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State-of-the-Art Endovascular Therapies for the Femoropopliteal Segment: Are We There Yet?

Ramya C. Mosarla, MD[a], **Ehrin Armstrong, MD, MSc**[b], **Yonatan Bitton-Faiwiszewski, MD**[b], **Peter A. Schneider, MD**[c], **Eric A. Secemsky, MD, MSc**[d,e,*]

[a]NYU Grossman School of Medicine, New York, New York;

[b]Adventist Heart and Vascular Institute, St Helena, California;

[c]University of California San Francisco, San Francisco, California;

[d]Harvard Medical School, Boston, Massachusetts;

[e]Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Abstract

Peripheral arterial disease is an increasingly prevalent condition with significant associated morbidity, mortality, and health care expenditure. Endovascular interventions are appropriate for most patients with either ongoing symptoms of intermittent claudication despite lifestyle and medical optimization or chronic limb-threatening ischemia. The femoropopliteal segment is the most common arterial culprit responsible for claudication and the most commonly revascularized segment. Endovascular approaches to revascularization of the femoropopliteal segment are advancing with an evolving landscape of techniques for arterial access, device-based therapies, vessel preparation, and intraprocedural imaging. These advances have been marked by debate and controversy, notably related to the safety of paclitaxel-based devices and necessity of atherectomy. In this review, we provide a critical overview of the current evidence, practice patterns, emerging evidence, and technological advances for endovascular intervention of the femoropopliteal arterial segment.

*Corresponding author: esecemsk@bidmc.harvard.edu (E.A. Secemsky).

Declaration of competing interest

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Ethics statement

The compilation of this comprehensive review did not require human or animal subjects research, therefore instiutional review board approval was not pursued.

Keywords

endovascular intervention; femoropopliteal; peripheral arterial disease

Introduction: Endovascular intervention of femoropopliteal disease

The femoropopliteal segment is the most commonly treated infrainguinal culprit in patients presenting with symptomatic peripheral arterial disease (PAD). Revascularization is indicated for lifestyle-limiting claudication after exhausting noninvasive measures and in chronic limb-threatening ischemia (CLTI).[1] Although the decision regarding surgical or endovascular revascularization relies on comprehensive evaluation of both anatomic and patient characteristics, technological advances have allowed an endovascular first approach in increasingly complex lesions. Comparative data for Transatlantic Society Classification (TASC) C and D lesions remain limited, but nonrandomized prospective data indicate that results with drug-coated balloons (DCBs), drug-eluting stents (DES), and covered stents may be competitive with the patency of femoropopliteal bypass. Although DCBs improve restenosis rates, there may be a need for bailout stenting when complications occur, such as flow-limiting dissections and vessel recoil. Conversely, scaffold placement, such as with DES and covered stents, can be used to reinforce the vascular lumen and improve patency; however, these devices are subject to complications such as stent fracture, restenosis due to femoropopliteal mechanical stresses, and stent thrombosis. Emerging technologies in vessel preparation, including atherectomy, specialty balloons, and intravascular lithotripsy, may enhance procedural outcomes and potentially allow avoidance of scaffold placement in the treatment of complex lesions. Intravascular imaging is also an important technology that can lead to more accurate vessel preparation and device sizing and reduce the risk of restenosis following intervention. The future of femoropopliteal intervention will be highlighted by continued innovation in stent technology, including a greater number of biomimetic stents that are more responsive to the stresses of the femoropopliteal segment as well as the resurgence of bioresorbable scaffolds. Furthermore, although the controversy associating paclitaxel-based devices with increased mortality has been all but refuted, there remains interest in exploring alternative antiproliferative agents such as limus-based devices. Herein, we review the current landscape of endovascular femoropopliteal interventions, including state-of-the-art techniques, the armamentarium of currently available devices, and the emerging technologies that we believe all vascular operators should be aware of (Central Illustration; Table 1.).

Vascular access

Techniques for vascular access in femoropopliteal interventions are evolving. Most femoropopliteal interventions are performed from a contralateral femoral approach, which provides favorable angulation for femoropopliteal cannulation.[2] The ipsilateral approach may be chosen in the face of anatomic constraints and offers better wire control, shorter distance to lesions, and more pushability; however, it is technically challenging with proximal superficial femoral arterial disease and flush occlusions.[3,4] Well-known complications of femoral arterial access include local hematoma, pseudoaneurysm, and

retroperitoneal bleeding; additionally, the presence of PAD is associated with an increased risk of access-site complications.[5] Although the use of ultrasound guidance can help to reduce the risk of access-site complications, the rates remain astoundingly high, ranging from 3.5% to 11%.[2,6,7–14] As such, there has been a movement for greater consideration of transradial access, similar to its adoption in coronary interventions. Transradial access for femoropopliteal interventions has been successful in limited studies, with lower rates of access-site complications without compromising outcomes.[15,16] However, transradial access has technical limitations related to the greater shaft lengths needed to reach distal lesions as well as a need for larger bore access that cannot be placed radially when intervening on more proximal arterial segments, such as aortoiliac disease. In these cases, brachial and axillary access may allow larger bore access and sufficiently short access-to-target distance that would allow the use of conventional equipment lengths. Further, limited device selection, such as long shaft length covered stents and drug-coated devices, has prevented more widespread adoption.

There has been significant growth in other sites of retrograde access, including the distal superficial femoral, popliteal, tibioperoneal, and pedal arteries, primarily in combination with antegrade access to assist in crossing chronic total occlusions. Many operators feel that these sites offer safe access options and can provide greater opportunities for procedural success in complex lesion subsets, such as long chronic total occlusions after failed antegrade-only approaches.[17] Cohort studies and systematic reviews of retrograde access approaches (including popliteal, tibioperoneal, pedal, and distal superficial femoral arteries) have demonstrated high rates of procedural success, ranging from 80% to 98%, with low rates of complications (3%−9%).[18–26]

Endovascular devices

Endovascular intervention of the femoropopliteal segment was first described by Charles Dotter[27] in 1964, during which he used coated dilators to perform angioplasty of stenotic lesions. Since the inception of endovascular intervention of the femoropopliteal segment, the armamentarium of devices has rapidly expanded. Despite advances, practical challenges due to unique mechanical stresses, including flexion/extension, compression/elongation and torsion (Figure 1), the high prevalence of chronic total occlusions, diffuse plaque, and heavy calcification, have all continued to impact procedural success and long-term vessel patency.[28] Innovation in this space is substantially needed and ongoing, with a number of novel devices purposely built with these issues in mind recently available to the market or near launching.

Percutaneous transluminal angioplasty

Plain balloon angioplasty (PBA) was the earliest method of percutaneous transluminal angioplasty (PTA). For primary PBA, balloon inflation is used for lumen enlargement, which occurs through compression of plaque, stretching of the external elastic lamina, and creation of dissections. PBA has high technical success rates, ranging from 98% to 100%.[29] However, frequent complications include residual stenosis, vessel recoil, and flow-limiting dissections, which require bailout stenting. Although PBA plays a role in primary

revascularization with provisional stenting, it is often used as an adjunct to other devices. The TASC II consensus document recommended that PBA be performed with provisional stenting in limited disease with stenosis or occlusion length <100 mm; however, it has been recommended that acute failure of PBA necessitates stent placement.[29] This is in accordance with contemporary appropriate use criteria, which grade the use of PBA as appropriate for lesions <100 mm and as may be appropriate for lesions >100 mm.[30] Thus, the primary clinical application is to short, focal lesions, particularly in no-stent preferred zones.

