# 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.

**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. ■