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IN.PACT SFA: benefits of a drug-coated balloon for the treatment of superficial femoral artery lesions persisting at 2 years

Drug-coated balloons are the latest addition to the endovascular toolbox for the treatment of peripheral artery disease. These balloons release an antiproliferative drug to limit restenosis of the vessel, a problem that is frequently seen after percutaneous transluminal angioplasty. *Confluence* spoke to Professor Thomas Zeller, Head of the Department of Angiology at the University Heart Centre Freiburg-Bad Krozingen, and Professor Frank Vermassen, Professor in Vascular and Thoracic Surgery at Ghent University, to discuss the recently presented 2-year results from the IN.PACT SFA study. The study investigated the use of the IN.PACT® Admiral® drug-coated balloon, compared with percutaneous transluminal angioplasty for the treatment of femoropopliteal lesions.

What is peripheral arterial disease?

Thomas Zeller (TZ): Peripheral arterial disease (PAD) is a systemic manifestation of arteriosclerosis. Besides the peripheral arteries, it can also affect the coronary and cerebral circulation. About 50% of patients suffering from PAD also have concomitant manifestation at the heart and the brain. For the last few years we have seen the incidence of PAD increase, because the disease is directly linked with the prevalence of diabetes mellitus, which we are also seeing increase due to rising body mass indexes.

In PAD in the lower limbs, we distinguish between claudication and critical limb ischaemia. Claudication is characterised by symptoms such as muscle pain, which may affect the calf or the entire leg, and limitation of walking distance. Critical limb ischaemia is an advanced stage of PAD, where the limb is at risk of amputation within weeks to months. Patients usually suffer from rest pain and/or wounds that heal slowly or not at all. The diabetic population, in particular, may progress directly to critical limb ischaemia without having had significant claudication, and such patients may not have complained of any limitation in walking distance prior to developing wounds.

What treatments are available for such patients?

TZ: We would use a staged treatment strategy starting with so-called conservative treatment, which includes risk factor modification, i.e. controlling hypertension and hyperlipidaemia – so statins are a key part of conservative management. Next, we would aim to control the diabetes, if present, and, of course, nicotine cessation. For claudicant patients, we also recommend supervised exercise training. If this basic, conservative treatment is not effective in improving the patient's quality of life sufficiently, the next step is revascularisation therapy.

Today, in the claudicant population, revascularisation means an endovascular revascularisation for more than 80% of the cases; the indication for surgical revascularisation has become rare. There are two main indications for surgical interventions; firstly, involvement of the common femoral artery (with or without involvement of the femoral bifurcation) is a valid indication for an endarterectomy, and secondly in some cases of aorto-iliac artery disease, particularly if the aorta is occluded, there is still an indication for bypass surgery. Due to the high primary success rates of endovascular therapy, femoropopliteal bypass has become a rare indication in the claudicant population.

Frank Vermassen (FV): It has been over 20 years since the first stents were used in the superficial femoral artery (SFA), and the history of stents in the SFA has been one of successes and failures. Stents are very good for treating problems such as dissection or early restenosis, but in the longer term, because the stent is a foreign object implanted in the vessel, it does not really prevent late restenosis. If you have restenosis in a stented area, it is more difficult to treat than restenosis in an artery where there is no stent.

Over the past few decades, we have been looking for methods to improve results after percutaneous transluminal angioplasty (PTA) in the SFA. Many strategies have been tried to prevent restenosis, including atherectomy, cryoplasty, lasering and covered stents, but none of these methods have proven to be more effective than simple balloon angioplasty and stenting.

We had the same problem with restenosis, as was seen after simple angioplasty in the coronary arteries, and to a large extent this was solved by drug-eluting stents; putting a drug that prevents late restenosis on the stent. In the beginning we thought that the same solution would work for every blood vessel, but that is not the case, illustrating that, although these are all blood vessels, vessels in one territory have other properties and need different treatments than vessels in another territory Now, for the first time, there is a method which might actually prove to be effective in the peripheral arteries. We use a drug-coated balloon (DCB) to deliver the drug to the blood vessel and not worry about stents. This seems to be at least as effective as drug-eluting stents in preventing late restenosis, while at the same time avoiding the presence of foreign material in the SFA.

We also see that the stent rate for acute problems, such as flow-limiting dissection and recoil, is far less in the DCB trials than historical studies, without negatively influencing the results.