The primary issue with the use of PBA as a standalone therapy is poor rates of long-term patency. A meta-analysis of 923 balloon interventions noted 3-year patency rates of 61% for stenotic lesions and 48% for occlusions in the setting of intermittent claudication.[31] Patency rates for primary PBA are lower compared with those for DCBs, bare-metal stents (BMS), DES, and covered stents, particularly with lesion lengths of >100 mm.[32–39] As a result, further innovation in angioplasty-based intervention was needed. Enter DCBs, which were specifically designed to improve durability of revascularization without necessitating the placement of a vascular scaffold. DCBs are coated with antiproliferative compounds that reduce neointimal hyperplasia, principal among which is paclitaxel.[40] A meta-analysis of 13 randomized controlled trials (RCTs), 6 global registries, and 3 global registries of long lesions found significantly better outcomes for paclitaxel-DCBs in terms of TLR (odds ratio [OR], 0.29; 95% CI, 0.20–0.40), primary patency (OR, 0.38; 95% CI, 0.27–0.54), and late lumen loss (mean diameter, −0.80 mm; 95% CI, −1.44 to −0.16) at 2 years.[41] This meta-analysis included pivotal trials that prompted Food and Drug Administration (FDA) market clearance of paclitaxel-DCBs, including Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis (LEVANT I), Extended Follow-up Post-Approval Study to evaluate the long-term performance of the Lutonix Drug Coated Balloon versus Percutaneous Transluminal Balloon Angioplasty (LEVANT II), Randomized Trial of a Novel Paclitaxel-Coated Percutaneous Angioplasty Balloon (ILLUMENATE), and Randomized Trial of IN.PACT Admiral(TM) Drug Coated Balloon vs Standard PTA for the Treatment of Superficial Femoral Artery and Proximal Popliteal Arterial Disease (IN.PACT SFA).[38,42–45] Paclitaxel-DCBs provide technical advantages in the treatment of longer and more complex lesions compared with PBA, which poses an attractive option to reduce extensive stenting and leaves less metal behind. For instance, in the superficial femoral artery (SFA)-Long Study, which included TASC C and D femoropopliteal lesions with a treated lesion length of 251 ± 71 mm and a 50% rate of chronic total occlusions, paclitaxel-DCBs were associated with a 70.4% primary patency rate at 2 years, with results that have also been corroborated in real-world cohorts.[46,47]

Paclitaxel-DCBs also have favorable cost-effectiveness profiles in the treatment of focal femoropopliteal disease. A cost-effectiveness analysis conducted by the National Health Service evaluated 5,167 procedures from 28 studies and found that paclitaxel-DCBs provided the most favorable incremental cost-effectiveness ratio (£3983) compared with DES and BMS (£4534 and £20,719, respectively).[48] A prospective economic analysis from IN.PACT SFA II compared paclitaxel-DCBs to PBA and found that paclitaxel-DCBs were economically attractive given similar limb-related costs and improved outcomes at 2 years.[37,49]

Given advantages in efficacy and cost effectiveness, along with the option of stent-free treatment of femoropopliteal lesions, paclitaxel-DCBs have been rapidly adopted into clinical practice.[50] However, a 2018 meta-analysis of RCTs evaluated the risk of late death after treatment with paclitaxel-coated devices (including stents) and found an alarmingly increased rate of all-cause mortality at 2 (7.2% versus 3.8%; hazard ratio, 1.68; 95% CI, 1.15–2.4) and 5 years (14.7% vs 8.1%; hazard ratio, 1.93; 95% CI, 1.27–2.93).[51] Although this study had an immediate impact on clinical practice, there were a number of methodologic concerns. For instance, the studies included in the meta-analysis were only designed to assess short-term limb outcomes, and there was significant missing death data in the majority of studies. Furthermore, patient level data were not used, which may have obscured important differences in patient characteristics comparing those receiving paclitaxel devices to those who did not. There was a very limited number of patients with 5 years of follow-up data. Since the publication of the meta-analysis, interim studies of RCT data, as well as observational data, have not corroborated the link between paclitaxel-coated devices and increased late mortality.[52–59] Because of a reasonable safety profile, 6 paclitaxel-coated devices (4 balloons and 2 stents) remain in continued use, but with caution. The FDA has advised judicious use of paclitaxel-coated devices for patients with a high risk for restenosis.[60]

In part, as a result of this controversy, the development of devices with novel antiproliferative agents has blossomed into an active area of exploration. Sirolimus, a macrolide compound with cytostatic properties and less vasculotoxicity than paclitaxel, has been successfully used on drug-eluting coronary stents for more than a decade.[61] Sirolimus allows more rapid endothelization and healing of vessel walls after intervention, which makes it favorable compared with paclitaxel.[62] The major limitation of sirolimus is reduced bioavailability compared with paclitaxel, requiring development of novel phospholipid nanocarriers to allow drug delivery in a DCB design and increase tissue concentrations.[63]

Three sirolimus-coated peripheral DCBs have received breakthrough device designations by the FDA to date, with limited data supporting their competitive efficacy. For instance, Clinical Use and Safety of the Xtreme Touch (Magic Touch PTA) - Neo Sirolimus Coated PTA Balloon Catheter in the Treatment of Infrainguinal Peripheral Arterial Disease (XTOSI) was a single-arm, open-label, single-center study evaluating the safety and efficacy of the MagicTouch DCB. More than 90% of patients had CLTI with Rutherford category 5 or 6, and approximately 80% of patients had at least 1 total chronic total occlusion in below-the-knee arteries. At 12 months, freedom from clinically driven target lesion revascularization (CD-TLR) was 89.7% and amputation-free survival was 81.6%.[64] First-in-human Evaluation of the SELUTION DCB, a Novel Sirolimus Coated Balloon in Peripheral Arteries (SELUTION) was a single-arm, open-label, multicenter study that evaluated the safety and efficacy of the SELUTION DCB. The rate of primary patency was 88.4% at 6 months, and freedom from TLR was 87.5% through 24 months.[65]

It is worth noting that paclitaxel-coated DCBs come with a theoretical risk of distal embolization of paclitaxel that may worsen ischemic injury and potentially delay wound healing because of deposition of antiproliferatives in tissue beds. The concern is more prominent with crystalline versus amorphous excipient formulations of paclitaxel and has

been primarily seen for older device iterations trialed for below-the-knee revascularization.[66] This concern has not yet been linked to sirolimus-coated DCBs.

Vascular scaffolds

The majority of peripheral vascular scaffolds utilized in clinical practice employ self-expanding, nitinol-based BMS. Nitinol is a nickel-titanium alloy with thermal shape-memory and superelasticity that allows for recovery of shape after deformation.[67] The benefit of nitinol-based self-expanding stents was established by the Balloon Angioplasty Versus Stenting With Nitinol Stents in the Superficial Femoral Artery (VIENNA) trial, which demonstrated decreased rates of restenosis at 6 and 12 months compared with those after PTA alone.[32] However, stent failure, in particular fracture caused by repeated torsional and rotational stresses, remains a major concern with these devices. As such, purpose-built stents that tolerate these biomechanical stresses have been developed. The Supera stent, a nitinol-woven stent with a reticular design, demonstrated a markedly low rate of stent fracture in the SUpera PERipheral System in the Superficial Femoral Artery trial (n = 264) and other real-world data and has been used to treat complex lesion subsets, including long lesions, heavy calcification, and the distal SFA/popliteal segments.[68–70] Although head-to-head data comparing the traditional BMS to the Supera stent are lacking, a propensity-matched analysis of the XPLAD registry found that Supera stents had lower rates of TLR (7.6% vs 13.6%; $P = .04$) and target vessel revascularization (7.6% vs 12.7%; $P = .08$) at 1 year.[71]

