Review

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Drug-coated balloons: a novel advance in the percutaneous treatment of coronary and peripheral artery disease

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Since the introduction of plain old balloon angioplasty, there have been several improvements in the treatment of coronary artery disease, with the advent of bare metal stents and drug-eluting stents being two notable milestones. Although these stents confer better acute gains in coronary interventions, the risk of in-stent restenosis (ISR) remains, especially with bare metal stents. Hence, the idea of delivering antiproliferative drugs via a drug-coated balloon (DCB) has been explored to hopefully avoid the need to implant another stent within an ISR. This review aims to summarize available clinical evidence and current guidelines in the use of DCB in ISR. Additionally, the roles of DCB in *de novo* small vessel and bifurcation coronary lesions, in ST-elevation myocardial infarction and in peripheral arterial disease are also reviewed.

Keywords: bare metal stents • bifurcation lesions • *de novo* small vessel disease • DCB • drug-coated balloon • drug-eluting stents • in-stent restenosis • paclitaxel-coated balloon • peripheral artery disease • plain old balloon angioplasty • POBA • ST-elevation myocardial infarction • STEMI

Plain old balloon angioplasty (POBA), once deemed an obsolete technique in the post-stenting era, has received revived interest in the recent decade owing to the development of drug-coated balloons (DCBs). DCB allows the delivery of drugs with antiproliferative properties, without the embedded mechanical struts. This paper provides a review of DCB, with particular focus on clinical trials that have evaluated its efficacy in in-stent restenosis (ISR), small vessel disease, ST-elevation myocardial infarction (STEMI), bifurcation lesions, and in the peripheral arteries.

POBA was first introduced in the 1970s for the treatment of coronary artery disease [1]. It was limited by its high rate of abrupt closure from vessel dissection and recoil often requiring urgent coronary artery bypass graft [2]. Clinical outcomes improved with the advent of bare metal stents (BMSs), which resulted in a dramatic reduction in the risk of acute closure compared with POBA [3]. BMS however came with the problem of ISR secondary to intimal hyperplasia [4], which prompted efforts to search for a solution. One of the original options included the use of intracoronary radiation [5,6]. Despite superior results in terms of intrastent luminal loss using intracoronary radiation, there was a large increase in the risk of very late stent thrombosis, a complication with a high mortality [7].

The development of drug-eluting stents (DESs), impregnated with outer polymer and drugs with antiproliferative properties, at the beginning of the millennium marked an important milestone in interventional cardiology owing to its dramatically lower rates of ISR compared with BMS [8,9]. An ongoing issue, however, especially with first-generation DES, was the persisting small but significant risk of malapposition and late stent thrombosis [10–12].

Similarly, percutaneous treatment of peripheral vascular disease of the lower limbs is increasingly the preferred treatment option

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over open vascular surgery. However, rates of restenosis with both plain balloon angioplasty and stent insertion remain high [13–15] because of the diffuse nature of the disease, marked vessel calcification and stent fracture, neointimal proliferation and thrombosis. Further, initial clinical trials with DES are not as encouraging as their application in coronary arteries [16,17]. Therefore, alternative percutaneous treatment options are also sought after in this vascular territory.

The concept of local delivery of drug is not a foreign one. Balloon catheters delivering antiproliferative drugs were first developed and shown to inhibit neointimal growth, both *in vitro* and *in vivo* in the late 1990s [18–20]. However, unlike DESs, DCBs face an inherent technological challenge of maintaining adequate levels of antiproliferative drug after balloon expansion. Following an observation that iopromide contrast agent adheres to vessel wall for a few seconds after injection, Scheller *et al.* found that paclitaxel delivery can be improved when given together with iopromide, suggesting the importance of an excipient or solvent [21]. This finding was further corroborated by later studies, which demonstrated that DCBs have different efficacy in reducing neointimal growth depending on the excipient used, the most potent were iopromide and butyryl-tri-hexyl citrate [22,23]. As with DES, the balance between effectiveness and potential toxicity, such as fibrin deposition, inflammation and delayed endothelialization, needs to be achieved.

Published randomized trials in human subjects have commonly employed several paclitaxel-excipient formulations: paclitaxel-shellac (Dior II), paclitaxel-urea (IN.PACT™ FALCON, Medtronic, MN, USA), paclitaxel-iopromide (SeQuent® Please, B Braun, Melsungen, Germany) and paclitaxel-polysorbate/sorbitol (Lutonix® DCB, BARD Peripheral Vascular, AZ, USA). Second-generation DCBs using zotarolimus have also been shown to achieve good tissue uptake in animal models [24,25], and future studies in human participants are eagerly awaited.

