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## Current evidence of drug-elution therapy for infrapopliteal arterial disease

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### Abstract

New and sophisticated endovascular devices, such as drug-eluting stents (DES) and drug-coated balloons (DCB), provide targeted drug delivery to affected vessels. The invention of these devices has made it possible to address the reparative cascade of arterial wall injury following balloon angioplasty that results in restenosis. DESs were first used for the treatment of infrapopliteal lesions almost 20 years ago. More recently, however, DCB technology is being investigated to improve outcomes of endovascular below-the-knee arterial procedures, avoiding the need for a metallic scaffold. Today, level IA evidence supports the use of infrapopliteal DES for short to medium length lesions, although robust evidence that justifies the use of DCBs in this anatomical area is missing. This review summarizes and discusses all available data on infrapopliteal drug-elution devices and highlights the most promising future perspectives.

**Key words:** Drug-elution therapy; Infrapopliteal arterial disease; Current evidence; Drug-coated balloons; Drug-eluting stents

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**Core tip:** Currently available level IA evidence justifies the use of infrapopliteal drug-eluting stents for short to medium length lesions in selected patients with specific anatomical criteria. The role of infrapopliteal drug-coated balloons remains to be determined.

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## INTRODUCTION

Infrapopliteal atherosclerotic arterial disease, either alone or combined with aortoiliac and femoropopliteal vascular disease, is the leading cause of critical limb ischemia (CLI) and severe, lifestyle-limiting, intermittent claudication (IC)<sup>[1]</sup>. In the western population, the incidence of infrapopliteal disease is strongly correlated with the prevalence of diabetes mellitus, and is continuously rising due to increased life expectancy in developed countries<sup>[2]</sup>. Foot ulceration with tissue loss and gangrene are some of the manifestations of CLI, which may lead to major amputation if the affected arteries are not promptly revascularized<sup>[3]</sup>. CLI is considered to be responsible for approximately 90% of the major amputations performed worldwide, and is a significant cause of morbidity and mortality<sup>[2,3]</sup>. In diabetic patients, CLI represents a medical emergency, as the concomitant foot architectural changes and potential infections can rapidly compromise limb salvage<sup>[4]</sup>. Besides, the long vessel occlusions combined with poor distal runoff, prevalent in diabetic CLI patients, represent a considerable challenge for healthcare specialists<sup>[5]</sup>.

Patients with ischemic rest pain, diabetic or non-healing foot ulcers, or gangrene involving any portion of the lower limbs should be evaluated with the WIFI classification system that assesses the three primary factors contributing to limb threat risk: wound (W), ischemia (I) and foot infection (FI)<sup>[6,7]</sup>. After considering these components and staging each patient, revascularization should be attempted<sup>[7]</sup>. The WIFI classification system is depicted in [Table 1](#). Femorodistal below-the-knee (BTK) bypass surgery with autologous vein grafts has been established in the past as the gold standard treatment for CLI<sup>[2]</sup>. However, the presence of various underlying comorbidities, as well as the scarcity of non-diseased donor and run-off vessels, render a significant number of CLI patients unsuitable for surgery. Direct comparison data between bypass surgery and percutaneous BTK procedures are limited, with only one randomized multi-center trial available in the literature. Nevertheless, the evolution of interventional techniques, along with the development of novel devices, contributed to a paradigm shift in CLI treatment; nowadays endovascular methods can be used for multiple vessel recanalization and are related to comparable clinical outcomes for open surgery<sup>[3,8-10]</sup>. Endovascular revascularization, by virtue of its minimally-invasive nature, is characterized by decreased perioperative complications and cardiovascular stress that result in both shorter hospital stays as well as low morbidity and mortality<sup>[11,12]</sup>.

Plain balloon angioplasty was the primary endovascular therapy utilized in the infrapopliteal territory. Although it appeared to be effective in the short-term, post-angioplasty elastic vessel recoil and flow-limiting dissection contributed to reocclusion and relapse of ischemic symptoms<sup>[13]</sup>. Despite the fact that balloon angioplasty may be repeated, each procedure involves an inherent risk of technical failure and yields additional cost<sup>[4]</sup>. Attempting to address this issue, Dorros *et al*<sup>[14]</sup> pioneered the placement of the first infrapopliteal bare metal stent (BMS) 25 years ago. However, BMS application has been associated with poor outcomes in the mid-term due to the phenomenon of in-stent restenosis<sup>[15]</sup>. Constant irritation of the vessel wall by the metal stent mesh results in inflammation, intimal hyperplasia, negative vessel remodeling and ultimate reocclusion<sup>[16,17]</sup>. Occlusion rates are high; half of the BMS become occluded within the first year and can lead to major amputation<sup>[18,19]</sup>. As a result, stenting in the infrapopliteal region has been reserved as a bail-out procedure in order to maximize acute lumen gain and avoid early vessel reocclusion.