The next generation of purpose-built vascular scaffolds includes the BioMimics 3-dimensional (3D) stent, which has a helical centerline and is designed to minimize shear stress and improve compatibility with femoropopliteal vasomotion. The MIMICS-2 trial (n = 271), a single-arm, device exemption study in de novo femoropopliteal disease, demonstrated promising results with freedom from adverse events of 79.2%, freedom from loss of primary patency of 70.2%, and freedom from CD-TLR of 83.0% at 24 months.[72] These results were corroborated in MIMICS-3D, which assessed the safety and efficacy of the device in a real-world population (n = 507) and showed sustained clinical improvement in 86.6% and freedom from CD-TLR in 82.8% (95% CI, 79.4%−86.4%).[73]

Although uncoated vascular scaffolds showed improved patency over PBA for complex lesion subtypes, in-stent restenosis remains a major concern. As such, DES were designed to minimize the impact of neointimal hyperplasia. Paclitaxel has been the dominant antiproliferative agent of choice in this domain, with 2 FDA-approved paclitaxel-eluting stents on the market: Zilver PTX and Eluvia.

Zilver PTX is a self-expanding, polymer-free, paclitaxel-coated, nitinol stent. It gained clearance in the United States based on the Zilver PTX RCT, with 480 femoropopliteal lesions randomized to Zilver PTX versus PBA with provisional stenting, with subgroups of provisional BMS versus provisional DES. Patients randomized to Zilver PTX had greater event-free survival (90.4% vs 82.6%; $P = .004$) and primary patency (83.1% vs 32.8%; $P < .001$) at 12 months, and extending to 5 years.[35,39] Cost-effectiveness studies have supported the use of the Zilver PTX over other commercially available devices. For instance, a French

cost-effectiveness model indicated that Zilver PTX would result in a net health care budget reduction of 6,807,202 euros per 82,316 patients based on decreased reintervention.[74] A study of 37,227 femoropopliteal interventions based on a Florida State Ambulatory Database supported these findings.[75]

However, it is worth noting that the recent Bare Metal Stent Versus Paclitaxel Eluting Stent in the Setting of Primary Stenting of Intermediate Length Femoropopliteal Lesions (BATTLE) trial, which randomized to Zilver PTX versus Misago Rx BMS, found no difference in freedom from in-stent restenosis (91% vs. 88.6%; $P = .64$) at 12 months.[76] This has raised questions regarding whether the kinetics of paclitaxel release, the majority of which is released in the first 24 hours after implantation in the Zilver PTX stent, provides continued efficacy against late restenosis over an uncoated scaffold.[76]

With this in mind, the Eluvia stent, which involves a durable polymer that slowly elutes paclitaxel over a period of months to years, was launched in the United States on 2018 as an alternative peripheral DES.[77] The FDA approval of Eluvia was supported by the A Randomized Trial Comparing the ELUVIA™ Drug-eluting Stent Versus Zilver® PTX® Stent for Treatment of Superficial Femoral and/or Proximal Popliteal Arteries (IMPERIAL) trial, which was a head-to-head randomized trial comparing the Eluvia stent to the Zilver PTX stent. This study found improved patency at 12 months with the Eluvia stent over the Zilver PTX stent (Eluvia 86.8% and Zilver 81.5%; difference, 5.3%; $P < .0001$) as well as greater freedom from major adverse events (Eluvia 93.9% and Zilver 91%; difference, 3.9%; $P < .0001$).[78] At 24 months, there was no significant difference in primary patency (Eluvia 83.0% and Zilver PTX 77.1%; [log rank $P = .1008$]), but CD-TLR remained significantly less with the Eluvia stent (Eluvia 12.7% vs Zilver PTX 20.1%; $P = .0495$). One concern that has since emerged with the Eluvia stent is the development of vessel wall or aneurysmal degeneration, termed the “halo sign” on duplex ultrasound.[79] Although there was no difference in vessel wall degeneration by hypoechogenic halo prevalence detection in the IMPERIAL study (33.7% for Eluvia vs 21.4% for Zilver PTX; $P = .153$), data were only available for 27.5% of patients.[80] In the recently published Clinical Impact of Intravascular Ultrasound-Guided Fluoropolymer-Based Drug-Eluting Stent Implantation for Femoropopliteal Lesions (CAPSICUM) study, aneurysmal degeneration was found in 16.8% of Eluvia stents placed by 1 year. However, the clinical impact of this finding has yet to be established.[81]

Similar to the exploration of limus-based DCBs, there has been growth in the development of limus-based DES. Early clinical data for sirolimusand everolimus-based DES have suggested the feasibility of drug delivery and early inhibition of neointimal hyperplasia; however, older device iterations failed to outperform BMS. For instance, in the Sirolimus-eluting versus bare nitinol stent for obstructive superficial femoral artery disease (SIROCCO) trial comparing the SMART-sirolimus-eluting stent versus BMS at 6 months, the sirolimus stent group showed a trend toward lower in-stent mean percent diameter stenosis than BMS (22.6% vs 30.9%; $P = .294$).[82] However, initial enthusiasm was dampened when results at 18 months indicated no significant differences in outcomes.[83,84] Similarly, the single-arm STRIDES study evaluating the Dynalink-everolimus-eluting stent found adequate primary patency at 6 months (94 ± 2.3%); however, the in-stent restenosis

rate at 12 months was 32%.[84,85] Contemporarily, novel limus-based stent technology has employed an abluminal reservoir releasing an amphiphilic formulation of sirolimus, coined amphilimus, and appears more favorable than its limus-based predecessors. For example, Innovative siroLimus seLf expanding drUg-eluting stent for the treatMent of perIpheral disease: evaluation of safety aNd efficAcy (ILLUMINA), a single-arm study assessing the efficacy of limus-based DES, found promising outcomes at 24 months, including a primary patency rate of 83.4% (95% CI, 73.9%−89.6%) and freedom from CD-TLR of 93.1% (95% CI, 85.3%−96.9%).[86] However, head-to-head comparisons with paclitaxel-based DES are warranted to establish the role these devices may play in clinical practice.[87]

While DES and DCBs attempt to reduce neointimal hyperplasia with antiproliferative agents, covered stents attempt to create mechanical barriers to the ingress of hyperplastic growth. The Viabahn endoprosthesis is the only FDA-approved covered stent for the treatment of symptomatic femoropopliteal disease. This endoprosthesis consists of a nitinol frame with internal polytetrafluoroethylene coating with more recent developments including heparin coating and contoured proximal edges. The primary role of covered stents is in the treatment of long segment disease, perforations, and aneurysms. However, a major limitation of these devices is the increased risk of stent thrombosis. An analysis of the Vascular Quality Initiative data set including 3721 infrainguinal procedures (3,338 BMS and 383 CS) found that patients who received covered stents presented with acute limb ischemia more frequently (12% vs 6.3%; $P < .001$) and underwent more major amputations (2.6% vs 1.0%; $P = .006$).[88] Although data against restenosis in the lumen of covered stents are promising, edge restenosis can also occur and is predicted by preprocedural characteristics such as poor distal runoff and stent oversizing, which may require adjunctive procedures such as DCB therapy.[89,90] Furthermore, covered stents can occlude collateral vessels. Although the appropriate approach to treatment and coverage of collateral arteries remain controversial, they are an important consideration when using covered stents.

