Endovascular Management of Femoropopliteal In-Stent Restenosis: A Systematic Review ☆,☆☆,★

Daniel L. Varela [a,*], Ehrin J. Armstrong [a,b]

[a] University of Colorado School of Medicine, Division of General Internal Medicine, 12631 East 17th Avenue, Aurora, CO 80045, USA
[b] Veterans Administration, VA Eastern Colorado Health Care System, 1055 Clermont Street, Denver, CO 80220, USA

ABSTRACT

Despite the development of new therapies for the treatment of femoropopliteal disease, nitinol stents remain a mainstay of therapy following balloon angioplasty. Consequently, femoropopliteal in-stent restenosis (FP-ISR) remains an important clinical problem. Interventions used to treat de novo lesions of the femoropopliteal segment have been used to treat ISR lesions, with disappointing outcomes. Early interventions focused on repeat balloon angioplasty, cryoplasty, and various debulking therapies. Recently, treatment has shifted towards the use of stent-grafts, drug-eluting therapies, and combination therapies. This review analyzes the evidence behind each treatment modality and provides insight into future directions for optimal endovascular management of FP-ISR.

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Contents

1. Background

The endovascular management of peripheral artery disease continues to improve following the advent and implementation of a wide variety of treatment modalities; however, treatment of femoropopliteal (FP) lesions continues to be particularly challenging. A number of factors, including continued disease progression, neointimal hyperplasia, and the unique anatomical location and complex mechanical forces imposed on these vessels (e.g., elongation, compression, flexion, and torsion) contribute to exceedingly high rates of restenosis of FP lesions following treatment relative to lesions involving other vascular beds [1]. Percutaneous transluminal angioplasty (PTA) of FP lesions is limited by a low primary patency rate of 30–61% at 3 years depending on lesion length and clinical stage. The poor patency following PTA has resulted in a move towards alternative strategies as a mainstay endovascular treatment for de novo lesions of the FP segment [2]. For complex lesions, stents may be used as either primary therapy, or as "bail out" after significant flow-limiting dissection or recoil. Unfortunately, femoropopliteal in-stent restenosis (FP-ISR) remains common following stenting of the FP segment.

Treatment of FP-ISR has been well studied, and while most of the early studies saw high rates of initial procedural success, long-term patency rates have been unsatisfying and rates of target lesion revascularization (TLR) remain quite high. To this day, there is no universally accepted method for the treatment of FP-ISR. We hypothesize that newer therapies such as drug coated balloons and stents, as well as combination therapy utilizing debulking devices plus balloons or stents, will result in the best long-term patency and freedom from TLR. This review discusses each currently available treatment option for the endovascular management of FP-ISR, highlighting the benefits and shortcomings of each modality, with the goal of helping clinicians identify the most effective treatment options and to identify future perspectives for ongoing research into the management of this challenging condition.

FP-ISR is very common after stenting of the FP segment, with an incidence between 19 and 37% at 1 year [2,3], 49% at 2 years [2], and 60% at 3 years [4]. The incidence of FP-ISR varies based on the type of stent used and the length of stent implanted, with rates as high as 19–35% at 1 year in patients treated with slotted-tube nitinol stents [5] and as low as 14–17% in patients treated with interwoven-wire nitinol stents [6]. The placement of longer or overlapping stents may further increase the risk of restenosis [7]. Additionally, the presence of stent fractures has also been implicated in the development of FP-ISR [8]. Stent fractures were particularly common with the older self-expanding stents but have become less common following the advent of newer nitinol stents [4].

Drug-coated balloon angioplasty (DCB) may also reduce the incidence of FP-ISR when used in place of PTA as the initial intervention for de novo lesions of the FP segment [6,9], at least during the first year following treatment. Unfortunately, the incidence of FP-ISR increases by 50% between the first and the second years of follow-up after treatment of de novo FP lesions with DCB plus stenting [10]. Another option for the treatment of de novo FP lesions is the Viabahn polytetraflouroethylene (PTFE)-covered nitinol stent-graft; use of the Viabahn stent-graft is associated with lower rates of FP-ISR (6–26% at 1 year) when compared with bare nitinol stents [11–13] Paclitaxel-eluting stents have shown superiority over older-generation bare metal stents, with restenosis rates of 10.1–14.6% at 1 year, 24.4% at 2 years, and 35.1% at 5 years [1,14].

In addition to the specific treatment modality employed, the characteristics of the FP lesions themselves also affect the rates of subsequent restenosis. Previous studies comparing the rates of FP-ISR between the different TransAtlantic Inter-Society Consensus (TASC) II classes saw similar 5-year restenosis rates of around 50% for TASC II class A-C lesions, while higher rates (66%) were seen for TASC II class D lesions [15]. Tosaka et al. [16] developed a classification system specific to the FP segment based on angiographic patterns of the restenotic lesion (Fig. 1). Tosaka class I consists of focal stenosis <50 mm within the stent body and/or edge. Tosaka class II includes diffuse stenosis >50 mm within the stent body and/or edge, and Tosaka class III refers to total stent occlusions. Tosaka et al. examined a cohort of patients who underwent treatment for FP-ISR with PTA and found that the prevalence of each lesion was evenly distributed between the three classifications: 29% of lesions were class I, 38% were class II, and 33% were class III. They also found that class III lesions were associated with a particularly high rate of recurrent restenosis (84.8%) and re-occlusion (64.6%) 2 years after treatment. By comparison, class I lesions had a 49.9% rate of recurrent restenosis and a 15.9% rate of re-occlusion, and class II lesions had a 53.3% rate of recurrent restenosis and an 18.9% rate of re-occlusion. Armstrong et al. [17] conducted a similar study, this time using multiple endovascular interventions, including laser atherectomy, excisional atherectomy, and repeat stenting. Despite the use of additional therapies, they found rates of restenosis that were similar to those reported by Tosaka et al.; recurrent restenosis was present in 39% of class I lesions, 67% of class II lesions, and 72% of class III lesions (Fig. 2). As was seen by Tosaka et al., Armstrong et al. also noticed a significantly higher rate of re-occlusion for class III lesions relative to class I and II lesions (hazard ratio = 5.8). Other lesion characteristics, such as the presence of critical limb ischemia (CLI) and poor distal runoff, along with patient comorbidities (e.g. diabetes, chronic kidney disease, and smoking) have been associated with higher rates of restenosis following treatment of the de novo lesion [7].

Unfortunately, there is no good means for preventing FP-ISR other than lifestyle modifications and dual-antiplatelet therapy, usually with aspirin indefinitely and clopidogrel for a minimum of 4 weeks post-intervention. The progression of restenosis is most pronounced during the first year following stenting, making this first year after intervention the most crucial period for aggressive anti-platelet therapy. In addition to aspirin and clopidogrel, some research has suggested that cilostazol may prevent FP-ISR [18]. Cilostazol, a phosphodiesterase type 3 inhibitor, increases the concentration of cyclic adenosine monophosphate. This has multiple effects, such as inhibition of platelet activation, vasodilation, antiproliferation of vascular smooth muscle cells, and improvement of endothelial cell function. It has been postulated that these effects may help delay or prevent the progression of restenosis following treatment of stenotic lesions [18]. Iida et al. [18] conducted a study that examined rates of TLR following treatment of de novo FP segment stenosis and found an absolute risk reduction of 20% for patients treated with cilostazol relative to patients who did not receive cilostazol. While no formal randomized controlled trial (RCT) has been conducted to further assess cilostazol's role in prevention of FP-ISR, this study suggests that there may be some benefit to adding cilostazol to anti-platelet therapy. Intravascular brachytherapy has also been studied, with good early and mid-term results for the prevention of FP-ISR, but disappointing long-term outcomes [18]. This, combined with the technical constraints of the procedure and necessary radiation safety measurements and staffing requirements, have led to brachytherapy not being adopted in usual practice.

