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EDITORIAL COMMENT

The Era of Drug-Coated Balloons

Are All Created Equal?*

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The optimal treatment of obstructive atherosclerotic disease in the femoropopliteal (FP) arterial segment remains elusive. Similar to the coronary space, endovascular devices have evolved in the FP territory from uncoated balloon percutaneous transluminal angioplasty (PTA) to bare-metal stenting to drug-eluting stents (DES), with the recent adoption of drug-coated balloon (DCBs) technology. Numerous randomized controlled trials (RCTs) have demonstrated superior short-term patency rates of DCBs over PTA alone, though midterm patency rates have varied. The cause of the varying DCB patency rates is uncertain. Given that all DCBs and their respective trials have not been created equal, the question of a class effect is challenging to answer. In this issue of *JACC: Cardiovascular Interventions*, Brodmann et al. (1) present the 2-year results of the ILLUMENATE EU RCT (European Randomized Clinical Trial), in which the Stellarex DCB (Philips Spectranetics, Colorado Springs, Colorado) showed a sustained treatment effect at 2 years (clinically driven target lesion revascularization [CD-TLR] rates of 12.1% with Stellarex DCB and 30.5% with PTA; $p < 0.001$), suggesting that not all DCBs are created equal.

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There are currently three commercially available DCBs in the United States: IN.PACT Admiral (Medtronic, Minneapolis, Minnesota), Lutonix (Bard, Tempe, Arizona), and Stellarex DCB. The dose of paclitaxel varies among DCBs and ranges from 2.0 μg/mm^2 (Lutonix and Stellarex) to 3.5 μg/mm^2 (IN.PACT Admiral). Although the reduced paclitaxel dose in the Lutonix DCB was initially thought to be the main reason for its lower patency rates (**Table 1**), we now have data from the ILLUMENATE trial suggesting that the difference in paclitaxel dose is not the whole story. What could lead to the different midterm CD-TLR and patency rates among different DCBs? First, to be effective, DCBs must be able to deliver a therapeutic drug dose to the target tissue, with drug being retained by the tissue for a prolonged period of time. The drug dose plays a role, and paclitaxel doses of >2 μg/mm^2 have been shown to effectively inhibit smooth muscle cell proliferation in preclinical models (2). However, it would be too simplistic to consider the concentration of the drug as the only contributor to these differences. Second, in DES, polymers dictate the rate of drug release, whereas in DCBs, excipients carry the drug to the target tissue. Excipients must be compatible with paclitaxel, able to generate uniform balloon coating, have stable adherence during device handling, but easy to transfer to the vessel wall upon balloon inflation as well as have optimal biocompatibility and biodegradation characteristics (3). The Lutonix balloon uses a combination of polysorbate and sorbitol, the Stellarex balloon uses polyethylene glycol, and IN.PACT Admiral uses urea. Could the difference in excipients be contributing to the difference in outcomes between DCBs? Finally, the differences in DCB trial design and endpoint definitions should not be overlooked. The commonly used primary patency endpoint in DCB trials, a combination of CD-TLR (a subjective endpoint) and duplex ultrasound-derived restenosis (an objective endpoint), can be affected by blinding. For instance, in the IN.PACT and ILLUMENATE trials, investigators were not blinded

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TABLE 1 Comparison of Current Drug-Coated Balloons

Current Drug-Coated Balloons	Stellarex (1,7)	Lutonix (5,8)	IN.PACT Admiral (4,9,10)
Primary patency at 12 months vs. PTA	83.9% vs. 60.6% ($p < 0.001$)	65.2% vs. 52.6% ($p = 0.02$)	82.2% vs. 52.4% ($p < 0.001$)
Primary patency at 24 months vs. PTA	75.9% vs. 61.0% ($p = 0.025$)	58.6 vs. 53% ($p = 0.05$)	78.9% vs. 50.1% ($p < 0.001$)
Primary patency at 36 months vs. PTA			69.5% vs. 45.1% ($p < 0.001$)
CD-TLR at 12 months vs. PTA	5.9% vs. 16.7% ($p = 0.014$)	12.3% vs. 16.8% ($p = 0.21$)	2.4% vs. 20.6% ($p < 0.001$)
CD-TLR at 24 months vs. PTA	12.1% vs. 30.5% ($p < 0.001$)	18.0% vs. 21.0% ($p =$ NS)	9.1% vs. 28.3% ($p < 0.001$)
CD-TLR at 36 months vs. PTA			15.2% and 31.1% ($p = 0.002$)
Bailout stent rate (DCB vs. PTA)	15.0% vs. 11.0% ($p = 0.38$)	2.5% vs. 6.9% ($p = 0.02$)	7.3% vs. 12.6% ($p = 0.11$)
Drug	Paclitaxel	Paclitaxel	Paclitaxel
Drug dose density ($\mu g/mm^2$)	2.0	2.0	3.5
Drug state + coating	Combination of crystalline and amorphous states	Amorphous	Highly crystalline
Excipient	Polyethylene glycol	Polysorbate and sorbitol	Urea
Company	Philips Spectranetics	Lutonix	Medtronic

