

# Drug-Coated Balloons Below the Knee: What Have We Learned?

Nearly a year and a half after the surprising trial results were presented, IN.PACT DEEP Principal Investigator, Prof. Thomas Zeller, MD, addresses lingering questions on DCBs in BTK lesions.



**How would you describe the challenges faced in enrolling patients in a critical limb ischemia (CLI) randomized trial, particularly those of higher Rutherford classifications?**

**Prof. Zeller:** Two main limitations exist. First, these patients are usually older, immobile, and suffering from comorbidities with an increased risk for follow-up angiography, such as diabetes mellitus and renal insufficiency. The immobile condition makes them dependent on other people to get them moved to the study site for follow-up visits.

Secondly, many of the patients qualifying for study participation according to lesion and wound morphology are suffering from dementia and must therefore be excluded from study participation.

**What else was learned from reviewing the results of IN.PACT DEEP and looking back at its design, both in terms of the individual factors that may have influenced outcomes, and in what should or should not be done in future trials?**

**Prof. Zeller:** The study design was appropriate. The only limitation of the IN.PACT DEEP study was basically the technically ineffective drug-coated balloon (DCB). If the test device is equally efficient as the control device, one can't expect any difference in clinical outcomes. If the test device is unsafe, that exposes the patient to a specific additional interventional risk.

Thus, for upcoming CLI/below-the-knee studies, a pilot study should be performed including a primary angiographic endpoint at 6 months, such as late lumen loss in patients with Rutherford category 3 and 4 disease who are fit enough for an invasive follow-up to verify the

efficiency of a new DCB before a sufficiently powered clinical endpoint study in real CLI patients will be started.

**What do post-trial analyses indicate as to the potential role of the coating or particulate matter in the IN.PACT DEEP DCB arm failure?**

**Prof. Zeller:** It seems as if the main reason for the insufficient drug release to the vessel wall was the material of the In.Pact Amphirion balloon (Medtronic), which is different from that of the Pacific and Admiral balloons (Medtronic). In a root-cause analysis using a preclinical study model, Medtronic identified this aspect as more relevant than the drug coating, which was only applied to the folded balloon surface, without any drug being located and protected in the balloon folds.

**In your opinion, why did the results of IN.PACT DEEP differ so considerably from the well-conducted single-center studies that preceded it?**

**Prof. Zeller:** I have no explanation for the different outcomes. All studies used the same DCB type. The only major difference is that the single-center study outcomes were not evaluated by an independent core lab.

**What can you tell us about the percentages of the patient populations who received self-administered postprocedural wound care versus those who underwent follow-up at a wound care clinic? How might this difference in wound care administration have affected outcomes?**

**Prof. Zeller:** The exact numbers are not available. It is unlikely, however, that the different wound care managements would have affected the outcome due to two reasons: (1) It is a randomized trial; thus, the different kinds of postinterventional foot and wound care should

be equally distributed in both study cohorts; and (2) the technical data (eg, restenosis rate and target lesion revascularization rate) are similar in the two groups, resulting in similar wound perfusion conditions.

### **How do you think future CLI trial designs will address wound care?**

**Prof. Zeller:** This will be a major challenge because it will not be possible to standardize wound care in a multicenter study setting. Excluding a bias related to wound care would only be possible in a single-center study setting, as was the case with the Italian single-center, randomized, controlled DEBATE-BTK study. On the other hand, as already mentioned, randomization should exclude this bias due to a similar distribution of wound care strategies in both study cohorts.

I believe the impact of wound care on the study outcome is overestimated.

### **What do you believe is the wound care standard that should be designated in all DCB CLI trials? Is this the same as for CLI trials of all kinds, or is it in any way specific to DCB in this setting?**

**Prof. Zeller:** I don't believe in a specific wound care standard for DCB trials. The wound care regimen should be as standardized as possible, independent of whether the patient receives self-administered postprocedural wound care or follow-up at a wound care clinic. This includes predefined time intervals for wound care, the type of wound dressing stratified to the individual wound condition, and most importantly, consultation of the study site before indicating any kind of amputation.

### **What level of data and/or personal experience do you think will ultimately be the appropriate measuring stick to determine whether and how DCB should be applied below the knee?**

**Prof. Zeller:** First, we need a study that proves the efficacy of a DCB in below-the-knee arteries. So far, no device has yet shown any technical benefit over standard balloon angioplasty. The next step will be a clinical endpoint-driven study that includes endpoints such as target lesion revascularization rates, re-hospitalization rates, time to wound healing, amputation rate, and time to complete ambulation.

### **What can you tell us about other DCB trials that are either underway or currently being planned?**

**Prof. Zeller:** Currently, the only randomized controlled trials that are still enrolling patients are the Lutonix BTK study (Lutonix 014 DCB [Bard Peripheral Vascular] vs standard balloon angioplasty) and the ADCAT study (Lutonix 014 DCB vs directional atherectomy and Lutonix DCB). In addition, a small single-arm study investigating the performance of the paclitaxel-coated Chocolate PTA balloon catheter (Chocolate Touch, TriReme Medical LLC) will start enrollment soon. ■

*Prof. Thomas Zeller, MD, is with Universitäts-Herzzentrum Freiburg–Bad Krozingen in Bad Krozingen, Germany. He has disclosed that he is a paid consultant to Medtronic and Covidien, as well as co-Principal Investigator of IN.PACT DEEP along with Dierk Scheinert, MD, and Iris Baumgartner, MD. Prof. Zeller may be reached at [thomas.zeller@universitaets-herzzentrum.de](mailto:thomas.zeller@universitaets-herzzentrum.de).*