2. Materials and methods

A systematic review of all published articles on the endovascular management of FP-ISR was conducted using PubMed. Search terms were:

1. Femoropopliteal in-stent restenosis OR superficial femoral artery in-stent restenosis

and

2. Percutaneous transluminal angioplasty OR cutting balloon angioplasty OR scoring balloon angioplasty OR cryoplasty OR brachytherapy OR percutaneous transluminal angioplasty with
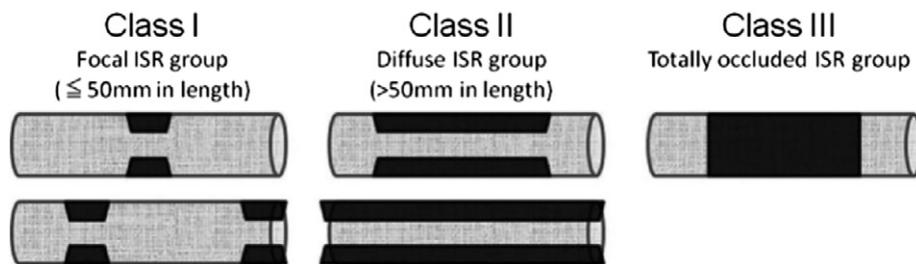
Fig. 1. FP-ISR classification scheme. Abbreviations: FP, femoropopliteal; ISR, in-stent restenosis. Reproduced, with permission, from Tosaka et al. [16].

nitinol stent OR covered stent-graft OR drug-eluting stent OR drug-coated balloon angioplasty OR mechanical thrombectomy OR directional and excisional atherectomy OR rotational and aspiration atherectomy OR laser atherectomy.

The resulting abstracts were reviewed, and full manuscript review was conducted for all manuscripts deemed to fall within the scope of this review. References from each manuscript were also reviewed and considered for inclusion to avoid missing any additional relevant articles. To be included, manuscripts must have studied the treatment of either FP-ISR or superficial femoral artery in-stent restenosis with at least one of the endovascular therapies listed above under "search term 2." Prospective studies conducted on just one intervention as well RCTs comparing two or more interventions were both included. Primary outcomes assessed were primary patency and freedom from clinically-driven TLR. Restenosis was defined as a >50% diameter stenosis by angiography or a peak systolic velocity ratio >2.4 by duplex at any point within the stent(s), plus the 5-mm segments proximally and distally. The requirement for any reintervention within 1 year was also considered as restenosis. ISR lesions were classified by visual estimate on angiography according to the Tosaka system. Mean lesion length and Tosaka classification were also recorded to serve as measures of lesion complexity and to help create a frame of reference for the variable results reported between the studies. Studies were excluded if they did not report at least one of the primary outcomes. Studies on the surgical management of FP-ISR were also excluded. Failure to report mean lesion length or Tosaka classification was not an indication for exclusion from this review.
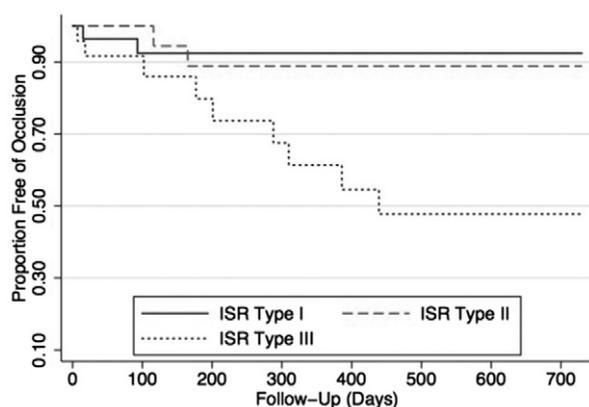

Fig. 2. Outcomes of FP-ISR treatment stratified by angiographic classification. Abbreviations: FP, femoropopliteal; ISR, in-stent restenosis. Reproduced, with permission, from Armstrong et al. [17].

3. Results

A total of 34 studies assessing 11 individual endovascular therapies and 3 combination therapies were included. The 11 individual therapies included were: PTA, cutting balloon angioplasty, brachytherapy, covered stent-grafts, DES, DCB, Rotarex mechanical thrombectomy, SilverHawk directional and excisional atherectomy, Pathway PV or JetStream rotational and aspiration atherectomy, and Excimer laser atherectomy. The 3 combination therapies were: laser atherectomy plus covered stent-grafts, laser atherectomy plus DCB, and SilverHawk atherectomy plus DCB. Some studies used PTA in combination with other therapies, such as laser atherectomy. However, the use of adjunctive PTA was not considered to be combination therapy in this review. Study durations ranged from 1 to 36 months, and the number of lesions treated in each study ranged from 14 to 169.

Before proceeding with the most well-studied treatments for FP-ISR, it is worth briefly mentioning a few interventions that have either been insufficiently studied or have shown no benefit in the management of this condition. Scoring balloon angioplasty has not been specifically studied in the treatment of FP-ISR, while cutting balloon angioplasty and cryoplasty have failed to show any benefit over PTA [19,23,24]. Brachytherapy with Rhenium-188 is a novel technique for the treatment of FP-ISR, and while one small study saw promising results at 12 months, this intervention has not been studied further and concerns about radiation-related complications and the time-consuming nature of the procedure have prevented brachytherapy from seeing more frequent use [25].

3.1. Percutaneous transluminal angioplasty

PTA, one of the first interventions utilized for the treatment of FP-ISR, has been associated with exceptionally poor primary patency (27–40% at 6 months and 13.4% at 12 months) [19,20] and freedom from TLR (20–60% at 6 to 12 months) [6,13,19–22]. PTA alone may be an acceptable choice for focal, class I FP-ISR, but the results for diffuse (class II) or occlusive (class III) FP-ISR are suboptimal. The poor long-term results following PTA may be the result of smooth muscle cell replication and extracellular matrix deposition within the stent. This extracellular matrix is composed of various collagen subtypes and proteoglycans that, over time, form a restenotic plaque; this collagen and proteoglycan plaque is less susceptible to PTA than the de novo lesion and may require more aggressive measures, such as debulking, particularly in longer lesions with greater degrees of occlusion [22]. While PTA may be acceptable for class I FP-ISR, its use for the treatment of more complex (class II and III) lesions should be discouraged [4,13,19–21].

3.2. Angioplasty plus covered stent implantation

The placement of an additional nitinol stent in cases of FP-ISR may prevent acute or subacute vessel closure; however, this is usually not done due to concerns about higher risks of recurrent ISR in vessels treated with overlapping stents. The placement of additional nitinol

stents has not been specifically studied in cases of FP-ISR, and outcomes following this treatment strategy are not well defined [17]. Two alternatives to treating FP-ISR with traditional nitinol stents include the use of newer Viabahn PTFE-covered nitinol stent-grafts and drug-eluting stents (DES), each of which has become increasingly popular and well-studied over the past several years.