Clinical trial data

DCB in ISR

The PACCOCATH ISR trials I and II were two independent randomized trials that first looked at the efficacy of paclitaxel-eluting balloons (PEBs) compared with POBA in the treatment of BMS–ISR (Table 1). Results from 6-month data [26] showed superiority with DCB with better in-stent minimal lumen diameter (MLD; POBA 1.53±0.81 mm vs DCB 2.30±0.61 mm, p = 0.003) and lower late lumen loss (POBA 0.81 ± 0.79 mm vs DCB 0.14 ± 0.46 mm; p = 0.001). The 1-year and 2-year follow-up also showed clear superiority of DCB with respect to target revascularization [27]. In 2012, Scheller *et al.* published a 5-year follow-up data from the original PACCOCATH series and showed that target vessel revascularization rate remained significantly lower when treated with DCB compared with POBA (9.3 vs 38.9%; p = 0.004) [28]. In addition, they also demonstrated that at 5 years, major adverse cardiac event (MACE) associated with DCB is significantly lower than POBA (27.8 vs 59.3%; p = 0.009). These studies are the first to demonstrate favorable results of DCB up to 5 years of follow-up.

The PEPCAD II trial [29] randomized 131 patients who had BMS–ISR to receive either paclitaxel-coated balloon or paclitaxel-eluting stents (PESs) and demonstrated higher in-stent late lumen loss in the DES cohort (0.19 ± 0.26 vs 0.45 ± 0.68 mm; p = 0.01) at 6 months. However, the in-stent minimal luminal diameters and binary ISR rates in the cohorts were not significantly different. One important consideration for the interpretation of this result is that stented lesions may be more likely to have higher late luminal loss, as the acute postprocedural gain in luminal diameter is greater in the stented cohort. Clinical follow-up at 12 months also showed no significant difference in target-lesion revascularization. The comparable results between DCB and DES provide evidence that DCB may be an alternative intervention to a second stent, especially in circumstances where a prolonged dual antiplatelet treatment is undesirable.

Several studies also investigated the efficacy of DCB in the treatment of DES–ISR. One such study is the PEPCAD-DES [30] multicenter trial, which randomized 110 participants to either DCB or POBA in DES–ISR (including sirolimus-, paclitaxel- and everolimus-eluting stents) and found that DCB provided superior results at 6 months in late lumen loss and binary restenosis rate (Table 1). Clinically, DCB group also experienced less MACE (16.7 vs 50%; p < 0.001) and target vessel revascularization (15.3 vs 36.8%; p = 0.005). Interestingly, the reported rate of late lumen loss is higher with these DES–ISR studies compared with the PACCOCATH study, which examined the use of DCB in BMS–ISR [26]. Potential explanations for why DES–ISR lesions were more difficult to successfully treat might include clinical factors, such as a higher prevalence of diabetes, diffuse disease and ostial lesion location, and mechanical factors related to the original DES such as under-expansion and stent fracture [31].

The ISAR DESIRE 3 trial [32] compared the efficacy of PEB to PESs in treating sirolimus-eluting ISR. Consistent with the findings of PEPCAD-DES, they also found that at 6–8 months, both PEB and PES performed much better than POBA in reducing binary restenosis and late lumen loss. In addition, they showed

Table 1. Drug-coated balloons in in-stent restenosis.

