Drug-Eluting Balloons and Drug-Eluting Stents in the Treatment of Peripheral Vascular Disease

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Abstract

Keywords

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- ▶ atherosclerosis
- ▶ paclitaxel
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In the last 20 years, peripheral artery disease (PAD) has been increasingly recognized as a significant cause of morbidity and mortality in the United States. The endovascular treatment of PAD has seen a marked rise as minimally invasive techniques and devices have been refined. Two newer devices, drug-eluting stents and drug-eluting balloons, are on the forefront of the battle against limb loss from PAD. This review focuses on the data backing the use of drug-eluting technologies for use in the peripheral arterial system.

Objectives: Upon completion of this article, the reader will be able to describe the current data for the use of drug-coated balloons and drug-eluting stents in infrainguinal peripheral artery intervention.

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Percutaneous transluminal angioplasty (PTA) has long been a treatment strategy for the management of symptomatic claudication and critical limb ischemia (CLI). PTA alone has a well-established initial success rate, but is plagued by a high incidence of short-term restenosis limiting its use.¹ Bare metal stents (BMSs) have also been described for use in the peripheral arteries with superior patency rates as compared to PTA; however, bare metal stenting is plagued with a 30 to

50% restenosis rate in the first year due to neointimal hyperplasia.² In addition to in-stent restenosis (ISR), thrombosis and stent fracture are among the commonly seen long-term complications in indwelling stents.^{3,4} In order to mitigate the limitations of both PTA and bare metal stenting, both drug-coated balloons (DCBs) and drug-eluting stents (DESs) were developed with the hopes of generating long-term patency without the common drawbacks of early treatments. The physiology and known data behind the use of DCB and DES in the peripheral circulation will be discussed.

Drug-Coated Balloons

Physiology

Angioplasty has several mechanisms for increasing the luminal diameter of a target vessel. Angioplasty invokes luminal gain by stretching or rupture of plaque and connective fibers in the intima and media, compression of plaque and thrombus, compression of the medial layers, redistribution of plaque or thrombus at the inner surface of an artery, and overstretching of the artery.⁵ Accordingly, restenosis of a target vessel is also the result of a variety of mechanical and biological processes that start immediately following the initial insult by the angioplasty balloon. Early vessel recoil, negative vascular remodeling, and neointimal hyperplasia all play significant roles in the pathophysiology

of restenosis.^{6,7} DCBs aim to control late restenosis by inhibiting neointimal growth by the delivery of antiproliferative material into the vessel wall.

The concept of delivering biologically active materials into a vessel wall during single treatment angioplasty has been around since the late 1980s.^{8,9} The ideal antiproliferative agent for DCB use would be expected to have certain biologic qualities. High lipophilicity is required to ensure quick delivery into target tissue while also maintaining retention in the vessel wall for longer-term antiproliferative action.⁷ Additionally, the agent must have minimal or no toxicity from drug delivery in the local vessel wall, downstream vascular bed, or in the systemic circulation. From a manufacturing standpoint, the chosen agent must create a uniform drug distribution during delivery, have a relatively stable configuration during transport and handling, have a reasonable shelf life, and demonstrate acceptable loss of drug on transition of the delivery device through the vasculature to the desired vascular bed. The practical use of coated balloon angioplasty has only recently gained a foothold as a mainstream treatment strategy as early studies showed a significant variability in site-specific uptake and rapid washout of delivered drug, which limited practical use of these materials.⁹

The majority of the current literature supporting antiproliferative local drug delivery on a balloon-mounted system surrounds the use of paclitaxel. Paclitaxel exerts its effects by binding to the beta subunit of tubulin, resulting in the cessation of microtubular function and the inhibition of cellular division.⁷ Paclitaxel is highly lipophilic, which limits its ability to transfer into the vessel wall. As a result, paclitaxel is paired with a co-drug “excipient” spacer to facilitate absorption. Several different DCBs have been developed which are largely differentiated by two factors: the particular excipient molecule bound to the drug and the concentration of paclitaxel.