The Viabahn PTFE-covered nitinol stent-graft is a flexible, self-expanding endoluminal stent graft consisting of a PTFE lining with an external nitinol support extending along its entire length. The advantage of the Viabahn stent-graft lies in its small pores, which allow the layer of graft material to serve as a direct barrier to neointimal in-growth, thereby minimizing the likelihood of restenosis within the stented region [5]. Additionally, this barrier is coated with a heparin bioactive surface that enhances hemocompatibility and decreases the risk of thrombus formation. Ansel et al. [26] treated FP-ISR (mean lesion length 271 mm) with the Viabahn stent and reported an 18-month primary patency of only 52%. Subsequent studies yielded more favorable results. Shammeri et al. [12] examined lesions with a mean length of 245 mm and reported 12 and 36-month primary patency rates of 85.1% and 81.4%, respectively. Gorgani et al. [27] treated FP-ISR (mean lesion length 215 mm) with the Viabahn stent-graft plus PTA and reported a primary patency of 63% after 40 months of follow-up; the authors noted that the mean time to recurrent restenosis was 6 months. There were also no cases of recurrent restenosis after 14 months of follow-up, suggesting favorable long-term sustained patency rates for this treatment.

The Gore Viabahn Versus Plain Old Balloon Angioplasty for Superficial Femoral Artery SFA In-Stent Restenosis (RELINE) trial [13] is the only RCT to date that has evaluated the use of the Viabahn stent-graft for the treatment of FP-ISR. This study compared Viabahn vs. PTA and found that the Viabahn group (mean lesion length 173 mm; 23.1% class III lesions) had a 74.8% 12-month primary patency rate, much higher than the 28.0% primary patency seen in the PTA group (mean lesion length 190 mm; 25.0% class III). 12-month freedom from TLR was 79.9% vs. 42.2% for the Viabahn and PTA groups, respectively.

While the Viabahn stent-graft has shown favorable outcomes relative to PTA, particularly in medium and long-segment FP-ISR, stent-grafts are predisposed to restenosis at the stent edges, where intimal injury is not covered completely by graft material. This pattern of restenosis, in which the main body of the graft is free of restenosis and the edges develop restenosis, appears to be characteristic of stent-grafts and has been reported to occur in 13.6% of lesions treated with the Viabahn stent-graft [28]. This edge restenosis is concerning because it can result in stent thrombosis and stent-graft failure [28]; to reduce the risk of restenosis at the stent-graft edge, the stent-graft should be properly sized to the reference vessel, and post-dilation should be avoided outside the edges of the stent-graft [4]. When stent thrombosis does occur at the stent-graft edge, there may be benefits from treating this lesion with JetStream XC atherectomy, as the combined thrombectomy and arherectomy capabilities may effectively remove the graft thrombosis and debulk restenotic tissue along the stent-graft edge [29].

3.3. Angioplasty plus drug-eluting stent implantation

Paclitaxel prevents microtubule formation, thereby inhibiting cell replication and smooth muscle cell proliferation and ingrowth after angioplasty. The Zilver PTX paclitaxel-eluting nitinol stent has been studied in the treatment of FP-ISR (mean lesion length 133 mm; 31% class III) with favorable results. 12-month primary patency was 78.8%; freedom from TLR was 81% at 12 months and 60.8% at 24 months [8]. The Zilver PTX was the first study to show that treatment of FP-ISR with paclitaxel-eluting stents results in favorable acute, midterm, and long-term outcomes. Murato et al. [30] subsequently conducted a retrospective study comparing outcomes following treatment of FP-ISR with either the Zilver PTX or PTA. Patients were stratified into

groups based on whether they had class III lesions. Among patients without class III lesions, there was no significant increase in 12-month primary patency following treatment with DES over PTA (59.5% vs. 54.3%). However, patients who had class III lesions and were treated with DES had substantially better 12-month primary patency than those treated with PTA (55.9% vs. 9.7%). The results of this study provide additional insight into the role of DES by suggesting an improvement in outcomes primarily for those patients with class III lesions. A drawback to the Zilver PTX stent is that it only comes in a limited number of sizes, so multiple stents may be required for treatment of long-segment FP-ISR. This limitation of the Zilver PTX may limit its potential utility and cost effectiveness for the treatment of long-segment FP-ISR, as multiple overlapping stents may be required for these cases.

3.4. Drug-coated balloon angioplasty

DCB may be the most extensively researched FP-ISR treatment modality in recent years. Drug coated balloons deliver paclitaxel locally at the site of balloon angioplasty. The ability to locally deliver an anti-restenotic agent without leaving behind additional scaffolding from a stent-based delivery system is an attractive option for the treatment of FP-ISR, given concerns regarding long-term stent durability, risk of stent fracture, and potential for increased risk of stent restenosis when overlapping stents are placed. Stabile et al. [31] treated FP-ISR (mean lesion length 83 mm; 20.5% class III) with DCB (IN.PACT, Medtronic, Minneapolis, Minnesota) and found a 1-year primary patency of 92.1% and freedom from TLR of 89.5%. Unfortunately, Virga et al. examined 2-year follow-up of patients from this study and found a significant reduction in both primary patency and freedom from TLR, with primary patency rates dropping from 92.1% to 70.3% while freedom from TLR dropped from 89.5% to 78.4% [10].

The Drug-Eluting Balloon in Peripheral Intervention for In-Stent Restenosis (DEBATE-ISR) trial [32] compared DCB (IN.PACT, Medtronic, Minneapolis, Minnesota) with PTA, specifically in patients with diabetes. Diabetic patients with FP-ISR (mean lesion length 132 mm; 51% class III) treated with DCB had a 1-year primary patency of 80.5% and freedom from TLR of 86.4%, while the PTA group (mean lesion length 137 mm; 65% class III) had significantly worse 1-year outcomes: primary patency was only 28.2% and freedom from TLR was 69.0%. DEBATE-ISR also reported even longer follow-up than the 2-year results reported by Virga et al. At 3-years, DEBATE-ISR revealed a progressive worsening of outcomes for the DCB group; freedom from TLR dropped from 86.4% at 12 months to only 60.0% at 3 years, nearly identical to the 57.0% freedom from TLR seen in the PTA comparator group [33]. This finding has raised concerns about a potential "late catch-up" phenomenon with DCBs, wherein the delay in neointimal growth following the use of antiproliferative drugs gradually wears off over time as the drugs progressively lose their therapeutic effect. This may be due to paclitaxel's known dose-dependent effect on the inhibition of neointimal proliferation, as well as the fact that paclitaxel retained in the arterial wall progressively washes out over time [33].

It is unclear when exactly this late catch-up phenomenon begins to set in, but the PLAISIR trial by Bague et al. [9] would suggest that DCB (IN.PACT Admiral, Medtronic, Santa Rosa, CA, USA) retain benefit for at least the first 18 months. The investigators in this study saw an impressive and nearly identical 12 and 18-month primary patency of 83.7% and 78.1% respectively. Rates of freedom from TLR were also identical, at 90.2% at both 12 and 18-month follow-up. However, the results must be considered in the context that the lesions treated in the PLAISIR trial were not as severe as those treated in DEBATE-ISR, with a mean lesion length of only 86 mm (mean lesion length in DEBATE-ISR was approximately 130 mm for both the DCB and PTA groups), and there were almost no class III lesions in the PLAISIR trial (2% for PLAISIR vs. 51–65% for DEBATE-ISR). Regardless of when the late catch-up phenomenon begins to take effect, the investigators of DEBATE-ISR still commented on the benefits of DCB over PTA, as the

initial delay in restenosis following DCB still allows for improved wound healing early on following intervention, and this can be particularly helpful for wound healing in diabetic patients and in those with CLI. Additionally, the authors speculate that higher doses of antiproliferative drugs, or implementation of a more effective drug-eluting platform, may help extend the antiproliferative effect of paclitaxel beyond its current therapeutic window.