Plaque modification

The goal of plaque modification is to maximize lumen gain, improve vessel compliance, and facilitate drug delivery, particularly in heavily calcified lesions and diffusely diseased segments. Improved vascular compliance allows for fewer high-grade and/or flow-limiting dissections, which can reduce the need for bailout stenting. The landscape for plaque modification at present is marked by 3 major device classes: atherectomy devices, specialty balloons, and intravascular lithotripsy. There may be added benefit when these devices are utilized in conjunction with intravascular ultrasound (IVUS) to clearly define concentric calcification and assess the adequacy of vessel preparation. While the practical benefit of improved vessel preparation is appreciable, there is a paucity of randomized data to definitively guide its application.

Atherectomy devices

The use of atherectomy for plaque modification is variable among operators but is primarily employed in the treatment of calcified lesions, in-stent restenosis, and unyielding or balloon uncrossable lesions. Atherectomy has been shown to reduce balloon inflation pressures

caused by improved vascular compliance, which may reduce flow-limiting dissections that require provisional stenting.[91] Atherectomy has also been proposed to overcome the effects of calcified disease hindering delivery of antiproliferatives to vessel walls.[92] Although numerous devices are available on the market, few have been evaluated in large prospective randomized studies. Although evidence to date does not suggest that adjunctive atherectomy improves long-term outcomes compared with PTA or stenting, there remains a benefit if the rates of dissection are reduced and to promote full-vessel expansion if stent implantation is being considered.[93,94] Furthermore, there is a possibility that intravascular imaging-guidance may improve selection of lesions requiring atherectomy and to optimize its use.

One of the more commonly used atherectomy devices is orbital atherectomy, which is supported by the Diamondback 360 platform and uses an eccentrically mounted diamond-coated crown. The longest follow-up data of orbital atherectomy, and atherectomy in general, comes from the post hoc analyses of the Observational Study to Evaluate PAD Treatment Clinical and Economic Outcomes (LIBERTY 360) real-world study, which noted low rates of bailout stenting and major amputation at 3 years of follow-up.[95] Conversely, rotational atherectomy uses front-cutting blades and is currently available via 5 FDA-approved platforms: Rotalink, Jetstream, Phoenix, Rotarex, and Revolution. Observational data suggest favorable outcomes, including freedom from CD-TLR with these devices; however, data are largely limited to 12 months of follow-up.[96] As these are front-cutting devices, they may be particularly useful for balloon uncrossable lesions. Directional atherectomy, on the other hand, uses side-cutting blades and is available via 4 devices: SilverHawk, TurboHawk, HawkOne, and Pantheris. Pantheris was studied in conjunction with optical coherence tomography in the single-arm Evaluation of the Pantheris Optical Coherence Tomography Imaging Atherectomy System for Use in the Peripheral Vasculature (VISION) study, which demonstrated that imaging guidance allowed for very high rates (<1%) of adventitial sparing.[97]

Laser atherectomy functions through an entirely different approach to plaque modification and is currently available via 4 devices: Turbo-Elite, Turbo-Power, Auryon, and DABRA. Turbo-Elite, Turbo-Power, and DABRA rely on excimer lasers that use short-wavelength energy to ablate plaque. The DABRA system has the added benefit of not requiring a guide wire and instead uses the excimer laser to cross lesions. The Auryon device uses a neodymium-doped yttrium aluminum garnet laser with the optional capability of continuous aspiration during atherectomy, which may minimize the need to deploy additional embolic protection devices. Auryon relies on laser technology that delivers longer wavelengths with shorter pulse width, concentrating ablative energy at superficial plaque and sparing thermal injury to the vessel, which may reduce the risk of restenosis. A common use of laser atherectomy has been in treating restenotic lesions, particularly in-stent restenosis, as it balances both an optimal safety profile with the ability to debulk mixed lesion subsets.[98–100]

The application of atherectomy is one of the more controversial techniques in the peripheral vascular space. First, from a safety standpoint, there is a possibility of distal embolization that may necessitate the use of embolic protect devices, although this is device-specific.[101,102] However, long-term data have not supported a great prevalence of

major adverse events with these devices.[103] In addition, newer generation devices, such as the Rotarex system, offer aspiration in addition to atherectomy capabilities, which may limit the amount of embolized material. This is particularly useful when employed in mixed calcific-thrombotic lesions. Second, there remains significant variation in the use of atherectomy among operators and clinical practice sites, which could be driven in some cases by reimbursement when used in the office-based lab setting.[104] Many efforts are ongoing to standardize atherectomy practices and disentangle reimbursement from device selection. Lastly, recent safety issues have prompted a Class I recall of the HawkOne device because of the risk of guidewire prolapse with tip separation and embolization, although corrections are in process to allow for this device to remain safely available for use.

Specialty balloons

Specialty balloons differ from atherectomy devices, although they share the primary goal of improving vessel compliance, lumen gain, and drug delivery.[105] They are often used in areas where bailout stenting is consequential (popliteal artery and common femoral artery), in smaller caliber vessels that are prone to dissection when subjected to higher balloon inflation pressures, and to treat in-stent restenosis and under-expanded stents.[105] Although initially limited by bulkier devices that resulted in delivery challenges, newer iterations allow for the creation of lower profile devices that can be used in more complex lesion subsets.

One class of specialty balloons includes scoring balloons, which have laser-cut nitinol scoring elements deployed over semicompliant balloons that crack atheroma. Retrospective data from the PANTHER registry found that among 124 femoropopliteal lesions treated with the AngioSculpt scoring balloon, strategies of scoring balloon monotherapy or in combination with DCBs and DES produced high rates of primary and secondary patency at 12 months of 81.2% and 91.8%, respectively.[106] Although prospective data to guide use remain limited to small single-center studies, forthcoming, prospective multicenter data of the Bard UltraScore device (NCT03693963) and the AngioSculpt balloon (MASCOT Study, NCT00619788) may offer further guidance.[105]

Cutting balloons are similar to scoring balloons but have longitudinally oriented microsurgical blades that cut into lesions with inflation. They were initially developed for the treatment of restenotic lesions involving neointimal hyperplasia but are used in a variety of lesion types. Their use may reduce the frequency of lesion recoil and has been associated with decreased inflammatory and proliferative responses.[107,108] Cutting balloons have been associated with increased lumen gain compared with PBA alone.[109] For instance, in a prospective study of 84 patients, cutting balloons had better efficacy than PBA at 12 months, with primary patency rates of 90.4% versus 83.1% ($P < .001$) at 12 months and 79.7% versus 66.6% ($P < .001$) at 2 years.[110]

Another specialty balloon is the Chocolate PTA balloon, a minimal trauma device that consists of a semicompliant balloon encased in a nitinol cage. The cage prevents focal distension of the balloon and transmits pressure to the vessel in a controlled manner, which minimizes the risk of dissection. Preliminary data with use prior to DCBs show a primary and secondary patency of 98.8% at a mean follow-up interval of 12.3 ± 5.6 months.[111]

Newer iterations of this device that involve coating of the Chocolate balloon with paclitaxel have demonstrated improved outcomes at 1 year compared with DCB alone.[112]

