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Combined Treatment of Native Femoropopliteal Occlusions in Chronic Limb-Threatening Ischemia Using Atherectomy Debulking and a New Sirolimus Drug-Coated Balloon (SELUTION SLR)

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Abstract

Objective The aim of this study was to report the primary outcomes of a pilot study investigating the safety and efficacy of sirolimus drug-coated balloons (SELUTION) for endovascular postatherectomy treatment of native occluded femoropopliteal lesions in patients with chronic limb-threatening ischemia (CLTI).

Materials and Methods This study analyzes a cohort of CLTI patients with femoropopliteal artery occlusions treated with combined rotational atherectomy and postatherectomy angioplasty using the SELUTION device. The primary outcome measures were amputation-free survival (AFS) defined as time to major limb (above ankle) amputation of the index leg or death from any cause. Secondary outcome measures included technical success, overall survival, major amputation of the index leg, major adverse limb event (MALE) defined as major amputation or any further major revascularization intervention of the treated segment during the follow-up period and primary patency at 12 months.

Results Between April 2021 and January 2022, nine patients (mean age: 64.0 ± 8.4, 66.7% male) with femoropopliteal occlusive lesions (mean lesion length: 141.1mm, range: 40–400) were treated with the above-combined approach. Technical success was 100%. At 12 months, the AFS was 88.9%, with one death and zero major amputations (88.9% survival and 100% limb salvage, respectively); only two patients (22.2%) suffered a MALE; primary patency was 75%. No adverse events related to the sirolimus drug-coated balloon nor to the atherectomy device were observed.

Keywords
- chronic limb-threatening ischemia
- peripheral arterial disease
- endovascular

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Conclusion Combining sirolimus drug-coated balloon and atherectomy for treatment of femoropopliteal occlusions in CLTI patients is a safe and effective approach achieving satisfactory patency and adverse event rates.

Introduction

Lower limb peripheral arterial disease (PAD) is a leading cause of cardiovascular morbidity.[1] Chronic limb-threatening ischemia (CLTI) occurs in the context of PAD, where the blood supply to the extremity is unable to match the tissue resting metabolic needs resulting in the more severe presentation with patients suffering from ischemic rest pain and/or tissue loss for a period greater than 2 weeks.[2] Clinically this grade of disease is staged as Rutherford categories 4 to 6.[3] Endovascular treatment is well-established in the management of CLTI[4–6] with endovascular-first approaches featuring positively in the BASIL-2 trial and presenting as lower risk alternatives to bypass surgery-first approaches, particularly in comorbid patients.[5,7]

Restenosis is a frequent concern with any revascularization procedure.[8] For example, neointimal hyperplasia can result in restenosis following plain balloon angioplasty.[9] The adjunctive use of drug-coated balloons (DCBs)—devices coated with antiproliferative agents which reduce neointimal hyperplasia and subsequent vessel restenosis[10,11]—is increasing as part of revascularization strategies to avoid this barotrauma-related phenomenon and decrease the associated late lumen loss.[12,13] Until recently, all commercially available DCBs for the treatment of PAD used the cytotoxic drug paclitaxel as the antiproliferative agent.[14] However, in 2020, the 6 month primary end-point results were published from the first-in-human clinical trial of a new DCB, called the SELUTION SLR (M.A. MedAlliance SA, Nyon, Switzerland), used to treat femoropopliteal lesions in PAD patients.[15] The antiproliferative coating for the SELUTION SLR is the cytostatic drug sirolimus (rapamycin), which had not previously been used on balloons for the treatment of peripheral vasculature lesions.[14] The 6 months results were promising, and the SELUTION SLR has since become commercially available for endovascular treatment of PAD.

