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Advances in Percutaneous Therapies for Peripheral Artery Disease: Drug-Coated Balloons

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Abstract
Purpose of Review This review paper provides a summary on the use of drug-coated balloons in peripheral artery disease. It covers the main drug-coated balloon (DCB) trials. It is divided into categories of lesions: superficial femoral artery and popliteal lesions, infra-popliteal lesions and in-stent restenosis. It also includes an overview of the future of DCBs, highlighting the main ongoing trials.
Recent Findings The latest research on DCB focuses on newer types of DCBs, mainly paclitaxel-coated but with lower doses. Another area of latest DCB research is its use in superficial femoral artery and popliteal artery in-stent restenosis, with superior outcomes.
Summary Drug-coated balloons produce better outcomes than percutaneous transluminal angioplasty alone in de novo and in-stent restenosis lesions of superficial femoral artery and popliteal arteries. More data are needed to demonstrate efficacy and safety of DCBs in infrapopliteal disease. Newer DCBs and adjunctive therapy may provide improved outcomes for peripheral artery disease interventions.

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Introduction

The optimal endovascular therapy for peripheral artery disease (PAD) has evolved over the last decade. Previous research has demonstrated that the long-term outcome is poor for percutaneous transluminal angioplasty (PTA) alone in the infrainguinal region, with restenosis rates exceeding 40% within 1 year [1–4]. Further studies have suggested that self-expanding stents may provide higher patency rates when compared to balloon angioplasty [5]. However, observations indicate higher than anticipated rates of stent fractures and in-stent restenosis (ISR), leaving room for an alternative strategy [6–9]. Drug-coated balloons (DCBs) have emerged as a mechanism to deliver pharmacotherapies to the arterial wall, while leaving no foreign material behind [10].

Drug-coated balloons are important innovations in the treatment of PAD. DCBs, like stents, offer potential greater treatment efficacy over standard PTA, but with the advantage of not leaving an implanted device (i.e., stent) in the artery. This provides number of potential advantages including preserving options for subsequent surgical bypass, should it be necessary, and improving the ease of percutaneous re-treatment, should initial treatment fail. Furthermore, DCBs allow for greater opportunity for percutaneous treatment strategies in areas where stents may be less desirable, such as the popliteal artery.

Several manufacturers have developed balloons coated with paclitaxel for the treatment of infrainguinal PAD. Employed as a chemotherapeutic agent, paclitaxel irreversibly binds to microtubules and inhibits cell division, thus hindering

neointimal proliferation and the resulting restenosis [10]. DCBs utilize an excipient or carrier substance to hold the drug on the balloon surface during transit to the target lesion. The excipient can also assist in delivery of the drug to the artery wall during balloon inflation. A paclitaxel-coated balloon using a urea excipient (Lutonix-Bard) was the first to be approved by the US Food and Drug Administration (FDA) for the treatment of superficial femoral artery (SFA) and popliteal lesions in October 2014. Another iteration (IN.PACT, Medtronic) from a different manufacturer uses polysorbate and sorbitol excipients and was subsequently approved for the same lesion substrate in December 2014; an indication for in-stent restenosis (ISR) was granted 2 years later (September 2016). Most recently, a third DCB (Stellarex, Spectranetics) was approved by FDA, and several others are currently undergoing evaluation in IDE trials. DCBs coated with drugs other than paclitaxel, including zotarolimus, sirolimus, and everolimus, have been studied in animal models, but have not been used clinically in humans for peripheral interventions [11–13]. The following review summarizes the currently available data regarding the use of DCBs for the treatment of infrainguinal PAD.

