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The value of introducing a new paradigm into lower extremity revascularisation for peripheral arterial disease

The treatment landscape for patients with peripheral arterial disease (PAD) shifted with the introduction of drug-coated balloons (DCBs). Three recent studies – the IN.PACT SFA, the IN.PACT Global and the DEB-SFA-LONG study – have investigated the safety and efficacy of the IN.PACT® Admiral® DCB and assessed how this technology can be applied across the spectrum of patients with PAD. *Confluence* spoke with Dr Antonio Micari, lead researcher of the DEB-SFA LONG study and GVM Care and Research at the Maria Cecilia Hospital, Cotignola, Italy, to discuss the 3-year results of the IN.PACT SFA study, 12-month results from the IN.PACT Global registry and 2-year findings from the DEB-SFA LONG study.

What is peripheral arterial disease (PAD)?

Dr Antonio Micari (AM): Peripheral arterial disease (PAD) is a condition where atherosclerosis causes chronic obstruction of arteries supplying the lower extremities, which can lead to intermittent claudication, chronic limb ischaemia and ischaemic ulcerations.[1] The disease is growing, both in terms of complexity and the number of patients affected. With the prevalence of diabetes expected to scale to huge numbers by 2030, we are anticipating a higher incidence of PAD in the near future. The disease remains a serious problem in the diabetic population, where it carries a worse prognosis compared with the general PAD patient population.

How has the PAD treatment landscape changed in recent years?

AM: Treatment of PAD started with a simple, plain balloon and shifted towards the use of stents in the early 2000s. We then realised that the metallic prosthetic scaffolding in stents could lead to problems in the mechanics of the femoropopliteal artery. This metal jacket is not prone to following the compression, distortion, expansion and flexion acting all at the same time. We had stent fractures, which caused occlusions of the stent and high levels of restenosis and patients ended up with a worse prognosis than they had before the angioplasty. These results have caused a general decrease in the number of patients that we now treat with a stent.

In the last several years, there has been a shift towards the use of drug-coated balloons (DCBs), and marked improvements in technology with regard to patient outcomes and rates of repeated revascularisation. More recently, we have paid a lot more attention to mid- and long-term outcomes when we perform angioplasty for these patients. Over the last 5 or so years, there have been a lot of rigorous studies demonstrating the efficacy and safety of drug-coated devices, which have helped to lower the rates of restenosis and show that we can achieve good results and a good outcome for PAD patients in the long term.

What was the IN.PACT SFA study?

AM: The IN.PACT Superficial Femoral Artery (SFA) study is a randomised, single-blinded, international trial, which has used a rigorous study design to compare the safety and efficacy of the IN.PACT® Admiral® paclitaxel-coated balloon (Medtronic Inc., Minneapolis, MN, US) versus percutaneous transluminal angioplasty (PTA). The study was for claudicants of mostly Rutherford class 2, 3 and 4, with an average lesion length close to 9 cm. We presented the 1-year results in 2014, and they really were amazing. After 2 years of strong results, a catch-up phenomenon might have been possible, with effects reaching

a plateau, but this was not the case. The 3-year results of the IN.PACT SFA study have again demonstrated a sustained effect and marked improvement in long-term outcomes with the use of the DCB compared with PTA. This is demonstrated by the significant differences observed in Kaplan–Meier curves for DCB versus PTA; at 3 years, higher patency was achieved with the DCB versus PTA (69.5% and 45.1%, respectively), as well as a lower level of clinically driven target lesion revascularisation (CD-TLR; 15.2% vs 31.1%, respectively).[2] I think that this is the only study to show that improvements in outcomes are either maintained or increased with this technology over 3 years. This is level 1A evidence without any bias, and should be regarded as a set of very high-value results.