The exact mechanism by which a single administration of paclitaxel inhibits long-term restenosis is still a matter of some debate. In all current iterations of DCBs, the drug delivered into the vessel wall represents a small fraction of the total dose loaded onto the balloon. In non-atherosclerotic pig models, only 10 to 15% of the initial loaded dose on the balloon is transferred into the target artery, with the remainder lost into the bloodstream either after or during balloon inflation.¹⁰ In addition, the same study demonstrated that after 72 hours the tissue concentration of paclitaxel in the target artery drops to less than 75% of its initial delivered value. After this initial washout period, it is suspected that prolonged tissue retention is attributable for the longer term biological effects of the drug.¹¹

While many DCBs exist in the current market, only three are available in the United States. IN.PACT (Medtronic, Minneapolis, MN) and Lutonix (Bard, Covington, GA) were approved by the Food and Drug Administration in 2014 for use in the peripheral vascular system with Stellarex (Spectranetics, Colorado Springs, CO) having gained approval in 2017.^{12,13} The main differences in these balloons lie within their excipient molecules, nature of coating, and concentration of drug. The IN.PACT DCB has a crystalline matrix of

paclitaxel with urea as the main excipient, with a paclitaxel concentration of 3.5 µg/mm². The crystalline coating of the IN.PACT balloon results in a higher degree of drug transfer to the vessel at the cost of a larger quantity of particulate being released into the systemic circulation with balloon inflation.¹⁴ In contrast, the Lutonix DCB has an amorphous matrix of paclitaxel with a polysorbate/sorbitol excipient and a concentration of 2 µg/mm². In theory, the amorphous coating offers the advantage of more uniform distribution of drug and a lesser degree of particulate released at the cost of reduced drug transfer to the target vessel. The newly approved Stellarex DCB asserts as an “optimal mix” ratio of amorphous and crystalline paclitaxel coating with a polyethylene glycol excipient at a concentration of 2 µg/mm². This reported “next-generation” DCB offers the advantages of improved tissue penetration seen with crystalline coatings with a smaller degree of particulate released into the systemic circulation.¹⁵

Supportive Data for Drug-Coated Balloons

The earliest use of DCBs in the systemic circulation was in the coronary circulation. Two early published randomized trials in 2008 showed efficacy of DCB in the peripheral circulation with a suggestion of a statistical advantage over PTA in the treatment of symptomatic femoral-popliteal (FP) atherosclerotic plaque.^{16,17} The PACIFIER trial was the first multicenter randomized control trial to be published on DCB versus PTA in the peripheral circulation. The primary endpoint of this study, late lumen loss (LLL) by angiography, was statistically significant between the PTA and DCB groups favoring the latter. Additionally, the PACIFIER trial also significantly favored DCB on a composite of death, amputation, and the need for target lesion revascularization (TLR) at 1 year (7.1 vs. 34.9%).¹⁸ The success of the IN.PACT balloon in the PACIFIER trial led to the further examination under global registries to determine large-scale feasibility and success of DCB use.

The largest and longest evaluation of DCB use in the FP system is the ongoing IN.PACT SFA trial. Despite the early success demonstrated by the PACIFIER trial, the trial was terminated at 12 months. The long-term efficacy of DCBs for use in the peripheral circulation therefore necessitated further study with comparison among different delivery systems. A total of 331 Rutherford classes 2- to 4-matched subjects in the IN.PACT SFA trial were randomized in a 2:1 fashion between DCB and PTA. Through 36 months of follow-up, the 12-, 24-, and 36-month rates of primary patency for DCB (87.5, 78.9, and 69.5%) and PTA (55.8, 50.1, and 45.1%) were statistically significant. Additionally, incidence of clinically driven target lesion recurrence (CD-TLR) was also statistically significant in favor of DCB (2.4, 9.1, and 15.2%) from PTA (20.6, 28.3, and 31.1%). One, 2, and 3 years of mortality data also favored DCB over PTA.¹⁹

