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IN.PACT SFA Trial: Overview of Study Design and 2-Year Clinical Outcomes

Sustained durability of IN.PACT™ Admiral™ DCB treatment effect with no late catch-up through 2 years.

BY PETER A. SCHNEIDER, MD

The IN.PACT SFA Trial is a level 1 clinical evidence trial evaluating the safety and effectiveness of the IN.PACT™ Admiral™ drug-coated balloon (DCB; Medtronic, Inc.) versus standard percutaneous transluminal angioplasty (PTA) for the treatment of superficial femoral artery (SFA) and proximal popliteal artery lesions. The IN.PACT SFA Trial was designed with utmost attention to clinical rigor, including external adjudication of major adverse events by an independent clinical events committee and interpretation of target lesion restenosis by independent angiographic and duplex ultrasound (DUS) core laboratories, as well as external monitoring (Table 1). The 2-year data from the IN.PACT SFA Trial were recently presented at the Transcatheter Cardiovascular Therapeutics (TCT) conference in October 2015 and simultaneously published in the *Journal of the American College of Cardiology*.[1]

The primary efficacy endpoint for IN.PACT SFA was primary patency, defined as freedom from clinically driven target lesion revascularization (CD-TLR) and DUS-derived restenosis (peak systolic velocity ratio [PSVR] ≤ 2.4) at 12 months and reported again at 24 months. The primary safety endpoint was a composite of freedom from device- and procedure-related mortality at 30 days and freedom from major target limb amputation and clinically driven target vessel revascularization (CD-TVR) at 12 months and reported again at 24 months. Select baseline, lesion, and procedural characteristics of the patients enrolled in the IN.PACT SFA Trial are shown in Table 2.

TABLE 1. IN.PACT SFA TRIAL DESIGN

Study type	Randomized, controlled, pivotal trial
Primary endpoints	Efficacy: Primary patency* Safety: Safety composite†
Rigor and quality	Prospective, multicenter Blinded independent clinical events committee Blinded independent core lab adjudication External monitoring
No. of patients	331 (220 DCB arm; 111 PTA arm)
No. of sites and location	57 (US + EU)
Key eligibility criteria	Single lesions ≤ 18 cm, CTO ≤ 10 cm TASC A–C SFA + proximal popliteal No ISR, Ca++

Abbreviations: ABI, ankle-brachial index; CTO, chronic total occlusion; ISR, in-stent restenosis; TBI, tibial-brachial index.
*Freedom from CD-TLR‡ and DUS-derived restenosis (PSVR ≤ 2.4) at 12 months.
†Freedom from device- and procedure-related death through 30 days and freedom from major target limb amputation and CD-TVR through 12 months.
‡Defined as reintervention at target lesion due to symptoms or drop of ABI/TBI of ≥ 20% or > 0.15 when compared to postprocedure baseline ABI/TBI.

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TABLE 2. IN.PACT SFA TRIAL PATIENT AND PROCEDURAL CHARACTERISTICS			
Patient and procedural characteristics	**DCB arm (n = 220)**	**PTA arm (n = 111)**	***P*-value**
Male gender	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
Current smoker	38.6% (85/220)	36.0% (40/111)	0.719
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% (18/221)	6.2% (7/113)	0.662
Provisional stenting	7.3% (16/220)	12.6% (14/111)	0.110

PATIENT POPULATION

The baseline clinical characteristics of patients enrolled in the IN.PACT SFA Trial are comparable to those of other SFA pivotal trials with a few notable exceptions. The mean lesion length of 8.9 cm is relatively long in the landscape of pivotal SFA populations, and the low provisional stenting rate of 7.3% may have been achieved through the procedural protocol of predilatation with a standard PTA balloon prior to a nominal pressure, 3-minute inflation with the DCB.

TWO-YEAR OUTCOMES FROM IN.PACT SFA

Figure 1 shows a Kaplan-Meier analysis of primary patency in the DCB and PTA arms of the IN.PACT SFA Trial. At 24 months, 78.9% of patients in the DCB group achieved primary patency compared to 50.1% who underwent standard PTA ($P < 0.001$).

Figure 2 shows a Kaplan-Meier analysis of freedom from CD-TLR in the DCB and PTA arms of the IN.PACT SFA Trial. At 24 months, 91.0% of patients in the DCB group were free of CD-TLR compared to only 72.2% in the PTA group.