The low levels of CD-TLR are very important for both the health and quality of life of the patient. CD-TLR is also important for payers – such as the Ministry of Health in Italy, for example, or Medicare in the US – because having to re-intervene every 12 or 18 months is very costly to a healthcare system. If you reduce the number of re-interventions, you reduce the overall cost. The procedure itself has been demonstrated as safe, it also has good efficacy, as we have seen in the trial results at 3 years. With these new technologies, the treatment is likely becoming more cost effective, and so it has the three key qualities – safe, efficacious and financially worthwhile – that make for a good technology.

What was the IN.PACT Global study?

AM: IN.PACT Global is a single-arm registry of patients treated with the IN.PACT® Admiral® DCB, and the largest independently-adjudicated DCB study of real-world patients with femoropopliteal PAD. Over 1,500 patients are included in the registry, covering the whole spectrum of the disease, including many diabetic patients, patients with risk factors for cardiovascular disease and patients with highly complex lesions. Claudicants are mostly included, and almost 10% of patients presented with critical limb ischaemia of Rutherford class 4. For this all-comers registry, there is very intensive monitoring of the data. All patients are treated with the same technology and the results checked by a core lab and a clinical event committee.

What were the results of the IN.PACT Global study?

AM: The first outcome of the 12-month results was that, again, we saw very low rates of CD TLR with the DCB (7.5%). Secondly, analysis of three pre-determined subgroups – the long lesion, the in-stent restenosis and the chronic total occlusion (CTO) patients – showed high levels of patency in all groups (91.1%, 88.7% and 85.3%, respectively).[3–5] It is important to highlight that good results were achieved even in the worst-case scenarios, such as the long-lesion cohort for lesions longer than 15 cm, where the average lesion length was 26.4 cm. Safety was another major success – so far in this study we have seen no procedure-related deaths and no amputations. The key message from these results is that IN.PACT DCB works for the whole spectrum of the disease, even highly complex lesions.

Overall, this is a very high quality registry with high quality data – I think it is important that medical data alone should be shaping the mind of the physicians, not marketing initiatives. All DCBs must demonstrate their own data; one cannot assume a class effect with another balloon that has not been rigorously studied.

How well do you think the results from the IN.PACT Global study reflect the outcomes that you see in your daily practice?

AM: My daily practice has already changed, as I have been using DCBs for the majority of my patients. The latest evidence of the IN.PACT Global study should cause a greater shift towards the use of DCBs. I would no longer feel comfortable treating a patient in my cath lab using a plain balloon, because I know that I would be giving them a treatment that provides a worse outcome than what I would be able to achieve with the DCB. It is ethical to treat the patient with the best technology available at the moment, and, when looking at the data, I would use a DCB.

You led a team of researchers in the DEB-SFA LONG study. What was the rationale behind this investigation?

AM: We decided that it was vitally important to assess the efficacy of DCBs in long lesions, as physicians will generally observe many more long lesions in the PAD population than they do short. This is especially true for the diabetic

cohort – I see long-lesion diabetic patients every day in my practice. Therefore, the purpose of the DEB-SFA LONG study was to investigate a registry focusing on PAD patients with lesion lengths and/or occlusions of anything more than 15 cm treated with IN.PACT DCB, so in that sense it was very similar to the long lesion cohort of the IN.PACT Global study. The results of our study showed primary patency rate at 89.3%, and the rate of CD-TLR at 360 days was 4%.[6] This means that we have two studies for long lesions in similar populations and with similar results – one is sponsored, and one is investigator-driven – which validates the efficacy of IN.PACT DCB. We think that it is very promising and very unique to have a set of results from two different studies that are so close to one another.

Were there any differences in rates of stenting of the DEB-SFA LONG study and the long-lesion cohort of the IN.PACT Global study?

AM: There was a difference in the approach to treatment between the two cohorts with regard to the rate of stenting. In the DEB-SFA LONG study, the proportion of patients treated using a stent was around 10%; for the long-lesion cohort of the IN.PACT Global study, this value was closer to 40%.

