REVIEW

Endovascular treatment of femoro-popliteal lesions

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Peripheral artery disease (PAD) is a major health concern affecting more than 200 million people worldwide and studies have shown PAD to be a strong predictor of mortality, morbidity, and disability. The management of PAD is multi-tiered and advancements in technology have given physicians more options for endovascular revascularization if medical therapy does not result in substantial improvement. Many randomized controlled trials have reported efficacy of various therapies including laser atherectomy, stent technology, and drug-coated balloons over standard percutaneous transluminal angioplasty; however, uncertainty regarding the best standard of care remains unclear because of a lack of head to head comparisons between novel therapies. Furthermore, variability in the reported clinical outcomes exists and makes it difficult to evaluate the superiority of any specific treatment modality, especially for functional capacity and quality of life. Recently established consensus definitions for clinical outcomes coupled with investigators incorporating direct comparisons within clinical trials will be crucial to establish consistent care and meaningful gain in treatment for these patients. This review will highlight the treatment modalities, literature supporting each treatment modality, and insight into why they are being used and why variation exists around the United States.

KEYWORDS

angioplasty, atherectomy, balloon, peripheral artery disease, revascularization, stent

1 | INTRODUCTION

Peripheral artery disease (PAD) is a major health concern affecting more than 200 million people worldwide.¹ PAD is defined as a partial or complete obstruction of ≥ 1 peripheral artery because of atherosclerotic occlusive disease.² Similar terms used in the literature include peripheral vascular disease, peripheral arterial occlusive disease, and lower extremity arterial disease. In patients with PAD, symptoms can range from none (asymptomatic state) to severe and life threatening. Intermittent claudication (IC) is the most frequent manifestation of PAD and is defined as ischemic leg pain associated with walking and relieved with rest. Many questionnaires have been developed to ascertain the presence and severity of IC in patients at risk for vascular disease including the Rose Questionnaire³ and the San Diego Claudication Questionnaire (modified to adjust for laterality of symptoms).⁴ The ankle-brachial index (ABI), that involves the calculation of the ratio of systolic blood pressure at the ankle vs at the arm, has become the diagnostic test of choice to identify patients with PAD. An ABI of ≤ 0.90 is both sensitive and specific for the diagnosis of PAD.

There are many risk factors associated with PAD. Cigarette smoking has shown to at least double the odds of PAD in most studies, although some estimates suggest that smoking increases an individual's risk nearly 4-fold.¹ Type 2 diabetes mellitus is also strongly associated with elevated risk. In one study, diabetic patients with PAD had a 5-fold higher odds of amputation and 3-fold higher odds of mortality when compared with patients with PAD but without diabetes mellitus. Other risk factors for PAD include advancing age, hypertension, dyslipidemia, and obesity to name a few.¹ There is a possible protective effect of moderate alcohol consumption on PAD, but data is not as consistent as for coronary artery disease.¹

The femoropopliteal arterial segment is the most common site of disease in patients with PAD and corresponds to the superficial femoral artery (SFA) and popliteal artery in the lower extremities.^{5,6} Patients with severe claudication or critical limb ischemia (CLI) often have multi-level disease, and typically have extensive femoropopliteal occlusion.⁵ Many factors make this area prone to disease. The femoropopliteal segment covers two major flexion points in the hip and knee, and the SFA is the longest artery in the human body and endures multiple external forces with leg movement.⁷ In addition, the

path of the SFA also goes through the adductor canal, a tight space enclosed by multiple muscles of the legs leading to additional compression during activity.⁷ Repeated injury leads to scar formation and calcification of atheromatous plaque. In fact, it is estimated that 50% of patients who undergo femoropopliteal intervention are found to have chronic total occlusions.⁸

The management of femoropopliteal disease is multi-tiered and is typically aimed at alleviating symptoms, improving functional capacity, and preventing limb events (eg, amputation) and cardiovascular events (eg, myocardial infarction, stroke, and death). Lifestyle modification involves smoking cessation, glycemic control, home and structured exercise training, and decreased alcohol consumption. Medical therapy includes anti-hypertensive medications, antiplatelet and antithrombotic medication, and 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase) medications (statins) to lower cholesterol. When patients have symptoms refractory to medical therapy, exercise training, and/or other supportive measures (eg, wound care), these patients are often then referred for surgical or endovascular revascularization to improve perfusion of the lower extremities.

