



Antonio Micari



Dierk Scheinert

## Medtronic drug-coated balloon for the treatment of peripheral arterial disease shows strong results in long lesions

The IN.PACT Admiral drug-coated balloon (Medtronic Inc., Minneapolis, MN, USA) for the treatment of treatment of peripheral arterial disease, including lesions in the superficial femoral artery and popliteal arteries, is coated with paclitaxel to limit the growth of cells and scar tissue. Urea in the coating helps transfer the paclitaxel to the artery wall. Two recent studies, the IN.PACT Global Study and DEB SFA-LONG Study, have assessed the efficacy of the balloon in patients, including difficult to treat patients, such as those with long lesions, to provide an indication of its performance in a more 'real world' population.

*Confluence* spoke with Dr Antonio Micari, Director of the GMV Care & Research, Maria Eleonora Hospital, Palermo, Italy, who led the DEB SFA-LONG study, and Professor Dierk Scheinert, Medical Director of the University Hospital Leipzig and Head of the Center for Vascular Medicine, Angiology and Vascular Surgery, who was involved in the IN.PACT Global Study, to hear their views on the initial findings from the studies.

**What does the typical patient with long lesions look like in the clinic?**

**Antonio Micari (AM):** I'm a cardiologist, so many of the patients I see already have advanced coronary artery disease, carotid artery disease or peripheral artery disease. They are mostly middle aged patients, 60 years old or more, and are often diabetic and active or previous smokers.

**What are the challenges in treating long lesions?**

**AM:** When we say 'long', we mean more than 15 cm, sometimes up to 40 cm. The problem with long superficial femoral artery (SFA) lesions is that the restenosis rate in this population has historically been very high, more than 40% up to 1 year. This is principally because the artery is not a good conduit, because many forces act at the same time – distortion, distension, flexion, compression – so that when you reopen and scaffold the artery with stents, the stents are not flexible enough to follow the artery movement during walking, bending the knee, or any movement of the leg. So, particularly with the first generation stents, we saw many

fractures in the stents. This was a great concern, because when it occurred there was occlusion or restenosis. I have to acknowledge that with the new stents the fracture rate has diminished, but the scientific community still doesn't believe that stenting the artery, the 'full metal jacket', so to speak, is a solution for this artery.

**Are drug-coated balloons (DCBs), also known as drug-eluting balloons (DEBs), currently used to treat long lesions?**

**AM:** The use of DCB is an emerging technique. Currently, there are scientific data from trials conducted in patients with short- or medium-length lesions in which DCBs show promising results with low restenosis and target lesion revascularisation (TLR) rates. However, you cannot translate the results from short to long lesions, because this is a different subset of patients. The new results from the IN.PACT Global Study long lesion cohort<sup>1</sup> and the DEB SFALONG study<sup>2</sup> show that even in patients with long lesions (often regarded as the worst kind of SFA disease), DCBs seem to work. Of course, to compare short and long lesions it is like comparing apples and

**fig. 1**  
IN.PACT Admiral  
Drug-Coated Balloon

oranges, but if you have data in patients with either short or long lesions showing that the DCB works well in both groups of patients, then this is a treatment that has the potential to become the standard of care for SFA.

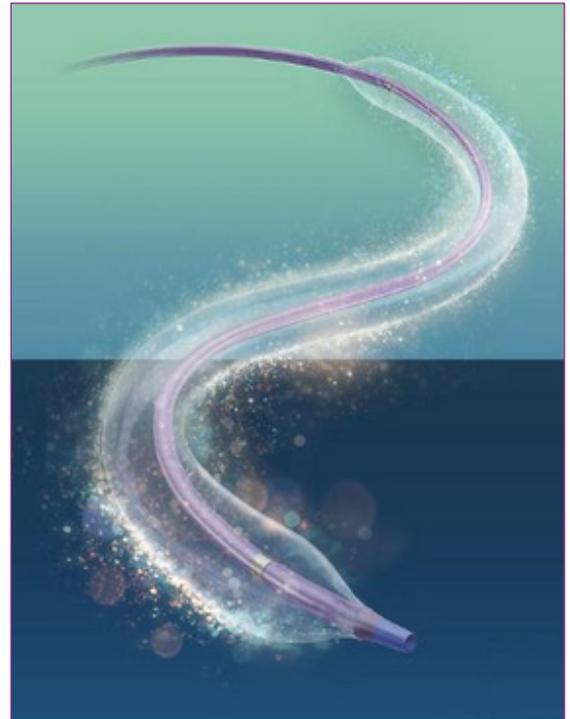
### Were the patients enrolled in the IN.PACT studies representative of the type of patients you see in the clinic every day?

