity, and reduction in the need for stenting. There are now 3 DCB platforms approved by the Food and Drug Administration for commercial use in the United States and many more available worldwide.<sup>11</sup> Despite the clinical benefits of DCB angioplasty demonstrated in clinical trials, the long-term safety and effectiveness of paclitaxel-coated balloons are unknown. There are no long-term data available beyond 3 years for any of the commercially available DCBs,<sup>4</sup> and only one small study has reported 5-year outcomes after DCB angioplasty.<sup>12</sup>

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]) evaluated the safety and effectiveness of the IN.PACT Admiral DCB (Medtronic, Dublin, Ireland) compared with standard PTA for the treatment of patients with symptomatic femoropopliteal artery disease. Early and mid-term 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.<sup>1,2,4</sup> In the current report, we describe the final 5-year outcomes from the IN.PACT SFA randomized trial.

### 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 was a prospective, multicenter, multinational, randomized, single-blind trial that was conducted in 2 consecutive phases. Three hundred thirty-one (331) subjects were enrolled between September 2010 and April 2011 (IN.PACT SFA phase I) and between April 2012 and January 2013 (IN.PACT SFA phase II). Eligible subjects were randomized in a 2:1 ratio to treatment with the IN.PACT Admiral DCB (n=220) or PTA (n=111) groups. Details of the IN.PACT SFA trial design and outcomes up to 3 years have been described previously.<sup>1,2,4</sup>

Subjects were followed for a total of 60 months according to the following schedule: 30 days and 6, 12, 24, 36, 48, and 60 months. Subjects underwent duplex ultrasonography or angiographic evaluations at 30 days and 6, 12, 24, and 36 months. Assessments at 48 and 60 months included the occurrence of reintervention, adverse events, and health status. 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.

An independent and blinded Clinical Events Committee (CEC; The Baim Institute for Clinical Research, formerly HCRI, Boston, MA) reviewed and adjudicated all major adverse events through the 60-month follow-up period. The CEC included interventional and noninterventional clinicians with pertinent expertise who were not participants in the trial and did not have conflicts of interest. Oversight of clinical sites was provided by an independent data safety monitoring board.

#### End Points and Definitions

Assessment through 60 months included freedom from CD-TLR, defined as reintervention at the target lesion due to symptoms or a decrease in the ankle-brachial index by  $\geq 20\%$  or  $>0.15$  when compared with post-procedure baseline ankle-brachial index or toe-brachial index, which was allowed in cases of incompressible vessels in the IN.PACT SFA phase II. The composite safety end point was defined as 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 60 months. The rate of major adverse events (a composite of death from any cause, CD-TVR, target limb major amputation, and thrombosis) was evaluated through 60 months. Additional end points included the rate of each individual component of the major adverse event composite. Primary patency, defined as freedom from CD-TLR and freedom from restenosis (duplex ultrasonography peak systolic velocity ratio  $\leq 2.4$ ), was analyzed through 36 months per study protocol.