Superficial Femoral Artery and Popliteal Disease

Drug-coated balloons were initially evaluated in superficial femoral artery and popliteal lesions. Beginning enrollment in 2004, the Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries (THUNDER) trial and the Femoral Paclitaxel (FemPac) trial were conducted in Europe. Both trials enrolled patients with symptomatic SFA and/or popliteal disease. THUNDER randomized 154 patients to three arms: paclitaxel "Paccocath" DCB (n = 48), standard PTA (n = 54), or standard PTA plus paclitaxel in the contrast medium (n = 52). FemPac randomized fewer patients (n = 87) in two arms: paclitaxel Paccocath DCB (n = 45) or standard PTA (n = 42). Lesions included in both trials were of relatively low complexity: 4–7 cm in length and 16–27% had total occlusions. The primary endpoint was late lumen loss (LLL) at 6 months, determined by angiography, which was performed in 83% of THUNDER patients and 75% of FemPac patients. The LLL at 6 months was significantly lower in DCB groups compared with patients who were treated with standard PTA: 0.4 versus 1.7 mm in THUNDER and 0.5 versus 1.0 mm in FemPac. In THUNDER, paclitaxel in the contrast medium provided no added benefit over standard PTA alone. Target lesion revascularization (TLR) up to 24 months was statistically significantly lower in the DCB groups compared to standard PTA groups, 15 versus 52% in THUNDER, and 13 versus 50% in FemPac. Long-term follow-up out to 5 years in the THUNDER follow-up trial demonstrated lower rates of target lesion revascularization among patients treated with DCB (21%) compared to those treated with standard PTA (56%) [14, 15••, 16].

Additional trials with novel DCBs, published subsequently, include the Paclitaxel-coated Balloons in Femoral Indication to Defeat Restenosis (PACIFIER) trial and Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis (LEVANT I) trial. They followed a similar design, randomizing patients with SFA/popliteal lesions to PTA with a standard balloon vs. DCB (Lutonix DCB in LEVANT I and IN.PACT Pacific DCB in PACIFIER). In PACIFIER, 85 patients with 91 lesions were randomized to DCB (n = 44) or PTA (n = 47). In LEVANT I trial, 101 patients were randomized to either PTA alone (n = 52) or Lutonix DCB (n = 49). The initial strategy incorporated into LEVANT I was different than previous trials. After pre-dilation, patients were stratified to PTA only or intended stenting and then patients were randomized under each category to either standard balloon or DCB. Mean lesion lengths were comparable to THUNDER, 6.6–7 cm in PACIFIER, and slightly longer, 8.1 cm in LEVANT I. Total occlusions were more common than in previous trials, 31% in PACIFIER and 42% in LEVANT I. PACIFIER also included ISR, which constituted 15.9% of the DCB group and 12.8% of the standard balloon group. The primary endpoint was angiographically driven LLL at 6 months for both trials, similar to prior studies. Once again, there was a significant benefit for those treated with DCB (LLL = 0.01 mm) compared to those treated with standard angioplasty (LLL = 0.65 mm, P = 0.001) in PACIFIER. Similar benefit was also demonstrated in LEVANT I, with LLL at 6 months of 0.46 and 1.09 mm in the DCB and control groups, respectively (P = 0.016), resulting in 58% reduction in LLL conferred by the DCB. In LEVANT I, the results were primarily driven by the balloon only stratum, as opposed to the intended-stenting stratum; the latter showed no significant difference between DCB and standard balloon, possibly due to limited statistical power from the small sample size. Primary patency in LEVANT I in the DCB group was 72, 67, and 57% at 6, 12, and 24 months, respectively. Primary patency in the control group was 49, 55, and 40% at 6, 12, and 24 months, respectively. However, the study had a small sample size for long-term clinical outcome assessment. Furthermore, neither study showed a statistical significant reduction in its secondary endpoint of TLR. There was a trend towards fewer TLR at 6 months in PACIFIER in the DCB group, 7.1% compared to control group, 21.4% (P = 0.12). LEVANT I showed fewer TLR at 24 months in the DCB group compared to controls; 15 and 20, respectively, at 24 months, but this did not reach statistical significance (P = 0.23). In PACIFIER, a composite secondary endpoint of TLR, death and amputations at 6–12 months, showed statistically significant lower rates in the DCB group (7.1%) vs. the control group (34.9%) (P = 0.003). However, such was not the case for LEVANT I, where the composite secondary

endpoint of major adverse events (death, thrombosis, amputation, and re-intervention) did not differ, 39 and 46% in the DCB and standard PTA groups, respectively ($P = 0.45$). There were no safety concerns or more amputations in the DCB groups in either study [17, 18•].

