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Drug-Coated Balloon and Stent Therapies for Endovascular Treatment of Atherosclerotic Superficial Femoral Artery Disease

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Abstract Endovascular management of superficial femoral artery disease has historically been limited to percutaneous balloon angioplasty, atherectomy, and bare-metal stents. However, these therapies have been plagued by high restenosis and target lesion revascularization rates. More recent technologies such as drug-coated stents and balloons are designed to combat restenosis by locally delivering antiproliferative drugs. Several randomized controlled trials have directly compared these antiproliferative drug-delivering devices to their non-drug-coated counterparts. Additionally, trials are currently ongoing to compare use of drug-coated technologies in combination with traditional therapies in hope of synergistic effects. This review gathers data from currently published clinical trials, provides an overview of upcoming clinical studies utilizing drug-coated technology, and explores the possible impact these devices may have on clinical practice.

Keywords Peripheral artery disease · Superficial femoral artery · Endovascular revascularization · Drug-coated stents · Drug-coated balloons · Chronic total occlusion

Introduction

Lower extremity atherosclerotic peripheral artery disease (PAD) affects nearly a third of individuals over the age of 60 years and is a growing clinical problem in nations with an aging population [1]. Symptomatic PAD in the form of intermittent claudication and critical limb ischemia (CLI) is present in nearly 20 % of individuals with PAD, and if treatment with optimal medical therapy and adherence to a walking regimen does not relieve symptoms, revascularization is often indicated [2]. The superficial femoral artery (SFA) is the most common site for development of PAD, since it experiences significant flexion and torsion that likely injures its *vaso-vasorum* and contributes to an exuberant local inflammatory response [3, 4]. Progressive atherosclerosis can lead to occlusive SFA lesions or chronic total occlusions (CTO), which completely block blood flow to the distal vasculature [5]. The SFA is of particular importance because nearly 50 % of patients presenting with either intermittent claudication or CLI referred for revascularization have a CTO in this location [6]. Furthermore, relief of these symptoms is dependent upon restoring flow through the SFA to distal, below-the-knee (BTK) vessels [6]. These procedures are increasingly being performed using minimally invasive percutaneous revascularization techniques over surgical bypass, given its ease, technical feasibility, and lower risk of complications [7].

Traditional endovascular methods of treating SFA disease are limited by the occurrence of restenosis, leading to 12-month target lesion revascularization (TLR) and loss of primary patency rates upwards of 35 % for treatment modalities such as percutaneous balloon angioplasty (PTA) [8–10], self-expanding nitinol bare metal stents (BMS) [11], covered stent grafts [12], and atherectomy which is used predominantly in medium-length, non-CTO lesions [13]. Improved balloon, stent, and atherectomy technologies have not been able to completely mitigate the risk of high restenosis, especially for the more complex SFA lesions (≥60 mm lesions length, heavily calcified, and/or CTO) [14]. Delivery of antiproliferative drugs to the target lesion using drug coated stents (DCS) and drug-coated balloons (DCB) are a recent development aimed at reducing restenosis [15••].

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Limus-based drugs halt the vascular smooth muscle cell proliferation by inhibiting the cell cycle at the G1-S checkpoint, preventing cellular encroachment of the vessel or stent lumen [16, 17]. Paclitaxel, on the other hand, combats inflammation by suppressing the release of growth factors, prevents smooth muscle cell migration by promoting the synthesis of stable, but dysfunctional cellular microtubules, and, at high doses, causes cell death by arresting mitosis at the G2-M phase [18, 19]. Combination therapies using these antiproliferative drug-delivering technologies with traditional therapies could potentially be synergistic. This review is aimed at critically appraising the clinical trial data involving DCS and DCB as stand-alone and combination therapies for SFA disease, as well as providing an overview of ongoing and upcoming clinical trials using such technologies.

Drug-Coated Stents

The first-generation DCS consisted of a stent scaffold composed of several possible metals (nickel-titanium, platinum–chromium, or stainless steel), a polymer matrix (a combination of silicone, cellulose esters, and polyurethane), and an antiproliferative drug. Release of the antiproliferative drug was controlled over time by degradation of the polymer matrix.