**Dierk Scheinert (DS):** This large registry (IN.PACT Global) really allowed the enrolment of what we would call 'all comers', including challenging subsets of lesions, which, to a large extent, does reflect clinical practice. Patients had symptomatic peripheral arterial disease with claudication and obstruction of the SFA; this is the most frequent location of atherosclerosis in the peripheral arteries and it is a common disease. The study aimed to assess a real-world population with a variety of lesions – short lesions, long lesions, complete occlusions and calcified lesions were all included. This is in contrast to the rather selected patient cohort that is typically studied in randomised trials. There were some standard exclusion criteria, in terms of patients who were too sick to be considered for a clinical study, patients who did not want to consent, or those who we would be unlikely to be able to be assessed during 1 or 3 years' follow up. Also, patients with very severe calcification were typically not considered for this study, but other than that all patients were considered eligible, even those with prior stenting and in-stent restenosis.

**AM:** Yes, these two specific studies, the Global Long Lesion and the DEB SFA-LONG Study, were much less selective than randomised clinical trials (RCTs), so we have a population that is closer to the real-world scenario. Patients with lesions longer than 15 cm or with restenosis were accepted, and these subgroups represent over 60% of the patients coming to our cath lab.

### Could you briefly outline the design of the IN.PACT Global Study?

**DS:** This study was set up as an expansion of a RCT carried out previously, investigating the IN.PACT Admiral DEB for the treatment of femoropopliteal lesions (figure 1). The study enrolled 1,538 patients in different countries across Europe, the Middle East, Latin America and Asia. It was intentionally very open, in terms of which patients could be enrolled, allowing all these different lesion subsets.



From a scientific standpoint, the study involved a very rigorous assessment of outcome results, including adjudication of all events by an independent Clinical Event Committee. Therefore, patency assessment was based on a core laboratory-adjudicated duplex ultrasound, for specific subsets. That was only done for a specific, pre-defined, challenging subsets of patients. In this imaging cohort, efficacy was assessed by primary patency grade, defined as freedom from clinically-driven reintervention, TLR, or freedom from restenosis, based on standard ultrasound criteria at 12 months. Then, of course, safety was assessed as another important primary objective of this study.

### And could you provide an overview of the DEB SFA-LONG study, in terms of the study population, trial design and endpoints?

**AM:** I was the PI for the DEB SFA-LONG study,<sup>2</sup> which included 105 patients with atherosclerotic SFA disease with lesions over 15 cm long. We enrolled claudicant patients in Rutherford class 2, 3, and 4. The procedure involved first creating a channel with a standard balloon to avoid wasting drug as the DCB goes through the vessel. Subsequently, the DCB was dilated 1 cm above and below the proximal and distal ends of the lesion. The DCB is inflated for 3 minutes to combine the mechanical effect of percutaneous transluminal angioplasty and the biological effect of the drug.

After the procedure, patients are followed up for 24 months. The primary end-point was patency, defined as freedom from TLR and from >50% restenosis at 12 months post-procedure.

### What were the efficacy results from these studies?

**AM:** In the DEB SFA-LONG Study, all patients were treated with DCB plus bailout stenting, which resulted in a very low stent rate of 10.9%. Patency was over 83% at 1 year, and we saw a very encouraging and satisfactory TLR rate of 4%. This means that using very few stents, we had great results in terms of high patency and very low restenosis. Additionally, when we looked at functional outcomes, assessed as walking impediment questionnaire score, ankle brachial index, or quality of life, we found a significant improvement from baseline to 1 year, and this improvement remained at 1 year. This is very encouraging, because when patients come to you because they have a low quality of life or they cannot walk and are claudicant, it's very important for them to achieve a clinical result, not just an angiographic or patency result. So we want to move towards a patient-centric approach. We care very much about the clinical benefits that patients get, but here we had both; we had patency and the clinical result, and both were very encouraging.

**DS:** In the IN.PACT Global Study imaging cohort,<sup>1</sup> patients were scheduled for visits during the follow-up window between 330 and 390 days and we also saw very high primary patency rates of 91% at 360 days and 80.7% at 390 days. This was particularly impressive given that this was a challenging patient cohort with a very long mean lesion length of 26 cm. Furthermore, 60% of patients had completely occluded vessels, which is also very high. Interestingly enough, the results do match the results of the RCTs for the DCB arm, which is impressive because the lesion length in this subgroup was much longer. We have shown that the initially encouraging results from RCTs could be reproduced in a much more challenging cohort with long lesions.