2 | OVERVIEW OF ENDOVASCULAR TREATMENT

The evolution of endovascular techniques and device technology over the last 20 years has led to an increase in endovascular revascularization procedures, with a subsequent reduction in the performance of open surgical revascularization procedures.⁹ Similar to patients undergoing coronary revascularization, endovascular treatment allows patients to return to normal activity more quickly and the risk of complications is markedly reduced when compared with surgical procedures.¹⁰ To give some historical context, in 1996, there was a 3:1 surgical revascularization:endovascular revascularization ratio in patients with PAD. By 2005, these numbers were almost at a 1:1 ratio, the likelihood of endovascular procedures over surgical procedures more than doubling from 12.7% to 28.3%, with the overall age- and sex-adjusted procedure rate increasing to 419.6 per 100 000 Medicare beneficiaries by 2011.^{9,11} With the advancements in technology and ever-changing methods of training for vascular surgeons, cardiologists, and radiologists alike, endovascular revascularization will likely continue to grow in the treatment of patients with PAD.

Endovascular revascularization of the femoropopliteal artery begins by obtaining vascular access, most commonly through a contralateral femoral artery retrograde approach.¹² A catheter is then used to steer guidewires up to the aortic bifurcation and over to the contralateral common iliac artery. A baseline angiogram is then completed to clearly define the extent and severity of the target lesion(s), identify where the distal vessel reconstitutes, and identify important collaterals. Before a treatment modality is chosen (eg, angioplasty, stenting, and atherectomy), a guide wire must be used to traverse the target lesion. This most often can be done intraluminally, but in circumstances, such as chronic total occlusions, special techniques such as subintimal crossing can be done.⁵ Once the target lesion has been traversed, a decision is then made to use either balloon angioplasty or atherectomy as the primary initial treatment device; direct stenting

has a Class IIIc recommendation in the ACC/AHA guidelines for SFA-popliteal lesions.¹³

The majority of studies compare one treatment modality or one device against either usual care or another modality or device. With many current options for endovascular treatment, and disparate studies investigating individual devices, it can be difficult to determine if there is a clear standard of care, and variation across the United States is quite high. This is highlighted in a recent review of treatment strategies for patients with PAD,¹⁴ which shows the strength of evidence often being low when evaluating endovascular treatment. Low strength of evidence can be because of multiple reasons, one of which is the number of observational studies that naturally suffer from a risk of bias based on treatment decisions and patient inclusion.¹⁴ Despite the predominance of observational studies in the PAD interventional literature, this review will strictly focus on randomized controlled trials (RCTs) comparing treatment modalities/devices against standard of care or another modality/device.

3 | TREATMENT MODALITIES

3.1 | Standard balloon angioplasty

In 1974, a German-born physician scientist named Andreas Grüntzig was the first to use a balloon-tipped catheter to open a severely stenosed femoral artery, a procedure that he then called “percutaneous transluminal dilatation” and is now known as percutaneous transluminal angioplasty.¹⁵ Since 2005, endovascular treatment for PAD has continued to become even more prevalent. Balloon angioplasty, also known as percutaneous transluminal angioplasty (PTA) in the medical literature, was established as the standard of care for endovascular procedures. As seen in Figure 1, the mechanism involves inflating a balloon in the target vessel and compressing the atheromatous plaque into and along the arterial wall.¹⁶ While this technique is temporarily able to restore blood flow, it can be prone to multiple problems. Abrupt vessel closure can happen early because no scaffold is left in place and can occur more commonly when chronic total occlusion is being treated.⁸ Vessel dissection occurs frequently with balloon angioplasty, especially when calcium is present and chronic total occlusion is being treated. Over time, target lesion restenosis can also occur, especially in longer lesions and when dealing with more severely calcified vessels. To date, no comparative studies have been done to establish PTA as the standard of care; however, it continues to be the method all other technologies are compared against.