Are efficacy and safety outcomes better with endovascular procedures than surgical procedures?

TZ: The main reason for not operating in claudication is basically safety. With surgical procedures there are certain complication risks, which are considered to be lower with endovascular procedures, and this is one reason why claudicants are mainly treated by endovascular means. The other reason is that over the last decade, the outcome of endovascular procedures has improved significantly, mainly as the result of the introduction of drug-eluting technologies, like drug-eluting stents and DCBs.

Critical limb ischaemia it is a somewhat different situation and bypass surgery is still considered a viable alternative option compared to an endovascular approach.

Could you give an overview of the study design, objectives and endpoints of the IN.PACT SFA study?

TZ: The IN.PACT SFA study was a pivotal study designed to support the approval of the IN.PACT® Admiral® DCB (Medtronic Inc. Minneapolis, MN, USA) from the US Food and Drug Administration in the US market.[1] The study compared the IN.PACT® Admiral® DCB against plain balloon angioplasty. We enrolled about 150 patients in Europe, followed by an additional 181 patients in the US.

FV: It was quite a large controlled trial with over 300 patients, randomised 2:1 to the active treatment, which was the DCB.

TZ: There were two primary endpoints. The efficacy endpoint was primary patency, so patents without a redo procedure. The safety endpoint was a composite, defined as freedom procedure or device-related death to 30 days and freedom from major amputation of a target limb or clinically-driven target vessel revascularisation (CD TLR) to 12 months.

The inclusion criteria allowed most of the indications that are commonly treated in the SFA. The mean lesion length, as compared to that in many previous studies, was actually quite long at almost 9 cm. Increasing lesion length results in a higher probability of developing restenosis. As such, the lesions permitted in the inclusion criteria of the IN.PACT SFA trial were somewhat more challenging compared to those in earlier bare metal stent trials. Despite the longer length, these lesions are still classified as Trans-Atlantic Inter-Society Consensus (TASC) II A or B lesions, which are not considered to be very challenging lesions. The IN.PACT Global study is a non-randomised study that enables us to look into complex lesions, such as very long length lesions or in-stent lesions.[2]

fig. 1

Kaplan–Meier estimate of primary patency (A) and freedom from clinically driven target lesion revascularisation (B) in the IN.PACT SFA trial at 2 years. Error bars represent 95% confidence interval.

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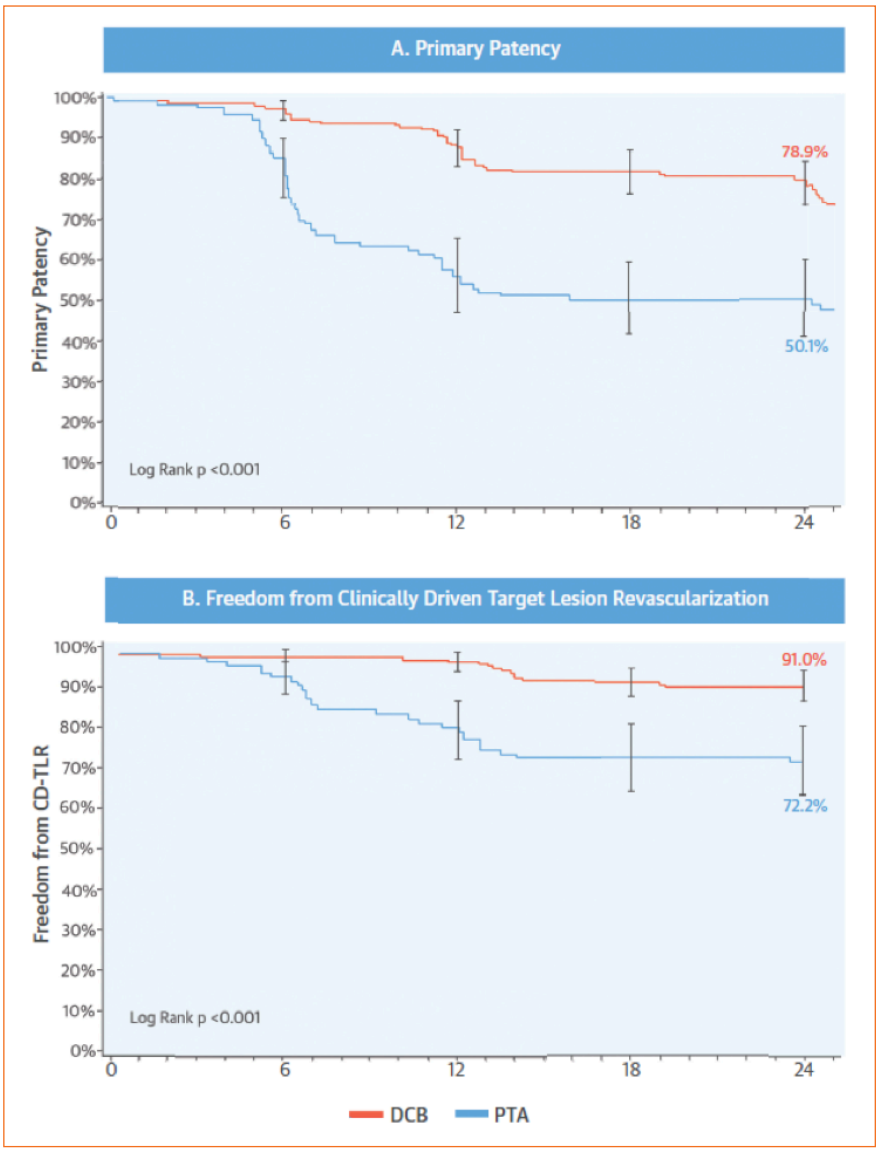