New and sophisticated endovascular devices, such as drug-eluting stents (DES) and drug-coated balloons (DCB), provide targeted drug delivery to affected vessels. The invention of these devices has made it possible to address the reparative cascade of arterial wall injury following balloon angioplasty that results in restenosis. BTK arteries share many characteristics with coronary arteries; this fact has motivated several investigators to apply this drug-eluting technology, widely used in percutaneous coronary interventions, in the infrapopliteal territory in order to improve clinical outcomes.

## DES

Table 1 Assessment of amputation risk: wound (W), ischemia (I) and foot infection classification<sup>[6,7]</sup>

Component	Score	Description		
W	0	No ulcer (ischemic rest pain)		
	1	Small, shallow ulcer on distal leg or foot without gangrene		
	2	Deeper ulcer with exposed bone, joint or tendon ± gangrenous changes limited to toes		
	3	Extensive deep ulcer, full thickness heel ulcer ± calcaneal involvement ± extensive gangrene		
I		ABI	Ankle pressure (mmHg)	Toe pressure or TcPO2
	0	≥ 0.80	> 100	≥ 60
	1	0.6-0.79	70-100	40-59
	2	0.4-0.59	50-70	30-39
	3	< 0.40	< 50	< 30
FI	0	No symptoms or signs of infection		
	1	Local infection involving only skin and subcutaneous tissue		
	2	Local infection involving deeper than skin/subcutaneous tissue		
	3	Systemic inflammatory response syndrome		

DESs were introduced into clinical practice by interventional cardiologists, and demonstrated favorable outcomes regarding late lumen loss (LLL) and rate-of-repeat revascularization procedures<sup>[20]</sup>. The comparable size of tibial to coronary arteries, and the superior efficacy of these stents compared to BMSs, led to the first clinical application of DES in the infrapopliteal arteries, with the goal of inhibiting restenosis and prolong uninterrupted blood supply to the foot<sup>[4]</sup>. The concept of DES technology is based on covering the stent's strut with a polymer matrix, such as silicone, polyethylene vinyl alcohol or cellulose ester, that is saturated with a specific drug. Some DESs are polymer-free, and the drug is applied directly onto the metallic strut<sup>[21]</sup>. DESs inhibit neointimal hyperplasia and smooth muscle cell proliferation by releasing the incorporated drug into the vessel wall over a standard period of time. The pharmaceutical agents that are most commonly used are immunosuppressants of the "-olimus family," *i.e.*, sirolimus, everolimus and tacrolimus, or the anti-mitotic agent paclitaxel. Sirolimus (rapamycin) is a natural lipophilic macrolide compound with both immunosuppressive and antiproliferative properties. Paclitaxel is a cytotoxic and antineoplastic drug that promotes microtubule stabilization, blocking M phase of the cell cycle, thus leading to cellular death<sup>[18]</sup>. The first clinical applications of DES in infrapopliteal arteries for the treatment of CLI demonstrated encouraging mid-term results<sup>[18,22-25]</sup>.

Following these initial promising single-center studies, multicenter randomized controlled trials (RCT) (YUKON-BTX, DESTINY and ACHILLES trials), reported low infrapopliteal vessel restenosis rate, higher event-free survival and improved quality of life. These provided level IA evidence for DES use in short focal infrapopliteal lesions (< 120 mm)<sup>[26-28]</sup>.

