Drug-Eluting Balloons in the SFA

Dierk Scheinert, MD, discusses the THUNDER and FemPac trial results and previews new studies that will evaluate drug-coated balloons versus plain old balloon angioplasty.

How would you briefly describe the current state of clinical studies evaluating drug-eluting balloon (DEB) use in the superficial femoral artery (SFA)?

DEBs are certainly one of the most exciting technologies that have become available in recent years, and based on the early randomized experience from the THUNDER study and the FemPac study, there is a lot of interest and promise for this technology.[1,2] In fact, both studies have shown a significant reduction of neointimal proliferation for the paclitaxel/iopromide-coated balloon as compared to standard balloon dilatation, measured by late lumen loss at 6 months. Moreover, standard efficacy parameters such as binary restenosis and target lesion revascularization (TLR) rates showed a significant and sustained improvement with this new technology up to 2 years.

Nevertheless, because the efficacy of a DEB may be largely dependent on the dose and formulation of the active coating, no general conclusions can be made for different DEB devices. It will be mandatory in the future that efficacy and safety data are provided for every individual commercially available product.

What are the major trials, and where are they in terms of their completion and follow-up?

The most relevant clinical publication to date is certainly the THUNDER trial, published by Dr. Gunnar Tepe in 2008 in *The New England Journal of Medicine*. This prospective, randomized, multicenter study compared the use of a paclitaxel/iopromide-coated balloon (n = 48) with plain old balloon angioplasty (POBA) (n = 54) and another control group with balloon angioplasty plus drug infusion and showed a significant reduction of the angiographic late lumen loss at 6 months for the actively coated balloon (0.4 ± 1.2 vs 1.7 ± 1.8 mm, $P < .001$). This also corresponded to a significant reduction of the 6-month binary restenosis rate (17% vs 44%, $P = .01$). To date, follow-up information has been published up to 24 months, confirming a sustained significant benefit as measured by binary restenosis and TLR rates.

The FemPac trial, published by Werk et al in 2008, can be considered a confirmatory study using a similar design with a total patient number of 87 randomized 1:1 into the two treatment arms: drug-coated balloon versus POBA. Although the lesion length was somewhat shorter in the FemPac study (4–4.7 cm) as compared to the THUNDER study (7.4–7.5 cm), the FemPac study showed a similar reduction in late lumen loss (0.3 vs 0.8 mm, $P = 0.031$). Also in this study, the effect was durable up to 2 years, as demonstrated by significant new reduced TLR rates in the drug-coated-balloon arm.

Other clinical investigations using similar clinical trial designs but new drug coating formulations with different dose and coating additives are currently underway. The Advance 18PTX trial uses a randomized comparison of a novel paclitaxel-coated balloon by Cook Medical (Bloomington, IN) as compared to their uncoated product. The originally planned study population of 100 patients has been enrolled; however, the study has recently been reopened to enroll another 50 patients to reach adequate statistical power.

The LEVANT I study by Lutonix, Inc. (Maple Grove, MN) has also recently completed enrollment of a total patient number of 100, randomized 1:1 into the treatment arms: drug-coated balloons versus POBA. Follow-up of both studies is ongoing, and initial results are expected to be presented in the fall of 2010.

Are the inclusion criteria and follow-up protocols fairly standard, or is there anything unique in terms of their design?

The study designs of the ongoing clinical trials indeed are fairly standardized with regard to their design and inclusion criteria, clearly focusing on intermediate length lesions up to 15 cm. All studies used the prospective, randomized, multicenter design in an attempt to allow direct comparisons for safety and efficacy with POBA. The use of a late lumen loss at 6 months as the primary efficacy endpoint has to be considered a surrogate, which has been adopted by all studies to be comparable to the initial publications of the THUNDER and FemPac studies. In the future, more typical endpoints such as binary restenosis and TLR rates should gain more attention to make these new technologies easier to compare with standard devices, including nitinol stents.

For those trials in which data are available, to what degree do the data support the use of a DEB over standard angioplasty? Over uncoated nitinol stenting?

