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Contents

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.

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

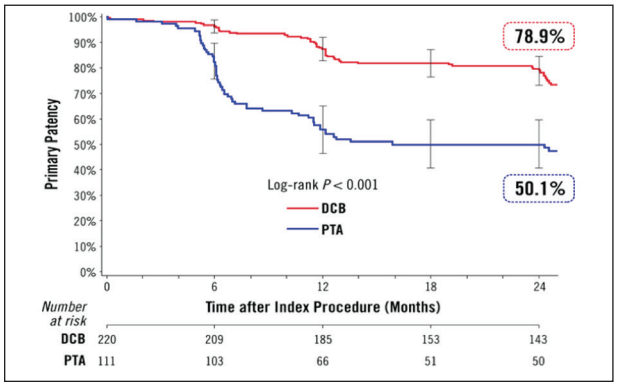

Figure 1. Kaplan-Meier analysis of primary patency in the DCB and PTA arms of the IN.PACT SFA Trial. Number at risk represents the number of evaluable subjects at the beginning of the 30-day window prior to each follow-up interval.

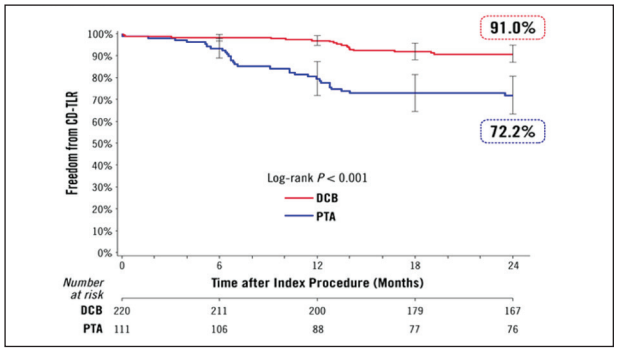

Figure 2. Kaplan-Meier analysis of freedom from CD-TLR in the DCB and PTA arms of the IN.PACT SFA Trial. Number at risk represents the number of evaluable subjects at the beginning of the 30-day window prior to each follow-up interval.

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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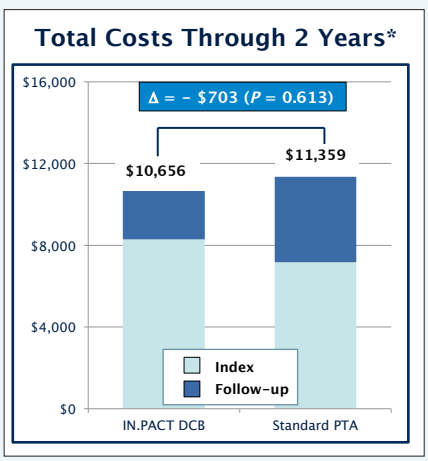

Figure 1. Analysis from the IN.PACT SFA economic substudy showed that postdischarge costs were higher for PTA as compared with IN.PACT Admiral DCB with the 2-year study period. *Winsorized—Costs for one extreme outlier reduced to next highest value.

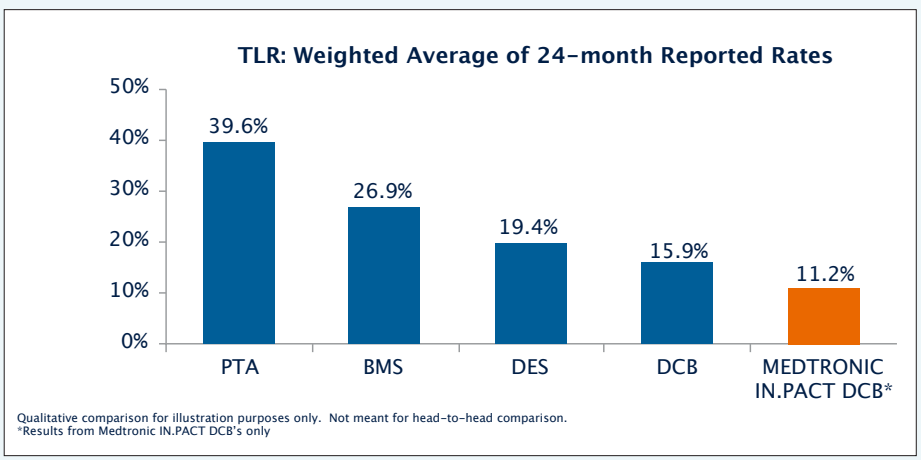

Figure 2. Two-year total cost of DCBs compared to various treatment strategies for the SFA.