The LEVANT II study examined the use of the Lutonix DCB for use in the femoral and popliteal arteries in a global, prospective, single-blind, randomized trial among Rutherford class 2 to 4 patients. The trial included 24-month data utilizing the Lutonix DCB to examine efficacy of conventional PTA

versus the Lutonix DCB. At 1 year, the study demonstrated statistically significant improvement in primary patency by Doppler in patients treated with the Lutonix DCB compared to standard PTA (73.5 vs. 58.8%; $p < 0.001$).²⁰ At 24 months, the rate of primary patency among patients treated with the Lutonix DCB remained superior to standard PTA (58.6 vs. 53%; $p = 0.05$) as reported at the Society of Vascular Surgery National meeting in 2015. The Lutonix-SFA global registry, however, had better 24-month outcomes in a globally selected population of 691 Rutherford 4 patients across 38 centers in 10 countries. Freedom from target lesion restenosis as defined by clinical parameters (CD-TLR) was 93.4%/89.3% for the overall population, 93.2%/88.2% for long lesions up to 500 mm, and 90.7%/84.6% for ISR at 12/24 months.²¹ Notably, the endpoints for this study were clinical (not Doppler, unlike LEVANT 2) based on ankle-brachial index and symptoms. This may account for the discrepancy in success rates between the two studies utilizing the same device.

The next-generation Stellarex balloon has also been recently studied, although the data are currently limited to 12-month follow-up. The ILLUMENATE trial was similarly structured in a 3:1 comparison of Stellarex DCB to PTA for FP lesions in a cohort of 294 Rutherford class 4 patients.²² The primary endpoint for this study was primary patency as defined by ultrasound, and was significantly better in the DCB group (83.9%) than in the PTA group (60.6%). Safety endpoints were also met, with the DCB group having a superior results in freedom from 30-day mortality and 12-month TLR (94.1 vs. 83.3%).

The results of the IN.PACT SFA, LEVANT II, and ILLUMENATE trials share a common theme of a significant improvement in both safety and efficacy when comparing DCB to PTA in the FP segment. There are, however, significant differences between the results of the three trials. The effectiveness of DCB angioplasty appears to be affected by numerous components, including the choice of excipient, balloon morphology, and pharmacokinetics relating to the specific type of coating. For instance, the LEVANT 2 data suggested that the lower dose Lutonix balloons may be less effective than the higher dose IN.PACT balloons when comparing 1-year results. In contrast to this, despite having a 75% decrease in total delivered dose, the use of the Stellarex balloon was associated with similar 1-year results as the IN.PACT balloon. It remains to be studied if the novel coating of the Stellarex balloon or the excipient may be accountable for these results. In addition, while the Stellarex balloon has shown similar 1-year results to the IN.PACT balloon, it remains to be seen whether these results will prove durable in the longer term.

DCB Plus Atherectomy for Treatment of Primary Lesions

Surgical endarterectomy is the gold standard in the treatment of common femoral and carotid atherosclerotic disease, as it offers complete plaque excision with acceptable postoperative patency rates. Endovascular atherectomy has recently emerged as a minimally invasive approach to debulk atheromatous plaque in difficult areas for surgical access. While endovascular atherectomy is not as complete as open

atherectomy, the alteration in plaque structure and removal of calcific components is thought to allow for a more uniform angioplasty with a decreased risk of plaque recoil and dissection.²³ Traditionally, hard to treat calcified or recoil-prone plaque has been treated with primary bare metal stenting. Unfortunately, as stated earlier, BMSs are prone to have LLL via ISR from endothelial hyperplasia. Therefore, the combination of minimally invasive techniques that do not result in the placement of a permanent implant would be a favorable strategy which would avoid the problems encountered with ISR. Debulking atherectomy combined with DCB angioplasty has logically been considered as an alternative treatment modality for these hard-to-treat lesions (► Fig. 1).