Occlusive lesions are more difficult to treat, and are less likely to remain patent, than stenotic lesions.[8] The length of the lesion also has a bearing on patency postintervention. A study found that patients with a chronic total occlusion longer than 10 cm had a lower primary patency rate.[16] Calcification also poses an independent issue with regard to restenosis[17]; it limits the delivery and absorption of the antiproliferative agent in DCB angioplasty.[18,19] Directional atherectomy has been shown to be a useful vessel preparation technique while also reducing the risk of dissection and bailout stenting associated with angioplasty of particularly heavily calcified vessels.[20,21] In addition, performing atherectomy prior to the use of a DCB has been shown to improve patency.[16,22,23] The use of the rotational atherectomy devices Jetstream (Boston Scientific, Marlborough, Massachusetts, United States) and Phoenix (Philips Healthcare, Cambridge, Massachusetts, United States) rather than directional atherectomy is also reported to result in low rates of distal embolization.[24,25]

This single-center retrospective study reports the results on the safety and efficacy of a sirolimus drug-coated balloon (SELUTION SLR) for endovascular treatment, following rotational atherectomy, in native occluded femoropopliteal lesions in patients with CLTI.

Materials and Methods

Study Population and Design

This is a single-center, retrospective pilot study analyzing a cohort of CLTI patients with femoropopliteal artery occlusions who were treated with atherectomy and postatherectomy angioplasty using the SELUTION SLR device. As this was a retrospective analysis, ethical approval was not required, but as per standard of care, all patients included in the study gave their written informed consent for both the procedure and for use of their patient data (including any imaging) for research purposes. The study was fully compliant with the ethical principles outlined in the Declaration of Helsinki.

All patients who had undergone endovascular treatment of the native, occluded femoropopliteal region for CLTI (Rutherford categories 4-6) with rotational atherectomy followed by SELUTION SLR between April 1, 2021 and January 31, 2022 were identified from the radiology information system. Inclusion criteria were as follows: documented CLTI in the electronic patient record prior to procedure; target lesion in the femoropopliteal region; target lesion treated with atherectomy followed by at least one SELUTION SLR balloon (as documented in procedural notes); and target lesion must have been fully occluded pre-procedure (as documented by preprocedural ultrasound angiology investigations or initial procedural angiogram). Exclusion criteria included patients treated for an in-stent restenosis/occlusion; hypercoagulation disorders; and cases where administration of anticoagulant or antiplatelet medications is contraindicated.

Data Collection

The hospital Electronic Patient Records, e-Noting, and Picture Archiving and Communication System (PACS) programs were reviewed to obtain baseline clinical information and procedural details for all patients that met the inclusion criteria. The same electronic platforms were then used to search the postprocedure period for each patient to record outcome events. Follow-up imaging performed in external hospitals was requested and imported to the local PACS.

Outcome Measures

Where appropriate, primary and secondary outcome measures were recorded at 6 and 12 months. The primary outcome

measure was amputation-free survival (AFS) with amputation defined as major (above the ankle) amputation of the index limb or death from any cause. Secondary outcome measures were as follows: technical success defined as flow restoration of the target lesion with residual stenosis less than 30%; 30-day mortality; overall survival; 30-day morbidity (including access site complications, target vessel reocclusion, major adverse cardiovascular event, any amputation of index limb); minor amputation (below the ankle) of the index limb; major amputation (above the ankle) of the index limb; major adverse limb event defined as major amputation of the index limb or any further major reintervention of the treated segment (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis); major adverse cardiovascular event defined as myocardial infarction, transient ischemic attack, stroke or death from any cause; limb salvage defined as the preservation of the index limb with no major amputation; primary patency defined as uninterrupted vessel patency on imaging with no re-intervention; primary-assisted patency defined as patency from the time of reintervention due to restenosis (without reocclusion) of the target lesion; secondary patency defined as patency from the time of reintervention due to reocclusion of the target lesion; and binary vessel restenosis defined as reduction in at least 50% of the vessel diameter.

Interventional Procedure

All procedures were performed in either an angiography laboratory or a hybrid operating theatre.

The SELUTION SLR DCB is an over-the-wire 0.018-inch guidewire percutaneous angioplasty balloon catheter with a coating of sirolimus at a dose density of 1µg/mm.[2,14,26] The sirolimus is mixed with a biodegradable polymer and a phospholipid blend to form the coating that aims to achieve a sustained release of sirolimus as well as optimize drug transfer to the vessel wall.[14,26] In this study, SELUTION SLR DCBs of 3 to 6 mm diameter were used.