Early trials focused mainly on an endpoint of LLL at 6 months, which ranged from approximately 0.01–0.5 mm for DCB and 0.65–1.7 mm for standard PTA, demonstrating approximately 70% mean reduction of LLL in the DCB group (Table 1). More recent trials have utilized a different primary endpoint, that of primary patency at 12 months, as defined by core lab adjudication, which is the absence of binary restenosis by duplex ultrasonography or freedom from target-lesion revascularization. With this in mind, LEVANT 2 trial is the largest DCB trial investigating the use of Lutonix DCB compared to PTA in patients with symptomatic SFA and/or popliteal artery lesions. This trial randomized 476 patients in a 2:1 fashion to DCB ($n = 316$) or standard PTA control ($n = 160$). Patients were randomized after initial conventional balloon angioplasty with a slightly undersized balloon; patients anticipated to require stent placement were excluded from randomization. Mean lesion length was 6.2 cm and 21% were total occlusions. The primary endpoint, patency at 12 months, was achieved in 65.2 vs. 52.6% ($P = 0.02$) in DCB and control groups, respectively. The primary safety measure was a composite endpoint including freedom from index-limb amputation or re-intervention, plus index-limb-related death at 12 months. This was achieved in 83.9% in DCB and 70% in controls ($P = 0.005$ for non-inferiority). However, notably, there was no statistically significant difference between the two groups in target lesion revascularization at 12 months: 12.3% in DCB and 16.8% in control group ($P = 0.21$). Although the trial was not powered to detect a difference, a greater difference might have been anticipated. This could be attributed to multiple reasons, one of which was the lower than expected rate of TLR in the control group compared to prior trials, masking the difference between the two groups. Furthermore, there was less stenting in the DCB group (2.5%) compared to the control group (6.9%) ($P = 0.02$), although the overall "bail-out" stenting rate was quite low [19••]. Finally, the rigorous blinding in LEVANT 2 of those making clinical decisions regarding revascularization may have reduced bias that may have influenced previous trials.

IN.PACT SFA, another large DCB trial published in 2015, investigated the use of the IN.PACT Admiral paclitaxel-coated balloon compared to standard balloon in treating SFA or proximal popliteal artery disease in patients with claudication or ischemic rest pain. This was a multicenter, single-blinded study, randomizing patients 2:1 between DCB ($n = 220$) and standard PTA ($n = 111$). IN.PACT SFA had two phases: IN.PACT SFA I was conducted in Europe and IN.PACT SFA II was conducted in the United States; these two were combined into one trial, IN.PACT SFA. Mean lesion length was 8.94 and 8.81 cm for DCB and control arms ($P = 0.82$), respectively. The percentages of total occlusion were 25.8 and 19.5% ($P = 0.22$) for DCB and control. The primary efficacy end-point, similar to LEVANT 2, was primary patency at 12 months, defined as freedom from restenosis or clinically driven TLR. The primary patency rate was 82.2% in the DCB group versus 52.4% in the standard PTA group ($P < 0.001$); this was primarily driven by the freedom from TLR, 2.4% in DCB and 20.6% in controls. The number of run-off vessels was significantly lower in the control group; however, propensity score matching indicated that the favorable results on primary patency with DCB remained significant. Provisional stenting was higher in the control (12.6%) vs. DCB (7.3%) group, but the difference was not statistically significant ($P = 0.11$) [20••]. These results further support the enhanced efficacy of DCBs in SFA and popliteal lesions.

Superficial Femoral Artery and Popliteal—Summary of Initial Trials

Initial trials of paclitaxel-coated balloons demonstrated a reduction in short-term late lumen loss for patients with superficial femoral artery and popliteal disease. Subsequent investigations in large registries seem to confirm the promising 1-year patency, as compared to conventional balloon angioplasty. These data are summarized in Table 2. Longer-term follow-up from the randomized trials, as well as real-world registry data, will further define the efficacy and role of DCB in this population.