Intravascular lithotripsy

Intravascular lithotripsy (IVL) is a novel angioplasty device that utilizes acoustic waves to fracture calcium deposits and increase vessel compliance. IVL has the added advantage of inducing fractures deep into medial calcification, which is often not addressable with atherectomy devices or specialty balloons that are limited to modification of intimal calcification. An additional strength of IVL is the safety profile, with infrequent complications such as vessel dissection or distal embolization. IVL has been supported by a number of randomized trials. For instance, the Shockwave Medical Peripheral Lithoplasty System Study for PAD (Disrupt PAD) II study enrolled 60 patients with severely calcified femoropopliteal artery disease, and, when used adjunctively, was associated with a 12-month primary patency rate of 54.5%, freedom from CD-TLR rate of 79.3%, and a low rate of bail out stenting (1.7%).[113] Furthermore, the Disrupt PAD III study randomized 306 patients to IVL + DCB and DCB alone and noted lower rates of the primary end point of residual stenosis ≤30% without flow-limiting dissection at 30 days when IVL was employed (65.8% of the IVL group compared with 50.4% of the PTA group; $P < .0065$).[114] More recent studies have shown that these short-term findings translate into longer-term benefits, including improved freedom from CD-TLR at 1 (80.5% vs 68.0%; $P = .017$) and 2 years (74.4% vs 57.7%; $P = .005$).[114,115]

Intravascular imaging

The use of peripheral intravascular imaging has grown over the past decade, with greater recognition that intravascular image-driven approaches to peripheral revascularization have the potential to improve short- and long-term outcomes. Intravascular imaging in the periphery has primarily consisted of IVUS. IVUS is an invasive imaging modality that creates cross-sectional images of the vascular lumen and surrounding structures and provides detailed characteristics, including plaque composition, presence of thrombus, and vessel wall injury.[116] IVUS also allows for precise vessel sizing with direct measurements of cross-sectional area based on the external elastic lamina, making it accurate at assessing reference vessel diameter and for sizing devices such as DCBs and stent implants.[117]

Evidence for IVUS use in peripheral interventions is developing. Data from nonrandomized studies suggest that IVUS has utility in femoropopliteal interventions in characterizing plaque morphology, accurate device, and vessel sizing, providing useful intraprocedural data, recognizing postprocedural complications, and impacting long-term procedural outcomes. Observational data suggest that IVUS and angiography-derived vessel sizing are frequently discrepant, with IVUS tending to demonstrate larger reference vessel diameter, which can have important implications for procedural outcomes such as stent sizing and expansion.[118] In a comparative study in which IVUS and angiography were performed before and after PTA of femoropopliteal lesions, IVUS showed higher sensitivity for detecting eccentric lesions, calcification, and vascular damage.[119] A retrospective analysis of 1,198 limbs with TASC A-C femoropopliteal lesions found that the propensity-matched

use of IVUS was associated with higher 5-year primary patency (65 ± 6% vs 35 ± 6%; $P < .001$), as well as decreased reintervention, improved freedom from adverse limb events, and event-free survival.[120] In a recent analysis of Medicare claims data including 697,794 peripheral interventions, IVUS use was found to be associated with a lower risk of major adverse limb events at a median of 425 days (hazard ratio, 0.68; 95% CI, 0.68–0.69; $P < .001$). Notably, a recent randomized trial of 150 patients undergoing femoropopliteal interventions demonstrated significantly higher freedom from binary restenosis at 12 months among patients who were randomized to the IVUS-guided intervention group (72.4% vs 55.4% in angiography alone group; $P = .008$). Although there was no difference in CD-TLR with the use of IVUS at 12 months (84.2% and 82.4%; $P = .776$), this study was not powered to detect differences in clinical outcomes. Notably, the use of IVUS resulted in a change to the treatment plan in nearly 80% of cases in the treatment arm in this study, demonstrating a high clinical impact. The primary change in response to IVUS-derived data was upsizing of DCBs based on vessel measurements. Angiography also overestimated the vessel diameter in 10.7% of cases, highlighting the limitations of angiography in accurate vessel sizing.

The use of IVUS also has the potential to increase the efficacy of devices that assist in vessel preparation. A retrospective analysis noted that when comparing IVUS versus angiography-guided directional atherectomy in femoropopliteal lesions, the use of IVUS was associated with lower rates of CD-TLR.[121] Furthermore, in the iDissection study, IVUS identified postatherectomy dissections more readily compared with angiography, which has important implications for target vessel patency.[122,123] With these advantages in mind, a recent multispecialty consensus document demonstrated that IVUS utilization was considered appropriate in the majority of clinical scenarios involving femoropopliteal artery revascularization.[124]

Future directions

The evolving landscape for endovascular femoropopliteal revascularization is robust and involves many areas of innovation. Some primary areas of current innovation include the development of bioresorbable scaffolds, refinement of antiproliferative agents, and creation of devices that allow for percutaneous bypass. Bioresorbable scaffolds rely on the ability to deliver synthetic, biopolymer stents that can provide a temporary scaffold and also allow for elution of antiproliferative compounds. In the short term, the scaffold provides vessel wall support and can be used to address issues such as vessel recoil and dissection. Over time, complete resorption of the polymer allows recovery of normal femoropopliteal vasomotion, decreasing late risks, including in-stent restenosis. At present, data on in vivo performance of bioresorbable scaffolds are sparse but encouraging in the treatment of short lesions.[125] The A Clinical Evaluation of the Abbott Vascular ESPRIT BVS (Bioresorbable Vascular Scaffold) System for the Treatment of Subjects With Symptomatic Claudication From Occlusive Vascular Disease of the Superficial Femoral (SFA) or Common or External Iliac Arteries (ESPIRIT 1) DA trial (n = 32) evaluated the performance of an everolimus-eluting poly-L-lactide scaffold in external iliac and femoropopliteal segments. Of the treated lesions, 89% were femoropopliteal, with rates of binary restenosis at 1 and 2 years of 12.1% and 16.1% and TLR of 8.8% and 11.8%, respectively. Importantly, there were no device-

or procedure-related safety issues.[126] Emerging data include Efemoral, a single-arm, open-label trial that is currently enrolling to evaluate a sirolimus-coated scaffold (NCT04584632).

As discussed previously, there remains interest in diversifying antiproliferative agents to prevent restenosis, particularly with exploration of limus-based compounds. Prior experiences with limus-based devices have been disappointing because of the inability to deliver therapeutic drug concentrations. However, more recent developments of lipophilic nanocarriers and amphiphilic sirolimus-based formulations show promise in overcoming prior limitations, with randomized data forthcoming.[63,86] Alternatively, adventitial delivery of dexamethasone may have future clinical utility in preventing vessel inflammation and the development of neointimal hyperplasia. The Dexamethasone to the Adventitia to Enhance Clinical Efficacy After Femoropopliteal Revascularization (DANCE) trial, a single-arm study (n = 263) of adventitial dexamethasone treatment after PTA or atherectomy of femoropopliteal lesions, noted high rates of primary patency of 75.5% and 78.4% and low rates of CD-TLR of 11% and 10%, respectively.[127]

Finally, percutaneous femoropopliteal bypass may become a viable option for treating complex femoropopliteal artery disease, avoiding the need for surgical revascularization. The PQ Bypass PQ Bypass Systems for Femoropopliteal Bypass (DETOUR) System involves utilization of the ipsilateral femoral vein to placed covered stent grafts as a conduit bypassing the SFA lesion. The safety and efficacy of this device has been demonstrated in the DETOUR I trial, with rates of primary, assisted primary, and secondary patency rates of 81 ± 4%, 82 ± 4%, and 90 ± 3%, respectively, and low rates of adverse events in complex lesions. These promising findings have prompted FDA approval as a breakthrough device, and the larger scale DETOUR 2 Clinical Study is ongoing (NCT03119233).[128]

Conclusion

The current state of femoropopoliteal revascularization allows for an endovascular approach to address most PAD lesions, regardless of clinical syndrome, reserving surgery for special cases or refractory lesions. Innovation in devices has resulted in improved patency rates comparable to those of surgical revascularization, with the added benefit of rapid recovery time, including allowing for outpatient-based procedures. Newer technologies, including plaque modification devices, DCBs, and intravascular imaging, have resulting in greater preservation of the native vessel without the need for stent implantation. These developments, combined with a general philosophy of “leave the least behind” with regards to stenting, have shown significant improvement in procedural technical success rates and freedom from TLR (Table 2). Looking to the future, newer stent technologies that employ different stent designs, including 3D systems that can better resist the shear forces of the femoropopliteal artery, coupled with drug-eluting technology, has brought femoropopliteal endovascular intervention through a revolution that is reminiscent of the progress coronary intervention underwent in the 2000s. The emerging application of bioresorbable scaffolds and novel antiproliferative technologies to overcome the challenges of complex femoropopliteal artery disease may further improve the durability of these interventions.