Table 3 compares safety and additional efficacy outcomes at 24 months in the two arms of the IN.PACT SFA Trial. Data indicate significant improvement in most outcomes for the DCB arm as compared with the PTA arm. The results of DCB use in IN.PACT SFA are remarkably good, despite the fact that lesions were longer (mean lesion length, 8.9 cm) in this trial than in previous randomized DCB trials. One of the most striking findings from IN.PACT SFA at 24 months was the remarkably low CD-TLR rate (9.1%), which is lower than rates reported in previous SFA device trials at the

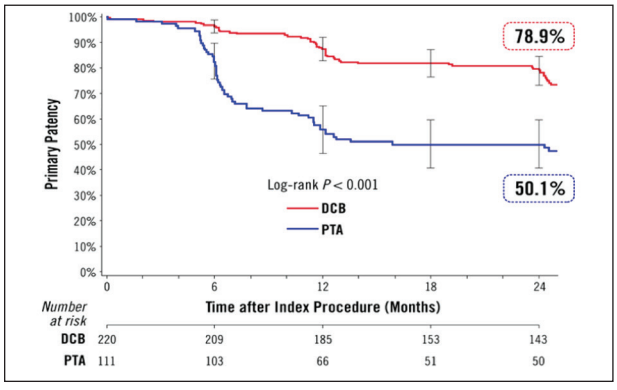

Figure 1. Kaplan-Meier analysis of primary patency in the DCB and PTA arms of the IN.PACT SFA Trial. Number at risk represents the number of evaluable subjects at the beginning of the 30-day window prior to each follow-up interval.

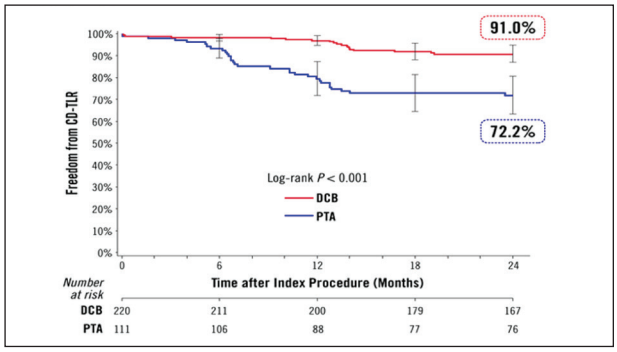

Figure 2. Kaplan-Meier analysis of freedom from CD-TLR in the DCB and PTA arms of the IN.PACT SFA Trial. Number at risk represents the number of evaluable subjects at the beginning of the 30-day window prior to each follow-up interval.

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DCBs: Cost-Effective Option for Treating Atherosclerosis in the SFA

IN.PACT SFA cost-effectiveness substudy finds the IN.PACT Admiral DCB is economically dominant compared to PTA.

Cost considerations are increasingly important when evaluating new endovascular treatment strategies. As a result, cost-effectiveness analyses are more commonly performed in parallel with clinical safety and efficacy studies to provide health care decision makers with further insight into the economic effectiveness of new technologies.

Recently, the positive results from the IN.PACT SFA cost-effectiveness substudy were presented at VIVA 2015.[1] This prospectively designed analysis evaluated costs and quality-adjusted life-years (QALYs) over 24 months of follow-up between the drug-coated balloon (DCB) and percutaneous transluminal angioplasty (PTA) arms in the US cohort of the pivotal study and found that the IN.PACT™ Admiral™ DCB (Medtronic, Inc.) is an "economically dominant"[2] (ie, highly cost-effective per QALY) strategy for the treatment of superficial femoral artery (SFA) disease compared to PTA.

Although the initial procedural cost is higher for patients treated with a DCB versus PTA, the data analysis demonstrated that the postdischarge costs (ie, additional physician fees, medications, and hospitalizations) were higher for PTA within the 2-year study period as compared with IN.PACT Admiral DCB, eliminating the early cost advantage of PTA (Figure 1). Results of this analysis confirm earlier models, which used published literature reviews to predict that DCBs would have the lowest 2-year total cost compared to various treatment strategies for the SFA, largely due to the significant difference in target lesion revascularization rates over 2 years of follow-up (Figure 2).[3]

IN.PACT Admiral DCB is a proven primary therapy for SFA disease; the latest durable safety, efficacy, and cost-effectiveness results will continue to drive a paradigm shift in SFA interventions. ■

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2. Cohen DJ, Reynolds MR. Interpreting the results of cost-effectiveness studies. J Am Coll Cardiol. 2008;52:2119-2126.
3. Pietzsch JB, Geisler BP, Garner AM, et al. Economic analysis of endovascular interventions for femoropopliteal arterial disease: a systematic review and budget impact model for the United States and Germany. Catheter Cardiovasc Interv. 2014;84:546-554.

