Drug-Eluting Technologies in Peripheral Arterial Disease With a Focus on Chronic Limb-Threatening Ischemia

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On behalf of the Critical Limb Ischemia Global Society Publications Committee

Abstract

Drug-coated technologies target the delivery of therapeutics directly to specific vascular segments with or without relying on a permanent scaffold. Paclitaxel remains the predominantly utilized antirestenotic medication in peripheral arterial treatment. This review provides a detailed discussion of research evaluating paclitaxel and alternative drug-coated therapies within the context of contemporary treatment of chronic limb-threatening ischemia.

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Introduction

Local drug delivery to prevent restenosis has long been a focus of technological advancement in the management of peripheral arterial disease (PAD) and has become one of the most widely studied topics of the last 2 decades. Paclitaxel, initially used in coronary drug-eluting stents (DES), has become the primary antirestenotic medication in peripheral arterial treatment. In this review, we seek to re-examine prior research efforts with paclitaxel and alternative drug-coated therapies in the context of modern treatment of chronic limb-threatening ischemia (CLTI).

Paclitaxel is an extract from the bark of Pacific yew trees and exhibits potent cytotoxic inhibition of cellular proliferation by disrupting cellular microtubule organization (**Figure**).[1] The first U.S. Food and Drug Administration (FDA)-approved coronary DES utilized sirolimus (Cypher, Cordis) and paclitaxel (Taxus, Boston Scientific), respectively, and were heralded for their significant reduction of in-stent restenosis (ISR) compared with bare-metal stenting (BMS).[2,3]

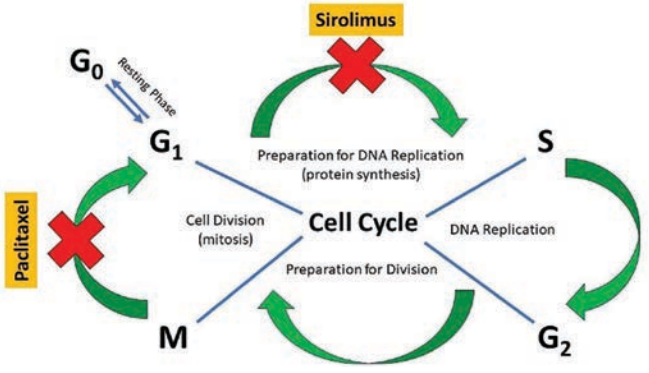

FIGURE. Cell cycle and mechanism of action of paclitaxel and sirolimus.

Sirolimus (or rapamycin), another natural compound, was derived in 1972 from a fungus found on Rapa Nui (Easter Island). Originally targeted as an antifungal agent, sirolimus was shown to exhibit cytostatic effects through receptor inhibition of the mammalian target of rapamycin, resulting in the cessation of cell-cycle progression in the late G1 to S phase (**Figure**).[4] Soon

TABLE 1. COMPARISON OF PIVOTAL RANDOMIZED CONTROLLED TRIALS AND STUDIES OF DRUG-COATED BALLOONS CURRENTLY APPROVED IN THE UNITED STATES

Trial name (year published)	N (intervention vs control)	Length of follow-up (years)	Lesion length (mm, intervention vs control)	Rate of primary patency* (*P*)	Freedom from target lesion revascularization* (*P*)
IN.PACT SFA (2015[11], 2018[12])	331 (220 vs 111)	1, 3	89.4± 48.9 vs 8.81 ± 5.12	82.2% vs 52.4% (<.001) at 1 year; 69.5% vs 45.1% (<.001) at 3 years	97.6% vs 79.4% (<.001) at 1 year; 84.8% vs 68.9% (.002) at 3 years
LEVANT 2 (2015)[5]	476 (316 vs 160)	1	62.7 ± 41.4 vs 63.2 ± 40.4	65.2% vs 52.6% (.02)	87.7% vs 83.2% (.21)
ILLUMINATE (2018)†[13]	371	1	75 ± 53	81.4%	94.8%
RANGER II SFA (2021)[14]	376 (278 vs 98)	1	82.5 ± 48.9 vs 79.9 ± 49.3	89.8% vs 74.0% (.0005)	94.5% vs 83.5% (.0011)
TRANSCEND (2022)‡[15]	446 (222 vs 224)	2	72.5 ± 48.4 vs 70.0 ± 50.5	70.8% vs 70.4% (.991)‡	85.3% vs 88.2% (.453)
CHOCOLATE TOUCH (2022)††[16]	313 (152 vs 161)	1	78.5+46.3 vs 77.8+47.7	78.8% vs 67.7% (*P* nonsignificant)	93.7% vs 88.6% (*P* nonsignificant)

