Drug-Coated Balloons
Current Outcomes and Future Directions

Ananya Kondapalli, MD[a], Barbara A. Danek, MD[b],
Houman Khalili, MD[a,b],
Haekyung Jeon-Slaughter, PhD[a,b],
Subhash Banerjee, MD[a,b,*]

KEYWORDS

• Drug-coated balloons • Paclitaxel • Endovascular intervention
• Femoropopliteal peripheral artery • Infrapopliteal peripheral artery

KEY POINTS

- Although outcomes with DCB in the femoropopliteal region are promising, the ideal treatment strategy for lesions in the infrapopliteal arterial distribution remains an unmet need.
- The ideal antiplatelet regimen after peripheral arterial interventions, including DCB, has not been adequately defined.
- Future iterations of the DCB will likely include improved drug formulations, allowing for greater efficacy and limiting systemic toxic effects.
- The importance of specific excipients is being explored.
- Cost-based analyses of treatment strategies explore an increasingly important aspect of medical care, and will no doubt factor into the future of drug-coated balloons.

INTRODUCTION

Endovascular intervention is the first-line therapy for peripheral artery disease (PAD) and is associated with decreased morbidity and mortality compared with surgical interventions.[1] The main disadvantage to percutaneous transluminal angioplasty (PTA) and stenting continues to be the high rates of in-stent restenosis and stent fracture that can affect long-term clinical outcomes.[2,3] Neointimal proliferation and restenosis occur in more than 60% of patients treated with PTA for PAD.[4] Use of drug-eluting stents (DES) to prevent restenosis has displayed varying results. Sirolimus-eluting stents show no difference in outcomes compared with bare metal stents (BMS),[5] but paclitaxel-eluting stents have improved outcomes and decreased rates of restenosis.[6] Paclitaxel may be more effective in preventing restenosis in peripheral arteries because of their high proportion of extracellular matrix compared with coronary arteries, leading to better drug penetration and retention with hydrophobic drugs, such as paclitaxel.

Paclitaxel is an antiproliferative agent that inhibits neointimal proliferation even at low doses.

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[a] Division of Cardiology, Department of Medicine, University of Texas Southwestern Medical Center, 4500 South Lancaster Road (111a), Dallas, TX 75216, USA; [b] Division of Cardiology, Department of Medicine, Veterans Affairs North Texas Health Care System, 4500 South Lancaster Road (111a), Dallas, TX 75216, USA
* Corresponding author. 4500 South Lancaster Road (111a), Dallas, TX 75216.
E-mail address: subhash.banerjee@utsouthwestern.edu

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Inhibition of neointimal proliferation leads to decreased rates of restenosis.[7,8] More recently, paclitaxel has been used as the drug of choice on drug-coated balloons (DCB). The advantage of using paclitaxel-coated balloons is the ability to deliver the necessary drug to the affected areas without a permanent vascular prosthesis. This article provides an overview of the clinical evidence for paclitaxel-coated balloons in the femoropopliteal and infrapopliteal peripheral artery distributions and future directions in this area.

TRIALS COMPARING DRUG-COATED BALLOONS WITH STANDARD PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY IN FEMOROPOPLITEAL LESIONS

The earliest trials comparing DCB with PTA for the treatment of femoropopliteal lesions are the FemPac (Paclitaxel-Coated versus Uncoated Balloon: Femoral Paclitaxel Randomized Pilot Trial), THUNDER (Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries), LEVANT I (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis), and PACIFIER (Paclitaxel-coated Balloons in Femoral Indication to Defeat Restenosis) trials. These were all randomized controlled trials with a primary end point of 6-month late lumen loss (LLL) defined as the difference between minimum luminal diameter after the procedure and at 6-month follow-up.[9–12] A study performed by Mauri and colleagues[13] demonstrated that LLL was the most sensitive marker for identifying restenosis because of neointimal proliferation. In each of these trials the DCB group was associated with significantly reduced LLL compared with the PTA group. Secondary outcomes including target lesion revascularization (TLR) were also significantly lower in the DCB group compared with PTA. Although these trials demonstrate the efficacy of DCB in treating femoropopliteal lesions, they do not provide information about long-term outcomes.

Micari and colleagues[14] examined 2-year outcomes after treatment with paclitaxel-coated balloons. The primary end point was primary patency rate defined as the absence of TLR, occlusions, or greater than or equal to 50% stenosis in the target lesions 24 months after treatment. Patients had a high primary patency rate (71%) and were observed to have significant improvements in ankle-brachial index and Rutherford class 2 years after treatment with DCB. The mean lesion length in the previously mentioned studies was 70 to 80 mm, with total occlusions representing less than 30% of the lesions. The DEBATE-SFA (Drug-Eluting Balloon in Peripheral Intervention for the Superficial Femoral Artery) trial compared treatment with DCB before insertion of a BMS with standard PTA before BMS in complex superficial femoral artery lesions.[15] Patients in the DEBATE-SFA trial had longer lesion lengths (>90 mm) and more than 50% of the lesions in the DCB group and 60% of the lesions in the PTA group were total occlusions. Patients in the DCB group had significantly lower rates of binary restenosis, defined as greater than or equal to 50% stenosis in the target lesion, 12 months after the procedure (17% vs 47%; $P = .008$). The use of nitinol self-expanding stents and inclusion of longer and more occluded lesions differentiates the DEBATE-SFA trial from previous trials in this area. Additionally, 69% of patients in the PTA group and 79% of patients in the DCB group had critical limb ischemia (CLI) in this trial compared with less than 10% of patients in the previous trials.

The LEVANT 2 (Moxy Drug Coated Balloon versus Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries) trial found higher primary patency rates in the DCB group compared with PTA in a study with a much larger sample size (n = 476). However, unlike the previous smaller randomized control trials, there was no significant difference in TLR between the two groups. This may be caused by several factors including the lower rate of TLR observed in the PTA group in this study compared with previous studies and exclusion of patients requiring stent placement.[16]

The findings from the IN.PACT SFA (Randomized Trial of IN.PACT Admiral Drug-Eluting Balloon versus Standard Percutaneous Transluminal Angioplasty for the Treatment of SFA and Proximal Popliteal Arterial Disease) trial support the earlier data showing higher primary patency rates and lower TLR with DCBs; however, there was a higher 24-month all-cause mortality rate in the DCB group. The mortality rate in the DCB group was 8.1%, which is in the range for the overall mortality rate for patients with PAD.[2] Three-year follow-up of IN.PACT SFA has confirmed superior patency and TLR with DCB, with no difference in the incidence of major adverse cardiovascular events. Higher all-cause mortality in the DCB group has persisted at 3 years, but these deaths occurred at a median of 1.8 years, and they were mostly unrelated to the procedure.[17] The FAIR (Femoral Artery In-Stent Restenosis) trial was the first to compare DCB with standard balloon angioplasty for treatment of SFA in-stent restenosis and reported