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

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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IN.PACT Global Study: Overview and 12-Month Outcomes of the Long Lesion and In-Stent Restenosis Imaging Cohorts

Positive overall safety and effectiveness for patients treated with the IN.PACT™ Admiral™ drug-coated balloon.

BY MARIANNE BRODMANN, MD

Peripheral artery disease is a complex disease that is progressive in nature, often requiring multiple treatments to maintain blood flow and save patients' limbs. Balloon angioplasty has been the historical endovascular standard for treating peripheral artery disease, and in some centers in the world, it is still the go-to treatment. However, angioplasty is associated with a high incidence of restenosis and reocclusion.[1] Angioplasty followed by stenting with bare-metal nitinol stents, and more recently drug-eluting stents, has vastly improved the low patency rates observed with angioplasty. Recent studies have reported 12-month patency rates ranging from 63% to 83% in short- to intermediate-length lesions.[2-6] Despite improved outcomes with stents, concerns still remain about performance in more complex lesions, including long lesions, chronic total occlusions (CTOs), and in-stent restenosis (ISR). These complex lesion subsets continue to pose unique treatment challenges, with no current treatment standard identified. Lesion length is shown to be a predictor of lower patency at 12 months, with rates ranging from 35% to 65% (mean lesion length, > 20 cm).[7,8] Up to 40% of bare-metal stents placed in the superficial femoral artery (SFA) will develop ISR or occlusion within 1 year.[9] There remains a desire for minimally invasive treatment strategies that provide effective and durable outcomes in complex lesions while preserving future treatment options. Drug-coated balloons (DCBs) have emerged as an attractive option with promising results.

OVERVIEW

The IN.PACT Global Study is an independently adjudicated and monitored prospective, multicenter, single-arm study designed to expand evidence of the IN.PACT™ Admiral™ DCB (Medtronic, Inc.) in the treatment of patients with real-world femoropopliteal lesions, including long lesions, ISR, and CTOs; more than 1,500 patients were enrolled in the study.[10] More than 1,400 patients were enrolled as part of the clinical cohort. A subset of these subjects underwent duplex ultrasound (DUS) imaging at 12 months to assess patency and were included in the imaging cohort. The imaging cohort consisted of three subgroups: (1) de novo ISR, (2) long lesion ≥ 15 cm, and (3) CTOs ≥ 5 cm. The primary efficacy endpoint for the imaging cohort was primary patency at 12 months, defined as freedom from clinically driven target lesion revascularization (CD-TLR) and freedom from restenosis as determined by DUS peak systolic velocity ratio

TABLE 1. CONSISTENT CLINICAL OUTCOMES WITH THE IN.PACT ADMIRAL DCB ACROSS STUDIES AND COMPLEX LESION SUBSETS

	IN.PACT SFA (DCB Arm) (N = 220)	IN.PACT Global Long Lesion Imaging Cohort (N = 157)	IN.PACT Global De Novo ISR Imaging Cohort (N = 131)
Lesion length	8.9 cm	26.4 cm	17.2 cm
Primary patency (12-month Kaplan-Meier)	87.5%	91.1%	88.7%
CD-TLR	2.4%	6.0%	7.3%
CD-TVR	4.3%	6.0%	8.9%
Thrombosis	1.4%	3.7%	0.8%

(PSVR) ≤ 2.4. The safety endpoint was a composite of freedom from device- and procedure-related mortality through 30 days and freedom from major target limb amputation and clinically driven target vessel revascularization (CD-TVR) within 12 months. Twelve-month outcomes from the long lesion imaging cohort were presented at EuroPCR in May 2015, and outcomes from the ISR imaging cohort were presented at the Vascular Interventional Advances (VIVA) conference in November 2015. Findings from these two complex lesion subsets are summarized as follows.

LONG LESION IMAGING COHORT

As presented by Prof. Dierk Scheinert, 157 patients (mean age, 69.5 years; 66.2% males) with 164 lesions ≥ 15 cm in length were enrolled in the long lesion imaging cohort of the IN.PACT Global Study.[10] The mean lesion length treated was 26.4 cm, markedly longer than that reported in traditional pivotal studies evaluating outcomes in the SFA, and included 60.4% total occlusions and 71.8% calcified lesions. At 12 months, the Kaplan-Meier estimate of primary patency was 91.1%. When stratified by lesion length subgroups (lesion lengths, 15–25 cm vs > 25 cm), primary patency was 97.7% in patients with lesion lengths of 15 to 25 cm and 79.2% in patients with lesion lengths > 25 cm. The CD-TLR rate at 12 months was 6.0%. The primary safety endpoint outcome was 94.0%. There were no major target limb amputations reported within 12 months, and the rate of thrombosis was low at 3.7%.

