Comprehensive Review

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, 1

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.

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 non-randomized 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 biodegradable 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).

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.

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

https://doi.org/10.1016/j.jscai.2022.100439
Received 4 April 2022; Received in revised form 18 July 2022; Accepted 1 August 2022
Available online 20 August 2022
2772-9303/© 2022 The Author(s). Published by Elsevier Inc. on behalf of the Society for Cardiovascular Angiography and Interventions Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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. 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. 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. Although the use of ultrasound guidance can help to reduce the risk of access-site complications, the rates remain astounding high, ranging from 3.5% to 11%. 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. 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

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.

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. 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. 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. Although the use of ultrasound guidance can help to reduce the risk of access-site complications, the rates remain astounding high, ranging from 3.5% to 11%. 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. 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

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.

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.
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 Dotter27 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.20 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.32-35 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 anti- proliferative compounds that reduce neointimal hyperplasia, principally 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.

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

PTA, percutaneous transluminal angioplasty.
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.64,65

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).66 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.67,68

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.69 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 higher rate of death than DES and BMS (€4534 and €20,719, respectively).66 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.67,68

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.69 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 mortality at 2 years (7.2% and 3.8% hazard ratio, 1.68; 95% CI, 1.15-2.45) and 5 years (14.7% and 8.1% hazard ratio, 1.93; 95% CI, 1.27-2.93).70 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.71,72 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.69

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 for better late lumen loss and freedom from restenosis.60 The FDA has advised judicious use of paclitaxel devices for patients with a high risk for restenosis.69

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 Infragenual Peripheral Arterial Disease (XTOSIS) was a single-arm, open-label, single-center study evaluating the safety and efficacy of the MagicTouch DCB. More than 90% of patients had CLI 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%.63 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 anti-proliferatives 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 Superfi mal Femoral Artery (VIENNA) trial, which demonstrated decreased rates of restenosis at 6 and 12 months compared with those after PTA alone.71 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 Superfi mal 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 potency over PBA for complex lesion subtypes, in-stent restenosis remains a major concern. As such, DES were designed to minimize the impact of neo-intimal 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.74,75 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.76 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
### Table 2. Summary of randomized trials in the treatment of femoropopliteal disease

| Reference, year | Center(s) | Patients | Outcome | Limitations |
|-----------------|-----------|----------|---------|-------------|
| **Access**      |           |          |         |             |
| Ruza et al. 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, 3.9% pedal, and 16.7% femoral) | Small sample size, closure devices not used |
| **Antiproliferatives** |           |          |         |             |
| Steiner et al. 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 85% 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. 2019 (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 (79.8% 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. 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. 2015 (IN.PACT SFA) | Multicenter (57 sites in 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 |
| **Stents**      |           |          |         |             |
| Baumbach et al. 2019 | Multicenter (5 sites in Germany and Belgium) | 75 to DCR; 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. 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. 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 to 2.5 velocity ratios may have resulted in higher patency rates) |
| Bosiers et al. 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. 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 |
| Goueffic et al. 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. 2006 (SIRROCCO) | 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. 2005 (SIRROCCO 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. 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 |

(continued on next page)
Table 2. (continued)

| Reference, year | Center(s) | Patients | Outcome | Limitations |
|-----------------|-----------|----------|---------|-------------|
| Müller-Hübbeck et al,40 2021 (IMPERIAL 2-year) | Multicenter (65 centers in Austria, Belgium, Canada, Germany, Japan, New Zealand, and the United States) | 309 to Eluvia 316 to Zilver 317 to LifeStent 156 to Zilver PTV | 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 PTV | 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,40 2018 | Multicenter (36 sites in the United States and Europe) | 197 to TIGRIS 70 to Lifesent | 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 (9% vs 32.7%; P = .60) | TIGRIS arm required more stents because of the limited device length as opposed to 17-cm devices available for Lifesent |
| Zeller et al,40 2016 (MIMICS) | Multicenter (8 investigational sites in Germany) | 50 to BioMimics stent 26 to Lifesent | 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