3.2 | Drug-coated balloons

Drug-coated balloons (DCBs) combine standard balloon angioplasty and anti-proliferative drug technology. A balloon coated with an anti-proliferative agent (eg, paclitaxel) and excipient is advanced to the target lesion. Once inflated, the excipient helps the drug of choice embed into the arterial wall, bind microtubules, and prevent cell growth. There are three DCBs available in the United States. The IN.PACT Admiral DCB is produced by Medtronic Inc (Minneapolis, MN) and is coated with the antiproliferative agent paclitaxel at a dose of

FIGURE 1 Three major categories of endovascular treatment for femoropopliteal disease

3.5 $\mu\text{g}/\text{mm}^2$ in a urea excipient.¹⁷ The Lutonix DCB is produced by C.R. Bard Inc, (New Providence, NJ) and is also coated with paclitaxel but at a lower dose of 2.0 $\mu\text{g}/\text{mm}^2$ with a polysorbate/sorbital excipient.¹⁸ Finally, the Stellarex DCB is produced by Spectranetics Corp. (Colorado Springs, CO) and is similarly coated with paclitaxel at 2.0 $\mu\text{g}/\text{mm}^2$ but with a novel excipient, polyethylene glycol.¹⁹

Many new trials have investigated different DCBs against PTA with encouraging results, as can be seen in Table 1. The THUNDER trial compared a paclitaxel-coated balloon to PTA and reported a significant difference in clinically-driven target lesion revascularization (CD-TLR) and primary patency.²⁰ This has been further supported by the PACIFIER, LEVANT II, BIOLUX P-1, AcoArt1, IN.PACT, and ILLUMENATE trials.^{17,19,21–24} Perhaps most interesting is the variance in patient-centric metrics: quality of life (QOL), walking impairment questionnaire (WIQ) score, and change in the 6-minute walking test (6MWT). Of these trials, LEVANT II, IN.PACT, and ILLUMENATE address these metrics. The LEVANT II trial compared Lutonix DCB vs PTA and reported a significant difference in QOL and maximum walking distance score from the WIQ. However, the ILLUMENATE and IN.PACT trials compared the Stellarex DCB and Medtronic Admiral DCB, respectively to PTA, and did not report a significant difference in QOL, WIQ, or 6MWT.^{17,19,24} Advantages of DCB over standard angioplasty include potential for homogenous drug delivery to the vessel and option of using in combination with metal stents.²⁵

Advantages of DCB over stent technology include drug release without the use of a stent; thus, possibly reducing restenosis (and potentially thrombosis) rates, no foreign object left behind in the body, and the ability to be used in anatomy where stent technology may not be possible (eg, across the knee joint).²⁵ However, DCB or PTA only treatment often leaves operators with a concern over no

scaffold in place (and subsequent fear of vessel recoil) and residual vessel dissection.²⁶

3.3 | Self-expanding nitinol stents

Nitinol (nickel/titanium alloy) bare metal, self-expanding stents (deployed without a balloon) are the most frequently used stents in the SFA-popliteal segment because of improved radial force and easy distensibility. As seen in Figure 1, Stents are inserted into the arterial system over a wire, advanced to the target lesion, and then deployed by retracting a sheath and allowing the stent to expand against the vessel wall to act as a scaffold, keeping the lumen open to blood flow. The results of trials involving stent technology are shown in Table 2. The femoral artery stenting trial (FAST) was one of the first RCTs to study bare metal stent (BMS) vs PTA. The FAST trial specifically looked at lesions less than 10 cm. The trial did not report a benefit in stenting short SFA lesions over PTA. A significant difference in maximal walking difference was reported, but the authors did mention that significance testing was performed on an exploratory basis, implying the difference could be because of random variance.²⁷ The ABSOLUTE trial studied BMS vs PTA in lesions greater than 10 cm.²⁸ Restenosis rate and maximal distance on treadmill were both able to demonstrate efficacy, suggesting that benefit of BMS over PTA possibly increases with lesion length. This conclusion was further supported by the RESILIENT trial.²⁹ Primary patency and CD-TLR both improved significantly as did relief from claudication pain in lesions greater than 5 cm.