Two atherectomy devices were available to the operators, Jetstream (Boston Scientific, Marlborough, Massachusetts, United States) and Phoenix (Philips Healthcare, Cambridge, Massachusetts, United States). Both devices feature a rotational atherectomy system with an aspiration mechanism to remove any debris created. The Jetstream atherectomy system is a rotational device that actively aspirates debris to avoid distal embolization; it also gives the operator control as to when the blades are engaged to allow for atraumatic manipulation within the vessel.[27] The Phoenix atherectomy system is also a rotational advice and employs the principle of the Archimedes screw to prevent distal embolization of debris.[28] Both devices are used over a wire.

Statistical Analysis

Continuous variables are summarized as mean ± standard deviation, with categorical variables summarized using frequency counts and percentages. Kaplan-Meier (K-M) analyses were used to estimate outcome measures at 6 and 12 months, and expressed as % ± Standard error of the mean. All statistical analysis was performed using GraphPad Prism (version 9.4.0 for Windows, GraphPad Software, San Diego, California, United States).

Results

Nine of the CLTI patients (see ►**Fig. 1**) treated in the department between April 1, 2021 and January 31, 2022 were found to meet the inclusion criteria (mean age: 64.0 ± 8.4 years, 66.7% male). As shown in ►**Table 1**, a number of comorbidities were present in the cohort including diabetes mellitus, hypertension, chronic heart failure, previous myocardial infarction, and previous stroke. A third of the patients were Rutherford category 4 at baseline and the remaining were Rutherford category 5 or 6. As per the inclusion criteria, all nine patients were treated for a native occluded vessel in the femoropopliteal region using SELUTION SLR balloons postatherectomy.

Baseline lesion characteristics and a comparison of baseline versus postprocedural infrapopliteal runoff are shown in ►**Table 2**.

One death occurred during the postprocedure period on day 178; however, no patients underwent a major index limb amputation. Our primary outcome measure, AFS, has a K-M estimate of 88.9 ± 10.5% at both 6 and 12 months. Technical success rate was 100% and there were no intraprocedural complications. Thirty-day mortality was 0%. K-M estimates for overall survival at 6 and 12 months were both 88.9 ± 10.5%. Two patients (22.2%) underwent minor amputations on day 6 and 11 postprocedure, respectively. No other adverse clinical events occurred in any patients during the first 30-day postprocedure; therefore, 30-day morbidity was 22.2%. No further minor amputations occurred during the study period. Major AFS was 100% at 12 months. Two patients (22.2%) underwent further major revascularization interventions of the treated segments (on day 163 and 365 postprocedure, respectively). The only cardiovascular event was the one death within the cohort. As no patients underwent a major index limb amputation, limb salvage was 100%.

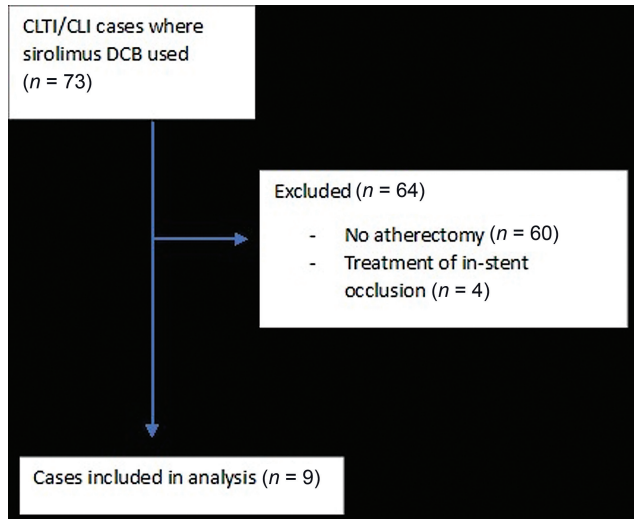

Fig. 1 Flowchart of cohort selection. CLTI, chronic limb-threatening ischemia; DCB, drug-coated balloon.

