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REVIEW

Drug-Coated Balloon in Peripheral Artery Disease

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Abstract

In the field of interventional cardiology and vascular surgery, drug-coated balloons (DCBs) are a type of medical device used to treat numerous cardiovascular diseases, notably in the peripheral arteries. The interventionist's toolkit has grown thanks to the use of DCBs, which has improved primary patency and freedom from target lesion revascularization. Which technologies may accomplish these goals while simultaneously lowering overall morbidity and mortality is still up for dispute. The purpose of this article is to highlight new developments in the literature pertaining to the usage of balloons with drugs.

Keywords: Drug-coated balloon, DCBs, paclitaxel, peripheral arterial disease.

Introduction

Peripheral artery disease (PAD) is a significant public health concern, affecting millions of people worldwide, particularly those aged 70 and older. It is associated with a 2–6% rise in cardiovascular and cerebrovascular incidents and a 4–6% rise in yearly mortality, of which 60% is attributable to cardiovascular death[1-3]. In recent years, advancements in technology and procedural skills have expanded treatment options for PAD. The three main categories of endovascular treatment for PAD are ballooning, stenting, and atherectomy. The early clinical experience with stenting in femoropopliteal segments revealed an increased risk of stent fracture due to the physiological torsion of the artery, which could lead to vessel wall damage and restenosis[4]. Moreover, preclinical studies have indicated that metallic implants permanently overstretch the arterial wall, causing sustained inflammation and persistent neointimal growth, which may contribute to the observed "catch-up" phenomenon in this vascular bed[5]. As a result, there has been significant interest in the use of drug-coated balloons (DCBs) for the treatment of PAD. These balloons are coated with cell-cycle arresting agents, primarily paclitaxel, which inhibit cellular remodeling and reduce the occurrence of neointimal hyperplasia and in-stent restenosis. There are several DCBs currently available on the market for the treatment of PAD (Table 1).

Table 1. Drug-coated Balloons.

Device name	Balloon diameter (mm)	Balloon length (mm)	Shaft length (cm)	Sheath compatibility (Fr)	Guidewire compatibility (inch)	Paclitaxel dose (μg/mm^2)
IN.PACT (Medtronic)	4–7	40–250	80, 130	5, 6, 7	0.035	3.5
Luminor (iVascular)	2–8	10–200	80, 100, 140, 150	5, 6	0.014, 0.018, 0.035	3
Lutonix (BD Interventional)	4–7	40–300	100, 130	4, 5	0.018, 0.035	2
Ranger (Boston Scientific Corporation)	4–7	40–200	80–150	5, 6	0.018	2
Stellarex (Phillips)	4–6	40–200	80, 135	6	0.035	2

Here is an overview of some of the DCBs and their characteristics:

1. *Lutonix(Bard Peripheral Vascular, Tempe, AZ):* The Lutonix DCB utilizes an immediate-release, non-polymer-based paclitaxel coating on an amorphous matrix. It aims to provide uniform drug distribution and decreased systemic drug exposure. Clinical trials such as LEVANT I and LEVANT II showed improved primary patency compared to plain-old balloon angioplasty (POBA) but did not demonstrate differences in clinical outcomes like death, amputation, or reintervention[6,7].
2. *Ranger (Boston Scientific Corporation):* The Ranger DCB uses a hydrophobic form of paclitaxel with a citrate ester excipient, known as the TransPax coating system. It is designed for sustained release of paclitaxel with increased stability and efficacy[8,9]. Initial studies showed improved target lesion revascularization(TLR) rates and primary patency compared to POBA. The COMPARE trial, prospective randomized controlled trial (RCT), compared the efficacy and safety of two different DCBs, Ranger DCB (lower-dose paclitaxel coating) and IN.PACT DCB (higher-dose paclitaxel coating), in the treatment of superficial femoral artery (SFA) or proximal popliteal lesions in patients with Rutherford classes 2-4. The 1-year results of the COMPARE trial showed no significant differences between the two DCBs in terms of primary patency or safety outcomes[10].
3. *IN.PACT Admiral (Medtronic, Minneapolis, MN)*: A unique FreePac coating, crystalline paclitaxel matrix, and urea excipient are all used in the IN.PACT Admiral DCB. The matrix has a higher rate of systemic drug release, despite being made to enhance drug transport to the vessel[11]. Clinical studies demonstrated improved primary patency compared to POBA, and long-term data showed higher rates of freedom from device and procedure-related adverse events[12].
4. *Stellarex: (Phillips, Amsterdam, the Netherlands):* The Stellarex DCB utilizes a hybrid amorphous/crystalline paclitaxel matrix with specific excipients. Its design aims to improve tissue penetration while minimizing systemic release of paclitaxel[13]. Clinical trials, including the ILLUMENATE European trial and pivotal study, showed improved primary patency and target lesion revascularization compared to POBA in patients with Rutherford classes 2 to 4[14-16]. A meta-analysis further demonstrated no evidence of increased mortality in the DCB arm[17].