The ongoing COPACABANA trial [34] is testing this hypothesis of increased paclitaxel dosing by looking into the role of higher doses of paclitaxel in the treatment of TLR when it occurs after initial treatment of FP-ISR. In this trial, when a previously treated FP-ISR lesion required TLR for the first time, the re-intervention was performed with DCB using twice the standard dose of paclitaxel used in the treatment of the initial FP-ISR lesion. While the final results are still pending, initial reports based on 2-year follow-up data are encouraging for this unique treatment strategy.

Recently, two additional RCTs further evaluated the efficacy of DCB compared with PTA for the treatment of FP-ISR. In the Femoral Artery In-stent Restenosis (FAIR) trial, Krankenberg et al. [6] compared DCB (IN.PACT Admiral paclitaxel-eluting balloon, Medtronic, Minneapolis, MN) vs. PTA in the treatment of FP-ISR (mean lesion length 82 mm; 28.6% class III) and found 12-month primary patency rates to be 70.5% in the DCB group vs. 37.5% in the PTA group. 12-month freedom from TLR was 90.8% vs. 52.8% for DCB and PTA, respectively. These results were comparable to those seen when DCBs were used to treat de novo stenosis of the FP segment as well as to the 12-month results reported by Stabile et al., Virga et al., and DEBATE-ISR for FP-ISR lesions of similar lengths (<150 mm) [10,31]. However, up until this point, there was little data to suggest how well DCB would hold up in the treatment of FP-ISR involving longer, more complex lesions. The PACUBA trial compared DCB (FREEWAY balloon 0.035; Eurocor, Bonn, Germany; Opto Eurocor Healthcare, Bangalore, India) to PTA in the treatment of longer FP-ISR lesions (>150 mm) [20]. In this study, the DCB group (mean lesion length 173 mm; 30.0% class III) saw a 12-month primary patency of only 40.7% and freedom from TLR of only 51.0%. The PTA group (mean lesion length 184 mm; 30.0% class III) fared even worse, with 12-month primary patency a dismal 11.1% and only a 22.1% freedom from TLR. The reasons for the significantly worse outcomes following treatment with both DCB and PTA in this study are not entirely clear but are likely due in part to the longer mean lesion length seen in this study than in the prior studies. In addition to the concerns about a late catch-up phenomenon reported previously, the outcomes of PACUBA raise another potential limitation of DCB: that DCB alone may not be sufficient for the treatment of long-segment FP-ISR. Assuaging these concerns, the most recent study on DCB, conducted by Brodmann et al. [35], provided some reassuring results; following treatment of long-segment FP-ISR (mean lesion length 172 mm; 34.0% class III), they reported some of the best outcomes for DCB (IN.PACT Admiral, Medtronic, Dublin, Ireland) thus far: a 12-month primary of 88.7% and 12-month freedom from TLR of 92.9%, which are comparable to the results reported for the treatment of shorter lesions [10,31,32]. Taken together, the current data on DCB support that this therapy produces mostly favorable midterm (approximately 1-year) outcomes that are similar to those seen with other popular treatment options, including Viabahn stent-grafts and DES.

Some of the most recent research on the treatment of FP-ISR is beginning to look into the role of DCB used in conjunction with debulking devices, such as laser or directional atherectomy [7,22,36,37], as discussed below.

3.5. Rotarex mechanical thrombectomy

Data on the use of thrombectomy devices for the treatment of FP-ISR are limited, which may be due to the fact that most of the material comprising these lesions is smooth muscle and collagenous extracellular matrix, rather than clot. As a result, thrombectomy is felt to be less effective than atherectomy for the treatment of these lesions. Regardless, a few studies have examined outcomes following treatment with mechanical thrombectomy. Silingardi et al. [38] employed the Rotarex mechanical thrombectomy system plus PTA to treat FP-ISR (mean lesion length 160 mm) and reported a 12-month primary patency rate of 58.1% and a 46.9% freedom from TLR. The following year, Wissgott et al. [39] treated patients (mean lesion length 147 mm) with mechanical thrombectomy (plus PTA in 68.4% of cases) and found a 12-month primary patency of 81.6%. Both studies were completed several years ago and no RCTs or other studies on the use of mechanical thrombectomy have been conducted since that time, with a much greater focus being placed on the various angioplasty, stent, and atherectomy-based treatment modalities.

3.6. SilverHawk directional and excisional atherectomy

Balloon angioplasty results in significant stretch injury (barotrauma) to the vessel wall, which stimulates smooth muscle cell migration, proliferation, and production of extracellular matrix, all factors which lead to gradual neointimal hyperplasia and restenosis. Catheter-based directional and excisional atherectomy have garnered significant attention over the past decade for its ability to increase luminal dimensions while minimizing barotrauma to the vessel wall [4]. In addition to reducing barotrauma, excisional catheters, such as the SilverHawk directional atherectomy device, may help treat FP-ISR by debulking thrombotic and hyperplastic tissue from the stent lumen, allowing for more effective angioplasty, stent expansion, and local delivery of anti-proliferative drugs. However, SilverHawk directional atherectomy is currently off-label use for the treatment of FP-ISR; while it carries the theoretical advantage of reducing the volume of restenotic tissue and may potentially delay the need for frequent repeat revascularization and additional stenting, there are concerns surrounding its use for FP-ISR due to rare reports of the device getting stuck on stent struts. Zeller et al. [40] reported an unimpressive 12-month primary patency of 54% and freedom from TLR of 53% following treatment of medium-length FP-ISR (mean lesion length 131 mm; 8.50% class III) with SilverHawk atherectomy. Fortunately, follow-up at 18 months revealed similar rates of primary patency (49%) and freedom from TLR (51%), indicating that the late catch-up phenomenon seen following DCB may not apply to SilverHawk atherectomy.

Trentmann et al. [41] treated FP-ISR (mean lesion length 108 mm) with SilverHawk atherectomy (plus adjunctive PTA in 46% of cases) and observed even worse outcomes; 12-month primary patency was only 25%. Shammas et al. [42] compared SilverHawk atherectomy (plus adjunctive PTA in 97% of cases) against excimer laser atherectomy and reported 12-month freedom from TLR to be 68.3% after treatment with SilverHawk atherectomy and 51.3% following treatment with laser atherectomy, though the mean lesion length was significantly shorter in the group treated with SilverHawk atherectomy (126 mm vs. 210 mm).

Overall, the results of excisional and directional atherectomy for the treatment of FP-ISR have been disappointing so far and the theoretical benefits of reduced barotrauma and increased luminal diameter have not borne out in clinical practice. Concerns have been raised that the better outcomes seen for SilverHawk atherectomy reported by Shammas et al. [42] compared to those reported by Zeller et al. [40] may be due to the increased utilization of PTA in the former study, rather than from the use of atherectomy itself [4]. Furthermore, distal embolization occurs with considerable frequency, with macrodebris being found in embolic protection devices in upwards of one-third of treated patients [42]. While this can be reduced by using embolic protection devices, rates of distal embolization following excisional atherectomy are still greater than those seen with other endovascular therapies. At this time, directional atherectomy has not produced satisfactory long-term patency rates following treatment of FP-ISR; this combined with the high rates of distal embolization and risk of

device entrapment within the stent has led to directional atherectomy not taking off as a mainstay treatment strategy for the management of FP-ISR.