What were the findings from the IN.PACT SFA study?

FV: Looking at the results obtained after the first year, these are already extremely good results. There were no device- or procedure-related deaths and no major amputations.[1] Primary patency was higher with DCB than PTA (82.2% vs 52.4%; p<0.001) and there was also a significantly lower rate of CD TLR with DCB than PTA (2.4% vs 20.6% p<0.001). Both arms had a low rate of vessel thrombosis (1.4% after DCB, 3.7% after PTA; p=0.10). These results have now been confirmed in the second year.[3] This means that not only is there a large difference between the DCB and the plain balloon, but also that the results with the IN.PACT® Admiral®, compared to studies performed in similar populations, are probably the best that have been achieved, with almost 80% primary patency at 2 years. Of course, as in every study, not all patients with femoral artery lesions could be included, but only those that fulfilled the inclusion criteria. We have to await the results of other studies, such as the IN.PACT Global study, to know whether these results can be extended to all lesions in the SFA.

TZ: In this well-matched, randomised study, the DCB clearly outperformed the plain balloon cohort in terms of a highly significant better primary patency rate at 2 years (78.9% in the DCB group vs 50.1% in the PTA group, p<0.001; figure 1).[3] In addition, significantly more patients reached the composite safety end point in the

DCB group than the PTA group (87.4 vs 69.8%, p<0.001). This was mainly driven by the TLR rate, which was clearly in favour for the DCB. In the DCB cohort, TLR rate at 1 year was only 2.4%, which is the lowest revascularisation rate ever reported for a peripheral artery trial so far, so the device has proven to be highly effective in improving patient outcomes. At 2 years, the TLR benefit was sustained, meaning there was still a difference of about 20% in absolute numbers in favour of the DCB (9.1% vs 28.3%, p<0.001). These data are in line with those from the ILLUMINATE FIM study,[4] which was a small, single-arm feasibility study using the Stellarex™ DCB (Spectranetics, Colorado Springs, CO, USA). Two-year outcomes from both of these studies outperformed those from the LEVANT 2 study,[5] in which the performance of the Lutonix™ 0.35 DCB (Bard Peripheral Vascular Inc., Tempe, AZ, USA) was investigated in almost 500 patients compared to regular balloon.

What do you think it is about the IN.PACT® Admiral® DCB that has given such good efficacy results?

FV: It is not only about the balloon, but also about the drug and the way the drug is delivered to the blood vessel. The balloon can deliver the drug to the vessel wall. There are a lot of DCBs in development and coming to the market now. A simple balloon is a purely, or mostly, mechanical device. This is not the case with DCBs. There is much more involved here; the way that the drug is delivered to the blood vessel, the way the drug is bonded to the balloon, the concentration and formulation of the drug, all can vary from one DCB to the next. All of this means that you cannot take for granted that results obtained with one DCB will be the same with another one. This might well be the reason why results from the LEVANT trial,[6] which are also positive for the Lutonix DCB (Bard Peripheral Vascular Inc.) are, let's say, less good than the results from the IN.PACT SFA study.