Table 1 provides details of SFA DCS trials included in this review. The earliest randomized controlled trial (RCT) utilizing DCS technology compared sirolimus-coated stents to uncoated SMART™ (Cordis Corp., Bridgewater, NJ) self-expanding BMS in the SIROCCO (Sirolimus-Coated Cordis Self-Expandable Stent) trial [20]. Overall, 47 patients received the DCS compared with 46 in the control, with lesion length (85±44 mm vs. 81±52 mm) and CTO (69 % vs. 57 %), both not significantly different, respectively. At a follow-up of 24 months, there were no significant differences in TLR (6 % vs. 13 %; p=0.30) or binary restenosis measured by duplex ultrasound (22.9 % vs. 21.1 %). Interestingly, a late catch-up effect was observed in the DCS arm, with restenosis rates increasing from 7.1 % to 18.4 % between 9 and 18 months compared with the control group, which stayed relatively constant at 11.1 % to 12.8 %. This effect was attributed to an inflammatory response to the polymer matrix of the DCS. The lack of significant differences in both TLR and restenosis rates could also be due to the surprisingly improved long-term performance of the control BMS.

The single-arm non-randomized STRIDES (Superficial Femoral Artery Treatment with Drug-Eluting Stents) trial implanted everolimus-coated Dynalink™ (Abbott Vascular, Santa Clara, CA) nitinol self-expanding stents in 104 patients [21]. Average lesion length was 90±43 mm; 45 % were CTO, and 87 % were Trans-Atlantic Society Classification (TASC) II A and B lesions. At 12 months post-procedure, primary patency was 55.0 %, and freedom from TLR was 70 %. The drug elution profile was designed to release 80 % of the 225 μg/cm^2 everolimus over the course of 3 months; during this time period, primary patency was 94 % and freedom from TLR 95 %. Dual antiplatelet therapy (DAPT) was mandated for at least 6 months, and 61 % of patients remained on DAPT for at least 12 months. The most significant drop in patency and freedom from TLR rates coincided following the 6-month timeframe, again raising concern about the possibility of late-onset restenosis induced by polymer degradation.

Next-generation DCS, such as the Zilver-PTX™ (Cook Medical, Bloomington, IN) paclitaxel-coated stent, eliminated the polymer matrix intermediary and instead coated the drug directly onto the stent struts. In the Zilver-PTX RCT, 238 patients were randomized to primary PTA and 236 to primary Zilver-PTX™ DCS [22•]. For those assigned to primary PTA, 120 had sub-optimal PTA and were secondarily randomized to receive provisional BMS (n=59) or Zilver-PTX™ (n=61). Lesion length (66.4±38.9 mm vs. 63.2±40.5 mm; p=0.31) and CTO (32.8 % vs. 27.4 %; p=0.20) were similar between the primary DCS and PTA cohorts. Two-year primary patency (primary endpoint), assessed by duplex ultrasound, was 74.8 % for the primary DCS cohort and 26.5 % for primary PTA (p<0.01). Subgroup analysis revealed similar significant advantages in primary patency for the DCS over the optimal PTA cohort (53.4 %; p<0.01). Provisional DCS had significantly higher 2-year primary patency compared with provisional BMS (83.4 % vs. 64.1 %; p<0.01), while no significant difference was observed between primary or provisional DCS (74.8 % vs. 83.4 %; p=0.11). The significant improvements in primary patency and freedom from TLR of the DCS over the overall PTA, optimal PTA, and provisional BMS cohorts were observed at 4 years [23]. Overall, the strong results from the Zilver-PTX™ trial has resulted in its United States Food and Drug Administration (FDA) approval and adoption into routine clinical practice, unlike the previously mentioned DCS. Nevertheless, the Zilver PTX trial was limited by inclusion of relatively short (~67 mm) lesions, under-representation of CTO (27 %), and inclusion of acute PTA failure as part of its primary endpoint.

The single-arm Zilver PTX trial incorporated a higher percentage of CTO (38.3 %), longer lesions (99.5±82.1), and included in-stent restenotic (ISR) lesions (13.2 %), and demonstrated similar 2-year freedom from TLR rates (80.5 % vs. 86.6 %) compared with the DCS arm in the RCT [22•]. Recently, results were presented from a 907 patient postmarket surveillance study conducted in Japan using the Zilver-PTX in real-world, more complex lesions compared with the RCT [24]. Average lesion length (147.0 mm) and ISR proportion (19.0 %) were significantly higher (p<0.01) compared with the RCT cohort. At 12-month follow-up, freedom from TLR was 91.4 % and primary patency 84.8 %, demonstrating promising results for challenging lesions using this treatment modality.