3.7. JetStream rotational and aspiration atherectomy

The JetStream atherectomy device is a rotational cutter with aspiration capacity and has been shown to cut and remove atherosclerotic and restenotic tissue [43]. JetStream atherectomy is currently off-label use for the treatment of FP-ISR [44]. The optimal technique for JetStream atherectomy in the treatment of FP-ISR was previously not well studied, but Shammas et al. [44] reported that maximal debulking was achieved when rotational atherectomy was performed with 2 blades down and 2 blades up runs followed by adjunctive PTA and that the addition of more blades up runs did not improve clinical outcomes but did increase the risk of distal embolization.

Few studies have assessed the outcomes following treatment of FP-ISR with JetStream atherectomy. Beschorner et al. [45] evaluated the use of the Pathway PV atherectomy system in patients with shorter lesions (mean lesion length 85.7 mm; 20.0% class III). 57% of patients required adjunctive PTA to achieve satisfactory results. 1-year primary patency was a disappointing 33% and dropped slightly to 25% at 2-year follow-up. Following the completion of this study, the Pathway PV atherectomy system was upgraded to the JetStream XC device, which has enhanced cutting ability and aspiration capacity. Shammas et al. [43] used JetStream XC atherectomy plus PTA in the treatment of FP-ISR (mean lesion length 195 mm; 25.0% class III) and reported a 6-month primary patency of 72%. The 6 and 12-month freedom from TLR rates were 86.2% and 58.6% respectively.

The results of the JetStream ISR feasibility study were superior to those reported by the studies on SilverHawk atherectomy and comparable to those seen by the most well-studied debulking strategy for FP-ISR: excimer laser atherectomy. However, data evaluating JetStream atherectomy's long-term outcomes and RCTs directly comparing JetStream atherectomy against other commonly used treatment modalities are currently lacking and limit our understanding of JetStream atherectomy's place in the management of FP-ISR.

3.8. Excimer laser atherectomy

Excimer laser atherectomy is currently the only atherectomy device approved for the treatment of FP-ISR [36]. Unlike PTA, which modifies obstructions through a disruptive stretching process, laser atherectomy vaporizes the plaque, neointimal tissue, thrombotic material, and calcium deposits comprising stenotic lesions. Because laser energy is emitted at the distal tip of the catheter, forward photoablation and atherectomy are possible, allowing the catheter to recanalize vascular blockages that are otherwise uncrossable or refractory to balloon dilation [46]. Excimer laser atherectomy may offer advantages specific to the treatment of FP-ISR, including significant debulking of neointimal tissue while simultaneously suppressing platelet aggregation and reducing or delaying the need for repeat revascularization [4,42].

Shammas et al. [47] reported freedom from TLR to be 49% at 12 months following treatment with laser atherectomy plus PTA in a patient population with complex FP-ISR (mean lesion length 210 mm; 48% class III); unfortunately, bailout stenting was required in 50% of cases. The Photo-Ablation using the TURBO-Booster® and Excimer Laser for In-Stent Restenosis Treatment (PATENT) trial [46] evaluated the use of laser atherectomy plus PTA in the treatment of less severe FP-ISR lesions (mean lesion length 123 mm; 34.1% class III) and reported a 12-month primary patency of only 37.8% but greater freedom from TLR than was seen by Shammas et al. (64.4% vs. 49.0%).

The Excimer Laser Randomized Controlled Study for Treatment of Femoropopliteal In-Stent Restenosis (EXCITE ISR) trial [21] was the first trial to compare laser atherectomy plus PTA head-to-head against

PTA monotherapy and found improved freedom from TLR (73.5% vs. 51.8%) at 6 months. Of note, the lesions treated in the laser therapy group were significantly longer (mean lesion length of 169 mm vs. 81 mm) while the percentage of class III lesions was slightly lower (30.5% vs. 36.8%). Following EXCITE-ISR, Armstrong et al. [48] conducted a similar study in which patients were treated with laser plus PTA or PTA monotherapy, but followed the patients over a longer period of time (2 years). After 2 years, the group treated with laser plus PTA (mean lesion length 222 mm; 31.0% class III) had a disappointing primary patency of 31.0%, but good freedom from TLR of 86.0%. In the PTA monotherapy group, outcomes were much worse: primary patency was 0% and freedom from TLR was 56.0%, despite these lesions being significantly shorter and less complex (mean lesion length 114 mm; 20.0% class III). Overall, excimer laser atherectomy, with or without adjunctive PTA, is felt to be inferior to Viabahn stent-grafts and DCB, the two therapies that have produced the best results for the treatment of FP-ISR to date [49], at least as far as endovascular monotherapy is concerned.

3.9. Combination therapy: excimer laser atherectomy plus stent-graft implantation

One of the most recent advances in the endovascular management of FP-ISR is the use of combination therapy. While excimer laser atherectomy by itself (or with PTA) has not seen comparable results to stent-grafting and DCB, it is beginning to see increasingly frequent use as part of combination therapy alongside these two treatment modalities. Combination therapy with laser atherectomy plus the placement of a stent-graft may provide additional benefit by ablating the intimal hyperplastic tissue and allowing for better stent-graft expansion and exclusion of the remaining neointima within a PTFE-covered stent-graft [4,50]. The Prospective, Multicenter Trial to Evaluate the Safety and Performance of Spectranetics Laser with Adjunct PTA and GORE VIABAHN Endoprosthesis for the Treatment of SFA ISR (SALVAGE) trial [50] treated FP-ISR lesions (mean lesion length 207 mm) with laser atherectomy plus PTA followed by placement of a Viabahn stent-graft. Unfortunately, study enrollment was terminated and financial support was withdrawn due to concerns surrounding potential safety issues related to the interaction between excimer laser and the stent-grafts; only a small subset of the intended population was enrolled as a result, and while no adverse interactions between the laser and stent-grafts were noted, the decision was made not to restart the study. Regarding the data that was acquired, the 12-month primary patency rate was disappointing at only 48%, though there was an impressive 82.6% freedom from TLR. The poor primary patency was attributed to a high frequency of edge restenosis rather than typical in-stent narrowing, as noted previously in studies that used Viabahn stent-grafts [22].

The results of the SALVAGE trial and earlier trials emphasize the importance of stent sizing when using covered stent-grafts, as an oversized stent is more likely to develop edge restenosis [28,50]. While laser atherectomy did not change the incidence of restenosis relative to stent-graft monotherapy, the debulking of neointimal tissue with laser atherectomy prior to covered stent-graft placement may have served to increase the cross-sectional area of the stented lumen, thereby preventing stent-graft in-folding and reducing the risk of thrombosis within the stented region [4]. It remains to be seen whether the combination of laser atherectomy with a covered stent-graft offers additional longer-term clinical benefit beyond the first year. It should also be mentioned that the SALVAGE trial did not include the newer version of the Viabahn device, which has a proximal contoured edge to reduce the potential for proximal edge restenosis and improved outcomes may be seen if future studies choose to evaluate this newer stent-graft.

3.10. Combination therapy: excimer laser atherectomy plus drug-coated balloon angioplasty

Following the introduction of combination therapy with laser atherectomy plus the Viabahn stent-graft, other endovascular therapy combinations have been tested, including the combination of laser atherectomy plus DCB. It is hypothesized that the addition of DCB to debulking therapy may mitigate the need to achieve 100% intraluminal debulking prior to angioplasty, because the cytotoxic effect of paclitaxel leads to smooth muscle cell apoptosis and prevents residual plaque from reaccumulating, a phenomenon known as the "positive remodeling effect." This phenomenon is thought to work synergistically with debulking to optimize the revascularization of the restenotic lesion [22].