Superficial Femoral Artery and Popliteal—Future Directions and Next Generation DCBs

Newer generations of DCBs have been developed. The Stellarex DCB, for example, utilizes a lower dose of paclitaxel. Stellarex was first studied in the ILLUMENATE Pivotal 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). This single-arm study

Table 1 Late lumen loss at 6 months based on angiography in earlier SFA, popliteal disease with DCB vs. PTA

Trial	DCB group	PTA group	*P* value
THUNDER	0.4 mm	1.7 mm	$P < 0.001$
FemPac	0.5 mm	1 mm	$P = 0.031$
Pacifier	− 0.01 mm	0.65 mm	$P = 0.001$
LEVANT 1	0.46 mm	1.09 mm	$P = 0.016$
DEBELLUM	0.5 mm	1.6 mm	$P < 0.01$

Table 2 Summary of DCB trials in SFA and popliteal lesions

Trial	Year published	Device used	Disease location	Number of patients	Average length of lesions	Primary outcome	Results	*P* value
THUNDER	2008	Paclitaxel Paccocath coated balloons vs. PTA with paclitaxel in the contrast medium vs. PTA alone	SFA, popliteal (de novo)	154 DCB = 48 PTA = 54 PTA and IV paclitaxel = 52	7.4 cm	Angiographic LLL after 6 months	0.4 mm in the DCB, 2.2 mm in the PTA and IV paclitaxel group, and 1.7 mm in the PTA only	$P < 0.001$ (DCB vs. PTA only)
FemPac	2008	Paclitaxel Paccocath DCB vs. PTA	SFA, popliteal (de novo and ISR)	87 DCB =45 PTA =42	4–4.7	Angiographic LLL after 6 months	0.5 mm in the DCB vs. 1.0 mm in the PTA group	$P = 0.031$
PACIFIER	2012	PTA vs. IN.PACT Pacific DCB	SFA, popliteal (de novo and ISR)	85 DCB = 41 PTA = 44	6.6–7.0	Angiographic LLL at 6 months	−0.01 mm for the DCB vs. 0.65 mm for the PTA group	$P = 0.001$
LEVANT 1	2014	PTA vs. Lutonix DCB	SFA, popliteal (de novo)	101 DCB = 49 PTA = 52	8.1 cm	Angiographic LLL in 6 months	0.46 mm for DCB vs. 1.09 mm for PTA	$P = 0.016$
IN.PACT SFA	2015	PTA vs. IN.PACT Admiral DCB	SFA, popliteal (de novo)	331 DCB = 220 PTA = 111	8.8–8.9 cm	Primary patency in 12 months	82.2% in DCB group vs. 52.4% in the PTA group	$P < 0.001$
LEVANT 2	2015	PTA vs. Lutonix DCB	SFA, popliteal (de novo)	476 DCB = 316 PTA = 160	6.2 cm	Primary patency in 12 months	65.2% in the DCB group vs. 52.6% in the PTA group	$P = 0.02$

enrolled 50 patients with SFA or popliteal disease to Stellarex. Mean lesion length was 7.2 cm, with 12.1% total occlusion lesions. The primary endpoint was LLL at 6 months, similar to early DCB trials, which was 0.54 mm. Primary patency after Stellarex was 89.5 and 80.3% at 12 and 24 months, respectively. The secondary endpoint of major adverse events (cardiovascular death, amputation, and ischemia-driven target lesion revascularization) occurred in 4%; there were no cardiovascular deaths at 24 months. This study was the platform for further Stellarex trials, including the ILLUMENATE European Randomized Trial and ILLUMENATE Pivotal Study [21••]. The recently presented ILLUMENATE US pivotal trial demonstrated 12-month primary patency rate of 82.3% and freedom from CD-TLR of 93.6% with the Stellarex balloon, despite reportedly complex calcified lesions and severe infrapopliteal disease. It was superior to standard balloon for safety endpoints [22]. The ILLUMENATE Global study of Stellarex DCB in obstructive SFA or popliteal lesions of ISR is estimated to have a primary completion date in November 2018.

