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Review

Progress on developing an effective below-the-knee drug-coated balloon

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Infrapopliteal atherosclerotic disease continues to present the greatest conundrum for effective endovascular therapies. To date, conventional angioplasty has been fraught with early restenosis and recoil in these complex, long, calcified, and occlusive lesions. The success of metallic drug-eluting stents in coronary arteries has not carried over to below-the-knee arteries. Initial promise in paclitaxel-coated balloons has not been demonstrated in large randomized clinical trials. Furthermore, the potential association between paclitaxel and mortality continues to generate tremendous controversy. The goal of this review article is to discuss the evolution and challenges of drug-coated balloon (DCB) science, present the clinical results of currently available tibial DCBs, and introduce new horizons in DCB technology.

Keywords

Drug-coated balloon; Device design; Below-the-knee; Infrapopliteal; Peripheral arterial disease

1. Introduction

Peripheral artery disease (PAD) represents a global health burden affecting 20% of the population over 80 years of age [1–3]. Its most severe form, chronic limb-threatening ischemia (CLTI) defined by ischemic rest pain, tissue loss, or gangrene is associated with a 25% incidence of limb loss and 25% risk of mortality at 1 year if left untreated [4]. Percutaneous peripheral intervention has become a vital treatment for many patients suffering from symptomatic PAD [5, 6]. While CLTI often results from multilevel disease [7], the addition of infrapopliteal disease most frequently leads to lower limb amputation and continues to present the greatest challenge for effective endovascular therapies [8]. The below-the-knee (BTK) endovascular therapeutic arsenal has, heretofore, evolved from plain balloon angioplasty [9, 10] to include bare metal stents [11], drug-eluting stents [12–16], bioresorbable stents [17], intravascular tacking [18], and drug-coated balloons.

The purpose of this review is to report the progress on developing a safe and effective BTK drug-coated balloon (DCB).

2. Infrapopliteal vascular occlusive disease

Infrapopliteal vascular occlusive disease bestows unique clinical and anatomic challenges. First, comorbidities such as diabetes and dialysis dependence are prevalent in patients with BTK disease. Unlike its coronary counterpart, infrapopliteal artery disease tends to be diffuse, severely calcified, and involve long-segment chronic total occlusions (CTO). The lower extremity vascular bed is also relatively low flow with a high resistance to outflow [19]. In women, the higher incidence of CLTI as a presenting symptom in addition to a smaller vessel size presents an additional therapeutic challenge [20].

Despite its broad applicability and usefulness, plain old balloon angioplasty (POBA) for the BTK arteries has produced generally suboptimal results, especially for long lesions and CTOs [21]. In their meta-analysis of infrapopliteal angioplasty, Romiti *et al.* [10] presented an immediate technical success as low as 89.0 $\pm$ 2.2%. Schmidt *et al.* [22] reported a 68.8% restenosis as early as 3 months post-intervention in 77 infrapopliteal artery lesions with a mean lesion length of 184 mm. Unfortunately, early failure is unlikely to match the need for prolonged patency required to heal foot wounds [23]. BTK POBA is also subject to elastic recoil and post-angioplasty dissection which remains unsolved in the absence of an arterial scaffold [23]. The primary patency of BTK POBA at 1 year averages 58.1 $\pm$ 4.6% with a 14% limb loss [10]. These suboptimal results have been consistent throughout more recent review. Mustapha *et al.* [24] reported a 63.1% primary patency and 14.9% major limb amputation at 1 year. The effect of neointimal hyperplasia or elastic recoil in small caliber and calcified distal arteries cannot be overstated. Patients with advanced disease (TransAtlantic Inter-Society Consensus (TASC) II D) [25] who are suitable candidates for an open operation could be better served by primary bypass rather than a failed attempt at POBA and this continues to be an area of active study [26, 27].