Gandini et al. [7] conducted a RCT comparing laser atherectomy plus DCB (FREEWAY balloon 0.035; Eurocor, Bonn, Germany; Opto Eurocor Healthcare, Bangalore, India) against DCB monotherapy in a group of patients who all had class III lesions (mean lesion length > 200 mm). Given the complexity of these lesions, 12-month primary patency was an impressive 66.7% following laser atherectomy plus DCB and only 37.5% for DCB monotherapy. 12-month freedom from TLR was greater in the laser plus DCB group (83.3% vs. 50.0%), and rates of major amputation were also significantly lower in the laser plus DCB group (8% vs. 46%). These results suggest that the addition of laser atherectomy to DCB may improve outcomes in the treatment of the most difficult cases of FP-ISR.

Van den Berg et al. [22] also reported very favorable 18-month outcomes with DCB (InPact Admiral and InPact Amphirion; Medtronic Invatec) in a small number of patients with FP-ISR (mean lesion length 133 mm; 78.6% class III); 18-month primary patency and freedom from TLR were both 91.7%. The most recent study on combination therapy with laser atherectomy plus DCB, conducted by Kokkinidis et al. [36], was also the only study to directly compare laser plus DCB [IN.PACT Admiral paclitaxel-eluting balloon (Medtronic Cardiovascular, Santa Rosa, CA, USA) or Lutonix (Bard Peripheral Vascular, Tempe, AZ, USA)] against laser plus PTA (Fig. 3). Kokkinidis et al. looked at patients with very long FP-ISR lesions (mean lesion length 256 mm; 74.2% class III) who were treated with laser atherectomy plus DCB and compared them to a similarly severe group of patients (mean lesion length 241 mm; 74.0% class III) who were treated with laser plus PTA. Combination laser plus DCB was associated with improved 12-month freedom from TLR (72.5% vs. 50.5%). While the rate of 12-month freedom from TLR reported in this study was lower than the 18-month freedom from TLR reported by Van den Berg et al. (72.5% vs.

91.7%), this may be due to the longer lesions treated in this study (mean length of 256 mm vs. 133 mm). The rate of freedom from TLR reported by both Van den Berg et al. (91.7%) [22] and Kokkinidis et al. (72.5%) [36] are comparable to that reported by Laird et al. following combination therapy with laser plus Viabahn (82.6%). The results of all three of these studies are superior to the results reported by the only other study conducted on laser plus PTA treatment for very long (>200 mm) FP-ISR lesions, which reported a 12-month freedom from TLR of only 49.0% [47]. These findings support a potential benefit of combination laser therapy plus additional modalities (e.g. Viabahn or DCB) over endovascular monotherapy for the treatment of FP-ISR, particularly for the treatment of very long lesions (>200 mm in length). Future studies assessing even longer follow-up (2 years and beyond) may be the next step to further support the use of combination laser atherectomy plus DCB for the treatment of FP-ISR.

3.11. Combination therapy: SilverHawk directional atherectomy plus drug-coated balloon angioplasty

Excimer laser atherectomy has been the best studied debulking therapy for use in combination with other treatment options, though less is known about the potential benefits of combination therapy utilizing other debulking devices, such as SilverHawk directional atherectomy. At this time, SilverHawk atherectomy has not produced satisfactory long-term patency and freedom from TLR when used by itself or in conjunction with PTA [37,40–42] The combination SilverHawk atherectomy with subsequent DCB may provide the benefits of both debulking and neointimal modification from atherectomy with the luminal expansion and anti-restenotic drug therapy of DCB. The combination of these interventions may lead to a synergistic effect whereby the improved debulking and clearance of thrombotic and hyperplastic material from within the stent helps pave the way for more effective local delivery of the anti-proliferative agent coating the balloon during angioplasty. Sixt et al. [37] randomized patients to treatment with either SilverHawk atherectomy plus DCB (brand and maker not specified) or SilverHawk atherectomy plus PTA. The mean lesion length was 153 mm in the SilverHawk plus DCB group and 180 mm in the SilverHawk plus PTA group. 12-month primary patency was 84.7% for SilverHawk plus DCB and 43.8% for SilverHawk plus PTA. The 12-month primary patency results seen with SilverHawk plus DCB in this study were substantially better than those seen with SilverHawk atherectomy with or without PTA reported in other studies (84.7% vs. 25–54%) and comparable to those seen for DCB monotherapy (84.7% vs. 70.3–92.1%). Unfortunately, this raises the same concern that was brought up in prior studies on SilverHawk atherectomy: the improved outcomes seen after combination therapy with Silverhawk atherectomy plus DCB may be driven more by the angioplasty itself rather than from a meaningful additive or synergistic effect from the combination of the two interventions. Nevertheless, the favorable outcomes reported by Sixt et al. are promising for this strategy of combination therapy, and future studies looking at long-term outcomes (i.e. beyond the first 12 months) following treatment with SilverHawk atherectomy plus DCB may provide additional insight into potential differences between combination therapy and DCB monotherapy, especially if the debulking capabilities of SilverHawk atherectomy can offset the late catch-up phenomenon and drastic reduction in primary patency seen at 3-year follow-up after DCB monotherapy.

4. Discussion

The endovascular treatment of the FP segment has been marred by alarmingly high rates of restenosis. Stenting has surpassed PTA as the preferred treatment for FP disease, and with this, there has been a significant increase in the number of cases of FP-ISR, and the advent of newer stents designed to reduce the risk of stent fractures and restenosis has been ineffective in reliably reducing the incidence of
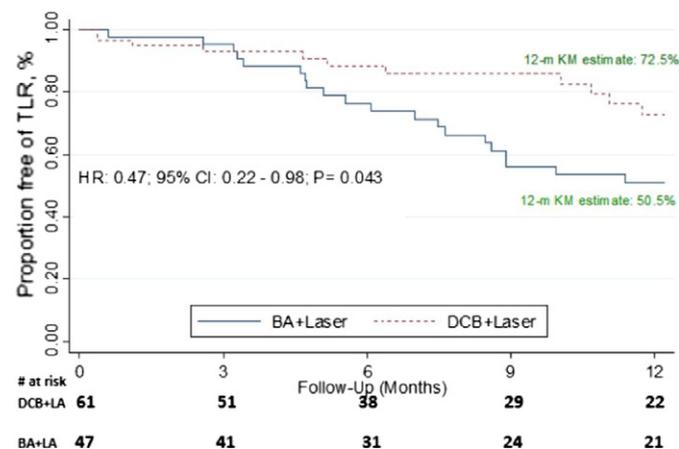

Fig. 3. One-year freedom from target lesion revascularization. Abbreviations: BA, balloon angioplasty; CI, confidence interval; DCB, drug-coated balloon; HR, hazard ratio; KM, Kaplan-Meier; LA, laser. Reproduced, with permission, from Kokkinidis et al. [36].
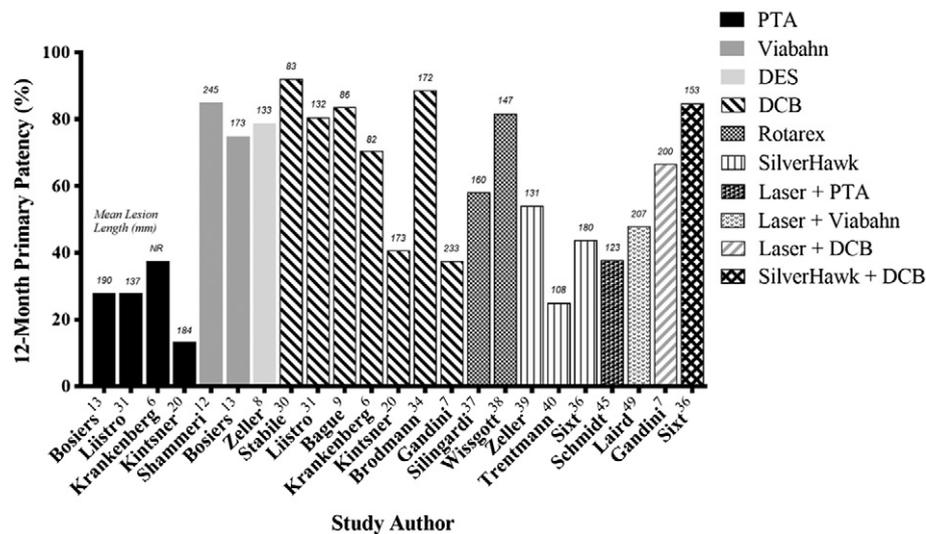
Fig. 4. 12-Month primary patency.

