

# Ask the Experts:

## Based on the Tibial DCB Trials, Is There Light at the End of the Tunnel?



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*Disclosures: Honoraria from Abbott Vascular, Bard Peripheral Vascular, Veyan, Biotronik, Boston Scientific Corporation, Cook Medical, Cordis Corporation, Gore & Associates, Medtronic, Spectranetics Corporation, Straub Medical, TriReme, VIVA Physicians; institutional grant/research support from 480 Biomedical, Bard Peripheral Vascular, Veyan, Biotronik, Cook Medical, Cordis Corporation, Gore & Associates, Abbott Vascular/Idev Technologies, Inc., Medtronic, Spectranetics Corporation, Terumo Interventional Systems, TriReme, Volcano; consultant to Abbott Vascular, Bard Peripheral Vascular, Boston Scientific Corporation, Cook Medical, Gore & Associates, Medtronic, Spectranetics Corporation; stockholder in QT Vascular.*

Unfortunately, no. Data regarding the efficacy and safety of drug-coated balloons (DCBs) for the treatment of tibial arteries are conflicting and inconclusive. Early, uncontrolled, single-center studies from Germany<sup>1</sup> and Italy<sup>2</sup> using the In.Pact Amphirion balloon (Medtronic) suggested a highly significant technical outcome benefit regarding primary patency up to 1 year as compared to plain-old balloon angioplasty (POBA). In the randomized Italian study, the complete wound healing rate

at 1 year was significantly higher in the DCB cohort, whereas in both studies, the amputation rates had been similar in the study cohorts. Liistro et al were so enthusiastic regarding the beneficial outcome of their study that they didn't believe a larger-scale multicenter trial was needed.<sup>2</sup>

However, the IN.PACT DEEP multicenter study, including 358 patients using the same DCB as in the single-center studies, did not show any technical benefit regarding late lumen loss, restenosis rate, and primary patency at 1 year.<sup>3</sup> The major amputation rate had been higher by trend in the DCB cohort, resulting in a safety concern, which led to the global recall of the In.Pact Amphirion below-the-knee (BTK) DCB.

Another independently randomized controlled pilot study, the BIOLUX P-II study, using the Paseo Lux DCB (Biotronik) as the test device, enrolled 72 patients with critical limb ischemia (CLI) who were randomized 1:1 to receive either a DCB or POBA and also failed to show any technical or clinical benefit at 1 year. Fortunately, in this study, no difference in the major amputation rate was found.

It is uncertain at this time whether DCBs using coating techniques similar to those used for femoropopliteal intervention will work below the knee. It is still unknown whether the differences in vessel wall architecture, including different degrees of calcification, smaller vessel diameter, or a loss of drug during the way down to the target lesion in the tibial artery, was responsible for the failure of the two previously mentioned randomized trials.

Currently, only one larger-scale randomized controlled trial, the Lutonix BTK study, is ongoing in evaluating the efficacy of DCBs in tibial interventions. Other companies, such as Boston Scientific Corporation (Ranger paclitaxel-coated balloon catheter) and TriReme Medical LLC (Chocolate Touch peripheral

DCB), are planning randomized controlled BTK studies comparing DCB with POBA to be started in 2016. Two smaller randomized controlled trials are ongoing and are investigating the role of atherectomy prior to DCB angioplasty: the ADCAT study (Turbohawk [Medtronic] plus a DCB vs DCB alone) and the OPTIMIZE study (Diamondback [Cardiovascular Systems, Inc.] plus a DCB vs DCB alone) are currently enrolling patients. However, it will take another couple of years before we may see any light at the end of the tunnel regarding beneficial outcomes of DCBs in tibial interventions.

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2. Liistro F, Porto I, Angioli P, et al. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia. *Circulation*. 2013;128:615-621.
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For years, tibial disease has been compared to coronary artery disease. I want to clarify this issue now: coronary arteries are very different from tibial arteries in so many ways. The most important difference is the fact that tibial arteries tend to have a tremendous amount of calcification. Tibial calcification has a clear-cut difference in the intimal and medial calcification. Intimal calcification in the tibials is always present in the lumen side and is associated with dense plaque formation. Medial calcification is localized to the media for the most part, with occasional migration toward the adventitia. When we discuss DCBs, and their pharmacokinetic ability to treat tibial arteries, we can reference the obstacles that might hinder the migration of drugs into the tibial vessel wall.

This leads me to the next and most important part of tibial DCB therapy, vessel preparation. Vessel preparation has been discussed in depth over the last 2 years, more so in the superficial femoral artery and popliteal than in the tibials. I want to take this opportunity to address this very crucial step in tibial DCB therapy. The tibial lumen is not as tolerant of plaque buildup as the vessels above the knee, and calcium deposition is higher compared to the above-the-knee vessels. Given these combined elements, tibial vessel preparation before DCB use becomes far more important than in above-the-knee vessels.

When we compared the average reported balloon sizes between the IN.PACT DEEP study and DEBATE BTK study, we found a 0.56-mm difference in the balloon to vessel wall ratio favoring DEBATE BTK. This serious undersizing can have grim consequences. Tibial intervention is still in its infancy when compared to above-the-knee vessel therapy. Balloon undersizing is mainly due to lack of experience with tibial percutaneous transluminal angioplasty and the lack of published data on actual tibial sizing.

Tibial DCBs will eventually prevail, but not until operators and trials treat the tibials with an adequate balloon to vessel ratio of 1.1:1 after robust tibial vessel preparation. There is no doubt in my mind that the antiproliferate drugs work; the problem is that we are not clearing the path for it first, hence the lack of proper drug dose delivery to the vessel wall.

In summary, tibial DCBs are an absolute must-have technology. It is our obligation as scientists to look and address previous failures and successes and merge the information into a clinical treatment pathway that can provide us with a multicenter trial result that is similar to the one resulting from DEBATE BTK.



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*Disclosures: None.*

The evidence for tibial DCB usage has been disappointing. It seems we mixed something up in the past—an anatomical area that we wanted to treat (infrapopliteal arteries) and a disease condition (CLI). The real drawback was the failure of the IN.PACT DEEP trial, with a malfunctioning DCB, but now we have some hints that the performance of DCBs are not quite as disappointing in treating infrapopliteal disease.

My understanding is that we need to separate the disease and the anatomical area. If we can prove that DCBs are working in infrapopliteal arteries as an anatomical region, we have proof of concept for that vessel region. The additional effect of CLI is something that we have to take into consideration.

Admittedly, mistakes were made by mixing up disease activity and anatomical region assessment/treatment with conflicting outcome parameters, such as CLI disease activity. I believe in the use of DCBs, in whatever peripheral field we want to use them, due to the sound concept of treating underlying atherosclerotic disease. So, I do believe it will also work in infrapopliteal arteries. ■