The patency success of drug-eluting stents (DES) in the treatment of coronary artery disease has not followed in small peripheral arteries [28–33]. The permanence of a metallic

Table 1. Commonly held views on paclitaxel vs. sirolimus (or analogs).

Characteristics	Paclitaxel	Sirolimus (or analogs)
Drug nature	Highly lipophilic	Less lipophilic
Mode of action	Cytotoxic	Cytostatic
Safety margin	10^2-fold	10^4-fold
Therapeutic range	Narrow	Wide
Anti-restenotic	Yes	Yes
Anti-inflammatory	No	Yes
Coating nature	Hydrophilic spacer	Drug encapsulation
Coating complexity	Simple	Complex
Tissue absorption	Fast	Slow
Tissue retention	Long	Short
Tissue deposition	Sub-intimal space with significant partition in adventitia	Throughout arterial wall
Acceptance	Mixed	Positive

Table 2. Coating properties.

Properties	Iopromide	Urea	BTHC*	Polysorbate/Sorbitol	Polymer
Uniform drug application		Yes	Yes	Yes	NA
Limited drug loss	No	No	Yes	NA	Yes
Efficient and rapid drug transfer	Yes	Yes	No	Yes	Yes
Controlled drug concentration	NA	NA	NA	NA	NA
Limited particulate degeneration with fragmentation	No	No	NA	Yes	NA

*, n-Butyryl tri-n-hexyl citrate.

implant has been linked to sustained arterial inflammation, a detrimental delay in endothelial coverage, and late thrombosis. Thick struts in small, calcified, low flow distal vessels pose a significant design limitation [34]. Malapposition of DES deployed in the tibial vasculature could significantly impair drug delivery and effect [35]. Therefore, below-the-knee disease still represents an endovascular therapeutic conundrum. Can biologic therapy be used in this hostile environment to improve the results of endovascular therapy? Drug-coated balloons offer real promise to address this unmet clinical need [36, 37].

3. Drug-coated balloon technology

3.1 Design principles

Drug-coated balloon angioplasty consists of a transfer of drug from the expanded balloon into the arterial mural surface by direct contact, followed by transport, diffusion, and uptake. Its success lies within the efficient delivery of therapeutic compounds while minimizing the need for a permanent implant [38]. However, questions persist on the dose of drug remaining in the arterial wall after balloon inflation [39]. Yazdani *et al.* [40] demonstrated therapeutic levels of paclitaxel in the arterial wall at 1 month without detectable plasma level after 1 day. In this swine femoral artery model, drug effect characterized by smooth muscle cell medial loss peaked at 90 days and was observed up 180 days after Lutonix balloon angioplasty. There is substantial preclinical animal evidence to demonstrate the inhibition of smooth muscle cell proliferation and neointima formation after a single DCB angioplasty [41, 42]. To date, paclitaxel has proposed numerous advantages including its lipophilic nature associated with a fast uptake and longer retention (Table 1) [38, 40, 43, 44]. In contrast, sirolimus presents unique questions related to its coating nature and complexity. Its slow absorption, fast elimination, and wide therapeutic range also account for some of its challenges. Nevertheless, drug is not the sole determinant of clinical response after DCB therapy [45].

3.2 Design challenges

The therapeutic success of DCB is based on a delicate balance of drug transport and transfer [45]. This balance requires an interaction between balloon, catheter, drug, and excipient [34]. Initial modifications in balloon fold geometry have proven insufficient to meaningfully enhance therapeutic level drug delivery [38]. Hence, coating appears to be the dominant design challenge in the manufacture of DCB.

Perceived ideal characteristics of utilized excipients are summarized in Table 2 [46]. Iterations of coating technology have resulted in improvement in preclinical model outcomes. Advancement in coating techniques have been geared towards increased homogeneity. When Buszman *et al.* [47] compared 2 generations of paclitaxel-coated balloon (PCB) coatings in their hypercholesterolemic iliofemoral porcine model, the more homogeneous second generation PCB yielded a significant reduction in percent diameter stenosis, percent area of stenosis, and neointimal proliferation. Microneedle coating generated a 1.7-fold increase in tissue retention of paclitaxel in a porcine femoral artery model when compared with amorphous/flaky-coating [48]. The goal of drug retention during tracking through a long sheath must be balanced with efficient drug transfer from the bal-

Table 3. Devices attributes in published BTK DCB clinical trials.