DE NOVO ISR IMAGING COHORT

To evaluate the effectiveness of the IN.PACT Admiral DCB in treating ISR lesions, 131 patients with pure de novo ISR lesions were enrolled into the ISR imaging cohort of the IN.PACT Global Study and underwent DUS imaging at 12 months.[11] The mean age was 67.8 years, and 69.5% of the patients were male. The mean lesion length treated was 17.2 cm, including 34.0% CTOs and 59.1% calcified lesions. The 12-month Kaplan-Meier estimate of primary patency was 88.7%. The CD-TLR rate at 12 months was 7.3%. The primary safety outcome was 91.1%. There were no major target limb amputations, no deaths, and a low (0.8%) thrombosis rate within the 12-month follow-up period.

DISCUSSION

The IN.PACT Admiral DCB has shown consistent clinical effectiveness across the IN.PACT Admiral clinical studies (Table 1). Very high patency was observed in the randomized trial and in the complex subsets in the IN.PACT Global Study. This is noteworthy, given that the mean lesion length in the randomized controlled trial was 8.9 cm compared to 26.4 cm in the long lesion imaging cohort. Restenosis after SFA interventions, particularly with stents, is common and remains an ongoing major challenge. Patency rates for reintervention are usually lower than those for the primary intervention with the exception of the results from the IN.PACT Global ISR imaging cohort. To the best of my knowledge, this is the highest 12-month primary patency rate reported for ISR interventions.

Intended for markets where mentioned products and indications are approved.

SUMMARY

DCBs have emerged as an important therapeutic modality for the treatment of femoropopliteal lesions. Results from the IN.PACT Global Study demonstrate positive overall safety and effectiveness for patients treated with the IN.PACT Admiral DCB. Importantly, the high patency and low CD-TLR rates were consistently observed across IN.PACT Admiral studies and SFA lesions, including the long lesion and ISR subsets. ■

Marianne Brodmann, MD, is from the Division of Angiology, Medical University Graz in Graz, Austria. She has disclosed that she has received honoraria from Bard Peripheral Vascular, Medtronic, Inc., Spectranetics Corporation, Bayer, Daiichi Sankyo, and Boehringer Ingelheim. Prof. Brodmann may be reached at marianne.brodmann@medunigraz.at.

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The Role of Preclinical Data in Drug-Coated Balloon Therapy

Drs. Virmani and Granada explain the importance of preclinical data, discuss key parameters for evaluation, and review the science behind clinical performance.

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ROLE OF PRECLINICAL SCIENCE

What can we learn from preclinical data?

Dr. Virmani: Preclinical data play a very important role, not only to evaluate safety, but also to understand toxic and biologic effects. Classically, in clinical studies you evaluate, "is it reducing the percent of neointimal stenosis?" This does not always apply to the preclinical work, because animals lack the atherosclerotic process. Preclinical data do, however, tell us about safety of DCBs—specifically if there is an inflammatory reaction. For paclitaxel, preclinical evaluation can determine: Is this toxic? Does toxicity relate to the level of drug we are putting in? Does it lead to thinning of the media? Does it lead to an aneurysm? In the case of DCBs, it is very important to know if we are seeing drug effects at 28 days, such as deposition, fibrin, and delayed healing. You also have to take into consideration that we are assessing juvenile animal models, not humans who are older (aged > 60 years) with peripheral vascular disease. So, at 28 days in humans, you will not see complete healing. Instead, you might see endothelialization on the surface, and below you may have very few smooth muscle cells.

Dr. Granada: In the era of local drug delivery, experimental device validation has become extremely important in understanding the basic principles of the technology and the potential benefits and challenges of the technology before it enters clinical testing. In DCBs, experimental research answers questions about the impact of coating on tissue pharmacokinetics and biological effect.

Why are preclinical data so important in the landscape of DCBs?

Dr. Virmani: In the landscape of DCBs, you also want to know about distal emboli and how drug dose affects drug delivery. DCBs attempt to deliver a large amount of drug in a very short time, typically 60 seconds to, at most, 3 minutes with balloon inflation. The IN.PACT™ Admiral™ DCB (Medtronic, Inc.) carries a 3.5-µg/mm^2 dose of drug, whereas Lutonix (Bard Peripheral Vascular) carries a 2-µg/mm^2 dose of drug. Drug dose and delivery may make a difference, but it is also important to ascertain how quickly the drug needs to be delivered, the time from entering the system to placing the DCB in the artery wall, and if emboli are produced in distal beds. These are things that we can evaluate in animal models that we cannot easily learn in humans.