One overall concern for stent technology is the risk of stent fracture because of movement, especially in the high usage area of the femoropopliteal artery.¹⁰ In addition to BMSs described above, there

TABLE 1 Drug-coated balloons vs percutaneous transluminal angioplasty

Trial name	THUNDER (2015)	IN.PACT (2015)	LEVANT II (2015)	PACIFIER (2012)	ILLUMENATE (2017)	Acort1 (2016)	BIOLUX P-1 (2015)
Randomized treatment	Paclitaxel-coated balloon vs PTA	2:1 Medtronic Admiral DCB vs PTA	2:1 Lutonix PCB vs PTA	Medtronic Pacific DCB vs PTAX	2:1 Stellarex DCB vs PTA	Acotec Scientific Orchid PCB vs PTA	Biotronik AG Passeo-18 Lux DCB vs PTA
Number of patients	154	331	476	85	300	200	60
Results timeline	5 years	24 months	12 months	12 months	12 months	12 months	12 months
Change in quality of life assessment (EQ-5D)	Not reported	0.0957 ± 0.2159 vs 0.0545 ± 0.2286, $P = 0.151$	Between-group difference: 0.01 ± 0.20, 95% CI (−0.03 to 0.05)	Not reported	Similarly improved 0.10 ± 0.23 vs 0.04 ± 0.21, $P = 0.2006$	Not reported	Not reported
Change in walking impairment questionnaire composite	Not reported	Similarly improved from baseline	Walking-distance score between-group difference: 9.3 ± 36.5, 95% CI (1.6 to 17.0). Otherwise similarly improved	Not reported	20.1 ± 29.4 vs 22.5 ± 28.1, $P = 0.5508$	Not reported	Not reported
Change in 6-min walk test (m)	Not reported	30.9 ± 87.7 vs 60.5 ± 97.6 $P = 0.117$	Not reported	Not reported	70 ± 114 vs 73 ± 178 $P = 0.8165$	Not reported	Not reported
CD-TLR	21% vs 56%, $P = 0.0005$	9.1% vs 28.3%, $P < 0.001$	12.3% vs 16.8%, $P = 0.21$	7.1% vs 27.9%, $P = 0.02$	7.9% vs 16.8%, $P = 0.023$	7.2% vs 39.6%, $P < 0.001$	15.4% vs 41.7%, $P = 0.064$
Primary patency (freedom from CD-TLR or restenosis)	Binary restenosis: 17% vs 54%, $P = 0.04$	78.9% vs 50.1%, $P < 0.001$	65.2% vs 52.6%, $P = 0.02$	Binary restenosis at 6 months: 8.6% vs 32.4% $P = 0.01$	76.3% vs 57.6%, $P = 0.003$	76.1% vs 33.7%, $P < 0.001$	Binary restenosis at 6 months: 11.5% vs 34.6% $P = 0.048$
Safety outcomes: freedom from 30 day device and procedure related death, major limb amputation, CD-TLR	Did not differ significantly	87.4% vs 69.8%, $P < 0.001$	83.9% vs 79.0%, $P = 0.005$ for noninferiority	7.1% vs 34.9%, $P < 0.01$	92.1% vs 83.2%, $P = 0.025$ for superiority	2% vs 3%, $P = 1.00$	Did not differ significantly

Abbreviations: BMS, bare metal stent; CMS, covered metal stent; CD-TLR, clinically-driven target lesion revascularization; PTA, percutaneous transluminal angioplasty. Trials comparing DCB technology against PTA.