Trials	Device	Company	Drug	Drug dose density (μg/mm^2)	Excipient
DEBELLUM [57]	IN.PACT Amphirion	Medtronic	Paclitaxel	3.5	Urea
DEBATE-BTK [52]	IN.PACT Amphirion	Medtronic	Paclitaxel	3.5	Urea
IDEAS-I [53]	IN.PACT Amphirion	Medtronic	Paclitaxel	3.5	Urea
IN.PACT DEEP [58]	IN.PACT Amphirion	Medtronic	Paclitaxel	3.5	Urea
BIOLUX P-II [54]	Passeo-18 LUX	BIOTRONIK	Paclitaxel	3	BTHC†
BIOLUX P-III [59]	Passeo-18 LUX	BIOTRONIK	Paclitaxel	3	BTHC†
Lutonix BTK [60]	Lutonix	Bard	Paclitaxel	2	Polysorbate/Sorbitol
APOLLO [61]	ELUTAX SV	Aachen Resonance GmbH	Paclitaxel	2.2	Dextran¶
Acotec [62]	Litos-Tulip	Acotec Scientific	Paclitaxel	3	Magnesium stearate
AcoArt II-BTK [56]	Litos-Tulip	Acotec Scientific	Paclitaxel	3	Magnesium stearate
PRESTIGE [63]	Selution SLR	MedAlliance SA	Sirolimus	1	Polymer-based
SINGA-PACLI [55]	Passeo-18 LUX	BIOTRONIK	Paclitaxel	3	BTHC†

†, n-Butyryl tri-n-hexyl citrate.

¶, no carrier.

IN.PACT Amphirion has been voluntary recalled. All other included devices (Passeo-18 LUX, Lutonix, ELUTAX SV, Litos-Tulip, Selution SLR) are Conformity Europeenne (CE) trademarked. None are currently Food and Drug Administration (FDA) approved.

loon to the artery after arrival at the target lesion. In a porcine coronary model, Kelsch *et al.* [49] confirmed a 30% drug loss during PCB angioplasty. Seidlitz *et al.* [44] presented an alarming 1% transfer of the total drug load.

A swine coronary model with very thin intima and moderately sized media is a poor model of human atherosclerotic distal peripheral vessels. In atherosclerotic animal models, the transfer of paclitaxel into arterial walls is significantly impaired. The need for higher inflation pressures to generate a pressure gradient against a rigid arterial wall to allow for efficient drug uptake may generate further arterial overstretch, injury, and dissection [38, 50]. The low solubility of paclitaxel combined with low flow in a distal peripheral arterial bed may favor drug retention and uptake [41]. Slow dissolution of coating for effective drug delivery must be balanced with the risk of forming embolizing particles in end narrow vessels [51].

Although the optimal drug preparation-excipient combination for an effective BTK DCB is a work in progress, several efforts have been undertaken in recent years with varying degrees of promise.