## Statistics

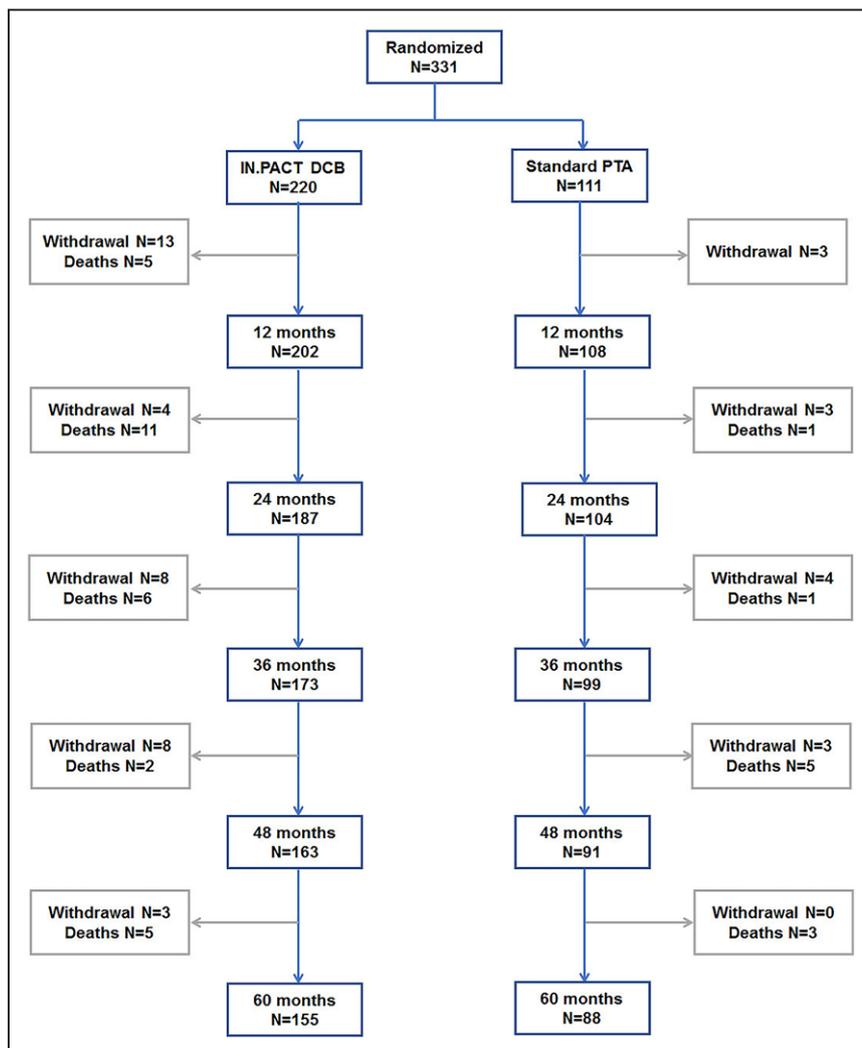
Analyses were based on the intent-to-treat principle. Baseline demographics and clinical characteristics were summarized on a per subject basis; lesion characteristics were summarized on a per lesion basis. For baseline characteristics, continuous variables were described as mean±SD and were compared 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 freedom from CD-TLR and freedom from all-cause death through the 60-month follow-up period. The difference in the survival curves between treatment groups was assessed using the log-rank test. For other outcomes, proportion rates were reported, and the Fisher exact test was used to compare between treatment groups for binary outcomes, and the Wilcoxon rank-sum test or Student *t* test was used for continuous outcomes.

To demonstrate the treatment effects within several selected clinical element subgroups, a forest plot of freedom from CD-TLR through 60 months was prepared.

Statistical analyses were performed using SAS (SAS Institute, NC) version 9.4. The level of statistical significance was set at  $P<0.05$ .

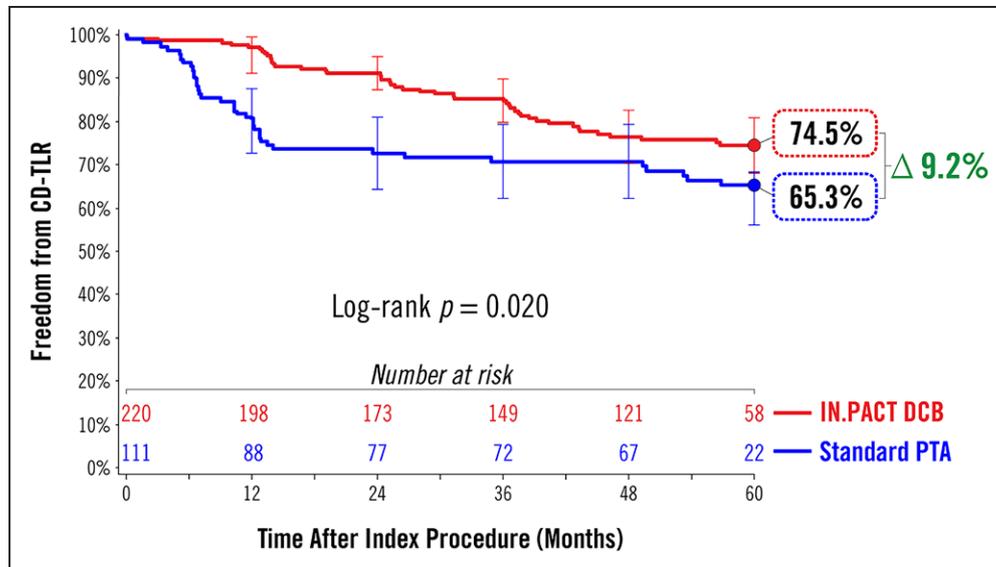
## RESULTS

In the IN.PACT SFA trial, 331 subjects were randomized to either DCB ( $n=220$ ) or PTA ( $n=111$ ). At 60 months follow-up, 155 subjects in the DCB arm and 88 subjects in the PTA arm were eligible for evaluation (Figure 1). The 60-month follow-up compliance rates were 94.8% (147/155) for the DCB group and 96.6% (85/88) for the PTA group. As reported previously,<sup>4</sup> demographic, clinical, and lesion characteristics were well matched between treatment groups at baseline (Table I in the [Data Supplement](#)). The mean age of subjects in the DCB and PTA groups were  $67.5\pm 9.5$  and  $68.0\pm 9.2$  years ( $P=0.612$ ), respectively. The mean lesion length was  $8.9\pm 4.9$  cm in the DCB and  $8.8\pm 5.1$  cm in the PTA groups ( $P=0.815$ ). Total occlusions were treated in 25.8% and 19.5% ( $P=0.222$ ) of subjects in the DCB and PTA arms, respectively (Table I in the [Data Supplement](#)).