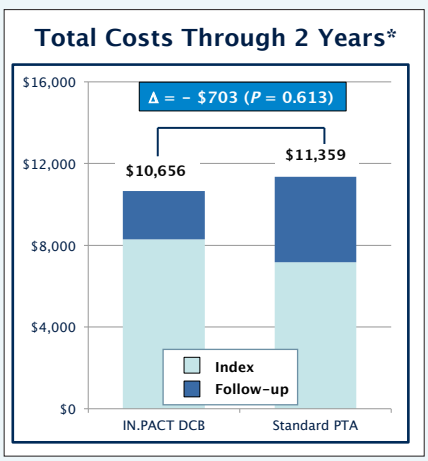

Figure 1. Analysis from the IN.PACT SFA economic substudy showed that postdischarge costs were higher for PTA as compared with IN.PACT Admiral DCB with the 2-year study period. *Winsorized—Costs for one extreme outlier reduced to next highest value.

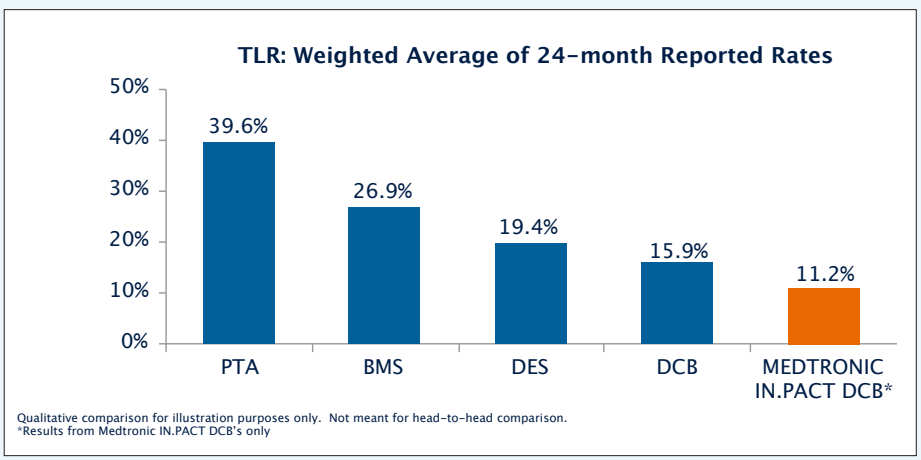

Figure 2. Two-year total cost of DCBs compared to various treatment strategies for the SFA.

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TABLE 3. IN.PACT SFA TRIAL 24-MONTH EFFICACY AND SAFETY OUTCOMES

Patient and procedural outcome	DCB arm (n = 220)	PTA arm (n = 111)	*P*-value
CD-TLR*	9.1% (18/198)	28.3% (30/106)	< 0.001
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
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
Device- or procedure-related mortality	0% (0/198)	0% (0/106)	> 0.999
All-cause mortality\\	8.1% (16/198)	0.9% (1/106)	0.008
CD-TVR**	12.6% (25/198)	30.2% (32/106)	< 0.001
Major target limb amputation	0% (0/198)	0% (0/106)	> 0.999
Thrombosis	1.5% (3/198)	3.8% (4/106)	0.243

Abbreviations: ABI, ankle-brachial index; TBI, tibial-brachial index; TVR, target vessel revascularization.
*Defined as reintervention at target lesion due to symptoms or drop of ABI/TBI of ≥ 20% or > 0.15 when compared to postprocedure baseline ABI/TBI.
†Freedom from target limb amputation, TVR, and increase in Rutherford class.
‡TBI allowed in cases of incompressible vessels in IN.PACT SFA II phase.
§Composite 30-day freedom from device- and procedure-related mortality and 12-month freedom from major target limb amputation and CD-TVR.
¶Composite of death, CD-TVR, major target limb 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.
**Defined as reintervention in target vessel due to symptoms or drop of ABI/TBI of ≥ 20% or > 0.15 when compared to postprocedure baseline ABI/TBI.