Table 1 Patient demographics and baseline clinical data

Variable	
Number of patients	9
Age (mean ± SD)	64.0 ± 8.4
Male gender	6/9 (66.7%)
Diabetes mellitus	7/9 (77.8%)
Hypertension	6/9 (66.7%)
Chronic heart failure	2/9 (22.2%)
Previous MI	1/9 (11.1%)
Previous stroke	1/9 (11.1%)
CKD > Stage 3	0/9 (0.0%)
COPD	1/9 (11.1%)
Current malignancy	1/9 (11.1%)
Peptic ulcer	0/9 (0.0%)
Dementia	0/9 (0.0%)
Hemiplegia	0/9 (0.0%)
Baseline CRP (mean ± SD)	50.7 ± 41.9
Baseline systolic BP (mean ± SD)	135.7 ± 21.4
Baseline eGFR (mean ± SD)	72.0 ± 23.9
Baseline CLTI stage/category	
- Ischemic rest pain (Rutherford 4)	3/9 (33.3%)
- Tissue loss (Rutherford 5/6)	6/9 (66.7%)

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CLTI, chronic limb-threatening ischemia; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; SD, standard deviation.

K-M estimates for all outcome measures are shown in ►**Table 3**, with survival curves for selected outcome measures shown in ►**Fig. 2**.

Two patients (22.2%) were found to have reocclusions of the treated vessel during the postprocedure period on day 155 and 246, respectively. As described above, both patients underwent revascularization procedures after the reocclusions were identified; both vessels were patent at latest follow-up (day 356 and 50 post redo angioplasty, respectively) giving secondary patency rates of 100% at 6 and 12 months. No cases qualified for primary-assisted patency. Six target vessels (66.7%) were found to have restenosed during the postprocedure period.

Discussion

The data from this retrospective observational study show no periprocedural and early period safety concerns relating to the combination use of rotational atherectomy and postatherectomy sirolimus-DCB angioplasty; there were no immediate procedural complications and no major adverse clinical events attributable to the therapy within 30 days of procedure. In addition, the 6 and 12 months clinical outcome and efficacy results are promising and within acceptable rates.

More specifically, in 2009, the SVS-CLI Working Group published a set of "objective performance goals" (OPGs) that were benchmark values for various clinical end-points against which novel endovascular therapies could be measured.[29] These OPG values for 1-year postprocedure were AFS 71%; survival 80%; and limb salvage 84%. When compared with these values, the K-M estimates from our cohort (at 1-year: AFS 88.9%; overall survival 88.9%; limb salvage 100%) present favorably.

The cause of death for the single diseased patient was sepsis secondary to infected leg ulcers caused by peripheral vascular disease. The patient had, with capacity, declined an above-knee amputation for the infection and had been referred to palliative care. The patient was a 76-year-old comorbid female and was the oldest in the cohort. She presented at baseline with tissue loss of the index limb, had the highest baseline C-reactive protein (103), the lowest baseline estimated glomerular filtration rate (37), and

Table 2 Baseline lesion characteristics and arterial runoff

Leg treated			
- Left	5/9 (55.6%)		
- Right	4/9 (44.4%)		
Lesion length (mm) (mean ± SD)	141.1 ± 145.6		
Site of lesion			
- SFA	5/9 (55.6%)		
- Popliteal	3/9 (33.3%)		
- Both	1/9 (11.1%)		
Baseline runoff		Postprocedural runoff	
No arteries	4/9 (44.4%)	No arteries	0/9 (0.0%)
One-vessel runoff	3/9 (33.3%)	One-vessel runoff	5/9 (55.6%)
Two-vessel runoff	1/9 (11.1%)	Two-vessel runoff	2/9 (22.2%)
Three-vessel runoff	1/9 (11.1%)	Three-vessel runoff	2/9 (22.2%)

Abbreviations: SD, standard deviation; SFA, superficial femoral artery.