*Outcomes are in comparison to percutaneous transluminal angiography alone unless otherwise stated.
†Single-arm study in the United States; original randomized controlled trial was performed in Europe.
‡Head-to-head comparison between Surmodics SurVeil drug-coated ballon (DCB) and Medtronic IN.PACT DCB; data presented in 2022 but has yet to be published online.
††Head-to-head comparison between Genesis MedTech Chocolate Touch DCB and BD Lutonix DCB.

after its approval for use in coronary DES, sirolimus-eluting self-expanding stents (S.M.A.R.T., Cordis) for superficial femoral artery disease were evaluated utilizing dose equivalents from those studied in the coronary arteries. Unfortunately, this stent failed to achieve a statistically significant reduction in restenosis compared with BMS.[5] This paved the way for translational research, transitioning paclitaxel from drug-eluting coronary stents to wide applications in PAD.

Drug-Coated Balloon Studies in Peripheral Arterial Disease

Historically, percutaneous transluminal angioplasty (PTA) has been the de facto treatment modality for both above-the-knee (ATK) and below-the-knee (BTK) endovascular interventions for PAD. Unfortunately, vessel patency rates as low as 33% at 1 year have been described in the femoropopliteal region with PTA alone.[6] Similar or worse outcomes have been described in the tibial arteries after PTA, with short-term patency rates ranging from 13% to 48% in the initial studies.[7,8] More contemporary studies have shown similarly low angiographic patency at 3 months in patients with CLTI and long lesions (31% patency, lesion length ≥80 mm).[9]

Drug-coated balloon (DCB) technology is intended to provide durable treatment results while foregoing the implantation of a permanent scaffold. Currently, several FDA-approved DCBs are available, with data supporting their use in both de novo and ISR lesions. Notably, while all the FDA-approved DCBs primarily use the same chemotherapeutic medications delivered to the vessel, they do so via alternate carrier molecules/mechanisms as well as different drug concentrations; therefore, a class effect should not be assumed.

Drug-coated balloon use in the femoropopliteal arteries

To date, multiple trials have shown the advantage of DCBs over uncoated balloon angioplasty for the treatment of femoropopliteal lesions (**Table 1**).[10] The initial studies comparing DCB use to PTA alone showed favorable primary patency rates at 1 year with a noninferior safety profile.[17] Longer-term data (extending to 2-3 years) comes primarily from the IN.PACT device (Medtronic). While still statistically significant, IN.PACT showed lower patency rates compared to PTA over time, compared with the initially published 1-year data (69.5% vs 45.1%, *P* <.001, for primary patency of DCB compared to PTA at 36 months, compared with 82.2% vs 52.4% primary patency, *P* <.001, at 12 months).[18,19]

In the femoropopliteal segment, randomized data from the EffPac program with the Luminor paclitaxel nano-coated DCB (iVascular) demonstrated superior short- and mid-term efficacy vs plain old balloon angioplasty, with higher 12-month primary patency (90.3% vs 65.3%). Luminor DCB had a sustained benefit at 2 years (primary patency 90.2% vs 62.7%; freedom from target lesion revascularization [TLR] 97.2% vs 78%) without an apparent safety signal. By 5 years, the treatment effect had attenuated, although primary patency remained statistically higher (61.4% vs 53.5%) and freedom from clinically driven TLR was numerically higher with DCB (82.1% vs 73.7%), with similar all-cause mortality between groups. Long-term effectiveness appears procedure- and lesion-dependent, with residual stenosis >30% identified as a key determinant of DCB failure.[20-24]

TABLE 2. RANDOMIZED CONTROLLED TRIALS EVALUATING THE USE OF DRUG-COATED BALLOONS VS PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY ALONE IN FEMOROPOPLITEAL IN-STENT RESTENOSIS

