Gunnar Tepe

Should drug-coated balloons be the primary treatment choice for upper leg obstructive disease?

As drug-coated balloons become ever more widely used in clinical practice, *Confluence* caught up with Professor Gunnar Tepe, Chief of Radiology at Klinikum Rosenheim in Germany, to find out more about how these devices are being used to manage peripheral artery disease.

Could you tell us about your work as an investigator and practitioner in peripheral artery disease?

Professor Gunnar Tepe (GT): I have carried out peripheral artery intervention for quite some time: for at least 12 years in Tübingen and right now for five years here at Rosenheim. The biggest patient cohort are those with claudication and who have superficial femoral artery (SFA) and popliteal artery lesions.

The problem in these patients is that even if the initial treatment is a technical success, the tendency to develop a longer occlusion or restenosis is very high. This is clearly a problem. A few years ago we were placing a lot of stents, which give good acute results, but stents have a tendency to restenose within 1 year, especially in longer lesions. In-stent restenosis is something that should be avoided as this can lead to the need for another intervention, and even after this there is very high chance of subsequent restenosis.

Due to the limitations with stenting, we needed to develop a therapy that prevented restenosis while leaving nothing behind: drug-coated balloons (DCBs) meet both requirements. We first tried a homemade, first-generation DCB together with Professor Speck in the THUNDER trial[1]; the balloon was then further developed by Medtronic, Inc., as the IN.PACT Admiral balloon. I had the chance to use that balloon in the IN.PACT SFA study[2] and, overall, I think this study strengthened my confidence in the use of DCBs.

How did the idea to use a balloon rather than using stenting come about?

Initially, Professor Speck and I were trying to find something to visualize plaque or stenosis with scintigraphy (used in nuclear medicine imaging) for diagnostic purposes. Later on, we progressed from only diagnostic indications to treatment and developed a radioactive stent. However, at the time when I was at the University of Tübingen, there was a group in cardiology who were investigating paclitaxel for local control of proliferation after percutaneous transluminal angioplasty (PTA); it turned out that this compound was rather effective.

We took this idea and thought 'Okay, what about just coating balloons?' and we developed the first DCBs. Initial animal experiments showed that the technology worked fine and we could show that paclitaxel is a very good compound, and that the so-called spacer on the surface of the DCB, which helps the paclitaxel to get into the vessel wall, is also very important. The first balloon developed for coronary artery disease was tested by Professor Scheller[3]; in the peripheral artery, I was the first to test the DCB in the THUNDER trial.[1]

Based on positive results in both coronary and peripheral arteries, there was a lot of enthusiasm and a lot of companies jumped on that idea and tried to develop DCBs. One of the balloons that was developed in a very close partnership with Professor Speck was the IN.PACT balloon.

What does the perfect drug-coated balloon look like for peripheral artery disease?

The perfect balloon is the balloon that works. While all DCBs available have paclitaxel, they are not all the same. The key is not how much paclitaxel is on the surface of the balloon, but the amount that goes into the vessel wall and has an effect on preventing restenosis. It is very important to have a DCB with high efficacy and I think that efficacy can only be shown if you have clinical

data, not in small patient cohorts but in big patient cohorts with a control. It is important to have even long-term follow-up beyond 1 year, for example up to 5 years. Right now we have the IN.PACT SFA data carrying out to 1 year but the patients will be followed up to five years. At least in our hospital we follow the patients, every patient has follow-up currently up to 3 years and there will be further follow-up for up to 5 years.

Thinking about SFA therapy, in the future it would be good to have balloons with more predictable dose delivery. At present, we only deliver to approximately 15% of the vessel wall but we never know whether it is 15% or 20%. Furthermore, we would like to have devices available in order to enhance the uptake of drug delivery in the vessel wall, for example cutting balloon technique or atherectomy to enhance the uptake. It would also be good to explore other drugs, apart from paclitaxel or even DCBs with different doses because some patients, such as those with restenosis or diabetes, might need a higher dose.