There are several atherectomy devices on the market currently. Strategies for atherectomy include directional cutting devices, rotational atherectomy, orbital atherectomy, and laser atherectomy. The debate regarding efficacy, safety, and device choice for atherectomy is beyond the scope of this article; however, a discussion of DCBs in the peripheral circulation warrants mention of the results of combined techniques with atherectomy. Recently, a registry of 30 patients treated with the TurboHawk (Medtronic) plaque excision system under filter protection followed by IN.PACT DCB treatment for long segment FP lesions was reported. While this study reported an excellent 1-year patency rate of 90%, 6.7% of these patients needed bailout stenting at the time of initial treatment.²⁴ The DEFINITIVE AR (Atherectomy Followed by Drug-Coated Balloon to Treat Peripheral Artery Disease) study sponsored by Medtronic compared atherectomy with the TurboHawk or SilverHawk plus DCB (DAART) versus DCB alone (Covantage Drug-Eluting Balloon) in the treatment of FP lesions. One-year patency with the DAART arm was 93.4% as compared to 89.6% with DCB alone group. Notably, the need for bailout stenting in the DAART arm was 4.1%.²⁵ The DEFINITIVE AR authors claimed a trend toward better outcomes in severely calcified long segment lesions and chronic total occlusions (CTOs), but no studies currently confirm or refute this benefit. Medtronic has recently launched the larger scale multicenter prospective REALITY study to answer this question. The REALITY study aims to address these lingering questions regarding the safety and efficacy profile of atherectomy plus DCB for the treatment of primary FP lesions. At this point, the data suggest limited 1-year patency benefit with an increased risk of dissection and bailout stenting as compared to DCB alone.

Use of DCB for In-Stent Restenosis

In-stent restenosis is characterized by cell-dense neointimal hyperplasia within the stent struts that has a tough elastic consistency. To the outer margin of the stent struts, the intima is defined by a cell-poor layer with a fibrous matrix. This distinctive “sandwich” structure overall results in a rubbery consistency of the lesions, which may account for their poor response to conventional balloon angioplasty.²⁶

There have been several studies that have evaluated the use of DCBs alone for superficial femoral artery ISR (SFA-ISR). In an Italian registry of 39 patients treated with the IN.PACT balloon, a 70% primary patency rate was noted at 2 years.²⁷

Fig. 1 A 66-year-old paraplegic diabetic with nonhealing foot ulcer. Initial angiography (a) shows multifocal high-grade stenoses (*arrowheads*) of the popliteal artery with preserved distal runoff (b). Rotational atherectomy (c) was performed followed by drug-coated balloon (d). Postintervention angiography (e) shows significant luminal gain. The patient had significant improvement in perfusion of the foot postintervention (f: preintervention and g: postintervention). He had initial reperfusion pain followed by slow healing of his ulcer. (Case courtesy: Scott Resnick.)

This encouraging data prompted three clinical trials for the use of DCBs in SFA-ISR. The Drug-Eluting Balloon in Peripheral Intervention for In-Stent Restenosis (DEBATE-ISR) trial enrolled 44 patients treated with IN.PACT balloons comparing DCB versus PTA. In this study, recurrent TLR at 1 year was 19.5% in the IN.PACT subgroup and 71.8% in the PTA group. Three-year TLR was similar (40 vs. 43%), suggesting DCB use only delays the redevelopment of ISR.²⁸ This study was combined with the results of two other prospective trials comparing DCB versus PTA for ISR in a recent meta-analysis of 278 patients. All trials evaluated recurrent ISR at 12 months, with the combined TLR in the DCB group having a significant advantage over PTA (34.8 vs. 73.1%, respectively).²⁹ Additionally, the IN.PACT Global SFA registry (1,535 patients) has also supported the use of DCBs in long segment complex ISR, with primary patency of 88.7% at

12 months.³⁰ While these data represent only a few small cohort studies, there appears to be a marked advantage to treating ISR with DCB as opposed to conventional PTA.