Dr. Granada: DCBs perform very differently compared to other local drug delivery technologies, as they aim to initially transfer drug "only once" via balloon dilatation but, at the same time, maintain drug levels in tissue over the long term. With experimental research, we were able to prove that first-generation DCBs were able to maintain tissue levels up to 90 days, which was an extremely important finding to validate the technology. Based on these findings, we were able to standardize the methodologies for DCB testing, and more importantly, we were able to determine the efficacy and safety boundaries of the technology through pharmacokinetic and tissue healing studies.

How does preclinical science relate to or work in partnership with clinical evidence?

Dr. Virmani: You look at the biology in the animal, whether healing is taking place and how quickly, as assessed by the location and quantity of fibrin, and if the drug is solid phase and how long drug persists in the arterial wall with one DCB compared to the other. If the drug persists without producing toxic effects, this can translate to the patient's outcome—the patient may do better because the drug will be there for a longer time. For instance, we know that the solid phase for IN.PACT Admiral DCB is greater than for the Lutonix DCB, and it remains in the arterial wall for a longer duration; thus, the drug is delivered for a longer time. However, head-to-head comparisons must be performed, both in terms of preclinical and clinical evaluation, to gain further knowledge.

Dr. Granada: It is important to highlight the profound differences between an animal's normal healthy artery and a human's atherosclerotic vascular environment. One has to be careful about extrapolating experimental findings into clinical lessons; however, we have learned that biological signals from experimental studies have translated into clinically measurable findings. For example, the pharmacokinetic behavior of DCBs is a good biological surrogate for clinical efficacy. Also, in the drug-eluting stent era, we learned that negative biological signals at the tissue level correlated with adverse clinical events in humans. Although one has to be careful about translating these findings between an animal and a human, we have learned to identify the signals that could potentially produce negative clinical events in humans.

SAFETY AND EFFICACY OF DCBs

What has your preclinical experience shown in terms of efficacy?

Dr. Granada: Pharmacokinetic studies have been the cornerstone of efficacy or the most important surrogate for efficacy. We have learned that maintaining stable, predictable tissue levels over time correlates with clinical efficacy in humans. Also, tissue efficacy studies evaluate the effect of paclitaxel on the vessel wall, as measured by the amount of fibrin that is accumulated and the amount of smooth muscle cells that are inhibited or killed by the drug over time. Tissue levels have been shown to correlate with the healing process over time and can be used as a surrogate of safety and efficacy in humans.

Dr. Virmani: I would say that the IN.PACT Admiral DCB has better efficacy as compared to Lutonix if you look at the depth of distribution of the drug or effects on the arterial wall. If you look at the circumference, there is better distribution. With IN.PACT Admiral DCB, there is 78.9% patency at 2 years, which is very high—higher than I would have expected. I think IN.PACT Admiral DCB is a very good system, and the clinical data speak for themselves.

What has your preclinical experience demonstrated in terms of safety?

Dr. Virmani: In terms of the preclinical work I did for IN.PACT Admiral DCB, I did not see much distal emboli,

even at three times the dose. In the preclinical work I have done for Lutonix, I did not see distal emboli when three balloons were deployed at the same site; however, I was blinded to how the balloon was delivered.

Dr. Granada: One of the important lessons about safety is to maintain therapeutic tissue levels over time that do not go beyond the boundaries of potential toxic effects. The biological effect of drug can be clearly identified and quantified through standard histologic methods.

What key parameters are most important for evaluation?

Dr. Virmani: For me, the most important parameter is delayed healing—specifically persistence of fibrin, fewer smooth muscle cells, and level of endothelialization. If healing is not complete, the area is not fully covered by smooth muscle cells, proteoglycan, and collagen. Instead, we still see persistence of fibrin, fewer smooth muscle cells, and more proteoglycan, which I call delayed healing. That tells me that the drug is effective.

Dr. Granada: A very important parameter that is being shown by Dr. Virmani's lab is the potential of paclitaxel to inhibit and kill smooth muscle cells in the media in the vessel wall. Most importantly, quantification of this effect throughout the entire vessel wall can define the biological effect of paclitaxel in smooth muscle cell proliferation and vessel healing. When you combine these parameters, you can essentially create a reproducible picture of the safety profile of DCB technologies.

