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Comprehensive Review

Surgical and Endovascular Therapies for Below-the-Knee Peripheral Arterial Disease: A Contemporary Review

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ABSTRACT

Peripheral arterial disease (PAD) represents one of the most prevalent cardiovascular disease processes and carries a high burden of morbidity and mortality. Patients with chronic limb-threatening ischemia (CLTI), the most severe manifestation of PAD, have the highest rates of cardiovascular morbidity and mortality of the overall PAD population. Patients with below-the-knee (BTK) PAD have an increased propensity toward CLTI due to small-vessel caliber and the frequently comorbid conditions of end-stage renal disease and diabetes mellitus, which tend to affect small artery beds preferentially. For those with BTK PAD with CLTI, the standard of care is revascularization. Early revascularization was performed using surgical bypass. However, endovascular techniques, starting with percutaneous transluminal angioplasty and expanding to the modern armamentarium of adjunctive devices and therapies, have become standard of care for most patients with CLTI due to BTK PAD. In this review, we will discuss the modern surgical and endovascular approaches to revascularization, as well as devices that are currently in development or preapproval study for the treatment of BTK PAD.

Introduction

Peripheral arterial disease (PAD) is one of the cardinal manifestations of atherosclerosis and carries a high burden of morbidity and mortality. Up to 29% of patients older than 50 years have hemodynamically significant PAD, diagnosed noninvasively by an ankle-brachial index (ABI) of $\leq$0.9.[1] Chronic limb-threatening ischemia (CLTI), defined by the presence of ischemic rest pain or tissue loss attributable to the presence of PAD, accounts for a small proportion of the overall population with PAD (500-1000 new cases per million per year) but represent the highest risk cohort of patients with 1-year major amputation and mortality rates of up to 30%.[2] This is the group to which the most investigative resources are allocated in an attempt to improve the burden of disease, quality of life, limb salvage, and short-term and long-term mortality. A significant portion of CLTI is due to infrapopliteal or below-the-knee (BTK) disease, in part due to comorbid conditions of diabetes mellitus and chronic kidney disease, which disproportionally affect small-vessel territories.[2] Historically, CLTI has been referred to as critical limb ischemia (CLI), and therefore, many of the older studies included in this review will use this terminology to describe patients with CLTI.

Although the mainstay of treatment in patients with intermittent claudication is risk factor modification and supervised exercise programs, endovascular and/or open surgical revascularization is available for patients with severe, lifestyle-limiting claudication refractory to guideline-directed medical therapy. However, either form of revascularization is considered compulsory for CLTI, where treatment of BTK PAD with endovascular therapy has been controversial owing to poor long-term patency.[3] Both endovascular and surgical interventions for BTK disease have advanced but have suboptimal intermediate-term and long-term target vessel patency rates and no significant effect on mortality. This review discusses the endovascular and surgical management of BTK PAD, some of the emerging data regarding treatment modalities, and future directions for investigation.

Abbreviations: BMS, bare metal stent; BTK, below-the-knee; CD-TLR, clinically driven target lesion revascularization; CLTI, chronic limb-threatening ischemia; DCB, drug-coated balloon; DES, drug-eluting stent; MALE, major adverse limb event; PAD, peripheral arterial disease; PTA, percutaneous transluminal angioplasty; RCT, randomized controlled trial.

Keywords: below-the-knee; peripheral artery disease; chronic limb-threatening ischemia.

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Table 1. Summary of trials comparing surgical bypass with endovascular intervention.

Study, year	Study design	Cohort size	Results
BASIL,[6] 2005	Prospective, multicenter randomized controlled trial	452 (228 surgery first, 224 angioplasty first)	Primary end point of amputation-free survival did not differ significantly between groups at 6 mo (unadjusted HR, 1.07; 95% CI, 0.72-1.6; adjusted HR, 1.04; 95% CI, 0.69-1.56) Signal for improved amputation-free survival in surgery-first group after 2 y (adjusted HR, 0.37; 95% CI, 0.17-0.77) No difference in quality-of-life measures throughout the course of the study
BASIL post hoc analysis,[7] 2010	Post hoc analysis of BASIL	452 (228 surgery first, 224 angioplasty first)	Surgery as the first intervention was associated with improved amputation-free survival (adjusted HR, 0.37; 95% CI, 0.17-0.77; $P = .008$) and improved all-cause mortality (adjusted HR, 0.34; 95% CI, 0.17-0.71; $P = .04$) at time periods beyond 2 y A follow-up analysis of patients who survived to 2 y was conducted later and confirmed that initial randomization to bypass surgery was associated with significantly improved overall survival (by 7.3 mo; $P = .02$)
BASIL Infrapopliteal Cohort,[8] 2017	Post hoc analysis of BASIL, infrapopliteal cohort	104 (56 surgery first, 48 angioplasty first)	There was no statistically significant difference in overall survival, although there was a trend toward significance favoring the bypass group (HR, 0.60; 95% CI, 0.36-1.02; $P = .06$) Surgical intervention was much more strongly associated with relief of rest pain than angioplasty (HR, 2.19; 95% CI, 1.27-2.78; $P = .005$)
BASIL Infrapopliteal Cohort,[9] 2022	Post hoc analysis of BASIL, infrapopliteal cohort	60 (20 surgery first, 20 angioplasty first, 20 major limb amputation)	Endovascular therapy (£329; 95% CI, £242-£390) was significantly less expensive than bypass surgery (£2551; 95% CI, £1934-£2807), likely owing to the length of the intervention and the number of staff required Over the course of the further 12 mo, the total cost of endovascular therapy (£12,298; 95% CI, £6961-£15,439) was also less than that of surgical revascularization (£20,401; 95% CI, £12,071-£23,926)
BEST CLI,[10] 2022	Prospective, multicenter randomized controlled trial	1830 (cohort 1: 709 surgery first, 711 endovascular first, cohort 2: 194 surgery first, 199 endovascular first)	In cohort 1 (available GSV), primary outcome event (major adverse limb event or death from any cause) occurred more frequently in the endovascular vs surgery group (57.4% vs 42.6%; HR, 0.68, 95% CI, 0.59-0.79; $P < .001$), driven by a statistically significant difference in major reintervention rates between surgery and endovascular (9.2% vs 23.5%) and a numerically higher rate of above-ankle amputations in the endovascular group (14.9% vs 10.4%) In cohort 2, primary outcome events were not significantly different between endovascular and surgical groups (47.7% vs 42.8%; HR, 0.79; 95% CI, 0.58-1.06; $P = .12$) No significant difference in adverse events between the groups or cohorts
BASIL-2,[11] 2023	Prospective, multicenter, randomized controlled trial	345 patients (172 surgery first, 173 endovascular first)	The primary outcome of amputation-free survival was statistically better in the endovascular-first group, with a primary event (major amputation or death) occurring in 53% in the endovascular arm vs 63% in the surgery arm (HR, 1.34; 95% CI, 1.02-1.8; $P = .037$) driven by higher mortality in the vein bypass arm (53% vs 45%) No between-group difference in individual components of the primary end point or 30-d MALE or MACE rates No between-group difference in rates of subsequent intervention after index procedure

GSV, greater saphenous vein; HR, hazard ratio; MACE, major adverse cardiovascular event; MALE, major adverse limb event.

Surgical revascularization

Bypass surgery is an open revascularization option for patients experiencing CLTI that predates endovascular approaches by decades.[4] Traditionally, autologous veins (ie, the ipsilateral single-segment greater saphenous vein [GSV]) are used to bypass areas with significant plaque burden and to revascularize threatened limbs. In patients without suitable ipsilateral or contralateral GSVs, other veins such as from the arm or prosthetic grafts may be used. Given substantially lower long-term patency rates for prosthetic grafts (3-year patency 55.5% vs 72.8% for femoro-below-the-knee-popliteal bypasses and 41.1% vs 68.3% for femorotibial bypasses), native veins remain the preferable option if available.[5]

BTK PAD is often characterized by long, multisegment lesions in small target vessels, which has posed a technical challenge for surgical revascularization. With the advent of endovascular revascularization over the preceding decades, there has been debate as to whether endovascular techniques may be able to better address the complexities of BTK PAD compared with bypass surgery. The BASIL trial was the first randomized controlled trial (RCT) evaluating the effectiveness of surgery versus endovascular treatment (Table 1).[6–11] In this trial, 452 patients with infrainguinal CLTI were randomized to receive either a surgery-first or angioplasty-first approach for treatment, with the primary end point of time to major amputation or death from any cause. Although surgery numerically performed better than endovascular intervention regarding reintervention rates, there was no difference in amputation-free survival (AFS). Post hoc analyses did reveal that surgery-first approach was associated with improvements in AFS and all-cause mortality and significantly longer overall survival in those surviving longer than 2 years (Table 1).[7] However, post hoc analyses found no difference in outcomes in patients with BTK PAD although surgery rendered more patients free of rest pain but at a higher cost (Table 1).[8,9] The most important limitation of the BASIL trial was that its endovascular arm was limited to balloon angioplasty only, excluding other options such as bare-metal and drug-eluting stents.

The recently reported BEST-CLI and BASIL-2 trials further add to the debate over which intervention offers the best outcomes for patients with CLTI.[8,11–14] BEST-CLI enrolled 1830 patients with infrainguinal PAD into 2 parallel cohorts, with the primary end point being a composite of major adverse limb events (MALE) or death from any cause. At a median follow-up of 2.7 years in the cohort with an available single-segment GSV conduit, surgical bypass had a lower primary event rate compared with endovascular therapy, driven by lower major reintervention rates with surgery and higher above-the-ankle amputation rates in the endovascular group. In the cohort without a GSV conduit, no significant difference between groups was seen at a median follow-up of 1.6 years. Adverse event rates were similar between groups and cohorts.[10] Several aspects of this trial make this a meaningful update to the prior BASIL trial. This trial enrolled more patients than any other in the space and did so across 150 sites in the United States, Canada, Finland, Italy, and New Zealand, making the data more generalizable. Moreover, whereas the

Table 2. A summary of trials evaluating the efficacy and clinical outcomes of percutaneous transluminal angioplasty (PTA) in BTK PAD.