Several novel paclitaxel DCBs are being studied. The Chocolate Touch study is an international multicenter trial for SFA/popliteal lesions, randomizing patients to Chocolate Touch DCB vs. Lutonix DCB for non-inferiority. The estimated completion date for this study is December 2018. The Safety and Feasibility of SurModics SurVeil (TM) Drug Coated Balloon (PREVEIL) study—an early feasibility study undertaken in the USA alone—assessed the efficacy and safety of SurModics SurVeil DCB [23]. This DCB incorporates a unique excipient, which has very high efficiency for drug transfer, and minimal loss of drug in transit. A pivotal trial has recently been approved and will begin in 2017.

There is great interest in delivering drugs other than paclitaxel, such as the "limus" compounds which have broader therapeutic windows. First-in-human Evaluation of the SELUTION DCB, a Novel Sirolimus Coated Balloon in Peripheral Arteries for SFA/popliteal disease, is a German study with an estimated completion in September 2017. This will be the first non-paclitaxel DCB studied in humans for SFA/popliteal lesions [23].

Finally, while DCB therapy alone improves luminal patency, treatment with other devices in conjunction with DCBs may further optimize patency. DiRectional AthErectomy + Drug CoAted BaLloon to Treat Long, CalcifIed FemoropopliTeal ArterY Lesions (REALITY), a study coordinated by VIVA physicians, is investigating the efficacy of combining directional atherectomy and DCB to treat long, calcified SFA/popliteal lesions [23].

Infrapopliteal Disease

Patients with infrapopliteal PAD often present with critical limb ischemia (CLI), defined as ischemic rest pain or non-healing wounds and gangrene with objective findings on non-invasive imaging that support low circulation distally to

the affected limb. Angiography is needed to determine the level of the disease and further intervention after imaging. CLI is usually a multi-level disease, causing an arterial occlusive disease in more than one vessel below the knee. Infrapopliteal vessels are of smaller caliber compared to popliteal and SFA and makes intervention more challenging.

Patients with CLI are at risk for amputations, and further innovations are necessary to improve outcomes in this population. Traditional balloon angioplasty has a high rate of restenosis or recurrent occlusion. Investigators have attempted to test DCBs in this challenging patient population; however, data supporting the use of paclitaxel-coated balloons for infrapopliteal lesions are limited and have shown mixed results. An initial evaluation by Schmidt et al. studied the use of DCB in 104 consecutive patients with infrapopliteal disease presenting with critical limb ischemia (CLI) or severe claudication. Mean lesion length was 176 mm and 77% of the population had complete or functional occlusion of all 3 tibial arteries. Patients were all treated with the IN.PACT Amphirion paclitaxel-coated balloon and underwent repeat angiography at 3 months to assess for binary restenosis. Surveillance studies were performed in 74 of the 104 patients; 73% of the arteries were patent, and 27% had binary restenosis, of which 8% were re-occlusions. TLR was 17.3% at 1-year follow-up; there were no major safety concerns. The authors concluded that DCB greatly reduced restenosis at 3 months, compared to the 69% reported previously with uncoated balloons [24, 25].

Subsequently, a randomized trial was conducted assessing the efficacy and safety of DCBs in infrainguinal lesion and included infrapopliteal lesions. Drug-Eluting Balloon Evaluation for Lower Limb MUltilevel TreatMent (DEBELLUM), published in 2012, randomized 50 consecutive patients to either DCB or standard balloon angioplasty. There were 122 lesions, of which 21% were total occlusions and 24.6% infrapopliteal. In the subpopulation with infrapopliteal lesions, 13 were treated with DCB and 17 with uncoated balloons. The primary endpoint was LLL at 6 months assessed by angiography, which was 0.5 mm in the DCB vs. 1.7 mm in the control group ($P < 0.01$). In a subgroup analysis of lesions below the knee (BTK), LLL at 6 months was 0.62 mm in the DCB vs. 1.65 mm in the uncoated balloons group ($P < 0.05$) [26]. However, sample size in DEBELLUM was too small to generalize the results.