In the ACHILLES trial, precisely 200 patients suffering from either CLI (> 60%) or Rutherford class 3 IC were enrolled in 17 European centers and were randomized to undergo primary DES with the CYPHER SELECT® PLUS sirolimus-eluting stent (Cordis, United States) or plain balloon angioplasty of the infrapopliteal arteries. Mean lesion length was 27 ± 21 mm. The device success rate was significantly higher for DES (95.5% *vs* 58.2%, *P* = 0.001), while DES at 12 mo achieved significantly lower restenosis rates (22.4% *vs* 41.9%, *P* = 0.019), superior patency (75.0% *vs* 57.1%, *P* = 0.025) and improved Rutherford class. Revascularization procedures and amputation rates were similar for both treatment options<sup>[28]</sup>. In a post hoc analysis of this trial, Katsanos *et al*<sup>[29]</sup> reported that DES use was found to accelerate wound healing compared with balloon angioplasty, a substantial outcome especially for patients with diabetes, to whom rapid wound healing is imperative to avoid superinfection and subsequent limb loss<sup>[29]</sup>. In the DESTINY multicenter RCT, 140 patients with CLI were randomized to receive either the XIENCE V Everolimus-eluting balloon-expandable stent or the Multilink vision bare balloon-expandable stent (ABBOTT, United States). The maximum lesion length allowed was 40mm, and primary patency was defined as the absence of > 50% restenosis assessed by quantitative analysis of contrast angiography. At 12 mo, both primary patency (85% *vs* 54%, *P* = 0.0001) and re-intervention (85% *vs* 54%, *P* = 0.0001) rates were significantly improved with DES use. Moreover, the Xience V DES significantly reduced both mean in-stent stenosis (21% ± 21% *vs* 47% ± 27%, *P* < 0.0001) and mean in-stent LLL (0.78 ± 0.63 mm *vs* 1.41 ± 0.89 mm, *P* = 0.001)<sup>[27]</sup>. Finally, the YUKON-BTK

multicenter, double-blind RCT randomized 161 suffering patients (CLI or IC) to receive endovascular treatment with either the YUKON-BTX polymer-free sirolimus-eluting stent (Translumina, Germany) or a placebo-coated bare-metal stent. Again, the 12 mo primary (80.6% *vs* 55.6%,  $P = 0.004$ ) and secondary (91.9% *vs* 71.4%,  $P = 0.005$ ) patency rates were significantly higher for the DES group, while changes in Rutherford-Becker classification were also significantly superior in the DES group<sup>[26]</sup>.

Meta-analysis of the above three multicenter RCTs confirmed these findings and demonstrated the superiority of DES over plain balloon angioplasty and BMSs<sup>[30]</sup>. Specifically, DESs were proven to be significantly superior in terms of 1 year primary patency [80.0% *vs* 58.5%; number needed-to-treat (NNT) = 4.8], improvement of Rutherford-Becker class (79.0% *vs* 69.6%; NNT = 11.1), target lesion revascularization (TLR) events (9.9% *vs* 22.0%; NNT = 8.3), wound healing (76.8% *vs* 59.7%; 2; NNT = 5.9), and event-free survival (72.2% *vs* 57.3%; pooled; NNT = 6.7).

Recently, data about long-term outcomes of DES application in infrapopliteal arterial disease were published in the PADI study; the only multicenter RCT study with the long-awaited 5-year follow up data<sup>[31]</sup>. In three vascular centers in the Netherlands, Paclitaxel-eluting stents (PES) (TAXUS Liberté; Boston Scientific, United States) were randomized *vs* both PTA and bail-out bare metal stenting. A total of 137 patients with CLI were included in the study. At 5 years follow-up, amputation-free survival and event-free survival rates were significantly superior in the PES group (26.2% *vs* 15.3%,  $P = 0.041$  and 31.8% *vs* 20.4%,  $P = 0.043$ , respectively), while amputation rate was also lower for PES (19.3% *vs* 34.0%,  $P = 0.091$ ). Survival rates were similar between the two groups, while the duplex-assessed patency rate was still significantly higher in the PES group after four years follow-up (13.5% *vs* 32.6%,  $P = 0.031$ ). All randomized controlled trials for infrapopliteal drug-eluting technologies are analytically reported in [Table 2](#).

Long-term outcomes of DES placement in diabetic patients with CLI were evaluated in a clinical study that reported a 90.4% amputation-free interval at 5 and 10 years after the procedure, while survival rate was 55.5% and 36.2% at 5 and 10 years follow-up, respectively<sup>[5]</sup>. Half of the patients (50.3%) underwent a repeat revascularization procedure due to clinical relapse at 10 years follow-up. Nevertheless, long-term data beyond a 1 year follow-up of infrapopliteal DES remain scarce, and further multicenter RCTs are required to prove whether the use of this technology can improve long-term clinical outcomes. Specifically, in a recent meta-analysis of ten studies (eight RCTs and two cohort studies), which included 927 patients assigned to either DES (484) or control treatment (443), primary patency was significantly in favor of DES at one year. However, this advantage was not evident at 3 years follow-up. The authors concluded that more high-level, long-term data are needed<sup>[32]</sup>.