Study, year	Study design	Cohort size	Results
Mustapha et al,[16] 2016	Systematic review and meta-analysis	6769 participants	Technical success was 91.1% (95% CI, 88.8-93.0) with PTA Incidence of flow-limiting dissections and bailout stenting was 5.6% (95% CI, 3.2-9.8) and 9.1% (95% CI, 6.3-12.9) Outcomes at 1 y were primary patency, 63.1% (95% CI, 57.3-68.6); repeat revascularization, 18.2% (95% CI, 14.5-22.6); major amputation, 14.9% (95% CI, 12.3-18.0); and all-cause mortality, 15.1% (95% CI, 12.8-17.7)
Romiti et al,[17] 2008	Systematic review and meta-analysis	2557 participants	Pooled estimate of technical success was 89.0% ± 2.2% with PTA Outcomes at 1 mo and 3 y were 77.4% ± 4.1% and 48.6% ± 8.0% for primary patency, 83.3% ± 1.4% and 62.9% ± 11.0% for secondary patency, 93.4% ± 2.3% and 82.4% ± 3.4% for limb salvage, and 98.3% ± 0.7% and 68.4% ± 5.5% for survival, respectively
Bosiers et al,[18,19] 2009	Retrospective cohort, single-center study	31 participants	Technical success of AngioSculpt balloon inflation was 100% 35.5% of participants required additional stenting for minor dissections or suboptimal stenosis reduction 1-mo complication-free survival was 96.8%; 1-y survival, primary patency, and limb salvage rates were 83.9 ± 6.6%, 61.0 ± 9.3%, and 86.3 ± 6.4%, respectively
Scheinert et al,[20] 2007	Retrospective cohort, multicenter study	43 participants	Technical success of AngioSculpt balloon inflation was 98.2% It was used as primary therapy without stenting in 89.3% There was no significant slippage or perforations. Postprocedural dissections occurred in 10.7% In 13 participants referred for amputation, the procedure led to limb salvage
Iezzi et al,[21] 2015	Retrospective cohort, single-center study	23 participants	Technical success was 100% with cutting balloon angioplasty No 30-d mortality or adverse events needing treatment were recorded No flow-limiting dissection was observed, so no stent implantation was necessary Primary and secondary patency rates were 89.3% and 93.5% at 6 mo and 77.7% and 88.8% at 1 y, respectively Primary and secondary patency rates at 1 y were 77.7% and 88.8%, respectively, with 1-y survival of 82.5% and 1-y limb salvage rate of 96% without flow-limiting dissections requiring stenting during the index procedure

BTK, below-the-knee; PAD, peripheral arterial disease.

endovascular arm in BASIL was treated with percutaneous transluminal angioplasty (PTA) only, endovascular and surgical operators, were able to use any currently accepted technique to achieve desired revascularization. Nevertheless, there were several notable limitations. The trial was underpowered owing to early termination of enrollment and had a lower-than-expected event rates in both arms, making it unclear whether the difference in major amputation rates between the 2 arms in cohort 1 are in fact significant. In subgroup analyses, the benefit of surgery over endovascular intervention was not significant in older patients, Black patients, and those with renal dysfunction. The 25% prevalence of renal dysfunction in both arms of cohort 1 was quite low and likely not representative of the overall CLTI population. The unbalanced early crossover across both arms of the trial from the endovascular arm to the surgical arm might further bias the results of the trial beyond the aforementioned statistical limitations. This highlights what is known in the field that, in select patient populations, surgical bypass may offer some upfront benefit over endovascular intervention, at least regarding reintervention rates.

The more recently published BASIL-2 trial, an open-label, pragmatic multicenter RCT run in the United Kingdom, Denmark, and Sweden, randomized 345 patients with BTK PAD and CLTI to surgical bypass-first vs endovascular-first approach (172 surgery, 173 endovascular) for revascularization.[11] The primary end point of this trial was AFS, defined by time to first major (above ankle) amputation or death from any cause over a minimum follow-up period of 2 years. As with BEST-CLI, BASIL-2 faced significant enrollment issues. An endovascular-first strategy was shown to be superior to surgery-first approach for the primary end point of AFS, with a primary event occurring in 53% in the endovascular first group vs 63% of the surgery first group (hazard ratio, 1.34; 95% CI, 1.02-1.8; $P = .037$). This difference in the primary end point was primarily driven by a higher rate of mortality in the vein bypass group than that in the endovascular group (53% vs 45%). There was no significant difference between groups in the individual components of the primary end point or 30-day MALE or major adverse cardiovascular event (MACE) rates. There was no difference in number of patients with subsequent intervention in the trial leg; however, reintervention rates were higher in the endovascular arm (19% vs 5% endovascular vs surgery). Similar to BEST-CLI, there were no differences in various general and disease-specific quality-of-life (QoL) metrics in either arm.

Some contend that the choice of initial revascularization strategy (endovascular vs surgical bypass) may influence the outcomes of subsequent revascularization procedures in the ipsilateral limb. In a 2022 study, Nolan et al[15] reported higher rates of 1-year amputation and graft occlusion in those with prior ipsilateral endovascular intervention compared with those without prior ipsilateral endovascular intervention. Importantly, this finding was the same in patients with prior ipsilateral surgical bypass. This importantly highlights the fact that reoperative surgical interventions are morbid and associated with worse outcomes than those with primary bypass surgery, as has been suggested by the outcomes of BEST-CLI.

Endovascular revascularization

The endovascular treatment of BTK PAD has grown dramatically over the past 30 years. Although PTA has been and remains the mainstay of endovascular treatment of BTK PAD, the arsenal of tools at the disposal of vascular specialists has expanded to include drug-coated balloons (DCB), intravascular lithotripsy (IVL), and various scaffolds such as bare metal stents (BMS), drug-eluting stents (DES), endovascular tacks, bioresorbable scaffolds, and other novel devices in the early stages of development. The following sections review the data for the existent endovascular treatment modalities and novel devices in development and various stages of early investigation.

Balloon-based intervention

BTK PAD is a difficult-to-treat disease process given the heterogeneity in the patient population, multivessel and multilevel involvement, small-vessel size, and external crush forces that contribute to ongoing difficulties with designing and deploying scaffolds post-PTA to maintain long-term patency. Although PTA is the standard of care for the endovascular treatment of BTK PAD, the data in this area are underwhelming. In meta-analyses by Mustapha et al and Romiti et al, pooled 1-year patency rates after PTA ranged from 58% to 69%, with 1-year limb salvage rates of 85% to 86% (Table 2).[16–21] The technical success of PTA is often subverted by flow-limiting dissections and heavily calcified lesions. Scaffolds such as BMS, DES, and bioresorbable

Table 3. A summary of trials evaluating the safety and efficacy of Shockwave intravascular lithotripsy (IVL) in PAD

Study, year	Study design	Cohort size	Results
Disrupt PAD III,[23] 2021	Prospective, single-arm, multicenter, nonrandomized study	306 participants	In heavily calcified and symptomatic (claudication or chronic limb-threatening ischemia) infrainguinal PAD lesions, the Shockwave IVL system was shown to have improved procedural success rates (65.8% vs 50.4%; $P = .01$), residual stenosis <30% (66.4% vs 51.9%; $P = .02$), and decreased flow-limiting dissections (1.4% vs 6.8%; $P = .03$) compared with PTA alone Major adverse events and clinically driven target lesion revascularization (CD-TLR) were similar
Disrupt PAD III,[24] 2021	Subanalysis of prospective, single-arm, multicenter, nonrandomized study	101 participants	There was a 99% success rate of achieving residual stenosis <50%, with average residual stenosis of 23.3% ± 12.5% and no flow-limiting dissections requiring adjunctive therapy with Shockwave IVL system
Disrupt BTK,[25] 2018	Prospective, single-arm, multicenter, nonrandomized study	20 participants	The Shockwave system was successful in 95% of participants The composite of major adverse events (death, myocardial infarction, emergency surgical revascularization of the target limb, target limb amputation, and efficacy end point of reduction in percentage of diameter stenosis) at 30 d was 0% The average reduction in percentage diameter stenosis was 46.5%
Disrupt PAD BTK II (NCT05007925)	Ongoing prospective, single-arm, multicenter study	Estimated 250 participants	Ongoing

PAD, peripheral arterial disease; PTA, percutaneous transluminal angioplasty.

scaffolds have been used to treat flow-limiting dissections resulting from PTA in BTK lesions.

Cutting/scoring balloons

Several balloon-based modalities exist for the treatment of heavily calcified lesions, including cutting/scoring balloons such as the AngioSculpt balloon (Philips), which uses nitinol wires on the surface of a minimally compliant balloon to grip and score the surface of atherosclerotic lesions to facilitate calcium fracture in target lesions. Although early studies with these balloons showed them to be safe and effective in balloon angioplasty of BTK lesions, the results did not differ considerably compared with those of standard PTA, with 1-year primary patency and limb salvage rates of 61% and 86.3%, respectively.[18,20] In a more recent study, Lezzi et al examined the use of cutting balloons in short-segment infrapopliteal bifurcation disease with more compelling results (Table 2).[21]

Additional studies have included the Chocolate Balloon Angioplasty Registry (Chocolate BAR), a large prospective cohort of patients with infrainguinal PAD treated with the Chocolate PTA balloon catheter (Medtronic) (NCT01589042), a semicompliant balloon within a nitinol cage allowing for formation of focal grooves/dissection within the atherosclerotic lesion facilitating adequate expansion. The registry included both above-the-knee (ATK) and BTK cohorts. The ATK cohort has been reported previously by Mustapha et al in 2018.[22]

Intravascular lithotripsy

The Shockwave IVL system (Shockwave Medical) has been studied in PAD for use in heavily calcified lesions. The results of the Disrupt PAD III trial demonstrated efficacy of IVL in heavily calcified and symptomatic (claudication or CLTI) infrainguinal PAD lesions, with significantly higher technical and procedural success rates and 80% lower rates of flow-limiting dissection (Table 3).[23–25] A recently published subgroup analysis of the BTK lesions included in the Disrupt PAD III trial demonstrated a 99% success rate for achieving residual stenosis of <50%, with an average residual stenosis of 23.3% ± 12.5% and no flow-limiting dissections requiring adjunctive therapy, and was similarly reinforced with the BTK substudy of the postmarket Disrupt PAD III observational study.[24] The Disrupt BTK trial was a small, single-arm safety and feasibility study examining the Shockwave IVL system in heavily calcified BTK PAD lesions, which reinforced the results of the subgroup analysis of the Disrupt PAD III trial with no major adverse events (MAEs) at 30 days and an average reduction of vessel diameter of 46.5% (Table 3).[25] The Disrupt PAD BTK II trial is an ongoing prospective, single-arm, multicenter study examining the safety and efficacy of the Shockwave IVL system in BTK lesions, the results of which should better define the role of IVL in BTK PAD (NCT05007925). Given the frequency of calcified lesions encountered in the BTK arteries, IVL may play a role in the future of BTK intervention.

Atherectomy

BTK lesions often pose technical challenges due to small-vessel diameters and extensive calcification. In contrast to techniques such as PTA, atherectomy was developed to debulk calcified plaque. This can function as either a primary treatment or an adjunctive therapy to facilitate lesion crossing or optimize the vessel for PTA or stenting. Several types of atherectomy devices have been developed over the past 30 years such as the following: rotational atherectomy (RA), directional atherectomy (DA), laser atherectomy (LA), and orbital atherectomy (OA).

Rotational atherectomy

RA devices use a concentrically rotating burr located at the tip of a catheter, which displaces plaque distally as it rotates. This plaque is then cleared by phagocytosis or by an aspiration device located proximal to the burr.

The Rotablator (Boston Scientific) was the first RA device to be studied in lower extremity (LE) PAD with promising with high rates of technical success, even in chronic total occlusion (CTO) lesions but was later found to be associated with high rates of early restenosis and was largely abandoned, now being not recommended for primary treatment of these types of lesions.[26,27] RESCUE-BTK is a prospective, multicenter clinical trial underway to evaluate the safety and efficacy of the Rotablator system as an adjunctive therapy in severely calcified BTK lesions.[28]

The PATHWAY PVD trial, a prospective, single-arm, multicenter clinical trial including 172 patients, showed more promising results with primary treatment using the Pathway Jetstream PV Atherectomy System (Boston Scientific). The authors demonstrated high technical success rates along with improved rates of restenosis and clinically driven target lesion revascularization (CD-TLR) at 1 year (Table 4).[29–45] In the 18 patients with BTK disease, the 1-year restenosis rate was only 11.1%.[29]

Two other RA devices, the Phoenix (Philips) and the Rotarex (BD Peripheral Vascular Inc), are currently being investigated but limited data are available regarding their efficacy in BTK intervention.