TABLE 2 Stent vs other technologies

	DES vs X		BMS vs X		Covered stent vs X			
Trial name	ZILVER-PTX (2016)	ABSOLUTE (2007)	FAST (2007)	RESILIENT (2010)	VIABAHN (2008)	VIBRANT (2013)	VIASTAR (2013)	
Randomized treatment	Zilver PTX Overall DES (primary and provisional) vs Standard care (PTA and provisional Zilver BMS)	Dynalink or Absolutese self-expanding nitinol stent (BMS) vs PTA	Bard Luminex 3 stent (BMS) vs PTA	2:1 LifeStent self-expanding stent (BMS) vs PTA	Viabahn covered stent (CMS) vs PTA	Viabahn covered stent vs bare nitinol stent (BMS)	Viabahn covered stent vs LifeStent/Protégé EverFlex Stent/SMART-Control Stent (BMS)	
Number of patients	474 (297:236)	104	244	206	197	148	141	
Results timeline	5 years	12 months	12 months	12 months	12 months	36 months	12 months	
Change in quality of life assessment (EQ-5D)	Not reported	Not reported	Not reported	Short form 8 question health survey used: Similarly improved	Not reported	Not reported	Not reported	
Change in walking impairment questionnaire composite	Both study arms significantly improved $P < 0.05$	Maximal distance on treadmill (m): 363 vs 270, $P = 0.04$	Maximal distance on treadmill (m): 185 vs 150, $P = 0.028$	More claudication pain in PTA group $P = 0.009$; Otherwise similarly improved	Not reported	Not reported	Walking distance (m): 785.8 vs 565.9 $P = 0.17$	
Change in 6-min walk test (m)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	
CD-TLR	16.9% vs 32.4%, $P < 0.01$	Not reported	14.9% vs 18.3%, $P = 0.595$	12.7% vs 54.8%, $P < 0.0001$	Not reported	Did not differ significantly, $P = 0.801$	13.4% vs 23.0%, $P = 0.37$	
Primary patency (freedom from CD-TLR or restenosis)	66.4% vs 43.4% $P < 0.01$	Binary restenosis rate: 37% vs 63%, $P < 0.01$	Binary restenosis rate: 31.7% vs 38.6%, $P = 0.377$	81.5% vs 36.7%, $P < 0.0001$	65% vs 40%, $P = 0.003$	24.2% vs 25.9%, $P = 0.392$	70.9% vs 55.1%, $P = 0.11$	
Safety outcomes: freedom from 30 day device and procedure related death, major limb amputation, CD-TLR	Freedom from persistent or worsening symptoms of ischemia: 79.8% vs 59.3% $P < 0.01$	Did not differ significantly	Did not differ significantly	Did not differ significantly	CLI 15% further improved for stent-graft group $P = 0.003$; Otherwise did not differ significantly	Did not differ significantly	Did not differ significantly	

Abbreviations: BMS, bare metal stent; CMS, covered metal stent; CD-TLR, clinically-driven target lesion revascularization; PTA, percutaneous transluminal angioplasty. Trials comparing drug-eluting, bare-metal, and covered stents against different techniques.

are two other categories of stents used in the SFA-popliteal segment: covered stents (often called stent grafts) and drug-eluting stents (DES).

3.4 | Covered stents

A covered metal stent, when compared with a bare metal, nitinol stent, utilizes the metal scaffold of a BMS and is also covered with expandable polytetrafluoroethylene (PTFE) on both the inside and outside. Since prosthetic bypass grafts for surgical revascularization utilize PTFE, it is for this reason that covered stents are often referred to as stent grafts or endoprostheses. A series of trials were conducted comparing covered metal stents, specifically the Viabahn endoprosthesis, to previous treatment options. In 2008, authors of the trial reported significant improvements in primary patency and safety outcomes for the endoprosthesis vs PTA.³⁰ In 2013, the VIBRANT trial reported results comparing the Viabahn endoprosthesis head to head with the nitinol bare BMS. Although no significant difference was reported, this was an important and necessary step to determining noninferiority of the Viabahn stent graft.³¹ The VIASTAR trial similarly compared endoprosthesis to a variety of BMS, and also reported no significant difference.³² A theoretical advantage of covered stents over BMS include the lack of ability for atheroma to invade through the cells of the stent and lead to neo-intimal hyperplasia and in-stent restenosis. A major disadvantage is that when covered stents fail, stent thrombosis and acute limb ischemia are often the presenting features, and frequently lead to urgent or emergent repeat revascularization.