| Reference, year | Center(s) | Patients | Outcome | Limitations |
|-----------------|-----------|----------|---------|-------------|
| Reijnen et al,41 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 |
| Lammer et al,41 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

| Reference, year | Center(s) | Patients | Outcome | Limitations |
|-----------------|-----------|----------|---------|-------------|
| Tepe et al,42 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,42 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

| Reference, year | Center(s) | Patients | Outcome | Limitations |
|-----------------|-----------|----------|---------|-------------|
| Shihshbhour et al,43 2022 | Multicenter (34 sites in United States, Europe, and New Zealand) | 152 to Chocolate Touch 161 to Luxtron DGB | Chocolate Touch met noninferiority and sequential superiority compared with Luxtron (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

| Reference, year | Center(s) | Patients | Outcome | Limitations |
|-----------------|-----------|----------|---------|-------------|
| Allan et al,44 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; CLT, chronic limb-threatening ischemia; COMPARE, Compare 1 Pilot Study for the Treatment of Subjects With Symptomatic Femoral 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 AdNipT® 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 Subjects With Symptomatic Peripheral Arterial Disease; PTA, percutaneous transluminal angioplasty; PTX, paclitaxel; SFA, superficial femoral artery; SIROCO, 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.

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 Trade 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 sirolimus- and 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%; \(P = .294\)). 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%; \(P = .006\)). 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 DGB therapy.88,89 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.77 Atherectomy has also been proposed to overcome the effects of calcified disease hindering delivery of antiproliferatives to vessel walls.72 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.77,78 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.86 Conversely, rotational atherectomy uses front-cutting blades and is currently available via 5 FDA-approved platforms: Rotaliink, 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.86 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.87

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.88,89

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. 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. 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. 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 AngioSculp 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. 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.

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. Cutting balloons have been associated with increased lumen gain compared with PBA alone. 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.

Another specialty balloon is the Chocolate PTA balloon, a minimal trauma device that consists of a semicompliant balloon encased in a stainless steel spring that unrolls and expands as the balloon inflates. The Chocolate PTA balloon is less traumatic than scoring balloons and is ideal for smaller vessels and vessels with a thin wall. Cutting balloons have been associated with increased lumen gain compared with PBA alone.

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 intra-procedural 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. 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.

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. 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.

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 intra-procedural 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. 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. 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.

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-guided derivation 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. Furthermore, in the iDissection study, IVUS identified postatherectomy dissections more readily compared with angiography, which has important implications for target vessel sizing.
patency. 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.

**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. 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 (SAF) or Common or External Iliac Arteries (ESPRIT 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. 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. 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 atherecetomy 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.

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 (NCT03119239).

**Conclusion**

The current state of femoropopliteal 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.

**Declaration of competing interest**

Dr Armstrong is a paid consultant for Abbott Laboratories, Boston Scientific, Cardiovascular Systems Inc, Gore Medical, Medtronic, Philips, and Shockwave Medical. Dr Schneider is a paid consultant for Boston Scientific, Cagent Vascular, Cardiovascular Systems Inc, InterVene Inc, LimFlow, Medtronic, Philips, Silk Road Medical, and Surmodics. Dr Secemsky is a paid consultant and member of the speakers bureau/advisory board for Abbott Laboratories, Bayer, BD, Boston Scientific, Cook Medical, Cardiovascular Systems Inc, Endovascular Engineering, Inari Medical, Janssen, Medtronic, Philips, and VentureMed. Dr Secemsky reports receiving grants to the institution from NIH/NHLBI (K23HL150290), the Food and Drug Administration, Harvard Medical School’s School Faculty Development Award, AstraZeneca, BD, Boston Scientific, Cook Medical, Cardiovascular Systems Inc, Lamine Medical Technologies Ltd, Medtronic, and Philips. Drs Mosarla and Bitton-Fawiszewski reported no financial interests.