Trial name (year published)	N (intervention vs control)	Length of follow-up (years)	Lesion length (mm, intervention vs control)	Rate of primary patency* (*P*)	Freedom from target lesion revascularization* (*P*)
DEBATE-ISR (2014[27]; 2016[8])	86 (44 vs 42)	3	132 ± 86 vs 137 ± 82	80.5% vs 28.2% at 1 year (<.001)	86.4% vs 69% (.045) at 1 year; 60% vs 57% (.8) at 3 years
FAIR (2015)[25]	119 (62 vs 57)	1	82.3 ± 70.9 vs 81.1 ± 66.2	70.5% vs 37.5% (.004) at 1 year	90.8% vs 52.6% (<.0001)
PACUBA (2016)[26]	73 (35 vs 38)	1	173 ± 113 vs 184 ± 88	40.7% vs 13.4% (.02) at 1 year	49% vs 22.1% (.11)
ISAR-PEBIS (2017)[28]	70 (36 vs 34)	2	132 ± 65 vs 146 ± 69	70% vs 41% (.03) at 6-8 months	81% vs 50% (.007) at 2 years
COPA CABANA (2020)[29]	88 (47 vs 41)	0.5	140 mean across both groups	86.5% vs 40.7% (<.001 reported for late lumen loss) at 6 months	51.4% vs 86% at 1 year

*Outcomes are in comparison to percutaneous transluminal angioplasty alone unless otherwise stated.

The use of DCBs for femoropopliteal disease extends beyond the treatment of de novo lesions. DCBs are currently 1 of only 3 FDA-approved interventions for femoropopliteal ISR, in addition to laser atherectomy and the Viabahn covered stent (Gore). Initial registry data utilizing the IN.PACT DCB showed promising primary patency rates for femoropopliteal ISR at 12 months as well as high levels of procedural success and safety.[25,26] Subsequent randomized controlled trials (RCTs) have confirmed markedly lower rates of recurrent restenosis with DCB than with PTA alone (**Table 2**). Unfortunately, both rates of restenosis and TLR increase with longer-term follow-up. For example, the Drug-Eluting Balloon in Peripheral Intervention for In-Stent Restenosis (DEBATE-ISR) trial, which had promising 1-year data, demonstrated no difference in TLR at 3 years (40% vs 43% for DCB vs PTA, respectively). Furthermore, shorter lesions tended to do better than longer lesions with regard to rates of recurrent restenosis.[28] Collectively, registry data and the available RCTs demonstrate DCB use for femoropopliteal ISR is associated with superior efficacy outcomes compared to PTA alone at 1-year follow-up.

Drug-coated balloon use in patients with chronic limb-threatening ischemia

The major trials in the femoropopliteal segments did not include significant numbers of patients with CLTI; for example, the IN.PACT SFA, EffPac, and ILLUMINATE pivotal trials had less than 5% of subjects enrolled with Rutherford 4-5 disease.[20,21] Conversely, nearly 10% of patients enrolled in the LEVANT-2 RCT of the Lutonix balloon (BD) had CLTI. DCB use resulted in improved primary patency when compared with angioplasty alone (65.2% vs 52.6%, *P*=.02).

Drug-coated balloon use in the infrapopliteal arteries

Given the success of DCBs in the femoropopliteal region, comparable results in the infrapopliteal arteries for patients with CLTI were highly anticipated. Unfortunately, the data did not corroborate this assumption. The first infrapopliteal trial involving DCBs was with the IN.PACT DCB, which did not show an improvement of DCB over PTA alone in the infrapopliteal arteries in regard to either TLR (9.2% vs 13.1%, *P*=.291 for DCB vs PTA, respectively) or late lumen loss (0.61 + 0.78mm vs 0.62 + 0.78mm, *P*=.950 for DCB vs PTA, respectively).[29] More concerning was a non-statistically significant safety signal for increased rates of major amputations through 12 months seen in the DCB vs PTA alone arm. The follow-up trial presenting 5-year data similarly showed no superiority of DCB compared with PTA. There was no significant difference in safety signals between groups at this time point, including risk of amputation in this longer-term data.[30]

The Lutonix BTK randomized trial demonstrated noninferior short-term safety at 30 days (short-term safety endpoint: freedom from major adverse limb events [MALE] and perioperative death [POD] 99.3% with DCB vs 99.4% with PTA; noninferiority *P*<.001). For short-term efficacy, the pre-specified 6-month composite endpoint (freedom from vessel occlusion, clinically driven TLR, and above-ankle amputation) showed benefit that was most evident in the proximal-segment cohort (proximal segment defined as the proximal two-thirds of the BTK artery: 76% DCB vs 62.9% PTA; one-sided *P*<.01), whereas the overall intent-to-treat analysis did not meet the pre-specified statistical success criterion despite numerically favorable results (74.5% vs 63.5%; one-sided *P*=.02). Secondary endpoints (including primary patency and clinically driven TLR) also favored DCB at 6 months. However, these early advantages were not maintained

at longer-term follow-up (12 months), contributing to the overall conclusion of limited durable efficacy for infrapopliteal DCB in this setting.[31]