CD-TLR = clinically driven target lesion revascularization; DCB = drug-coated balloon; PTA = percutaneous transluminal angioplasty.

to treatment assignments, while LEVANT 2 blinded the research coordinators and follow-up physicians to the treatment arm, which may have affected CD-TLR rates.

The 2-year patency rates of the Stellarex DCB (1) (75.9% with DCB vs. 61.0% with PTA; $p = 0.025$) are similar to those of the IN.PACT Admiral balloon (78.9% with DCB vs. 50.1% with PTA; $p < 0.001$) (4) (Table 1). To date, 2-year outcomes of the LEVANT 2 (Moxy Drug Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries) trial have not been published but have been presented, with lower primary patency rates of 58.6% with DCB versus 53.0% with PTA (log-rank $p = 0.05$) and freedom from CD-TLR of 82% with DCB versus 79% with PTA ($p =$ NS) (5). Given a lack of randomized head-to-head DCB trials, cautious direct comparison among DCBs should be made, as the inclusion and exclusion criteria, clinical and anatomic characteristics, and analysis of the endpoints in the trials did differ. Overall, RCTs have examined somewhat similar clinical (Rutherford class 2 to 4 disease) and anatomic cohorts with short lesions and about 20% total occlusions. The ILLUMENATE EU RCT enrolled patients with a mean lesion length of 7.2 cm, with a 19% total occlusion rate. The IN.PACT SFA trial had a mean lesion length of about 9 cm, with a total occlusion rate of 20% to 26%, whereas the LEVANT 2 trial had a mean lesion length of 6.3 cm, with 21% of the lesions being total occlusions. However, other differences in baseline characteristics and delivered treatment may have affected trial results.

The investigators allude to potential toxicity of a higher dose of paclitaxel from local effects and the potential for distal embolization. However, there have been no data published to date to suggest that paclitaxel dose toxicity is of clinical concern among the commercially available DCBs in the FP territory. The current report adds to the available body of safety data on DCBs and suggests that the Stellarex DCB has an evolved synergistic combination of excipient and drug dosing that permits a lower drug dose to be effective. However, as mentioned previously, multiple factors are required for a successful DCB, including drug formulation and dosing, excipient(s), DCB coating, and manufacturing methods as well as proper patient selection and procedural application.

Although the optimal treatment for FP arterial disease remains elusive, clearly DCBs provide an important “leave nothing behind” treatment option with superb short- and mid-term outcomes over plain “old” angioplasty. DCBs will continue to evolve in their drug formulation and dose, coating, deliverability, efficacy, and cost. Longer (>3 to 5 years) follow-up studies are needed to confirm the durability of reported outcomes with low-dose DCBs. Randomized comparisons of different DCBs are necessary given each DCB’s distinctive characteristics in terms of excipient, drug dose and delivery, balloon material, and manufacturing process, which may produce different outcomes. Further studies are needed to better understand the contribution of each of these factors and their role in DCB effectiveness. Given the significant body of RCT data for DCBs and their superiority over non-drug-coated PTA, current endovascular guidelines give DCBs a Class I recommendation for most FP lesion subsets (6). Despite the effectiveness of DCBs, stenting may result in better outcomes in certain anatomic subsets. RCTs are needed to compare DCBs and DES in the FP territory as well as DCB pre-treatment prior to DES versus BMS. Also needed are studies that examine the cost-effectiveness of strategies that avoid the need for permanent scaffolds, such as the combined use of plaque modification devices (e.g., atherectomy) and

DCBs. Such trials should recognize that not all DCBs are created equal and examine hard clinical endpoints of efficacy, safety, durability of treatment, quality of life, and cost-effectiveness in specific clinical circumstances and lesion subsets.

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