The safety and superiority of DES in short to medium length lesions has been demonstrated by level IA evidence. Nevertheless, the polymorphic nature of BTK disease, which usually presents with very long lesions (> 20 cm) and requires treatment of bifurcations and flexion points, such as the distal anterior tibial artery and the pedal arch, still has several controversies and thus requires further investigation. Specifically, the YUKON-BTX, DESTINY, and ACHILLES trials excluded patients with infrapopliteal trifurcation lesions, lesions in juxta-articular regions or lesions subject to external compression. In an attempt to address these issues, Spiliopoulos *et al*<sup>[33]</sup> reported the treatment outcomes of 39 patients with infrapopliteal bifurcation disease using techniques of coronary DES placement. The mean clinical follow-up period was  $47.56 \pm 14.8$  mo, while the mean angiographic follow-up period was  $17.56 \pm 12.5$  mo. The application of DES across the origin of tibial vessels was proven as a safe and effective method, and was associated with satisfactory long-term angiographic and clinical outcomes. Specifically, the overall amputation-free survival and TLR-free survival at 5 years were 84.3% and 58.0%, respectively. Two-vessel primary patency (no revascularization and no > 50% angiographic restenosis of either vessel forming the target bifurcation) was 77.2%, 47.5% and 33.9%, at 12, 24 and 36 mo follow-up, while primary patency of at least one of the treated vessels was 84.0%, 65.5% and 54.5%, at 12, 24 and 36 mo. In a study that was published the following year, similar results were reported of 54.5% two-vessel primary patency and 81.8% one-vessel primary patency at 6 mo<sup>[34]</sup>.

Another challenging issue commonly faced by medical providers is the deployment of DES in anatomic flexion points. Severe compression resulting in DES fracture at the distal third of the anterior tibial artery has been related to in-stent restenosis/reocclusion, as well as the inability to recanalize the lesion with either endovascular or surgical means. Therefore, stent placement in this area, as well as the pedal arteries, must be avoided<sup>[35]</sup>. The concern of treating infrapopliteal DES in-stent restenosis/reocclusion has also been addressed. In a retrospective analysis of 367 patients treated with infrapopliteal DES, 54 cases of DES occlusion were noted (re-

Table 2 Summary of randomized controlled trials investigating infrapopliteal drug-eluting technologies

	Trial	Study design	Patients	Follow-up	CLI	Lesion length (cm)	Primary endpoints
DES	Falkowski <i>et al</i> <sup>[25]</sup> , 2009	Single-centre BMS vs SES	50 patients (25 vs 25)	6 mo	32%	1.8 ± 2.4	LLL: SES 0.46 ± 0.72 vs BMS 1.70 ± 0.94 mm; <i>P</i> < 0.001 6-mo restenosis: SES 16% vs BMS 76%; <i>P</i> < 0.001 6-mo TLR: SES 12% vs BMS 14.56%; <i>P</i> < 0.05
	ACHILLES Scheinert <i>et al</i> <sup>[28]</sup> , 2012	Multicentre PTA vs SES	200 patients (101 vs 99)	1 yr	39%	both 2.7 ± 2.1	1-yr in-segment binary restenosis by quantitative angiography: SES 22.4% vs PTA 41.9%, <i>P</i> = 0.019
	Below Tepe <i>et al</i> <sup>[39]</sup> , 2010	Single-centre SES BMS vs PTA	63 limbs (4-arm trial; PTA pooled)	6 mo	100%	3.4 ± 0.3	6-mo restenosis: SES 9%, BMS 67% and PTA 75%
	YUKON-BTX Rastan <i>et al</i> <sup>[26]</sup> , 2012	Multicentre BMS vs non-polymer SES	161 patients (79 vs 82)	3 yr	46.60%	3.1 ± 0.9	Event-free survival: 65.8% SES vs 44.6% BMS; <i>P</i> = 0.02
	DESTINY Bosiers <i>et al</i> <sup>[27]</sup> , 2012	Multicentre BMS vs Everolimus stent	140 patients (66 vs 74)	1 yr	100%	1.7 ± 1.0	Angiographic primary patency: 85% DES vs 54% BMS; <i>P</i> = 0.0001
	PADI van Overhagen <i>et al</i> <sup>[31]</sup> , 2017	Multicentre PTA vs PES	137 patients (64 vs 73)	5 yr	100%	2.2 ± 2.0	Major amputation: DES 19.3% vs 34.0% PTA; <i>P</i> = 0.091 Amputation-free survival: DES 26.2% vs PTA 15.3%, <i>P</i> = 0.041 Event-free survival: 31.8% DES vs 20.4% PTA, <i>P</i> = 0.043
PCB	DEBATE-BTK Liistro <i>et al</i> <sup>[45]</sup> , 2013	Single-centre PTA vs PCB	132 patients (67 vs 65)	1 yr	100%	13.0 ± 8.0	
	IN.PACT DEEP Zeller <i>et al</i> <sup>[46]</sup> , 2014	Multicentre PTA vs PCB	358 patients (119 vs 239)	1 yr	99.70%	11.1 ± 9.0	TLR: 9.2% PCB vs 13.1% PTA; <i>P</i> = 0.291 LLL: 0.61 ± 0.78 mm DCB vs 0.62 ± 0.78 mm PTA; <i>P</i> = 0.950
	BIOLUX P-II Zeller <i>et al</i> <sup>[47]</sup> , 2015	Multicentre PTA vs PCB	72 patients (36 vs 36)	1 yr	77.80%	11.4 ± 8.7	6 mo patency loss: 17.1% PCB vs 26.1% PTA; <i>P</i> = 0.298
	IDEAS Siablis <i>et al</i> <sup>[52]</sup> , 2014	Single-centre PCB vs DES	50 patients (25 vs 25)	6 mo	100%	DES 12.7 ± 4.6 PCB 14.8 ± 5.6	Angiographic binary restenosis: DES 28% vs 57.9% in PCB; <i>P</i> = 0.0457