Table 3 Kaplan-Meier estimates for outcome measures

	6 months (% ± SEM)	12 months (% ± SEM)
AFS	88.9 ± 10.5	88.9 ± 10.5
Overall survival	88.9 ± 10.5	88.9 ± 10.5
Major AFS	100.0	100.0
Minor AFS	77.8 ± 13.9	77.8 ± 13.9
MALE free survival	88.9 ± 10.5	74.1 ± 16.1
MACE free survival	88.9 ± 10.5	88.9 ± 10.5
Primary patency	87.5 ± 11.7	75.0 ± 15.3
Secondary patency	100.0	100.0
Freedom from binary restenosis	76.2 ± 14.8	50.8 ± 17.7

Abbreviations: AFS, amputation-free survival; MACE, major adverse cardiovascular event; MALE, major adverse limb event; SEM, standard error of the mean.

demonstrated no arterial runoff at baseline. She went on to have first, second, and third toe amputation of the index limb on day 6 postprocedure. However, on latest imaging (day 31 postprocedure), the target vessel was still patent with no binary restenosis, and so, our conclusion is that this death was very unlikely to have been attributable to our index therapy.

With regard to the other minor amputation, this patient was a 54-year-old diabetic male who had also presented with tissue loss of the index limb. He had a very long lesion (380mm) extending from the mid-superficial femoral artery into the popliteal artery with no arterial runoff at baseline. He underwent a transmetatarsal amputation of the index limb on day 11 postprocedure; however, on the latest follow-up imaging (day 508 postprocedure), the target vessel still showed primary patency (albeit showing binary restenosis at this time). Both minor amputations occurred shortly after the index procedures, and it is deemed that these were likely inevitable despite the endovascular interventions.

In terms of patency data, Zeller et al[15] in their first-in-human trial of the SELUTION SLR for the treatment of femoropopliteal lesions presented a primary patency rate of 88.4% at 6 months that compares well with our 6-month K-M estimate of 87.5 ± 11.7%. Zeller et al[15] also presented a 6-month freedom from binary restenosis rate of 91.2% for which our K-M estimate (76.2 ± 14.8%) compares less favorably. However, the cohort in the study by Zeller et al were Rutherford categories 2 to 4, with lower comorbidity rates than our cohort, only 30% had total occlusions, lesion lengths were all less than or equal to 150mm, and all patients had to have at least one patent infrapopliteal artery at baseline. In addition, they were not investigating the combination therapy of atherectomy and postatherectomy angioplasty; theirs was an investigation solely of SELUTION SLR angioplasty.

In their 2021 PRESTIGE study, Tang et al[26] published 6-month outcomes from their investigation of using the SELUTION SLR balloon for the treatment of tibial occlusive lesions in patients with CLTI. Despite this study differing from ours in terms of the vessels of interest and the treatment protocol