TABLE 4. IN.PACT SFA TRIAL 24-MONTH PRIMARY PATENCY SUBGROUP OUTCOMES

Subgroup (N [DCB], [PTA])	DCB arm	PTA arm	*P*-value
Diabetic (89, 54)	73.3%	45.8%	< 0.001
Nondiabetic (131, 57)	82.5%	54.5%	< 0.001
Female (77, 36)	76.7%	42.3%	< 0.001
Male (143, 75)	80.2%	53.7%	< 0.001

same time point. Although there were no device- or procedure-related deaths in either arm of the trial, the rate of all-cause mortality in the DCB group was higher than that in the PTA group (8.1% vs 0.9%; $P = 0.008$). The 0.9% all-cause mortality rate in the PTA group was anomalously low for this population, and the median post–index days to death was 564.5 days in the DCB arm and 397.0 days in the PTA arm, confirming that deaths were not related to the device or procedure. The clinical events committee adjudicated all deaths and also confirmed that none of the deaths were device- or procedure-related.

In a subgroup analysis, 2-year results also showed clinical superiority and consistency across various patient types that have been proven difficult to treat based on historical data, including patients with diabetes and the female population. The 24-month primary patency rates for gender and diabetic subgroups are shown in Table 4.

COMMENTARY

The key takeaway on the 2-year data from the IN.PACT SFA Trial is the lack of catch-up effect on both primary patency and CD-TLR. If anything, the

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groups may have diverged just a little, and this goes a long way toward alleviating concern about the efficacy of this "minimal implant" approach to SFA disease. The absolute difference in primary patency between DCB and PTA at 2 years was 28.8% (78.9% vs 50.1%). By all measures, PTA was well conducted, rigorous, and performed as prescribed, and the results in the PTA group were in line with the best that PTA has to offer. Despite this, the advantage in the DCB arm remained significant and did not decrease. With respect to CD-TLR, the difference between the groups was 18.2% at 1 year (2.4% vs 20.6%). There was some concern that there may have been bias in the DCB group, with some resistance to reintervention until after the all-important 1-year endpoint. There was no rush to reintervention in the DCB group, and at 2 years, the absolute difference between the DCB and PTA groups was 19.2% and actually increased slightly (9.1% vs 28.3%, respectively).

The broader body of SFA data has matured significantly over the past 5 years. These data show that some consideration of the use of antiproliferative drugs will be included in day-to-day management of most patients going forward. The major emphasis on implant-based therapy for SFA disease in recent years must be called into question at this point.

Earlier DCB data from other studies of female patients suggested a lesser effect than in males. In IN.PACT SFA at 2 years, the patency benefits were dramatic in both genders and were about the same magnitude in males and females. Diabetic patients had lower patency rates than nondiabetic patients for both PTA and DCB, but the magnitude of the patency benefit was similar in both diabetics and nondiabetics.

The higher mortality rate in the DCB arm of the trial is the one anomaly. This cannot be dismissed and requires more study as DCB data are collected; however, a common sense look at the data is useful. The mortality rate in the comparative group of PTA patients of 0.9% (among only 111 patients) was very low compared to what is expected in this population, which is usually 5% to 10%. All-cause mortality among the DCB patients was 8.1%, more consistent with what is usually seen. None of the deaths occurred in the early period after use, and most were beyond 1 year of follow-up. Paclitaxel is one of the most commonly used chemotherapeutic agents worldwide, and usually at much higher doses, and there is no identified link with increased mortality.

This premarket approval study was extremely useful for identifying medication effect and offers a lot of promise for this therapy. The US Food and Drug Administration rapidly reviewed the data once they were accumulated. The lesion lengths and types are consistent with previous SFA studies and, if anything, the lesion lengths were more challenging in IN.PACT SFA than some recent studies. More information about the "real world" can be elucidated with the IN.PACT Global Study, which allows for evaluation of longer, more complex lesions and those more challenging to the therapy.

CONCLUSION

The IN.PACT SFA Trial provides rigorous independently adjudicated level 1 evidence supporting DCB therapy for patients with disease in the SFA and proximal popliteal arteries. At 24 months, the IN.PACT Admiral DCB demonstrates durability and continued superiority of DCB treatment effect, including strong primary patency and low CD-TLR. Additionally, IN.PACT Admiral proves a strong safety profile, with statistically superior outcomes relative to PTA. The IN.PACT Admiral DCB is a proven primary therapy for SFA disease, and these clinical results will drive a paradigm shift in SFA intervention. ■

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