Directional atherectomy

DA devices use a cutting blade located on one side of the catheter, which is directed toward the portion of the vessel containing the plaque. As the device is passed over the lesion, ribbons of plaque are removed and captured in the nosecone of the device.

The SilverHawk Atherectomy Catheter (Medtronic) was the first DA device to be studied in BTK PAD. Zeller et al demonstrated the safety and efficacy of the device in 17 patients with BTK PAD, with a technical success rate of 93%, significant reductions in stenosis, and significant improvements in ABI before discharge (Table 4).[30] The multicenter TALON registry is a prospective real-world experience of the SilverHawk device, with midterm outcomes demonstrating procedural success in 94.7% of lesions and primary patency rates of 80% at 1 year (Table 4). Notably, the use of adjunctive therapy was only required in 26.7% of lesions.[31] Zeller et al published a follow-up study evaluating 49 BTK lesions and found similar technical success rates but slightly lower primary patency rates and higher rates of adjunctive therapy use (Table 4).[32]

The DEFINITIVE LE study was the first prospective, multicenter, independently adjudicated study to investigate the effectiveness of the SilverHawk device in LE PAD. Medtronic's TurboHawk device was allowed to be used as an alternative to the SilverHawk device in the trial; 799 patients with 1022 lesions were included, 189 of which were BTK. Device success was achieved in 89% of cases without adjunctive procedures and with low rates of perforation and embolization. The 1-year primary patency rate was 78% in patients with claudication, and the rate of freedom from major unplanned amputation at 1 year was 95% in the CLTI cohort (Table 4).[33] A formal subgroup analysis of the 189 BTK lesions in the DEFINITIVE LE study was published 1 year later, demonstrating similar results. Patients also demonstrated significant improvements in Rutherford class (RC) and quality of life at 1 year (Table 4).[34] Recently, the SilverHawk and TurboHawk devices were investigated as adjuncts to DCB in the treatment of long BTK lesions with the hope that plaque removal may allow for improved drug delivery into the vessel wall. Rastan et al[35] published a prospective, randomized, multicenter trial including 80 patients randomized to either receive DA+DCB or DCB alone and found similar rates of primary patency at 6 months and TLR at 6 months and 1 year (Table 4).

Laser atherectomy

LA devices use an excimer laser located on the tip of a catheter. The laser delivers pulses of ultraviolet radiation to the atheromatous plaque, removing it from the vessel wall. Devices in this category include the Turbo-Tandem, Turbo-Elite, and Turbo-Power systems (Spectranetics).

Gray et al[37] were the first to evaluate the use of LA in 23 patients with CLTI, 32% of which had BTK lesions. This study used the CVX-300 (Philips) LA device and demonstrated a procedural success rate of 88% with a 6-month limb salvage rate of 69% (Table 4). This was followed by the much larger prospective LACI trial, with 145 patients with CLTI treated with an excimer laser. LA was most often used as an adjunct to PTA and/or stenting and demonstrated a similar overall success rate with a higher 6-month limb salvage rate of 93% (Table 4).[38] The retrospective LIPS study included 726 patients treated with LA + PTA or PTA alone with infrapopliteal and popliteal PAD. Although patients in the LA + PTA group had worse baseline lesion characteristics, use of LA + PTA was associated with an almost 5 times greater likelihood of improvement in BTK lesion severity and a 7 times greater likelihood of achieving ≤50% residual stenosis postintervention when compared with that of PTA alone.[39] The LIPS2 trial followed up the same population of patients after intervention and found similar rates of 3-year major ipsilateral amputation repeat revascularization between the 2 groups, despite worse differences in baseline lesion characteristics.[40]

Orbital atherectomy

OA devices use a diamond-coated crown, which moves eccentrically within the vessel lumen to remove plaque. With increased rotational speed of the crown, the device debulks a greater diameter of vessel, which differentiates it from RA devices.

The OASIS trial was the first prospective, nonrandomized multicenter trial to evaluate the safety and effectiveness of OA in BTK intervention. This study used the Diamondback 360° Orbital Atherectomy System (Abbott) and included 124 patients with 201 BTK lesions. High rates of procedural success were observed along with low rates of MAEs at 30 days and 6 months. At 6 months, patients also demonstrated sustained improvements in ABI and RC (Table 4).[41] furthermore, the CALCIUM 360 trial investigated the use of OA as an adjunct to PTA. Fifty consecutive patients were randomized to receive either OA + PTA or PTA alone. Rates of procedural success were high in both groups, and bailout stenting rates were similar, but freedom from target vessel revascularization at 1 year trended toward significance in the OA + PTA group, and freedom from all-cause mortality at 1 year was significantly higher in the OA + PTA group (Table 4). None of the patients in the study underwent amputations related to the index procedure by 1 year.[42]

Using the CONFIRM registry, a group of 3 registries sponsored by Cardiovascular Systems, to evaluate the performance of their 3 OA devices—Diamondback 360°, the newer Predator 360°, and Stealth 360°—Lee et al[43] analyzed procedural outcomes for 712 RC 4-6 BTK lesions and found a composite rate of procedural complications of 17.8%, which was significantly lower than ATK lesions, and driven mainly by rates of spasm and slow flow (Table 4). The CONFIRM registries were subsequently used to inform technique optimization for the OA devices to help minimize rates of slow flow and spasm.[46] Subgroup analyses have demonstrated device safety and efficacy in diabetic patients[47] and those aged older than 75 years.[48] Most recently, Giannopoulos et al[44] published a subgroup analysis of 503 patients from the LIBERTY 360 study who were treated with adjunctive OA and showed promising 3-year survival estimates and 3-year freedom from amputation estimates, supporting the use of adjunctive OA in patients with both claudication and CLTI (Table 4).[49]

Similar to DA, OA was studied as a vessel preparation technique before DCB in calcified BTK lesions. In the recently published OPTIMIZE BTK pilot trial, 66 subjects were randomized to undergo OA + DCB or DCB alone. At 12 months, the primary patency rate was higher in the OA + DCB group when compared with the DCB-alone group, but this did not reach statistical significance. Rates of freedom from MAE, CD-TLR, major amputation, and all-cause mortality did not differ significantly between the groups (Table 4).[45] This pilot study is being followed by a more adequately powered RCT to investigate the potential benefit of OA as an adjunct to PTA.

Drug-coated balloons

Long-term patency of BTK PAD lesions after PTA is limited by 3 main factors: elastic recoil of the target vessel, flow-limiting dissection, and restenosis due neointimal hyperplasia. Drug-eluting scaffolds have not been as successful in BTK PAD as in the coronary vasculature due to differential in the legs leading to stent fracture and late stent thrombosis.[50,51] DCBs have been developed to deliver antiproliferative agents to vessels post-PTA to prevent the inflammatory cascade

Table 4. A summary of trials evaluating the safety and efficacy of atherectomy in PAD.

Study, year	Study design	Cohort size	Results
PATHWAY PVD,[29] 2009	Prospective, single-arm, multicenter, nonrandomized study	172 patients with LE PAD, 210 lesions	In the entire population of patients with LE PAD, the authors demonstrated technical success rates of 99% and 1-y restenosis and clinically driven target lesion revascularization rates of 38.2% and 26%, respectively In the subpopulation of 18 patients with BTK disease, the 1-y restenosis rate was only 11.1% At 1 y, patients also demonstrated sustained improvements in ABI (0.59 ± 0.21 to 0.82 ± 0.27; $P < .05$) and mean Rutherford class (3.0 ± 0.9 to 1.5 ± 1.3; $P < .05$)
Zeller et al,[30] 2003	Prospective, single-arm study	17 patients with BTK PAD	Technical success rate of 93%; stenosis was reduced from 87% ± 9% to 14% ± 22% after intervention, and ABI improved from 0.5 ± 0.27 to 0.86 ± 0.40 before discharge
TALON Registry,[31] 2006	Observational, multicenter, nonrandomized registry	601 patients with LE PAD, 1258 lesions	Procedural success (≤50% residual stenosis) was demonstrated in 94.7% of lesions, and primary patency rates were 80% at 1 y Use of adjunctive therapy (PTA or stenting) was only required in 26.7% of lesions
Zeller et al,[32] 2007	Observational, single-center, nonrandomized registry	36 patients with 49 BTK lesions	Technical success rates were 98% Primary patency rates were 67% at 1 y and 60% at 2 y Adjunctive PTA or stenting was also performed in 42.8% of lesions
DEFINITIVE LE,[33] 2014	Prospective, single-arm, multicenter, nonrandomized study	799 patients, 1022 lesions, 189 BTK	Device success (≤30% residual stenosis) was achieved in 89% of cases without adjunctive procedures Rates of perforation and embolization were 5.3% and 3.8% The 1-y primary patency rate was 78% in patients with claudication, and the rate of freedom from major unplanned amputation at 1 y was 95% in the CLTI cohort
DEFINITIVE LE BTK Cohort,[34] 2015	Prospective, single-arm, multicenter, nonrandomized study	145 patients, 189 BTK lesions	Procedural success rates were 84% 1-y primary patency was 84% and freedom from major unplanned amputation at 1 y was 97.1% Patients also demonstrated significant improvements in Rutherford class (3 to 1; $P < .001$) and quality of life at 1 y (mean EQ-5D visual analog score, 65.1 ± 18.2 at baseline to 71.8 ± 18.5 at 1 y; $P = .004$)
Rastan et al,[35,36] 2021	Prospective, multicenter, randomized study	80 patients with BTK PAD	Patients were randomized to either receive DA + DCB or DCB alone Rates of primary patency at 6 mo (DA + DCB 49% vs DCB 34%; $P = .24$) and TLR at 6 mo (8% vs 14%; $P = .475$) and 1 y (30% vs 43%; $P = .308$) were similar
Gray et al,[37] 2002	Prospective, single-arm, multicenter, nonrandomized study	23 patients with CLTI, 32% BTK	This study utilized the CVX-300 (Philips) LA device and demonstrated a procedural success rate (≤50% stenosis) of 88%, with a mean reduction in wound area of 89% and a 6-mo limb salvage rate of 69%
LACI,[38] 2006	Prospective, multicenter registry	145 patients, 432 lesions, 41% BTK	LA was most often used as an adjunct to PTA (96%) and/or stenting (45%) The overall success rate was 86% with a 6-mo limb salvage rate of 93%
LIPS,[39] 2014	Retrospective cohort study	731 patients with popliteal or BTK lesions	Patients in the LA + PTA group had worse baseline lesion characteristics (26% more TASC D lesions, 37% more CTOs), but use of LA + PTA was associated with an almost 5 times greater likelihood of improvement in BTK lesion severity by Yamasaki score (OR, 4.77; $P < .0001$) and a 7 times greater likelihood of achieving ≤50% residual stenosis postintervention (OR, 7.59; $P < .0001$) when compared with BA alone
LIPS2,[40] 2015	Retrospective cohort study	726 patients with popliteal or BTK lesions	Despite worse baseline lesion characteristics as described above, groups had similar rates of 3-y major ipsilateral amputation (LA + PTA 4.1% vs PTA 5.1%; $P = .48$) and 3-y repeat revascularization (24.1% vs 22.4%; $P = .56$) between the 2 groups
OASIS,[41] 2009	Prospective, multicenter, nonrandomized study	124 patients, 201 BTK lesions	Authors demonstrated rates of procedural success of 90.1% along with low rates of major adverse events (death, MI, amputation, repeat revascularization) at 30 d (3.2%) and 6 mo (10.4%) At 6 mo, patients demonstrated sustained improvements in ABI (0.68 ± 0.2 to 0.82 ± 0.10; $P < .001$) and Rutherford class
CALCIUM 360,[42] 2012	Prospective, multicenter, randomized, controlled study	50 patients with popliteal or BTK PAD	Rates of procedural success were high in both groups (OA + PTA 93.1% vs PTA 82.4%; $P = .27$) and bailout stenting rates were similar (OA + PTA 6.9% vs PTA 14.3%; $P = .44$) Freedom from target vessel revascularization at 1 y trended toward significance in the OA + PTA group (93.3% vs 80%; $P = .14$) and freedom all-cause mortality at 1 y was significantly higher in the OA + PTA group (100% vs 68.4%; $P = .01$)
CONFIRM Registry,[43] 2016	Prospective, multicenter registry	523 CLTI patients, 712 BTK lesions	The composite rate of procedural complications was 17.8%, driven mainly by rates of spasm (10.3%) and slow flow (7.7%) Compared with complication rates for Rutherford class 4-6 ATK lesions, BTK lesions had significantly higher composite complication rates (17.8% vs 12.1%; $P = .001$) with significantly higher rates of spasm (10.3% vs 4.2%; $P < .001$), slow flow (7.7% vs 5.0%; $P = .03$), and perforation (1.5% vs 0.2%; $P = .005$)
Giannopoulos et al,[44] 2020	Prospective, observational, multicenter registry	503 patients, 272 with BTK lesions	During the 3-y follow-up period, Kaplan-Meier estimates for survival from all-cause death were 84.6% patients with Rutherford class 2-3 lesions, 76.2% for Rutherford class 4-5 lesions, and 63.7% for Rutherford class 6 lesions 3-y freedom from amputation estimates were 100%, 95.3%, and 88.6%, respectively
OPTIMIZE BTK,[45] 2022	Prospective, multicenter, randomized study	66 patients with BTK PAD	At 12 mo, the primary patency rate was 88.2% in the OA + DCB group compared with 54.5% in the DCB-alone group ($P = .07$) Rates of freedom from MAE, CD-TLR, major amputation, and all-cause mortality did not differ significantly between the groups