Do you have any safety concerns regarding DCBs as a class? Regarding IN.PACT Admiral in general?

Dr. Virmani: For a one-time dose, no, I don't think there are safety concerns with either DCB.

Dr. Granada: I think the most important thing is to go back to the clinical data. If you look at group class effect, DCBs in the superficial femoral artery (SFA) have not really shown any safety concerns. I think it is fair to say that DCBs are safe for that particular application. At the present time, we have not seen evidence of arterial thrombosis or aneurysm formation in the SFA after DCB treatment despite the wide use of the technology. In the territory below the knee, it is still an open question because it is a very difficult territory to treat—there is a lot of plaque burden, and there is the potential for embolization into a territory that has very poor vascular runoff. I think it is fair to say that the overall safety for DCBs below the knee is still under investigation.

THE SCIENCE BEHIND CLINICAL PERFORMANCE

Pivotal trial evidence proves the safety and efficacy of DCB therapy through 2 years; however, there is variability in efficacy across the technologies. What makes a DCB effective, and what mechanism of action is critical to success?

Dr. Granada: As previously discussed, the pharmacokinetic profile of each DCB depends on the type of coatings developed by the device manufacturer, and it will determine the clinical efficacy of the technology. Specifically for the IN.PACT Admiral DCB, we know that paclitaxel levels in tissue remain within therapeutic levels beyond 28 days. Clinical data show the sustainability of patency rates up to 2 years, but it is challenging to compare results between technologies and trials because the methodologies and the patients enrolled are different. Therefore, head-to-head comparisons between technologies are very difficult to make at the present time. It is fair to say that for DCB technologies, it is remarkable that we can achieve sustainable patency rates up to 2 years with a single drug application, as recently shown.

Dr. Virmani: The duration of time paclitaxel stays in the vessel wall is critical to success. For the IN.PACT Admiral DCB, it is claimed that because of its solid phase, paclitaxel remains in tissue longer, and we have shown that crystals are seen much longer. Both DCBs deliver crystalline paclitaxel. One has larger crystals and the other has smaller crystals, so you could argue that with one, we can see the crystals, and in the other, we cannot see the crystals; however, that does not mean it is not effective. You can argue either way. I think in vitro testing has shown that the solid phase stays around more than 24 hours as far as the IN.PACT Admiral DCB is concerned.

What product differences may play a role in these clinical outcomes?

Dr. Virmani: Solid state makes the difference—how much drug is delivered to the vessel wall and how long it stays there. When delivering a DCB, contact with the vessel wall is important. Pressure can be applied; the longer the pressure, the more drug will be delivered. You could also argue that not only is the pressure important, but it is important how long the balloon is inflated. If the balloon is inflated for 30 seconds versus

180 seconds, it will make a difference. These are all factors that can be tested.

Dr. Granada: I emphasize pharmacokinetics because if you talk about clinical efficacy, you need to make sure that you not only transfer drug but also that tissue levels are maintained over time. The sustainability and reproducibility of the pharmacokinetic profile in each individual patient is extremely important. The second difference is the concept of tissue distribution. If you look at stents, the stents essentially release drug into the tissue in a very uniform and predictable fashion. DCBs essentially maintain tissue levels by adhering crystalline particles on the vessel wall, and those particles release drug into the tissue over time. This distribution is not as organized or predictable as that observed in drug-eluting stents, but it works. The ability to reproduce homogeneous distribution of paclitaxel transfer and sustainability over time is certainly an important concept. The last concept that is important but still poorly understood is the concept of particle dislodgement occurring upon balloon inflation. As part of the process of coating transfer, particles are produced and dislodged off the surface of the balloon and can potentially produce adverse effects, especially in areas with very poor vascular runoff. The development of DCBs that demonstrate lower embolization potential while still achieving reproducible therapeutic tissue levels is warranted.

Based on your preclinical evaluation, which of these technology differences is most critical, and how might it affect clinical outcomes?

Dr. Granada: The most impactful technologic difference that can improve outcomes is the ability to maintain tissue levels that are therapeutic, reproducible, and reliable over time. Finding the right balance between therapeutic effect and safety will be a key technical specification for the development of future-generation DCB technologies.