For our treatment algorithm in the DEB-SFA LONG study, we believed strongly in the value of the balloon dilation and the mechanical angioplasty. We decided that we would do at least a 3-minute dilation with the DCB and if results from the angiography were sub-optimal we would go back inside the drug-coated area with a long balloon for post-dilation instead of using a stent. The inflated balloon would then be kept there for up to 5 to 10 minutes to try and optimise the angiography. Any residual dissection was checked; if the dissection was non-flow limiting, it was left as it was. From both past experience and the Italian registry we knew that dissections heal over time if they are non-flow limiting. We saw many examples where the dissection was resolved after 3 or 6 months.

Stents were only used as a bailout and for spot stenting. From the beginning we wanted to reduce the number of stents used, as we didn't believe that stents were the right solution for long lesions, so we are very proud to have achieved a high standard of results with low rates of stenting.

Were any studies affected by antithrombotic therapy?

AM: Antithrombotic therapy, such as dual antiplatelet therapy (DAPT), is used after intervention to help prevent thrombotic complications. There is a lot of variability in the recommended duration of DAPT; usually, the average duration is around 1 month if patients are treated using a balloon alone, or 3–6 months if one or more stents are deployed. I think that no patients in these trials have been significantly affected by different pharmacological regimens, but this was not an outcome studied.

How do you think that results from these studies will impact physicians' daily practice?

AM: I hope that they will impact a great deal. Physicians should always rely on evidence-based medicine; the results in SFA and popliteal artery are clear and there should be a shift towards DCBs because of them. I expect to see a steep increase in the number of DCBs being used to treat PAD patients globally, in the US and Europe, as well as in Asia where the diabetic population is expected to grow in the next few years. Improved outcomes with the use of DCBs below the popliteal artery in patients with critical limb ischaemia is still currently not supported by clinical data. Previous studies demonstrated no significant benefit of DCBs vs PTA in patients with chronic limb ischaemia,[7,8] but further trials with different and more evolved devices may provide evidence to justify a broader indication for use of DCBs.

How do you expect the treatment landscape to change in the future?

AM: The best available technology should always be used to try and give patients the best possible outcome. Some could even consider it unethical to knowingly use a device that is less effective. This mindset leaves little residual room for the role of a plain balloon, except in the treatment of very short lesions of less than 4 cm. For all other lesions, I would recommend DCBs as the first line of treatment. In the case of restenosis, I would go directly to the DCB, even for patients with a lesion length of less than 4 cm.

There are always ways to help optimise DCB technology. For example, developing a longer DCB at say 300 mm would likely allow for easier treatment of patients, which could help to reduce

the time of the procedure. Being able to use just one balloon is always more beneficial, and optimising drug release could increase efficacy.

Overall, I foresee complementary use of DCBs and stenting. I don't think it is a case of one versus another; they are not fighting. The results of the SFA studies have shown rigorous and robust evidence for the IN.PACT DCB technology and given physicians data that they can rely on and use in their daily practice. I expect to see a large role for DCBs in the future; however, we cannot give up the chance to have a wider portfolio of technologies to treat the whole spectrum of the disease.

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REFERENCES:

1. Olin JW, et al. *Mayo Clin Proc* 2010;85(7):678–692.
2. Krishnan P. Presented at Vascular InterVentional Advances (VIVA) 2016, Las Vegas, NV, USA.
3. Scheinert D. Presented at EuroPCR 2015, Paris, France.
4. Brodmann M. Presented at Vascular InterVentional Advances (VIVA) 2015, Las Vegas, NV, USA.
5. Tepe G. Presented at Charing Cross Symposium 2016, London, UK.
6. Micari A, et al. *JACC Cardiovasc Interv* 2016;9(9):950–6.
7. Zeller T, et al. *J Am Coll Cardiol* 2014;64(15):1568-76.
8. Zeller T, et al. *J Am Coll Cardiol Intv* 2015;8(12):1614-22.

DISCLOSURES: Dr Micari is a consultant to Medtronic and Spectranetic, and is on speaker bureaus for AstraZeneca, Bard, Boston, Spectranetics and Terumo. He has an institutional grant from Medtronic and offers research support to Medtronic.