Trial name	Size (n)	Lesion	Angiographic follow-up (months)	Binary restenosis rate	In-stent late lumen loss (mm)	Clinical follow-up (months)	TLR	MACE
POBA vs paclitaxel DCB								
PACCOCATH I and II	108	BMS–ISR	6	49 vs 6%; p = 0.001	0.81 ± 0.79 vs 0.14 ± 0.46; p = 0.001	24	37 vs 6%; p = 0.001	46 vs 11%; p = 0.001
Habara *et al.*	208	BMS/DES–ISR	6	31.9 vs 4.3%; p < 0.001	0.49 ± 0.50 vs 0.11 ± 0.33; p < 0.001	6	31.0 vs 2.9%; p < 0.001	31.0 vs 6.6%; p < 0.001
PEPCAD DES	110	DES–ISR	6	58.1 vs 17.2%; p < 0.001	1.03 ± 0.77 vs 0.43 ± 0.61; p < 0.001	6	36.8 vs 15.3%; p = 0.005	50.0 vs 16.7%; p < 0.001
ISAR DESIRE III	271	DES–ISR	6–8	57 vs 27%; p < 0.0001	0.70 ± 0.69 vs 0.37 ± 0.59; p < 0.0001	12	43.5 vs 22.1%; p < 0.0001	46.2 vs 23.5%; p < 0.0001
Paclitaxel DES vs paclitaxel DCB								
PEPCAD II	131	BMS–ISR	6	16.9 vs 7%; p = 0.17	0.45 ± 0.68 vs 0.19 ± 0.39; p = 0.01	12	15.4 vs 6.3%; p = 0.15	21.5 vs 9.1%; p = 0.08
ISAR DESIRE III	268	DES–ISR	6–8	24 vs 27%; p = 0.61	0.34 ± 0.61 vs 0.37 ± 0.59; p = N/A	12	13.5 vs 22.1%; p = 0.09	19.3 vs 23.5%; p = 0.50
PEPCAD China ISR	220	DES–ISR	9	18 vs 17%; p = 0.51	0.62 ± 0.68 vs 0.54 ± 0.46; p = 0.36	12	13 vs 17%; p = 0.48	25 vs 26%; p = 0.96
Everolimus DES vs paclitaxel DCB								
RIBS V	189	BMS–ISR	6–9	4.7 vs 9.5%; p = 0.22	0.04 ± 0.5 vs 0.14 ± 0.5; p = 0.14	12	1 vs 6%; p = 0.09	6 vs 8%; p = 0.60
RIBS IV	309	DES–ISR	6–9	11 vs 19%; p = 0.06	0.18 ± 0.6 vs 0.30 ± 0.6; p = N/A	12	4 vs 13%; p = 0.008	10 vs 18%; p = 0.044

Binary restenosis rate: Diameter stenosis ≥50% at follow-up; DCB: Drug-coated balloon; DES: Drug-eluting stent; In-stent late lumen loss: The difference between minimal luminal diameter immediately after the procedure and at follow-up; MACE: Major adverse cardiac event (TVR, MI, stent thrombosis, death); POBA: Plain old balloon angioplasty; TLR: Target lesion revascularization.

that both Paclitaxel-DCB and PES attained similar clinical outcomes at 1 year in target vessel revascularization (Table 1).

Another multicenter randomized trial in Japan by Habara *et al.* examined the efficacy of DCB compared with POBA in the treatment of both BMS- and DES-related ISRs [33]. They analyzed 213 lesions, 123 of which were BMS–ISRs and the remaining 90 were DES-related ISRs (sirolimus n = 62, zotarolimus n = 24 and everolimus n = 4). The study participants were randomized to receive either paclitaxel-DCB or POBA, and the primary end point was late lumen loss at 6 months. In the overall cohort, they showed that DCB was associated with less late lumen loss than POBA (0.11±0.33 vs 0.49±0.50 mm, p < 0.001). As noted in previous studies, an important finding in this study was that DCB was observed to be more effective in treating BMS-related ISRs than DES–ISRs. In a subanalysis examining the DCB-treated cohort only, a significantly smaller late lumen loss at 6 months was achieved in BMS–ISR lesions (0.05 ± 0.28 vs 0.18 ± 0.38 mm; p = 0.03) compared with DES–ISR.

A recent noninferiority trial in China also showed comparable outcomes when using Paclitaxel-DCB compared with Paclitaxel-DES in the treatment of DES-related ISR [34]. This study is in keeping with the ISAR DESIRE 3 trial results.

Perhaps more relevant to contemporary practice, the Restenosis Intra-stent of Drug-eluting Stents (RIBS) V trial compared the efficacy of PEBs with everolimus-

eluting stents (EESs) in the treatment of BMS–ISR [35]. At 6–9 months, EES achieved a lower percent diameter stenosis (13 ± 17 vs 25 ± 20%; p < 0.001) and larger MLD (2.36 ± 0.6 vs 2.01 ± 0.6 mm; p < 0.001) than DCB. The absolute difference in MLD in favor of EES remained after adjusting for differences in baseline characteristics (adjusted for age, diabetes, smoking and degree of lesion stenosis; p < 0.001). However, binary restenosis rates did not differ significantly (EES 4.7 vs DEB 9.5%; p = 0.22).

Led by the same group of investigators, Alfonso *et al.* compared the efficacy of Paclitaxel DCB with EES in DES–ISR lesions as well in the RIBS IV trial [36,37] presented at the Transcatheter Cadiovascular Therapeutics meeting in 2014. Similar to RIBS V, EES achieved a lower MLD (2.03 vs 1.80 mm; p = 0.004) and late loss (0.18 ± 0.6 vs 0.30 ± 0.6 mm; p < 0.05) than DCB. However, binary restenosis rates showed no significant differences (11 vs 19%; p = 0.06). Clinically at one year, EES had higher rates of freedom from target-lesion revascularization (TLR; (96 vs 87%; p = 0.008) and MACE (90 vs 82%; p = 0.044). Collectively, the evidence presented from RIBS IV and V trials strongly suggests that EES is superior to DCB in the treatment of both BMS and DES–ISR. However, a class effect should not be assumed for the other second-generation stents, for example, the zotarolimus stents.