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Abbreviations:

BMS	bare-metal stent
CD-TLR	clinically driven target lesion revascularization
CLTI	chronic limb-threatening ischemia
DCB	drug-coated balloons
DES	drug-eluting stents
IVUS	intravascular ultrasound
PAD	peripheral arterial disease
PBA	plain balloon angioplasty
PTA	percutaneous transluminal angioplasty
RCT	randomized controlled trial
SFA	superficial femoral artery
TASC	TransAtlantic Inter-Society Consensus

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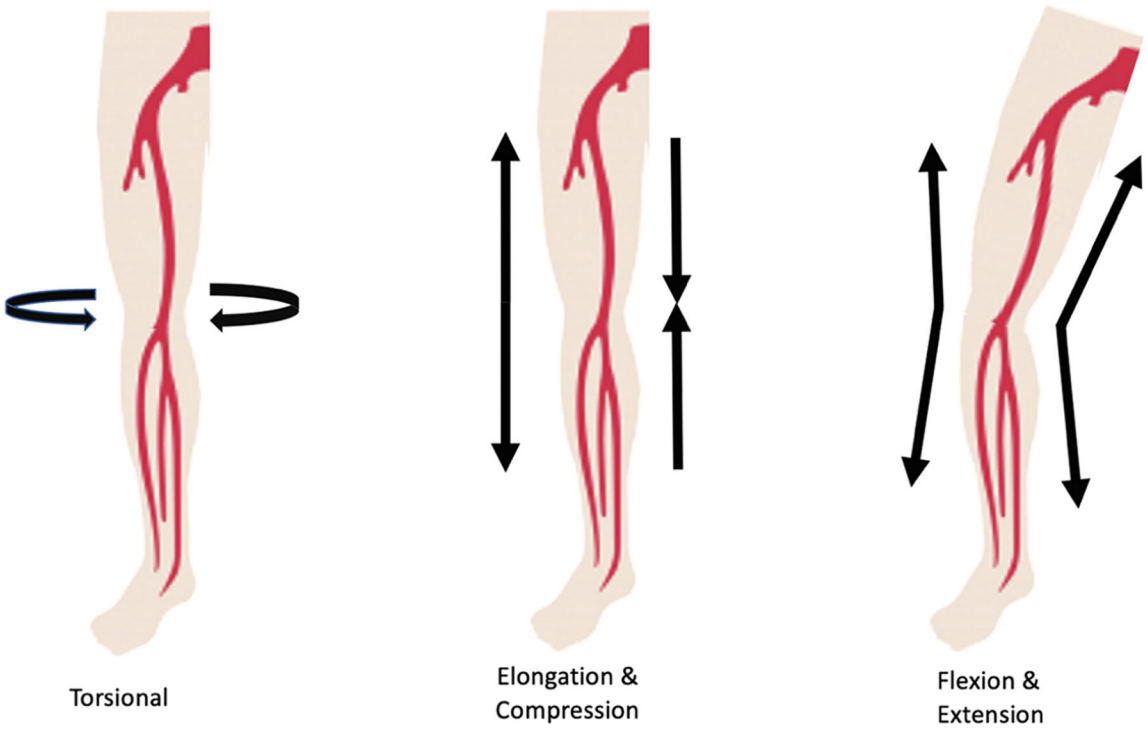
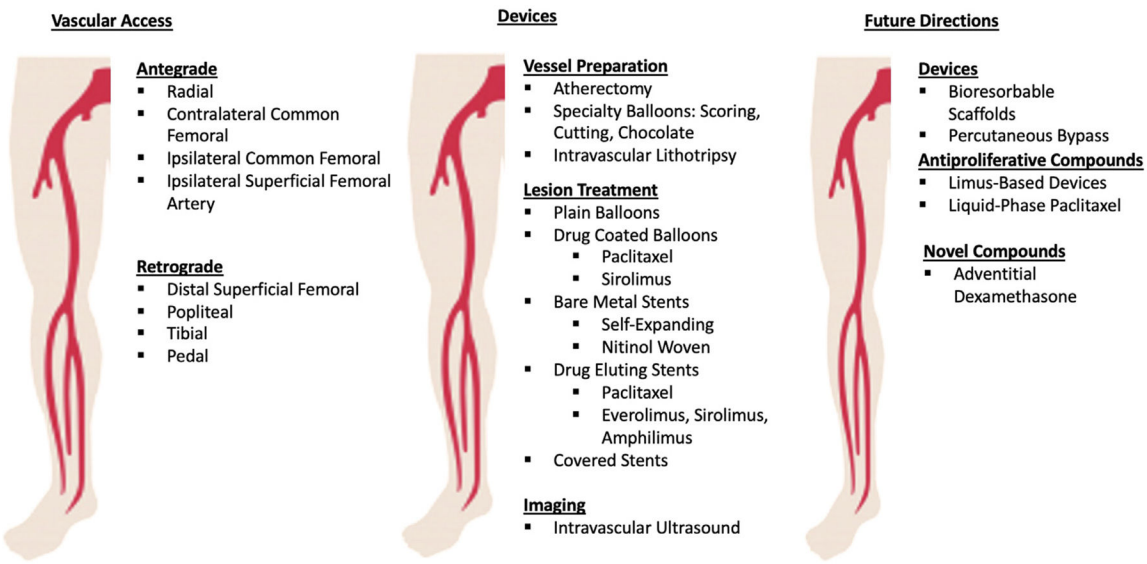


Figure 1. Mechanical stress on the femoropopliteal segment.

The femoropopliteal segment is subject to unique mechanical stress, including torsion, elongation, compression, flexion, and extension. This increases the risk of potential stent fractures and in-stent restenosis.



Central Illustration. Landscape of endovascular femoropopliteal interventions.

The landscape of endovascular interventions in femoropopliteal disease is evolving with innovations in arterial access, device-based therapies, vessel preparation, and intraprocedural imaging. Future directions include development of novel antiproliferative compounds, development of bioresorbable scaffolds for vessel support, and methods for entirely percutaneous bypass.

Table 1.

