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Endovascular TODAY

GLOBAL

THE LATEST IN DCB DATA

TRANSLATING EVIDENCE TO PRACTICE

Experts weigh in on the latest findings from US and worldwide studies on the role of drug-coated balloon therapy in treating SFA and popliteal lesions.

THE LATEST IN DCB DATA

TRANSLATING EVIDENCE TO PRACTICE

To kick off 2015, Medtronic proudly announced US Food and Drug Administration approval of the IN.PACT™ Admiral™ drug-coated balloon for the interventional treatment of peripheral arterial disease (PAD) in the superficial femoral and popliteal arteries. The availability of this technology in the United States will result in a greater standard of care for patients.

The data produced from the various trials conducted around the globe have consistently shown reliable results. The IN.PACT SFA Trial demonstrated the lowest 12-month clinically driven target lesion revascularization rate ever reported for interventional treatment of PAD in the superficial femoral artery, as well as the highest reported rates of primary patency to date. It is an exciting next step to embark upon in PAD treatment, and this supplement to *Endovascular Today* assembles a knowledgeable team of experts in order to share their perspectives on the very latest data and how it affects their daily practice. Hopefully, you will find these articles useful and informative as you continue to assess the best treatments for your patients in this ever-changing (and hopefully, improving) world.

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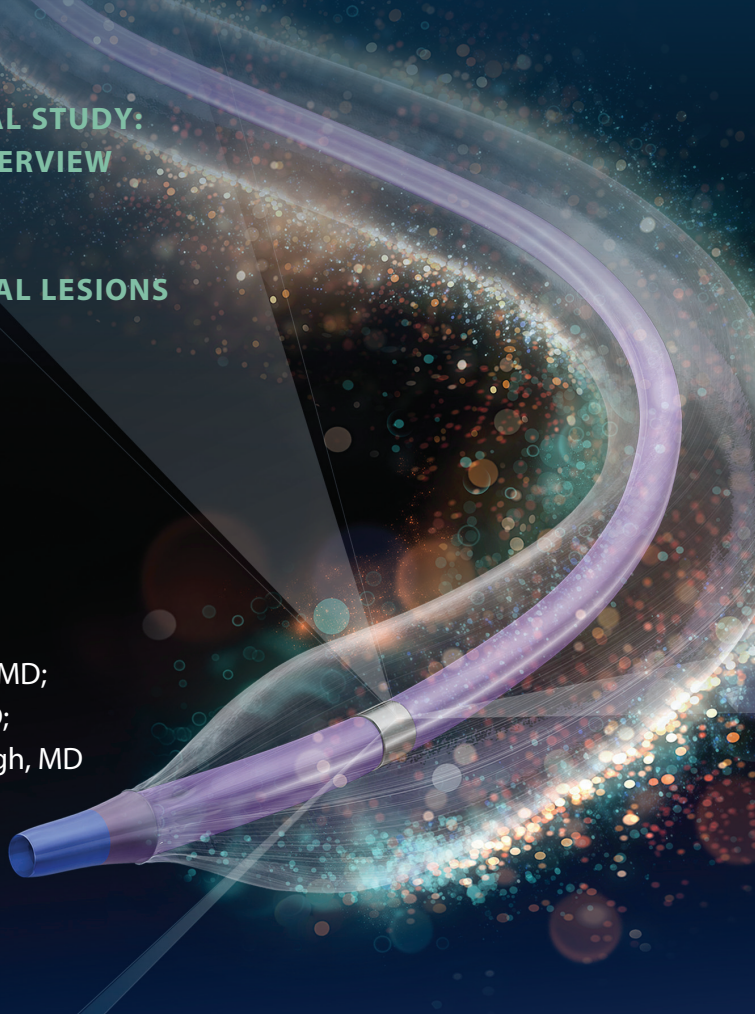

IN.PACT SFA Trial and IN.PACT Global Study: Study Design and Clinical Data Overview

Creating rigorous studies to produce meaningful data for use in everyday clinical practice.

BY JOHN R. LAIRD JR, 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 plc) versus standard percutaneous transluminal angioplasty (PTA) for the treatment of superficial femoral artery (SFA) and proximal popliteal artery lesions.

The IN.PACT Global Study is a single-arm study that reflects a complex, real-world patient population. Both the IN.PACT SFA Trial and the IN.PACT Global Study were designed with utmost attention to clinical rigor, and each has a prospective, multicenter design. Although IN.PACT SFA is a randomized controlled trial and IN.PACT Global is a single-arm study,

TABLE 1. COMPLEMENTARY STUDY DESIGNS

	IN.PACT SFA Trial	IN.PACT Global Study
Study type	Randomized controlled pivotal trial	Single-arm study
Primary endpoints	Efficacy: primary patency* Safety: safety composite†	Efficacy: freedom from CD-TLR‡ (all patients) Efficacy: primary patency (imaging cohort) Safety: safety composite†
Rigor and quality	Prospective, multicenter Independent clinical events committee (blinded in IN.PACT SFA) Independent core lab adjudication (blinded in IN.PACT SFA) External monitoring	
No. of patients	331 (220 DCB arm)	> 1,500 > 150, ISR subset > 150, long lesion subset > 150, CTO subset
No. of sites and location	57 (US + EU)	~67 global
Key eligibility criteria	Single lesions ≤ 18 cm, CTO ≤ 10 cm TASC A–C SFA + proximal popliteal No ISR, Ca^{++}	Single or multiple lesions ≥ 2 cm All TASC SFA + full popliteal ISR, Ca^{++}

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

TABLE 2. SELECT BASELINE, LESION, AND PROCEDURAL CHARACTERISTICS		
Patient and Procedural Characteristics	**IN.PACT SFA Trial (n = 220 patients)**	**IN.PACT Global Study (n = 655 patients)**
Male sex	65% (143/220)	67.2% (440/655)
Diabetes	40.5% (89/220)	41.2% (269/653)
Coronary artery disease	57% (122/214)	43.3% (270/624)
Current smoker	38.6% (85/220)	33.6% (220/655)
Predilatation	96.4% (212/220)	75.4% (494/655)
Provisional stenting	7.3% (16/220)	24.7% (160/648)

they both utilize adjudication of major adverse events, including target lesion and target vessel revascularizations, by independent clinical events committees. In the IN.PACT SFA Trial and the imaging cohort of the IN.PACT Global Study, there is also interpretation of target lesion restenosis by independent core laboratories (blinded in the IN.PACT SFA Trial), as well as external monitoring (Table 1). The 12-month data from the IN.PACT SFA Trial were recently published, and 12-month data from the first 655 enrolled IN.PACT Global Study patients were presented at the Vascular Interventional Advances conference this past November.