Debulking and DCB for ISR

Use of DCB has been combined with various atherectomy devices in an attempt to obtain superior patency in patients with ISR. To date, only one study has evaluated the combination of DEB and laser atherectomy for treatment of ISR, with a primary patency rate and freedom from TLR of 86% at 18 months.³¹ Directional atherectomy has also been evaluated for the treatment of infrainguinal ISR. In a recent multicenter nonrandomized study, 33 patients were treated with both DCB and directional atherectomy with a resultant primary patency of 33% at 1 year and 25% at 2 years.³² A separate retrospective analysis treated FP ISR with excisional

atherectomy followed by either PTA or DCB. One-year TLR rates were 15.3% in the DCB/atherectomy group and 56.2% in the PTA group. The results of these studies suggest that atherectomy combined with DCB may have at most modest advantage to the use of DCB alone for ISR.³³

DCBs for Below-the-Knee Atherosclerosis

Infrapopliteal (or below-the-knee [BTK]) atherosclerosis is the most common cause of CLI, which ultimately can lead to high morbidity, mortality, and amputation rates for its sufferers. Due to the increased risk of complications of open surgical revascularization of the infrapopliteal arteries, an endovascular-first strategy is commonly employed in treating symptomatic BTK peripheral artery disease (PAD).³⁴ PTA alone has been a longstanding strategy for treatment of BTK atherosclerosis; however, the long-term patency of these arteries after treatment is suboptimal. In a recent meta-analysis of 6,769 patients treated with PTA alone for BTK disease, primary patency was 63.1% at 1 year. In this same study, 14.9% of patients necessitated a repeat vascularization procedure, 14.9% underwent amputation, and 15.1% of these patients died as a result of all-cause mortality.³⁵ Clearly, there is room for significant progress in treatment of BTK lesions, and as such, DCBs are currently undergoing evaluation for the treatment of infrapopliteal lesions.

The IN.PACT Ampherion balloon was evaluated for use in patients with BTK CLI in a recent trial where it was compared to conventional PTA. This multicenter prospective study of 358 patients found comparable efficacy of IN.PACT Ampherion DCB to PTA. Unfortunately, there was a trend toward major amputation at 12 months as compared with conventional PTA, thought to be secondary to embolic events.³⁶ One hypothesis is that there may be a greater downstream risk of embolization due to the increased paclitaxel dose and crystalline conferred by the IN.PACT balloon. In contrast to the negative result of the IN.PACT balloon, Steiner et al reported more favorable results. In an analysis of 248 patients treated with the Lutonix 0.014 platform DCB for symptomatic PAD in the BTK vessels, the overall freedom from TLR was 84.1% and a freedom from major amputations of 96% at 12 months.³⁷ These encouraging data have spurred interest in a multicenter trial for BTK use of the Lutonix 0.014 system. In the most recent published 6-month data from a cohort of 314 BTK CLI patients across 26 sites, Medtronic reported freedom from all-cause death of 91.2%, above ankle amputation of 97.1%, reintervention for thrombosis of 95.2%, reintervention for distal embolization of 100.0%, and target vessel revascularization of 88.0%.³⁸ Twelve-month data for these patients have yet to be published; however, the Lutonix 014 system appears to have some early advantages in the treatment of BTK lesions. Despite the encouraging results of this study, long-term outcome data are needed prior to widespread implementation.

Drug-Eluting Stents

Percutaneous revascularization has a very high technical success rate in the coronary arteries as well as the periphery. DESs were developed in an effort to reduce restenosis rates.³⁹ Drugs

such as paclitaxel, sirolimus, and everolimus coat the surface of the stent and are released at variable rates. These drugs inhibit postintervention inflammation and neointimal hyperplasia.^{40–42} DESs were initially developed for the coronary circulation, and a wide body of evidence supports their safety and efficacy in the coronary arteries.³⁹ Coronary DES significantly reduce reintervention rate in 5-year follow-up studies compared to BMS with similar long-term safety profile.^{43,44}