ABI, ankle-brachial index; ATK, above-the-knee; BA, balloon angioplasty; BTK, below-the-knee; CLTI, chronic limb-threatening ischemia; CTO, chronic total occlusion; DA, directional atherectomy; DCB, drug-coated balloon; LA, laser atherectomy; LE, lower extremity; MAE, major adverse event; OA, orbital atherectomy; PAD, peripheral arterial disease; PTA, percutaneous transluminal angioplasty; TLR, target lesion revascularization.

leading to long-term restenosis while obviating the need for scaffold placement.

DCB angioplasty involves delivery of antiproliferative drug directly to the endothelial surface post-PTA. The theoretical key to successful DCB angioplasty is in efficient delivery of an appropriate dose of drug directly to the effected endothelium with a minimal systemic drug delivery. Two types of DCBs have been studied; paclitaxel-based DCBs and limus-based (sirolimus, everolimus, and zotarolimus) DCBs. Initial experience with DCBs in BTK PAD predominantly used paclitaxel-eluting DCBs. The major clinical trials including DCB treatment of BTK PAD lesions are included in Table 5. The results of the first prospective randomized trial comparing DCB with PTA, DEBATE-BTK, were encouraging. This randomized, open-labeled single-center study comparing the IN.PACT Amphirion (Medtronic) paclitaxel-based DCB with standard PTA in BTK PAD in diabetic patients. Binary restenosis, TLR, and target vessel occlusion at 1 year were significantly improved in DCB versus PTA, with no difference in major amputation rates (Table 5).[52–65] Subsequent randomized trials have shown heterogeneous results, with several trials showing similar superior 1-year patency rates of DCBs compared with standard PTA (Table 5).[54] However, in the IN.PACT DEEP trial, the IN.PACT Amphirion DCB (Medtronic) was shown to have no significant difference in CD-TLR, late lumen loss (LLL), or 1-year binary restenosis rate compared with standard PTA (Table 5). Moreover, the investigators noted a trend toward increased major amputation rate in the DCB arm compared with that in PTA (8.8% vs 3.6%; $P = .08$).[55] Further trials have shown no significant difference in 12-month primary patency rates compared with standard PTA, suggesting heterogeneity in different balloon performance and trial design.[56,57] The concerning trend toward increased major amputation with DCB was again observed in the SINGA-PACLI trial, using a paclitaxel-coated balloon.[58] More concerning than increased major amputations with DCB therapy was a possible association between paclitaxel-based drug-eluting technology (both DCB and DES) used in the periphery and late mortality, first noted to Katsanos et al,[59,60] in 2 meta-analyses published in 2018 and subsequently in 2020. There has been decreased utilization of paclitaxel-based DCBs and the US Food and Drug Administration (FDA) convened an advisory panel in 2019 advising that paclitaxel-coated balloons only be used in select high-risk populations (2019 FDA advisory update). These concerns have now been laid to rest by subsequent analyses and trials, which have failed to demonstrate this mortality signal and have resulted in withdrawal of the FDA's warning. This topic is covered in greater detail by Mosarla et al in their *JSCAI* review of endovascular therapies for femoropopliteal PAD and is summarized in Table 5.[61,63,66] Although controversy exists surrounding paclitaxel-coated DCBs, DCBs using alternative antiproliferative drugs such as sirolimus, everolimus, and zotarolimus may show promise in furthering the role of DCBs in BTK PAD.

Limus-coated balloons are new and have limited data in PAD, but their use in DES and bioresorbable scaffolds in both the coronary vasculature and BTK PAD have shown impressive results compared with BMS or PTA.[36,67,68] The PRESTIGE trial, a single-arm, nonrandomized trial, studied the use of the SELUTION Sustained Limus Release sirolimus-coated DCB in 25 patients with BTK PAD with RC 5 symptoms and TASC II C and D lesions demonstrated impressive 6-month primary patency (81.5%), freedom from CD-TLR (83.3%) and AFS (84%) rates.[64] The 12-month data of the Safety and Feasibility of Surmodics SUNDANCE Drug Coated Balloon (SWING) trial were recently presented at the 2022 Vascular and Endovascular Issues Techniques and Horizons meeting by Dr Ramon Varcoe.[65] This prospective, multicenter, single-arm, feasibility study enrolled 35 patients with RC3-5 BTK PAD in Australia, New Zealand, and Europe for treatment with the SUNDANCE sirolimus-coated balloon (Surmodics). In the per-protocol analysis, performed due to the loss of 10 patients for planned angiographic follow-up owing to the COVID 19 pandemic (Table 5), the primary safety end point of freedom from MALE and postoperative death (POD) at 30 days was achieved in all but 1 patient and the primary efficacy end point of LLL was 1.0 ± 0.79 mm. Primary patency was 80% at 12 months. The ongoing FUTURE-BTK (NCT04511247) trial is an RCT comparing the MagicTouch PTA sirolimus DCB (Concept Medical) plus PTA with standard PTA alone in BTK PAD. The primary end point of this trial is primary patency at 6 months. The role of DCB therapy in BTK interventions remains unclear, with heterogeneous results and safety concerns driving operators toward other means of antiproliferative drug delivery. There may still yet be a more prominent role for DCB therapy in BTK PAD, but this will first need to be further defined by the ongoing trials with newer generation balloons and non–paclitaxel-based therapies.

PTA with scaffolding

The standard of care for BTK PAD has been and for the present remains PTA. Owing to the small-vessel, long-segment, and multivessel and level nature of BTK PAD, stenting with either metallic or bioresorbable scaffolds has not been nearly as successful as it has been in the coronary, aortoiliac, and femoropopliteal vasculature. In the following sections, we will discuss BMS including tacks, DES, and bioresorbable scaffolds in BTK PAD.

Bare metal stents

The use of BMS in PAD began in 1985 to address restenosis and recurrent ischemic symptoms frequently seen after PTA.[69] At the time, repurposed coronary artery stents were mainly reserved as bailout therapies for poor angioplasty outcomes, predominantly flow-limiting dissection, in the extremities. The major trials in this space are summarized in Table 6.[70–74] The first randomized prospective trial in this space was reported in 2005 by Rand et al, comparing primary PTA with BMS placement in 51 patients with Fontaine III-IV symptoms, and found that primary patency at 6 months was significantly higher in the BMS group compared with PTA alone.[70] This was followed by a single-arm multicenter clinical trial of 50 patients utilizing a cobalt chromium alloy coronary stent, demonstrating favorable 12-month primary patency (83.3%) and limb salvage (89.3%) rates.[71]

The Chromis Deep stent (Medtronic) was the first BMS designed specifically for use in BTK arteries, engineered to be more flexible and lengthier than coronary stents, and was shown to have similar outcomes to prior BMS trials (Table 6).[72] The EXPAND Study, published in 2015, was the first multicenter RCT evaluating the efficacy of primary BMS placement with PTA with or without bailout stenting, which failed to demonstrate a significant difference in sustained clinical improvement, TLR, or amputation.[73] Given these underwhelming results, the use of traditional BMS in infrapopliteal PAD has all but disappeared.

Flow-limiting dissections remain a hindrance to long-term vessel patency post-PTA. In stark contrast to the long-segment BMS and its poor performance in the BTK territory is the Tack Endovascular System (Philips), a small, short segment nitinol scaffold designed for tacking up intimal dissection flaps to maintain vessel patency after PTA. The Tack system for BTK lesions uses a 4-F system with 4 independent Tack implants for vessels ranging in diameter from 1.5 to 4.5 mm.

Geraghty et al[74] reported the 12-month results of the TOBA II BTK study in 2020, using the Tack endovascular system for the treatment of flow-limiting dissections post-PTA in the BTK intervention (Table 6). The composite primary efficacy end point of 6-month freedom from MALE and 30-day POD was achieved in 93.4% of patients with impressive rates of tacked segment patency (81.3%), limb salvage (96.8%), and AFS (89.3%) at 12 months (Table 6). The Tack endovascular system was the first scaffold to receive FDA approval for use in BTK PAD following the results of this study.

Table 5. A summary of trials examining the safety and efficacy of drug-coated balloon (DCB) angioplasty in BTK PAD.

