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EDITORIAL COMMENT

Drug-Coated Balloons for Treatment of Femoropopliteal Disease

A Step Toward an Elusive Goal*

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Percutaneous treatment of atherosclerotic disease in the femoropopliteal (FP) segment remains one of the most challenging subsets for endovascular operators. The experience of unacceptably high restenosis rates with plain balloon angioplasty (POBA) and nitinol self-expanding stents (SES) generated considerable interest in a variety of atherectomy technologies as a complement or replacement for angioplasty/stenting over the last decade (1). However, it has become clear that these technologies suffer from the same problem of high restenosis rates (2). In addition, application of atherectomy technologies was generally expensive, introduced greater technical challenges in performing the procedure, leading to a greater degree of variability in outcome based on operator experience and skill level, and probably increased the risk of distal embolization during treatment, necessitating the use of embolic protection devices (3). More recently, the pendulum has swung back toward the use of angioplasty and stents with the availability of drug-coated balloons (DCB) and a drug-eluting nitinol stent (DES) system with proven superiority over POBA and non-drug-eluting SES, respectively (4-6).

Most endovascular specialists are inherently attracted to the use of DCB angioplasty as the primary strategy for revascularization of the FP segment. This is driven by several considerations. Primarily, the greatest concern is to avoid the specter of in-stent restenosis (ISR), for which there is no good therapy (7,8). If a durable result can be achieved with drug-eluting balloon (DEB) angioplasty, even if it has lower primary patency rates compared with DES, then this option would generally be favored. In addition, from a technical standpoint, angioplasty is very straightforward, resulting in a reasonably predictable outcome across a broad range of operators. There is no issue with DEB angioplasty of the distal superficial femoral artery (SFA) or popliteal segments where most operators are reluctant to place stents due to the physical forces in this location and the need to avoid the possible touch-down site of a surgical graft in the future. Avoiding stents when treating ostial SFA disease minimizes the risk of plaque shift toward the profunda femoral artery and eliminates the challenge of precise positioning of the proximal end of the stent to cover the ostium.

Currently, there are 2 Food and Drug Administration-approved DCB systems available for clinical use in the FP segment. Each system was tested in pivotal randomized trials (LEVANT II [Moxy Drug Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries] and IN.PACT SFA [Randomized Trial of IN.PACT Admiral Drug Coated Balloon vs Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease] trials) comparing DEB with POBA (5,6). The design of both studies was fairly similar, with recruitment of patients with Rutherford class 2 to 4 and de novo lesions with lengths of 10 to 15 cm. Patients with ISR were excluded. Randomization occurred in a 2:1 fashion between DCB and POBA following initial successful pre-dilation of the lesion. Ultimately, the lesion lengths treated in these randomized studies was very modest compared with real-world practice (6.3 ± 4.1 cm in the LEVANT II trial vs. 8.9 ± 4.9 cm in the IN.PACT SFA trial). Primary patency of the target lesion at 12 months was the primary endpoint of both trials but was adjudicated slightly differently.

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Freedom from binary restenosis by ultrasound and *any* target lesion revascularization was used in the LEVANT II trial, whereas freedom from binary restenosis by ultrasound and *clinically driven* target lesion revascularization was used in the IN.PACT SFA trial. This difference may explain the higher primary patency rates reported in the DCB arm of the IN.PACT SFA trial (82.2%) compared with the LEVANT II trial (65.2%). The primary patency rate for the POBA arm in both trials was similar at ~52%. Both trials showed statistical superiority of the DCB therapy over POBA. At 24 months, the benefit of the DCB arm over POBA for primary patency was maintained (78.9% vs. 50.1%; $p < 0.001$) in the IN.PACT trial (9).

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In an effort to demonstrate the generalizability of the results of randomized studies to real-world practice and the safety of DCB therapy, it has been important to examine both DCB systems in "real-world" registries. In this issue of *JACC: Cardiovascular Interventions*, Thieme et al. (10) report the 24-month follow-up data from the Lutonix Global SFA registry using the Lutonix DEB (Bard, New Hope, Minnesota) that was used in the LEVANT II trial. This was a large (691 patients) and rigorous registry with prospective collection of data and independent adjudication of adverse events by a blinded clinical events committee. As in the LEVANT II trial, this registry largely enrolled patients with peripheral artery disease of Rutherford class 2, 3, and 4. Pre-specified lesion subsets excluded in the original randomized trial were included (long lesions >14 cm and ISR lesions). The overall mean lesion length was 10.1 ± 8.4 cm, with mean lesion lengths in the long-lesion and ISR subsets of 21.2 ± 6.5 cm and 15.4 ± 9.7 cm, respectively. Bailout spot stenting was required in one-quarter of cases. Retention of patients in the registry for assessment of follow-up was reasonable (~84% at 2 years). Remarkably, freedom from target lesion revascularization was 93.4% at 1 year, and 89.3% at 2 years. There was only a marginal decrement in these figures for the long-lesion and ISR subsets. There was no signal of any safety concerns at 30 days. Freedom from target vessel revascularization, major limb amputation, and device- and procedure-related deaths at 1 and 2 years was estimated at 92.1% and 86.7%, respectively.

These data are certainly reassuring with respect to the safety of DCB therapy in the treatment of FP disease. For short lesions <10 cm in length, the difference in patency rates compared with POBA in randomized studies probably justifies the added expense of these balloons. However, despite the rigor of the current registry, we still need randomized data to confirm the efficacy of DCB therapy for the treatment of patients with long lesions and in-stent restenosis. In the meantime, endovascular specialists are likely to continue to apply DCB therapies aggressively in these clinical scenarios, given the absence of proven alternatives.

Moving forward, there is a need to perform a head-to-head comparison between the 2 DCB systems to explore whether the superior patency rates reported for the DCB arm of the IN.PACT SFA trial (using the IN.PACT Admiral DCB [Medtronic, Santa Rosa, California]) reflects a real difference or was due to differences in patient population and/or lesion type, or trial design. This may help to move the field forward by determining whether the dose of paclitaxel and the excipient used can have a significant clinical impact on restenosis rates.

Finally, it must be accepted that DCB therapy will always suffer from the major Achilles heel of not being able to deal with the issue of elastic recoil or development of flow-limiting dissections following angioplasty. In addition, it would be naive to think that DCB therapy will reliably prevent restenosis in the most severe lesion types that are encountered in the FP artery. Although DCB therapy is a welcome addition to the options for revascularization in the FP segment, there is a long way to go before endovascular therapy that includes DCB angioplasty can rival the patency rates of surgical bypass. It is hard not to feel that an inert biodegradable metal scaffold combined with an antiproliferative agent still offers the best chance of achieving this goal. Unfortunately, the many failures to date for nonbiodegradable DES in the FP segment have hampered investment and investigation, and may continue to do so for some time.

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