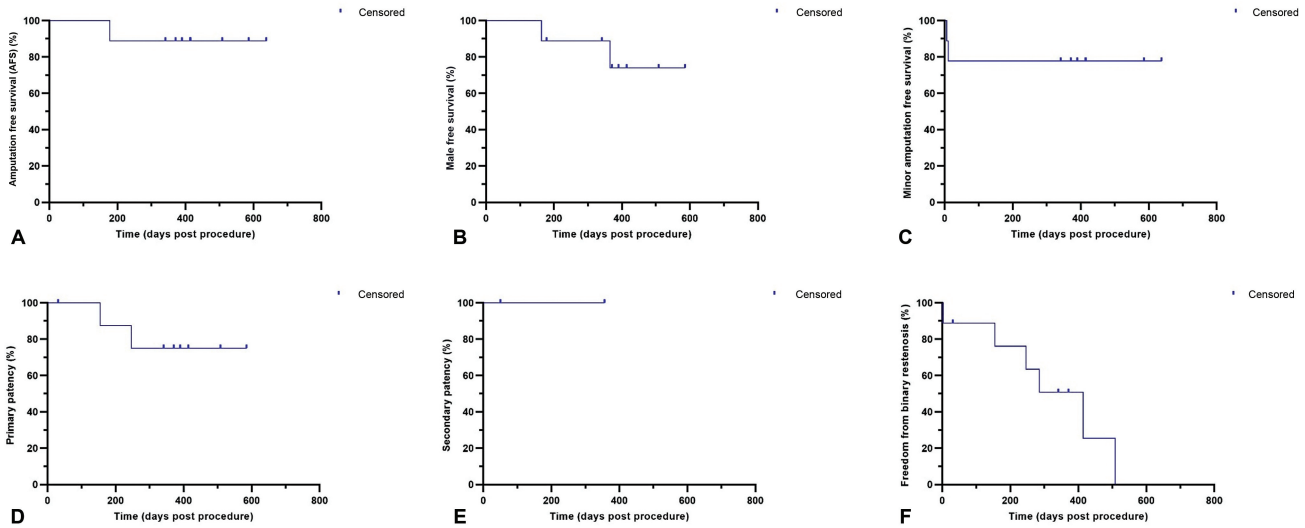

Fig. 2 Kaplan-Meier curves for (**A**) amputation-free survival (AFS; %), (**B**) major adverse limb event (MALE)-free survival (%), (**C**) minor AFS (%), (**D**) primary patency, (**E**) secondary patency (%), and (**F**) freedom from binary restenosis.

(the use of sirolimus balloon angioplasty without atherectomy), the cohort characteristics were very similar, and so it is interesting to compare their data with this study. At 6 months, primary tibial patency was 81.5% and AFS was 84.0%, which again compares well with the K-M estimates we present above, 87.5 and 88.9%, respectively. In their report of the 12-month outcomes of the PRESTIGE study,[30] both primary tibial patency and AFS rates had held at 81.5 and 84.0%, respectively. Our K-M estimates at 12 months of 75% primary patency and 88.9% AFS are again interesting to compare.

Also in 2021, Feng et al[16] published their 6- and 12-month primary patency data from an investigation of directional atherectomy combined with paclitaxel-coated balloon angioplasty of femoropopliteal artery lesions in patients with PAD (Rutherford categories 2-6). Although their cohort's comorbidities were similar to ours, 28% of patients only had stenoses and the average length of the lesion was much shorter, at an average of 83 mm compared with 141 mm in this study. In addition, this was not an investigation of just CLTI patients; indeed 34.2% of patients did not have CLTI; therefore, comparing results with our own is not a comparison of two identical cohorts. Nevertheless, the work by Feng et al[16] does present the most similar treatment technique to our own. At 6 and 12 months, K-M estimates for primary patency were 93.3% (95% confidence interval [CI]: 82.7–97.2%) and 80.8% (95% CI: 67.3–79.7%), respectively. Again, this is interesting to compare with our own results at 6 and 12 months of $87.5 \pm 11.7\%$ and $75.0 \pm 15.3\%$, respectively. While less favorable, it is important to note that the lesions treated were considerably more severe, therefore, our results remain encouraging. A comparison of all values presented in this section is provided in ►**Table 4**.

Until the end of 2019, all commercially available DCBs for the treatment of PAD used the cytotoxic drug paclitaxel as their anti-re-stenotic agent.[14] An antimicrotubular, cytotoxic agent, paclitaxel was originally approved as an antineoplastic treatment for carcinomas in the 1960s.[31] It is thought that the antiproliferative effects of paclitaxel are a result of the drug's cytotoxic effects in the smooth muscle cells.[31] However, in 2018 a meta-analysis suggested that PAD patients treated with paclitaxel-coated devices (either stents or balloons) had higher all-cause mortality than patients treated with bare (noncoated) devices, at both 2 and 5 years.[32] It has been suggested that this possible increased risk of late mortality may be due to long-term, low-level exposure to the cytotoxic paclitaxel.[14,32] Although the conclusions of the meta-analysis were very controversial, with multiple more recent studies finding no increased mortality associated with paclitaxel-coated device use,[33–35] this has led to an inevitable loss of confidence in paclitaxel-devices among vascular physicians.[14]

Sirolimus, in contrast to paclitaxel, is a cytostatic agent and was first approved by the U.S. Food and Drug Administration in 1999 as Rapamune, used for the purpose of preventing organ transplant rejection.[14] It was later incorporated into drug-eluting stent (DES) technology due to its