PTA: Percutaneous transluminal angioplasty; CLI: Critical limb ischemia; BMS: Bare metal stent; PCB: Paclitaxel-coated balloon; DES: Drug-eluting stent; PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent; TLR: Target lesion revascularization; CLI: Critical leg ischemia; LLL: Late lumen loss.

occlusion rate 11.4% within a 7 year study period), and the technical success of uneventful endovascular recanalization of DES occlusions was 90.7%. The authors concluded that intraluminal recanalization of infrapopliteal DES occlusions is safe and not technically demanding in the majority of cases<sup>[36]</sup>.

DES occlusions have been studied using optical coherence tomography (OCT), which reveals in-stent neoatherosclerosis. The concept that antiproliferative properties of DES alter endothelial formation and function has been discussed but never proven. However, it's thought that these properties result in increased lipid insudation and macrophage activation, which precipitate both atherosclerosis of the neointima and vascular lumen loss<sup>[37,38]</sup>. Furthermore, the stent's durable polymer matrix acts as a source of continuous vessel irritation that triggers a local inflammatory reaction and can precipitate in-stent thrombosis. In the field of coronary disease, the phenomenon of neoatherosclerosis following both bare metal or DES has been correlated with very late acute stent thrombosis, and many authors advocate the prescription of long-term dual antiplatelet therapy to avoid late thrombotic events. Nevertheless, late stent thrombosis has never been investigated following infrapopliteal BMS placement and, therefore, whether this phenomenon is as frequent as in cases of DES placement remains to be addressed<sup>[38]</sup>. However, according to current knowledge, the need for long-term antiplatelet coverage to reduce the risk of acute or late thrombosis after DES placement might pose some restrictions on the use of these devices<sup>[20]</sup>. Tepe *et al.*<sup>[39]</sup> have investigated the administration of GP IIb/IIIa blockade with sirolimus-eluting stents (SES), bare-metal stents and PTA. SES were correlated with significantly reduced restenosis, as the 6 mo restenosis rate was 9%, 67%, and 75%, respectively<sup>[39]</sup>.

The development of novel DES with biodegradable polymer technology aims to improve vessel re-endothelialization and further decrease complications<sup>[40]</sup>. Initial outcomes of the application of bioabsorbable DES in 33 patients suffering from either CLI (68.4%) or claudication due to infrapopliteal vessel disease were excellent. The primary patency rates were 96% and 84.6%, and freedom from clinically-driven target lesion revascularization rates were 96% at 12 and 24 mo, respectively. Although mean lesion length was only  $19.2 \pm 11.6$  mm, most likely due to the current availability of very short bioabsorbable DES, these results may soon lead to the implementation of this technology for CLI management<sup>[41]</sup>.