3.5 | Drug-eluting stents

DES utilizes a standard, self-expanding nitinol scaffold, but added to the scaffold is an anti-proliferative drug that is slowly released and designed to prevent cell proliferation. The Zilver-PTX produced by Cook Medical releases paclitaxel from a polymer-free scaffold within 72 hours of placement. Paclitaxel is absorbed and remains in the arterial wall acting as an antiproliferative agent. Studies have shown that after approximately 1 month, the intimal layer of the artery grows over the scaffold, reducing the risk of thrombus formation.³³ In 2016, the Zilver-PTX trial reported 5-year results comparing DES (primary and provisional) vs standard care (defined as PTA with provisional Zilver BMS). Results were able to show a significant improvement favoring DES in many outcome measures including CD-TLR and primary patency. Both study arms also showed significant improvement in their WIQ composite score. However, other patient-centric metrics, such as QOL assessment or 6MWT remained unreported.³³

3.6 | Atherectomy

The primary mechanism of action of atherectomy devices is to obliterate atheromatous plaque rather than compressing it onto the arterial wall. This provides the advantage of increasing luminal diameter without leaving a foreign body, such as a stent, in the vessel. Endovascular atherectomy devices can further be divided into four categories: directional, rotational, orbital, and laser atherectomy. Each of these techniques, outlined in Figure 1, provides unique advantages and disadvantages with the overall goal of removing plaque burden. Table 3

provides an overview to trials evaluating atherectomy against other techniques.

3.7 | Directional atherectomy

As seen in Figure 1, a catheter with the cutting device is guided to the target lesion, once activated the device shears atheromatous plaque in a longitudinal plane, and the plaque is collected in a section of the device called a nosecone. In order to achieve maximum debulking, directional atherectomy requires multiple passes through the target lesion. Advantages include efficacy for eccentric and severely calcified lesions and the ability to use the device in vessel segments which typically are not stented (eg, common femoral or popliteal arteries). Disadvantages include risk of vessel trauma, longer procedural times because of multiple passes of the device, and risk of distal embolization that necessitates the use of an embolic protection device. In 2011, Shammas et al. reported results comparing directional atherectomy vs PTA using the Medtronic SilverHawk. The study did not report a significant difference in either CD-TLR or safety outcomes.³⁴ The DEFINITIVE AR study most recently compared atherectomy plus DCB vs DCB alone and did not report a significant difference in any of these same metrics or in QOL.³⁵

3.8 | Rotational atherectomy

A single, diamond-tipped, rotating burr is advanced to the target lesion and then when activated, this rotating burr is advanced into and through the target lesion. The burr grinds plaque into small particulate matter that can either be safely eliminated by the body or aspirated by the device. This process can be seen in Figure 1. Advantages include technical ease of use, speed of use, and ability to target severely calcified lesions. Disadvantages include difficulty to adjust to atheroma depth, as the luminal gain will match the burr diameter, as well as danger of particulate debris becoming embolized down the leg.³⁶

3.9 | Orbital atherectomy

A high-speed rotating shaft and debulking crown are utilized by advancing the device to the target lesion and when activated, the rotating crown is advanced into and through the target lesion. The difference between rotational atherectomy and orbital atherectomy is that debulking area (ie, the "orbit") increases with increasing rotational speed of the crown. This allows luminal gain to more closely match atheroma depth and completeness of plaque obliteration. Operative speed remains a procedural advantage with orbital atherectomy, along with improved luminal gain. Disadvantages include inability to address in-stent restenosis and possible high risk for barotrauma if operator does not properly manage rotational speed.³⁶ The COMPLIANCE 360 trial investigated orbital atherectomy vs PTA and did not report a significant difference in primary patency, as seen in Table 3.³⁷