Considering use below the knee, there are a number of areas where further development of DCBs will be required. First of all in critical limb ischemia (CLI) patients, only 10% or 15% of the drug is really delivered to the vessel wall and there is a lot of downstream of paclitaxel, so this might not do any good to wound healing and might be a problem.

Also, it might affect efficacy if you don't have enough drug on the balloon, so for below the knee I think the coating should be different and also the surface of the balloon might be different. That might be a top coat or something like that because right now, when pushing the balloon towards the lesion, you lose a lot of drug and then of course, due to the coating, there is no hydrophilicity so it is very difficult to push a balloon towards the lesion. Below the knee we will have to look for much more improvement because the current versions have a lot of limitations.

What is the treatment algorithm and pathway for a typical patient being treated with a balloon for femoropopliteal artery disease?

The current data strongly suggest the use of a DCB first-line. Currently in our hospital, only the very short and very easy lesions are treated by plain balloon angioplasty because those do quite well with only 20% or 30% restenosis and it is unlikely that DCBs would provide a considerable benefit in these patients.

However, if the lesion gets more challenging and a little bit longer – at least a TransAtlantic Inter-Society Consensus (TASC) B or C lesion, then a DCB should be used. In these patients we only rarely carry out primary stenting; we just do spot stenting if necessary. Pre-dilatation of the lesions is not necessary unless we cannot pass the lesion with a DCB.

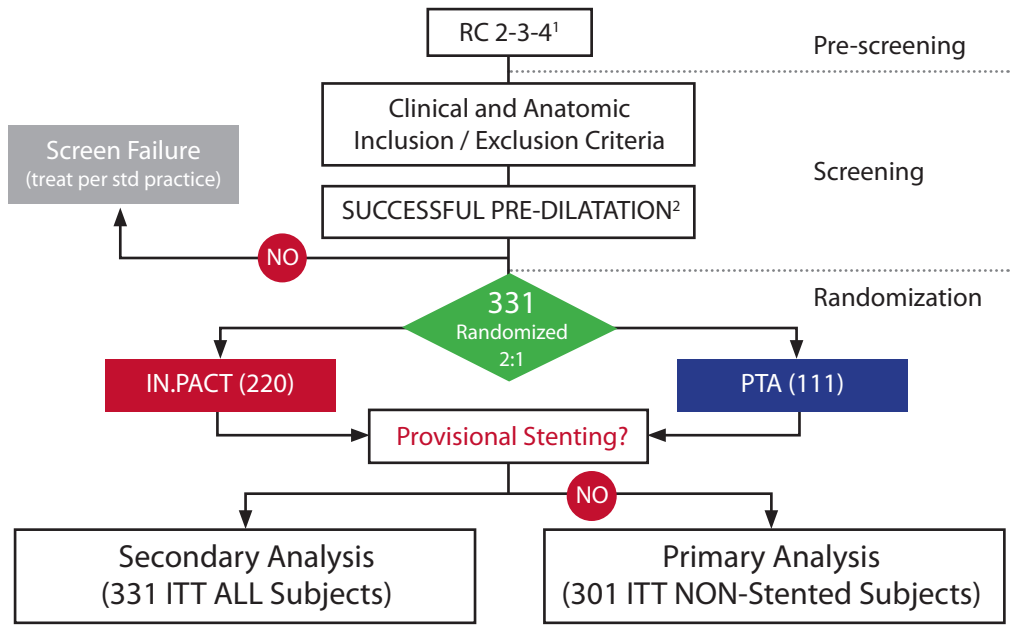
Could you perhaps give us an overview of the IN.PACT SFA trial and its results?

The IN.PACT SFA trial was a very robust trial because it was prospective, multi-centre, randomized blinded and controlled trial. To ensure data accuracy and reliability, patency endpoints underwent evaluation by an independent imaging core lab (including ultrasound and angiography), while all clinical events were adjudicated by an independent clinical events committee. Both the imaging core lab and the clinical events committee were blinded to the randomization of the patients. In addition to that, we had 100% source data verification, so that made the results very strong.