**Funding sources**

Dr Secemsky is funded in part by NIH/NHLBI K23HL150290.

**Ethics statement**

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

**References**

1. Zeller T. Current state of endovascular treatment of femoro-popliteal artery disease. Vasc Med. 2007;12(3):223–234.
2. Ortiz D, Jahangir A, Singh M, Allaqaband S, Bajwa TK, Mewissen MW. Access site complications after peripheral vascular interventions: incidence, predictors, and outcomes. Circ Cardiovasc Inter. 2014;7(6):821–829.
3. Cagg J, Lowry D, Hopkins J, et al. Safety and outcomes of ipsilateral antegrade angioplasty for femoropopliteal disease. Vasc Endovascular Surg. 2018;52(2):93–97.
4. Eleisazawy MI, Elbarbary AH, Elwagih MM, Elhenedy MA, Santoro C, Foumeau I. Ipsilateral antegrade angioplasty for flush superficial femoral artery occlusion versus open bypass surgery. Ann Vasc Surg. 2019;61:55–64.
5. Dencker D, Pedersen F, Engstrom T, et al. Major femoral vascular access complications after coronary diagnostic and interventional procedures: a Danish register study. Int J Cardiol. 2016;202:604–608.
6. Sheikh IR, Ahmed SH, Mori N, et al. Comparison of safety and efficacy of bivalirudin versus unfractionated heparin in percutaneous peripheral intervention: a single-center experience. JACC Cardiovasc Interv. 2009;2(9):871–876.
7. Mamas MA, Nolan J, de Belder MA, et al. Changes in arterial access site and association with mortality in the United Kingdom: observations from a national percutaneous coronary intervention database. Circulation. 2016;133(17):1655–1667.
28. Thukkani AK, Kinlay S. Endovascular intervention for peripheral artery disease.
27. Dotter CT, Judkins MP. Percutaneous transluminal treatment of arteriosclerotic
angiography and intervention in patients with acute coronary syndromes (RIVAL): a
randomised, parallel group, multicentre trial. Lancet. 2013;377(9775): 1409–1420.
11. Di Santo P, Simard T, Wells GA, et al. Transradial versus transfemoral access for
percutaneous transluminal coronary intervention with balloon angioplasty: a
randomised trial. J Am Coll Cardiol. 2012;59(7):671–678.
22. El-Sayed H, Bennett ME, Loh TM, Davies MG. Retrograde pedal access and
accompanying review of current literature. Ann Vasc Surg. 2019;56:33–41.
20. Mustapha JA, Diaz-Sandoval LJ, Jaff MR, et al. Ultrasound-guided arterial access:
evaluation of clinical effectiveness with paclitaxel-eluting stents in the femoropopliteal artery: 5-year results of the Zilver PTX randomized trial. Circulation. 2016;133(15):1472–1483. discussion 1483.
34. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation versus balloon
angioplasty for treatment of superficial femoral artery and proximal popliteal
artery: twelve-month results from the RESILIENT randomized trial. Circ Cardiovasc Interv. 2010;3(3):267–276.
33. Dick P, Wallner H, Sabeti S, et al. Balloon angioplasty versus stenting with nitinol
stents in intermediate length superficial femoral artery lesions. Catheter Cardiovasc Interv. 2009;74(7):1090–1095.
29. Schillinger M, Sabeti S, Dick P, et al. Sustained benefit at 2 years of primary
femoropopliteal stenting (REVOLUTION): 2-year follow-up with balloon angioplasty with optimal stenting. Circulation. 2007;117(21):2745–2749.