Table 1 Drug coated stent and balloon trials in the superficial femoral artery

Trial	Study design	Lesion characteristics (DCS vs. control)	Outcomes (DCS vs. control)	Comments
SIROCCO (2006)	DCS (n=47) vs. BMS (n=46), RCT	Length (mm): 85±44 vs. 81±52 CTO: 69 % vs. 57 %	24-month TLR: 6 % vs. 13 %; p=0.30; 24-month restenosis: 22.9 % vs. 21.1 %	DAPT: 3–4 months; 85% received ≤2 stents; 100 % Rutherford ≤4
STRIDES (2011)	DCS (n=104) single-arm trial	Length (mm): 90±43 CTO: 45 %	12-month TLR: 30 %; 12-month primary patency: 55 %	DAPT: 6 months; 94 % received ≤2 stents; 87 % TASC II A and B
Zilver-PTX (2013)	DCS (n=236) vs. PTA (n=238), RCT optimal PTA (n=118) provisional BMS (n=59) provisional DCS (n=61)	Length (mm): 67±39 vs. 63±41; p=0.31 CTO: 33 % vs. 27 %; p=0.20	[a]24-month primary patency: 75 % vs. 27 %; p<0.01; [b]24-month primary patency: 83 % vs. 64 %; p<0.01; [c]48-month TLR: 17 % vs. 31 %; p<0.01; [b]48-month primary patency: 75 % vs. 58 %; p=0.04	3-year stent fracture: 2.1 %; DAPT: ≥60 days; 91 % Rutherford ≤3
Zilver PTX (2013)	DCS (n=787) single-arm trial	Length (mm): 99.5±82.1 CTO: 38.3 %	24-month TLR: 19.5 %	Study included 13.2 % ISR lesions, compared with 0 in RCT
FemPac (2008)	DCB (n=45) vs. PTA (n=42), RCT	Median length (mm): 40 vs. 47; p=0.45 CTO: 13 % vs. 19 %; p=0.56	24-month TLR: 13 % vs. 50 %; p=0.001; 24-month primary patency: 78 % vs. 46 %; p=0.001	66 % de novo lesions; 43 % TASC II C and D
THUNDER (2008)	DCB (n=48) vs. PTA+paclitaxel contrast (n=52) vs. PTA (n=54), RCT	[d]Length (mm): 74±65 vs. 74±67; p=0.73 [d]CTO: 14 % vs. 14 %; p=1.0	[a]24-month TLR: 40 % vs. 52 %; p<0.001	TLR similar for paclitaxel contrast vs. PTA at all time periods
PACIFIER (2012)	DCB (n=41) vs. PTA (n=44), RCT	[e]Length (mm): 70±53 vs. 66±55 [e]CTO: 23 % vs. 38 %	12-month TLR: 7 % vs. 28 %; p=0.02	96 % Rutherford ≤3
BIOLUX P-I (2013)	DCB (n=30) vs. PTA (n=30), RCT	Length (mm): 51±47 vs. 69±57; p=0.307 CTO not reported	12-month TLR: 13 % vs. 42 %; p=0.064	As-treated 12-month TLR: 16 % vs. 53 %; p=0.020
LEVANT I (2014)	DCB (n=49) vs. PTA (n=52), RCT	Length (mm): 81±37 vs. 80±38; p=0.89 CTO: 41 % vs. 42 %; p=0.88	24-month TLR: 36 % vs. 49 %; p=0.23; [b]24-month primary patency: 57 % vs. 40 %	8 DCB failed to deploy

BMS bare metal stent, *CTO* chronic total occlusion, *DAPT* dual antiplatelet therapy, *DCB* drug coated balloon, *DCS* drug coated stent, *FemPac* Femoral Paclitaxel, *ISR* in-stent restenosis, *LEVANT* Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis, *PACIFIER* Paclitaxel-Coated Balloons Reduce Restenosis After FemoroPopliteal Angioplasty, *PTA* percutaneous transluminal angioplasty, *RCT* randomized controlled trial, *SIROCCO* Sirolimus Coated Cordis Self-Expandable Stent, *STRIDES* Superficial Femoral Artery Treatment with Drug-Eluting Stents, *TASC* Trans-Atlantic inter-society consensus, *THUNDER* Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries, *TLR* target lesion revascularization

*Comparison of primary DCS to PTA

[b] Comparison of provisional DCS to provisional BMS

[c] Comparison of primary DCS to optimal PTA

[d] Comparison between DCB and PTA cohorts

[e] *P* value not reported

Drug-Coated Balloons

There are several potential advantages of DCB over DCS: avoid implantation of an intravascular scaffold, conceptually more homogenous delivery of drug to vessel wall, ability to reach tortuous lesions, and ability to treat in-stent restenotic lesions where placement of additional stents may not be preferred. The drug is coated onto the balloon along with an excipient, such as urea, iopromide, or polysorbate/sorbitol, to control the drug's release rate in a timely manner onto the vessel wall.