The primary efficacy endpoint for IN.PACT SFA was primary patency (defined as freedom from clinically driven target lesion revascularization (CD-TLR) and duplex ultrasound (DUS)-derived restenosis (peak systolic velocity ratio [PSVR] ≤ 2.4) at 12 months. For IN.PACT Global, the primary efficacy endpoint in the clinical cohort is freedom from CD-TLR within 12 months. In the imaging cohort of the IN.PACT Global Study, the primary efficacy endpoint is primary patency within 12 months, defined as freedom from CD-TLR and freedom from restenosis as determined by DUS PSVR ≤ 2.4. Both studies were analyzed with a composite safety endpoint defined as 30-day freedom from device- and procedure-related mortality and 12-month freedom from major target limb amputation and clinically driven target vessel revascularization (CD-TVR).

Select baseline, lesion, and procedural characteristics of the patients who were treated in the two studies are shown in Table 2.

PATIENT POPULATION COMPARISON

Compared to the IN.PACT SFA Trial, the first 655 subjects enrolled in the IN.PACT Global Study tended to have higher Rutherford classification scores, longer

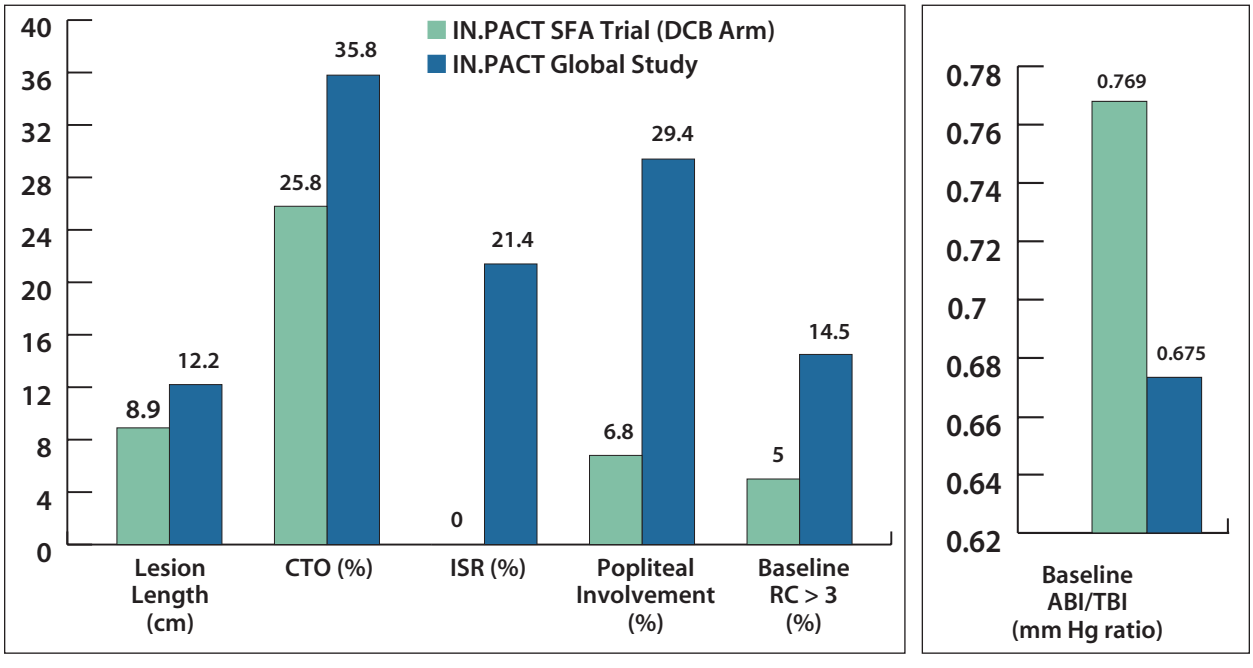

Figure 1. IN.PACT SFA Trial and IN.PACT Global Study patient population comparison.