TZ: The technical performance of DCBs, in terms of drug delivery to the vessel wall and drug persistence in the vessel wall, depends on multiple components, such as the interaction of the antiproliferative drug, paclitaxel, with the excipient, the binding energies between the balloon material and the drug, and the crystallinity of the drug coating (as compared to a more amorphous condition of the drug coating). All of these factors seem to be balanced with the IN.PACT® Admiral® coating, resulting in the positive clinical outcomes in femoropopliteal lesions treated with IN.PACT® DCBs.

We understand that the results from the IN.PACT SFA study have been analysed in different subgroups. Were any differences identified for specific populations?

TZ: The subgroup analysis showed that all patient groups benefitted from the use of DCBs. What we know from other trials is that there are some interventional procedures where, for example, diabetics do not benefit as much as non-diabetics. This has been found in earlier bare-metal stent studies.[7] The IN.PACT SFA study is unique in that all patient groups benefitted from the use of the DCB. This includes both female and male patients, diabetics and non-diabetics, and every lesion length. This differs from the findings of, for example, the LEVANT 25 study, where female patients in particular did not benefit from the use of the Lutonix DCB (Bard Peripheral Vascular Inc.). It is a unique finding from IN.PACT SFA, that there were no exceptions in terms of benefit, regardless of which subcohort of patients was investigated. The lesson here is that not every DCB is alike. There are differences in performance between different DCBs and, in terms of their efficacy, there is no generalisable effect. Therefore, the performance of each individual DCB has to be investigated individually and every new device which comes to the market has to show that it is effective. You cannot simply refer to another study outcome to demonstrate a class effect.

What effect do you think these positive outcomes from the trial will have on clinical practice?

FV: I believe these results will change practice. When the 1-year results were published, everybody was a bit astonished that this difference had been obtained. There were already a lot of smaller studies indicating that this would probably work, but the fact that the concept was shown to work in larger studies was important. With a lot of studies, after 1 year you start to see a catch-up effect, so although the 1-year results were promising, this is a bit short. Now we have seen that the treatment effect is sustainable at 2 years, so yes, I think that

this proves in the longer term that these DCBs will be effective. I think that this will convince quite a lot of people who were a bit reluctant to use it at first, because once we have the 2-year results, these are usually also confirmed in the longer term.

TZ: In my institution we have adopted the use of DCBs as the first-line strategy for more than 3 or 4 years now. This means that about 90% of all patients with superficial femoral artery disease seen at our institution are treated with DCBs. There are also other German centres, for example Leipzig, where they do the same. There are some indications for atherectomy device or for primary stenting but, besides that, the mainstream treatment strategy is to use DCBs in this indication. Stenting should be reserved as a last resort.

We have good evidence that DCBs, in particular the IN.PACT® Admiral®, do work in all kinds of lesions, including short lesions, called TASC II type A lesions, which, in the past, have been considered an indication for plain balloon angioplasty. The IN.PACT SFA study clearly showed that even short lesions do better if a DCB is used as compared to a plain balloon. Furthermore, based on the outcome of the IN.PACT SFA Global study,[2] which included long lesions and in-stent restenotic lesions, we see that the performance of DCBs seems to be almost independent of lesion length. That means even long lesions show exciting benefits in terms of high primary patency rates (91.1% at 1 year) and low re-intervention rates (6.0%). It seems that the IN.PACT technology, in particular, is extremely effective in almost every kind of femoral popliteal lesion morphology.

Is there a need for treatment guidelines to change to reflect this?

TZ: Yes, of course, and this will come soon. The next time international guidelines are updated, the published evidence on DCB angioplasty will be implemented in those guidelines. The European Society of Cardiology (ESC) is in the process of updating their guidelines, and the German Vascular Society has recently finished an update of their guidelines, which will be published in the first quarter of 2016.

The problem with publishing guidelines is that they only include data published in peer reviewed journals; data presented at congresses are not allowed. This means that if up-to-date study outcomes are presented at global meetings, those data cannot be included in a guideline paper, and this basically means that guidelines are not up-to-date. Usually, the process of publishing new guidelines takes about 3 years, so after finishing the analysis of the published literature, it will take 1.5–3 years for those guidelines to be published, and in the meantime, new, more up-to-date data are published or presented.