Table 1 provides an overview of the SFA DCB trials included in this review. The Femoral Paclitaxel (FemPac) trial randomized 45 patients to receive a paclitaxel coated balloon and 42 PTA [25]. Median lesion lengths were similar between the DCB and PTA cohorts (40 mm vs. 47 mm; p=0.45), as

was CTO distribution (13 % vs. 19 %; p=0.56). Overall, 11.5 % of patients received provisional stents. The study reported only 6.4±2.9 % residual paclitaxel on the DCB following inflation, although it is unclear how much was lost into the bloodstream. TLR at 24-months (13 % vs. 50 %; p=0.001) and primary patency (78 % vs. 36 %; p=0.001) significantly favored the DCB.

The THUNDER (Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries) trial randomized 48 patients to receive DCB therapy, 54 to PTA, and 52 to PTA+paclitaxel in contrast medium [26]. The paclitaxel in contrast arm was included in anticipation of producing similar results to animal studies. Patients in the PTA arm received significantly more provisional stents compared to the DCB (22 % vs. 4 %; p=0.009) and paclitaxel contrast (22 % vs. 6 %; p=0.02) groups. Although angiographic findings showed significant improvement in 6-month late lumen loss favoring DCB over both comparator arms, clinical improvement in terms of ankle-brachial index and Rutherford category were not significantly different. Twenty-four-month TLR, however, significantly favored the DCB over PTA (40 % vs. 52 %; p<0.001).

The PACIFIER (Paclitaxel-Coated Balloons Reduce Restenosis After Femoro-Popliteal Angioplasty) RCT randomized 41 patients to receive DCB therapy and 44 PTA [27]. Lesion lengths were similar at 70 mm on average, although CTO was more common in the PTA cohort (38 % vs. 23 %; p value not reported). Provisional stenting was similar between DCB and PTA (20.5 % vs. 34.0 %; p=0.17), and DCB procedures required significantly more devices (1.6±0.9 vs. 1.1±0.4; p<0.001) due to necessity for multiple DCB for longer lesions. At 12 months post-procedure, DCB exhibited significant improvements in TLR (7 % vs. 28 %; p=0.02).

The LEVANT I (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) RCT utilized a lower-dose 2 μg/mm^2 paclitaxel DCB in 101 patients [28]. All patients received PTA pre-dilation, and patients were then randomized according to whether the operator decided upon another round of balloon inflation or placement of a nitinol stent. If the former was chosen, the patient was randomized to DCB (n=37) or PTA (n=38). If the latter was chosen, the post-dilation strategy was randomized to DCB (n=12) or PTA (n=14). Overall, 49 patients received DCB and 52 PTA, with lesion lengths (80.8±37.0 mm vs. 80.2±37.8 mm; p=0.89) and CTO (41 % vs. 42 %; p=0.88) well matched, respectively. The primary endpoint of late lumen loss was significantly lower for the DCB compared with PTA in the balloon-only arm (0.45±1.18 vs. 1.19±1.15; p=0.024), while no significant improvement was observed with DCB as a post-dilation strategy. Overall, 24-month TLR was similar following use of DCB versus PTA (36 % vs. 49 %; p=0.23). This study highlighted the differences between DCB that deployed fully and those that failed. Of the eight that failed, 63 % required TLR and 0 % maintained primary patency at 24 months.

The BIOLUX-PI (A Prospective, Multi-center, Randomized Controlled, First in Man Study to Assess the Safety and Performance of the Passeo-18 Lux Paclitaxel Releasing PTA Balloon Catheter vs. the Uncoated Passeo 18 Balloon Catheter in Patients with Stenosis and Occlusion of the Femoropopliteal Arteries) RCT compared 30 patients each treated with DCB or PTA for femoropopliteal stenosis [29]. Importantly, an exclusion criterion was the presence of heavy calcification upon angiography. Mean lesion length was 51.4±47.2 mm for the DCB and 68.5±57.0 mm for PTA (p=0.307), with one-third of all patients having diabetes mellitus. Binary restenosis rates at 6 months (11.5 %) compared favorably with aforementioned DCB RCT, as did freedom from TLR at 12 months (84.6 % DCB vs. 58.3 % PTA; p=0.064).

A potential application of DCB could be within ISR SFA lesions, with the advantage of avoiding a second layer of stents using stent-based strategies. The DEBATE-ISR (Drug Eluting Balloon in Peripheral Intervention for In-Stent Restenosis) RCT utilized DCB in 44 and PTA in 42 patients, with similar lesion lengths (175±90 mm vs. 160±82 mm; p=0.4), percentage of CLI patients (75 % vs. 67 %; p=0.8), and provisional stent use (16 % vs. 26 %; p=0.2), respectively [30]. Of note, the disease severity was markedly higher in this study compared with aforementioned de novo RCT examining DCB. The long lesion lengths resulted in 1.6±1.2 DCB used per procedure, and over 40 % of patients required concomitant BTK vessel revascularization. At 12 months, freedom from TLR was significantly higher for the DCB arm (86 % vs. 69 %; p=0.045), as was binary restenosis assessed by duplex ultrasound (19 % vs. 72 %; p<0.001). The advantages of DCB for this clinical presentation, especially given the high ISR rate for stent-based SFA procedures, are promising.