### Were there any factors that affected response rates to treatment?

**AM:** The population size in DEB SFA-LONG was only 105 patients, meaning the study was not

powered to assess subgroups, so any trends are not conclusive. Of course, what is very interesting is the difference between stenotic versus occluded lesions. There was a trend towards poorer outcomes in patients with occluded lesions, but the difference was not significant. We also looked at patients with popliteal involvement versus non-popliteal involvement, but lesion location did not affect outcomes. Only 11 patients were stented, vs 94 non-stented, so we cannot draw any conclusions between groups of these patients in terms of efficacy. It is a challenge to try to figure out if there are some variables or subgroups in whom a better response to DCBs can be achieved.

**DS:** We did a comparison of patients with 15–25 cm lesion and those with lesions longer than 25 cm. In patients with lesions up to 25 cm, TLR rate was almost identical to the much shorter lesions in the randomised IN.PACT SFA DCB arm. Only the patients with extremely long lesions – longer than 25 cm – had a somewhat higher restenosis and reintervention rates, but this was still in a very favourable range.

Some patients needed stenting as an adjunct to the DCB treatment and, interestingly, those patients who received stents had identical results compared to patients who were treated without stents. However, in this subgroup analysis of 157 patients in the imaging cohort,<sup>1</sup> only non-stented patients with long lesions were assessed. In-stent restenosis was excluded, and this will be assessed separately in a future presentation.

### What were the safety results?

**AM:** Our results showed the procedure to be very safe. There was no toxic effect from paclitaxel, no amputations, no deaths related to the procedure, and in a sample of 105 patients, that means it had a good safety profile.

**DS:** The rate of clinically-driven TLR reinterventions was only 6% at 12 months, which is actually a very low value, showing that very few patients had to undergo repeat hospital admission, stenting and intervention. We also assessed all other standard safety endpoints, such as death, limb amputation and thrombosis, and recorded very low numbers, which were consistent with expected values from RCTs. This reassured us of the safety of the procedure.

How do you think these results will translate into the clinic? Do you think people will take up this practice immediately?

**DS:** Yes, there is huge potential for DCBs to be used as first-line therapy for a wide range of lesion subsets, including very long lesions. I envisage that in the future, in particular for long-lesions, treatment will involve full lesion drug delivery via DCB, and a very patient-tailored spot-stenting approach in patients with mechanical challenges that cannot be addressed with the balloon treatment alone.

There has been a great deal of well-conducted clinical research into DCBs – probably more than with most other technologies in the peripheral vascular space. There is very good scientific evidence and a good basis to update national and international guidelines, and this is an important next step to ensure that these technologies are adopted by physicians, but also by paying agencies. In Germany at least, vascular surgery and interventional radiology societies are working together in this field to make sure that this important therapy is recognised.

**AM:** Physicians have been using stents for many years, and I think it will take some time for them to fully change their mind. However, if we consider the data coming from these studies, evidence-based medicine shows that we should use this DCB as a first-line treatment for SFA.

Are there any other studies to support the use of DCBs for the treatment of patients with peripheral arterial disease?

**DS:** DCBs are a very well investigated field. Several proof-of-concept studies have confirmed the approach, using different coating formulations in a number of smaller studies, using surrogate endpoints. Then we have seen two large RCTs, the IN.PACT SFA trial, and the LEVANT-2 study with the Lutonix device. Both studies met their primary endpoints, reconfirming in large-scale clinical trials that DCBs achieve significantly better results than standard PTA, at least at 1 year. We now have the chance to report at PCR the first insights into treating these challenging cohorts from IN.PACT Global, which show very encouraging results in a real-world patient population. The IN.PACT clinical trial programme is very comprehensive and, together with the data from Dr Micari, we see a great deal of reproducibility, which is very reassuring.

What impact will this procedure have on patient's lives, and are there any consequences of treatment?

**AM:** Recovery should be quick as patients don't have stents placed, which requires endothelialisation process, which was a concern with the stent. This means that you can shorten the anticoagulant therapy period from 6, to 1 or 3 months, and this of course reduces the haemorrhagic risk, which can be a problem for older or very fragile patients.

Do you currently use DCBs to treat patients in your clinic?