**Figure 1. Subject flow chart in the IN.PACT SFA trial through 60 mo.**

Three hundred thirty-one subjects were randomized 2:1 into groups that received angioplasty with a paclitaxel drug-coated balloon (DCB) or a standard percutaneous transluminal angioplasty (PTA). Subjects were followed for 5 y. IN.PACT SFA indicates 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).



**Figure 2. Treatment effect of a drug-coated balloon (DCB) in femoropopliteal lesions at 60 mo.**

Freedom from clinically driven target lesion revascularization (CD-TLR) by Kaplan-Meier estimate was significantly higher in the DCB group than in the percutaneous transluminal angioplasty (PTA) group (74.5% vs 65.3%; log-rank  $P=0.020$ ) at 60 mo. Bars represent 95% CI. All target lesion revascularization events were adjudicated by the independent and blinded Clinical Events Committee.

## Effectiveness Outcomes Through 60 Months

The Kaplan-Meier estimate of freedom from CD-TLR was significantly higher with DCB than PTA (74.5%

versus 65.3%; log-rank  $P=0.020$ ) through 60 months (Figure 2). The proportion rates of CD-TLR observed at 60 months were 25.5% and 35.6% in the DCB and PTA arms, respectively ( $P=0.080$ , Table 1). Kaplan-Meier estimates of CD-TLR through 60 months were 25.5%

**Table 1. Safety and Effectiveness Results at 60 Months**

End Points at 60 mo	DCB (N=220 Subjects)	PTA (N=111 Subjects)	Difference [95% CI]	P Value*
Safety parameters				
Primary safety composite end point†–freedom from:	70.7% (130/184)	59.6% (62/104)	11.0% [−0.5%, 22.5%]	0.068
Device- and procedure-related death through 30 d	0.0% (0/219)	0.0% (0/111)	NA	NA
Target limb major amputation within 1800 d	0.5% (1/184)	0.0% (0/104)	0.5% [−0.5%, 1.6%]	1.000
CD-TVR‡ within 1800 d	29.3% (54/184)	40.4% (42/104)	−11.0% [−22.5%, 0.5%]	0.068
Death (all-cause) within 30 d	0.0% (0/219)	0.0% (0/111)	NA	NA
Safety events within 60 mo				
MAE composite§	42.9% (79/184)	48.1% (50/104)	−5.1% [−17.1%, 6.8%]	0.459
Death (all-cause)	15.8% (29/184)	9.6% (10/104)	6.1% [−1.6%, 13.9%]	0.156
CD-TVR	29.3% (54/184)	40.4% (42/104)	−11.0% [−22.5%, 0.5%]	0.068
Major target limb amputation	0.5% (1/184)	0.0% (0/104)	0.5% [−0.5%, 1.6%]	1.000
Thrombosis	2.2% (4/184)	4.8% (5/104)	−2.6% [−7.3%, 2.0%]	0.292
Secondary effectiveness end points within 60 mo				
CD-TLRI	25.5% (47/184)	35.6% (37/104)	−10.0% [−21.2%, 1.1%]	0.080
Any TVR	29.9% (55/184)	40.4% (42/104)	−10.5% [−22.0%, 1.0%]	0.091
Any TLR¶	26.6% (49/184)	37.5% (39/104)	−10.9% [−22.2%, 0.4%]	0.063

Values are mean±SD or % (n/N). CD-TLR indicates clinically driven target lesion revascularization; CD-TVR, clinically driven target vessel revascularization; DCB, drug-coated balloon; MAE, major adverse events; NA, not applicable; PTA, percutaneous transluminal angioplasty; TLR, target lesion revascularization; and TVR, target vessel revascularization.

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

†Defined as freedom from device- and procedure-related death through 30 d and freedom from target limb major amputation and CD-TVR through 60 mo.

‡Defined as any reintervention within the target vessel due to symptoms or drop of ankle-brachial index  $\geq 20\%$  or  $>0.15$  when compared with post-procedure baseline ankle-brachial index/toe-brachial index.

§A composite of death from any cause, CD-TVR, target limb major amputation, and thrombosis.

