Leave No Stent Behind

Are Drug-Coated Balloons Enough for Femoropopliteal Disease?

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Endovascular revascularization is recommended for patients who fail medical and exercise therapy for lifestyle-limiting claudication secondary to peripheral arterial disease.[1] The cornerstone of endovascular intervention has been percutaneous transluminal angioplasty (PTA) since the advent of the procedure over 50 years ago.[2] However, restenosis rates for PTA in the femoropopliteal circulation remain up to 50% at 2 years, resulting in the development of alternate techniques to improve postintervention patency.[3,4] Stenting with nitinol self-expanding stents and drug-eluting nitinol self-expanding stents has reduced restenosis in the femoropopliteal artery compared with PTA; however, long-term patency even with stents remains suboptimal.[3–5] In theory, stents may not maintain long-term patency because of the mechanical strain exerted from torsion, flexion, and extension of the femoropopliteal artery. Consequently, enormous resources have been devoted to the development of drug-coated balloons (DCBs) which deliver an antiproliferative drug to mitigate neointimal hyperplasia after PTA while also avoiding the continuous hazard of a chronic indwelling metallic endoprosthesis.

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DCBs which deliver paclitaxel have now been studied for over a decade as one potential option of facilitating antirestenotic drug delivery while avoiding the implantation of a stent.[6] To date, long-term data on patency after DCB angioplasty have been lacking. The IN.PACT SFA trial (Randomized Trial of IN.PACT Admiral Paclitaxel-Coated Percutaneous Transluminal Angioplasty [PTA] Balloon Catheter vs Standard PTA for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery [SFA] and/or Proximal Popliteal Artery [PPA]) randomized 331 patients in a 2:1 fashion to DCB versus standard PTA.[7,8] The patient demographics were consistent with other studies with an average age of 68 years, 65% men and 45% with diabetes mellitus. The average lesion length was just under 9 cm with almost 60% of the lesions calcified. The study sponsor and subjects remained blinded for 1 year, whereas the clinical events committee and the core laboratories remained blinded for 3 years. In this issue of *Circulation: Cardiovascular Interventions*, the investigators report the 3-year results of the study.[9] Primary patency adjudicated by duplex Doppler ultrasound was superior in the DCB group (69.5%) compared with the PTA group (45.1%). It is notable that there has been a loss of primary patency from 1 (82%) to 2 years (78%) and now to 3 years.[7–9] Over 3 years, primary patency rates after PTA hovered around 50% suggesting that after the first year, PTA patients that remained patent had a similar trajectory when compared with the DCB group. Similarly, 85% of patients in the DCB group remained free from clinically driven target lesion revascularization (TLR) at 3 years compared with 69% in the PTA group. Again, this difference seems to occur in the first 6 months to 1 year and remains sustained out to 3 years. There is no late catch-up effect. Observations from preclinical models indicate that paclitaxel remains resident in the artery for up to 180 days after the index procedure, providing a plausible mechanistic explanation for why the peak biological benefits of DCBs occur in the first 6 months.[10]

Despite the clear sustained improvement in primary patency and a decrease in TLR, there was a statistical increase in the number of deaths in the DCB arm. Independent adjudication by a blinded clinical events committee suggests that this difference was likely because of factors not related to the DCB procedure; however, this observation has not been noted in other DCB trials. Moreover, both groups had similar improvements in symptom measures compared with baseline including walking distance and stair climbing. The authors attribute the similarity to less reinterventions in the PTA arm; however, to verify this, data that suggested a symptom difference before reintervention would be necessary and are not shared.

DCBs are not the only therapies beyond PTA that have been used in the femoropopliteal circulation. Five-year data have been published for the Zilver PTX drug-eluting stent (Cook), revealing a 66.4% primary patency rate and an 83.1% freedom from TLR.[11] These numbers rival those of the IN.PACT Admiral DCB (albeit at 3 years); however, there was a 1.9% rate of stent fracture at 3 years. In an effort to reduce stent fractures, the SUPERA (Abbott) wire interwoven nitinol vascular mimetic stent performed well in a single-arm study relative to a Federal Drug Administration mandated objective performance goal. The stent had a 12-month primary patency of 79%, whereas freedom from TLR was 89% at 12 months and 82% at 3 years.[12,13] Again, these numbers are similar to those achieved in this study using DCB. However, comparing outcomes between trials is difficult given different outcome measures, lesion characteristics, patient populations, and follow-up

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methodology. Discerning optimal advanced therapies beyond PTA would require direct head-to-head randomized controlled clinical trials, which heretofore have not been published.