Study, year	Study design	Cohort size	Results
DEBATE-BTK,[52] 2013	Prospective, open-labeled, single-center, randomized study	132 participants	Binary restenosis rates at 1 y with DCB vs PTA were 27% vs 74% ($P < .001$); target lesion revascularization, 18% vs 43% ($P = .002$); and target vessel occlusion, 17% vs 55% ($P < .001$) No significant differences were noted in major amputation rate
ACOART-BTK,[53] 2020	Prospective, multicenter randomized, controlled study	105 participants	At 1 y, target lesion revascularization rate was 10% in DCB-treated lesions vs 41% of plain old balloon angioplasty (POBA)-treated lesions ($P < .001$) Complete healing at 1 y was observed in 89.4% of DCB-treated limbs vs 74.5% of POBA-treated limbs ($P = .05$)
ACOART-II BTK,[54] 2021	Prospective, multicenter randomized, controlled study	120 participants	Primary patency at 6 mo was 75.0% in the DCB group and 28.3% in the control group ($P < .001$) 1-y freedom from CD-TLR was 91.5% in the DCB group vs 76.8% in the control ($P = .03$) There was no significant difference in mortality (1.7% DCB vs 3.6% control; $P = .53$)
IN.PACT DEEP,[55] 2014	Prospective, multicenter randomized, controlled study	358 Participants	No significant difference in CD-TLR, LLL, or 1-y binary restenosis rate in the DCB arm compared with those in the standard PTA arm Increased major amputation rate was found in the DCB compared with that in the PTA arm (8.8% vs 3.6%, $P = .08$)
BIOLUX P-II,[56] 2015	Prospective, multicenter randomized, controlled study	71 participants	The primary safety end point (all-cause mortality, target extremity major amputation, target lesion thrombosis, and CD-TLR at 30 d) was 0% with DCB vs 8.3% with PTA ($P = .239$) The primary performance end point (patency loss at 6 mo) was 17.1% with DCB vs 26.1% with PTA ($P = .298$) Major amputations of the target extremity occurred in 3.3% vs 5.6% of participants at 1 y, respectively
Lutonix BTK,[57] 2019	Prospective, multicenter randomized, controlled study	442 participants	Freedom from major adverse limb events and perioperative death with DCB (99.3%) was noninferior to those of PTA (99.4%) ($P < .001$)
SINGA-PACLI,[58] 2021	Prospective, 2-center, randomized study	70 participants	There was no difference in primary patency of treated lesions at 6 mo (43% in PTA vs 38% in DCB; $P = 048$) Through 1 y, mortality was 21% in the DCB group vs 16% in PTA ($P = .43$) Amputation-free survival rate differed through 1 y: 59% of the DCB group vs 78% of PTA ($P = .01$)
Katsanos et al,[59] 2018	Systematic review and meta-analysis	4663 participants	All-cause mortality at 1 y was similar between paclitaxel-coated devices and control arms (2.3% vs 2.3% crude risk; risk ratio, 1.08; 95% CI, 0.72–1.61) There was progressively increasing risk of mortality with each passing year from index paclitaxel-based interventions compared with that of PTA
Katsanos et al,[60] 2020	Systematic review and meta-analysis	1420 participants	Using a composite end point of amputation-free survival, paclitaxel-based DCBs performed worse than that of PTA (13.7% crude risk of death or limb loss with DCB vs 9.4% in PTA; $P = .008$) Neither individual end point (all-cause death or major amputation) met statistical significance on its own
Secemsky et al,[61] 2019	Retrospective cohort study	16,560 participants with femoropopliteal PAD	36.2% of participants were treated with drug-coated devices There was no difference in all-cause mortality between participants treated with drug-coated and those treated with non–drug-coated devices (HR, 0.97; 95% CI, 0.91-1.04; $P = .43$) These findings were consistent across all subgroups including critical limb ischemia, DCB alone, and drug-eluting stent ± DCB
Schneider et al,[62] 2019	Meta-analysis	1980 participants	There was no difference in 5-y mortality between low, moderate, and high dose terciles of paclitaxel exposure There was no difference in 5-y mortality between paclitaxel-based DCB and standard PTA
Secemsky et al,[63] 2021	Retrospective cohort study	16,796 participants	26.4% of participants were treated with drug-coated devices There was no significant difference in long-term mortality with treatment with drug-coated devices and non–drug-coated devices (adjusted HR, 1.03; 95% CI, 0.96-1.10; $P = .39$) Results were comparable for participants treated with balloons alone (adjusted HR, 1.00; 95% CI, 0.92-1.08; $P = .96$) or stents (adjusted HR, 1.02; 95% CI, 0.88-1.18; $P = .78$)
PRESTIGE,[64] 2020	Prospective, single-arm, multicenter, nonrandomized study	25 participants	Technical success was 100% with drug-coated balloons 6-mo primary patency was 81.5%. Freedom from CD-TLR was 83.3%, and amputation-free survival was 84%
SWING,[65] 2022	Prospective, single-arm, multicenter, nonrandomized study	35 participants	ITT and PP analyses reported owing to loss to follow-up angiography in 10/35 patients Safety end point of freedom from MALE achieved in 97% and 100% of patients in PP and ITT analyses, respectively 6-mo LLL 1.0 ± 0.79 mm in both ITT and PP 6-mo primary patency 80% in PP analysis

CD-TLR, clinically driven target lesion revascularization; ITT, intention-to-treat; LLL, late lumen loss; MALE, major adverse limb event; PAD, peripheral arterial disease; PP, per-protocol; PTA, percutaneous transluminal angioplasty; TLR, target lesion revascularization.

Table 6. A summary of trials examining the safety and efficacy of bare-metal stents (BMS) in BTK PAD.

Study, year	Study design	Cohort size	Results
Rand et al,[70] 2006	Prospective, randomized, controlled study	51 participants	Primary patency at 6 mo was significantly higher in the BMS group compared with that in the PTA-alone group, at both the 70% restenosis threshold (83.7% vs 61.1%, respectively) and the 50% restenosis threshold (79.7% vs 45.6%, respectively)
Bosiers et al,[71] 2008	Prospective, single-arm, multicenter, randomized study	50 participants	83.3% of participants were alive at 12 mo with a limb salvage of 89.3% and primary patency of 62.8% with use of BMS
Deloose et al,[72] 2009	Prospective, single-center, randomized study	50 participants	At 1-y follow-up, 79.8% of the study population was alive and limb salvage rate was 91.5% with BMS The primary patency rate was 52.9% Subgroup analysis determined that residual stenosis ≥50% after predilation was a significant risk factor for patency loss at 1-y follow-up
EXPAND,[73] 2015	Prospective, multicenter, randomized, controlled study	92 participants	There was no significant difference in sustained clinical improvement at 1 y between those treated with primary BMS and those treated with PTA and bailout stenting Secondary end points were also negative: primary placement of BMS did not significantly reduce rates of target lesion revascularization, amputation, or mortality at 1 y
TOBA II BTK,[74] 2020	Prospective, single-arm, multicenter study	233 participants	There was successful resolution of 100% of treated dissections At 1 y, 93.4% of participants remained free of the composite end point of major adverse limb events and all-cause perioperative death Tacked segment patency was 81.3%, and limb salvage was 96.8% at 1 y; freedom from CD-TLR and amputation-free survival were 83.1% and 89.3%, respectively Rutherford category improvement was reported in 82.4% of participants, with 62.4% improving ≥3 categories ($P < .001$) 72.5% of wounds healed or improved

BTK, below-the-knee; CD-TLR, clinically driven target lesion revascularization; PAD, peripheral arterial disease; PTA, percutaneous transluminal angioplasty.

Drug-eluting stents

As with the coronary vasculature, the use of BMS is associated with increased rates of restenosis, in part due to arterial wall inflammation following angioplasty, neointimal hyperplasia, and smooth muscle proliferation.[75] Coronary DES have been repurposed in the BTK vasculature to good effect. DES are designed to deliver a scaffold capable of maintaining luminal gains from PTA while simultaneously delivering antiproliferative drug such as everolimus, sirolimus, or paclitaxel to dampen the inflammatory response induced by PTA. Treatment of BTK lesions with DES therapy has been associated with improved outcomes in primary patency and target limb amputation rates.[76,77]

Several trials have evaluated the efficacy of coronary DES in patients with severe claudication and CLTI in BTK PAD. In a small single-center trial, 60 patients with symptomatic BTK PAD (RC 3-6) were treated with either a BMS or a sirolimus-eluting stent (SES) and saw improvement in CD-TLR (23.3% BMS vs 0% SES), MAEs (46% vs 10%), and stent occlusion or restenosis (17.4% vs 0%) with SES placement (Table 7).[78–87]

In a 2007 trial by Siablis et al[79] examining the use of SES vs BMS as a bailout strategy for suboptimal angioplasty results following PTA in BTK PAD, DES outperformed BMS once again (Table 7). Subsequent small prospective trials have continued to demonstrate improved binary restenosis rates with DES in appropriately selected patients.[80,81]

Severe large prospective trials have confirmed these early and promising findings (Table 7).[67,68,88] Although promising, other trials including the PADI trial, comparing paclitaxel-eluting stent with BMS in 137 patients with CLTI, have found no difference in outcomes (Table 7).

The IDEAS trial, an RCT comparing paclitaxel-coated balloons with DES in 50 patients with RC 3-6 symptoms was the first trial comparing DCB with DES, and reported lower rates of binary restenosis with DES vs DCB (28% vs 57.9%; $P = .0457$) without significant difference in mortality, major amputation, or TLR.[85] The difference in restenosis between 2 antiproliferative drug delivery methods support the notion that outside of inflammation, elastic recoil plays a prominent role in restenosis in BTK PAD, having been improved by scaffolding.

In a recent meta-analysis of DES in BTK PAD by Changal et al,[86] the authors examined 9 controlled trials encompassing 945 patients in whom DES was compared with conventional therapies including PTA, BMS, and DCBs. The primary outcome of primary patency was superior in DES (hazard ratio, 2.17; 95% CI, 1.58-2.97; $P = .0008$). DES outperformed conventional therapies for TLR without significant difference in major amputation or all-cause mortality (Table 7). There was significant heterogeneity of the studies included in this analysis.

While these trials have shown promise in the repurposed use of coronary DES to the BTK vasculature, the variable target vessel size and external crush forces of the LE that are not present in the coronary vasculature require a purpose-built DES designed for the local anatomy and biology of the infrapopliteal arteries.

The SAVAL DES (Boston Scientific) is a self-expanding paclitaxel-based DES specifically designed for use in the BTK arteries, longer than traditional coronary stents, specially engineered to be durable in infrapopliteal arteries. The SAVAL stent was designed based on the Eluvia stent, a self-expanding paclitaxel-eluting stent designed for and tested for use in femoropopliteal PAD.[89,90] Phase A of the SAVAL pivotal trial, examining the SAVAL DES in BTK PAD, randomized 201 patients in a 2:1 fashion (SAVAL:PTA) with 12-month primary patency as the primary end point, defined by duplex ultrasound flow in the absence of CD-TLR or surgical revascularization. Primary patency of the SAVAL DES was not superior to PTA alone (68.0 vs 76.0%; $P = .8552$) and did not meet its safety noninferiority end point of 12-month freedom from MAEs either (91.6% vs 95.3% SAVAL vs PTA; noninferiority $P = .0433$).[87] Patient follow-up will continue through 3 years in-office with vital status assessment through 5 years, as defined in the study protocol. It is not clear why the SAVAL stent has not performed as well as those in previous BTK DES trials. The self-expanding nature of the SAVAL stent compared with prior repurposed balloon-expandable coronary DES may have played a role in the differential performance. A significantly greater proportion of patients in the SAVAL DES group had moderate or severe calcification (57.0%) than those in the PTA group (40.8%; $P = .0221$), which may lead to increased risk for in-stent restenosis.

Bioresorbable scaffolds

Although DES have shown promise as a bailout strategy in BTK interventions, the question remains of how to maintain luminal gains of PTA and deliver antiproliferative drug without leaving a permanent scaffold behind. To meet this demand, bioresorbable scaffolds have been developed and studied in multiple vascular beds, including the

Table 7. A summary of trials examining the safety and efficacy of drug-eluting stents (DES) in BTK PAD.