Superficial Femoral Artery

Early trials evaluating DES in the SFA and proximal popliteal artery were performed in the early to mid-2000s. The SIROCCO trial compared sirolimus-eluting stents to bare SMART stents (Cordis, Miami Lakes, NJ). The trial showed no difference in restenosis rate at 24 months; however, the restenosis rate in the BMS arm was noted to be unexpectedly low. DESs were shown to be safe and effective.⁴⁵ The STRIDES single-arm trial evaluated an everolimus-eluting stent, and suggested improved primary patency at 6 months, though improvement was not sustained at 12 months.⁴⁶

The Zilver PTX (Cook Medical, Bloomington, IN) nitinol self-expanding polymer-free paclitaxel-eluting stent is currently approved by the United States Food and Drug Administration for use in the SFA (→ Fig. 2).³⁹ The Zilver PTX single-arm clinical study was performed to evaluate safety and efficacy of the stent. The study enrolled 787 patients with SFA disease, 24% of which represented restenotic lesions, and 38% of which were CTOs. At 1 year, event-free survival was 89%, 90% were free from TLR, and primary patency was 86%.⁴⁷

The Zilver PTX randomized trial followed the single-arm study. A total of 474 patients were randomized to receive treatment with DES or PTA. Those who acutely failed PTA underwent a second randomization to either provisional BMS or DES. Most patients were claudicants (91%) with greater than 50% vessel stenosis. Average lesion length was approximately 6 cm. Comparison of the DES and BMS arms gives an estimate of the effect of paclitaxel coating in the SFA. Eighty-nine percent of patients treated with Zilver PTX were free from repeat intervention at 2 years compared with 77% in those treated with BMS. DES was very effective at preventing restenosis when compared with PTA alone, with 2-year primary patency rates of 74.8 and 26.5%, respectively.³⁹

The Zilver PTX randomized trial is one of few available DES trials that has long-term follow-up data. At 5 years, DES had significantly improved freedom from clinically driven TLR (83 vs. 67%) and primary patency (66 vs. 43%) when compared with standard treatment. Advantages of DES over BMS were also durable over time with higher freedom from TLR and significantly improved primary patency. Treatment with DES had greater than 40% in relative risk reduction of reintervention or restenosis at 5 years when compared to PTA and provisional BMS. Patients enjoyed sustained clinical improvement, and had patency outcomes that compare favorably to venous and synthetic surgical bypass.³⁹

Two large Japanese post-market cohort studies have been undertaken to further evaluate Zilver PTX outcomes in real-world settings. The ZEPHYR registry (Zilver PTX for the femoral artery and proximal popliteal artery) evaluated

Fig. 2 A 67-year-old man with prior femoral-popliteal bypass graft and right superficial femoral artery (SFA) occlusion and severe claudication. Complete occlusion (*arrowhead*) of the mid and distal SFA with numerous collaterals and distal reconstitution (*arrow*) (*a* and *b*). The lesion was unable to be crossed antegrade. Pedal access was obtained followed by successful crossing with a Viance catheter (*c*). Zilver PTX drug-eluting stents were placed, restoring in-line flow. Note old bypass hood (*arrowhead*) (*d* and *e*). (Case courtesy: Kush Desai.)

690 patients. Lesions were longer and more heavily calcified, with greater proportion of CTO than those studied in the Zilver PTX randomized trial.^{48,49} One-year primary patency was 68%. Major adverse limb event rate defined as major amputation or any surgical or endovascular reintervention was 22%. Stent thrombosis rate was 2%.⁴⁸ The ZEPHYR registry determined long lesion length (>16 cm) and small diameters of treated segments to be risk factors for restenosis.^{48,49} Patients without these risk factors had 1-year primary patency rate of 85%, while primary patency fell to 49% in those with two risk factors.^{48,49} ZEPHYR investigators were encouraged to use intravascular ultrasound for their procedures to better define lesions. A subanalysis of the ZEPHYR CTO patients showed intraluminal versus subintimal lesion crossing which did not have significant impact on 2-year restenosis rates.⁵⁰ Yokoi et al conducted a cohort study of 907 patients treated with Zilver PTX. Patency and reintervention rates were excellent with freedom from TLR of 91%, clinical benefit of 87%, and primary patency of 86%. Differences between the ZEPHYR registry and Yokoi et al's cohort are likely related to patient selection, as Yokoi et al's cohort was composed largely of claudicants with low proportion of CLI.⁵¹ Reported stent fracture rates are less than 2% across the available SFA Zilver PTX trials.^{39,47,51}