Dr. Virmani: I would say that the DCB that delivers the most drug is the winner in terms of clinical outcomes. The DCB that has the lowest risk of distal embolization may be important in some patients, but may not be important in other patients, so these factors have to be weighed. ■

Perspectives on 2-Year Drug-Coated Balloon Data

A panel of experts discusses how the 2-year IN.PACT SFA and 1-year IN.PACT Global Study data affect decisions in real-world clinical practice.

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DURABILITY

At 2 years, the IN.PACT™ Admiral™ drug-coated balloon (DCB; Medtronic, Inc.) has demonstrated the highest reported primary patency rate and lowest reported reintervention rate in the landscape of superficial femoral artery (SFA) pivotal trials. What does this mean in the real world of peripheral practice?

Prof. van den Berg: We now have randomized evidence that DCBs are more effective than percutaneous transluminal angioplasty (PTA) alone in the treatment of short- to intermediate-length SFA lesions. Patency rates are similar and, in some instances, even better than those of randomized trials that investigated the use of nitinol-slotted tube stents in the same type of lesions. However, it is important to note that comparing trials, although

attractive, has its limitations. The IN.PACT study results are therefore an important step toward the concept of leaving nothing behind.

Dr. Schneider: Each DCB will have to be studied and evaluated on its own. Although they seem simple enough in theory, the reality of differences in the drug preparation, excipient, balloon, and delivery are significant enough that we must understand the differences and benefits of each. Going forward, it is highly likely that some drug will be included in the management of most patients. The story is just now unfolding, but our next round of development is likely to capitalize on new information about how to get better patency rates.

Prof. Brodmann: Given the data, plain old balloon angioplasty is no longer a standard of care treatment for SFA/peripheral artery lesions, at least not in the P1 segment. DCB is the new standard of care for those lesions.

Dr. Rundback: Treatment in the SFA represents a common clinical challenge due to high restenosis rates related to intimal hyperplasia after endovascular device injury or surgical bypass. The IN.PACT study data suggest that drug delivery on a dedicated and proprietary balloon platform substantially inhibits this process, with dramatically improved rates of both treatment vessel patency and clinical durability. This evolution should now be considered the treatment standard for moderate- to intermediate-length SFA disease in the absence of severe calcification and potentially for long-segment obstructions as well. Practically speaking, this translates to fewer reinterventions, longer periods of health for our patients, and possibly a lower threshold for therapy in patients who have even modest debility from femoral peripheral artery disease.

Do you believe these longer-term results will influence the incorporation of and increase adoption of DCBs in practice?

Dr. Rundback: The 2-year IN.PACT SFA Trial data should drive increased utilization of DCBs for femoropopliteal disease. Earlier data of drug-eluting stents (DESs) from the SIROCCO studies had noted a "rebound" or late "catch-up" phenomenon at 2 years with loss of the initial benefit seen compared to conventional balloon angioplasty. The preserved benefit at this same interval seen in the IN.PACT SFA Trial attests to the impressive properties of the excipient urea and the crystalline paclitaxel dosing used on this platform and provides convincing data for interventional physicians to consider the IN.PACT Admiral DCB as a first-line strategy in appropriate patients.

Prof. Brodmann: Yes, definitely! With three different DCBs providing long-term (2-year) results (IN.PACT Admiral, Lutonix [Bard Peripheral Vascular], and Stellarex [Spectranetics]), we see important differences that count at the end of the day. Differences in patency rates between 80% and on the lesser end, 50%, are important. In my opinion, these differences give us no choice other than to use the DCB with more impressive patency rates.

Prof. van den Berg: As mentioned previously, the results should—and will—influence the use of these DCBs in the primary treatment of SFA occlusive disease. The push toward adoption can be further supported by the 2-year cost-effectiveness analysis recently presented at Vascular Interventional Advances (VIVA) in November 2015. Previous studies had already determined the cost-effectiveness of DCBs at 1 year, and this benefit seems to be sustained according to this recent analysis.

Dr. Schneider: Yes. Collecting multiyear data in the SFA is new, and we should be pleased about this so we can understand the longer-term effects.

CONSISTENCY

Based on available evidence and your own practice, are you comfortable treating a wide range of patient and lesion types with IN.PACT Admiral DCB?

Prof. Brodmann: Yes, there is no question about that. We now have a 6-year experience with the IN.PACT Admiral DCB at our site. I oversee and manage every patient in the different trials and registries, and without looking to the treatment modality, I know which DCB has been used based on the reintervention rate. Patients treated with the IN.PACT Admiral DCB have better outcomes at my institution.