**DS:** Yes, we do. We believe that delivering the drug throughout the whole lesion really offers a great advantage in terms of taking a biological approach to reducing restenosis of the vessel wall. We believe that minimising the use of metallic implants as far as possible is advantageous. This is of particular importance when considering potential future treatment needs of those patients who will typically require surveillance over their lifespan. By using DCBs, we reserve many options for future use.

**AM:** I strongly believe in this new technology and so my first choice would be to treat most of my patients with SFA lesions with a DCB. I might exclude, for economic reasons, the very simple lesions, so non-occluded stenotic lesions of less than 4 cm, which I would probably treat with a standard PTA. I would treat all other lesions with DCB and try to avoid stenting in these patients by using long inflation or prolonged PTA, and to reserve the bailout stenting for restenosis or patients with residual stenosis of more than 30% after prolonged inflation and aggressive post-dilation.

What are the key take home messages from the results of these studies?

**AM:** I would highlight the importance of the strategy in that it is minimally invasive and we are not leaving anything in the vessel. I think this is a winning strategy in terms of patency, clinical benefit and one's ability to carry out the procedure again in the future. This is very important because these are quite young patients, in their 60s or 70s, who have a lifespan of 10–20 years, and will probably need further intervention in later life, for example revascularisation or surgery if revascularisation fails.

**DS:** For me, the really exciting point was that, for the first time, we had really good quality scientific data on this new treatment approach in long, challenging lesions. This clearly indicates that the trend for this treatment is away from a lot of metallic implants and Dr Micari has pointed out the benefits of this. We are moving towards a more biological approach with full lesion drug delivery and very patient-tailored, focal, end-implantation. To me, this sounds like a very appealing and realistic future concept for these long diseased segments.

### What about longer-term outcomes, how long do you think patency will last and when will these patients require revascularisation?

**DS:** At this point in time it is not possible to answer that but it will be very important to see the IN.PACT 2-year data, which I believe is scheduled to be presented at Transcatheter Cardiovascular Therapeutics congress in the fall. For the moment, we are confident that this will be a treatment which has significant advantages at the 2-year time point, but that remains to be proven.

**AM:** Like Dr Scheinert, I cannot tell you at the moment. However, I'm running the 2-year follow up, and next year I will probably be able to tell you more. I can say that in the short lesion patients we have seen that results are still good at 3 years. I expect it to last similarly in long lesions but until we have the data, we cannot be sure.

### Are there any remaining challenges and do you think that any further data are required to convince people?

**AM:** In some subset of patients more data is needed. For example, in calcified lesions some reports showed there may be problems with the drug penetrating the calcification and reaching the vessel wall. There is a question over whether to use

a DCB alone, or a combination therapy approach. One option is to debulk the calcium first by cutting the plaque and then progress to DCB use.

**DS:** Yes, there are always challenges that need to be addressed. Highly calcified lesions are probably not the sweet spot for balloon-based therapy, including DCBs. There is a slightly increased risk of rupture when using balloons in highly-calcified lesions, particularly if you take them to very high pressure. However, this is no different with a DCB than with any other balloon. Calcified lesions present a mechanical challenge that requires a mechanical solution, which can be either a mechanical implant like an optimised stent, or potentially an approach with a dedicated intermediary device, which would remove part of the calcium to make the vessel more treatable with other modalities. This is really a work in progress and it is an important focus for the years to come. There are still challenges for the interventional approach in general, and dedicated devices are playing a big role here, including dedicated stent devices.

In addition, as we see from the study results, there is still a higher re-obstruction rate in the very long lesions (over 25 cm), so we may need to focus on those lesions eventually. We are pushing the limits substantially further, but I am confident that there is always still work ahead of us.

**AM:** More research on in-stent restenosis is required; there are some reports, but they are not conclusive. Last but not least, we need to understand what we should do after DCB restenosis. Should we treat a second time with DCB? Or should we do more? We also need to understand how often and when to use stenting. Are we using too few stents? When should we stent? Should stenting be reserved for bailout stenting, as I strongly believe, or provisional stenting?

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**DISCLOSURES:** DS is a Consultant to / on an Advisory Board for Abbott, Biotronik, Boston Scientific, Cook Medical, Cordis, Covidien, CR Bard, Gardia Medical, Medtronic/Covidien, TriReme Medical, Trivascular, Upstream Peripheral Technologies. He is a Stockholder/Consultant to IDEV Technologies. AM is a Consultant to Medtronic, Endocross, Spectranetics. He is on Speaker's Bureaus for Boston, Bard, terumo, Spectranetics, AstraZeneca and has an Institutional Grant / offers Research Support from Medtronic.