5. *Luminor (iVascular):* Luminor is a newer DCB that has not yet received FDA approval. It uses nanodrop technology to encapsulate paclitaxel in an ultrathin layer to prevent drug loss prior to balloon insufflation. Trials such as EffPac and MERLION demonstrated high freedom from target lesion revascularization rates, including below-the-knee interventions [18-20].

DCBs in Femoropopliteal arterial disease

The challenges associated with endovascular therapy in femoropopliteal (FP) arteries such as high restenosis rates (20-40%) after stenting, have led to the recommendation of DCBs as a standard treatment option for femoropopliteal artery disease, according to the Society for Cardiovascular Angiography and Interventions (SCAI) guidelines[21].

Several clinical trials have demonstrated the efficacy of DCBs compared to POBA in reducing late lumen loss (LLL). The FemPac Pilot trial[22] and THUNDER trial[23] conducted in 2008 showed significant reductions in LLL with DCBs compared to POBA. Meta-analyses, including studies with a total of 381 patients and eight RCTs with 1,341 patients, have confirmed the effectiveness of DCBs in terms of angiographic restenosis and TLR reduction[24,25].However, heterogeneity in treatment effect for TLR was observed, particularly in the LEVANT 1 and 2 studies. The LEVANT I (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) trial was a multicenter, randomized controlled trial that compared the use of Lutonix DCB with POBA for the treatment of femoropopliteal artery disease. The trial included 101 patients and assessed the primary efficacy endpoint of angiographic late lumen loss at 6 months. At 6 months ,late lumen loss was 58% lower for the Lutonix DCB group than for the control group[6]. The LEVANT II trial was a larger, multicenter, randomized controlled trial that further investigated the use of Lutonix DCB in femoropopliteal artery disease. This trial included 476 patients and aimed to assess the primary safety endpoint of a composite of freedom from major adverse events at 1 year. The trial evaluated the primary efficacy endpoint of binary restenosis at 6 months. The results demonstrated that the Lutonix DCB group had similar safety outcomes compared to the POBA group, with no significant difference in the primary safety endpoint. The Lutonix DCB group showed significantly lower rates of restenosis at 6 months compared to the POBA group. However, they could not find a significant difference between the two trial groups in the clinically important end point of target-lesion revascularization at 12 months[7]. Lutonix DCB was found to have lower paclitaxel tissue bioavailability compared to other DCBs like IN.PACT and Stellarex DCBs[26]. This difference in drug delivery might have contributed to lower primary patency and freedom from TLR at the 1-year follow-up in the LEVANT 2 study[27,28].

The COMPARE multicenter RCT have compared different DCBs. In this prospective, multicenter, non-inferiority clinical study 414 patients with symptomatic femoropopliteal lesions (Rutherford classification2-4) were randomized in a 1:1 ratio to receive endovascular therapy with either high-dose (IN.PACT) or low-dose (Ranger) DCBs after lesion length stratification. At 12 months, non-inferiority was established for the key effectiveness and safety endpoints. Primary patency varied between 81.5 percent in the high-dose DCB group and 83.0 percent in the low-dose DCB group. In the high-dose DCB group, freedom from serious adverse events was found in 92.6 percent, and in the low-dose DCB group, in 91.0 percent. Therefore according to the study, the Ranger DCB was equally effective at treating symptomatic femoropopliteal lesions as the IN.PACT DCB[10]. The COMPARE trial's 2-year results also showed that PCBs in both low- and high-dose forms were effective for treating femoropopliteal interventions with a variety of lesion lengths[29]. Other studies like ILLUMENATE and CONSEQUENT demonstrated superior safety and effectiveness of DCBs compared to POBA-only groups at longer-term follow-up (> 2 years)[17,30]. Consistent findings from various meta-analyses support the use of DCBs over bare-metal stents (BMS) and POBA alone, demonstrating a significant reduction in TLR when DCB strategies are employed in the treatment of femoropopliteal arteries[25,31].

