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EDITORIAL COMMENT

Drug-Coated Balloons for Infrapopliteal Disease

Digging Deep to Understand the Impact of a Negative Trial*

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Over the past decade, drug-coated balloons (DCBs) have emerged as an effective treatment for atherosclerosis in multiple vascular beds. Initial attempts to deliver antirestenotic agents locally without a stent scaffold included use of infusion balloons, injection into the arterial wall, and admixing drug with contrast media (1). Each of these approaches suffered from technical limitations or unpredictable systemic drug dosing. The insight that paclitaxel can be coated on an angioplasty balloon provided an important breakthrough in local drug delivery (2). DCBs rely on 3 mechanisms related to paclitaxel's lipophilicity. First, crystalline paclitaxel can be combined with an excipient, such as contrast media, to coat an angioplasty balloon. Second, paclitaxel stays largely bound to the excipient and balloon during advancement to the target vessel. Third, a brief (1 to 3 min) inflation of the balloon at the target vessel is sufficient for local delivery of a therapeutic dose of paclitaxel, which then resides in tissues for months (3,4). All currently available paclitaxel-coated balloons rely on a specific excipient (e.g., iopromide, shellac, urea, butyryl trihexyl citrate) and paclitaxel at doses ranging from 2.0 to 3.5 $\mu g/mm^2$.

DCBs were shown to be effective in treatment of both coronary and femoropopliteal lesions. In coronary arterial circulation, DCBs can be used to treat in-stent restenosis with efficacy similar to that of a paclitaxel-eluting stent and superior to standard balloon angioplasty (5,6). Coronary DCBs are also useful for the treatment of lesions in small coronary arteries and bifurcation lesions (7). In the peripheral arteries, DCBs improve the rates of primary patency for de novo femoropopliteal lesions compared to percutaneous transluminal angioplasty (PTA) (8-11), and may be particularly beneficial in the treatment of femoropopliteal in-stent restenosis (12).

These positive results have led to speculation that DCBs could also be efficacious in the treatment of infrapopliteal occlusive disease in patients presenting with critical limb ischemia (CLI). While PTA has historically provided acceptable angiographic results and reasonable limb salvage rates when used to treat infrapopliteal disease, it is plagued by high rates of restenosis and need for repeat interventions. Schmidt et al. demonstrated an angiographic restenosis rate of 68.8% at 3 months following PTA of long infrapopliteal lesions and a need for reintervention in 50% of cases (13). These same investigators later showed significantly better outcomes when treating a similar cohort of patients with DCBs. Angiographic restenosis was only 27.4%, with a significant reduction to 17.3% in the need for target lesion revascularization (TLR) (14). Liistro et al. (15) subsequently performed a single-center randomized trial of DCB versus PTA in diabetic patients with CLI, which demonstrated a significant reduction in 12-month angiographic restenosis (27% vs. 74%) and need for reintervention (18% vs. 43%).

These encouraging, but preliminary, findings led to the development and conduct of a larger, multicenter, randomized clinical trial. In this issue of the *Journal*, Zeller et al. (16) report the results of the

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IN.PACT DEEP trial (Study of IN.PACT Amphirion™ Drug Eluting Balloon vs. Standard PTA for the Treatment of Below the Knee Critical Limb Ischemia). This

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well-designed, industry-sponsored trial included an independent data safety monitoring board and clinical events committee, as well as independent, blinded core laboratories for angiography, duplex ultrasound, and wound assessment. A total of 358 patients were randomized (2:1) between DCB and PTA. The 2 coprimary efficacy endpoints of the trial were clinically driven TLR (CD-TLR) and angiographic late lumen loss. The primary safety endpoint through 6 months was a composite of all-cause mortality, major amputation, and CD-TLR.

Despite use of the same DCB (IN.PACT Amphirion, Medtronic, Santa Rosa, California) that was evaluated in the aforementioned single-center retrospective and prospective studies, the IN.PACT DEEP trial investigators were unable to demonstrate any benefit of DCB in this randomized trial. There were no significant differences with regard to CD-TLR or angiographic late lumen loss. While the study met its noninferiority hypothesis with regard to the primary safety endpoint, there were more complications in the DCB arm of the trial and a trend toward more major amputations (8.8% vs. 3.6%; $p = 0.080$) and lower amputation-free survival (81.1% vs. 89.2%; $p = 0.057$).

How do we explain the disparate results between the IN.PACT DEEP trial and previous investigations of DCB in infrapopliteal and femoropopliteal vascular territories? Was there a problem with the trial design? Was there a problem with this particular DCB platform? Or was this just 1 more example of a well-done randomized trial failing to reproduce the results from smaller or nonrandomized studies? It is difficult to be too critical of this well-conducted clinical trial. However, as the authors point out, the trial was not powered to demonstrate differences in major amputation rates, and there was not a predefined and consistent approach to wound care. The differences with regard to safety between DCB and PTA are perhaps most easily addressed. While the amputation rate was 2.4-fold higher in the DCB arm of the trial, the 3.6% major amputation rate in the PTA arm is remarkably low and certainly an outlier compared to major amputation rates from previous studies of PTA and other endovascular therapies for CLI (17–19). These outstanding PTA outcomes were achieved despite inclusion of a high percentage of Rutherford class 5 patients and likely reflect good PTA results followed by excellent wound care.

There are important differences between the IN.PACT Amphirion DCB platform and other DCBs studied in the SFA. The balloon is constructed of different material and the coating process is entirely different. The IN.PACT Amphirion balloon is manually coated *after* it is folded, resulting in nonuniform paclitaxel distribution on the balloon. The bulk of the adherent drug is in an exposed position (not protected by balloon folds) and subject to loss during advancement through the sheath and tracking to the lesion. The lack of an observed treatment effect in the current study might well be explained by an insufficient paclitaxel dose delivered into the vessel wall. These limitations of the balloon coating process, together with concerns regarding the trend toward a higher amputation rate with DCB, led to Medtronic's withdrawal of the IN.PACT DCB from the market.

Where do we go from here? On the basis of the IN.PACT DEEP trial's results, it is premature to conclude that there is no role for DCBs in infrapopliteal disease in patients with CLI. While the results of PTA in this trial were remarkably good, there is still a need for a therapy that provides more durable patency in this vascular bed and reduces the need for repeat interventions. DCBs that can deliver therapeutic levels of paclitaxel into the vessel wall may still play a role. We await the results of additional trials, including the results of an ongoing randomized trial in the United States.

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