12. Valgimigli M, Gagnor A, Calabrò E, et al. The femoral artery access site
society for cardiovascular angiography and interventions joint committee on clinical practice guidelines. J Am Coll Cardiol. 2019;73(2):161–179.
9. Mehta SR, Jolly SS, Cairns J, et al. Effects of radial versus femoral artery access in
patients with acute coronary syndromes with or without ST-segment elevation. J Am Coll Cardiol. 2015;66(24):2490–2499.
19. Montero-Baker M, Schmidt A, Brehm A, et al. Tibio-pedal arterial minimally invasive
angioplasty to the infrapopliteal arteries: analysis of 222 patients. Heart. 2013;99(1):69–75.
31. Schillinger M, Sabeti S, Dick P, et al. Sustained benefit at 2 years of primary
femoropopliteal stenting (REVOLUTION): 2-year follow-up with balloon angioplasty with optimal stenting. Circulation. 2007;117(21):2745–2749.
5. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary
disease after revascularization. J Am Coll Cardiol. 2019;73(2):161–179.
4. Mustapha JA, Saab F, McGoff T, et al. TRIACCESS study: randomized comparison
between radial, femoral, and pedal access for percutaneous femoro-popliteal artery
revascularization: final results from the Radial accEss for nAvigation to your CHosen lesion for Peripheral artery intervention trials. J Endovasc Ther. 2015;22(2):215–225.
32. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of
durably durable stents to 3 years in the femoropopliteal arteries: evidence from the SPA-long study. J Am Coll Cardiol. 2016;68(1):161–169.
30. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus stenting with nitinol
stents in intermediate length superficial femoral artery lesions. Catheter Cardiovasc Interv. 2009;74(7):1090–1095.
10. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary
angiography and intervention in patients with acute coronary syndromes (RIVAL): a
randomised, parallel group, multicentre trial. Lancet. 2011;377(9775): 697–706.
345. Schillinger M, Sabeti S, Dick P, et al. Sustained benefit at 2 years of primary
femoropopliteal stenting (REVOLUTION): 2-year follow-up with balloon angioplasty with optimal stenting. Circulation. 2007;117(21):2745–2749.
14. Fukuda K, Okazaki S, Shiozaki M, et al. Ultrasound-guided puncture reduces
bleeding-associated complications, regardless of calcified plaque, after
devascular treatment of femoropopliteal lesions, especially using the antegrade
procedure: a single-center study. PLoS One. 2021;16(3):e0249416.
35. Dick P, Wallner H, Sabeti S, et al. Balloon angioplasty versus stenting with nitinol
stents in intermediate length superficial femoral artery lesions. Ann Vasc Surg. 2019;62:345–352.
36. Dick P, Wallner H, Sabeti S, et al. Balloon angioplasty versus stenting with nitinol
stents in intermediate length superficial femoral artery lesions. Ann Vasc Surg. 2019;62:345–352.
37. Dick P, Wallner H, Sabeti S, et al. Balloon angioplasty versus stenting with nitinol
stents in intermediate length superficial femoral artery lesions. Ann Vasc Surg. 2019;62:345–352.
38. Rosenfield K, Jaff MR, White CJ, et al. Treatment of a paclitaxel-coated balloon for
devascular treatment of femoropopliteal artery disease. N Engl J Med. 2015;373(2):145–153.
39. Laird JR, Schneider PA, Tepe G, et al. Effect of balloon angioplasty and drug-eluting stents on