¶Defined as any reintervention at the target lesion due to symptoms or drop of ankle-brachial index of  $\geq 20\%$  or  $>0.15$  when compared with post-procedure baseline ankle-brachial index/toe-brachial index.

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

**Table 2. Safety and Effectiveness Results Through 60 Months by Kaplan-Meier Estimate**

End Points Through 60 mo by K-M	DCB (N=220 Subjects)	PTA (N=111 Subjects)	K-M Rate Difference	Log-Rank P Value
Safety parameters				
Primary safety composite end point*—freedom from:	70.9% (54)	60.5% (42)	10.5%	0.012
Device- and procedure- related death through 30 days	0.0% (0)	0.0% (0)	...	...
Major target limb amputation	0.6% (1)	0.0% (0)	0.6%	0.452
CD-TVR†	29.1% (54)	39.5% (42)	−10.5%	0.012
Safety events within 60 mo				
MAE composite‡	39.8% (79)	46.7% (50)	−6.9%	0.090
Death (all-cause)	14.6% (29)	10.2% (10)	4.5%	0.201
CD-TVR†	29.1% (54)	39.5% (42)	−10.5%	0.012
Major target limb amputation	0.6% (1)	0.0% (0)	0.6%	0.452
Thrombosis	1.9% (4)	4.6% (5)	−2.7%	0.176
CD-TLR§	25.5% (47)	34.7% (37)	−9.2%	0.020
Any TVR	29.5% (55)	39.4% (42)	−9.8%	0.014
Any TLR	26.6% (49)	36.5% (39)	−10.0%	0.012

CD-TLR indicates clinically driven target lesion revascularization; CD-TVR, clinically driven target vessel revascularization; DCB, drug-coated balloon; K-M, Kaplan-Meier; MAE, major adverse events; PTA, percutaneous transluminal angioplasty; TLR, target lesion revascularization; and TVR, target vessel revascularization

\*Defined as freedom from device- and procedure-related death through 30 days and freedom from target limb major amputation and CD-TVR through 60 mo.

†Defined as any reintervention within the target vessel due to symptoms or drop of ankle-brachial index  $\geq 20\%$  or  $>0.15$  when compared with post-procedure baseline ankle-brachial index/toe-brachial index.

‡A composite of death from any cause, CD-TVR, target limb major amputation, and thrombosis.

§Defined as any reintervention at the target lesion due to symptoms or drop of ankle-brachial index of  $\geq 20\%$  or  $>0.15$  when compared with post-procedure baseline ankle-brachial index/toe-brachial index.

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

and 34.7% for the DCB and PTA arms, respectively (log-rank  $P=0.020$ , Table 2)

A post hoc analysis was performed to compare freedom from CD-TLR through 60 months in subgroups defined by the baseline demographic or clinical characteristics (Figure 3). In the nondiabetic subgroup, Kaplan-Meier estimates of freedom from CD-TLR through 60 months were 77.1% for DCB and 66.3% for PTA (log-rank  $P=0.046$ ), respectively (Figure 3A). In the diabetic subgroup, the Kaplan-Meier estimate of freedom from CD-TLR through 60 months was 70.3% in DCB versus 64.4% in PTA (log-rank  $P=0.243$ ; Figure 3B).