Table 4 Comparison of outcome measures

	Primary patency (% ± SEM)		Freedom from binary restenosis (% ± SEM)		AFS (% ± SEM)		Vascular territory	CLTI patients only?	Total occlusions only?	Treatment
	6 months	12 months	6 months	12 months	6 months	12 months				
Sumner et al	87.5 ± 11.7	75.0 ± 15.3	76.2 ± 14.8	50.8 ± 17.7	88.9 ± 10.5	88.9 ± 10.5	Fem-Pop	Yes	Yes	Atherectomy + sirolimus DCB (SELUTION SLR)
Zeller et al[15]	88.4	–	91.2	–	–	–	Fem-Pop	No	No	Sirolimus DCB (SELUTION SLR)
Tang et al[30]	81.5	81.5	–	–	84.0	84.0	Tibial	Yes	Yes	Sirolimus DCB (SELUTION SLR)
Feng et al[16]	93.3 (95% CI 82.7–97.2)	80.8 (95% CI 67.3–79.7	–	–	–	–	Fem-Pop	No	No	Atherectomy + paclitaxel DCB

Abbreviations: AFS, amputation-free survival; CI, confidence interval; CLTI, chronic limb-threatening ischemia; DCB, drug-coated balloon; SEM, standard error of the mean.

antiproliferative vascular effects for use in the coronary vasculature[36] and later in the peripheral vasculature for treatment of PAD.[15] Thus, while a relatively new player in the setting of DCBs in peripheral vasculature, many DES studies have demonstrated its safety and efficacy and have now become a well-established antiproliferative drug-coating used for endovascular procedures in both the coronary and peripheral vessels.[14] While the efficacy of sirolimus over paclitaxel is still subject to investigation, with only limited pilot studies published on DCBs in the peripheral vasculature,[31] it has been suggested that it has a preferential therapeutic safety margin compared to paclitaxel and it has become the preferred drug coating for devices used in coronary artery intervention.[31,37] This could be setting a precedent for what is to occur in the peripheral vascular field. If sirolimus is to become the preferred drug-coating for DCBs used in peripheral vascular disease, investigation into its combined use with other techniques and devices is just as critical.

The combination of DCB and atherectomy especially in heavily calcified lesions is beneficial for several reasons. As discussed previously, the technical success rate of endovascular treatment of stenoses is greater than occlusions.[38] By "downgrading" the lesion from an occlusion to a stenosis by debulking the lesion with atherectomy, long-term patency rates may be increased. The use of a DCB following atherectomy also has the potential to reduce neointimal hyperplasia as a result of the traumatic effects of atherectomy on the intima and therefore reduce restenosis rates.[22] Lastly, by debulking the calcific portion of the plaque with atherectomy drug transfer from the DCB to the vessel wall is improved.[19]

Limitations

The small cohort size is an important limitation and extrapolation should be exercised with caution. Procedural protocol also varied between operators and the use of two different atherectomy devices, while similar, may further affect the outcomes.

Conclusion

This single-center retrospective pilot study has analyzed the outcomes of a cohort of CLTI patients with native femoropopliteal artery occlusions treated with rotational atherectomy and postatherectomy angioplasty using the SELUTION device. This study was designed as a pilot investigation to gain an initial insight into the safety and efficacy of the combination therapy in a particular disease setting. The combined use of sirolimus DCBs and atherectomy for the treatment of femoropopliteal occlusions is a safe and effective technique yielding satisfactory patency and adverse event rates. Overall, this calls for larger scale studies to compare the efficacy of this management algorithm against other treatment protocols.

Conflict of Interest

N.T. reported Consulting fees received from Philips and Payment or honoraria received from Boston Scientific, Cordis and Philips, Abbott. Received Support from Shockwave Medical for attending meetings and/or travel. A.S. reported Support for the present manuscript from Abbott Ltd., Shockwave Ltd. (as Research funding). A.D. reported Grants or contracts from Co applicant for an NHIR grant for the EVOCC trial for "Investigating the treatment of aortoiliac occlusive disease". Payment or honoraria from MILBrooks for "CORE PAD meeting". Support for attending meetings and/or travel from CIRSE 2022 for (CORDIS). Leadership or fiduciary role in CIRSE as "Member of the membership Committee". Other financial or non-financial interests with Chief investigator for SUCCESS trial in the UK.

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