Guidelines have been published to guide the treatment of BMS and DES restenosis. The American Heart Association (AHA) suggests the use of DES in BMS–ISR [38]. However, in DES–ISR, intravascular ultrasound is recommended to further characterize the stenosis, and focal restenosis can be treated with POBA, BMS, coronary artery bypass graft or DES. By contrast, the European Society of Cardiologists (ESC) suggests the consideration of DCB in the treatment of BMS–ISR [39] only, but not for DES–ISR. In summary, there is favorable data for Paclitaxel DCB over POBA in the treatment of BMS–ISR, but not for DES–ISR. In addition, they do not perform better than Paclitaxel DES and seem to be inferior to second-generation EES. Nonetheless, the use of DCB warrants further research, especially with the newer DCB technologies, such as the zotarolimus-eluting balloons.

DCB in small vessel coronary artery disease

Small vessel disease, defined as a lumen diameter of ≤2.75 mm, occurs in an estimated 20–30% of patients who present with symptomatic coronary artery disease, with a higher prevalence in patients with diabetes and renal impairment [40]. It presents a therapeutic dilemma for cardiologists as these lesions have higher rates of restenosis and stent thrombosis following percutaneous coronary intervention [41–44].

The initial trials with POBA on small vessel intervention provided very poor results [45], and the adverse events were still very high with BMS [46]. As a result, the European Society of Cardiology and ACC Guidelines on Intervention mandate that DES is the preferred interventional treatment for small vessel intervention [38,39]. This is due to the significantly lower rates of mid-term restenosis [47–49]. However, late stent thrombosis remains a concern [50]. Therefore DCB were proposed as a possible alternate approach to deliver the drug to the lesion [51], avoiding the complications of implantable stents.

Two randomized trials to date have examined this scenario with contrasting results. The PICCOLETO study (paclitaxel-coated balloon vs DES during percutaneous coronary intervention of small coronary vessels) [52] compared paclitaxel-eluting DCB with the PES for the treatment of small vessel stenosis. The study was stopped prematurely after enrollment of two-thirds of the intended patient number due to a clear superiority of the PES group. In the follow-up angiography at 6 months, the DCB group had higher angiographic binary restenosis (32.1 vs 10.3%; p = 0.043) and TLR (32.1 vs 10.3%; p = 0.15).

A larger multicenter Italian study (BELLO) was then published 2 years later by Latib *et al.* [53], which randomized patients to receive Paclitaxel-urea balloon or PES. At 6 months, Latib *et al.* found that although the percent diameter stenosis was marginally higher in the DCB group, it was not statistically significant (32.31 ± 16.66 vs 26.69 ± 20.38%; p = 0.06). Binary restenosis was similar in both arms, and so was the rate of TLR.

The contrasting results of PICCOLETO and BELLO trials could be related to the specific DCB technologies used, namely paclitaxel-shellac (Dior II) and paclitaxel-urea (IN.PACT FALCON). It is possible that these excipients were less efficacious than the paclitaxel-iopromide preparations used in ISR studies. Further research examining the role of paclitaxel-iopromide or zotarolimus DCBs in *de novo* small vessel disease may result in better outcomes. Current recommendations from AHA and the ESC strongly suggest the use of DES in the treatment of small vessel disease [38,39] as there is insufficient evidence to support the use of DCB.

DCB in STEMI

Drug-eluting balloon angioplasty is potentially an attractive treatment option in STEMI because of the concern regarding stent malapposition and acute stent thrombosis in underdeployed and undersized stents [54] in the acute infarct vessel. The DEB-AMI multicenter trial [55] was a three-arm trial that compared the use of

DES alone, DCB followed by BMS and BMS alone in 150 patients who presented with STEMI, with reference diameter of target vessel between 2.5 and 4.0 mm. DES was shown to have significantly lower angiographic stenosis (percent diameter stenosis) at 6-month follow-up, compared with the other treatment strategies (DES 19.0 ± 11.6 vs DCB + BMS 35.7 ± 20.9 vs BMS 41.2 ± 23.5; $p < 0.01$). An analysis of efficacy of neointimal growth inhibition was also performed using coronary ocular coherence tomography (OCT). By comparing the mean neointimal volumes at 6 months, DES was shown to exert a far greater antiproliferative effect than DCB + BMS (1.07 vs 2.75 mm^3; $p < 0.01$).