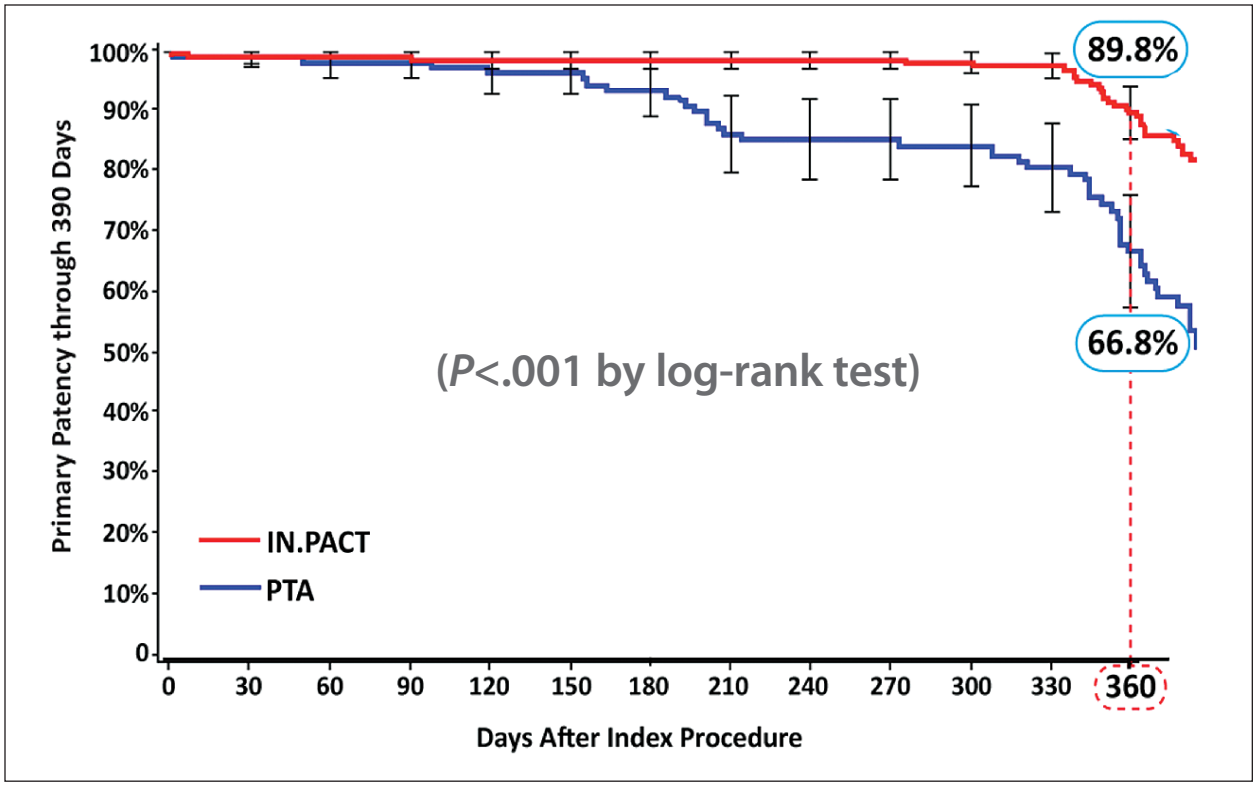

Figure 2. Twelve-month primary patency rates from the IN.PACT SFA Trial. Primary patency is defined as freedom from CD-TLR and restenosis as determined by DUS PSVR ≤ 2.4.

lesions, greater involvement of the popliteal artery, and included patients with in-stent restenosis* (ISR) (Figure 1). ISR is a very important potential application for DCBs. The IN.PACT Global Study included a large number of femoropopliteal ISR lesions (21.4% in the first 655 subjects) and will provide important data regarding this challenging clinical problem.

TWELVE-MONTH OUTCOMES FROM IN.PACT SFA AND IN.PACT GLOBAL

Figure 2 shows a Kaplan-Meier analysis of primary patency in the DCB-treated and PTA-treated arms of the IN.PACT SFA Trial. At 360 days, 89.8% of patients in the DCB group achieved primary patency compared to 66.8% who underwent standard PTA ($P < .001$).

Table 3 compares safety and efficacy outcomes at 12 months in the two arms of the IN.PACT SFA Trial. The data indicate significant improvement in most outcomes for the DCB arm as compared to the PTA arm in the IN.PACT SFA Trial. 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. The most striking finding from IN.PACT SFA was the remarkably low CD-TLR rate (2.4%), which is lower than those reported in any previous SFA device trial.

Outcomes from the first 655 patients enrolled in the IN.PACT Global Study are also presented in Table 3. The 12-month safety and efficacy outcomes from these subjects confirm the safety and effectiveness of IN.PACT Admiral in a complex, real-world patient population and reinforce the excellent outcomes from IN.PACT SFA. The CD-TLR rate was only 8.7%, despite the inclusion of longer and more complex lesions, with 14.5% patients at Rutherford classification > 3. The CD-TLR rate in the IN.PACT Global Study compares very favorably with the TLR rate seen in previous device trials (DCB, stent, atherectomy) that included shorter and less complex lesions.

The patients were predefined by sex in subgroups that were analyzed in the IN.PACT SFA Trial. The primary safety, primary effectiveness, and CD-TLR outcomes for these subgroups are shown in Table 4. The results of an interaction analysis indicate that the treatment differences between the IN.PACT Admiral DCB and PTA groups are consistent between men and women. This occurred despite the historically worse outcomes of endovascular procedures in women. These

*In-stent restenosis is not an approved indication in the United States.

TABLE 3. TWELVE-MONTH SAFETY AND EFFECTIVENESS OUTCOMES				
IN.PACT SFA Trial				IN.PACT Global Study
Outcomes	**IN.PACT Admiral (n = 220)**	**Standard PTA (n = 111)**	***P* Value**	**IN.PACT Admiral (n = 655)**
CD-TLR	2.4% (5/207)	20.6% (22/107)	< .001	8.7% (50/577)
All TLR	2.9% (6/207)	20.6% (22/107)	< .001	9% (52/577)
CD-TVR	4.3% (9/207)	23.4% (25/107)	< .001	9.5% (55/577)
Primary safety composite	95.7% (198/207)	76.6% (82/107)	< .001	89.6% (517/577)
Thrombosis	1.4% (3/207)	3.7% (4/107)	.096	3.8% (22/577)
Target limb major amputation	0% (0/207)	0% (0/107)	> .999	0.3% (2/577)
All-cause death	1.9% (4/207)	0% (0/107)	.926	3.3% (19/577)

TABLE 4. TWELVE-MONTH SAFETY AND EFFECTIVENESS OUTCOMES BY IN.PACT SFA PATIENT SEX SUBGROUP			
Women			
Outcome	**IN.PACT Admiral (n = 77)**	**Standard PTA (n = 36)**	***P* Value**
Primary safety endpoint	94.6% (70/74)	68.6% (24/35)	< .001
Primary effectiveness endpoint (primary patency)	75.7% (53/70)	43.8% (14/32)	.004
CD-TLR	4.1% (3/74)	25.7% (9/35)	< .001
Men			
Outcome	**IN.PACT Admiral (n = 143)**	**Standard PTA (n = 75)**	***P* Value**
Primary safety endpoint	96.2% (128/133)	80.6% (58/72)	< .001
Primary effectiveness endpoint (primary patency)	86% (104/121)	56.3% (40/71)	< .001
CD-TLR	1.5% (2/133)	18.1% (13/72)	< .001

findings are particularly important because another DCB trial (LEVANT 2), failed to show a benefit of DCB use in women who were treated with the Lutonix device (Bard Peripheral Vascular).

