Name of the journal: World Journal of Cardiology

Manuscript ID: 02664735

Manuscript Type: Minireview

Current evidence of drug-elution therapy for infrapopliteal arterial disease

Spiliopoulos et al. Infrapopliteal drug-elution devices

Authors: Stavros Spiliopoulos, Nikiforos Vasiniotis Kamarinos, Elias Brountzos

2nd Radiology Department, Interventional Radiology Unit, University of Athens, Attikon University General Hospital, Athens, Greece.

Author contributions: Spiliopoulos S conceived the review and made critical revisions to its content. Nikiforos Vasiniotis Kamarinos drafted the manuscript and made critical revisions to its content. Brountzos E drafted the manuscript and made critical revisions to its content. All authors approved the final version of the article.

Supported in part by: ‘no specific source of funding’

Conflict of interest statement: ‘The authors have no conflict of interest to declare.’

Correspondence to:

Stavros Spiliopoulos, MD, PhD, EBIR

Assistant Professor of Interventional Radiology

Address:

2nd Department of Radiology,

Division of Interventional Radiology

National and Kapodistrian University of Athens, School of Medicine,

Attikon University General Hospital, Athens, Greece

Tel: +306937403468 (mobile)

+302105831832 (office)

email: stavspiliop@med.uoa.gr

stavspiliop@upatras.gr

Abstract

The advent of new and sophisticated endovascular devices such as the drug-eluting stents (DES) and the drug-coated balloons (DCB), both of which provide targeted drug delivery to the affected vessels, made possible to address the reparative cascade of arterial wall injury following balloon angioplasty that results in restenosis. DES were first used for the treatment of infrapopliteal lesions almost 20 years ago, while more recently, DCB technology is being investigated in order to improve outcomes of endovascular below-the-knee arterial procedures, avoiding the use of a metallic scaffold. Today, level IA evidence supports the use of infrapopliteal DES for short- to medium length lesions, although robust evidence to justify 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.

Keywords: Drug-elution therapy; Infrapopliteal arterial disease, Current evidence

Core tip: Currently available level IA evidence justify the use of infrapopliteal DES for short to medium length lesions in selected patients with specific anatomical criteria. The role of infrapopliteal DCBs remains to be determined.

Spiliopoulos S, Vasiniotis Kamarinos N, Brountzos E. Current evidence of drug-elution therapy for infrapopliteal arterial disease.

**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)[1]. In the western population, the incidence of infrapopliteal disease is strongly correlated with the prevalence of diabetes mellitus and is continuously rising due to the increase in life expectancy in developed countries[2]. 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 revascularized promptly[3]. CLI is considered to be responsible for approximately 90% of the major amputations performed worldwide and is a significant cause of morbidity and mortality[2,3]. In diabetic patients, CLI represents a medical emergency as the concomitant foot architectural changes and potential infections can rapidly compromise limb salvage[4]. Besides, the long vessel occlusions combined with poor distal runoff, prevalent in diabetic CLI patients, represent a considerable challenge for healthcare specialists[5].

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

Plain balloon angioplasty was the primary endovascular therapy that utilized in the infrapopliteal territory. Although it seemed effective in the short-term, post-angioplasty elastic vessel recoil and flow-limiting dissection contributed to reocclusion and relapse of ischemic symptoms[13]. Despite the fact that balloon angioplasty may be repeated, each procedure involves an inherent risk of technical failure and yields additional cost[4]. Attempting to address this issue, Dorros et al. pioneered in placing the first infrapopliteal bare metal stent (BMS) 25 years ago[14]. However, BMS application has been associated with poor outcomes in the mid-term due to the phenomenon of in-stent restenosis[15]. The constant irritation of the vessel wall by the metal stent mesh results in inflammation, intimal hyperplasia, negative vessel remodeling and ultimately reocclusion[16,17]. Occlusion rates are high; half of the BMS become occluded within the first year and can lead to major amputation[18,19]. 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.

The advent of newer and more sophisticated endovascular devices such as the drug-eluting stents (DES) and the drug-coated balloons (DCB), both of which provide targeted drug delivery to the affected vessel, made possible to address the reparative cascade of vessel wall injury that results in restenosis. Below the knee arteries share many characteristics of 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.