4. Clinical trials of BTK-DCB

4.1 Summary of PCB clinical trials

In 2013, DEBATE-BTK compared PCB with POBA with encouraging results. Both target-lesion revascularization (18% vs. 43%; $p = 0.002$) and binary restenosis (27% vs. 74%; $p < 0.001$) were significantly lower in limbs treated with PCB [52]. In the following years, IDEAS-1 evaluated DES against PCB. While there was no significant difference in target-lesion revascularization (TLR) between groups ($p = 0.65$), arteries treated with PCB exhibited significantly higher post-procedure residual stenosis (24.8 ± 3.5% vs. 9.6 ± 2.2%; $p < 0.0001$) and subsequent binary restenosis at 6 months (57.9% vs. 28%; $p = 0.0457$) [53]. In BIOLUX P-II, the Passeo-18 LUX (Biotronik, Berlin, Germany) drug-releasing balloon catheter showed no significant difference in 6-month patency loss (17.1% vs. 26.1%; $p = 0.298$) or major amputation (3.3% vs. 5.6%; $p = 0.631$) compared with POBA [54]. More recently, Patel *et al.* [55] related a similarly low 6-month primary patency after Passeo-18 LUX BTK angioplasty compared with POBA (43% vs. 38%; $p = 0.48$). AcoArt II (Acotec, Beijing, China) BTK reported a significantly superior 6-month primary patency (75.0% vs. 28.3%; $p < 0.001$) and late lumen loss (0.43 ± 0.62 mm vs. 0.99 ± 0.55 mm; $p < 0.001$) with PCB vs. POBA [56]. Additional published clinical trials are tabulated (Tables 3 (Ref. [52–63]),4 (Ref. [52–63]),5 (Ref. [52–63]),6 (Ref. [52–63])). Comparisons of DCB and POBA have so far yielded heterogeneous results (Fig. 1).

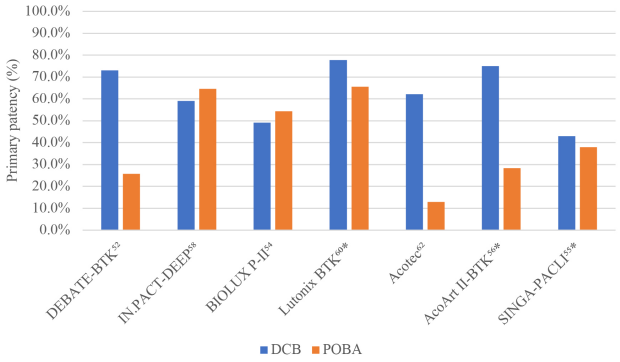

Fig. 1. Comparison of 12-month primary patency in DCB vs. POBA clinical trials. *, primary patency at 6 months.

4.1.1 IN.PACT DEEP

In the initial study of IN.PACT Amphirion against POBA, the IN.PACT DEEP trial investigators failed to demonstrate a superiority of DCB in clinically-driven TLR (9.2% vs. 13.1%;

Table 4. Patient demographics in published BTK DCB clinical trials.

Trials	Patients, n*	Age, years	Men, %	Diabetes, %	Renal disease, %	Rutherford stages 5–6, % or median Rutherford stage
DEBELLUM [57]	25	66	76	52	NA	8
DEBATE-BTK [52]	65	74	83	100	10.8	97.2
IDEAS-I [53]	25	67.6	80	76	44	4.5†
IN.PACT-DEEP [58]	239	73.3	76.2	75.7	8.6	85.8
BIOLUX P-II [54]	36	72.9	75	61.1	27.8	72.2
BIOLUX P-III [59]	151	72.3	73.5	62.9	36.4	63.6
Lutonix BTK [60]	287	72.9	70.4	71.1	23.7	56.1
APOLLO [61]	164	74.7	66.5	79.9	57.3	78.1
Acotec [62]	52	75.4	75	100	40	92.8
AcoArt II-BTK [56]	61	70.7	59	74	NA	54
PRESTIGE [63]	25	63.7	68	88	44	100
SINGA-PACLI [55]	70	61	61	94	54	97

*, n = patients treated with DCB.

†, Median Rutherford stage.

Table 5. Lesion characteristics in published BTK DCB clinical trials.