Contradicting the above negative results was the AcoArt-BTK trial of the Litos DCB (Boston Scientific), which showed markedly superior reduction in late lumen loss on routine follow-up angiography at 6 months (0.51 ± 0.60 mm in the DCB group vs 1.31 ± 0.72 mm in the angioplasty arm). These results carried forward for a pivotal randomized trial of 120 patients with CLTI randomized to DCB vs angioplasty (primary patency with DCB 75.0% vs 28.3%, *P*<.001).[32] This was followed by the AcoArt II-BTK trial, which was a prospective, multicenter, randomized, single-blinded study of 120 patients with CLTI undergoing infrapopliteal (BTK) revascularization, comparing the Litos Tulip DCB angioplasty with plain balloon PTA. At 5 years, the DCB group had higher freedom from all-cause death (74.6% vs 57.2%; *P*=.04) and a lower composite major adverse event rate (34.5% vs 56.1%; *P*=.013). Freedom from clinically driven TLR was numerically better with DCB angioplasty (70.5% vs 53.7%; *P*=.058), while major amputation rates were not significantly different (5.2% vs 1.8%; *P*=.347).

Overall, the findings of the two AcoArt studies support favorable long-term outcomes with DCB angioplasty compared with plain balloon PTA in the BTK segments.[33] Furthermore, a meta-analysis of DCB in the infrapopliteal segment found overall benefit in TLR and complete wound healing compared to angioplasty alone.[34]

The absence of consistently positive data surrounding DCBs in the infrapopliteal arteries may be attributed to factors such as composition of the plaque (eg, higher thrombus burden compared to femoropopliteal arteries), early elastic recoil, insufficient uptake of the chemotherapeutic drug into the vessel wall, or increased distal embolization into wound beds in patients. Supporting the plausibility of a thrombotic component in BTK CLTI, histopathologic assessment of amputation specimens has demonstrated that severe infrapopliteal occlusive disease is frequently associated with luminal thrombi, often in the setting of limited atherosclerosis.[35-37]

Particulate embolization

Paclitaxel DCBs may underperform in CLTI because clinically meaningful amounts of coating/drug can be lost during delivery, embolizing distally as particulates. In patients with limited tibial runoff and impaired microcirculatory reserve, this downstream particulate burden may contribute to microvascular obstruction, vasospasm, or inflammatory responses, manifesting as slow-flow/no-reflow and potentially reducing healing.[38] Limus-based balloons (eg, sirolimus/everolimus) are proposed as an alternative because limus drugs are predominantly cytostatic with anti-inflammatory effects, theoretically lowering the risk of distal tissue injury. Furthermore, contemporary limus balloon platforms often use carrier or microreservoir technologies to improve arterial wall uptake and prolong tissue residence while minimizing coating loss—features that could translate into less distal embolization-related microvascular compromise in CLTI, although definitive comparative clinical evidence in CLTI needs further study.[39,40]

Removable scaffolds coupled with drug-coated balloons

In a novel approach to BTK treatment with DCB, the DEEPER OUS study described the use of a removable self-expanding Spur stent with external penetrating spikes (Reflow Medical) followed by a DCB, which demonstrated a primary patency of 85.7% (95% confidence interval [CI]: 78.2-93.2%; *P*<.001 vs 51% performance goal).[41] More recently, the DEEPER LIMUS trial extended this concept by combining a retrievable scaffold with a sirolimus-coated balloon in Rutherford class 3-5 infrapopliteal disease (88% Rutherford 5; 36% occlusions; 54% TASC B/C), reporting a 6-month MALE-POD composite safety event rate of 11.5% and a 12-month primary patency of 89.5%, with no additional major amputations or clinically driven TLR reported through 12 months.[42] Although limited by a small sample size and a single-arm design, these early studies support the feasibility of scaffold-assisted vessel preparation followed by limus-coated balloon angioplasty as a strategy to mitigate recoil and optimize drug delivery in BTK interventions.