Furthermore, a new generation of polymer-free, dedicated BTK DES is presently under investigation. Specifically, the Alvimedica Cre8™ BTK is a polymer-free, balloon-expandable platform-loaded stent with the Amphilimus™ antirestenotic agent (Sirolimus + Fatty Acid). Furthermore, the Angiolite BTK sirolimus-eluting peripheral stent (iVascular, Spain) is another balloon-expandable device consisting of a cobalt chromium alloy coated with a mix of sirolimus and last generation biostable fluorinated acrylate polymer. Clinical results from these devices are pending.

The cost-effectiveness of DES should indeed be placed under scrutiny; the direct cost of DES is higher than that of a plain balloon, while most CLI patients suffer from long multilevel tibial vessel lesions that cannot be treated with the short DES presently available. However, despite the increased direct cost, DESs appear cost-effective for the management of long infrapopliteal lesions due to the significantly reduced number of re-interventions that are required<sup>[42]</sup>. It is generally accepted that the direct cost-reduction resulting from deeper market penetration, combined with the development of longer devices, would further improve DES cost-effectiveness.

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## DCB

DCBs were first introduced in coronary artery procedures, and the applications of this technology have subsequently been expanded with the goal of confronting the endovascular treatment obstacles of femoropopliteal artery atherosclerotic disease. Today, there is strong level IA evidence derived from multiple multicenter RCTs and their meta-analysis demonstrating that femoropopliteal angioplasty using DCB significantly reduces restenosis rates<sup>[43]</sup>. This new technology to inhibit neointimal hyperplasia by administering a single dose of an antiproliferative agent within the vessel wall without the use of a permanent metallic scaffold ("leave nothing behind" concept) is rather appealing for the infrapopliteal vascular bed. As previously discussed, the distal third of the anterior tibial artery is not readily amenable to stent placement due to the compressive forces of the osseous and musculotendinous tissues in this area that can lead to stent deformations and fractures, and ultimately decreased patency rates<sup>[35]</sup>. DCB could provide a valid solution to such limitations presented by the utilization of DES in this territory. Furthermore, long lesions can be easily treated with DCBs as the available lengths reach up to 150 mm. DCB combines balloon angioplasty with local, high-dose, cytotoxic drug delivery. The drug is coated on the balloon using special excipients, and is delivered within the arterial layers during balloon inflation to both achieve a uniform application to the vessel wall and promote the death of smooth muscle cells in the media. This allows for early intimal re-endothelialization and vessel healing<sup>[4]</sup>. The pharmaceutical agent that is most