Published the following year, the Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation (DEBATE BTK) was a dedicated trial for infrapopliteal lesions. It was a single-center trial that randomized 132 diabetic patients with CLI with significant stenosis or occlusion > 40 mm of 1 BTK vessel (158 lesions). Mean lesion length was 129 and 131 mm in the DCB and standard PTA groups, respectively ($P = 0.7$). The primary endpoint was binary restenosis at 12 months by angiography (performed in > 90% of patients) or Duplex ultrasound. Restenosis occurred in 27 vs. 75% in the DCB and PTA groups, respectively ($P < 0.001$). Secondary endpoints included clinically driven TLR, which was also significantly lower in DCB (18%) vs. controls (43%) ($P = 0.002$). Target vessel occlusion was also lower in DCB (17%, compared to 55%) ($P < 0.001$). There was one major amputation in the PTA group, not statistically significance ($P = 0.9$). Overall relative risk reduction in this study was 64% with DCB [27].

Despite promising early results in tibial vessel, concerns have risen for use of DCB BTK, primarily in the wake of the RandomIzed AmPhirion DEEP DEB vs StAndard PTA for the treatment of below the knee CriTical limb ischemia (IN.PACT DEEP). IN.PACT DEEP was a large multicenter trial of infrapopliteal DCB, randomizing 358 patients with critical limb ischemia 2:1 to either IN.PACT Amphirion DCB ($n = 239$) or standard balloon ($n = 119$). The primary endpoints were LLL and clinically driven TLR at 12 months. Target lesions were significantly longer in the control arm (12.9 cm) compared to those treated with DCB (10.9 cm) ($P = 0.002$). Total occlusions were similar in the two groups: 38.6% in the DCB arm and 45.9% in controls ($P = 0.114$). There was more inflow disease in the DCB group (40.7%) compared to the standard PTA group (28.8%) ($P = 0.035$). The primary endpoint of LLL at 12 months was no different statistically between study groups, 0.61 mm ($P = 0.95$). Similarly, clinically driven target lesion revascularization (CD-TLR) was 11.9% in the DCB and 13.5% in the control group ($P = 0.682$). There was no difference in binary restenosis (e.g., ≥ 50%) at 12 months—41 vs. 35.5%—between DCB and standard PTA ($p = 0.609$). Nor was there a difference in re-occlusion rates: DCB 11.5% vs. controls 16.1% ($P = 0.531$). The composite endpoint of death, amputation and CD-TLR at 6 months was 17.7% for DCB and 15.8% for controls ($P = 0.021$). The study met non-inferiority for the primary safety endpoint. However, at 12 months, amputation-free survival: was 81% for DCB vs. 89% for controls ($p = 0.057$), and the 12-month individual secondary safety endpoint did not meet non-inferiority. This trial raised concerns regarding the safety of DCB in tibial vessels among patients with CLI [28••]. Explanations regarding the lower amputation-free survival in DCB patients have included—among other things—distal embolization of drug, excipient, coating, improper drug dosing, and patient selection bias.

More recently, a smaller DCB trial (BIOLUX P-II) was conducted for tibial vessels. This study was designed to assess the safety and efficacy of a newer type of paclitaxel DCB, Passeo-18 Lux. In this multicenter trial, 72 patients with infrapopliteal disease and CLI were randomized 1:1 to DCB vs. standard PTA. The DCB group included more calcified lesions than controls. The primary safety endpoint, 30-day major adverse event rate (composite of all-cause mortality, major amputation and TVR) trended better in the DCB (0%) vs. standard PTA (8.3%) ($P = 0.239$). The primary efficacy endpoint, defined as *loss* of angiographic patency at 6 months (measured earlier than IN.PACT DEEP and DEBATE-BTK,

in which angiographic patency was measured at 12 months), was 17.1% for DCB vs. 26.1% for controls, not statistically significant ($P = 0.298$). Secondary endpoints were also not different between DCB and controls, including binary restenosis at 6 months (DCB 53.1%, control 41.4%; $P = 0.359$), late lumen loss at 6 months (DCB 0.56 mm, control 0.54 mm; $P = 0.93$), and TVR at 12 months (DCB 30.1%, control 30.6% [29•]. BIOLUX P-II, small in sample size, showed no primary efficacy benefit to using DCB, but it was underpowered. Importantly, the safety concerns raised by IN.PACT DEEP were not duplicated.