Drug-eluting stents for the above-the-knee (femoropopliteal) segment

The first successful treatment in the femoropopliteal arterial segment with a dedicated DES was the Zilver PTX (Cook Medical). Zilver PTX applies a relatively high dose (3 μg/mm²) of paclitaxel directly to a nitinol self-expandable stent without a polymer. The Zilver PTX demonstrated sustained clinical benefits at a 5-year follow-up in an RCT compared with standard care (balloon angioplasty or BMS). Five-year primary patency was significantly higher in the DES cohort (83.1% vs 67.6%, *P*<.01).[43]

Multiple important subsequent reports have been published regarding the Zilver PTX. In the ZILVERPASS study, a randomized trial comparing Zilver PTX with bypass surgery using prosthesis graft, non-inferiority was shown in the rate of 12-month primary patency (74.5% vs 72.5%, *P*=.998). This result suggested that Zilver PTX can serve as an alternative to bypass surgery with prosthesis graft in complex lesions.[44] Several single-arm trials in real-world complex lesions have also been conducted; however, heterogeneous patency rates (60% to 85%) were observed.[45-47] This suggests that procedural quality may influence the outcome of Zilver PTX in addition to patient and lesion characteristics.

The ZEPHYR study of the Zilver PTX stent helped identify the predictors of restenosis with DES: 1) lesion length >16 cm, 2) distal external elastic membrane area ≤27 mm², and 3) minimum stent area (MSA) ≤12 mm².[45] Following the ZEPHYR study, the concept of "lesion preparation" became more recognized given the ISR associated with a smaller residual MSA. Although Zilver PTX marked a significant progress, the patency rate of Zilver

PTX still did not match that of coronary DES. Therefore, a new generation of peripheral DES with a novel concept emerged.

Eluvia (Boston Scientific) is a second-generation femoropopliteal-dedicated DES that uses a biocompatible fluoropolymer developed from coronary DES technology. It applies a low dose of paclitaxel (0.167 μg/mm²) using fluoropolymer to the surface of the Innova nitinol self-expandable stent (Boston Scientific). In the MAJESTIC trial, a 12-month primary patency of 96.4% was reported.[48]

Due to the promising results of the MAJESTIC trial, early market introduction was anticipated. The IMPERIAL trial, conducted as an FDA approval study, was an RCT comparing Eluvia with Zilver PTX. While designed to demonstrate non-inferiority, initial 12-month results reported superior primary patency (88.5% vs 79.5%, *P*=.0119) in the Eluvia cohort,[49] though this superiority disappeared during the 24-month follow-up (83.0% vs 77.1%, *P*=.10).[50] These extended results were confirmed by the REALDES 3-year outcomes, which again showed no difference between Eluvia and Zilver PTX in the treatment of symptomatic femoropopliteal disease (3-year patency: 65.2% Eluvia and 70% Zilver PTX, *P*=.74).[51]

The 1-year superiority of Eluvia may be explained by its durable fluoropolymer coating, creating a controlled, sustained elution profile designed to target prolonged drug availability out to approximately 12 months. In contrast, Zilver PTX is polymer-free (paclitaxel applied without a binder), which leads to much earlier drug wash-off. Preclinical pharmacokinetic data show that about 95% of paclitaxel is delivered from the stent within 24 hours, with tissue levels persisting for weeks but with far less prolonged release than polymer-based systems.[52] At greater than 1-year follow-up, after elution is complete, Zilver PTX and Eluvia stents may perform similarly to BMS, resulting in comparable outcomes.

When evaluating the DES literature, it is also important to distinguish how loss of patency occurs (restenosis vs complete stent occlusion) because occlusions may present more abruptly, be more difficult to treat, and carry a greater risk of limb-threatening ischemia than nonocclusive restenosis. Thus, the finding of greater occlusive failures with Eluvia despite similar patency rates suggests that patency alone may obscure clinically meaningful differences in failure mode and supports reporting occlusions as a separate endpoint alongside patency and TLR.[53]

Halo sign

One concern following Eluvia stent implantation is the reported aneurysmal degeneration known as the "halo sign". Initially reported in the CAPSICUM study, the halo sign was seen in association with subintimal guidewire passage with subsequent Eluvia placement.[54] Data from multiple studies have shown no significant safety signal associated with the halo sign.[53] A pooled analysis of the IMPERIAL and EMINENT studies showed no significant association between the presence of the halo sign and primary patency in 659 patients.[55] A 5-year follow-up study confirmed higher patency rates with a halo sign compared to without (87% vs 59%; hazard ratio [HR] 2.48, 95% CI 1.19-5.16; *P*=.015), although confirmation in larger cohorts is warranted given study design limitations.[53]