devascular treatment of femoropopliteal artery disease: 12-month results from the RESILIENT randomized trial. Circulation. 2016;133(15):1472–1483. discussion 1483.
40. Schiller M, Speck U, Abramshki C, Bernhardt U, Böh m M, Nickenig G. Paclitaxel
balloon coating, a novel method for prevention and therapy of restenosis. Circulation. 2004;110(7):810–814.
21. El-Sayed H, Bennett ME, Loh TM, Davies MG. Retrograde pedal access and
accompanying review of current literature. Ann Vasc Surg. 2019;56:33–41.
23. Mustapha JA, Saab F, McGoff T, et al. Tibio-pedal access for crossing of
infranigual artery occlusions: a prospective multicenter observational study.
J Endovasc Ther. 2016;23(6):839–846.
24. Mustapha JA, Díaz-Sandoval LJ, Jaff MR, et al. Ultrasound-guided arterial access:
occlusion of peripheral artery disease. Lancet. 2016;388(10056): 1536–1547.
26. Bazzan HA, Le I, Donovan M, Sidhom T, Smith TA, Sternberg 3rd WC. RETROgrade
access for patients with critical limb ischemia. J Vasc Surg. 2014;60(2):375–381.
27. Dotter CT, Judkins MP. Percutaneous transluminal treatment of arteriosclerotic
obstruction. Radiology. 1965;84:631–643.
28. Thukkani AK, Kinlay S. Endovascular intervention for peripheral artery disease. Circ Res. 2015;116(4):e1599–1613.
29. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management
of peripheral arterial disease (TASC II). Eur J Vasc Endovasc Surg. 2007;33(suppl 1):S1–75.
30. Bailey SR, Beckham DA, Dao TD, et al. ACC/AHA/SCAI/SIR/SCVM 2018 appropriate use
criteria for peripheral artery intervention: a report of the American College of
Cardiology Appropriate Use Criteria Task Force, American Heart Association,
Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, and Society for Vascular Medicine. J Am Coll Cardiol. 2019;73(2): 214–237.
31. Murad GN, Bosch JL, Stijnen T, Hunink MG. Balloon dilation and stent
implantation for treatment of femoropopliteal arterial disease: meta-analysis.
Radiology. 2003;228(1):114–125.
32. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of
nitril stents in the superficial femoral artery. N Engl J Med. 2006;354(18):1789–1798.
33. Dick P, Wallner H, Sabeti S, et al. Balloon angioplasty versus stenting with nitinol
stents in intermediate length superficial femoral artery lesions. Catheter Cardiovasc Interv. 2009;74(7):1090–1095.
34. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation versus balloon
angioplasty for treatment in the superficial femoral artery and proximal popliteal
artery: twelve-month results from the RESILIENT randomized trial. Circ Cardiovasc Interv. 2010;3(3):267–276.
35. Dave MD, Ansel GM, Tepe G, et al. Paclitaxel-eluting stents show superiority to
balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month
Zilver PTX randomized study results. Circ Cardiovasc Interv. 2011;4(5):495–504.
36. Schillinger M, Sabeti S, Dick P, et al. Sustained benefit at 2 years of primary
femoropopliteal stenting (REVOLUTION): 2-year follow-up with balloon angioplasty with optimal stenting. Circulation. 2007;117(21):2745–2749.
114. Tepe G, Brodmann M, Werner M, et al. Intravascular lithotripsy for peripheral artery calcification: 30-day outcomes from the randomized Disrupt PAD III trial. *JACC Cardiovasc Interv.* 2021;14(12):1352–1361.