Trials	Lesion length, mm	Diameter stenosis, %	Severe calcification, %	Chronic total occlusion, %
DEBELLUM [57]	76	85	NA	12.2
DEBATE-BTK [52]	129	97.2	25	77.5
IDEAS-I [53]	148	85.3	NA	12
IN.PACT DEEP [58]	102	83.9	13.7	38.6
BIOLUX P-II [54]	113.1	72.5	4.7	NA
BIOLUX P-III [59]	79.2	86.2	9.8	18.4
Lutonix BTK [60]	111.8	86.7	15.1	36.1
APOLLO [61]	107.2	89.4	27	42
Acotec [62]	169	91.5	61.3	68
AcoArt II-BTK [56]	169.95	95	12.3	75
PRESTIGE [63]	191	88.9	30.3	NA
SINGA-PACLI [55]	90.3	77.2	70	35

$p = 0.291$) or late lumen loss (0.61 ± 0.78 mm vs. 0.62 ± 0.78 mm; $p = 0.950$). Moreover, binary restenosis wasn't significantly different at 12 months (41.0% vs. 35.5%; $p = 0.609$). The authors also noted an alarming safety signal driven by a higher incidence of major amputations at 12 months (8.8% vs. 3.6%; $p = 0.08$) [58]. As a result, Medtronic (Minneapolis, MN, USA) subsequently voluntarily recalled the IN.PACT Amphirion DCB. Of note, there was no significant difference in amputation rate at 5 years (15.4% vs. 10.6%; $p = 0.106$) [64].

4.1.2 Lutonix-BTK

The Lutonix balloon demonstrated a trend toward improved freedom from major amputation 6 months post-intervention (95.5% vs. 93.8%; $p = 0.268$). However, the primary efficacy endpoint of combined vessel occlusion, clinically driven-TLR (CD-TLR), and above-ankle amputation was only superior in the proximal-segment DCB group (76% vs. 62.9%; $p = 0.0085$) [60]. In femoropopliteal revascularization, a "slow-flow phenomenon" has been observed after DCB angioplasty and associated with worse 6-month primary patency (71% vs. 91%; $p = 0.09$), freedom from TLR (71% vs. 97%; $p < 0.01$), and amputation free-survival (71% vs. 95%; $p = 0.02$) [65]. The incidence of "slow-flow phenomenon" after infrapopliteal POBA has been reported as high as 18.6% and its occurrence has been associated with reduced 2-year major limb amputation (60% vs. 86%; $p < 0.01$) and decreased wound healing (77% vs. 91%; $p = 0.03$) [66]. Perhaps, the consequences of slow flow after PCB angioplasty could be even more pronounced in smaller, distal arteries and therefore result in the observed better results of PCB in proximal and larger tibial vessels. At 1 year, there was no longer a statistical difference in the primary efficacy endpoint between DCB and POBA (60.3% vs. 60.9%; $p = 0.54$). The Lutonix balloon is still awaiting U.S. Food and Drug Administration (FDA) approval for the tibial vasculature.

4.1.3 Systematic reviews and meta-analyses

The lack of clear benefit of PCB has since then been confirmed by Ipema *et al.* [67] in their review of 10 studies including 1593 patients. The authors did not reveal a significant difference in their primary outcomes of 12-month limb salvage or secondary endpoints (survival, restenosis, TLR, amputation-free survival). Similarly, Cassese *et al.* [68] showed no difference in clinical outcomes with a favorable

Table 6. Clinical and anatomic outcomes of published BTK DCB clinical trials.

Trials	Primary patency, %	Primary patency time-point, months	TLR*, %	TLR* time-point, months	Amputation, %	Amputation time-point, months	Death, %	Death time-point, months	LLL†, mm	LLL† time-point, months
DEBELLUM [57]	NA	NA	5	6	5	0	0	12	0.62	6
DEBATE-BTK [52]	73	12	18	12	0	12	7.7	12	NA	NA
IDEAS-I [53]	42.1	6	13.6	6	4	6	8	6	1.15	6
IN.PACT DEEP [58]	59	12	9.2	12	8.8	12	10.1	12	0.605	12
BIOLUX P-II [54]	49.2	12	34.9	12	3.3	12	NA	NA	0.56	6
BIOLUX P-III [59]	86.6	12	9.1	12	9	12	NA	NA	NA	NA
Lutonix BTK [60]	77.8	6	8.7	6	1.1	6	5	6	NA	NA
APOLLO [61]	68.5	12	9.4	12	4.6	12	12.2	12	NA	NA
Acotec [62]	62.1	6	10	6	0	6	7.7	6	0.51	6
AcoArt II-BTK [56]	75	12	8.9	12	1.7	6	1.7	12	0.43	6
PRESTIGE [63]	81.5	6	16.7	6	8	6	12	6	NA	NA
SINGA-PACLI [55]	43	6	20	12	25	12	21	12	NA	NA