Summary of endovascular technology classes available for treatment of the femoropopliteal segment

Device class	Mechanism	Utility	Limitations
Plain balloons	Vessel dissection, stretching, and radial compression of plaque	Efficacious when treating lesions <100 mm	- High rates of restenosis - Flow-limiting dissections, vascular recoil, and residual stenosis require provisional stenting
Drug-coated balloons	Vessel dissection, stretching, and radial compression of plaque with local delivery of antiproliferative compound in excipient	Improved patency compared with results achieved by plain balloons; recommended for lesions at high risk for restenosis	- Residual controversy about safety of paclitaxel-coated devices - Theoretical concerns about paclitaxel distal embolization
Bare-metal stents	Metal alloy scaffold to compress and stabilize plaque/stenoses	Improved patency when treating lesions >100 mm	- High rates of restenosis with long lesions >200 mm
Drug-eluting stents: paclitaxel-based	Metal alloy scaffolds coated with paclitaxel in excipient	May have equivalent outcomes to bypass and improved patency compared with PTA and bare-metal stents (may not apply to newest generation)	- Residual controversy about safety of paclitaxel-coated devices - Concerns about aneurysmal degeneration
Drug-eluting stents: limus-based	Metal alloy scaffolds coated with limus-based antiproliferative agents in excipient	Limus-based antiproliferative agents have less vasculotoxicity compared with paclitaxel	- Prior generation of everolimus- and sirolimus-based stents with high rates of restenosis in follow-up (may be overcome by amphilimus-based devices)
Covered stents	Impose mechanical barrier to restenosis with polytetrafluoroethylene	Can treat long lesions with stent patency not correlating with lesion length	- Increased risk of stent thrombosis - Still prone to edge restenosis - No data to support incremental benefit over bare-metal stents
Atherectomy devices	Debulk plaque and calcium	Reduce inflation pressures with angioplasty to limit dissections and improve results of PTA and stenting	- Scarce randomized trial data to support use
Specialty balloons and intravascular lithotripsy	Induce fractures in plaque and calcium (moderate to severe)	Reduce inflation pressures with angioplasty to limit dissections and improve results of PTA and stenting	- Scarce randomized data and limited prospective data
Intravascular ultrasound	Invasive intraluminal imaging providing cross-sectional vascular representation	Improved characterization of plaque characteristics, thrombus morphology, and postprocedural complications	- Limited evidence to support use

PTA, percutaneous transluminal angioplasty.

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Table 2.

Summary of randomized trials in the treatment of femoropopliteal disease

Reference, year	Center(s)	Patients	Outcome	Limitations
Access				
Ruzsa et al,[16] 2022	Multicenter	60 to radial 60 to femoral 60 to pedal	Radial and pedal access associated with lower access-site complications compared with femoral access (3.3% radial, 3.3% pedal, and 16.7% femoral)	Small sample size, closure devices not used
Antiproliferatives				
Steiner et al,[129] 2020	Multicenter (15 centers in Germany)	207 to high-dose paclitaxel 207 to low-dose paclitaxel	Low-dose paclitaxel DCB not inferior to high dose for primary patency (81.5% in high dose vs 83% in low dose; $P < .01$) at 12 mo or freedom from major adverse events (92.6% in high dose vs 91% in low dose; $P < .01$)	Lack of operator blinding, vessel preparation devices not used, higher attrition rate in high-dose DCB arm
Devices Drug-coated balloons				
Laird et al,[37] 2015 (IN.PACT SFA 2-year)	Multicenter (57 sites in European Union and United States)	220 to DCB 111 to PTA	Higher rates of primary patency DCB compared with PTA (78.9% vs 50.1%; log rank $P < .001$), lower rates of CD-TLR for DCB (9.1% vs 28.3%; $P < .001$), composite safety end point of freedom from 30 d device and procedure-related death, amputation and target vessel revascularization lower for DCB vs PTA (12.6% vs 30.2%; $P < .001$)	Treating physicians not blinded to treatment arm
Iida et al,[130] 2019 (IN.PACT SFA Japan)	Multicenter (11 centers in Japan)	68 to Admiral DCB 32 to PTA	DCB group with higher 24 mo patency compared with PTA (79.8% vs 46.9%; $P < .001$) and similar to CD-TLR (9.1% vs. 20.7%; $P = .177$)	Small subgroup size
Tepe et al,[131] 2015	Multicenter (57 sites in European Union and United States)	220 to DCB 111 to PTA	DCB group with higher 12 mo primary patency rate compared with PTA (82.2% vs 52.4%; $P < .001$), lower CD-TLR (2.4% vs 20.6%; $P < 0.001$), and no significant difference between change from baseline quality of life (0.1059 vs 0.0730; $P = .10$)	Quality of life outcomes assessed using patient questionnaires, which can be subjective; treating physicians not blinded to treatment arm
Steiner et al,[132] 2018 (COMPARE)	Multicenter (10 European centers)	71 to Ranger DCB 34 to PTA	Ranger DCB with greater primary patency at 12 mo (86.4% vs 56.5%; log-rank $P < .001$), longer time to patency failure, and freedom from TLR (91.2% in DCB and 69.9% in control; $P = .010$)	Small subgroup sizes; lack of blinding of treating investigator
Teichgräber et al,[133] 2020	Multicenter	85 DCB 86 PTA	Late lumen loss at 6 mo, 0.93 mm lower in DCB group (95% CI, −1.36 to −0.49 mm; $P < .001$)	Small subgroup sizes
Stents				
Bausback et al,[134] 2019	Multicenter (5 sites in Germany and Belgium)	75 to DCB 75 to DES	Patency rates at 12 mo (79% DCB vs 80% DES; $P = .96$) comparable, but trend toward improvement with DES at 36 mo (54% DCB vs 38% DES; $P = .17$)	High loss of follow-up, various types of DCBs with different paclitaxel doses, and small sample size
Dake et al,[35] 2011 (ZILVER PTX)	Multicenter (55 centers in United States, Japan, and Germany)	241 to Zilver PTX 238 to PTA	Zilver PTX primary (88.3% vs 75.8%; $P < .001$) and provisional stenting (90.5% vs 72.3%; $P = .009$) with superior patency at 12 mo compared with angioplasty	High rate of PTA failures (50.4%), exclusion of long segment disease (>140 mm), randomization of Zilver PTX against angioplasty rather than bare-metal stents
Dake et al,[39] 2016 (ZILVER PTX 5-Year)	Multicenter (55 centers in United States, Japan, and Germany)	236 to Zilver PTX 238 PTA	Freedom from persistent or worsening ischemia (79.8% vs 59.3%; $P < .01$), patency (66.4% vs 43.4%; $P < .01$), and freedom from TLR (83.1% vs 67.6%; $P < .01$) were better with Zilver PTX than with PTA at 5 y	Similar to Zilver PTX (above), further conservative peak systolic velocity ratio < 2.0 was used to evaluate patency (use of <2.4 to 2.5 velocity