Drug-Coated Balloons in Combination with Traditional Therapies

Over 70 % of SFA PAD, especially in patients with diabetes mellitus, presents as complex atherosclerotic disease that includes long (≥60 mm) diffusely diseased arterial segments, heavily calcified lesions, and/or CTO that require additional scaffolding with intravascular stents [14]. Balloon angioplasty of such lesions has traditionally been associated with poor clinical outcomes, and the need for a vascular scaffold makes such lesions not ideal for stand-alone treatment even with DCB [31]. These limitations of DCB can be minimized with the use of adjunctive therapies such as stenting and atherectomy. Therefore, some clinical trials have incorporated such combination therapies into the study design. The DEBATE-

SFA (Drug Eluting Balloons in Peripheral Intervention for the Superficial Femoral Artery) RCT compared DCB to PTA as a pre-dilation strategy and randomized 53 patients (55 lesions) to DCB+BMS and 51 patients (55 lesions) to PTA+BMS [31]. Lesion lengths were 94±60 mm for DCB and 96± 69 mm for PTA (p=0.8), with a trend towards more CTO in the PTA arm (69 % vs. 55 %; p=0.1). At 12 months, the primary endpoint of binary restenosis was reached in 17 % DCB vs. 47 % PTA (p=0.008), and TLR in 17 % DCB vs. 33 % PTA (p=0.07). An upcoming RCT, RAPID (Randomized Trial of Legflow Paclitaxel-Eluting Balloon and Stenting Versus Standard Percutaneous Transluminal Angioplasty and Stenting for the Treatment of Intermediate and Long Lesions of the Superficial Femoral Artery), will also compare DCB versus PTA as a pre-dilation strategy, but in intermediate (5–15 cm) and long (>15 cm) lesions more closely resembling clinical practice [32]. An ongoing RCT is comparing DCB to PTA as a post-dilation strategy following nitinol stent implantation, and 12-month interim results favor lower TLR rates with the DCB (8 % vs. 17 %; p value not reported) [33].

Several trials are exploring the "leave nothing behind" benefits of DCB and/or atherectomy. The DEFINITIVE-AR (Directional Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis and Maintain Vessel Patency) RCT is an ongoing study examining the efficacy of DCB after directional atherectomy to DCB alone in minimally calcified, non-CTO lesions [34]. The study randomized 48 patients to atherectomy+DCB and 54 to DCB alone, with the former having longer lesion lengths (112 vs. 97 mm; p=0.05). Angiographic patency assessed at 12 months showed a trend towards increased patency following atherectomy+DCB

Table 2 Ongoing drug-coated device trials in femoropopliteal arteries

Trial	Study design	Notes
LEVANT 2	Lutonix™ DCB vs. PTA	12-month PP: 65 % DCB vs. 53 % PTA; p=0.015
IN.PACT SFA	IN.PACT Admiral™ DCB vs. PTA	12-month TLR: 2 % DCB vs. 21 % PTA; p<0.001; 12-month PP: 82 % DCB vs. 52 % PTA; p<0.001
FREERIDE	Freeway™ DCB vs. PTA	6-month TLR: 5 % DCB vs. 20 % PTA; p=0.07; bail-out stenting: 9 % DCB vs. 26 % PTA; p=0.04
ADVANCE 18 PTX	Advance 18LP™ DCB vs. PTA	Advance 18LP™ DCB lacks excipient; 6-month LLL (mm): 0.9±1.1 DCB vs. 1.3±1.2 PTA; p=0.12
CONSEQUENT	SeQuent® Please P DCB vs. PTA	De novo and restenotic lesions allowed
ILLUMENATE	Cardiovascular Ingenuity™ DCB vs. PTA	360 estimated enrollment by July 2015
MDT-2113 SFA	MDT-2113™ DCB vs. PTA	Maximum length 20 cm
FREEWAY	BMS+Freeway™ DCB vs. BMS+PTA	12-month TLR: 8 % DCB vs. 17 % PTA; p=N/A
RAPID	Legflow™ DCB+BMS vs. PTA+BMS	Supera™ stenting after DCB or PTA pre-dilation
PHOTOPAC	Laser+DCB vs. laser+PTA for ISR	No maximum target lesion length required; ≥70 % stenosis inclusion criteria
ISAR-STATH	IN.PACT Pacific™ DCB vs. PTA for ISR	≥70 % SFA stenosis inclusion criteria
FAIR	IN.PACT Admiral™ DCB vs. PTA for ISR	Inclusion criteria: maximum 20 cm lesion; lesion cannot extend into popliteal or beyond stent lengths
PACUBA I	Freeway™ DCB vs. PTA for ISR	6-month PP: 78 % vs. 37 %
COPA-CABANA	Cotavance™ DCB vs. PTA for ISR	≥70 % SFA stenosis inclusion criteria; maximum lesion length, 27 cm