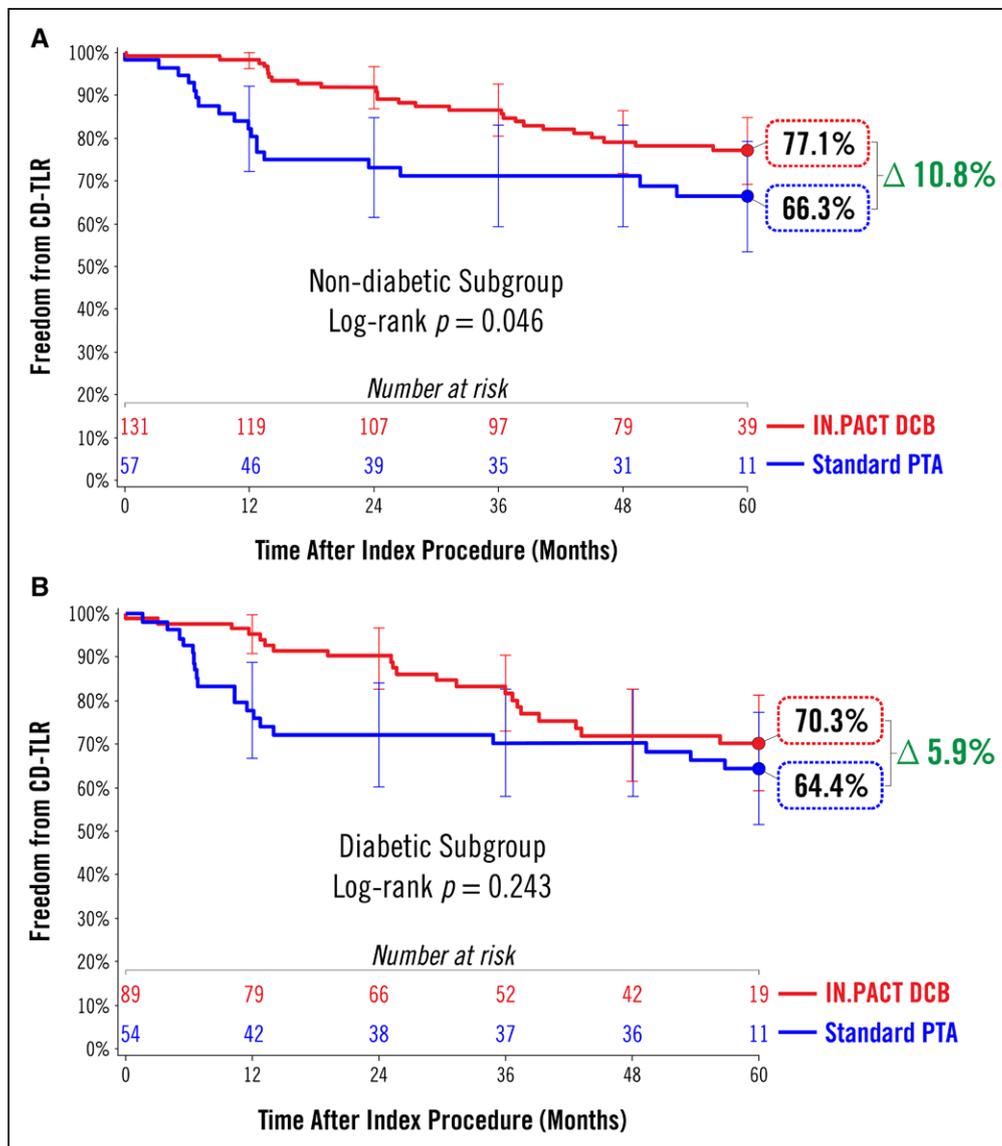
Post hoc analyses of other subgroup categories are presented in a forest plot (Figure 4). Through 60 months, freedom from CD-TLR favored DCB treatment over PTA across numerous clinical and anatomic subgroups, including Rutherford category 4, patient age  $\geq 75$ , female sex, lesion length  $\geq 10$  cm, and total occlusions.

## Safety Outcomes Through 60 Months

Safety outcomes through 60 months are reported in Tables 1 and 2. The primary safety composite end point within 60 months was achieved in 70.7% (130/184) of subjects in the DCB group and 59.6% (62/104) of subjects in the PTA group ( $P=0.068$ ). The all-cause mortality rate was 13.5% (39/288) for all subjects and was not

significantly different between the DCB arm and the PTA arm (15.8% versus 9.6%;  $P=0.156$ , Table 1). These rates were consistent with the Kaplan-Meier estimates of freedom from all-cause death in the DCB and PTA arms (Table 2 and Figure I in the [Data Supplement](#)). There was no procedure- or device-related death in this study as adjudicated by the CEC (Table 3). Additional analyses were performed to examine the effect of paclitaxel dose on survival. The results demonstrated that there was no correlation between mean paclitaxel dose and mortality rate (Figures II and III in the [Data Supplement](#)). Causes of deaths included cardiac-, malignancy-, neurological-, respiratory-, hepatobiliary-, renal-, infection-, or gastrointestinal-related events, and other/unknown (Table 3).

Major adverse events composite rates were 42.9% (79/184) in the DCB group and 48.1% (50/104) in the PTA ( $P=0.459$ , Table 1). Vessel thrombosis occurred in 2.2% (4/184) of the patients with DCB and 4.8% (5/104) in the patients with PTA ( $P=0.292$ , Table 1). These findings were consistent with Kaplan-Meier estimates (Table 2). One major target limb amputation was reported in the entire IN.PACT SFA trial. A 79-year-old male patient in the DCB group underwent an above-the-knee amputation of the treated limb 3.5 years after DCB for popliteal artery occlusion. He was noted to have restenosis at the popliteal artery site as well as severe lesions in the common femoral artery and SFA. He underwent successful



**Figure 3.** Subgroup analysis of freedom from clinically driven target lesion revascularization (CD-TLR) by Kaplan-Meier estimate at 60 mo.