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Reference, year	Center(s)	Patients	Outcome	Limitations
				ratios may have resulted in higher patency rates)
Bosiers et al,[135] 2020 (ZILVERPASS)	Multicenter (13 clinical sites in Belgium, Germany, Italy, Brazil)	107 to Bypass 113 to Zilver PTX	12-mo primary patency (74.5% Zilver vs 72.5% bypass; $P = .998$) and freedom from TLR (80.9% Zilver vs 76.2% bypass; $P = .471$) noninferior for Zilver PTX compared with bypass	Patients in the surgical arm had more hypertension, HLD, obesity, and CLTI
Enzmann et al,[136] 2019	Single center	55 limbs to nitinol stent 55 limbs to bypass	At 24-mo patency rates, limb salvage and survival were not different between stent vs bypass but clinical improvement was better with bypass	Small size as is an ongoing single-center trial that is still recruiting
Gouëffic et al,[76] 2020 (BATTLE)	Multicenter (10 centers)	91 Misago 90 Zilver PTX	Zilver PTX not superior to Misago BMS in freedom from in-stent restenosis at 1 y (91.0% vs 88.6%; $P = .64$)	Functional testing not included in secondary end points, treating physicians not blinded, lesions <10 cm
Duda et al,[137] 2006 (SIROCCO)	Multicenter (8 centers in Europe and Australia)	47 patients to sirolimus-eluting SMART stent 46 to bare SMART stent	No difference in restenosis rates at 24 mo between groups (21.1% in BMS vs 22.9% in sirolimus; $P > .05$)	Small treatment group size, approximately half of the patients were Rutherford categories 1 or 2
Duda et al,[83] 2005 (SIRROCO II)	Multicenter (8 centers in Europe and Australia)	29 to sirolimus-eluting stent 28 to bare-metal stent	No difference between groups in in-stent mean lumen diameter at 6 mo (4.94 ± 0.69 mm for BMS and 4.76 ± 0.54 mm for sirolimus; $P = .31$)	Small treatment groups, approximately half of patients were Rutherford categories 0,1, or 2, short follow-up
Gray et al,[78] 2018 (IMPERIAL)	Multicenter (65 centers in Austria, Belgium, Canada, Germany, Japan, New Zealand, and the United States)	309 to Eluvia 156 to Zilver PTX	Noninferiority of Eluvia for primary patency (Eluvia 86.8% vs Zilver 81.5%; $P < .0001$ for noninferiority) and major adverse events (Eluvia 94.9% vs Zilver 91.0%; $P < .0001$ for noninferiority) at 12 mo	Noninferiority margin was based on expert opinion
Müller-Hülsbeck et al,[80] 2021 (IMPERIAL 2-year)	Multicenter (65 centers in Austria, Belgium, Canada, Germany, Japan, New Zealand, and the United States)	309 to Eluvia 156 to Zilver PTX	At 2 y, Eluvia had lower CD-TLR (12.7% vs 20.1%, $P = .0495$), higher primary patency (83% vs 77.1%; log rank $P = .1008$), and similar hypogenic halo prevalence (33.7% vs 21.4%; $P = .153$) compared with Zilver PTX	Hypogenic halo prevalence was only assessed in a small subset: 86 in Eluvia and 42 in Zilver because of the imaging protocol being added later
Laird et al,[138] 2018	Multicenter (36 sites in the United States and Europe)	197 to TIGRIS stent 70 to LifeStent	No difference in primary patency at 12 mo (60.6% vs 63.2%; $P = .73$) or 24 mo or in TLR (70.5% vs 67.2%; $P = .85$), with rate of stent fracture lower for TIGRIS (0% vs 32.7%; $P = .60$)	TIGIRIS arm required more stents because of the limited device length as opposed to 17-cm devices available for LifeStent
Zeller et al,[139] 2016 (MIMICS)	Multicenter (8 investigational sites in Germany)	50 to BioMimics stent 26 to LifeStent	Primary safety endpoint of freedom from death, target limb amputation and TLR at 30 d (1-sided $P < .01$), and effectiveness end point of freedom from CD-TLR at 6 mo (1-sided $P < .001$) were met	Small subgroup size, more patients with Rutherford category 3 but none with rest pain in straight stent group, limited lesion length (mean of 7 cm)
Stent grafts				
Reijnen et al,[140] 2017	Multicenter (6 centers in the Netherlands)	63 endoluminal stent graft 62 surgery	Greater improvement in quality of life in endoluminal group; at 1 y, no differences in primary patency (endoluminal: 64.8%; surgical: 63.6%), secondary patency (endoluminal: 85.9%; surgical: 83.3%), or target vessel revascularization (endoluminal: 72.1%; surgical: 71.0%)	Study was powered for quality of life outcome but not for noninferiority in patency outcomes, high rates of loss to follow-up, small subgroups

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Reference, year	Center(s)	Patients	Outcome	Limitations
Lammer et al,[141] 2013	Multicenter (7 centers in Europe)	72 Viabhan 69 BMS	12-mo patency with Viabhan significantly longer than BMS in intention-to-treat (71.3% vs 36.8%; $P = .01$) and treatment per protocol (73.3% vs 33.3%; $P = .004$)	8.5% had a major study protocol violation
Intravascular lithotripsy				
Tepe et al,[114] 2021 (Disrupt PAD III)	Multicenter (45 centers in Austria, Germany, New Zealand, and United States)	153 to IVL 153 to PTA	Higher primary patency with IVL (80.5% vs 68.0%, $P = .017$), freedom CD-TLR (IVL: 95.7% vs PTA: 98.3%, $P = .94$), and restenosis (IVL: 90.0% vs PTA: 88.8%, $P = .48$) were similar at 12-mo	Patency follow-up available for 80.4% in IVL arm and 83.7% in PTA arm
Tepe et al,[114] 2021 (Disrupt PAD III 30-day)	Multicenter (45 centers in Austria, Germany, New Zealand, and United States)	153 to IVL 153 to PTA	Residual stenosis ≤ 30% without flow-limiting dissection (≥ type D) superior in IVL group relative to PTA (65.8% vs 50.4%; $P < .0001$) at 30 d	Short-term outcomes, investigators and research staff not blinded, compared IVL to PTA rather than other plaque modifying devices
Specialty balloons				
Shishehbor et al,[112] 2022	Multicenter (34 sites in United States, Europe, and New Zealand)	152 to Chocolate Touch 161 to Lutonix DCB	Chocolate Touch met noninferiority and sequential superiority compared with Lutonix (78.8% vs 67.7%; $P < .0001$ for noninferiority and $P = .04$ for sequential superiority) at 12 mo	Mean lesion length limited to 78.1 ± 46.9 mm
Intravascular ultrasound				
Allan et al,[142] 2022	Single center	74 to angiography 76 to IVUS	Improved freedom from binary restenosis at 12 mo for IVUS-guided vs non-IVUS-guided group (72.4% vs 55.4%; $P = .008$)	Lack of functional outcomes, cost analysis, procedure factors (ie, fluoro time), core lab adjudication

BATTLE, Bare Metal Stent Versus Paclitaxel Eluting Stent in the Setting of Primary Stenting of Intermediate Length Femoropopliteal Lesions; BMS, bare-metal stent; CD-TLR, clinically driven target lesion revascularization; CLTI, chronic limb-threatening ischemia; COMPARE, Compare I Pilot Study for the Treatment of Subjects With Symptomatic Femoropopliteal Artery Disease; DCB, drug-coated balloons; DES, drug-eluting stents; Disrupt PAD III, Randomized Study of the Shockwave Medical Peripheral Lithoplasty System Used in Combination With DCB Versus Standard Balloon Angioplasty Used in Combination With DCB to Treat Moderate and Severely Calcified Femoropopliteal Arteries; HLD, hyperlipidemia; IN.PACT, IN.PACT Global Clinical Study for the Treatment of Comprehensive Superficial Femoral and/or Popliteal Artery Lesions Using the IN.PACT Admiral™ Drug-Eluting Balloon; IMPERIAL, A Randomized Trial Comparing the ELUVIA Drug-eluting Stent Versus Zilver PTX Stent for Treatment of Superficial Femoral and/or Proximal Popliteal Arteries; IVL, intravascular lithotripsy; IVUS, intravascular ultrasound; MIMICS-2, Evaluation of Safety and Effectiveness of the BioMimics 3D Stent System in the Femoropopliteal Arteries of Patients With Symptomatic Peripheral Arterial Disease; PTA, percutaneous transluminal angioplasty; PTX, paclitaxel; SFA, superficial femoral artery; SIRROCO, Sirolimus-eluting versus bare nitinol stent for obstructive superficial femoral artery disease;; TLR, target lesion revascularization; ZILVERPASS, The Cook Zilver PTX Drug-eluting Stent Versus Bypass Surgery for the Treatment The Cook Zilver PTX Drug-eluting Stent Versus Bypass Surgery of Femoropopliteal TASC C&D Lesions.

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