DESs have also been shown to be beneficial in the treatment of ISR. A subgroup analysis of the Zilver PTX single-arm trial was performed, demonstrating 78% primary patency at 1 year in patients with DES stent-in-stent treatment for in-stent stenosis. Data for ISR are favorable when compared to other available methods.⁵²

The ISAR-STATH trial did not include a DES arm. Rather, it compared DCB plus BMS, PTA plus BMS, and directional atherectomy in 155 patients with de novo SFA lesions. The trial found that the combination of DCB and BMS resulted in improved 6-month angiographic stenosis and 24-month freedom from TLR.⁵³ The study supports the use of antiproliferative agents in combination with a mechanical scaffold.

The Eluvia (Boston Scientific, Natick, MA) DES has been designed to elute paclitaxel over longer periods of time. Paclitaxel is bound to the stent using a fluoropolymer coating.⁵⁴ The stent is currently available in Europe and is pending approval in the United States. Eluvia uses a lower paclitaxel dose (0.167 $\mu\text{g}/\text{mm}^2$) than Zilver PTX (3.0 $\mu\text{g}/\text{mm}^2$).⁵⁵ In a swine model, fluoropolymer-bound paclitaxel-eluting stents had lower levels of neointimal hyperplasia and sustained biological effect when compared to free paclitaxel-eluting stents and BMS.⁵⁵ Fluoropolymer DESs deliver approximately 40% of the available drug within the first 30 days and continue to release drug over time with an estimated 90% eluted at 12 months.⁵⁵ In contrast, polymer-free DESs such as Zilver PTX release 95% of the available drug within the first 24 hours with sustained paclitaxel levels in the artery wall up to 56 days.⁵⁵ Fluoropolymer stents are also used in cardiac circulation (Xience V; Abbott, Santa Clara, and Promus, Boston Scientific).⁵⁵

The MAJESTIC trial showed promising initial results with the Eluvia stent. This single-arm nonrandomized trial evaluated 57 patients with Rutherford 2 to 4 diseases, 46% of

which had total occlusions. At 12 months, primary patency was 96%.⁵⁴ Two-year primary patency was 83%, and 3-year freedom from TLR was 85%.⁵⁶ No stent fractures were identified at 3 years, though this may be attributable to small sample size.^{54,56} Given 2-year DCB patency rates close to 80%, DES compares favorably as DES trials included more highly calcified lesions and greater proportion of CTO.⁵⁶ The IMPERIAL trial is ongoing to further evaluate Eluvia.⁵⁶

Infrapopliteal

The infrapopliteal arteries present unique challenges due to their small size. The current standard of care is PTA with bailout BMS.⁵⁷ Reported patency of PTA and bailout BMS is less than surgical bypass, though midterm limb salvage outcomes are equivalent. There is overall decreased morbidity and mortality due to the minimally invasive nature of the procedure.⁵⁷⁻⁶¹ Patients often have significant comorbidities with high operative risk which make surgical bypass challenging or not offered.⁶² A recent meta-analysis by Mustapha et al examined contemporary outcomes of infrapopliteal PTA. Flow-limiting dissection and bailout stenting were reported in 5.6% of cases. Outcomes are suboptimal at 1 year with primary patency of 63%, reintervention in 18%, and major amputation in 14%. All-cause mortality at 1 year was 15%.³⁵ Initial technical success is high, though these vessels are prone to restenosis due to neointimal hyperplasia.³⁵ Recent DCB data from the In.Pact DEEP trial are troubling with a trend toward increased amputation rate.³⁶ DESs have proven effective in the coronary circulation. The infrapopliteal arteries are similar in size to the coronary vessels, prompting study of coronary DES BTK.^{63,64}