115. Ormiston W, Dyer-Hartnett S, Fernando R, Holden A. An update on vessel preparation in lower limb arterial intervention. *CVR Endovasc.* 2020;3(1):86.

116. Nishanian G, Kopchok GE, Donayre CE, White RA. The impact of intravascular ultrasound (IVUS) on endovascular interventions. *Semin Vasc Surg.* 1999;12(4):285–299.

117. Secemsky EA. Consensus for the appropriate use of intravascular ultrasound in femoropopliteal arterial dissections post atherectomy: results from the iDissection study. *J Invasive Cardiol.* 2019;31(5):121–126.

118. Shammas NW, Shammas WJ, Jones-Miller S, Radaideh Q, Shammas GA. Femoropopliteal arterial dissections post femoral and proximal popliteal artery: 2-year results of the MDT-2113 prospective, randomized, non-inferiority trial of high- vs. low-dose paclitaxel drug-coated balloons for femoropopliteal interventions. *Endovascular Ther.* 2019;3(1):86.

119. Secemsky EA, Parikh SA, Kohli M, et al. Intravascular ultrasound guidance for lower extremity arterial and venous interventions. *Europ. Intervention.* Published online Apr 19, 2022. https://doi.org/10.4244/EJIT-D-21-00698.

120. Iida O, Takahara M, Soga Y, et al. Vessel diameter evaluated by intravascular ultrasound versus angiography. *J Endovasc Ther.* 2022;29(3):343–349.

121. van Lankeren W, Gussenhoven EJ, Pieterman H, van Sambeek MB, van den Luit J. Comparison of angiography and intravascular ultrasound before and after balloon angioplasty of the femoropopliteal artery. *Cardiovasc Intervent Radiol.* 1998;21(5):367–374.

122. Zeller T, Gaines PA, Ansel GM, Caro CG. Helical centerline stent improves patency: two-year results from the randomized Mimics trial. *Circ Cardiovasc Interv.* 2016;9(6):e1640–e1649.

123. Ormiston W, Lamer J, Zeller T, Hausegger KA, et al. Heparin-bonded covered stents versus bare-metal stents for complex femoropopliteal artery lesions: the randomized VIASTAR trial (Viaibahn endoprosthesis with PROPATEN bioactive surface [VIA] versus bare nitinol stent in the treatment of long lesions in superficial femoral artery occlusive disease). *J Am Coll Cardiol.* 2013;62(15):1520–1527.

124. Lamer J, Zeller T, Hausegger KA, et al. Heparin-bonded covered stents versus bare-metal stents for complex femoropopliteal artery lesions: the randomized VIASTAR trial (Viaibahn endoprosthesis with PROPATEN bioactive surface [VIA] versus bare nitinol stent in the treatment of long lesions in superficial femoral artery occlusive disease). *J Am Coll Cardiol.* 2013;62(15):1520–1527.

125. van Haelst ST, Peeters Weem SM, Moll FL, de Borst GJ. Current status and future imaging results. *Semin Vasc Surg.* 2019;32(4):464–472.

126. Razavi MK, Donohoe D, Dua MB, et al. ZILVERPASS study: ZILVER PTX stent versus drug-coated balloon revascularization in patients with femoropopliteal arterial disease. *J Am Coll Cardiol.* 2019;73(6):667–679.

127. Bosiers M, Setacci C, De Donato G, et al. Zilver PTX study: ZILVER PTX stent versus bypass surgery in femoropopliteal lesions. *J Endovasc Ther.* 2020;27(3):287–295.

128. Enzmann FK, Nierlich P, Apfalter M, et al. Nitinol stent versus bypass in long femoropopliteal lesions: 2-year results of a randomized controlled trial. *JACC Cardiovasc Interv.* 2019;12(24):2541–2549.

129. Steiner S, Schmidt A, Zeller T, et al. COMPARE: prospective, randomized, non-inferiority trial of high- vs. low-dose paclitaxel drug-coated balloons for femoropopliteal interventions. *Circ Cardiovasc Interv.* 2016;9(6):e002930.

130. Reijnem MMPJ, van Walraven LA, Fritschi WM, et al. 1-year results of a multicenter randomized controlled trial comparing heparin-bonded endoluminal to femoropopliteal bypass. *JACC Cardiovasc Interv.* 2017;10(22):2331–2338.

131. Lammer J, Zeller T, Hausegger KA, et al. Heparin-bonded covered stents versus bare-metal stents for complex femoropopliteal artery lesions: the randomized VIASTAR trial (Viaibahn endoprosthesis with PROPATEN bioactive surface [VIA] versus bare nitinol stent in the treatment of long lesions in superficial femoral artery occlusive disease). *J Am Coll Cardiol.* 2013;62(15):1520–1527.

132. Allan RB, Puckridge PJ, Spark JI, Delaney CL. The impact of intravascular ultrasound on femoropopliteal artery endovascular interventions: a randomized controlled trial. *JACC Cardiovasc Interv.* 2022;15(5):536–546.