*, Target-lesion revascularization.

†, Late lumen loss.

Table 7. Planned BTK DCB clinical trials.

Trial	Clinicaltrials.gov identifier	Device	Company	Design	Patients, n	Primary endpoint
PRISTINE	NCT04534257	Selution SLR	MedAlliance SA	Single arm	75	6-month TLR*
SELUTION BTK IDE	NA	Selution SLR	MedAlliance SA	FDA IDE	330	NA
STEP	NA	Selution SLR	MedAlliance SA	Single arm	20	Freedom from occlusion at 30 days
Future BTK Asia-Choke	NCT04511247	MagicTouch DCB	Concept Medical	Randomized	219	6-month primary patency
Future BTK EU	NA	MagicTouch DCB	Concept Medical	NA	153	NA
LIMES Germany-Teichgraber	NCT04772300	MagicTouch DCB	Concept Medical	Randomized	244	Compositive of 6-month primary patency and limb salvage
Debate BTK DUelL-Liistro	NA	MagicTouch DCB	Concept Medical	Randomized	172	6-month LLL†
SWING	NCT04107298	SUNDANCE DCB	Surmodics	Single arm	35	6-month LLL†

*, Target-lesion revascularization.

†, Late lumen loss.

late lumen loss (LLL) at 12 months in 641 patients enrolled in 5 clinical trials comparing PCB with POBA. In this study, the discordance between angiographic and clinical results of PCB in BTK arteries raised additional concerns related to the reliability of angiographic findings in small calcified arteries, and the merit of angiographic success [69].

4.2 Failure of paclitaxel

Although paclitaxel has consistently shown improved efficacy over conventional devices in the treatment of femoropopliteal disease, its success in tibial disease so far is rather modest [70–75]. The effectiveness of DCB in the treatment of long complex femoropopliteal lesions [76, 77] has not carried onto the infrapopliteal vasculature. No significant difference was demonstrated in 12-month binary restenosis between IN.PACT and POBA. In Lutonix BTK, the combined freedom from amputation, unhealed wounds, rest pain, target-vessel occlusion, and CD-target-vessel revascularization was not significantly different between groups (76% vs. 62.9%; $p = 0.13$).

In 2018, the highly controversial summary-level meta-analysis by Katsanos *et al.* [78] noted an increased late mortality in patients with femoropopliteal disease treated with paclitaxel devices. The FDA issued a first warning letter to physicians in January 2019 and eventually convened an advisory panel in June 2019. Patient-level data analyses questioning this mortality signal along with its mechanism swiftly followed [79–85].

In 2020, Katsanos *et al.* [86] focused on PCBs targeting infrapopliteal disease. In this second systematic review and meta-analysis of randomized controlled trials, PCBs were associated with significantly worse outcomes using a composite endpoint of amputation-free survival (86.3% vs. 90.6%; $p = 0.008$). Although no significant differences were encountered when separating all-cause death (odds ratio (OR) = 1.39 [0.94–2.07]; $p = 0.10$) or major amputation (OR = 1.63 [0.92–2.90]; $p = 0.09$), the authors commented on the need for adequately powered multicenter studies with long-term follow-up data. More recently, the same group reported a significantly higher amputation rate after PCB angioplasty in CLTI patients (hazard ratio = 1.56 [1.04–2.33]; $p = 0.03$). In this systematic review and meta-analysis, the authors hypothesized that both paclitaxel systemic release, and an underlying inflammatory process were responsible for an observed 4% crude risk of major amputation [87]. Several systematic reviews and meta-analysis with contradictory findings consequently followed [88–90]. But this turmoil led to a natural decrease in paclitaxel use in the wide medical community along with a reconsideration of its role in the treatment algorithm of PAD. The further identification of mechanistic shortcomings of paclitaxel including its potential for downstream release and distal embolization [87, 91] along with an ongoing debate on its systemic safety supported by limited animal studies [92] led to a growing interest in favor of sirolimus or its analogs.