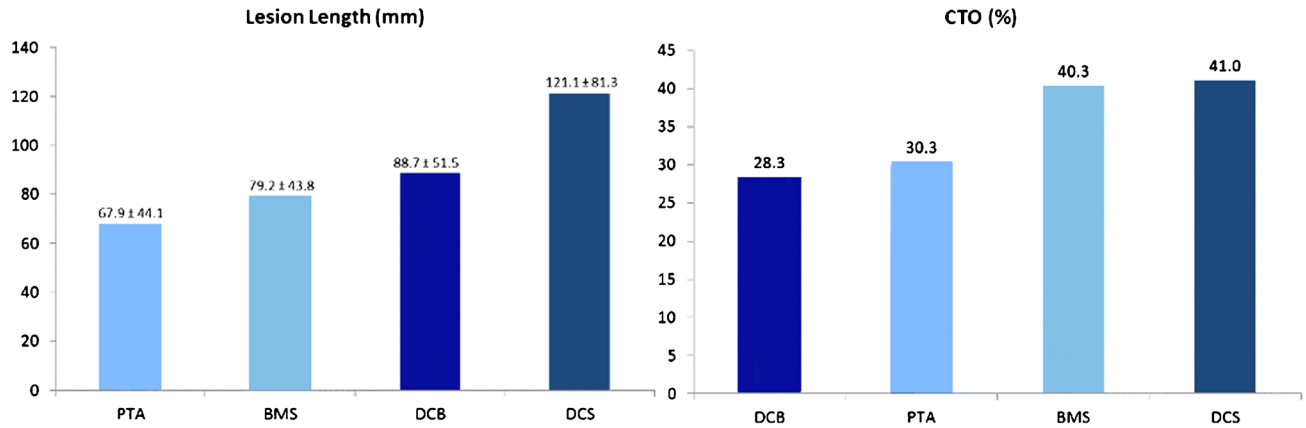
ADVANCE 18 PTX Treatment of Lesions in Superficial Femoral Artery/Popliteal Artery With a Paclitaxel-Coated Balloon, *BMS* bare metal stent, *CONSEQUENT* Clinical Trial on Peripheral Arteries Treated With SeQuent Please P Paclitaxel-Coated Balloon Catheter, *COPA CABANA* Cotavance Paclitaxel-Coated Balloon Versus Uncoated Balloon Angioplasty for Treatment of In-Stent Restenosis in SFA and Popliteal Arteries, *CTO* chronic total occlusion, *DAPT* dual antiplatelet therapy, *DCB* drug-coated balloon; FAIR: Femoral Artery In-Stent Restenosis, *FREERIDE* Freeway Paclitaxel-Coated Balloon Catheter to Treat Peripheral Artery Disease, *FREEWAY* The Freeway Drug-Eluting Balloon for Treatment of De Novo Lesions in the SFA or Popliteal Arteries, *ILLUMENATE* Prospective, Randomized, Single-Blind, U.S. Multi-Center Study to Evaluate Treatment of Obstructive Superficial Femoral Artery or Popliteal Lesions With A Novel Paclitaxel-Coated Percutaneous Angioplasty Balloon, *IN.PACT SFA* Randomized Trial of IN.PACT Admiral Drug-Eluting Balloon vs. Standard Percutaneous Transluminal Angioplasty for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery and/or Proximal Popliteal Artery, *ISAR-STATH* Efficacy Study of Stenting, Paclitaxel Eluting Balloon or Atherectomy to Treat Peripheral Artery Disease, *ISR* in-stent restenosis, *LEVANT* Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis, *LLL* late lumen loss, *MDT-2113 SFA* MDT-2113 Drug-Eluting Balloon vs. Standard PTA for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery and/or Proximal Popliteal Artery, *PACUBA* Paclitaxel Balloon Versus Standard Balloon in In-stent Restenosis of the Superficial Femoral Artery, *PHOTOPAC* Photoablative Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis in In-Stent Femoropopliteal Obstructions, *PP* primary patency, *PTA* percutaneous balloon angioplasty, *RAPID* Randomized Trial of Legflow Paclitaxel-Eluting Balloon and Stenting Versus Standard Percutaneous Transluminal Angioplasty and Stenting for the Treatment of Intermediate and Long Lesions of the Superficial Femoral Artery, *SFA* superficial femoral artery, *TLR* target lesion revascularization