There was no significant difference in late luminal loss between the entire DCB + BMS and BMS cohorts. However, in a subgroup analysis confined to patients who only required one stent, patients who received DCB + BMS did have less late luminal loss compared with BMS alone (0.43 ± 0.45 vs 0.74 ± 0.60 mm; $p = 0.047$). It is plausible that patients who only required one stent performed better because the risk of geographic mismatch between the predilated and stented segments was less. Interestingly, a proportion of patients within the DCB + BMS group who received predilation of the lesion with POBA before DCB + BMS had lower late luminal loss compared with those who did not (0.49 ± 0.52 vs 0.85 ± 0.56 mm; $p = 0.04$). This may be due to vessel micro-injury caused by predilation with POBA, which may have improved local drug delivery from the DCB.

In the treatment of STEMI, the AHA and ESC recommend the use of DES, provided the patient is able to tolerate dual antiplatelet for at least 6 months [38,39], but not DCB. A recent pilot study has demonstrated the feasibility of DCB in STEMI [56]; however, further studies are still required to increase the body of evidence for the potential role of DCBs in patients with STEMI who cannot tolerate longer-term dual antiplatelet therapy, either in conjunction with a BMS implantation or on its own.

DCB in bifurcation lesions

Studies of DCB in bifurcation lesions have not been as encouraging. In the Drug-Eluting Balloon in Bifurcations Trial (DEBUIT) [57], patients with *de novo* bifurcation lesions with a main branch (MB) of ≥2.5 mm diameter and length of <32 mm and a side branch (SB) of ≥2 mm diameter were recruited. They all received predilatation with POBA of both MB and SB, and then were randomized to one of three arms: BMS implantation, additional dilatation with DCB before BMS implantation, or DES. At 6 months, in the proximal MB, late luminal loss was lowest in the DES group (DES 0.13±0.45 mm), and there was no difference between the BMS and DCB + BMS groups (BMS 0.60 ± 0.65 mm, DCB + BMS 0.58 ± 0.65 mm; $p = 0.87$). Likewise, DES was superior in the distal main and side branches. Similar trends were also observed in binary restenosis and percentage diameter stenosis. Notably, the investigators did not find any difference when BMS was implanted with or without predilatation with DCB.

Other novel strategies involving the use of DCB in bifurcation lesions have also been explored and recently reported. The first study randomized 64 patients to DCB of POBA without a stent in bifurcation lesions that either involved the SB or distal MB but not the proximal MB. Bail out stenting was discouraged but allowed. Angiographic restenosis at 9 months trended lower in the DCB than POBA (6 vs 25%; $p = 0.08$), and late lumen loss was significantly lower with DCB (0.15 vs 0.48 mm; $p = 0.0035$). The second study was an observational report of 50 patients with a strategy of paclitaxel DES in the MB and a DCB in the SB. The TLR in the SB was only 2% with virtually no late loss (0.0065 ± 0.4 mm).

Currently, the recommended treatment strategy by AHA for bifurcation lesion is stenting of the MB with DES, with additional balloon angioplasty or stenting of the SB, depending on the risk of SB occlusion [38], and therefore there is no role for DCB on the available evidence.

DCB in peripheral artery disease in the lower limb

The problem of restenosis and occlusion in the peripheral arteries is similar to that faced in coronary arteries [58]. Recently, trials examining the use of newer generation-limus DES in the treatment of femoro-popliteal peripheral vascular disease showed no significant difference in outcomes when compared with BMS [16,17]. Furthermore, complications of very late stent thrombosis and stent fracture may occur in the peripheral vascular beds [59,60]. This has led to considerable interest in a possible role for DCB to treat the often long segments of diffuse disease in femoro-popliteal arteries, for both *de novo* and restenotic lesions.

Several papers have shown encouraging results for the use of DCB in peripheral vessel disease. The first study is the Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries (THUNDER) trial [61], which randomized 154 patients with stenosis or occlusion of the superficial femoral and/or popliteal artery to receive either POBA, POBA with regional intra-arterial paclitaxel injection dissolved in contrast or paclitaxel-eluting balloons. It demonstrated lower late lumen loss at 6 months in the PEB group compared with plain balloon angioplasty (0.4 ± 1.2 vs

1.7 ± 1.8 mm; p < 0.001). However, no benefit was seen when paclitaxel was delivered in the contrast medium. TLR was also less in the DCB group at 6, 12 and 24 months (Table 2).