The optimal revascularization therapy for in-stent restenosis (ISR) in femoropopliteal arteries is still a matter of debate, and there is currently insufficient statistical power in randomized trials to thoroughly investigate the clinical outcomes of DCBs versus POBA for this indication. However, patient-level data from three randomized trials published in 2018 involving 263 patients with ISR of femoropopliteal arteries showed that the DCB arm had a lower risk of TLR and recurrent ISR compared to the POBA group[32]. These findings suggest a potential benefit of DCB angioplasty for ISR. On the other hand, the DEBATE-ISR trial demonstrated that while recurrent TLR at 1 year was significantly lower in the DCB group compared to POBA, the 3-year TLR rates were similar between the two groups[33].

In cases where restenotic or heavily calcified lesions are present, the use of debulking devices in combination with DCBs offers another treatment option. This approach combines the benefits of removing excessive tissue or calcified plaques with atherectomy or laser, along with the suppression of neointimal proliferation through the use of DCBs[34]. Studies such as the DEFINITIVE AR study have shown promising results in patients with calcified superficial femoral artery lesions, suggesting the potential benefit of performing debulking atherectomy before using DCBs[35].Additionally, studies have demonstrated encouraging mid-term clinical outcomes with the use of atherectomy in combination with DCBs compared to DCB therapy alone[36]. Combining laser debulking with DCBs has also shown improved outcomes in patients with critical limb ischemia and SFA in-stent occlusion[37].

A recent analysis of four prospective multicenter studies supported the use of DCB over bare-metal stents (BMS), demonstrating higher 12-month patency (90.4% vs 80.9%), higher freedom from 36-month CD-TLR(85.6% vs 73.7%), and cumulative 36-month major adverse events (MAE)(25.3% vs 38.8%)[38].

Study that was just published by Tepe et al. [39] evaluated the 5-year clinical outcomes of DCBs for the treatment of challenging FP lesions, ISRs, long lesions (LLs), and chronic total occlusions (CTOs)[39].The results showed that DCB treatment for LLs and CTOs had acceptable clinical outcomes. The 5-year rate of freedom from clinically driven target lesion revascularization (CD-TLR) for LLs was similar to that reported in the overall clinical cohort of the IN.PACT Global study. The clinical outcomes of DCB for LLs appeared comparable to those of bypass surgery using prosthetic conduit or saphenous vein. The study suggests that DCB could be a first-line treatment for long FP lesions. For CTOs, the 5-year rate of freedom from CD-TLR was high(69.8%), but it should be noted that approximately half of the lesions underwent stent-supported DCB therapy. The POPCORN (PrOsPective multiCenter registry Of dRug coated ballooN for FP disease) registry, which was the largest DCB study with rare bailout stenting (3.5%) and no atherectomy use, demonstrated that the presence of CTO was significantly associated with the loss of primary patency[40]. Vessel preparation with directional atherectomy before DCB treatment and the use of stents might have contributed to the better outcomes in the CTO cohort. However, this study showed suboptimal outcomes for DCB treatment of ISRs. The 5-year rates of freedom from CD-TLR and thrombotic occlusion were the worst among the ISR subset. This suggests that DCB therapy for ISRs is challenging, and additional measures such as plaque modification by atherectomy and intensive antithrombotic medications may be needed to improve outcomes.

Drug-Coated Balloons versus Drug Eluting Stents

DCB is typically chosen for non-challenging, mild to moderate FP lesions, while Drug Eluting Stents (DES) is often selected for challenging, severe lesions. DES, which uses a fluoropolymer-based coating, effectively inhibits neointimal hyperplasia and reduces the risk of restenosis and CD-TLR. However, DES raises concerns regarding acute stent thrombosis and aneurysmal degeneration. Acute stent thrombosis can lead to adverse limb events, and the optimal antithrombotic treatment for prevention is still debated. The clinical significance of aneurysmal degeneration remains inconclusive.

In contrast, DCB treatment carries lower risks of acute stent thrombosis and aneurysmal degeneration. This makes DCB a preferred option for the treatment of both non-challenging and challenging FP lesions in terms of safety. The lower risk profile of DCB makes it an attractive choice,

particularly in clinical settings where minimizing adverse events is crucial. The evaluation of DCBs versus DESs for the treatment of peripheral artery disease can be challenging due to various factors, including patient crossover between treatments and a lack of long-term data on patency.

Several studies have attempted to compare DCBs and DESs in PAD treatment. A multicenter, randomized trial by Bausback et al. [41] demonstrated comparable effectiveness and safety profiles between DES and DCB, with a trend favoring DES after 36 months[41]. This finding was further supported by additional studies and a meta-analysis comparing DES and DCB to other treatment options[42,43].

Koifman et al compared all treatment options for femoropopliteal disease, including surgical options, and found that all treatments were superior to POBA[44]. However, no treatment showed superiority in terms of amputations or survival. Financial implications also play a role, as the use of multiple DCBs or the need for a stent can significantly decrease cost-effectiveness[45].