Conclusions Regarding Use of DCB Below the Knee

Results from infrapopliteal DCB studies are summarized in Table 3. Preliminary small trials utilizing DCB in tibial disease were promising, demonstrating a significant reduction in LLL at 6 months and in binary stenosis at 12 months. However, those findings were not reproducible in a subsequent large randomized trial, IN.PACT DEEP. Furthermore, whether well-founded or not, the failure to meet non-inferiority for secondary safety outcomes raised enough concerns that the device has since been withdrawn from the market. The use of DCB is currently not recommended in BTK disease, pending the availability of more data and new trials with devices tailored to this region.

Infrapopliteal Future Directions

A randomized, multicenter, international study randomizing patients with BTK disease to Lutonix DCB vs. PTA is currently underway multicenter. It will complete its enrollment of 480 patients in 2017. In addition, the European BTK registry is accruing patients to evaluate the efficacy and safety of Lutonix DCB in BTK. Additional investigation is underway to evaluate the use of infrapopliteal DCB with adjunctive therapies, such as atherectomy. One such trial is the Orbital Vessel Preparation to Maximize DCB Efficacy in Calcified Below the Knee (BTK) Lesions (OPTIMIZE-BTK). This is a multicenter European pilot study randomizing patients with calcified BTK lesions to orbital atherectomy followed by DCB vs. DCB alone; the estimated study completion is June 2018 [23].

In-Stent Restenosis

Initial trials have generated enthusiasm for utilizing paclitaxel-coated balloons in the treatment of in-stent restenosis in the SFA and popliteal arteries. Drug-Eluting Balloon in Peripheral Intervention for In-Stent Restenosis (DEBATE ISR) is a registry that included 44 diabetic patients with ISR. There was no control

Table 3 Trials with infrapopliteal DCB

Trial	Year published	Device used for infrapopliteal lesions	Disease location	Number of patients, lesions	Average length of lesions	Primary outcome	Results
DEBELLUM	2012	IN.PACT Amphirion vs. PTA	SFA, popliteal (75.4%), infrapopliteal (24.6%)	50 patients, 122 lesions	7.5 cm	LLL at 6 months	0.5 mm in the DCB group vs. 1.6 mm in the PTA group ($P < 0.01$)
DEBATE-BTK	2013	IN.PACT Amphirion vs. PTA	Infrapopliteal with CLI and DM	132 patients, 158 lesions	12.9 cm in the DCB 13.1 cm in the PTA group ($P = 0.7$)	Angiographic binary restenosis at 12 months	27 vs. 75% in the DCB and PTA groups respectively ($P < 0.001$)
IN.PACT DEEP	2014	IN.PACT Amphirion vs. PTA	Infrapopliteal with CLI	358 patients	10.2 cm in the DCB 12.9 cm in the PTA group, ($P = 0.002$)	LLL and CD-TLR at 12 months	LLL = 0.61 mm for each group ($P = 0.95$), CD-TLR = 11.9% in the DCB and 13.5% in the PTA group ($P = 0.682$)
BIOLUX P-II	2015	Passeo 18 Lux DCB vs. PTA	Infrapopliteal with CLI	72 patients 105 lesions	11.3 cm in the DCB group 11.5 cm in the PTA group ($P = 0.96$)	Patency loss at 6 months	17.1% in the DCB vs. 26.1% in the PTA group ($P = 0.298$)

arm, but a matched comparison was made to 42 similar diabetic patients previously treated with uncoated balloons for SFA or popliteal ISR. Average lesion lengths were 132 mm in the DCB group and 137 mm in the comparison group. At 1-year follow-up, there was no statistical significant difference in mortality or amputations. Two thirds of patients had an angiogram and a third had ultrasound follow-up at 1 year; the binary restenosis rate was 19.5% in the DCB versus 71.8% in the comparison group ($P < 0.001$). Target lesion revascularization was also significantly lower in the DCB group, 13.6 vs. 31% ($P = 0.045$). There were no safety concerns [30••].