Drug-Eluting Stents in Below-the-Knee Lesions

Given the overall lack of efficacy of drug-coated technology BTK, standard percutaneous angioplasty has become the default treatment. In cases of severe recoil or dissection requiring bail-out, placement of coronary-specific DES has become the most utilized strategy. Several trials have supported this technique, including the Achilles trial, which randomized 200 patients to DES with a sirolimus-eluting stent vs PTA. At 1 year, the rate of restenosis was markedly reduced in the coronary DES arm vs PTA (22.4% vs 41.9%; *P*=.019).[56] These results were bolstered by the YUKON and DESTINY RCTs, which similarly showed benefit of sirolimus- and everolimus-based DES over BMS.[57]

Balancing these strongly positive studies were the SAVAL and PADI trials, which showed a lack of benefit of DES in long lesions (SAVAL) and with long-term follow-up (PADI) in patients with BTK CLTI. In SAVAL, the neutral results for the efficacy endpoint occurred in the context of a high 12-month patency rate in the PTA arm (76%), which likely narrowed any incremental benefit achievable with DES.[58,59] In the PTA arm, optimal PTA was performed rather than standard of care PTA (as in other contemporary trials such as LIFE-BTK).[60] SAVAL and PADI highlight the challenging patient subset that is BTK CLTI.

Bioresorbable Drug-Eluting Stents in Below-the-Knee Arterial Disease

BTK lesions remain challenging, given increased lesion complexity and worse patient-level comorbidities (ie, diabetes and end-stage renal disease), resulting in poor post-intervention patency. Patency of BTK disease is constrained by 4 main factors: elastic recoil of the target vessel, flow-limiting dissection, restenosis due to neointimal hyperplasia, and impaired inflow or outflow. The clinical need for improved outcomes with an ideal device that can combat recoil, deliver antiproliferative drugs, and treat significant dissections, while "leaving nothing behind", has led to the rapid development of drug-eluting bioresorbable scaffolds (DRS).

Composition of bioresorbable stents

Several DRS platforms are under study to evaluate optimal biocompatibility and degradation profile. Components of DRS for BTK interventions include scaffolds and the drug. The scaffolds may be made of polymers, usually poly-L-lactic acid, and corrodible metals such as magnesium and iron.

DRS also utilizes antiproliferative drugs, paclitaxel or rapamycin derivatives, to inhibit neointimal hyperplasia. Drug elution occurs by hydrolysis of the polymer matrix coating the scaffold backbone, followed by scaffold dissolution over several years.

Clinical studies

Bosiers et al published the first large clinical study of BRS in BTK interventions in 2005, examining an absorbable metal stent. This initial investigation showed 1-year primary patency, limb salvage, and survival rates of 73.3%, 94.7%, and 85%. The follow-up AMS INSIGHT trial, which compared the absorbable metal stent to PTA alone, showed no difference in 30-day safety endpoints and had worse 6-month patency compared to PTA alone.[61]

Next, Varcoe et al showed encouraging outcomes in patients with BTK disease with the ABSORB scaffold. The study reported 12-month survival of 84.8%, freedom from clinically driven TLR of 96%, and a primary patency rate of 96% at 12 months. The 5-year follow-up results of this trial continued to demonstrate favorable outcomes over PTA alone.[62,63]

The LIFE-BTK trial was an RCT studying the Esprit BTK DRS (Abbott) compared to PTA alone in Rutherford 4-5 BTK disease. At 12 months, 74% of patients in the scaffold group achieved the composite primary endpoint, compared with 44% in the PTA group (absolute difference 30%; 95% CI, 15%-46%; *P*<.001). Importantly, these benefits appeared durable at 2 years, with higher freedom from the revised composite efficacy endpoint in the DRS group vs PTA (68.8% vs 45.4%; *P*=.0004), driven in part by lower binary restenosis (28.5% vs 48.2%; *P*=.005) and lower clinically driven TLR (9.7% vs 18.6%; *P*=.034), while maintaining a comparable safety profile (freedom from MALE-POD 91.6% vs 95.6%; *P*=.16). Given the strength of these clinical trial results, the ESPRIT study potentially represents a major shift in the endovascular management of CLTI.[60,64]

The MOTIV BVS BTK pilot study was a single-arm, multicenter trial evaluating 76 scaffolds in 60 limbs over 36 months. The 6-month data demonstrated 99% technical success, 90% primary patency, and a 3% clinically driven TLR.[65] The 3-year follow-up was recently reported, with a primary patency of 80%.[66]

RESOLV I was a prospective, single-arm, multicenter trial examining the Magnitude DRS bioresorbable scaffold (R3 Vascular) in infrapopliteal interventions. The study enrolled 50 patients with Rutherford category 3-5 disease. Six-month data showed 100% (n = 28/28) achievement of primary safety endpoints, defined as freedom from MALE and POD. Primary efficacy endpoints, including angiographic primary patency and freedom from TLR, were met in 93% (n = 27/29) of lesions at 6 months.[67]

Bioresorbable stents for BTK PAD represent an important breakthrough, providing a treatment that addresses both the need for immediate scaffolding and the need for long-term vessel health.