The "As Less As Reasonably Achievable Stenting (ALARAS)" strategy has been proposed as an approach to minimize stenting and preserve the natural motion and geometry of the superficial femoral artery (SFA)[46]. Placement of a stent following balloon angioplasty, guided by the ALARAS principle, aims to avoid stent fractures and high TLR rates.

The use of adjuvant therapies like atherectomy in conjunction with DCB further complicates the comparison between DCB and DES. In a study by Lee et al[47], 32% of patients in the DCB arm underwent atherectomy with the DCB arm showing higher primary patency and freedom from TLR[47].

DCBs in Atherosclerotic disease of below-the-knee (BTK) arteries

In below-the-knee (BTK) lesions, coronary drug-eluting stents (DES) have shown superiority over POBA and bare-metal stents (BMS)[48]. However, the diffuse nature of atherosclerotic disease in this long vascular segment limits the routine use of many coronary DES. The clinical performance of DCBs in this area has yielded less conclusive results.

Early experience from a single-center observational study by Schmidt et al. and the randomized DEBATE-BTK trial reported superior mid-term results with the use of DCBs compared to POBA[49,50]. However, the IN.PACT-DEEP multicenter RCT released in 2015 did not demonstrate the superiority of the IN.PACT Amphirion DCB over POBA in terms of TLR and late lumen loss (LLL). Moreover, the IN.PACT-DEEP trial showed a higher incidence of amputation and a trend towards higher mortality in the DCB arm, resulting in the withdrawal of the device from the market[51].

A meta-analysis conducted in 2016, including five trials with 641 patients, reported that DCBs in BTK lesions had similar clinical efficacy and superior angiographic performance compared to POBA or DES at 1-year follow-up. The analysis revealed lower LLL with DCBs but no improvement in clinical outcomes such as amputation and wound healing. The study concluded that a dedicated wound care management approach should be implemented for patients with advanced-stage atherosclerotic BTK disease to evaluate the net clinical benefit of different revascularization strategies[52].

Regarding the use of Lutonix DCB versus POBA in BTK lesions, a prospective, global, multicenter, single-blind RCT demonstrated no significant difference in freedom from mortality, freedom from major amputation, or amputation-free survival between the two groups. The study concluded that Lutonix DCB provided statistically significant efficacy outcomes at 6 months without observed safety issues up to 3 years[53]. However, it is important to note that the Lutonix DCB has not received market approval from the FDA for the treatment of peripheral arterial disease (PAD) in BTK vessels.

More prospective studies are needed to clearly establish the merits of DCB-based strategies in the treatment of BTK lesions. The current evidence does not provide a definitive consensus, and further research is required to assess the long-term safety and efficacy outcomes in this specific patient population.

Mortality Risk

The safety concerns surrounding paclitaxel-coated devices for PAD interventions emerged following a systematic review by Katsanos et al[54]. This review demonstrated an increase in all-cause mortality in patients treated with paclitaxel-coated devices, leading to global avoidance of these devices and a reassessment of their safety.

However, reactions to the results of the review were mixed, and questions were raised about the limitations of the study and statistical analysis. The original review was not specifically designed to evaluate mortality, but rather patency outcomes, and there were limitations in patient-level data, long-term follow-up, and accountability for crossover treatment arms. These limitations make it challenging to establish a causal relationship between paclitaxel exposure and increased mortality based solely on the study by Katsanos et al. [54]

Subsequent studies have provided conflicting results regarding the association between paclitaxel-coated devices and mortality. Some studies have shown no difference in mortality, while others have reported a small absolute increased mortality risk without identifying a clear causal mechanism[42,55-59].

Interpretation and clinical application are quite difficult for the endovascular professional because of these contradictory results. In exchange for a higher quality of life and a lesser need for revascularization, some patients may find the risk tolerable. It is necessary to continue monitoring paclitaxel-coated devices in order to assess the technology's safety; in the interim, patients must receive the right patient counseling regarding these issues.

Conclusion

Current clinical data consistently show a significant reduction in TLR with the use of DCBs compared to bare-metal stents (BMS) and POBA. DCB treatment appears to be a preferred modality for non-challenging FP lesions, while DES is often chosen for challenging, severe lesions. DCB shows acceptable outcomes for LLs and CTOs. However, the treatment of ISR with conventional methods remains challenging, and there is no clear frontline strategy. The use of debulking devices, such as atherectomy and laser debulking, in combination with DCBs has shown improved outcomes compared to using DCBs alone. Long-term safety outcomes of patients treated with paclitaxel-based devices should continue to be monitored.

Conflicts of Interest

The author have no conflicts of interest to declare.

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