this complication. The increasing prevalence of FP-ISR has become quite problematic, as many of the tried-and-true treatment modalities for revascularization of de novo lesions have not been nearly as successful in the treatment of FP-ISR (Fig. 4, Table 1). PTA alone has yielded terrible outcomes, with <50% primary patency as early as 6 months following revascularization and alternative angioplasty techniques (cutting balloon angioplasty and cryoplasty) have shown to be similarly ineffective [19,24]. By themselves, debulking devices (SilverHawk, Jetstream, and laser atherectomy) have achieved better short-term success, but have largely demonstrated less satisfactory outcomes by midterm follow-up, with rates of primary patency and freedom from TLR around 40–60% at 1 year in most studies (Fig. 5, Table 1) [39–43,45,46].

The most recent studies on the treatment of FP-ISR, which have focused largely on more intricate stent platforms and combination therapies, have produced more favorable outcomes and have provided valuable insight into the future direction of the management of FP-ISR. The Viabahn stent-graft has produced excellent outcomes, with midterm and long-term primary patency and freedom from TLR generally >60%, even after treatment of longer and more complicated lesions [12,13,27]; the major drawback of stent-grafts lies in the high rates of edge restenosis. DES therapy has been shown to be more effective than repeat nitinol stenting, but is currently hindered by the short available stent lengths, which may preclude their use in long FP-ISR lesions [8]. DCB has also shown superior outcomes relative to conventional PTA and debulking strategies and is the most extensively studied treatment option for FP-ISR [6,9,10,20,31,32,35]; however, the initial benefits of this therapy may diminish over time and may also be less effective for the treatment of long-segment FP-ISR [20,32]. Finally, the recent implementation of combination therapies, particularly those combining laser atherectomy with DCB, has shown the greatest promise in treating the longest FP-ISR lesions and may become the treatment of choice for handling these most challenging cases in the years to come [7,22,36,37,50].

Future directions for the management of FP-ISR may be guided by studies that aim to fill in key gaps in our understanding of these new treatment options. For example, future studies may opt to evaluate the use of higher doses of drug-eluting therapies, as is being studied in the ongoing COPACABANA trial [34], to teach us whether this approach can overcome the late catch-up phenomenon previously reported with lower doses of drug-eluting therapy [20,32]. While combination therapy has produced some of the best short and midterm outcomes, long-term outcomes (beyond 12 months) are lacking for each of the combination therapies discussed in this review. Also, there is still much to be learned regarding which combination therapies are most effective. No RCTs have been conducted that have directly compared various combination therapies head-to-head, and there are many potential combination therapies, such as laser atherectomy plus DES, which have yet to be studied at all. While effective treatment of FP-ISR has already reaped significant benefits from prior investigations into the endovascular management of this condition, there remains much to be learned about how to best treat restenosis after stent implantation in the FP segment.

5. Limitations

This review is limited by several factors which varied across studies. First, there was considerable variability in the sample size of each study (Table 1), ranging from as few as 14 to as many as 169 lesions treated per study. Lesion complexity also varied considerably across studies, making it difficult to make direct comparisons between studies with markedly different lesion characteristics. To account for this, we reported the mean lesion lengths and percentage of patients with Tosaka class III lesions for each study, where this information was available (Table 1). Similarly, the risk of selection bias exists for RCTs and other studies that compared two different treatments against each other, as having more severe lesions in one group could make the treatment used in the other group appear superior; fortunately, most of those studies reported similar lesion characteristics between groups (Table 1), which should minimize the risk that the difference in outcomes for each treatment were the result of uneven distribution of complex lesions between groups. Also, the location of the lesion along the FP segment has significant prognostic implications, as stents within the popliteal or infrapopliteal segments may be more predisposed towards FP-ISR due to shear stress and compressive trauma from repetitive knee flexion and extension. DEBATE-ISR, EXCITE-ISR, and FAIR all included infrapopliteal interventions, either in addition to above the knee interventions or as the primary lesion. Fortunately, each of these studies were RCTs, and the percentage of infrapopliteal interventions was similar between treatment groups, so the inclusion of infrapopliteal interventions should not have confounded results within these studies. However, knowing the percentage of infrapopliteal disease in these studies, but not in other studies, makes it harder to directly compare outcomes across different studies. The Zilver-PTX single-arm study was the only study that was not an RCT that distinguished between above- and below-the-knee interventions; in this study, the percentage of patients with below-the-knee disease was low at only 9%. The remaining studies in this review did not specify the locations of the restenotic lesions within the FP segment, and it is

Table 1
Comparison of trials for the endovascular treatment of femoropopliteal in-stent restenosis.