A second study, the FemPac Trial [62], also demonstrated similar results, favoring DCBs over POBA. In this study, 87 patients with both *de novo* or restenotic lesions ≥70% diameter stenosis of the superficial femoral and/or popliteal artery were randomized to either POBA or paclitaxel-eluting balloons. Six month late lumen loss was less in the DCB group (0.5 ± 1.1 vs 1.0 ± 1.1mm; p = 0.031). TLR was significantly lower with DCB (7 vs 33%; p = 0.0024) at 6 months and trended lower (23 vs 50%; p = 0.12) at 24 months (Table 2). Notably, a subgroup analysis showed similar late lumen loss for both *de novo* (DCB 0.4 ± 1.2 mm vs POBA 0.9 ± 1.2 mm; p = 0.12) and restenosic lesions (DCB 0.6 ± 0.5 mm vs POBA 1.1 ± 0.9 mm; p = 0.095).

More recently, the PACIFIER Trial [63] compared the use of PEBs with plain angioplasty and found favorable outcomes with DCB. It was a multicenter, randomized trial, with 44 and 47 participants in the DCB and control arms, respectively. All candidates had either *de novo* or restenotic femoro-popliteal artery stenosis of ≥70%. Late lumen loss was less for the DCB arm at 6 months (-0.01 mm [95% CI: -0.29–0.26] vs 0.65 mm [95% CI: 0.37–0.93]; p = 0.001). TLR was also significantly lower in the DCB group than POBA at 12 months (Table 2).

Another study published recently, the LEVANT I trial [64], utilized a lower concentration of Paclitaxel-coated balloons (2 μg/mm^2) compared with prior studies. Participants with both *de novo* and restenotic femoro-popliteal lesions were stratified into two arms, those intended for balloon angioplasty only (n = 75) and those intended for stent revascularization (n = 26), based on the operators' discretion after initial predilation. Within each arm, the subjects were then randomized 1:1 to receive either paclitaxel-eluting or plain balloon angioplasty. The 6-month late lumen loss was less in the DCB cohort, irrespective of whether they received a stent (0.49 ± 1.01 vs 0.9 ± 0.91 mm; p = 0.37) or angioplasty alone (0.45 ± 1.18 vs 1.19 ± 1.15 mm; p = 0.024). Statistical significance was only achieved in the angioplasty group, likely related to the small numbers in the stent subgroup. There was no statistical significance between the groups in target vessel revascularization at 6, 12 and 24 months.

Some trials also included patients with infrapopliteal lesions as well. In the DEBELLUM trial, 24.6% of the recruited patients had infrapopliteal disease, while the rest were femoro-popliteal. The investigators showed that DCB, compared with POBA, achieved lower late lumen loss (0.5 ± 1.4 vs 1.6 ± 1.7 mm; p < 0.01), lower binary restenosis rates (9.1 vs 28.9%; p = 0.03) and

Table 2. Drug-coated balloons in peripheral artery disease in the lower limb.

Trial name	Size (n)	Lesion	Angiographic follow-up (months)	Binary restenosis rate	Late lumen loss (mm)	Clinical follow-up (months)	TLR	Major amputations
POBA vs Paclitaxel DCB								
THUNDER	102	SFA	6	44 vs 17%; p = 0.01	1.7 ± 1.8 vs 0.4 ± 1.2; p < 0.001	6–12	48 vs 10%; p < 0.001	0 vs 4%; p = 0.22
FemPac	87	SFA	6–8	47 vs 19%; p = 0.035	1.0 ± 1.1 vs 0.5 ± 1.1 ; p = 0.031	18–24	50 vs 13%; p = 0.001	2 vs 0%; p = 1.00
PACIFIER	85	SFA	6	32.4 vs 8.6%; p = 0.01	0.65 (0.37–0.93) vs -0.01 (-0.29–0.26); p = 0.001*	12	27.9 vs 7.1%; p = 0.02	0 vs 0%; p = 1.00
LEVANT I	101	SFA	6	51 vs 28%; p = N/A	1.09 ± 1.07 vs 0.46 ± 1.13; p = 0.016	12	33 vs 29%; p = N/A	0 vs 2%; p = N/A
DEBELLUM	50	SFA/BTK	6	28.9 vs 9.1%; p = 0.03	1.6 ± 1.7 vs 0.5 ± 1.4; p < 0.01	6	24 vs 6%; p = 0.02	8 vs 3%; p = 0.36
DEBATE-BTK	120	BTK	12	74 vs 27%; p < 0.001	N/A	12	43 vs 18%; p = 0.002	1.5 vs 0.0%; p = 0.9
IN.PACT DEEP	358	BTK	12	35.5 vs 41.0; p = 0.609	0.62 ± 0.78 vs 0.61 ± 0.78; p = 0.95	12	13.5 vs 11.9; p = 0.682	3.6 vs 8.8%; p = 0.08