**A.** Freedom from CD-TLR was significantly higher in the drug-coated balloon (DCB) group than percutaneous transluminal angioplasty (PTA; 77.1% vs 66.3%;  $P=0.046$ ) in the nondiabetic subgroup. **B.** Freedom from CD-TLR was numerically higher in the DCB group than PTA but not statistically significant (70.3% vs 64.4%;  $P=0.243$ ) in the diabetic subgroup. Bars represent 95% CI. All target lesion revascularization events were adjudicated by the independent and blinded Clinical Events Committee.

balloon angioplasty of all lesions but developed progressive gangrenous necrosis leading to amputation.

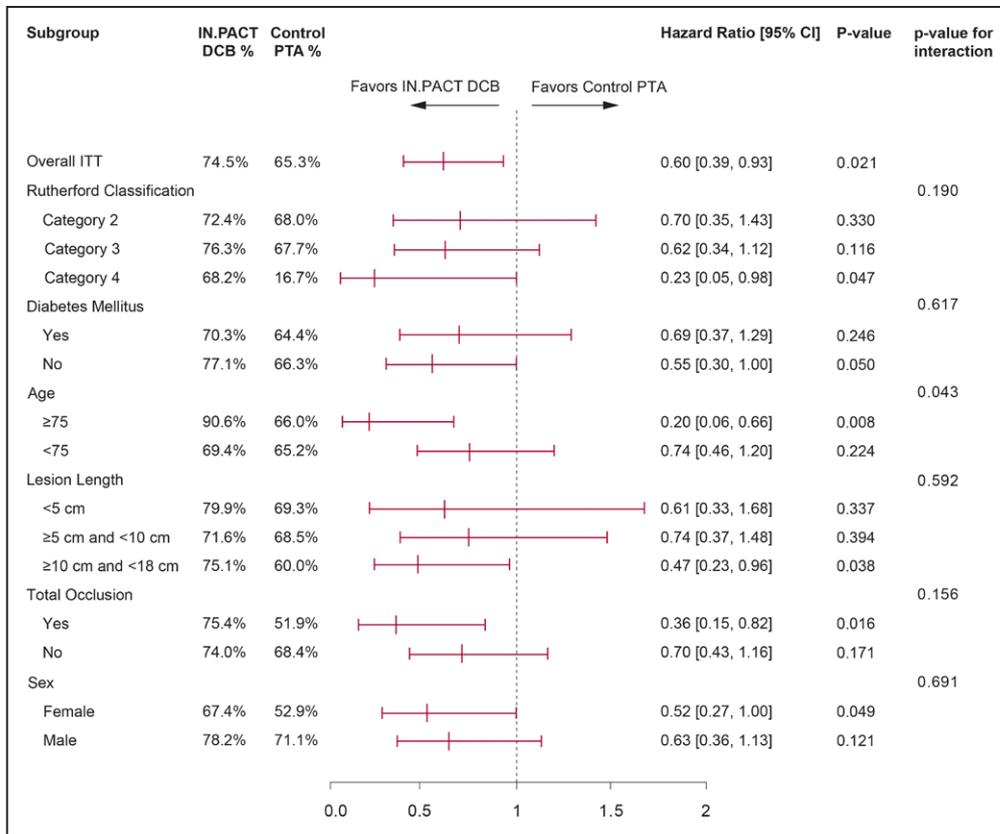
A summary of the safety and effectiveness outcomes through 5 years in the IN.PACT SFA trial<sup>1,2,4,13</sup> is reported in Table 4.

## DISCUSSION

In this final report from the IN.PACT SFA randomized trial, a paclitaxel-coated DCB was shown to provide superior outcomes compared with PTA through 5 years in subjects with symptomatic femoropopliteal artery disease. Five-year freedom from CD-TLR was superior following DCB, though the incremental benefit of DCB over PTA has narrowed over time. These results support the hypothesis

that short-term exposure to paclitaxel, an antiproliferative drug indicated to inhibit neointimal hyperplasia, provides long-term benefit with regard to avoidance of target lesion revascularization that persists for up to 5 years.

In recent years, there has been tremendous innovation in endovascular therapies for lower extremity PAD, and a wide variety of approaches have been used, including bare-metal stents (BMS), covered stents, atherectomy, drug-eluting stents (DES), and DCB.<sup>14,15</sup> Despite this proliferation of endovascular therapies for PAD, there are limited comparative data regarding these devices and only a few randomized studies have reported long-term (5 years) results.<sup>12,16–18</sup> There are inherent difficulties in comparing outcomes across device trials, given the differences in study end points,