CONCLUSION

The IN.PACT SFA Trial was a well-conducted, large, prospective, randomized trial that confirmed the benefits of the IN.PACT Admiral DCB compared to standard PTA for patients with disease in the SFA and proximal popliteal arteries. Twelve-month primary patency was excellent, and there was an extremely low rate of CD-TLR. The IN.PACT Global Study has added to our understanding regarding the effectiveness of DCBs for more complex lesions often seen in real-world clinical practice. The 12-month outcomes on the first 655 subjects confirm the safety and effectiveness of IN.PACT Admiral in a complex, real-world patient population and reinforce the excellent outcomes from IN.PACT SFA. ■

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Managing Complex Femoropopliteal Lesions

The latest data demonstrating the benefit of including drug-coated balloons in the interventionist's toolbox.

BY THOMAS ZELLER, MD; ALJOSCHA RASTAN, MD; ROLAND MACHARZINA, MD; ULRICH BESCHORNER, MD; AND ELIAS NOORY, MD

Peripheral arterial disease is a common manifestation of atherosclerosis, and the majority of patients suffer from lifestyle-limiting or disabling claudication. The main goal of treating patients with claudication is a sustained relief from their lifestyle-limiting claudication, as opposed to preventing amputations, as in critical limb ischemia. Thus, the treatment applied must be safe, durable, and cost effective.

BACKGROUND ON COMPLEX LESION TREATMENTS

Anatomically, approximately 50% of these arterial lesions are located in the femoropopliteal tract. Using dedicated crossing and reentry devices, the technical success rate increased to > 95% for percutaneous transluminal angioplasty to recanalize the femoropopliteal artery.[1,2] Recanalization procedures had been limited by restenosis rates of 40% to 80% after 12 months, depending on lesion complexity.[3,4] The benefits seen with first- and second-generation nitinol stents in femoropopliteal vessels were only fair, with 1-year restenosis rates remaining in the range of 20% to 50%, increasing with lesion length.[4-6] Long stent chains are at significant risk for diffuse in-stent restenosis (ISR), which represents its own class of complex femoropopliteal lesions.

Bypass surgery is still considered as a gold standard for the treatment of complex femoropopliteal lesions such as long TASC II C and D lesions, severely calcified occlusions, and in-stent reocclusions.[1,7,8] Those lesion entities are associated with high restenosis rates for established endovascular treatment modalities. However, recent advances in stent design (interwoven nitinol stents, helical stents), drug device combination technologies such as drug-coated balloons (DCBs) and drug-eluting stents (DES), and endografts (ie, Viabahn, Gore & Associates) have resulted in a significant improvement of longer-term technical success in revascularization of complex femoropopliteal lesions.[9-17] The attractiveness of a stent-less strategy using DCBs lies in the opportunity to easily reintervene in the future when longer-term patency failure occurs. Moreover, stent-based treatment solutions have their limitations in vessel segments exposed to high mechanical forces such as the femoropopliteal transition zone (kink and bending forces) and the distal popliteal segment (compression forces).

The common characteristic of complex femoropopliteal lesions is the limited durability of current therapies in terms of a high restenosis rate. The longer the lesion, the more likely it is that local severe dissection, elastic recoil, and plaque shift will occur. The major limitation in treating calcified lesions is their eccentricity and acute and subacute recoil due to reduced vessel compliance. Finally, ISR is characterized by an overwhelming hyperproliferative vessel wall reaction to injury from neointimal proliferation.

AVAILABLE DCB DATA TO DATE

To address these challenges, DCBs are designed to specifically target the main reason for midterm failure of endovascular treatment, which is neointimal hyperproliferation. Recently published pilot studies and two larger-scale pivotal trials investigating DCBs have shown a substantial improvement in the durability of endovascular treatment for TASC II A and B lesions.[9,10] The randomized IN.PACT SFA Trial[17] is supplemented by the single-arm IN.PACT Global Study, which represents the largest study in peripheral vascular interventions today, with more than 1,500 patients with femoropopliteal artery disease enrolled at 67 sites in Europe, the Middle East, Asia, Canada, Australia, and South America. The objective of this prospective study is to characterize the IN.PACT™ Admiral™ DCB (Medtronic plc) clinical outcomes in a real-world patient population. The large sample size allows for ample subset analyses and offers the ability to detect low event rates, which might be missed in smaller-scale randomized controlled trials. The specific predefined subgroups (each with at least 150 patients) include de novo ISR, long lesions (≥ 15 cm), and chronic total occlusions (≥ 5 cm) are assessed by a core lab. More

than 100 patients who underwent treatment with the 150-mm-length IN.PACT Admiral DCB were also enrolled.*

For IN.PACT Global, the primary efficacy endpoint in the clinical cohort was freedom from clinically driven target lesion revascularization (CD-TLR) within 12 months. In the imaging cohort of the IN.PACT Global Study, the primary efficacy endpoint is primary patency within 12 months, defined as freedom from CD-TLR and freedom from restenosis as determined by DUS PSVR ≤ 2.4. The primary safety endpoint is a composite of the 30-day freedom from device- and procedure-related mortality and 12-month freedom from major target limb amputation and CD-TVR.