Dr. Schneider: We do not have enough data related to occlusions, especially long occlusions, lesions that are recurrent, and those involving the arteries distal to the P1 segment. However, I am willing to at least consider using a DCB in some of these situations based upon what we know so far. It is likely that we will have more information on this fairly soon.

Prof. van den Berg: The evidence that has been built up over the last few years with the IN.PACT

Admiral DCB (the randomized data and the global registry data) has made me feel more at ease to treat more patients with DCBs. The data from the global registry are very helpful in that respect, because they are more a reflection of "real life" compared to the "artificial" environment of a randomized trial.

Dr. Rundback: The drug delivery era has arrived. The results reported with the IN.PACT SFA Trial, combined with approval from the Centers for Medicare & Medicaid Services for incremental reimbursement of DCBs in the United States, support consideration for DCB use across a diverse spectrum of SFA and popliteal occlusive disease. However, there are two important caveats to this statement. The first is that aggressive vessel preparation is necessary to optimize drug delivery and was a mandate of the US investigational device exemption studies. The second is that patients with moderate-to-severe calcification may not achieve the benefits seen in the IN.PACT study, and this cohort was not well represented in the randomized trial. Further data are needed to determine the role of the IN.PACT Admiral DCB in treating densely calcified lesions.

Complex lesions, including long lesions and in-stent restenosis (ISR), continue to present a challenge for available SFA therapies. Are you more confident treating these lesions with IN.PACT Admiral DCB based on the IN.PACT Global cohort data?

Prof. Brodmann: Sure, there are data indicating that DCBs are promising in long lesions and ISR. However, I usually avoid stenting, instead choosing to leave the dissections that often occur in challenging lesions behind. There is a learning curve associated with leaving what may not appear to be a perfectly favorable angiographic result as is, but at the end of the day, low stenting rates and high patency rates have proven this strategy.

Prof. van den Berg: The challenges of long lesions were already addressed during the first presentation on the global registry during EuroPCR in May 2015. Combined with the good data of the ISR lesion subgroup presented during VIVA in November 2015, this creates a good basis for more confidence in treating these complex lesions. With regard to long ISR total occlusions, I strongly believe in additional treatment with debulking, because the preliminary studies that looked into the use of DCBs for ISR long lesions demonstrated a higher restenosis rate in the subgroups of Tosaka class II and III at 1 and 2 years and an absence of effect at 3 years.

Dr. Rundback: Results of Kaplan-Meier analysis in the IN.PACT Global Study showed a 91.1% patency rate and 94% freedom from clinically driven target lesion revascularization (CD-TLR) rate for SFA lesions with mild-to-moderate calcification and an average length of 26.4 cm. Although 40% of cases required a stent for bailout, results are absolutely remarkable and potentially set a new standard for therapy in this cohort. With regard to restenotic lesions, data from the ISR imaging cohort showed maintained patency in 88.7% of patients 1 year after treatment. In an increasingly evidence-based practice environment, this information has raised our confidence in using the IN.PACT Admiral DCB in both of these scenarios if predilation does not result in a pattern of restenosis mandating an alternative scaffold-based therapy. Although not widely reported in the global experience, we have also found a role in our interventional lab to utilizing debulking strategies in these lesions, with the option of using atherectomy in part based upon angiographic appearance. In my practice, the feeling is that debulking may allow better drug delivery and lower stent usage, either for de novo or secondary treatment, affording a reasonable long-term cost-effectiveness. Early data from the DEFINITIVE AR trial have provided a weak signal that this combination strategy may provide differential benefit in longer and calcified lesions, and this is going to be tested in the near future by REALITY, a VIVA-run trial to be led by Dr. Krishna Rocha-Singh, which will specifically look at directional atherectomy and DCB use in these complex patients.

SAFETY

Given the recently published IN.PACT SFA 2-year outcomes, combined with available preclinical work by Drs. Renu Virmani and Juan Granada, do you feel there are any safety concerns with the IN.PACT Admiral DCB relative to other SFA therapies?

Prof. van den Berg: The preclinical work done is of paramount importance and already gave a good indication of the safety. The recently published outcomes of the IN.PACT SFA Trial have confirmed the absence of safety issues. I think this is important mainly because a lot of questions on adverse outcomes were raised following the publication of the IN.PACT DEEP trial results. This is not really a surprise, since we already knew that the balloon and coating technology of the two balloons studied is not identical.

Prof. Brodmann: No. As previously mentioned, I now have a 6-year experience with the IN.PACT Admiral DCB, and I feel confident using it. Based on our experience in trials, registries, and daily practice, there were no safety issues with IN.PACT Admiral DCB in the SFA population. The only issue I ever experienced was a pelvic procedure with an introducer sheath that was too small.