*Reported as mean (95% CI).
BTK: Below theknee; N/A: Not available; N/S: Not significant; POBA: Plain old balloon angioplasty; SFA: Superficialfemoral artery; TLR: Target-lesion revascularization.

lower TLR (6.1 vs 23.6%; p = 0.02) at 6 months. The DEBATE-BTK recruited diabetic 120 patients with infrapopliteal disease alone. Compared with POBA, DCB was also shown to achieve much less binary restenosis (27 vs 74%; p<0.001) and TLR (18 vs 43%; p = 0.002) at 1 year. However, these results were not replicated in a recent, larger IN.PACT DEEP trial, which examined 358 patients with critical limb ischemia. There were no differences in binary restenosis or late lumen loss between DCB and POBA, and notably there was a trend toward higher rate of major amputation at 12 months in the DCB arm (8.8 vs 3.6%; p = 0.08) [65]. As noted by Laird and Armstrong [66] in an accompanying editorial, the 3.6% of amputation rate in the POBA group was much lower than anticipated from previous studies. This may have reflected good contemporary wound care in the POBA arm, and there was no predefined protocol in wound management across the recruitment centers.

Taken together these studies, evidence available to date appears to favor the use of DCB over POBA in femoro-popliteal peripheral artery disease. Based on the 2005 [67] (and an updated 2011 [68]) guidelines from the AHA, percutaneous transluminal angioplasty remains the recommended first-line treatment for femoro-popliteal disease. The use of stents can be considered if percutaneous transluminal angioplasty alone failed or provided suboptimal results. A recent press release by C. R. Bard, Inc. announced the approval of Lutonix 035 DCB Catheter for the treatment of suitable *de novo* or restenotic lesions (up to 150 mm in length) [69] by theUS FDA in the USA, based on as yet unpublished results from the LEVANT 2 trial at 1 year [70]. This exciting development may well see DCBs being increasingly used in the treatment of femoro-popliteal arterial diseases in the coming years. At present, there is insufficient evidence to support the use of DCB in infrapopliteal lesions.

DCB in arterio-venous fistulas, carotid ISR & intracranial arteries

In patients with arterio-venous hemodialysis access, Paclitaxel DCB has been evaluated in the treatment of native arterio-venous fistula and juxta-anastomotic arterio-venous graft stenotic lesions. In a randomized trial of 40 patients, at 6 months, primary patency was higher in the DCB group (70% DCB vs 25% POBA; p < 0.001), and longer-term follow-up data are still awaited [71]. Another smaller case series (n = 26) also reported safety and feasibility in the use of DCB in juxta-anastomotic arteriovenous fistula stenosis [72]. DCB has also been demonstrated to be feasible in the treatment of carotid ISR [73,74] and in intracranial atherosclerotic disease [75]. These studies, however, do need to be followed up with larger trials to further evaluate the potential clinical advantage of DCB in these vascular territories.

Conclusion

In the treatment of ISR, the available evidence seems to favor DCB over POBA, but they are not superior to DES. The advantage of DCB is that it precludes the need for additional metallic scaffold within an ISR. It is an attractive option in BMS–ISR, given the observation that DCB achieves better results in BMS–ISR than DES–ISR. However, DESs – both first and second generations – are increasingly being used in contemporary practice, and data supporting the efficacy of DCB in these ISRs is still lacking. In addition, the DCB technology studied in randomized trials thus far utilized paclitaxel as the antiproliferative agent. Further evidence with sirolimus-eluting balloons may lead to better outcomes.

For *de novo* small vessel disease, initial studies examining the efficacy of DCB have been equivocal, but ongoing trials such as the BASKET-SMALL 2 and RAMSES trials are awaited with interest. Trials that have examined the use of DCB in STEMI and bifurcation lesions have been less encouraging, but they may still have a future role in the small subset of patients who are unable to tolerate prolonged dual antiplatelet therapy.

In peripheral arterial beds, DCB has proved efficacious compared with POBA. Since DES in the treatment of femoro-popliteal disease is not as effective as in coronary arteries, DCB appears a promising and attractive treatment modality. While feasibility in infrapopliteal, A-V fistula and carotid arteries has been shown with DCB, more data are required.