Study, year	Study design	Cohort size	Results
Scheinert et al,[78] 2006	Prospective, single-center registry	60 participants	At a mean follow-up of 10 mo, 23.3% of patients treated with BMS required CD-TLR, compared with 0% treated with DES ($P = .0049$) The number of major adverse events was lower in the DES group vs BMS ($P = .0016$) The mean degree of in-stent restenosis in the DES group was only 1.8% vs 53.0% in the BMS group ($P < .0001$) Owing to the limited sample size and follow-up time, no statistical difference was detected in the rates of limb amputation between the 2 groups, although a numerically greater number in BMS group (10%) experienced major amputation than that in the DES group (0%)
Siablis et al,[79] 2007	Prospective, single-center, nonrandomized, controlled trial	58 patients with 131 BTK lesions (29 patients with 65 lesions in BMS group; 29 patients with 66 lesions in the DES group)	Stenting performed as bail out procedure for all patients for suboptimal angioplasty results SES with significantly higher primary patency compared with BMS at 6 mo (OR, 5.625; 95% CI, 1.711-18.493; $P = .004$) and 1 y (OR, 10.401; 95% CI, 3.425-31.589; $P < .001$) SES had lower in-stent binary restenosis compared with BMS at 6 mo (OR, 0.067; 95% CI, 0.021-0.217; $P < .001$) and 1 y (OR, 0.156; 95% CI, 0.06-0.407; $P < .001$) SES was associated with significantly fewer TLR at 6 mo (OR, 0.057; 95% CI, 0.008-0.426; $P = .001$) and 1 y (OR, 0.238; 95% CI, 0.067-0.841; $P = .026$) No between-group differences in mortality, minor amputation, or limb salvage
Falkowski et al,[80] 2009	Prospective, single-center, randomized study	50 participants	Only 32% of the participants included in this study had chronic limb-threatening ischemia At 6 mo, the participants in the DES group performed significantly better than the participants in the BMS group; the restenosis rate for participants in the DES group was 16%, compared with 76% in the BMS group ($P < .001$)
BELOW,[81] 2010	Prospective, single-center, randomized study	60 participants	After 6 mo, the restenosis rates were 58%, 75%, 67%, and 9%, respectively, with the DES providing the lowest restenosis rate
YUKON-BTX,[36] 2012	Prospective, multicenter, randomized study	161 participants	At 1-y follow-up, there was a statistically significant difference in primary patency rate between the 2 groups, favoring treatment with a DES (80.6% in DES vs 55.6% in BMS; $P = .004$) At a follow-up time of 1000 d, the event-free survival rate was 65.8% in the DES group vs 44.6% in BMS ($P = .02$) Additionally, the rate of limb amputation was significantly lower in the DES group than that in the BMS group
DESTINY,[68] 2012	Prospective, multicenter, randomized study	140 participants	At 1-y follow-up, the primary patency in the DES group was 85.4%, compared with only 54.4% in the BMS group ($P = .0001$) Patency was superior in the DES group for those who had both proximal and distal lesions At 1-y follow-up, 91.3% of participants in the DES group were free from target lesion revascularization, compared with 66.4% in the BMS group ($P = .001$) There was no difference in survival between the 2 groups at 1 y
ACHILLES,[67] 2012	Prospective, multicenter, randomized study	200 participants	In the intention-to-treat analysis, 41.9% of participants in the PTA group had in-segment restenosis, compared with 22.4% in the DES group ($P = .019$) Statistically significant reductions in restenosis rate were also apparent in the as-treated population ($P = .004$) and in the subset of diabetic participants ($P < 0.001$) Other end points, such as percentage diameter of stenosis ($P = .001$) and minimal lumen diameter ($P = .044$), favored intervention with the DES The clinical end point of vessel patency, defined as absence of hemodynamically relevant restenosis and/or CD-TLR, also favored treatment with DES (75.0%) vs PTA (57.1%) ($P = .025$) Freedom from a composite end point of death, target lesion revascularization, bypass, amputation, and Rutherford class ≥ 4 also favored the DES group over the PTA group at 1 y (log rank $P = .028$)
PADI,[82] 2016	Prospective, double-arm, multicenter, randomized, controlled study	137 participants	At 6 mo, a signal toward benefit for the DES treatment was seen, with significantly worse treatment failure noted in the PTA $\pm$ BMS group than that in the DES group, as graded by an ordinal score of both angiographic and clinical end points (modified intention-to-treat $P = .041$) The lesion patency rate at 6 mo showed a trend toward better outcomes in the DES group than that in the PTA $\pm$ BMS group (35.1% vs 48.0%), but this did not reach statistical significance ($P = .096$) There was similarly a trend toward reduction in amputations for those treated with a paclitaxel-eluting stent by 2 y follow-up; however, again, this did not reach statistical significance ($P = .066$)
PADI,[83] 2017	Prospective, double-arm, multicenter, randomized, controlled study	137 participants	At 5 y follow-up, the differences in outcomes between participants treated with a DES or a BMS became more pronounced. There was a statistically significant improvement in a composite major amputation or death rate end point ($P = .043$) and event rate per patient ($P = .041$) The rate of amputations in the PTA $\pm$ BMS group (34.0%) remained higher than that in the DES group (19.3%); however, this, again, did not reach statistical significance ($P = .091$)

(*continued on next page*)

Table 7 (continued)

Study, year	Study design	Cohort size	Results
			The survival rate at 5 y remained comparable between both groups (37.0% and 37.7% for the PTA ± BMS and the DES groups, respectively; $P = .45$)
PADI,[84] 2020	Prospective, double-arm, multicenter, randomized, controlled study	137 participants	There were poor mortality outcomes in both patients treated with PTA ± BMS and DES, with no statistically significant difference between both groups at 10 y (log rank $P = .12$) Similarly, the authors reported no total dose-related mortality associated with paclitaxel (unadjusted HR, 1.0; $P = .90$)
IDEAS,[85] 2014	Prospective, randomized, controlled trial	50 patients (25 arteries in 25 limbs in the DCB group; 30 arteries in 27 limbs in the DES group)	At 6 mo, angiographic binary restenosis rate was significantly lower in DES than that in PCB group (28% vs 57.9%; $P = .047$) No significant differences in TLR (7.7% DES vs 13.6% PCB; $P = .65$) No difference in death or major amputation between groups ($P = 1.00$ for both comparisons)
Changal et al,[86] 2022	Systematic review and meta-analysis	945 patients across 9 controlled trials	Primary patency superior with DES compared with conventional therapies such as PTA, BMS, and DCBs (HR, 2.17; 95% CI, 1.58-2.97; $P < .0001$) DES was associated with lower rates of TLR compared with controls (HR, 0.48; 95% CI, 0.22-0.68; $P < .0001$) No significant difference in major amputation rates and mortality between groups
SAVAL,[87] 2023	Prospective, multicenter, randomized, controlled study	201 Participants (130 DES, 71 PTA)	The SAVAL DES did not meet its primary safety of efficacy end points Primary patency in the DES group was 68% vs 76% in the PTA group (difference 8%, 95% CI, −22.9% to 6.8%, *P* for superiority = .8552) 12-mo MAE-free rate 91.6% in DES vs 95.3% in PTA group (difference, −3.7%; 95% CI, −10.9% to 3.5%; *P* for noninferiority = .0433)

BTK, below-the-knee; BMS, bare-metal stent; CD-TLR, clinically driven target lesion revascularization; DCB, drug-coated balloon; PAD, peripheral arterial disease; PCB, paclitaxel-coated balloon; PTA, percutaneous transluminal angioplasty; SES, sirolimus-eluting stent; TLR, target lesion revascularization.

BTK vasculature. These scaffolds maintain vessel patency post-PTA and enable sustained antiproliferative drug delivery, while deploying a scaffold that will ultimately be resorbed with time.

The first study of bioresorbable drug-eluting scaffolds for BTK indications, using the Absorbable Metal Stent (AMS) (Magic; Biotronik) was reported in 2005 by Bosiers et al,[91] reporting 12-month outcomes of 20 patients with RC 4-6 using the AMS in BTK PAD. The 1-year primary patency, limb salvage, and survival were 73.3%, 94.7%, and 85%, respectively. The follow-up AMS INSIGHT trial, a large multicenter randomized trial comparing AMS with PTA alone in 117 patients with BTK PAD and CLTI found no difference in the primary safety end point of 30-day freedom from major amputation or death but demonstrated inferior 6-month patency of AMS vs PTA (31.8% vs 58%; $P = .013$).[19] Enthusiasm for bioresorbable scaffolds did not die with the failure of the AMS.

The ABSORB Bioresorbable Vascular Scaffold (BVS) (Abbott Vascular)[92,93] is a widely studied bioresorbable scaffold in BTK PAD with several studies comparing the ABSORB BVS with standard-of-care therapies. In 2016, Varcoe et al presented the 1-year results of a prospective, single-center experience using the ABSORB BVS in BTK PAD (Table 8).[19,92–97] In 33 patients with RC 3-5 symptoms, the ABSORB BVS was associated with 12-month survival of 84.8%, freedom from CD-TLR (96%), and primary patency of 96%, 96%, and 84.6% at 6, 12, and 24 months, respectively (Table 8). The 5-year outcomes of these data were recently reported with similarly encouraging results.[94] Additional retrospective data have demonstrated similar efficacy.[95]

In a recent systemic review and meta-analysis of studies utilizing bioresorbable scaffolds in BTK PAD with 12-month data available, Ipema et al[96] report pooled 1-year primary patency rate of 90%, freedom from CD-TLR of 96%, limb salvage rate of 97%, and survival of 90%. In a more recent pooled analysis of 3 cohorts using the Absorb BVS in BTK PAD, Huizing et al[98] reported outcomes for 121 patients receiving 189 ABSORB BVS with similar outcomes (Table 8).

The recently published LIFE-BTK trial was the first large, multicenter, multinational RCT comparing drug-eluting bioresorbable scaffolds (DRS) with standard-of-care balloon angioplasty. LIFE-BTK assessed the safety and efficacy of the ESPRIT DRS (Abbott Vascular) in BTK PAD compared with PTA.[97] In total, 261 patients with RC4-5 symptoms due to lesions in the proximal two-thirds of the BTK arteries were randomized in a 2:1 fashion (173 DRS vs 88 PTA) and followed up for 1 year for the composite primary efficacy end point of freedom from above-ankle amputation in target limb, occlusion of target vessel, CD-TLR, or binary restenosis. The primary safety end point was 6-month freedom from MALE or POD. The primary efficacy end point was observed in 74% in the DRS arm versus 44% in the PTA arm (30% absolute difference; 95% CI, 15%-46%; $P < 0.001$ for superiority, number needed to treat = 4). The primary safety end point was noninferior in the DRS arm compared with that of the PTA arm. The results of this trial mark a potential turning point in the treatment of BTK PAD, offering a solution to the problem of maintaining luminal gains with a scaffold alongside sustained delivery of antiproliferative drug, which may play a prominent role in the future of device therapy in endovascular interventions in BTK PAD. Other ongoing trials including MOTIV BVS BTK (MOTIV bioresorbable scaffold; REVA Medical; NCT03987061), and RESOLV I (MAGNITUDE Bioresorbable Drug-Eluting Scaffold and Delivery System; R3 Vascular; NCT04912323) will better define the role of BVS in the BTK space.