3.10 | Laser atherectomy

The excimer laser ablates or obliterates atheromatous plaque through ultraviolet radiation, as seen in Figure 1. Current technology is able to remove 10- μ m thickness in depth with each pulse of energy without

TABLE 3 Atherectomy vs other technologies

	Atherectomy vs PTA			Atherectomy vs PCB
Trial name	Shammas et al. (2011)	COMPLIANCE 360 (2014)	EXCITE-ISR (2015)	DEFINITIVE AR (2017)
Randomized treatment	Medtronic SilverHawk directional atherectomy vs PTA	Orbital atherectomy vs PTA	2:1 Spectranetics Turbo Tandem laser catheter vs PTA	Medtronic SilverHawk/TurboHawk DA + Medtronic Cotavance PCB vs PCB alone
Number of patients	46	50 (65 lesions)	250	102
Results timeline	12 month	12 month	6 month	12 month
Change in Quality of Life Assessment (EQ-5D)	Not reported	Not reported	Not reported	EQ-5D index at 1 year: 0.87 ± 0.20 vs 0.87 ± 0.19 $P = 0.72$
Change in walking impairment questionnaire composite	Not reported	Not reported	Not reported	Similarly improved
Change in 6-min walk test (m)	Not reported	Not reported	Not reported	Not reported
CD-TLR	8.0% vs 22.2% , $P =$ not significant	Not reported	26.5% vs 48.2% $P < 0.005$	7.3% vs 8.0%, $P = 0.90$
Primary patency (freedom from CD-TLR or restenosis)	Not reported	81.2% vs 78.3%, $P > 0.99$	Maintained superiority through available follow-up $P < 0.005$	84.6% vs 81.3%, $P = 0.78$
Safety outcomes: freedom from 30 day device and procedure related death, major limb amputation, CD-TLR	Did not differ significantly	Not reported	5.8% vs 20.5%, $P < 0.001$	89.3% vs 90.0%, $P = 0.86$

Abbreviations: CD-TLR, clinically-driven target lesion revascularization; PTA, percutaneous transluminal angioplasty; PCB, paclitaxel coated balloon. Trials comparing different atherectomy devices against different techniques.

damaging arterial tissue. As seen in Table 3, the EXCITE-ISR trial compared laser atherectomy vs PTA and was able to show a significant difference in CD-TLR, primary patency, and safety outcomes.³⁸ Due to these results, the U.S. Food and Drug Administration granted the device an indication for treatment of in-stent restenosis. Other advantages include the ability to obliterate thrombus (when present) and the ability to use laser atherectomy in long segments of atheroma. However, a disadvantage includes an increased procedural time due to slow energy pulse.¹⁶

4 | LIMITATIONS OF CURRENT DATA

Newer endovascular therapies, such as atherectomy devices, stent technology, and DCBs have been the subject of many recent trials and ongoing discussion among experts. The field of endovascular SFA-popliteal revascularization has clearly made great strides over the past 2 decades; however, major limitations of the current data remain. The first is primarily because of the lack of head to head comparisons. Results of trials outlined in this review highlight clinical benefit vs the former standard of care (ie, PTA), but a lack of randomized head to head studies (ie, which atherectomy device is better) continues to make it difficult for specialists to choose the appropriate treatment option for patients. A recent network-meta analysis has attempted to combine separate RCTs to provide comparisons among therapies; however, the heterogeneity in patient populations, severity of disease,

and treatment choices limit the results and its impact on clinical decision-making.³⁹ In fact, treatment recommendation is unclear even when taking each treatment modality separately. For example, looking at DCBs, there need to be future trials comparing different designs. Although separate DCBs have been able to show efficacy vs PTA, it remains difficult to form a clear recommendation in the operative setting.