The 1-year interim data from the first 655 IN.PACT Global patients confirm the safety and efficacy of the IN.PACT Admiral DCB for the treatment of femoropopliteal disease. IN.PACT Global patients were inclined to have higher Rutherford classification, longer lesions, involvement of the popliteal artery, and included ISR, which is an approved CE indication.* This confirms the positive results seen in other superficial femoral artery lesion studies and supports the IN.PACT Admiral DCB as a front-line therapy, even in complex femoropopliteal lesions. Furthermore, the IN.PACT Global Study sets a new standard in the real-world assessment of femoropopliteal arterial revascularization.

A recent single-center study has reported 1-year patency outcomes for femoropopliteal lesion treatment with DCBs in a range of 75% to 84% for mean lesion lengths of 19.5 and 24 cm, respectively.[18]

In this retrospective study, 228 patients presenting with femoropopliteal lesions longer than 10 cm who were suffering from peripheral arterial disease Rutherford stages 1 through 5 were treated with either DCB (n = 131) or DES (n = 97). Propensity score stratification analysis was employed to minimize the biases in baseline demographics, as well as clinical, anatomical, and procedural characteristics between the two study arms. The mean lesion length was 194.4 ± 86.3 mm (range, 100–450 mm) and 195 ± 64.5 mm (range, 100–350 mm) in the DCB and DES cohorts, respectively. Restenotic lesions were treated in 51.9% and 44.3%, and total occlusions were treated in 52.7% and 62.9%, respectively. Provisional stent placement was performed in 18.3% of the lesions in the DCB cohort. At 1 year, the binary restenosis rate was 23.9% in the DCB cohort and 30.4% in the DES cohort (P = .319), and the CD-TLR rate was 15.6% versus 19% (P = .543), respectively. The combination of a DCB with (provisionally implanted) bare-metal stents did not affect the primary patency in the DCB arm and eventually showed a tendency to slightly improve freedom from death and TLR. Clinical outcomes throughout 1 year did not significantly differ.[18]

In the Leipzig DCB registry,[19] 260 patients with femoropopliteal lesions, including ISR and those with a mean lesion length of 24 cm, were analyzed.* The provisional stent rate was 23.3%. The duplex ultrasound–based 1-year primary patency rate was 77.6% for the entire population, 82.4% for strictly superficial femoral artery lesions, and 85.2% for ISR. Thus, DCBs are an attractive option for treating complex femoropopliteal lesions with a low provisional stent rate. ■

*In-stent restenosis and lesions > 18 cm are not approved indications in the United States, and the 150-mm device is not approved or available in the United States.

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IN.PACT™ Admiral™ DCB Case Study

BY GUNNAR TEPE, MD

The patient was a 62-year-old man who was a current smoker. He had a baseline ankle-brachial index of 0.73 and a Rutherford category of 3. His preprocedure reference vessel diameter was 4.86 mm.

The total lesion length was 13.9 cm, which was located in the mid-superficial femoral artery and included a totally occluded segment. We employed 4-mm X 120-mm and 4-mm X 60-mm IN.PACT™ Admiral™ drug-coated balloons (Medtronic plc) to treat the target lesion.

The patient had a favorable procedural outcome, with a peak systolic velocity ratio ≤ 2.4. Postprocedure stenosis was reduced to 22%. The patient also had a postprocedure dissection grade of A (per core lab).

At 6 months, the patient's ankle-brachial index had improved to 0.93, and at 12 months, continued to improve to 1.05. Primary patency and primary sustained clinical improvement (defined as freedom from target limb amputation, target vessel revascularization, and increase in Rutherford class) were demonstrated at 12 months. At 6, 12, 24, and 36 months, the Rutherford category was a consistent 0. There have been no revascularizations reported to date. ■

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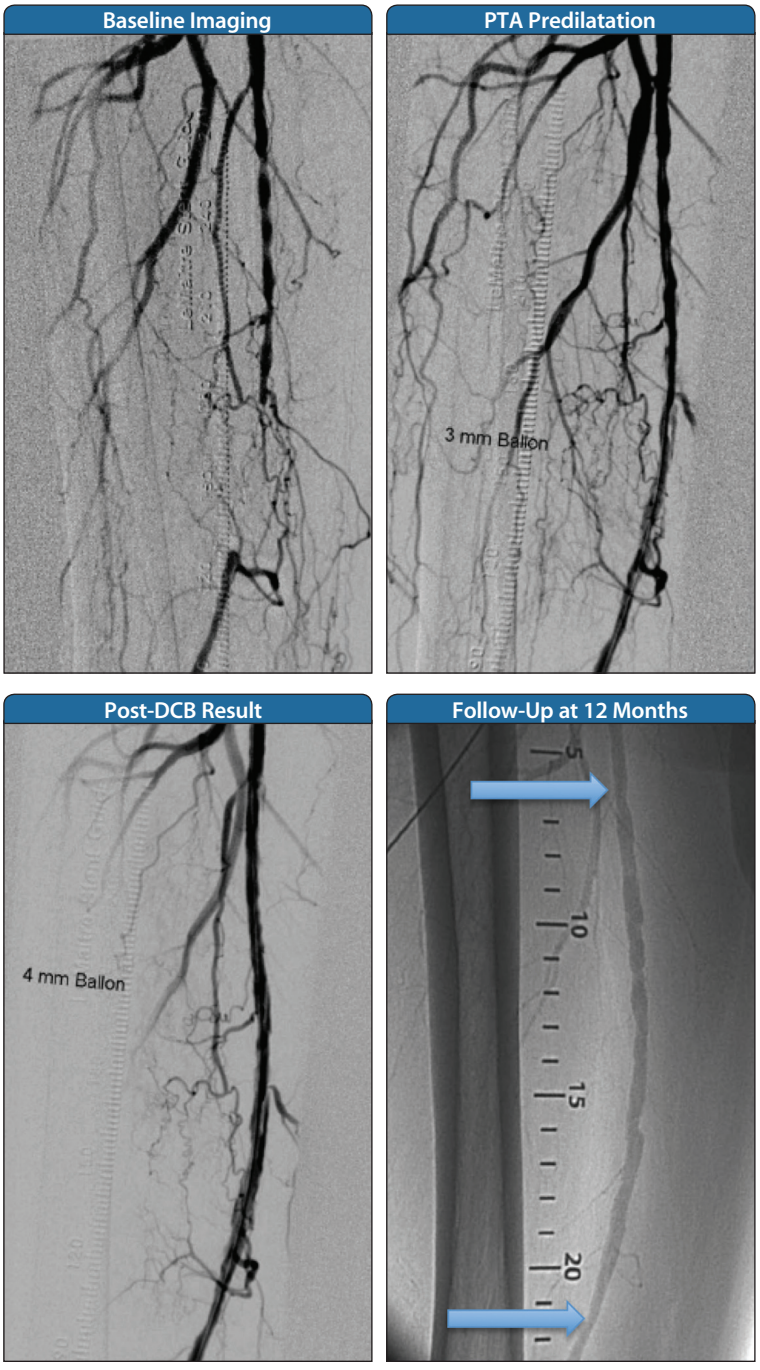