commonly used in DCB is paclitaxel, owing to its lipophilic properties that can generate high local tissue concentrations. Although the application of DCB is less likely to compromise any future surgical revascularization procedures and can achieve a drug distribution to the target lesion that is not affected by malapposition, as in the case of DES, available evidence about the efficacy of DCB in the BTK territory has been conflicting<sup>[44-47]</sup>. Despite the initial promising results deriving from single-center studies, two industry-driven, large-scale, multicenter RCT studies failed to prove any clinical or angiographic superiority of DCB over plain PTA. Precisely, the IN.PACT DEEP study was a prospective, multicenter, RCT designed to undergo independent clinical event adjudication as well as angiographic and wound core laboratory analysis. The trial included 358 CLI patients that were randomized 2:1 to receive IN.PACT Amphirion™ paclitaxel-coated balloon (Medtronic, USA) or PTA. Despite randomization of a considerably large population, significant baseline differences were noted between the two arms in important parameters, such as mean lesion length (10.2 cm for DCB *vs* 12.9 cm for control,  $P = 0.002$ ), impaired inflow (40.7% for DCB *vs* 28.8% for control,  $P = 0.035$ ), and previous target limb revascularization (32.2% for *vs* 21.8% for control,  $P = 0.047$ ). No statistically significant differences were detected in the primary efficacy outcomes of clinically-driven target lesion revascularization (CD-TLR: 9.2% PCB *vs* 13.1% control,  $P = 0.291$ ) and late lumen loss (LLL:  $0.61 \pm 0.78$  mm for PCB *vs*  $0.62 \pm 0.78$  mm for control,  $P = 0.950$ ) at 1 year follow-up. The composite primary safety endpoint (6 mo all-cause mortality, major amputation, and CD-TLR) was similar between PCB (17.7%) and control (15.8%), and the non-inferiority hypothesis was met ( $P = 0.021$ ). However, major amputations at 12 mo were more than double in the PCB arm and on the verge of statistical significance (8.8% *vs* 3.6%,  $P = 0.080$ )<sup>[46]</sup>. After safety issues were raised, the study was interrupted, and the Amphirion™ paclitaxel-coated balloon was withdrawn from the market. It has been suggested that distal embolization due to loss of balloon coating during insertion may have contributed to these poor outcomes<sup>[48]</sup>. The company is currently recruiting patients in an RCT to investigate a novel PCB for BTK use<sup>[49]</sup>. In the BIOLUX P-II multicenter RCT study, 72 patients were randomized in a 1:1 ratio to undergo treatment with either the Paseo-18 Lux DCB (Biotronik AG, Switzerland) or Paseo-18 PTA. In this trial, the primary endpoint of 6 mo patency loss was not significantly inferior in the DCB group *vs* plain balloon angioplasty (17.1% *vs* 26.1%, respectively,  $P = 0.298$ ), while major amputations were also similar (3.3% *vs* 5.6% at 12 mo, respectively). The 30 d composite primary safety endpoint (all-cause mortality, target extremity major amputation, target lesion thrombosis, and target vessel revascularization) was marginally superior in the DCB group (0% PCB *vs* 8.3% PTA,  $P = 0.239$ )<sup>[47]</sup>. The authors would like to comment that the patency rates of plain balloon angioplasty in both studies were unexpectedly high, taking into consideration reported data from previous infrapopliteal plain balloon angioplasty studies, a fact that potentially contributed to the inability to prove the anti-restenotic effect of PCB. The reason for this discrepancy remains to be clarified. Outcomes from a new generation of DCB are also pending. Lutonix® 014 DCB (paclitaxel dose 2  $\mu\text{g}/\text{mm}^2$ ) has been tested in a large-scale multicenter, single-arm registry, which included 314 patients from 26 sites and 12 countries. Patients suffered from either CLI or claudication due to infrapopliteal disease. Interim 6 mo results demonstrated an excellent safety profile, as freedom from major adverse limb events and perioperative death was 98.6% at 30 d and 96.0% at 6 mo, while freedom from TLR was 87.9% at 6 mo<sup>[50]</sup>. The final 24 mo results are expected in late 2019. The Ranger™ (Boston Scientific Corporation, United States), a new-generation 2  $\mu\text{g}/\text{mm}^2$  DCB, is also under investigation. The single-center, open-label prospective trial sponsored by Boston Scientific has enrolled 30 CLI patients with infrapopliteal disease treated with the Ranger DCB. The study's efficacy primary outcome measures will be primary patency at 6 mo follow-up (no stenosis > 50% of the target lesion measured by quantitative vascular angiography). The safety outcome measurement will be the number of deaths and major amputations at 6 mo follow-up. The estimated study completion date is November 2018<sup>[51]</sup>.

## DES VS DCB FOR INFRAPOPLITEAL ARTERIAL DISEASE

In 2014, Siablis *et al*<sup>[52]</sup> sought to compare the efficacy of the two emerging drug-eluting technologies for long infrapopliteal lesions. The authors randomized 50 CLI patients to receive DES or DCB infrapopliteal treatment<sup>[52]</sup>. Among the inclusion criteria was a minimum lesion length of 70 mm. The primary endpoint of 6 mo angiographic > 50% restenosis, adjudicated by quantitative vessel analysis, was significantly less in the DES group (28% *vs* 57.9%,  $P = 0.0457$ ). Nonetheless, LLL, TLR