Future perspective

The idea of using a DCB in conjunction with a BMS is potentially an attractive one as it allows local delivery of antiproliferative drug while taking advantage of the acute gains in luminal diameter from a stent implantation. An initial study of the application of DCB in conjunction with BMS was the PEPCAD III multicenter, noninferiority trial [76]. Although DCB + BMS was shown to perform better than just BMS alone, it failed to surpass DES. In another study, *de novo* lesions were first predilated with POBA, followed by Paclitaxel DCB, and finally implantation of BMS. That treatment arm was compared with Everolimus DES [77]. The study was halted early due to a higher ischemia-driven target vessel revascularization and MACE at 9 months in the DCB+BMS group (25 vs 4%; p = 0.01 and 29 vs 6%; p = 0.01, respectively). Therefore, current evidence does not favor the use of DCB + BMS

over DES. However, in clinical circumstances where dual-antiplatelet cannot be tolerated, the DCB + BMS may conceivably be an attractive option, especially as the optimal duration of dual antiplatelet therapy after DES is a matter of ongoing debate [78].

When DCB is used in conjunction with BMS, their sequence of deployment appears to be important. Kaul *et al.* recently published a pilot study (n = 97) examining the effect of predilatation with a Paclitaxel DCB before deployment of cobalt–chromium BMS and vice versa on late lumen loss and target lesion related MACE [79]. While statistical significance was not achieved, lower in-segment late lumen loss was demonstrated for the stent-before-DCB cohort (0.36 ± 0.56 vs 0.51 ± 0.56 mm; p = 0.23). One possible explanation is that in a DCB-before-stent approach, there is geographic mismatch between the segment receiving antiproliferative drug and the segment stented. Another hypothesis is that initial stent implantation causes micro-dissections to the vessel wall, which allows greater consequent uptake of antiproliferative drugs from the DCB [80]. The ISAR DESIRE 4 study [81] is currently being undertaken to further investigate this hypothesis.

For the treatment of ISR, a small, recent study has demonstrated promising results using the newer antiproliferative–limus nanoparticle DCBs [82]. Three sirolimus nanoparticle polymer matrices have been examined in porcine models for the treatment of BMS–ISR – two anionic preparations (poly D,L-lactide acid [PDLLA] and polylactic-co-glycolic acid-based formulations) and one cationic-based formulation (copolymer of ethyl acrylate, methyl methacrylate, and chloro-trimethylammonium ethyl methacrylate). These preparations were compared with POBA. At 28 days, all three formulations of sirolimus showed less luminal volume loss when compared with POBA, with the greatest effect seen in the PDLLA matrix. Further trials with sirolumus-based DCB in the treatment of BMS–ISR are required to ascertain the efficacy of this generation of antiproliferatives and translate its use in human subjects.

In small vessel coronary artery disease, the two existing trials had relatively small sample sizes, which limited their ability to detect a significant difference. This will be addressed in the multicenter trial in Switzerland, which is currently recruiting participants. This BASKET-SMALL 2 trial compares paclitaxel DCB with PESs, with an expected sample size of 649 patients [83].

Several other trials are also underway to ascertain the role of DCB in *de novo* disease. Of note, the DEBUT [84] and the PEPCAD-NSTEMI [85] trials are designed to compare paclitaxel-iopromide balloons to BMSs. However, the results of these studies will need to be interpreted in light of recent evidence showing superior short- and mid-term results with DES compared with BMS [47].

For direct comparison with the second-generation DESs, the RAMSES trial [86] compares zotarolimus-eluting stents with paclitaxel-urea balloons. The chosen primary outcome is target vessel revascularization, which is arguably better than earlier studies, which primarily measured angiographic outcomes. In addi-

Practice points

Background
- Drug-coated balloons (DCB) provide a means of delivering antiproliferative agents in the treatment of coronary artery disease, without the need to implant a stent *in situ*.

DCB in in-stent restenosis
- DCBs performed better compared with plain old balloon angioplasty in the treatment of coronary in-stent restenosis, but were not superior to drug-eluting stent (DES).

DCB in *de novo* small vessel disease
- In *de novo* small vessel disease, DCBs may be an attractive option, given concerns of very late stent thrombosis with DES. However, larger studies are required to examine the efficacy of DCB.

DCB in ST-elevation myocardial infarction
- In ST-elevation myocardial infarction predilatation of coronary lesion with a DCB prior to implantation of a bare metal stent may have a future role where dual antiplatelet therapy is contraindicated.

DCB in bifurcation lesions
- In coronary bifurcation lesions, DES in the main branch with additional angioplasty or stenting of the side branch is the recommended approach.

DCB in peripheral artery disease
- DCB appears to be superior to plain old balloon angioplasty in the treatment of femoro-popliteal peripheral vascular disease.

Future perspective
- Further trials utilizing second-generation sirolimus and zotarolimus DCBs, and further comparisons with newer generation stents are eagerly awaited.

tion, it aims to provide a cost–effectiveness analysis with DCBs.

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