The trial was done in two phases. The first phase, called IN.PACT SFA I, was done in Europe with 150 subjects, and the second phase called IN.PACT SFA II was done in the US with 181 subjects using a similar trial design. Therefore, in total we had 331 subjects randomized to the trial and those patients were randomized to receive either DCB therapy with an IN.PACT Admiral balloon or PTA (figure 1). Inclusion/exclusion criteria were similar to those in other DCB trials. Interestingly, however, there was a lower limit of lesion length allowed, so patients with a lesion length less than 4cm (and not longer than 18cm) were not randomized. This had an impact on the baseline characteristics with a mean lesion length of almost 9cm in IN.PACT SFA, while other DCB studies have 6cm or 7cm lesions. This is very important because lesion length correlates with outcomes and so we were dealing with a more challenging cohort. We had a primary efficacy endpoint and a safety endpoint for the study population: efficacy was primary patency throughout 12 months defined as freedom of clinically-driven target lesion revascularization (CD-TLR) and restenosis. The safety endpoint was a freedom from device- and procedure- related death

fig. 1

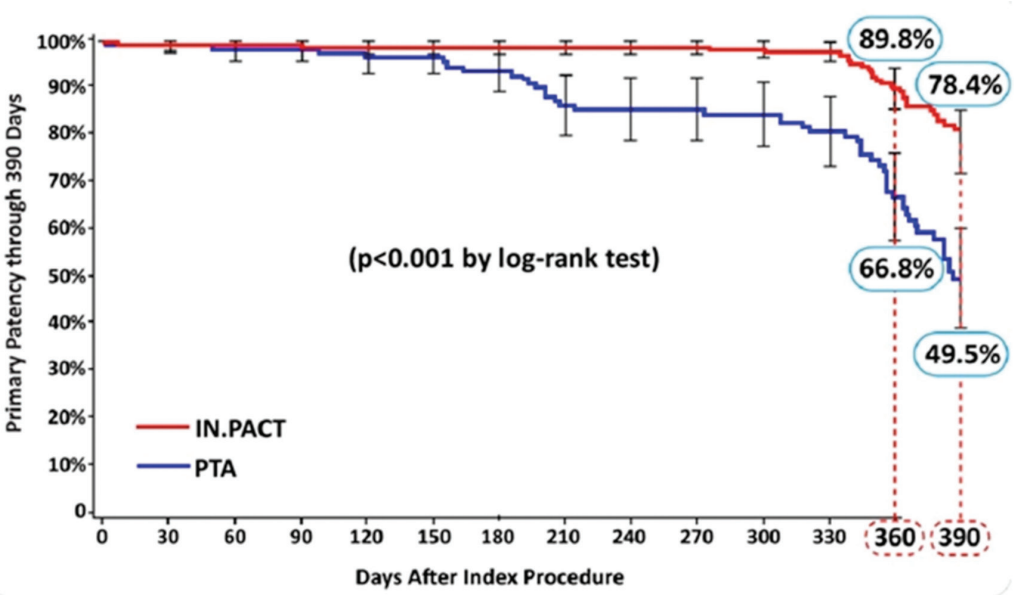
Study design and patient flow in the IN.PACT SFA trials



1. With symptoms of claudication and/or rest pain and angiographic evidence of SFA/PPA stenosis
2. Pre-dilation mandatory for all subjects in IN.PACT SFA II phase only

fig. 2

Primary patency at 12 months in the ITT population. Primary patency was defined as freedom from clinically driven TLR and freedom from restenosis as determined by duplex ultrasound peak systolic velocity ratio ≤2.4



through 30 days, and freedom from target limb major amputation and clinically driven target vessel revascularization through 12 months.

The primary patency was significantly better in the DCBs. After one year we have almost a 90% primary patency rate by Kaplan Meier in the IN.PACT Admiral group versus 66.8% for the uncoated balloons (figure 2). This translated to a highly statistically significant difference in the clinically driven TLR rate; it was only 2.4% in the IN.PACT balloons versus 20.6% in the uncoated balloons. The balloons were also shown to have good safety profiles; no major amputations, a low thrombosis rate, and no other safety concerns were noted for the IN.PACT balloon.