and major amputation rates at 6 mo follow-up were similar between the two study groups. This is the only study directly comparing infrapopliteal DES *vs* DCB that reported that DCBs are associated with increased vessel restenosis at 6 mo, even though LLL was similar between the two groups. The authors can assume that reduced binary restenosis following DES deployment was due to a significantly superior initial luminal gain compared to DCB angioplasty. In addition, they can also assume that for small-vessel disease, maximizing the initial luminal gain could lead to less short-term binary restenosis. Nevertheless, better vessel preparation using atherectomy devices or less traumatic semi-compliant balloon catheters could also improve infrapopliteal DCB angioplasty outcomes. Indeed, the combination of DCB use with debulking atherectomy devices for the management of long, heavily calcified femoropopliteal de novo or restenotic lesions is supported by an increasing level of evidence. Orbital and directional atherectomy have been employed to remove occlusive intimal or neointimal tissue, allowing DCB to act directly on the vessel wall<sup>[53]</sup>. Moreover, in a recent Bayesian network meta-analysis by Katsanos *et al*<sup>[54]</sup>, data from RCTs investigating all endovascular treatment options for BTK arterial disease were elaborated. In total, 16 RCTs with 1,805 patients were analyzed. Median follow-up was 1 year. The authors created a network of comparisons between infrapopliteal DES, DCB, plain balloon angioplasty and BMS, and calculated the cumulative rank probabilities to provide hierarchies of these treatments. Outcomes were found to be stable upon sensitivity and meta-regression analyses. No significant publication bias or inconsistency was detected. DESs were found to significantly reduce restenosis, amputations and revascularization procedures compared to BMSs and plain balloon angioplasty. Specifically, DES reduced restenosis compared with BMS [OR 0.26, 95% Credible Interval (CrI): 0.12 to 0.51] and plain balloon angioplasty (Odds Ratio (OR) 0.22, 95%CrI: 0.11 to 0.45), and also reduced TLR compared with plain balloon angioplasty (OR 0.41, 95%CrI: 0.22 to 0.75) and BMS (OR 0.26, 95%CrI: 0.15 to 0.45) (quality of evidence high). DCBs reduced TLR compared with plain balloon angioplasty (OR 0.55, 95%CrI: 0.34 to 0.90) and BMS (OR 0.35, 95%CrI: 0.18 to 0.67) (quality of evidence low to moderate), while plain balloon angioplasty resulted in significantly less TLR than BMS (OR 0.63, 95%CrI: 0.40 to 0.99) (level of evidence high). Furthermore, DES significantly reduced limb amputations compared with plain balloon angioplasty (OR 0.58, 95%CrI: 0.35 to 0.96), DCB (OR 0.51, 95%CrI: 0.26 to 0.98), or BMS (OR 0.38, 95%CrI: 0.19 to 0.72) (quality of evidence moderate to high), and improved wound healing compared with plain balloon angioplasty (OR 2.02, 95%CrI: 1.01 to 4.07) or BMS (OR 3.45, 95%CrI: 1.41 to 8.73) (quality of evidence high). The abovementioned high level of evidence establishes DES as the dominant endovascular treatment modality for BTK disease, although these outcomes mainly relate to short-to-medium length lesions and short-to-midterm follow-up.

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## DRUG INFUSION CATHETERS

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New elution technologies for BTK treatment include catheters that can deliver therapeutic agents directly to the vessel wall, eliminating drug loss in the circulation. The Occlusion Perfusion Catheter (Advanced Catheter Therapies, Chattanooga, TN) is a universal delivery catheter capable of delivering paclitaxel to the media by forming a treatment chamber between two occlusion balloons. Results from a small multicenter study are promising<sup>[55]</sup>. Moreover, the infusion of dexamethasone in the adventitia of infrapopliteal arteries is also being studied. The LIMBO-PTA prospective, multicenter RCT is currently recruiting CLI patients (up to 120 participants) in up to 30 sites throughout Europe and the US in order to document the effects of adventitial delivery of dexamethasone via the Bullfrog Micro-Infusion Device (Mercator MedSystems, Inc., United States) after balloon angioplasty of infrapopliteal lesions<sup>[56]</sup>. Patients will be randomized 1:1 to receive either the active treatment or control therapy. The study is currently recruiting patients, and the estimated study completion date is February 2020.

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## CONCLUSION

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Level IA evidence supports the use of infrapopliteal DES for short-to-medium length lesions. New developments in DES, such as bioabsorbable, polymer-free or even longer self-expanding DES, could maximize outcomes. Large trials to prove their superiority over other endovascular technologies in longer lesions are required. DCBs are a very appealing endovascular solution for infrapopliteal artery disease due to their inherent features, which enable metal-free inhibition of vessel restenosis.

However, data to prove the superiority of DCBs over plain balloon angioplasty are scarce. In a single-institution randomized comparison with DES in long infrapopliteal lesions, DES resulted in significantly less 6 mo binary restenosis. Multicenter RCTs and long-term results from large-scale registries are awaited in order to justify the use of DCBs in BTK disease. New-generation drug elution and drug infusion devices are also under investigation.

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