First author Trial name	Intervention	Duration (months)	Number of lesions treated	Mean lesion length (mm)	Tosaka class III lesions (%)	Primary patency at end of study (%)	Freedom from TLR at end of study (%)
Viabahn stent-graft							
Ansel [26]	Viabahn	18	39	271	NR	52.0	NR
Shammeri [12]	Viabahn	12	27	245	52.0	85.1	NR
	Viabahn	36	27	245	52.0	81.4	NR
Gorgani [2]	Viabahn + PTA	40	27	215	NR	63.0	NR
Bosiers [13]	Viabahn	12	39	173	23.1	74.8	79.9
RELINE	PTA	12	44	190	25.0	28.0	42.2
Drug-eluting stent							
Zeller [8]	DES	12	119	133	31.0	78.8	81.0
Zilver PTX	DES	24	119	133	31.0	NR	60.8
Murata [30]	DES	12	62	170	0	59.5	NR
	DES	12	57	250	100	55.9	NR
	PTA	12	89	90	0	54.3	NR
	PTA	12	44	200	100	9.7	NR
Drug-coated balloon angioplasty							
Stabile [31] and	IN.PACT	12	39	83	20.5	92.1	89.5
Virga [10]	IN.PACT	24	39	83	20.5	70.3	78.4
Liistro [32] and	IN.PACT	12	44	132	51.0	80.5	86.4
Grotti [33]	PTA	12	42	137	65.0	28.2	69.0
DEBATE ISR	IN.PACT	36	44	132	51.0	NR	60.0
	PTA	36	42	137	65	NR	57.0
Bague [9]	IN.PACT	12	55	86	2	83.7	90.2
PLAISIR	IN.PACT	18	55	86	2	78.1	90.2
Krankenberg [6]	IN.PACT	12	62	82	28.6	70.5	90.8
FAIR	PTA	12	57	NR	NR	37.5	52.8
Kintsner [20]	FREEWAY	12	35	173	30.0	40.7	51.0
PACUBA	PTA	12	39	184	30.0	13.4	22.1
Brodmann [35]	IN.PACT	12	149	172	34.0	88.7	92.9
Rotarex mechanical thrombectomy							
Silingardi [38]	Rotarex	12	32	160	NR	58.1	46.9
Wissgott [39]	Rotarex	12	78	147	NR	81.6	NR
SilverHawk directional and excisional atherectomy							
Zeller [40]	SilverHawk	12	43	131	8.50	54.0	53.0
	SilverHawk	18	43	131	8.50	49.0	51.0
Trentmann [41]	SilverHawk + PTA (in 46% of cases)	12	35	108	NR	25.0	NR
Shammas [42]	SilverHawk + PTA (in 97% of cases)	12	41	126	NR	NR	68.3
	Laser	12	40	210	NR	NR	51.3
JetStream rotational and aspiration atherectomy							
Beschorner [45]	Pathway PV + PTA (in 57% of cases)	12	40	86	20.0	33.0	NR
	Pathway PV + PTA (in 57% of cases)	24	40	86	20.0	25.0	NR
Shammas [44]	JetStream + PTA	1	15	167	NR	100	100
Shammas [43]	Jetstream + PTA	6	29	195	25.0	72	86
JETSTREAM-ISR	Jetstream + PTA	12	29	195	25.0	NR	59
Excimer laser atherectomy							
Yeo [5]	Laser + PTA	12	22	NR	NR	NR	77.0
Shammas [47]	Laser + PTA	12	40	210	48	NR	49.0
Schmidt [46]	Laser + PTA	12	90	123	34.1	37.8	64.4
PATENT							
Dippel [21]	Laser + PTA	6	169	196	30.5	NR	73.5
EXCITE-ISR	PTA	6	81	193	36.8	NR	51.8
Armstrong [48]	Laser + PTA	24	54	222	69	31	86
	PTA	24	81	114	20	0	56
Combination therapy							
Laird [50]	Laser + Viabahn	12	27	207	NR	48	82.6
SALVAGE							
Gandini [7]	Laser + DCB (FREEWAY)	12	24	200	100	66.7	83.3
	DCB (FREEWAY)	12	24	233	100	37.5	50.0
Van den Berg [22]	Laser + DCB (IN.PACT)	19	14	133	78.6	91.7	91.7
Kokkinidis [36]	Laser + DCB (IN.PACT or Lutonix)	12	62	256	74.2	NR	72.5
	Laser + PTA	12	50	241	74.0	NR	50.5
Sixt [37]	SilverHawk + DCB	12	29	153	NR	84.7	NR
	SilverHawk + PTA	12	60	180	NR	43.8	NR

Abbreviations: DCB, drug-coated balloon; DES, drug-eluting stent; NR, not reported; PTA, percutaneous transluminal angioplasty; TLR, target lesion revascularization.

Fig. 5. 12-Month freedom from TLR. Abbreviations: DCB, drug-coated balloon; DES, drug-eluting stent; NR, not reported; PTA, percutaneous transluminal angioplasty; TLR, target lesion revascularization. *Studies that do not report 12-month outcomes are excluded.
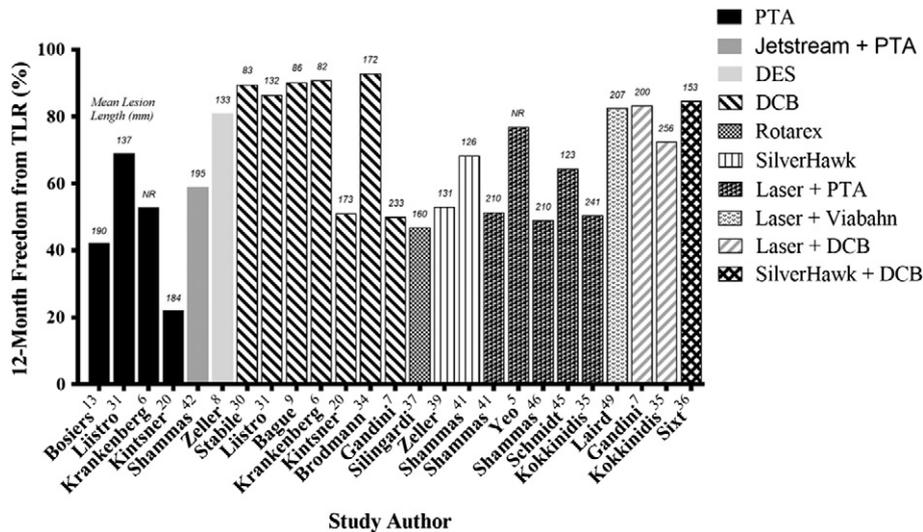
unclear how many, if any, of the cases in these studies involved infrapopliteal FP-ISR.

For cases of recurrent restenosis following treatment of FP-ISR, the included studies did not specify whether these were simply cases of restenosis or complete in-stent re-occlusion, which may have additional implications in terms of what secondary interventions would need to be performed (e.g. higher rates of limb amputation for cases of in-stent re-occlusion). However, one study on laser atherectomy vs. PTA did distinguish cases of in-stent occlusion after treatment of the initial FP-ISR; they found that while rates of TLR were similar for patients treated with laser atherectomy or PTA (44% vs. 48%), the rate of in-stent re-occlusion was lower for the group treated with laser atherectomy (33% vs. 71%) [48], thereby suggesting a potential benefit for laser atherectomy over PTA that would not have been identified had the study not made this distinction between recurrent restenosis and occlusion. Unfortunately, the failure to report on this distinguishing feature in other studies may have prevented those studies from identifying similar potential benefits for laser atherectomy, or other specific therapies, following the initial treatment of FP-ISR.

Operator proficiency with each device may also vary both within and across each study, potentially introducing bias as the result of differing skill levels between operating physicians. Similarly, while most of the studies were able to discretely study the treatment of FP-ISR with just a single device or with a combination of two specifically chosen devices (combination therapy), several studies utilizing debulking devices also involved the use of adjunctive PTA in anywhere between 50 and 100% of lesions treated. Adjunctive PTA was used either at the discretion of the operating provider or when the debulking device was unable to adequately treat the restenotic segment by itself; the indication was not always explicitly stated in the studies that utilized adjunctive PTA. The intermittent use of adjunctive PTA makes it harder to compare the efficacy of these debulking devices across studies, as those studies which used adjunctive PTA may have had an advantage when it comes to procedural success and long-term patency and freedom from TLR. Fortunately, most studies were explicit in stating when, and how often (listed as percentages in parentheses in Table 1), adjunctive PTA was utilized, and several studies which used adjunctive PTA also included a PTA monotherapy comparison group. Funding bias may have affected the results reported by some of the studies, as several of them were funded by manufacturers of specific devices.

Another limitation of this review is that the studies included consist of a mixture of prospective clinical experiences, retrospective analyses, and RCTs, some of which were conducted at a single center while others were part of multicenter registries. This may further limit the ability to make comparisons across studies, though conducting a systematic review of just a single study design would not be feasible given the overall paucity of studies on the endovascular management of FP-ISR.

6. Conclusion

The implementation of intricate stent-grafts and coated stents and balloons has resulted in more successful outcomes following treatment of FP-ISR, though there remains room for improvement, especially when it comes to long-term outcomes and the management of particularly long lesions. The use of combination therapy has already shown promising results in the management of long and complex lesions and may eventually prove to be the most successful treatment strategy for this challenging disease. Further research is necessary to investigate the long-term outcomes of combination therapy as well as the potential role for high-dose drug-eluting therapies and a variety of as-of-yet untested combination therapies.

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