In fact, "limus" drug has already displaced paclitaxel in the coronary world as the preferred antiproliferative agent. "Limus" drugs have already been used in tibial drug-eluting stents [30, 93–96]. In YUKON-BTK, 1-year primary patency was significantly improved in DES compared with bare-metal stents (80.6% vs. 55.6%; $p = 0.004$). The primary endpoint of freedom from target vessel revascularization, myocardial infarction, and death similarly favored the DES group [12, 30]. The Destiny trial also revealed a primary patency advantage of the Everolimus polymer-coated Xience V stent in contrast to bare-metal stenting (85.2% vs. 54.5% at 1 year; $p = 0.0001$) [14, 97]. The "limus" analog Everolimus has also being used in a drug-eluting bioresorbable vascular scaffold in tibial vessels with an impressive 8% incidence of binary restenosis after a mean 24-month period [98]. While "limus"-based technology presents some challenges in drug dose density and tissue uptake [99], they may offer an effective therapeutic solution to this clinical puzzle. Pharmacokinetic differences between paclitaxel and sirolimus (or analogs) are summarized in Table 1 [38, 43].

4.3 SELUTION SLR

The SELUTION SLR consists of a sirolimus-coated balloon that utilizes micro-reservoirs made of biodegradable polymer. Its purpose is to achieve controlled and sustained drug release via a long-term tissue distribution. In the pilot physician-initiated, prospective, non-randomized, single arm PRESTIGE, the investigators assessed the safety and efficacy of the SELUTION SLR in TASC II C and D tibial occlusive disease. The authors presented favorable 6-month freedom from CD-TLR (83.3%), primary patency (81.5%) and amputation free-survival (84%) in high-risk CLTI patients with long lesions (mean lesion length 191 mm). Wound healing was achieved in 81% of patients at 6 months in the 25 included patients with Rutherford class 5 wounds [63].

5. Future directions

5.1 Beyond PRESTIGE

After encouraging initial clinical results, the SELUTION SLR is currently under investigation in Asia (PRISTINE) and Austria (STEP). The SELUTION SLR BTK IDE trial will debut enrollment in the U.S. and Europe this calendar year (Table 7). Sirolimus-coated balloons may provide an alternative to PCBs in other forms [100].

5.2 MagicTouch DCB

In an effort to improve the lipophilic profile and bioavailability of sirolimus, Concept Medical has developed nanolute technology. This proprietary design relies on the conversion of sirolimus into sub-micron sized particles and its encapsulation into a phospholipid drug carrier. In the XTOSI first in man clinical trial presented at Leipzig Intervention Course (LINC) 2020, investigators reported a 74% primary patency at 6 months in 30 BTK lesions. Further trial results including FUTURE BTK Asia, FUTURE BTK EU, LIMES Germany, and DEBATE BTK-DUelL are awaited (Table 7).

5.3 Surmodics Sundance

The Surmodics Sundance balloon presents a unique hydrophilic shaft coating and is currently being investigated. The SWING trial (A Prospective, Multi-Center, Single-Arm, Feasibility Study to Access the Safety and Performance WIth the SUNDANCE^{TM} DruG Coated Balloon (Surmodics, Inc., Eden Prairie, MN, USA) for the Treatment of De Novo or Restenotic Lesions in Infra-Popliteal Arteries) will be reporting a primary endpoint of 6-month late lumen loss (Table 7).