It should be pointed out that, unlike in my clinical practice, pre-dilatation was mandated by the protocol in almost every IN.PACT patient: 96.4%

in DCB versus 85.6% in PTA. Post-dilatation was also carried out: 26.8% DCB versus 18.9% PTA. This led to a very low stenting rate in both groups at 7.3% in DCB versus 12.6% in PTA. There was only one dissection greater than a Grade D in the PTA group identified by the core lab.

In conclusion, we now have robust, level one evidence for the IN.PACT DCB demonstrating the lowest TLR rates and highest patency rates in the SFA ever reported. This really drove a lot of the enthusiasm at the Charing Cross Meeting (April 2014, London, UK), where the results were presented. This treatment with the IN.PACT balloons has the potential to become the standard of care for SFA treatment.

How do you feel these data will be applied to clinical practice? Are the results going to be relevant to the person working in the cath lab?

I think it's very relevant and the message is that IN.PACT Admiral balloon significantly better performs than normal treatment with PTA in the patients included in the SFA study and, therefore, patients should be given the opportunity to receive DCB treatment. I think DCBs will be the standard of care in almost every patient in the future and this trial helps to drive this paradigm shift.

Considering the LEVANT 2 trial results in which patients with stenotic femoro-popliteal arteries randomized to either a DCB (Lutonix, Bard) or standard balloon angioplasty where it appears that different DCB technologies have differing results. What perhaps could account for this?

The drug is the same; it's just the coating that is different. Of course there is not so much drug on the surface of the Lutonix balloon but I don't think this is the main point. The different coating may lead to a lower rate of drug uptake in the vessel, which may have an impact on the TLR rates. This may also explain the limited benefits of the DCB in this trial comparing with PTA.

What are the remaining unmet needs for patients with this peripheral artery disease and what can we do to overcome those problems?

There are still a lot of unmet needs. We have made great strides with DCB but we still have a restenosis rate after 1, 2 or 3 years of 15–20%: this is still higher than in the coronary arteries, so there is a lot of room for improvement here. Also as I said, we have to do more research on patients with calcified arteries or long lesions.

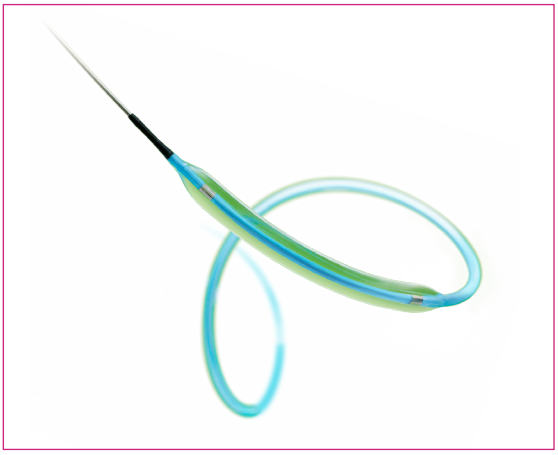
Then there is the big area of below the knee artery disease, in which we see good results after PTA but high restenosis rates; at present we do not know what we should do about those restenosis rates because we do not have any balloon with proven outcomes available in this area.

Are there any other trials needed do you think to convince physicians of the value of this technology?

Long-term data are very important up to five years. It can be a challenge to convince physicians because during the intervention you have just a balloon-like result, nothing else, not like a stent for example. It is only once the patient is followed that he learns that the patency is very good six months or one year later. Once they see really great results either with ultrasound, angiography or MRI, the physicians will be convinced.

The second thing is patients have to be convinced, and patients have to really come back to the physician and say 'Hey, I am doing really well even after one year, no problem with restenosis and I can do sports'. If they can resume their normal life and do whatever they want, this also convinces the physicians.

We have to have data to support the use of DCBs, but it is also personal experience both in the cath lab and the patients that is crucial.



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