Aside from comparisons against other therapeutic modalities, there are important differences between current US Federal Drug Administration approved DCBs. The IN.PACT Admiral DCB (Medtronic) uses a higher coating density of paclitaxel (3.5 mg/mm^2) relative to other Federal Drug Administration approved DCBs such as the Lutonix (CR Bard) and Stellarex (Philips/Spectranetics) DCBs, which have a paclitaxel coating density of 2.0 mg/mm^2. Each device also uses a different carrier or excipient and morphology of paclitaxel with respect to composition of crystalline or amorphous drug which contributes to differential arterial pharmacokinetics. The LEVANT 2 trial (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis), which evaluated the Lutonix DCB (CR Bard), published 1-year data in 2015.[14] Longer-term follow-up of this cohort has not been published. More recently, the Stellarex DCB (Phillips/Spectranetics) 1-year data were published in the ILLUMENATE trial (Prospective, Randomized, Single-Blind, US Multi-Center Study to Evaluate Treatment of Obstructive Superficial Femoral Artery or Popliteal Lesions With a Novel Paclitaxel-Coated Percutaneous Angioplasty Balloon).[15] Longer-term follow-up on this cohort is ongoing. Similarly, safety data are important as well. One area which has not been fully elucidated is the extent to which various DCBs cause embolism into distal arterial beds. In 1 preclinical study, the IN.PACT and Lutonix DCBs were directly compared with one another and the IN.PACT DCB demonstrated evidence of a greater degree of particulate embolization.[16] No clinical sequelae have clearly been identified. Similarly, the impact of calcification and atherectomy before DCB angioplasty on patency rates and TLR has yet to be completely clarified. Finally, clinical trial patients studied to date have relatively short lesion lengths (up to 15 cm), whereas real-world patients frequently have significantly longer lesion lengths. One would predict reduced primary patency as a function of lesion length. Longer-term data in more real-world cohorts will be needed to properly assess DCBs rightful place in our therapeutic algorithm for femoropopliteal disease.

With multiple randomized controlled trials confirming improved primary patency and decreased TLR with DCB versus PTA, DCB angioplasty has become a preferred treatment strategy for many operators in the femoropopliteal arterial bed. Although direct comparisons to drug-eluting or nitinol biomimetic stents are lacking, the absence of a scaffold avoids stent fractures and subsequent in-stent restenosis. To encourage use of this technology, the Centers for Medicare and Medicaid Services had been adding an additional payment for DCB angioplasty. However, the existing pass-through payment for DCB angioplasty will expire starting January 2018. Furthermore, the rule suggests packaging the device costs of the DCB into the costs of the procedure, implicating that DCB will be reimbursed at the same rate as PTA. The repercussions of this change may discourage the use of DCB, despite cost-effectiveness studies and real-world analyses suggesting a reduction in overall healthcare costs. An analysis from the IN.PACT SFA trial revealed that initial costs were about $1000 higher per patient with DCB angioplasty than standard PTA. At 12 months, target limb-related costs were $1212 per patient lower with DCB angioplasty.[17]

In summary, the current study demonstrates that the IN.PACT Admiral DCB has improved primary patency compared with PTA over a 3-year period. Although a prespecified 3-year follow-up would have been a more rigorous study design when compared with a 3-year follow-up of a 1-year trial, we commend the investigators on maintaining core laboratory blinding and publishing long-term outcome data of DCB angioplasty. The observed results for the first time demonstrate stent-like patency rates without the purported disadvantage of a permanent metallic indwelling scaffold of a stent. With these clinical results, one might argue that PTA without DCB is no longer a tenable clinical strategy for treatment of femoropopliteal stenosis for the management of intermittent claudication. However, without appropriate comparative effectiveness data of DCB head-to-head against stents and other DCB, clinicians will remain unsure which therapy should be applied for treatment of femoropopliteal lesions. Moreover, further regulatory and reimbursement changes may make DCB angioplasty cost-prohibitive even though its clinical application has been supported by high-quality randomized controlled clinical trials. Future reimbursement models may need to adapt to affirm the use of DCB.

Disclosures

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