5.4 Substitute "limus" drug

Sirolimus is not the only member of the "limus" family to have shown promise in the search for an optimal DCB. The highly lipophilic nature of zotarolimus and potential for enhanced drug uptake has been tested in a porcine coronary overstretch model. In this preclinical evaluation, zotarolimus-coated balloons demonstrated a significant reduction in inflammation scores, and neointimal area when compared with control polymer coated stents without drug or zotarolimus-eluting stents [101].

5.5 Alternative methods of drug delivery

Novel therapeutic modalities have emerged with the goals of minimizing arterial injury while designing an effective platform for antiproliferative drug delivery.

Administration of antiproliferative drug dissolved in contrast medium has shown promise in reducing restenosis due to neointimal hyperplasia in a porcine artery overstretch model [102]. In this light, the Mercator Bullfrog catheter was developed to directly administer "limus" drugs in the arterial bed. In the TANGO trial presented at Transcatheter Cardiovascular Therapeutics (TCT) 2020, temsirolimus was used in 41 patients with TASC II B-C-D infrapopliteal lesions. The investigators reported a significant improvement in remaining transverse lumen area which assesses late lumen loss along the entire length of the treated artery when compared with 20 controls (24% vs. 46%) at 6-month follow-up.

The appeal of an effective device without the need for a permanent metallic implant has been explored in the coronary arteries. In ABSORB II, an Everolimus-containing poly-D, L-lactide scaffold initially demonstrated promising results with no significant difference in the composite endpoint of 1-year cardiac death, myocardial infarction, or target lesion revascularization vs. the best in-class DES Xience (Abbott, Chicago, IL, USA) [103]. In contrast, the significantly higher rate of target-lesion failure at two years led to its withdrawal [104]. Below the knee, excellent early results were noted with an astoundingly low binary restenosis (6%) and CD-TLR (4% at 2 years) [17]. Primary patency (81.1%) and freedom from CD-TLR (87.3%) have remained satisfactory at 36 months [98].

6. Limitations

Several limitations prevail in the study and design of an effective BTK DCB. High-fidelity models incorporating flow are lacking [45]. Compressive forces created by adjacent bones, muscles, and tendons are rarely accounted for [23, 105]. Study endpoints are heterogeneous and challenging to interpret [106]. The impact of vessel preparation and balloon inflation protocol on technical and clinical outcomes remains unknown, particularly to treat lesions with poor run-off [50, 105, 107]. Efficacy may vary based on lesion location, length, and pattern of calcification. The role and potential advantage of BTK DCB in the treatment of high-risk lesions or restenosis is still undefined. Drivers of clinical success in PAD span beyond devices and include the management of underlying metabolic disorders as well as optimal and standardized wound care. Finally, paradigm shifts in post-procedural antithrombotic and antiplatelet therapy may play a larger role in success after high-risk infrapopliteal revascularization [108].

7. Conclusions

The endeavor to develop additional tools in the management of infrapopliteal occlusive disease is driven by limited efficacy of currently available devices [105]. Improvements in device design, drug delivery, possibly drug choices, along with the identification of demographic and lesion risk factors will allow for patient-specific targeted and effective therapy delivery [29, 109, 110].

Author contributions

Conceptualization—REK and PAS; investigation—REK and PAS; resources—REK, MB, and PAS; writing—original draft preparation—REK and PAS; writing—review and editing—REK, MB, and PAS; visualization—REK, MB, and PAS; supervision—MB and PAS; project administration—REK and PAS. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

PAS has served as a consultant for Silk Road Medical, Surmodics, Boston Scientific, Medtronic, Philips, CSI, Cagent, Cordis, and LimFlow. MB is a consultant for Medtronic, BD Bard, Boston Scientific, Biotronik, and Cook Medical.

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