Drug-Eluting Stents (DES)

Drug-eluting stents were introduced in clinical practice by interventional cardiologists and demonstrated favorable outcomes regarding late lumen loss and rate of repeat revascularization procedures[20]. The comparable size of tibial to coronary arteries and the superior efficacy of these stents compared to bare metal stents, led to the first clinical application of DES in the infrapopliteal arteries, with a view to inhibit restenosis and prolong uninterrupted blood supply to the foot[4]. The concept of DES technology is based on the coverage of the stent’s strut with a polymer matrix such as silicone, polyethylene vinyl alcohol and cellulose ester, saturated with a specific drug. Some DES are polymer-free, and the drug is applied directly on the metallic strut[21]. Drug-eluting stents inhibit neointimal hyperplasia and smooth muscle cell proliferation by releasing the incorporated drug to the vessel wall over a standard period of time. The pharmaceutical agents that are most commonly used are the 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 the cell cycle in the M phase, and thus leading to cellular death[18]. The first clinical applications of DES in infrapopliteal arteries for the treatment of CLI demonstrated encouraging mid-term results[18,21,23-25].

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

Precisely, in the ACHILLES trial, 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, USA) 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 at 12 months DES 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[28]. In a post hoc analysis of this trial, Katsanos et al. 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 as to avoid superinfection and subsequently limb loss[29]. 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, USA). 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 months both primary patency (85% vs. 54%; p=0.0001) and re-intervention (85% vs. 54%; p=0.0001) rates were significantly improved with the use of DES. Moreover, the Xience V DES significantly reduced both mean in-stent stenosis (21% ± 21% vs. 47% ± 27%; p <0 .0001) and mean in-stent late lumen loss (LLL) (0.78 ± 0.63 vs. 1.41 ± 0.89 mm; p= 0.001)[27]. Finally, the YUKON-BTK multicenter, double-blind RCT, randomized 161 patients suffering (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-month 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[26].

Meta-analysis of the above three multicenter RCTs confirmed these findings and demonstrated the superiority of DES over plain balloon angioplasty and bare metal stents[30]. Specifically, DES were proved 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 revescularization (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[31]. Paclitaxel-eluting stents (TAXUS Liberte; Boston Scientific, USA) were randomized versus PTA and bail-out bare metal stenting, in three vascular centers in the Netherlands. In total 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 paclitaxel-eluting stent (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 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[5]. 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 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 10 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, but this advantage was not shown at 3-years follow up. The authors concluded that more high-level, long-term, data are needed[32].

Despite the fact that the safety and superiority of DES in short to medium length lesions has been demonstrated by level IA evidence, 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, certainly requires further investigation, as several controversies remain. Specifically, the YUKON- BTX, the DESTINY, and the 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. reported the treatment outcomes of 39 patients with infrapopliteal bifurcation disease using techniques of coronary DES placement[33]. The mean clinical follow-up period was 47.56 ± 14.8 months, while the mean angiographic follow-up period was 17.56 ± 12.5 months. The application of DES across the origin of tibial vessels was proven 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 were 84.3%, and 58.0%respectively, at 5- years. 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 months 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 months. In a study that was published in the following year, similar results of 54.5% two-vessel primary patency and 81.8% one-vessel primary patency at 6- months, were reported[34].

Another challenging issue, commonly faced by medical providers, is the deployment of DES in anatomic flexion points. Severe compression resulting to DES fracture at the distal third of the anterior tibial artery has been related with in-stent restenosis/reocclusion, as well as 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[35]. 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-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 vast majority of the cases[36].

DES occlusions have been studied by means of optical coherence tomography (OCT) which revealed in-stent neoatherosclerosis. It has been discussed, but still not proven, that the antiproliferative properties of DES alter endothelial formation and function, resulting in increased lipid insudation and macrophage activation that precipitate atherosclerosis of the neointima and vascular lumen loss[37,38]. 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 drug-eluting stents 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 bare metal stent placement and therefore whether this phenomenon is as frequent as in cases of DES placement remains to be addressed.[38] 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[20]. Tepe et al. 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-month restenosis rate was 9%, 67%, and 75% respectively[39].

The development of novel DES with biodegradable polymer technology aims to improve vessel re-endothelialization and further decrease complications[40]. 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, with primary patency rates of 96% and 84.6% and freedom from clinically driven target lesion revascularization rates of 96% at 12 and 24 months, respectively. Even though mean lesion length was only 19.2 ± 11.6 mm, most likely due to the current availability of very short bioabsorbable DES, these results may lead soon to the implementation of this technology for the management of CLI[41].

Furthermore, a new generation of polymer-free, dedicated BTK drug-eluting stents is presently under investigation. Specifically, the Alvimedica Cre8TM BTK , is a polymer-free, balloon-expandable platform-loaded stent with the AmphilimusTM antirestenotic agent (Sirolimus + Fatty Acid), while the Angiolite BTK sirolimus-eluting peripheral stent (iVascular, Spain) is another balloon-expandable device consisted of a cobalt chromium alloy that is coated with a mix of sirolimus and last generation of biostable fluorinated acrylate polymer. Clinical results from these devices are awaited.