When the last ESC guidelines were published in 2011, only first-in-man studies for DCBs had been published. What is considered class I evidence, i.e. randomised, controlled trials or meta-analyses, had not been published at that time. The new, upcoming guidelines will include the evidence from the published data of IN.PACT SFA 1- and 2-year outcomes, and also the LEVANT 2 study.[5] Those studies have shown a benefit as compared to plain balloon angioplasty and that means those DCBs will be added as a first-line strategy in the treatment of femoropopliteal disease in future guidelines.

There is a move towards trying to avoid stenting in peripheral lesions. How often do you find yourself having to resort to adding a stent in particularly challenging lesions?

TZ: Two different schools of thought exist in the interventional community. One school believes in stents and uses them in almost every lesion, either drug-eluting stents or bare-metal stents, like the Supera stent (Abbott Vascular, Santa Clara, CA, USA). The other opinion is to avoid stenting as much as possible and it is this school that is promoting the use of DCBs. If indicated, prepare the vessel up front with atherectomy or plaque modulation balloons, such as Cutting Balloon (Boston Scientific, Marlborough, MA, USA) or Scoring Balloon (Spectranetics), in order to avoid secondary stent placement as much as possible, so that patients do not have a foreign body *in situ* in the long term. The beauty of DCBs is that their use results in really outstanding patency results in almost all lesion morphologies without a clear need for stents.

Studies have shown that as lesion length increases, the stent rate also increases. In the IN.PACT SFA study, stent use was about 7% in the DCB arm with a mean lesion length of about 9 cm. If you look

at the Long Lesion cohort of the IN.PACT Global study, where the mean lesion length was 26 cm, the stent rate was about 40% for the entire cohort. Within this registry there was a subgroup analysis looking at lesions 15–25 cm, and another cohort with lesions longer than 25 cm. In the shorter lesions cohort (up to 25 cm), the stent rate was 33%, so that means every third patient received at least a focal stent. In the really long lesions cohort (over 25 cm, up to 40 cm), every second patient (about 53%) needed a stent.

However, another study from an Italian registry was recently presented by Antonio Micari, also looking at long lesions with a mean lesion length of 26 cm.[8] They used a dedicated balloon angioplasty protocol, resulting in much lower stent rates of about 10%. They used an aggressive protocol with prolonged pre-dilatation of the lesion (3 minutes), prolonged DCB inflation (3 minutes) and even post-dilatation with a plain balloon if the outcome was not satisfactory after the DCB up to 5 minutes. If you follow such dedicated balloon angioplasty protocols, the need for stenting is still in the range of only 10–20%, even in long lesions. This is due to persisting dissection or acute recoil, mainly induced by severe vessel calcification.

There are a number of different DCBs on the market. What factors do you think should influence a physician's choice around which particular balloon to use?

FV: As I already mentioned, you cannot assume that the results for one balloon will also be obtained with another one. This is because the excipient is different, the concentration of the drug can be different, the way the drug is applied to the balloon may be different, so there are a lot of parameters which can vary from one balloon to the next. Physicians should use whichever DCB has been shown to be effective during clinical studies.

Do you think that the DCB will become the standard of care for SFA disease?

FV: I think it will for the vast majority of cases, yes. The subgroup analysis from IN.PACT Global study shows that it is also effective in long lesions of over 20 cm. We know that in very calcified lesions it might be less effective so some additional treatment might be indicated, and there are still some lesion types in which we do not yet know for sure. For instance, in restenosis we are expecting more data soon, but I am convinced that for the vast majority of native lesions it will prove to be effective.

There is still the issue of price, and perhaps for people with very simple lesions it might still be appropriate to use a simple PTA, but for the vast majority of lesions, and maybe even for all lesions, this will become the first choice of treatment.

TZ: Reimbursement is one of the challenges to the adoption of DCBs. Some countries, such as France and Italy, will only reimburse stents, while in Germany and some other countries, they will also reimburse DCBs. In my view, DCBs do have many advantages over stenting and there is no reason not to switch.

Are there any further studies needed in order to convince us of the effectiveness and usefulness of this type of treatment?

FV: We not only have the randomised clinical study, but also the IN.PACT Global study, which is a registry with a lot of patients. These registry data will provide more information about subgroups that were not included in the IN.PACT SFA study.

Of course, you can always argue that more studies are necessary. For example, there are no randomised head-to-head comparisons between two different DCBs. You could consider doing studies investigating a combination of, for instance, atherectomy and DCB, or DCB and bioresorbable stent, but for clinical practice, we already know a lot from the IN.PACT SFA and the IN.PACT Global studies, these already tell us a lot.

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