**Figure 4. Post hoc analysis of freedom from clinically driven target lesion revascularization (CD-TLR) at 60 mo.**

Forest plot shows CD-TLR based on Kaplan-Meier estimate in key subgroups at 60 mo. Subjects with Rutherford category 4, nondiabetic, age greater than 75 y, longer lesion length (≥10 cm and ≤18 cm), total occlusion and female sex favored drug-coated balloon (DCB), while both DCB and percutaneous transluminal angioplasty (PTA) performed nonsignificantly in remaining subgroups. P value of hazard ratio between DCB and PTA was calculated using Cox Proportion Hazards model for each subgroup. Treatment-by-subgroup interactions were tested using a Cox proportional hazards model containing the main effects of treatment (IN.PACT DCB and Control PTA), subgroup and the treatment-by-subgroup interaction. ITT indicates intent-to-treat.

definitions, vascular territories included, patient demographics, and lesion characteristics. Nonetheless, outcomes found in the DCB group of femoropopliteal trials are superior to those reported for PTA and other endovascular interventions in the same vascular bed, and DCB have a Class 1 recommendation per the newly

released SCAI Guidelines (The Society for Cardiovascular Angiography and Interventions).<sup>14,15,19,20</sup> In the literature, only 2 contemporary endovascular device studies evaluating drug-eluting platforms for the treatment of femoropopliteal artery disease (THUNDER trial [Local Taxane With Short Exposure for Reduction of Restenosis in Distal

**Table 3. Causes of Death Through 60 Months**

Causes of Death	DCB (N=184)	PTA (N=104)	CEC-Adjudicated*	
			Device-Related	Procedure-Related
Cardiac-related	3.26% (6)	0.96% (1)	No	No
Malignancy-related	2.72% (5)	3.85% (4)	No	No
Respiratory-related	1.63% (3)	0.00% (0)	No	No
Neurological-related	2.17% (4)	0.00% (0)	No	No
Hepatobiliary-related	0.54% (1)	0.00% (0)	No	No
Gastrointestinal-related	1.63% (3)	1.92% (2)	No	No
Renal-related	0.54% (1)	0.00% (0)	No	No
Infection-related	1.08% (2)	0.00% (0)	No	No
Other	0.54% (1)	1.92% (2)	No	No
Unknown	1.63% (3)	0.96% (1)	No	No

CEC indicates Clinical Events Committee; DCB, drug-coated balloon; and PTA, percutaneous transluminal angioplasty. \*CEC adjudications through 12 mo included drug relatedness which there were none.

**Table 4. Final Report—IN.PACT SFA Trial Through 60 Months**

	12 mo*			24 mo†			36 mo‡			48 mo			60 mo		
	DCB	PTA	P Value	DCB	PTA	P Value	DCB	PTA	P Value	DCB	PTA	P Value	DCB	PTA	P Value
Primary patency§	87.5%	55.8%	<0.001	79.0%	50.1%	<0.001	69.5%	45.1%	<0.001	Not assessed			Not assessed		
Freedom from CD-TLR§	97.5%	79.3%	<0.001	91.0%	72.2%	<0.001	84.5%	70.4%	<0.001	76.8%	70.4%	0.040	74.5%	65.3%	0.020
CD-TLR	2.4%	20.6%	<0.001	9.1%	28.3%	<0.001	15.2%	31.1%	0.002	23.4%	31.1%	0.164	25.5%	35.6%	0.080
Target limb major amputation	0.0%	0.0%	>0.999	0.0%	0.0%	>0.999	0.0%	0.0%	N/A	0.0%	0.0%	>0.999	0.5%	0.0%	1.000
Thrombosis	1.4%	3.7%	0.100	1.5%	3.8%	0.243	2.0%	4.9%	0.283	2.2%	4.9%	0.290	2.2%	4.8%	0.292
All-cause death	1.9%	0.0%	0.930	8.1%	0.9%	0.008	10.7%	1.9%	0.006	13.0%	6.8%	0.116	15.8%	9.6%	0.156

CD-TLR indicates clinically driven target lesion revascularization; DCB, drug-coated balloon; and PTA, percutaneous transluminal angioplasty.

\*All data from Tepe et al 2015<sup>2</sup> unless specified.

†All data from Laird et al 2015<sup>1</sup> unless specified.