It is difficult to draw final conclusions of the value of DEBs from the limited clinical trial experience. However, as I described, both the THUNDER and the FemPac studies demonstrated significant reduction of binary restenosis and TLR rates, which where sustained at up to 2-year follow-up, supporting a claim for general superiority of drug-coated balloons over plain angioplasty. Comparative data to nitinol stenting, which recently has become more and more a first-line treatment option for complex SFA lesions, are not yet available.

In which patients and lesions have there been the greatest benefit?

There have been attempts by the clinical investigators to provide efficacy comparisons for different lesion subgroups. In fact, it has been shown that the late lumen loss in the THUNDER study was fairly comparable for easier and more complex lesions subsets; however, there is no adequate statistical power for such subgroup comparison.

Have the trials shown any patient or lesion subsets in which the use of DEBs does not improve over the results with standard angioplasty?

So far, there has been no subgroup of lesions identified that would not respond to a DEB treatment; however, there is probably a relevant proportion of complex lesions that cannot be treated by angioplasty alone. Particularly calcified and bulky lesions may require additional mechanical treatment approaches, such as stenting or atherectomy, to optimize the acute luminal gain. The efficacy of a combined treatment approach of DEBs plus stenting or atherectomy has not yet been studied. However, there are several projects underway that will specifically focus on the combination of atherectomy procedures and drug-coated balloons.

Do the results with DEBs support the use of a potentially more expensive technology? In other words, are the patient outcomes better or more durable than standard angioplasty to the degree that they are still cost-efficient?

I am not aware of a health economic assessment of the use of DEBs compared to balloon angioplasty and other adjunctive treatments. However, if the significant reduction of restenosis and subsequent TLR can be confirmed by the ongoing clinical trials, a health economic benefit of DEBs seems to be very likely. To further elucidate this benefit, it would be, from my perspective, very appealing to design other studies in the future that would compare DEBs with other established treatment modalities, such as primary stenting. I believe this would allow potentially interesting conclusions on the cost effectiveness of DEBs.

Is there any increased potential for adverse outcomes related to the presence of a drug in the vessel or lesion, such as a thrombosis?

The use of DEBs has been shown to be safe, and no systemic or local complications have been reported. Because the current experience is limited, it remains mandatory to systematically monitor patients after treatment with drug-coated balloons for adverse outcomes. Based on the relatively low systemic plasma level, systemic complications related to the local drug delivery seemed to be relatively unlikely because these drugs have been used in much higher concentrations for other clinical indications. It should not be underestimated that the local tissue concentrations at the treatment site are quite considerable and may not be fully predictable. Extensive preclinical work has been done by most of the manufacturers; however, it remains to be crucial for the manufactures and the approving authorities to validate the information for every individual device.

Are there additional promising drugs for DEB application other than paclitaxel, or are the properties of paclitaxel such that it is uniquely suited to work with DEBs?

Currently, all of the active clinical programs are using paclitaxel, which seems to have unique chemical and physical properties to be effective as an active coating for balloons. However, based on the positive experience with drug-eluting stents, there are certainly other drugs on the horizon that may also have suitable antiproliferative capabilities; preclinical tests are still ongoing, and as far as I

know, none of these alternative drugs are currently entering a clinical human application.

How will the DEB studies deal with crossover stenting?

The interaction of DEBs with stenting of the target lesion remains an area of concern. Currently, most of the positive clinical experience supporting the efficacy of DEBs has been achieved in studies using a very low stenting rate. In this setting, the proliferative response to the acute balloon trauma can be effectively suppressed by the locally delivered drug. In contrast, an implanted self-expanding metallic stent represents a more chronic stimulus for neointimal proliferation, and therefore, it is not clear whether a single drug administration at the time of angioplasty can provide an effective and durable suppression of neointimal proliferation. Further studies will be necessary to specifically address this issue.

Should there be a trial of DEB use before stenting, or perhaps studies of DEBs used after debulking with atherectomy devices?

Yes, absolutely. We are certainly only at the beginning of our experience with DEBs in peripheral arteries and there are still a lot of open questions. In particular, the combination of DEBs with other modalities that could be necessary to achieve a good mechanical result particularly in complicated lesions needs to be studied. The combinations of DEBs and stenting or DEBs and pretreatment with atherectomy are obvious concepts that need further investigation. As mentioned, those projects are currently in the design process and will start in the foreseeable future. ■

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