Liquid Drug Delivery

Various types of liquid drugs have been employed to prevent and treat restenosis-encompassing antiproliferative, anticoagulant, and anti-inflammatory agents. In the 1960s, heparin was initially utilized for thrombosis treatment using polyvinyl alcohol applied to the adventitia.[68] Over subsequent decades, heparin became widely adopted as an anticoagulant to inhibit excessive platelet and smooth muscle cell aggregation, which contributes to vessel narrowing following endothelial injury.[69] Historically, local drug delivery systems aimed at targeted heparin delivery have included polyvinyl alcohol, other polymer sheets, and various catheters such as the InfusaSleeve (LocalMed).[70] However, the use of heparin declined over time, partly due to the high dosages required for effective therapy, which occasionally led to bleeding complications.

Although significant progress was achieved in the late 1990s and early 2000s in enhancing liquid drug delivery systems, the development and success of DES in treating lower extremity restenosis diverted almost all attention away from liquid delivery devices. Consequently, exploration of catheters such as the InfusaSleeve, Infiltrator (InterVentional Technologies), and iontophoretic catheters for treating local lesions in the peripheral vasculature nearly ceased.[71,72] However, recent advances in liquid delivery systems have led to marked improvements in outcomes for endovascular treatment of infrainguinal lesions, including challenging femoropopliteal and infrapopliteal lesions.[73] Current examples of liquid drug delivery systems in use include 1) the Bullfrog micro-infusion device (Mercator MedSystems), 2) the ClearWay rapid-exchange therapeutic infusion catheter (Atrium Medical), and 3) the Occlusion Perfusion Catheter (OPC) (Advanced Catheter Therapies).

The Bullfrog was created to inject therapeutic drugs directly into the adventitia, either through blood vessel walls or perivascular areas. When the balloon is sealed, the microneedle on its surface remains flat, ensuring safe passage through vessels to the target lesion. Upon low-pressure inflation (2 atm) at the target site, the microneedle penetrates the vessel wall without causing damage, allowing the selected therapeutic agent to be injected into the adventitial tissue. Several clinical studies have highlighted the potential for this liquid drug delivery device, including the Temsirolimus Adventitial Delivery to Improve Angiographic Outcomes Below the Knee (TANGO) trial, which evaluated local drug delivery following revascularization of lesions in patients presenting with CLTI.[74-76] The TANGO-3 BTK randomized trial is ongoing and will evaluate delivery of temsirolimus BTK after revascularization in patients with CLTI compared to placebo infusion.

The ClearWay catheter is designed to deliver therapeutic drugs directly to target lesions in both coronary and peripheral vasculature. Drug infusion occurs through micropores in the polytetrafluoroethylene balloon, which temporarily occludes

blood flow for precise drug delivery to the target site. The ClearWay catheter has been successfully used to administer liquid paclitaxel, glycoprotein IIb/IIIa inhibitors, thrombolysis agents, and urokinase.[77,78]

The OPC is an advanced drug-delivery device equipped with a built-in fiberoptic pressure sensor for precise targeting. It features 2 occlusion balloons that, when inflated, create a controlled "treatment chamber". This chamber allows continuous monitoring of applied pressure and precise control over the volume of therapeutic agent administered. Clinical studies have demonstrated the effectiveness of the OPC, achieving a 96.4% rate of clinically driven TLR at 6 months.[79,80]

Role of Plaque Modification and Atherectomy to Enhance Drug Delivery

Atherectomy and plaque modification are important tools that may enhance vessel compliance promoting DCB expansion and may enhance wall porosity allowing for deeper penetration of antiproliferative agents. The use of DES and DCB for intra-arterial drug delivery faces the challenge of transferring drugs across calcified atherosclerotic plaques, resulting in reduced therapeutic concentration in the desired treatment area. Paclitaxel is highly hydrophobic and requires significant vascular penetration to be efficiently absorbed by surrounding tissues, gain cellular entry, and bind tightly to proteins within cells and the interstitium.[75]