‡All data from Schneider et al 2018.<sup>4</sup>

§Kaplan-Meier estimate.

||IN.PACT Admiral instructions for use.<sup>13</sup>

Arteries] and Zilver PTX Randomized trial [Evaluation of the Zilver PTX Drug-Eluting Stent in the Above-the-Knee Femoropopliteal Artery]) have reported target lesion revascularization (TLR)/freedom from TLR through 5 years.<sup>12,16</sup> The 5-year freedom from TLR rate was 79% for a DCB in the THUNDER trial,<sup>12</sup> compared with a freedom from CD-TLR rate of 74.5% for the DCB arm in the present study. In the Zilver PTX Randomized trial, the 5-year freedom from TLR was 83.1% for the Zilver PTX DES.<sup>16</sup> It should be noted that the mean lesion length in the DCB arm of IN.PACT SFA was 8.9 cm compared with 6.6 cm in the Zilver PTX Randomized trial and 7.4 cm for the DCB arm in THUNDER trial. The slightly higher 5-year freedom from TLR seen with Zilver PTX comes at the cost of a permanent metallic implant and the risk of problematic in-stent restenosis.<sup>21,22</sup>

Throughout the 5-year follow-up period, all major adverse events, including TLR and TVR, were adjudicated by an independent and blinded CEC in the IN.PACT SFA trial. The results demonstrated a durable safety profile for DCB with low thrombosis rates and only one amputation through 5 years in this PAD population. There was a trend towards a higher number of patients achieving the primary safety composite end point in the DCB arm as compared with PTA. While at 2 and 3 years follow-up there was a significantly higher mortality observed in the DCB arm,<sup>1,4</sup> this was no longer statistically significant at 4 and 5 years albeit a numerically higher rate in the DCB group. Causes of death were varied, age-appropriate for this treatment population, and adjudicated by the CEC to not be related to the study device and procedure. A recent summary-level meta-analysis reported an association between paclitaxel devices (DCB and DES) and mortality<sup>23</sup>; however, 5 more-recent meta-analyses (3 of which include patient-level data) have contradicted these findings.<sup>24–28</sup> The supplemental paclitaxel dose analysis results concurred with the latter 5 meta-analyses. There was no

correlation between the paclitaxel dose effect on survival status analysis (Figure II in the [Data Supplement](#)) or mortality rate across trials with varying mean paclitaxel dosing (Figure III in the [Data Supplement](#)).

A post hoc analysis was performed evaluating outcomes in important subgroups (Figure 4). Results in challenging lesions (longer lesions and total occlusion), advanced PAD (Rutherford category 4) or high-risk patients (age older than 75 years) favored DCB over PTA. Of particular interest is the apparent independent relationship between lesion length and CD-TLR through 5 years in subjects treated with DCB, though the small number of subjects means this deserves further study. Recent data from prospective as well as retrospective registries/studies also demonstrated that DCB angioplasty provides consistent clinical benefit in cohorts of long lesions,<sup>7,29</sup> in-stent restenosis,<sup>8</sup> and other complex lesions.<sup>9,30,31</sup> Although only short-term outcomes (1 and 2 years) are available for these registries/studies; these results provide additional evidence that DCB is a viable treatment option for complex lesion/patient cohorts. Previously, we reported a superior treatment effect of DCB in patients with diabetes mellitus as compared with PTA.<sup>1</sup> Although freedom from CD-TLR was numerically higher in diabetic patients treated with DCB, there was no statistically significant difference between these 2 treatment groups at 5 years.

In the current study, women treated with DCB had a better outcome as compared with women treated with PTA. A similar result was also observed in the THUNDER trial at 5 years.<sup>12</sup> These encouraging findings highlight the promise of DCB for improving outcomes in women with symptomatic femoropopliteal disease, although further study is required.

## Limitations

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. Subjects were randomized in a 2:1 ratio to the DCB or PTA group resulting in fewer patients in the PTA arm. Another limitation of this study is that core lab-adjudicated duplex ultrasonography assessments were not performed at 4 and 5 years, hence patency rates were reported through 3 years only. The present study was not powered to resolve statistically any differences in mortality between the 2 treatment arms. Finally, the results of this trial were restricted to certain patient populations that would fit the enrollment criteria and cannot be generalized to all patients with femoropopliteal artery disease.

## Conclusions

The IN.PACT SFA randomized trial demonstrates that the IN.PACT Admiral DCB continues to perform better than PTA through 5 years with higher freedom from CD-TLR. The sustained safety and effectiveness profile of this DCB supports its use as a preferred treatment choice compared with PTA for femoropopliteal lesions.

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## Disclosures

Dr Laird is a consultant and advisory board member for Abbott Vascular, Bard, Boston Scientific, and Medtronic. Dr Schneider is consultant and advisory board member to Medtronic. Dr Jaff is a noncompensated advisor for Abbott Vascular and Boston Scientific; advisor for Biotronik, Medtronic, Philips, Vactronix, and Vascular Therapies. Dr Brodmann has received speaking honoraria from Bard Peripheral Vascular, Biotronik, Medtronic, Spectranetics, and VIVA Physicians and is a consultant for Bard Peripheral Vascular, Biotronik, Medtronic, and

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