DCB Use in the Real World

A panel of experts discusses recommendations for optimizing outcomes when treating complex SFA and popliteal lesions with drug-coated balloon technology.

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From the IDE to the Real World

Featuring Drs. Schneider, Rocha-Singh, Krishnan, and Tepe.

Do you believe that the IN.PACT SFA Trial data are translatable to real-world practice?

Dr. Schneider: Yes, but it is not a perfect fit for every patient who will walk through your door. There is no such thing as a successful trial with clearly measurable outcomes that will perfectly translate to everyday life. The good news is that drug-coated balloons (DCBs) work. The pivotal trial was sizeable and was extremely well controlled and adjudicated, was carried out in a broad geographic area with many investigators of different specialties, and included lesions up to 18 cm in length, occlusions, as well as both claudication and rest

pain. In terms of pivotal trials that have been done in the past, IN.PACT SFA is as "real world" as it gets in the development of endovascular technologies. DCBs were a lot better than plain old balloon angioplasty, which we considered the standard of care not long ago.

Dr. Rocha-Singh: The clinical results obtained from a randomized, controlled, prospective, clinical trial never mirror the actual results from real-world practice. The diversion from the randomized controlled trial's inclusion and exclusion criteria rarely reflect the clinical and angiographic patient cohorts seen in real-world practice, which is just one reason for this divergence. Additionally, it is impossible to discern the number of patients who failed entry criteria for the randomized controlled trial, as these numbers and the reasons for exclusion are rarely captured. Although I believe that the results of the IN.PACT SFA Trial are an excellent start in selecting patients who may achieve optimal results through 1 year, postmarketing surveillance trials and registry studies will capture a larger cross-section of the patient population with severe atherosclerotic femoropopliteal disease and lifestyle-limiting claudication.

IN.PACT Global is a single-arm study evaluating a real-world population. How important is this study?

Dr. Krishnan: I believe that the IN.PACT Global will confirm what we've already learned from IN.PACT SFA in a real-world population. Obviously, the lesion lengths are longer, and the inclusion/exclusion criteria are less rigid, thereby allowing us to use the IN.PACT™ Admiral™ DCB (Medtronic plc) in more difficult patients with longer lesion segments that have significantly more calcium and less runoff. This is closer to the type of patients that we treat on a day-to-day basis.

IN.PACT Global is not only going to confirm what we've learned from IN.PACT SFA—that the IN.PACT Admiral is effective—but it's also going to be complementary because it will allow us to see that in real-world lesions, this balloon does work.

Dr. Rocha-Singh: Single-arm registries add to our understanding of the appropriate patient cohorts that may receive an optimal clinical benefit from this therapy. However, if patients are not consecutively enrolled in such studies, an inherent operator selection bias exists, as the physician could only enroll patients who are easiest to treat or whom they think might have the best clinical outcomes. In the IN.PACT Global Study, the sponsor enforced consecutive enrollment as much as possible in order to minimize biases in the patient selection process.

Also, the IN.PACT Global Study is independently adjudicated, which is in contradistinction to recent global registries that relied on site-directed, unadjudicated reporting of patient demographic and angiographic specifics, procedural success, complications, and primary patency through follow-up. As such, the full contribution of the IN.PACT Global Study can only be fully realized when we understand how it builds upon the results of the IN.PACT SFA Trial. Specifically, the divergence of lesion lengths, percentage of patients with "severe" calcium, length of chronic total occlusions, in-stent restenosis, TASC II C and D lesions—all were excluded from the randomized controlled trial.

Taken together, I believe that the randomized controlled trial, along with the global registry, which will include more challenging patient subsets, will provide us with a more complete assessment of the capabilities of this first-generation device and the patient cohort in which it should be applied.

How does DCB use fit into your practice? Where are you using DCBs as your standalone therapy when treating superficial femoral artery (SFA) and popliteal lesions?

Dr. Rocha-Singh: In general, I suspect that my use of DCBs will reflect the use of these devices by my colleagues. Clearly, patients who have failed primary angioplasty with adjunct therapies (specifically, atherectomy) will be ideal candidates for the application of the IN.PACT Admiral DCB as a standalone device.

Prof. Tepe: In the presence of heavy calcium, in Europe, we might try an adjunct therapy (cutting balloon or atherectomy) in order to prepare the vessel for better drug uptake. If there is a very long lesion, we might also use covered stent grafts, but this is very rare. I would say that most of our patients receive DCBs as the primary therapy.

Dr. Schneider: DCBs are being integrated into our practice now—our usage is increasing based upon available data. I believe that over time, the paradigm of "DCB as standalone whenever possible" will replace the paradigm of "plain old balloon angioplasty plus/minus implant" that has been our practice over the past 10 years or more. This will be a major shift in our approach. How far it goes, we don't know. The concern is with the angioplasty mechanism itself. It is apparently good at delivering the drug; however, the acute damage caused by balloon angioplasty must be understood better. The idea that we can create extensive dissections and somehow that doesn't matter is counterintuitive. At the very least, we need to understand what happens when dissections

are left behind. We also know that occlusions and longer lesions are more likely to require some type of scaffolding.