(82.4 % vs. 71.8 %; *p* value not reported). A retrospective study compared atherectomy+DCB to atherectomy+PTA in restenotic (in-stent or native vessel) lesions [35]. Following atherectomy, a total of 60 patients were treated with PTA and 29 with DCB, with similarly long lesion lengths (180±136 mm vs. 153±93 mm; $p=0.276$), respectively. Multivariable Cox-proportional hazards modeling was performed to compare 12-month target lesion restenosis, and after adjusting for clinically significant covariates, a 0.28 hazard ratio for treatment with DCB over PTA was found (95 % confidence interval, 0.12–0.66; $p=0.004$).

As the DCB is a fairly recent innovation with a versatile application, several ongoing studies are continuing to examine its efficacy compared, and in combination, with traditional therapies. A summary of ongoing trials is listed in Table 2. With DCS and DCB available, contemporary clinical practice is expected to develop around widespread use of these technologies for SFA revascularization. Based on the clinical evidence presented (Fig. 1), it is likely that DCB will be used predominantly for endovascular treatment of short- or intermediate-length and non-CTO SFA lesions that are less likely to require a vascular scaffold. Its use in such lesions has also been shown to be cost-effective in one recently published study [36]. For more complex lesions, DCS is likely to be the default strategy. However, well-powered randomized clinical trials comparing DCS and BMS in more complex SFA lesions that are routinely encountered in clinical practice are needed to cement the role of DCS and justify the incremental cost associated with its use. An important limitation of the DCS and DCB technologies also includes the current lack of robust evidence for their cost-effectiveness.

Discussion

Overall, these data suggest a marked improvement in mid- and long-term SFA TLR and patency rates with drug delivering technologies compared with its bare or non-drug-coated counterparts. However, the aforementioned trials raise interesting questions about comparisons between DCS and DCB. When comparing DCB, it is important to note that not all DCB are created equal due to the varying excipients used. Optimal



PTA: SUPER, ASTRON, FAST, RESILIENT, ABSOLUTE, Schillinger et al, Zilver PTX, LEVANT 1, THUNDER, FemPac, PACIFIER, LEVANT 2, IN.PACT SFA, BIOLUX-PI
BMS: SUPER, ASTRON, FAST, RESILIENT, ABSOLUTE, Schillinger et al., *DURABILITY, *COMPLETE, *STROLL, *SUPERB, *OSPREY, SIROCCO
DCB: *Micari et al., LEVANT 1, LEVANT 2, THUNDER, FemPac, PACIFIER, *Zeller et al., IN.PACT SFA, BIOLUX-PI
DCS: Zilver PTX, *Zilver PTX Single Arm, SIROCCO, *STRIDES, *Zeller et al., *Zilver Japan
***Not a randomized trial**

Fig. 1 Comparison of lesion length and chronic total occlusion percentages of clinical trials examining various endovascular revascularization strategies. *ABSOLUTE*: The Balloon Angioplasty Versus Stenting with Nitinol Stents in the Superficial Femoral Artery; *ASTRON*: The Balloon Angioplasty Versus Stenting with Nitinol Stents in Intermediate Length Superficial Femoral Artery Lesions; *BIOLUX-PI*: A Prospective, Multi-centre, Randomized Controlled, First in Man Study to Assess the Safety and Performance of the Passeo-18 Lux Paclitaxel Releasing PTA Balloon Catheter vs. the Uncoated Passeo 18 Balloon Catheter in Patients With Stenosis and Occlusion of the Femoropopliteal Arteries; *COMPLETE*: The Medtronic Complete Self-Expanding SFA Stent System for the Treatment of Atherosclerotic Lesions in the Superficial Femoral and/or Proximal Popliteal Arteries; CTO: chronic total occlusion; *DCB*: drug-coated balloon; *DCS*: drug-coated stent; *DURABILITY*: The United States Study for Evaluating Endovascular Treatments of Lesions in the Superficial Femoral Artery and Proximal Popliteal By using the Protégé Everflex Nitinol Stent System; *FAST*: Femoral Artery Stenting Trial; *FemPac*: Femoral Paclitaxel; *IN.PACT SFA*: Randomized Trial of IN.PACT Admiral Drug Eluting Balloon versus Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease; *LEVANT*: Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis; *PACIFIER*: Paclitaxel-Coated Balloons Reduce Restenosis After Femoro-Popliteal Angioplasty; *RESILIENT*: Nitinol Stent Implantation Versus Balloon Angioplasty for Lesions in the Superficial Femoral Artery and Proximal Popliteal Artery; *SIROCCO*: Sirolimus Coated Cordis Self-Expandable Stent; *STRIDES*: Superficial Femoral Artery Treatment with Drug-Eluting Stents; *STROLL*: SMART Nitinol Self-Expandable Stent in the Treatment of Obstructive Superficial Femoral Artery Disease; *SUPER*: Randomized Trial of the SMART Stent versus Balloon Angioplasty in Long Superficial Femoral Artery Lesions; *SUPERB*: Comparison of the Supera Peripheral System to a Performance Goal Derived From Balloon Angioplasty Clinical Trials in the Superficial Femoral Artery; *THUNDER*: Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries

excipients should not only release the vast majority of the drug from the balloon during inflation, but also should minimize drug loss into the bloodstream and ensure drug delivery to the vessel wall. Reports from trials have shown as much as 86± 12 % of the paclitaxel being released from the balloon during inflation, while animal studies have shown that only 10–20 % of the drug is delivered to the vessel wall, suggesting room for improvement [27, 37]. Without standardized reporting of such excipient efficacy criteria, the generalization of DCB trial results would be limited by this caveat.

However, general comparisons of DCB and DCS can be made due to the differing natures of balloon- and stent-based revascularization. SFA lesions frequently present as heavily calcified and/or long-segment CTO. Such lesions are more likely to require vascular scaffolds using stent-based strategies, and DCS may prove more practical and cost-effective than combination therapies with DCB for several reasons [38]. The presence of vascular calcification, ubiquitous in complex SFA lesions (≥60 mm and/or CTO) may hinder drug delivery to the vessel wall via DCB [39, 40]. In fact, the DEFINITIVE-AR trial accounted for this limitation by excluding heavily calcified lesions from randomization to DCB, and used directional atherectomy prior to DCB for lesions that were heavily calcified [34]. Moreover, long lesion lengths may increase the cost of using DCB. Because the full dose of the drug is released upon first inflation, several DCB may be required to optimally treat a long lesion. Lastly, the high degree of atherosclerotic burden of CTO frequently requires adjunctive therapies such as atherectomy and/or stenting following PTA to minimize residual stenosis, treat flow-limiting dissections, and prevent acute arterial recoil. The lesions represented in the aforementioned DCB RCT, which averaged 40–80 mm in length with less than 30 % CTO, suggest limited generalizability to more complex lesions. In fact, the ongoing LEVANT 2 RCT, which compares DCB to PTA, accounts for such disparities between balloon- and stent-based therapies by requiring operators to randomize treatment to DCB or PTA after an optimal initial PTA result [41]. Suboptimal initial PTA is deemed a screen failure and necessarily inflates the patency results compared with trials that do not include a "stopgap" after suboptimal PTA. As such, judicious interpretation of the results of this and similar DCB trials may be warranted when deciding upon an optimal strategy within a real-world setting. Stenting is commonplace in today's practice, especially for complex lesions, and the use of a vascular scaffold may be necessary in many situations, despite the potential benefits conferred by a DCB. The REAL-PTX RCT, currently the only ongoing trial directly comparing DCS to DCB in femoropopliteal lesions, will shed more light upon the optimal situations for use of each device [42]. In terms of their bare counterparts, RCT comparing BMS to PTA showed that stents fared significantly better in longer lesion lengths and CTO lesions, and may translate similarly to drug-coated devices [8–10].

Conclusion

Overall, these data show a marked improvement in mid- to long-term outcomes using drug-coated technologies compared with traditional therapies. In comparing DCS with DCB, perhaps these data suggest treatment should be stratified based on lesion complexity, with DCB reserved for in-stent restenotic, relatively short, non-CTO lesions, and DCS for long, heavily calcified and CTO target lesions. To definitively compare DCS with DCB, a large-scale randomized trial will be necessary. With DCB recently receiving approval from the United States FDA, the likelihood of such a trial should undoubtedly increase. However, until then, deciding between DCB, DCS, and traditional therapies will have to rest on our clinical judgment.

Compliance with Ethics Guidelines

Conflict of Interest Subhash Banerjee reports research grants from Boston Scientific and Medicines Company; consultant/speaker honoraria from Gilead, St. Jude Medical, Cordis, Boehringer Ingelheim, Sanofi, and Medtronic; ownership with MDCARE Global (spouse); intellectual property with HygeiaTel.

Karan Sarode and Atif Mohammad declare that they have no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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