Intravascular ultrasound

The use of intravascular ultrasound (IVUS) imaging in coronary artery interventions has been an area of active investigation for many years and has been well demonstrated to improve both periprocedural results

Table 8. A summary of trials examining the safety and efficacy of bioresorbable vascular scaffolds (BVS) in BTK PAD.

Study, year	Study design	Cohort size	Results
AMS INSIGHT,[19] 2009	Multicenter, randomized, controlled study	117 participants	Procedural success was achieved in 100% of absorbable metal stent participants and 96.4% of PTA participants There was no significant difference in the primary safety end point of 30-d freedom from major amputation or death between the groups In the intention-to-treat analysis, the absorbable stent failed to outperform and was inferior to PTA alone, with 6-mo primary patency rate of 31.8% in the absorbable stent arm compared with 58% in PTA ($P = .013$)
Dia et al,[92] 2019	Retrospective, single-center case series	31 Participants	There was 100% procedural success with Absorb bioresorbable vascular scaffold Freedom from clinically driven target vessel failure was 95.1% at 1 y, driven by 1 revascularization, and 1 amputation Primary patency was 96.7% at 12 mo All participants were alive at 1 y, and 96.8% of participants showed improvements their Rutherford classification
Varcoe et al,[93] 2016	Prospective, single-center study	33 participants	79% of patients showed clinical improvement defined by either wound healing or improvement in Rutherford class with the Absorb BVS 12-mo survival was 84.8% Freedom from CD-TLR was 96% at 6, 12, and 24 mo. Primary patency was 96%, 96%, and 84.6% at 6, 12, and 24 mo, respectively 64% of patients with Rutherford class 5-6 had complete healing of their wounds during follow-up period
Varcoe et al,[94] 2021	Prospective, single-center study	48 participants	Binary restenosis occurred in only 15.5% of bioresorbable scaffolds at 5 y Primary patency in 72.3% was reported at 5 y Freedom from CD-TLR of 90.7% at 5 y After a follow-up period of 35.2 ± 20.4 mo, 54.2% of participants were alive
DISAPEAR,[95] 2020	Retrospective registry	41 participants	There was 100% technical success with the Absorb BVS 6- and 12-mo primary patency rates was 95% and 86%, respectively 1-y freedom from CD-TLR and major amputation was 93% and 98%, respectively, and amputation-free survival was 85% at 1 y 79% of participants with Rutherford class 5-6 symptoms had wound healing by 1 y
Ipema et al,[96] 2021	Systemic review and meta-analysis	155 participants	The pooled 1-y primary patency rate with the use of bioresorbable scaffolds was 90%; freedom from CD-TLR, 96%; limb salvage rate, 97%; and survival, 90%
LIFE-BTK,[97] 2023	Prospective, multicenter, randomized, controlled trial	231 patients (173 BVS vs 88 PTA)	The primary efficacy end point of freedom from ipsilateral above-ankle amputation, target vessel occlusion, CD-TLR, or binary restenosis was observed in 135/173 (74%) patients in the BVS arm and 48/88 (44%) in the PTA arm (30% absolute difference; 95% CI, 15-46; $P < .001$ for superiority) The primary safety efficacy end point of freedom from MALE or POD was observed in 165/170 in the BVS arm and 90/90 in the PTA arm ($P < .001$) for noninferiority Serious adverse events occurred in 2% of patients in the BVS group and 3% of those in the PTA arm

BTK, below-the-knee; CD-TLR, clinically driven target lesion revascularization; MALE, major adverse limb event; PAD, peripheral arterial disease; POD, postoperative death; PCB, paclitaxel-coated balloon; PTA, percutaneous transluminal angioplasty; TLR, target lesion revascularization.

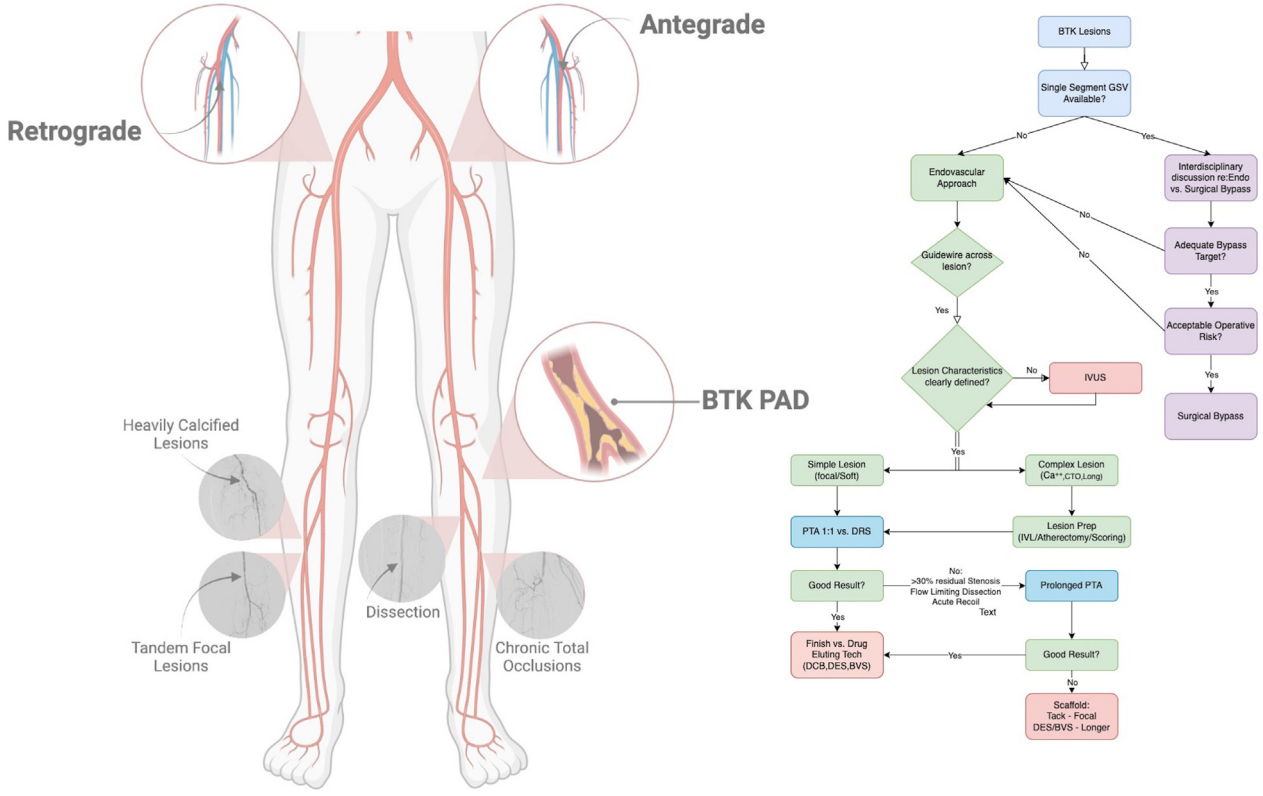
and postprocedural outcomes. Only recently have studies suggested that the utility of IVUS may extend to peripheral interventions.[99] The literature in BTK interventions is currently limited to several small cohort studies.

Three studies in BTK interventions have suggested that IVUS imaging provides more accurate estimations of reference vessel diameter than traditional angiography. Shammas et al performed a prospective single-center cohort study including 20 patients undergoing BTK PTA or atherectomy and found that quantitative vascular angiography (QVA) arterial diameter measurements were on average 1.1 mm smaller than measurements derived using IVUS for the same treated artery (mean 2.9 vs 4.0 mm; $P < .001$).[100] Pliagas et al[101] performed a similar cohort study ($n = 43$) comparing measurements from digital subtraction angiography (DSA) to IVUS measurements and found that DSA provided significantly smaller vessel lumen estimates across all above-ankle BTK segments.

Accurate estimates of vessel size are a critical component of successful BTK interventions as this facilitates appropriate device sizing, which directly affects procedural results. In a single-center, retrospective cohort study of 216 patients with BTK CLTI undergoing PTA, Fujihara et al[102] found that significantly larger balloon sizes were chosen in IVUS-guided procedures than those of angiography-guided procedures (mean 2.45 ± 0.4 mm vs 2.23 ± 0.4 mm; $P < .001$) and significantly better postprocedural skin perfusion pressures (all $P < .02$) and improved wound healing rates ($P = .006$). Soga et al[103] performed a similar study in 155 patients with BTK CLTI undergoing PTA and found very similar results, in addition to higher rates of limb salvage without any reintervention ($P = .0028$), when compared with procedures guided by angiography alone.

Two studies have also suggested that IVUS may have utility in BTK CTO intervention. In 2017, Takahashi et al[104] performed a retrospective cohort study ($n = 50$ limbs) investigating technical success rates and 1-year outcomes for femoropopliteal and BTK CTOs treated with transvenous IVUS-guided endovascular therapy. This procedure, which uses an IVUS catheter in a vein parallel to the target artery to provide imaging guidance during recanalization achieved successful recanalization (TIMI 3 flow) in 96% of limbs and had a 77.9% rate of freedom from TLR at 1 year.[104] A new IVUS system (AnteOwl WR; Terumo) has been specifically developed for CTO intervention and was recently shown to be helpful in recanalizing even long CTOs in a case series published by Hayakawa et al.[105] Natesan et al have recently published a systematic review of the use of IVUS in peripheral vascular disease in 2022, offering a comprehensive evaluation of IVUS in both PAD and iliofemoral venous disease.[106]

These data emphasize the need for randomized trials in this area. The first such RCT evaluating IVUS in PAD interventions was published in JACC by Allan et al in 2022.[99] In total, 150 patients were randomized in 1:1 fashion to angiography alone vs angiography plus IVUS-guided femoropopliteal intervention with the primary outcome of freedom from binary restenosis at 12 months by duplex ultrasound significantly favoring the addition of IVUS (72.4% vs 55.4%; $P = .008$). There was no



Central Illustration.
Algorithm for the management of BTK PAD. BTK, below-the-knee; BVS, bioresorbable vascular scaffold; CTO, chronic total occlusion; DCB, drug-coated balloon; DES, drug-eluting stent; DRS, drug-eluting bioresorbable scaffold; GSV, greater saphenous vein; IVL, intravascular lithotripsy; IVUS, intravascular ultrasound; PAD, peripheral arterial disease; PTA, percutaneous transluminal angioplasty.

significant difference in CD-TLR. However, other secondary outcomes including mean vessel diameter (5.6 vs 5.1 mm; $P < .001$) and binary restenosis at 12 months when combined with DCB (9.1% vs 37.5%; $P = .001$) favored IVUS guidance as well. This study has paved the way for further RCTs of intravascular imaging in the PAD space, focusing now on the BTK segments and reinforces the promise that IVUS guidance may hold in guiding PAD interventions to optimize technical results and long-term patency.

Devices in development

With the recent successes of drug-eluting devices and IVL in maintaining target vessel patency, there is much enthusiasm for new and novel devices to meet the ever-expanding need for durable revascularization in BTK PAD. In this final section, novel devices and therapies currently in various stages of development and study for use in BTK PAD will be reviewed.