In which SFA or popliteal lesions will you not use a DCB as the primary treatment option, and why?

Dr. Schneider: We actually don't know yet how DCBs or long subintimal angioplasty will work for heavily calcified lesions, as these types of lesions were not included in the studies that have been done to date. Patients with gangrene and those who have extensive femoropopliteal disease that could be treated with DCBs have also not been well studied in randomized controlled trials. Right now, each clinician will have to make the call in these situations.

Complex Lesion Considerations

Featuring Drs. Schneider, Garcia, Krishnan, and Rocha-Singh.

Can you briefly explain what the term "complex lesions" means to you?

Dr. Schneider: Complex lesions are summarized in the TASC II classification. Lesions longer than 20 cm, those that involve the common femoral artery or the popliteal artery contiguous with a long superficial femoral artery (SFA) occlusion, or those with heavy calcification are all complex, in my opinion.

Dr. Garcia: Lesions that are > 20 cm in overall length, those that have moderately heavy calcification (which again has not been well defined in the endovascular market to date), chronic total occlusions that have difficult-to-cross caps (either proximally or distally), multilevel disease in terms of inflow and outflow SFA, popliteal, and infrapopliteal disease. They can still be presenting as simple claudicants, but these are the more complex lesions that we have to deal with from day to day.

What are some of the most common challenges of treating complex lesions in a real-world setting?

Dr. Krishnan: The challenges of treating complex lesions depend on the morphology of the lesion. The most common complexities that we encounter are long lesions, calcific lesions, and chronic total occlusions in the femoropopliteal segment. I believe the greatest challenge now is not technical success—it is long-term patency and economic sensibility. This long-term patency was demonstrated in the IN.PACT SFA Trial patients, and I believe will be validated by the IN.PACT Global Study in a real-world setting.

The DCB has given operators the technology to maintain patency, thereby improving patient outcomes and reducing repeat procedures.

Dr. Garcia: One of the challenges is simply in crossing these lesions, but I think one of the bigger challenges we face today is the financial burdens that limit our opportunity to use all of the available tools in the more difficult cases. So, not only do you have the anatomic challenges, such as an ostial SFA lesion that extends all the way through the popliteal occlusion, which is a good 35-cm or 40-cm lesion that has moderate to heavy calcification—that's a challenge no matter what. But then, once you've crossed the lesion, you also have to consider how best to treat it while keeping the cost in my hospital minimal while still providing the patient with the best outcome. In other words, is the marginal cost going to trump everything and still get the patient the best outcome, or do I have to mitigate the marginal cost in order to achieve the best outcome? The problem lies in getting those two things to come together so that you can have a good overall outcome with durability (ie, patency), but with the least amount of money out of pocket for the patient.

Dr. Rocha-Singh: Treating more complex lesions in the real-world setting will present the practicing interventionist with a significant conundrum. We do not have important outcomes data in these patients, who, in my practice, are more common; specifically, patients with severe or diffuse intimal and medial calcification, high-grade disease associated with chronic total occlusions, and small-caliber vessels with limited runoff. Typically, these patients are technically challenging, requiring the use of more adjunct technologies (multiple specialized wires, potential use of reentry devices, and use of adjuncts to angioplasty and potentially provisional nitinol stenting). These cases are longer in duration, exposing patients to increased radiation and contrast. Additionally, managing patient expectations with chal-

lenging and complex lesions is essential, as the incidence of clinically driven target lesion revascularizations will likely be higher in these cohorts.

What data do you still need in order to determine how to treat complex lesions?

Dr. Schneider: I think IN.PACT Global will help with this. There are other drug-coated balloons (DCBs) in development that will also be studied, and the results of these studies will help to build our database of knowledge on these devices. In addition, there are many single-center or small multicenter studies looking at specific issues like in-stent restenosis or heavy calcification. We need to know how DCBs work in these settings. If a lesion requires scaffolding in order to achieve an acceptable posttreatment result, I believe that spot stenting and minimizing metal is best. The randomized controlled trials of DCBs were intended to understand the effect of the medication, not to answer the question of when we should stent in the setting of DCBs. That remains under consideration.

Dr. Rocha-Singh: At present, we have no peer-reviewed, appropriately powered, independently adjudicated, long-term follow-up data on the use of DCBs in complex lesions. It should be emphasized that the current technology available to us in the United States was derived from very circumscribed and well-defined patient cohorts, and we only have 1-year follow-up data. In contradistinction to bare-metal stents, we understand that the durability of nitinol stents, particularly in longer lesions, followed over 3 years, is clearly suboptimal.

We must remember that the current Lutonix (Bard Peripheral Vascular, Inc.) and Medtronic drug-coated technologies are first-generation devices, and although we have some understanding of their mechanism of action, we know little about their potential mechanisms of failure and which patients should and should not be treated with the technology. We must explore the interesting hypothesis of adjuncts to DCBs, specifically vessel pretreatment with atherectomy to maximize the potential elution of paclitaxel into the vessel wall, the impact of varying degrees of vessel wall calcification on primary patency, and their use in long occlusive disease, all which may drive the use of adjunct technologies and procedural costs.

Is the prospect of leaving no permanent implant behind compelling?

Dr. Krishnan: Absolutely. As we know, this is a disease process that is ongoing and unrelenting. Any permanent implant we leave behind may complicate future therapies. Mechanical implants may have structural problems such as stent fracture and in-stent restenosis, whereas DCBs allow treatment of a similar cohort of patients without these risks.

Treating SFA and Popliteal Lesions With IN.PACT Admiral DCB Technology

Featuring Drs. Schneider, Krishnan, van den Berg, Tepe, Rocha-Singh, and Garcia.