The only true randomized trial addressing efficacy and safety of DCB in SFA and popliteal lSR is the Femoral Artery In-Stent Restenosis (FAIR). The study randomized 119 patients with symptomatic SFA ISR, 1:1 to either IN.PACT Admiral DCB ($n = 62$) or standard PTA ($n = 57$). Mean lesion length was 8.1–8.2 cm and 28.6% had total occlusion. The primary endpoint, recurrent ISR at 6 months, was significantly lower in the DCB group (15.4%) compared to the control group (44.7%) ($P = 0.002$). Freedom from TLR was higher among the DCB group compared to controls: 96.4% compared to 81% at 6 months ($P = 0.0117$) and 90.8% compared to 52.6% at 12 months ($P < 0.001$) [31••].

ISR Summary and Future Directions

Although the data are limited in the use of DCB in SFA/popliteal ISR, overall findings suggest a significant benefit of DCB, with no safety concerns. Indeed, the FAIR trial led to FDA approval for use of IN.PACT Admiral DCB in treating SFA/popliteal ISR in September 2016. A similar ongoing multicenter, randomized study of Lutonix DCB vs. standard balloon in SFA/popliteal ISR has an estimated completion date of December 2016 [23].

Medical Therapy After Peripheral Vascular Interventions with DCBs

All patients with PAD should receive the standard of care and guideline-determined medical therapy. This includes structured exercise program, smoking cessation and guideline-based pharmacotherapy as recommended by the ACC/AHA latest recommendations.

There is a mortality benefit in patients with symptomatic PAD who enroll in a 12-week supervised exercise-training programs, and therefore, it is given a class IA recommendation based on ACC/AHA latest PAD practice guidelines. Structured community- or home-based exercise programs have been studied more recently and have promising results given a class IIa recommendations less favorable compared to supervised programs. However, unstructured exercise recommendations have not been efficacious. In terms of pharmacotherapy: ASA alone or clopidogrel alone has been shown to reduce cardiovascular events and given a class IA recommendation in symptomatic PAD patients. There is unclear benefit of dual-antiplatelet therapy in patients with unrevascularized symptomatic PAD. However, patients treated with drug-coated balloons should be treated with dual-antiplatelet therapy for at least a month based on the DCB trials and at least 3 months if they require bailout stenting. Statin remains an important pharmacotherapy and also given a class IA recommendation in patients with PAD. Cliostazol is recommended for patients with claudication and mainly for quality improvement but no mortality benefits. It is also important to have optimal management of hypertension and diabetes in PAD patients. Oral anticoagulation is not routinely recommended and may be harmful with the exception of their limited role in prosthetic bypass and autologous veins.

Penotxifylline, chelation therapy, and B-complex vitamins to lower homocysteine levels have not shown benefits and therefore are not recommended [32, 33].

Conclusions

In summary, DCBs as a class of devices represent a significant advance in the therapeutic armamentarium for treating PAD. In particular, DCBs have been shown to be safe and effective for the treatment of native lesions in the SFA and popliteal arteries. Additional data suggest that a similar benefit may exist for the treatment of in-stent restenosis. The data regarding treatment of infrapopliteal lesions are more ambiguous, with some investigations showing a benefit, but at least one study raising a safety concern. Further studies are needed to better define the role of DCB in this subpopulation. Overall, DCBs have increased the treatment options for patients with PAD and provide operators with an additional tool for percutaneous revascularization for PAD.

Compliance with Ethical Standards

Conflict of Interest Rasha F. Al-Bawardy declares that he has no conflict of interest.

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- • Of importance
- •• Of major importance

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