Optimization of drug delivery through bigger balloon expansion, which may be promoted by atherectomy or plaque modification, has also been established. In an ex vivo study, scanning electron microscopy images demonstrated that the drug was mostly retained within grooves and gaps of the luminal surface of the arteries treated with the DCB-artery-ratio of 1.25:1, as compared to 1:1. The overexpansion of the artery allowed deeper penetration of the drug coating within the intimal layer, strengthening its adhesion to the luminal surface.[81] Furthermore, plaque modification with arthrectomy, specialty balloons, intravascular lithotripsy, and temporary stents can enhance deep cracking of the plaque and, theoretically, improve drug delivery to deeper layers, promoting retention of the antiproliferative agent within the treated areas.

Current clinical data: atherectomy plus drug-coated balloons

Although the potential therapeutic benefit of using atherectomy with DCB is clear, clinical data has been conflicting. In 2 randomized trials, use of atherectomy was safe and effective with higher technical success rates, decreasing dissection, and overall bailout stenting. In the DEFINITIVE AR study, atherectomy plus DCB was not associated with a significant improvement in the 1-year primary outcome of percent diameter stenosis, clinically driven TLR, and freedom from major adverse events; however, the trial underscored the importance of achieving an optimal acute angiographic result, particularly residual stenosis <30% (ie, technical success). When technical success was achieved, 12-month patency was 94.1% vs 68.8% when technical success was not achieved.[82,83] Cai et al revealed similar outcomes with no difference in amputation rates, 12-month and 24-month primary patency, and overall mortality rate.[84] A meta-analysis, including 2 RCTs and 4 retrospective cohort studies, comparing atherectomy plus DCB vs DCB alone in the treatment of femoropopliteal lesions showed no significant difference between the 2 groups at 12 months in terms of distal embolization, perforation, hematoma, primary patency, TLR, leg amputations and mortality (relative risk for mortality: 2.18, 95% CI: 0.71-6.64, P=.17).[85] Finally, Rodoplu et al retrospectively evaluated atherectomy plus DCB vs DCB alone and showed that combined usage of rotational atherectomy plus DCB for the treatment of CLTI resulted in reduced 1-year TLR (6.1% vs 17.4%, P=.001).[86] Larger RCTs with longer-term follow-up are required to determine the benefits of atherectomy as an adjunctive therapy with drug-coated devices.

Katsanos Controversy

In 2018, Katsanos et al published a meta-analysis purporting to show increased mortality associated with paclitaxel-coated balloons (PCBs) in peripheral arterial angioplasty. The study included 28 RCTs with 4663 patients randomized to PCB vs PTA alone. At 1 year, the safety signals were similar; however, at 2 years, the mortality rate in the PCB arm was significantly higher than the PTA arm (7.2% vs 3.8%, relative risk 1.68; 95% CI 1.15-2.47), with a reported number needed to harm of 29 patients. The manuscript also postulated a potential dose-time relationship but failed to provide a clear causal mechanism for the results.[12] The concerns surrounding DCB were bolstered by a second meta-analysis[87] examining PCB use specifically in the infrapopliteal arteries for treatment of CLTI. The study-level meta-analysis showed that amputation-free survival was significantly worse with PCB use (13.7% vs 9.4%, P=.008). Particulate embolization was raised as a mechanism for the higher adverse event rate with PCBs. These publications led to negative publicity and an FDA warning letter regarding the use of PCBs. The Katsanos controversy led to a significant shift in practice, with an approximate 50% reduction in the use of PCBs for PAD in the United States over the 6 months after the FDA warning.

The Katsanos meta-analysis results were challenged by several manuscripts.[5] Most importantly, a large-scale meta-analysis was conducted in which much of the missing data and loss to follow-up from the initial Katsanos paper were rectified and showed no perceived mortality signal with PCBs: intent-to-treat analysis (HR 1.14, 95% CI 0.93-1.40); as-treated analysis (HR 1.13, 95% CI 0.92-1.39).[88] This data led the FDA to withdraw its warning about the use of paclitaxel in 2023.

Conclusion

Drug-coated technologies enable the proceduralist to deliver therapeutic agents directly to specific arterial segments via multiple mechanisms. Drug technologies, with or without a scaffold, in the peripheral arteries will remain a key area of focus as we work to improve patency and optimize outcomes for our patients with PAD.

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