Dr. Rundback: There has been extensive preclinical work to support the clinically observed safety of the IN.PACT Admiral DCB when treating SFA lesions. There have been no reported embolic events or major limb amputations with the DCB, and thrombotic events are lower than seen with the plain old balloon technology.

Dr. Schneider: I don't have any safety concerns. We need to follow through and monitor all-cause mortality in DCB patients and look for any potential links, but I believe the likelihood that they are connected is extremely low.

SUPERIORITY/COMPETITIVE ADVANTAGE

How do the IN.PACT SFA 2-year outcomes compare to other antiproliferative therapies at the same time point?

Dr. Rundback: Directly comparing data from different trials is always difficult. On the surface, the IN.PACT Admiral DCB has a better primary patency rate than the Lutonix DCB at 1 year. However, the LEVANT 2 trial, which evaluated the Lutonix balloon, had three times as many restenotic lesions and slightly more lesions with heavy calcium or involving the more distal popliteal artery. The 2-year primary patency rate of 78.9% and CD-TLR rate of 9.1% from the IN.PACT SFA Trial compares favorably to the 74.8% and 19.5% seen with the Zilver PTX DES (Cook Medical). It is less certain whether there is a difference in benefit between DCB and DES technology for longer and calcified lesions in which bailout stents and concomitant cost differences are common when using a primary DCB strategy.

Dr. Schneider: The preparation used in the IN.PACT SFA Trial gave a sustained effect, at least to 2 years. We have also had a number of drug-mediated therapies that have failed to show a sustained effect, both with DESs and DCBs. I think each preparation needs to be proven on its own.

Prof. Brodmann: I think the published and presented data stand on their own. The 2-year data are impressive and confirm the safety and efficacy of the IN.PACT Admiral DCB.

Prof. van den Berg: At this point in time, there are data available from two other studies at a 2-year follow-up. One study (nonrandomized) showed similar results, while the other (randomized) trial demonstrated results that do not favor the use of DCBs. Again, all of the limitations previously mentioned apply. Having 2-year data available means that any other DCB technology coming to the market should meet this standard.

In your opinion, what differences in these products potentially translate to variation in clinical outcomes?

Prof. Brodmann: The variations in clinical outcomes relate to amount of drug, coating, and excipient.

Dr. Rundback: We are still using both commercially available DCB platforms when treating noncalcified or minimally calcified intermediate to longer SFA lesions with a satisfactory initial vessel preparation. Our use of DESs has been reduced to the management of lesions with dissections or recoil in which a mechanical scaffold is mandated for acute success. As we gain more real-world data, we may be better informed as to unique advantages of specific drug delivery technologies based upon a wide variety of factors including gender, diabetic status, Rutherford classification, lesion location, and runoff score. With the potential emergence of additional DCB and DES platforms to the marketplace over the next few years, it will be critical to obtain this information to guide best patient care.

Prof. van den Berg: The previously mentioned studies both used a DCB with a lower dose of paclitaxel (2 µg/mm^2), so given the difference in outcomes between those two DCBs, I believe drug dose is not the issue. It is therefore important to look at the efficiency of drug transfer, which depends on a lot of factors (eg, use of solid-state paclitaxel, the type of carrier, and balloon characteristics). We are continuously learning about the impact of these factors, and although an explanation may not be available right know, the data show that some DCBs are more equal than others.

Given these longer-term clinical results, do you believe IN.PACT Admiral should be the DCB of choice for femoropopliteal therapy?

Prof. van den Berg: There are a lot of factors that influence my decision making—clinical outcome

(demonstrated in large randomized trials) and cost-effectiveness are the most important. Other factors that play a role are sheath size compatibility and available sizes, especially length. Therefore, I place the IN.PACT Admiral DCB in the top three of the DCBs I use.

Prof. Brodmann: Yes, given the clinical results, the IN.PACT Admiral should be the DCB of choice for femoropopliteal therapy.

Dr. Rundback: All in all, we have adopted DCB angioplasty as initial therapy for a large percentage of patients with femoropopliteal disease, and we look very favorably upon the IN.PACT Admiral DCB for its clinical performance and durable randomized and registry results. We eagerly await further long lesion, calcified femoral, and adjunctive atherectomy data over the next several years to potentially further expand our choice of the IN.PACT Admiral DCB as primary therapy across the many patterns of stenotic and occlusive disease we see in our practice. ■

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