In which patients are you most confident in using an IN.PACT Admiral DCB?

Dr. Schneider: I believe that once the technology is widely diffused into the medical community, most patients will be candidates for DCBs for treatment of a femoropopliteal lesion. I would not recommend a DCB when it's reasonably clear that angioplasty balloons cannot be used as standalone therapy. Patients with very heavily calcified arteries or with common femoral artery occlusive disease may not derive a benefit. Patients with in-stent restenosis and with multiple different kinds of endovascular failures will probably be treated with DCBs because we are desperate for treatment options in these patients, but we don't yet know whether DCBs will be the best tool, nor are DCBs approved for an in-stent restenosis indication in the United States.

What is the role of predilatation before using an IN.PACT Admiral DCB, and why is this important?

Dr. Krishnan: That's a very interesting question. Predilatation was mandated in the United States phase of the trial by the US Food and Drug Administration. In the United States, we predilated the lesion with a bare balloon, 1 mm less than the reference vessel diameter. The strategy being to prep the vessel in order to facilitate the delivery of paclitaxel by way of the IN.PACT Admiral DCB. We routinely perform predilatation for all DCB

cases; however, in Europe, this is not the case. In Europe, DCBs are being used without predilatation. Clinical judgment is necessary and is dependent upon lesion morphology and characteristics to determine the need for predilatation. As our experience grows in the United States, we will arrive at an algorithm for this practice as a society of endovascular interventionists.

Dr. van den Berg: Predilatation is necessary in order to prepare the vessel for optimal drug uptake into the vessel wall in a homogeneous manner. To reduce barotrauma to the vessel wall, an undersized balloon is typically used. Without predilatation, especially in total occlusions, there may be an issue of losing some of the drug while crossing a lesion that is not pretreated.

What are your strategies with regard to lesion length, predilatation balloon length, and IN.PACT Admiral DCB length, and what inflation techniques are you using?

Dr. Krishnan: In order to formulate a strategy, one must understand the nuances of DCB use. The common problems encountered are geographic miss and dissection. From the trial, we have learned the following algorithm. The lesion needs to be predilated in its entirety. Predilatation should be done using a balloon that is 1 mm < reference vessel diameter, be completed with glow tape, and then the image must be stored in the monitor. The DCB treatment balloon should be placed 10 mm distal and proximal to the location of the predilatation site to ensure avoidance of geographic miss. Predilatation also enables us to avoid under- or oversizing of the treatment balloon, thus ensuring optimal drug delivery and minimizing the occurrence of dissection. Finally, when using multiple DCBs, the balloons must overlap by at least 10 mm to avoid geographic miss.

We're also learning about how to perform adequate balloon angioplasty. This means proper expansion of the lesion and also prolonged balloon inflation, even with predilatation. Here at Mount Sinai Heart, we recommend leaving the balloon inflated for at least a minute during predilatation, after which, we use imaging to make sure there is no flow-limiting dissection. The point here is that you want to make sure that the lesion is expanded. Once this has been confirmed, we send in the DCB and inflate to nominal pressure. We try not to go to high pressures, and then we deploy the DCB for 3 minutes in order to allow adequate entry of the drug into the vessel.

What sizing considerations do you make when using IN.PACT Admiral?

Dr. van den Berg: DCB sizing should be one to one with respect to vessel diameter.

When and how do you handle post-dilatation with a balloon after use of an IN.PACT Admiral DCB?

Prof. Tepe: Postdilatation after DCB use should be considered in cases of residual stenosis > 30%. In order to achieve good angiographic results without stenting, I very often use a shorter, uncoated balloon in the area of residual stenosis. In general, I leave this balloon inflated for 5 to 6 minutes.

When and how will stents be used along with the IN.PACT Admiral DCB?

Prof. Tepe: I use stents for spot stenting, meaning that I use stents, but I don't cover the entire lesion with stents.

How do you prevent geographic miss? Why is this important to understand when using an IN.PACT Admiral DCB?

Dr. Rocha-Singh: The prevention of geographic miss, either within the lesion or at its margins, is essential to maximize the clinical benefit of DCBs. Before treatment, the appropriate product diameters and lengths should be available to avoid suboptimal use of the technology. Appropriate positioning of the patient's extremity on the cath lab table and the use of the adhesive radiopaque tape applied to the index extremity to fully define the treatment zone and the radiopaque numbers is an important technique to avoid geographic miss. It is important to realize that a DCB is a balloon platform used as a drug-delivering device.

As such, appropriate understanding and expectations of a satisfactory balloon angioplasty result is essential. In this regard, many physicians who are unaccustomed with pursuing a primary angioplasty result, with or without the use of adjunct angioplasty technologies, must measure their expectations. Achieving a stent-like result is a bar too high to set, particularly in lesions excluded in the premarket approval trials. Paying close attention to minimizing any impedance to inflow and maximizing, where clinically appropriate and feasible, treatment runoff is an important concept as much as moderating expectations with regard to an acute angioplasty result after DCB use.

Dr. Krishnan: It's important to ensure full coverage of the entire lesion; the balloon diameter must match the reference vessel diameter distal to the lesion; and the balloon length must exceed the lesion length by approximately 1 cm on both ends.

Because the acute result is often not the same as the results seen immediately after stenting, how do you manage angiographic expectations? Is positive remodeling a real consideration?

Dr. Krishnan: We have learned that vessel beautification does not correlate with positive outcomes. The IN.PACT SFA Trial demonstrated that non–flow-limiting dissections did not affect patency. We must trust in the data and not our desire for a beautiful angiographic picture.

Dr. Garcia: Being able to look into the future and imagine what the result may look like becomes critical. It is important that you can walk away from something that doesn't look "stent-like" and understand that it will look better than a stent result at 6 months and 1 year, being able to pull back from saying, "I need to stent this," that's when people's experience will become most critical to being able to usher in acceptance of this tool, as well as to allow the opportunity for growth in this industry. ■

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