The MicroStent system developed by Micro Medical Solutions was purpose-built for use in BTK PAD. The continual outward radial force exerted by balloon-expandable stents on the atherosclerotic plaques and vessel walls is felt to be a contributing factor in neointimal hyperplasia. The MicroStent system, utilizing a self-expanding woven nitinol stent, is meant to overcome this limitation by exerting lower radial force than that by balloon-expandable stents while maintaining luminal gain and vessel patency after PTA. A safety and feasibility study of 15 patients with RC 4-5 symptoms demonstrating 100% freedom from MALE and POD at 30 days, 91.7% primary patency at 30 days, and 100% freedom from CD-TLR led to the US FDA granting the device an investigational device exemption in 2019.[107] At 6 months, there was no change in primary patency with 90.9% of patients maintaining target vessel patency. The follow-up STAND randomized trial will enroll 177 patients comparing the MicroStent system with standard PTA in BTK PAD (clinicaltrials.gov NCT NCT03477604). The primary outcome of this trial will be primary patency at 6 months, defined as freedom from target vessel occlusion, CD-TLR, or major amputation in the target limb. This will be one of the first trials comparing primary stenting with PTA following on the disappointing results of the SAVAL Pivotal trial.

ReFlow Medical has developed the Spur device for use in BTK PAD, consisting of a temporary stent with spikes designed to penetrate atherosclerotic lesions with the goal of delivering antiproliferative drug deeper into the arterial wall. The DEEPER LIMUS trial is a pilot study being conducted in 30 patients with BTK PAD to assess safety and efficacy of the Spur device (NCT04162418). The primary end point in this study is a 6-month composite end point of all-cause mortality, freedom from CD-TLR, and major amputation. This device may serve to bridge the gap between DCB and DES technology, delivering local antiproliferative drug deep into the arterial wall without the need for a retained scaffold.

The ultimate goal of any revascularization strategy in BTK PAD, whether surgical or endovascular, is the restoration of straight in-line flow to a target angiosome. However, in some patients, there are neither adequate distal bypass targets, nor a means of establishing flow via an arterial endovascular approach. These no-option patients often require major amputation. The final device in this section was designed with these patients in mind. The LimFlow stent graft system (LimFlow) is designed for endovascular interventionalists to perform percutaneous deep vein arterialization (DVA) in patients with no-option BTK PAD. The procedure is performed via simultaneous retrograde pedal access to the desired deep vein and antegrade arterial access to the diseased tibial vessel. A needle is passed from

the artery into the vein, creating an arteriovenous fistula and is then lined with a covered stent, resulting in in-line flow from the diseased tibial vessel to the foot. The PROMISE I trial, a study of 32 patients with no-option CLTI undergoing DVA with the LimFlow system was reported in 2021.[108] The authors report 97% technical success rate and 30-day, 6-month, and 12-month AFS rates of 91%, 74%, and 70%, respectively, with 75% of wounds healed or healing at 12 months. However, 52% of patients required reintervention. AFS decreased to 59% by 2 years, driven in large part by all-cause mortality rather than major amputation; 85% of patients had fully healed wounds. The follow-up PROMISE II trial was recently reported, encompassing 105 patients with no-option BTK PAD who underwent DVA with the LimFlow system with the primary end point of 6-month AFS with a performance goal of 54%.[109] As with PROMISE, the investigators had high rates of technical success (99%), with AFS at 6 months of 66% (posterior probability of AFS at 6 months $>$ 54% performance goal 0.993 − greater than prespecified threshold of 0.977).

Standardization of outcomes

In this final section, we discuss standardization of patient selection, ascertainment of imaging end points, and choice of end points in future clinical trials in the BTK PAD space to ensure that emerging data are broadly applicable and clinically relevant.

As the field of BTK PAD intervention has evolved, most operators and expert consensus agree that only patients with CLTI should undergo revascularization given the high rates of restenosis, stent failure, and need for repeat revascularization in the patient population with BTK PAD. However, within CLTI, those with minor and major tissue loss (RC 5-6) experience significantly higher rates of major amputation and death when compared with patients with ischemic rest pain alone (RC 4), partly because of the blurred lines between RC 3 and RC 4.[110,111] Patients with RC 5-6 PAD are more likely to have clinical events and, thereby, are the group in which we would expect to see the greatest clinical effect. However, the inclusion of patients with RC 4 PAD at significantly lower risk of amputation and death may serve to dilute the overall effect of an intervention under study. Therefore, the question of how best to manage patients with RC 4 PAD in future studies remains. Should we have higher thresholds for ischemic burden (ie, lower ABI cutoffs for inclusion) in patients with RC 4 PAD? Should outcomes be reported separately for patients with RC 4 vs those with RC 5-6 PAD? How we manage this requires expert consensus to ensure reproducibility of trial outcomes in real-world populations.

For most contemporary trials in the BTK PAD space utilizing imaging end points, the standard for ascertainment of binary restenosis and occlusion has been duplex ultrasonography, due to its ease of use, noninvasive nature, and general reproducibility. However, there are limitations to its use as the means by which binary restenosis ($>$50% stenosis) is assessed, including seemingly arbitrary cutoffs for certain vascular beds, differences in vessel compliance, inflow disease effecting the proximal velocity, and differences in velocity cutoffs for stented vs unstented lesions. The generally applied standard of a peak systolic velocity ratio of $>$2.4 within a given arterial segment has been used to define a $>$50% stenosis based on the work of Ranke et al[112] in 1992, wherein the authors showed that a peak systolic velocity ratio of $\geq$2.4 identified a $\geq$50% stenosis with sensitivity and specificity of 87% and 94%, respectively. However, others have reported different values depending on the segment and population to which this is applied.[113–115] Previous studies have utilized standard DSA as the gold standard of comparison, which remains a subjective measure of vessel stenosis. Several studies have examined the use of QVA to determine correlation between duplex ultrasonography–derived vessel stenosis and a more objective angiographic measure in QVA. These studies demonstrated that the predictive values of peak systolic velocity ratios vary by single-segment vs multisegment stenoses and whether the previously treated artery was stented or not.[116,117] Although these studies were conducted in the femoropopliteal space, it is clear that many factors affect the reliability of duplex ultrasonography in determining restenosis. Several contemporary trials have utilized follow-up angiograms to ascertain binary restenosis or LLL, but there is no standardization of this practice, and duplex ultrasonography is utilized equally as much if not more. It is important to note that, when discussing LLL, this is only a valid end point when either addressing stented lesions, where recoil is not an issue, or in cases where a follow-up angiogram has been performed shortly after the index procedure to account for acute recoil. We likewise cannot compare a scaffolding strategy with a balloon-based strategy with LLL as the end point due to the consequences of acute recoil in PTA-based strategies. We therefore need to standardize the choice of imaging modality for ascertainment of restenosis. If duplex ultrasonography is to be the standard of care, further quantitative validation of peak systolic velocity ratios and the presence of *parvus et tardus* waveforms and spectral broadening in each vessel segment and in scaffolded and nonscaffolded arteries needs to be undertaken to refine and or validate our current standards.

Finally, the choice of end points in clinical trials in the PAD space, not just BTK, not only needs to better address the safety and efficacy of a new device or intervention but should also include end points that demonstrate the clinical and QoL benefit to the patient. Binary restenosis, AFS, and CD-TLR are clinically meaningful but do not reflect the patient's experience. Understanding time to reintervention, time to wound healing, sustained improvement in RC, and patient-reported outcomes (PROs) would give a more holistic view of not only the safety and efficacy of the treatment but also the clinical benefit derived by a patient undergoing a specific treatment. The abovementioned end points have been used sporadically throughout the BTK literature but should become standard in clinic trials of new BTK technology. The American Heart Association recently published a scientific statement on the role of patient-reported outcome measures (PROMs) and the push to develop PROM performance goals to ensure consistent quality of care in PAD care.[118] Given the noninvasive nature of QoL questionnaires, monitoring of wound healing, and assessment of RC, the seamless integration of these measures into routine protocol follow-up visits should not put undue burden on investigators going forward.

As the armamentarium of endovascular technologies for BTK PAD continues to expand, we must be able to speak to the relative cost effectiveness of one treatment over another to ensure appropriate and cost-efficient care is delivered. Without well-validated PROMs and regular use in clinical trials, we cannot give a realistic assessment of the utility and quality-adjusted life years gained or lost from a given intervention. The recent BEST-CLI trial demonstrated the need for standard use of PROMs in the clinical trial setting, wherein the authors found no difference in PROs despite a higher rate of major amputation in the endovascular arm of cohort 1, suggesting the QoL cost associated with surgical intervention compared with endovascular is so high that the cost associated with the increase in amputation rate is offset. Without these measures, the clinical difference between groups would be apparent without understanding the QoL ramifications for the patient.[10] There is a dearth of well-validated PAD-specific PROMs, but several tools are in development. In the short term, much of contemporary literature has utilized the Euro Quality of Life 5 Dimension (EQ-5D) health status assessment, which is not disease specific and, therefore, may lack the granularity to ascertain the level of benefit of an intervention in patients with PAD.

Conclusion

The past 3 decades of research in BTK PAD have been marked by advances in both surgical and increasingly endovascular techniques. While several modalities, predominantly antiproliferative therapies including DCBs, DES, and bioresorbable scaffolds, have shown impressive results in short-term patency and freedom from CD-TLR, short-term, and long-term mortality remain essentially unchanged. Scaffold deployment in BTK PAD has proven fraught with intermediate-term and late-term complications with the notable exception of the recent LIFE-BTK trial. Patients with CLTI due to BTK PAD are one of the highest risk patient cohorts for cardiovascular morbidity and mortality and often die not of complications of their PAD but rather of stroke or myocardial infarction due to their pan-vascular disease. The role of surgical bypass vs endovascular intervention for BTK PAD remains to be fully defined, even with the recently published results of both the BEST-CLI and BASIL-2 trials. PTA remains the standard of care for endovascular intervention in BTK PAD but continues to have high rates of restenosis. The past decade has seen significant growth in the tools available, including endovascular tacks, coronary DES, DCBs, and plaque-modifying therapies such as IVL, atherectomy, and cutting balloons. Unfortunately, the story of DCBs in the BTK vasculature has been disappointing compared with the femoropopliteal vasculature, where DCBs represent a large portion of the market share. In addition to lower rates of primary patency, concerns regarding a possible signal for harm have pushed some operators away from their use, although these concerns now been laid to rest. Likewise, the use of coronary DES in the crural arteries is essentially limited to the treatment of focal, proximal stenoses owing to concerns over late stent failure in longer and more distal lesions. With the recently published LIFE-BTK trial, there appears now to be a viable option for scaffolding with sustained antiproliferative drug release, without the attendant concerns of metallic scaffolds, with durable long-term effects. The Central Illustration represents one of several possible approaches to the treatment of BTK PAD. Although this algorithm is not meant to be prescriptive, it demonstrates both the need for interdisciplinary care in the management of this complex patient population to determine whether surgery or endovascular intervention is best and the growing armamentarium of endovascular devices and their potential roles in revascularization. There are several exciting devices in development, which have shown promising results in small nonrandomized observational studies. The role of these therapies in the future of endovascular therapy for BTK PAD remains to be elucidated by upcoming RCTs. Although we are still in the early stages of this progression, it appears that scaffolds will play a prominent role in the treatment of BTK PAD. What the optimal scaffold is and when it is appropriate for use remains to be fully delineated. What is clear is that we may be entering an era in the treatment of BTK PAD where we may move the needle on long-term patency, wound healing, and limb salvage—a progression that has not been seen in 30 years.

Declaration of competing interest

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