The cost-effectiveness of drug-eluting stents 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 which cannot be treated with the short drug-eluting stents that are presently readily available. However, despite the increased direct cost, DES appear cost-effective for the management of long infrapopliteal lesions, due to the significantly reduced number of re-interventions that are required[42]. It is generally accepted that the direct cost reduction resulting from deeper market penetration, combined with the development of longer devices, would further increase DES cost-effectiveness.

Drug-Coated Balloons (DCB)

Drug-coated balloons have been first introduced in coronary artery procedures, and subsequently, the applications of this technology have been expanded with a view to confronting the endovascular treatment obstacles of femoropopliteal artery atherosclerotic disease. Today there is strong level IA evidence deriving from multiple multicenter RCTs and their meta-analysis, demonstrating that femoropopliteal angioplasty using drug-coated balloons reduces restenosis rates significantly[43]. This new technology that targets 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 consequently to decreased patency rates[35]. Drug-coated balloons could provide with 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 150mm. Drug-coated balloons combine 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 achieving a uniform application to the vessel wall and leading the smooth muscle cells of the media to cellular death; this allows for early intimal re-endothelialization and vessel healing[4]. The pharmaceutical agent that is most commonly used in drug-coated balloons is paclitaxel owing to its lipophilic properties that can generate high local tissue concentrations. Although the application of drug-coated balloons 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[44-47].

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 AmphirionTM paclitaxel-coated balloon (Medtronic, USA) or PTA. Despite randomization in a considerably large population, significant baseline differences were noted between the two arms in substantial parameters such 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 versus 13.1% control; p= 0.291) and late lumen loss (LLL: 0.61 ± 0.78 mm for PCB versus 0.62 ± 0.78 mm for control; p= 0.950) at 1 year follow up. The composite primary safety endpoint (6 months 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 months were more than double in the PCB arm and on the verge of statistical significance (8.8% vs. 3.6%; p = 0.080)[46]. After safety issues were raised, the study was interrupted, and the AmphirionTM paclitaxel-coated balloon was withdrawn from the market. It has been suggested that distal embolization due to loss of balloon’s coating during insertion may have contributed to these poor outcomes[48]. The company is currently recruiting patients in an RCT investigating a novel PCB for BTK use[49]. In the BIOLUX P-II multicenter, RCT study 72 patients were randomized in a 1:1 ratio, to undergo treatment with either the Passeo-18 Lux DCB (Biotronik AG, Switzerland) or Passeo-18 PTA. Again in this trial, the primary endpoint of 6-month patency loss was not significantly inferior in the DCB group versus plain balloon angioplasty (17.1% vs. 26.1%, respectively; p = 0.298), while major amputations were also similar (3.3% versus 5.6% at 12 months, respectively). The 30-days 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)[47]. The authors would like to comment that in both studies the patency rates of plain balloon angioplasty were unexpectedly high, taking into consideration reported data from previous infrapopliteal plain balloon angioplasty studies, a fact that has possibly 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 awaited. The Lutonix® 014 DCB (paclitaxel dose 2µg/mm2) 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-month results demonstrated an excellent safety profile, as freedom from major adverse limb events and perioperative death was 98.6% at 30 days and 96.0% at 6- months, while freedom from TLR was 87.9% at 6- months[50]. Final 24-months results are awaited in late 2019. The RangerTM (Boston Scientific Corporation, USA), a new-generation 2 µg/mm2 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- months follow up (no stenosis >50% of the target lesion measured by quantitative vascular angiography). The safety outcome measure will be the number of deaths and major amputations at 6- months follow up. The estimated study completion time is November 2018[51].

DES vs DCB for infrapopliteal arterial disease

In 2014, Siablis et al. sought to compare the efficacy of the two emerging drug-eluting technologies in long infrapopliteal lesions. The authors randomized 50 CLI patients to receive DES or DCB infrapopliteal treatment[52]. Among the inclusion criteria was a minimum lesion length of 70 mm. The primary endpoint of 6-months 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- months follow up were similar between the two study groups. This is the only study directly comparing infrapopliteal DES versus DCB that reported that DCB are associated with increased vessel restenosis at 6- months, 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 and that for small-vessel disease, maximizing the initial luminal gain could lead to less short-term binary restenosis. Having said that, better vessel preparation, using atherectomy devices or less traumatic semi-compliant balloon catheters could also improve outcomes of infrapopliteal DCB angioplasty. 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 as well as directional atherectomy has been employed to remove the occlusive intimal or neointimal tissue, allowing drug-coated balloons to act straight to the vessel wall.[53] Moreover, in a recent Bayesian network meta-analysis by Katsanos et al. data from RCTs which investigated all endovascular treatment options for BTK arterial disease were elaborated[54]. In total 16 RCTs with 1805 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 stable on sensitivity and meta-regression analyses. No significant publication bias or inconsistency was detected. DES were found to significantly reduce restenosis, amputations and revascularization procedures compared to bare metal stents and plain balloon angioplasty. Specifically, DES reduced restenosis compared with BMS (OR 0.26, 95% CrI 0.12 to 0.51) and plain balloon angioplasty (Odds Ratio (OR) 0.22, 95% Credible Interval (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 data 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-mid-term follow-up.