The second major limitation of the current evidence is a lack of consensus over consistent clinical definitions of outcome measures, and a general lack of patient-centric measures used in SFA-popliteal intervention studies. PAD is not only associated with a high mortality rate, it also has a significant impact on functionality and QOL. Although studies have consistently reported outcomes such as CD-TLR and primary patency, metrics that ultimately matter to patients such as QOL and walking distance have failed to see this same consistency. The Peripheral Academic Research Consortium (PARC) and other groups such as the Society for Vascular Surgery recently laid a framework addressing this issue.^{40,41} The overall goal of the PARC group was to develop standardized definitions for patients with PAD to better allow for clinical characterization and evaluation of therapies. Definitions for clinical outcomes for this population were agreed upon based on a dichotomy separating patients suffering from IC or other exertional limb symptoms from CLI. Functional definitions for clinical outcomes of the IC population included both the 6MWT and WIQ as consensus tools to measure walking/functional capacity and QOL, respectively. Additional tools included peak walking time as

assessed by a treadmill walking protocol and the Peripheral Artery Questionnaire (PAQ) that quantifies the patient's physical limitations, symptoms, social functions, treatment satisfaction, and QOL.⁴⁰ With a clear set of guidelines, future trials must now make it a priority to report clinical outcomes that affect this population on a daily basis.

5 | FUTURE RESEARCH

Although atherectomy devices require more evidence, stent technology, and DCBs have both proven to be superior to PTA when treating femoropopliteal lesions. In order to establish a standard of care, it is now important for randomized trials to focus on head to head comparisons (eg, laser atherectomy vs directional atherectomy), study treatment strategy comparisons (eg, DCB/stent vs atherectomy/DCB), and include standardized, consistent patient-centric outcomes. An informal review of clinicaltrials.gov revealed a number of ongoing, comparative effectiveness studies. A RCT from the University of Leipzig, Germany is currently recruiting participants and comparing the Ranger DCB and IN.PACT DCB. The study design includes up to 414 participants (1:1 ratio) and outcomes include patency rate, freedom from death and amputation, CD-TLR and walking capacity (WIQ). Similarly, SurModics, Inc. is currently recruiting for the TRANSCEND RCT, comparing its own Surmodics SurVeil DCB to the Medtronic IN.PACT Admiral DCB. The study design includes 446 participants (1:1 ratio) and outcomes include lesion patency at 12 months, safety composite, WIQ, 6MWT, and PAQ scores. Shockwave Medical Inc. is investigating its Shockwave lithotripsy balloon vs Medtronic IN.PACT DCB in DISRUPT PAD III RCT. The study design includes 334 participants (1:1 ratio) with outcomes including procedural success, freedom from CD-TLR, clinical success, and QOL (EQ5D questionnaire).

In addition, research is being done to investigate stent technology. Cook Medical is currently recruiting for the XPEDITE RCT comparing different models of the Zilver PTX stent including one with slower-dissolving coating and one with higher dose coating. The study design includes 150 participants and the primary outcome is percent diameter stenosis at 6 months. Finally, the FOREST trial is a proposed randomized, controlled, single blind, multicenter trial comparing DCB, and provisional bare-metal stenting to primary stenting with DES. The study design includes 254 patients (1:1 ratio) with outcomes of freedom from binary restenosis, TLR, changes in ABI, safety outcomes, and QOL as measured by PAQ.⁴² The path forward in this field includes more head to head trials, standardized data entry, and an industry willingness to fund these important studies.

6 | CONCLUSIONS

PAD, and specifically SFA-popliteal disease, continues to remain a major health concern significantly affecting mortality, functionality, and QOL. Endovascular treatment has increasingly become a more popular therapy over the past two decades. Many RCTs have reported the effectiveness of various therapies including laser atherectomy, stent technology, and DCBs over PTA. A new standard of care remains unclear; however, due to a lack of head to head comparisons

between novel therapies. Furthermore, a large degree of heterogeneity exists in the clinical and patient-centric outcomes reported in these studies, and it has continued to make it difficult to evaluate functionality and the impact on QOL - important metrics when evaluating overall the comparative effectiveness of various treatment modalities. Recently established guidelines and consistent definitions for clinical outcomes, coupled with the field taking steps towards direct comparisons, will be crucial to establish consistent care and meaningful gain in the treatment approach for these patients.

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