A number of different DES have been studied in the infrapopliteal arteries. These stents are coronary balloon-expandable stents that are used off-label. As such, they are available in shorter than optimal lengths for typical long diffusely diseased infrapopliteal pathology. Multiple stents are often required, quickly adding to the cost of the procedure.⁶⁵

The PADI trial compared the TAXUS Liberté DES (Boston Scientific) to PTA in patients with CLI. At 6 months, DES demonstrated improved primary patency of 48% compared with 35%.⁶⁶ Patients were followed up up to 5 years or until a clinical endpoint was reached. At 5 years, patients treated with DES had a significantly reduced major amputation rate and reintervention rate, with no difference in overall survival. At 4 years, patency rate was higher in the DES group, though results were not statistically significant.⁶⁷

The YUKON trial similarly compared sirolimus-eluting DES to BMS. At long-term follow-up, event-free survival and amputation rates were improved in the DES group. The YUKON investigators also reported significantly better clinical improvement in the DES group as reflected by Rutherford class.⁶⁸

Several additional trials have compared DES to BMS in the infrapopliteal circulation. A nonrandomized prospective registry by Siablis enrolled 103 patients, and followed up them for 3 years. DES was found to have improved primary patency, less binary restenosis, and better repeat intervention-free survival when compared to BMS. There was no difference in mortality or limb salvage rates.⁶⁹ The ACHILLES

randomized controlled trial enrolled 200 patients, randomized to sirolimus DES (Cypher, Cordis) or PTA. At 1 year, DES demonstrated lower angiographic restenosis rates (22.4 vs. 41.9%) and greater patency (75 vs. 57%). There was no difference in mortality, repeat revascularization, or amputation rates.⁷⁰ The DESTINY prospective randomized controlled trial compared the Xience V everolimus-eluting stent to BMS and enrolled 140 patients. At 12 months, the study demonstrated significant improvements in primary patency (85 vs. 54%), rate of in-stent stenosis (21 vs. 47%), and freedom from TLR (91 vs. 66%).⁷¹ Falkowski et al compared the Cypher (Cordis) sirolimus-eluting stent to BMS. Angiographic follow-up at 6 months showed significantly lower restenosis rate in DES when compared with BMS.⁷²

Comparison of DES and DCB has also been performed. The IDEAS prospective randomized controlled trial compared intrapopliteal with DES in long (>70 mm) lesions.⁶² DES had significantly lower immediate postprocedure stenosis (9 vs. 24%) and had significantly less angiographic restenosis (>50%) at 6 months (28 vs. 57%).⁶²

Several meta-analyses have been performed, examining available data on intrapopliteal DES. These meta-analyses all report improved freedom from TLR and primary patency with DES when compared with PTA and BMS without impact on overall survival.^{41,73–75} Two meta-analyses report improvement in amputation rate,^{41,74} while a third⁷³ reports no difference. Of note, the majority of studies included in these meta-analyses reported 12-month data.

The available data support the off-label use of coronary DES in the intrapopliteal arteries, and emerging stent technology has the opportunity to further improve patient outcomes. Long self-expanding DESs are currently in development at Boston Scientific and Micro Medical Solutions. The Boston Scientific SAVAL self-expanding DES pivotal trial is set to enroll imminently.

Conclusion

DCB and DES have been developed to ameliorate the problem of postintervention restenosis. Drug-eluting technologies have a clear benefit over PTA. While atherectomy combined with DCB may provide superior results, a randomized trial of DCB versus atherectomy plus DCB is needed. The next generation of fluoropolymer SFA DES and intrapopliteal DCB and DES are on the horizon. The goals of long-term vessel patency, improved clinical outcomes, and increased limb salvage are becoming reality, as these technologies are refined.

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