Drug Infusion Catheters

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 multi-center study are promising [55]. 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 in Europe and in the US, to document the effects of adventitial delivery of dexamethasone via the Bullfrog Micro-Infusion Device(Mercator MedSystems, Inc. USA) after balloon angioplasty of infrapopliteal lesions[56]. 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.

Conclusion

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, while in a single-institution randomized comparison with DES in long infrapopliteal lesions, DES resulted in significantly less 6-month 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.References

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Table 1 Assessment of the risk of amputation: the WIFI classification[6,7]

| Component | Score | Description | | |
| --- | --- | --- | --- | --- |
| Wound (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 | | |
| Ischemia (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 |
| Foot Infection (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 | | |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| Table 2. Summary of randomized controlled trials investigating infrapopliteal drug-eluting technologies | | | | | | | |
| DES | Trial | Study design | Patients | Follow-up | CLI | Lesion  Length  (cm) | Primary endpoints |
| Falkowski A,  et al. 2009[25] | Single-center  BMS vs SES | 50 patients  (25 vs 25) | 6 months | 32% | 1.8±2.4 | LLL:SES 0.46 ±0.72 vs. BMS 1.70 ± 0.94mm; p<0.001  6-month restenosis: SES 16% vs. BMS 76%; p< 0.001  6-month TLR: SES 12% vs BMS.14 56%; p<0.05 |
| ACHILLES Scheinert D, et al. 2012[28] | Multicenter  PTA vs SES | 200 patients  (101 vs 99) | 1 year | 39% | both  2.7±2.1 | 1-year in-segment binary restenosis by quantitative angiography: SES 22.4% vs. PTA 41.9%, p= 0.019 |
| BELOW  Tepe G, et al. 2010[39] | Single-center  SES BMS vs PTA | 63 limbs  (4-arm trial; PTA pooled) | 6 months | 100% | 3.4±0.3 | 6-months restenosis:  SES 9%, BMS 67% and PTA 75% |
| YUKON-BTX Rastan A, et al. 2012[26] | Multicenter  BMS vs non-polymer  SES | 161 patients  (79 vs 82) | 3 years | 46.6% | 3.1±0.9 | Event-free survival: 65.8% SES vs.44.6% BMS; p= 0.02 |
| DESTINY Bosiers M, et al. 2012[27] | Multicenter  BMS vs Everolimus stent | 140 patients  (66 vs 74) | 1 year | 100% | 1.7±1.0 | Angiographic primary patency: 85% DES vs.54% BMS; p=o .0001 |
| PADI van Overhagen H, et al. 2017[31] | Multicenter  PTA vs PES | 137 patients  (64 vs 73) | 5 years | 100% | 2.2±2.0 | Major amputation: DES 19.3% vs.34.0%  PTA; p=0.091  Amputation-free survival: DES 26.2% vs. PTA  15.3%, p=0.041  Event-free survival: 31.8% DES vs 20.4% PTA, p=0.043 |
| PCB | DEBATE-BTK Liistro F, et al. 2013 [45] | Single-center  PTA vs PCB | 132 patients  (67 vs 65) | 1 year | 100% | 13.0±8.0 |  |
| IN.PACT DEEP  Zeller T, et al. 2014[46] | Multicenter  PTA vs PCB | 358 patients  (119 vs 239) | 1 year | 99.7% | 11.1±9.0 | TLR: 9.2% PCB vs.13.1% PTA; p=0.291  LLL: 0.61±0.78mm DCB vs. 0.62±0.78mm PTA;  p= 0.950 |
| BIOLUX P-II Zeller T, et al. 2015[47] | Multicenter  PTA vs PCB | 72 patients  (36 vs 36) | 1 year | 77.8% | 11.4±8.7 | 6 months patency loss: 17.1% PCB vs. 26.1% PTA; p = 0.298 |
| IDEAS  Siablis D et. al 2014[52] | Single-center  PCB vs DES | 50 patients  (25 vs. 25) | 6 months | 100% | DES 12.7±4.6  PCB 14.8± 5.6 | Angiographic binary restenosis  DES 28% vs.57.9% in PCB p= 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 men loss | | | | | | | |