Endovascular treatment of femoropopliteal arterial occlusive disease with drug-eluting balloon angioplasty: A prospective cohort of 100 consecutive interventions

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ABSTRACT

Introduction

Drug-eluting balloons (DEBs) have proven to possess antirestenotic features in the treatment of femoropopliteal arterial occlusive disease in multiple randomized controlled trials. However, is this high-quality evidence applicable to a real-life clinical practice?

Methods

This retrospective analysis of a prospectively maintained database included all consecutive patients with femoropopliteal arterial stenoses and occlusions treated with DEB angioplasty from April 2014 to March 2016. Patients were monitored for 12 months, with a treadmill test and duplex ultrasound imaging at 6 and 12 months. The primary end point of this study was primary patency at 12 months. Secondary end points were technical success, freedom from binary restenosis, freedom from clinically-driven target lesion revascularization (cd-TLR), major amputation, mortality, changes in the ankle-brachial index, and changes in Rutherford-Baker category.

Results

The analysis included 100 procedures. There were 37 lesions (37%) treated for critical limb ischemia, and 41% of the lesions were chronic total occlusions. The mean lesion length was 105.7 ± 94.3 mm. The primary patency was 72.6% at 12 months. The freedom from binary restenosis rate was 78.8% at 12 months, and freedom from cd-TLR was 91.7%. Periprocedural complications occurred in 5.0% of patients. Two major amputations were performed in the first year.

Conclusions

In a real-world vascular population in the Netherlands, DEB angioplasty was a feasible technique for endovascular treatment of femoropopliteal arterial stenoses and occlusions. Lesions >150 mm have a significantly higher chance of binary restenosis; however, this does not affect the freedom from cd-TLR rate.

INTRODUCTION

Percutaneous transluminal angioplasty (PTA) has become an established treatment for various indications of femoropopliteal arterial occlusive disease.[1–3] PTA has low morbidity and mortality rates compared to bypass surgery, though patency rates of uncoated balloon angioplasty are disappointing, especially in long and calcified lesions.[4,5] Randomized controlled trials demonstrated superior patency of bare-metal stents compared with plain balloon angioplasty in the femoropopliteal arteries, in quest of more durable results after angioplasty.[6,7] However intra-arterial stenting is also associated with late complications such as stent thrombosis, in-stent restenosis or even stent fracture.[8–10]

Focal administration of anti-proliferative drugs limits neo-intimal hyperplasia after angioplasty.[11] Drug-eluting balloons (DEBs) have been designed to provide transfer of antiproliferative drug to the arterial without leaving an implant, omitting the late complications of stenting.

Recent systematic reviews with meta-analyses have demonstrated superior results of DEBs in the femoropopliteal arteries compared with uncoated balloon angioplasty.[12–14] Nevertheless, most of these trials are industry driven and include highly selected patient groups, the majority of which consists of patients with intermittent claudication and short lesions.

The aim of this study was to evaluate the treatment of femoropopliteal arterial occlusive disease with DEBs in a prospective all-comers registry from a vascular referral center in the Netherlands.

MATERIALS AND METHODS

Study design

This study was a prospective, single-center, all-comers registry to assess the safety and clinical performance of the Passeo-18 Lux DEB (Biotronik AG, Bulach, Switzerland) in patients with femoropopliteal arterial occlusive disease. Because this treatment strategy and follow-up was standard of care in our institution, the local ethics commission approved this registry and issued a waiver for patient informed consent.

Patients

All patients aged >18 years with symptoms suggestive of peripheral artery disease (PAD) were screened in the outpatient clinic. An ankle-brachial index (ABI) or treadmill test, as well as duplex ultrasound imaging, computed tomography angiography, or magnetic resonance angiography, were performed at the outpatient clinic to assess the severity and the location of the disease.

Patients with intermittent claudication were treated with supervised walking therapy and medical therapy. If symptoms persisted or deteriorated after 6 months of supervised walking therapy, patients were scheduled for angiography. Patients with CLI were immediately scheduled for angiography. If a significant stenosis (>50% reduction of lumen diameter assessed by angiography) or occlusion was noted on the angiogram, the patient was treated with DEB angioplasty and provisional stenting.

We included all patients with at least one de novo, restenotic, or in-stent stenotic lesion in the femoropopliteal arteries. Rutherford-Baker classifications 2 to 6 were included. There was no maximum length of the lesion. Exclusion criteria included thrombus within the target lesion, failure to cross the lesion with a guidewire, and, aspirin, clopidogrel, or heparin allergy.

Procedure

Patients were treated under local or general anesthesia. Access was obtained by a 4F to 6F sheath, preferably in the common femoral artery. Antegrade and crossover approaches were both allowed. Also allowed were all other additional approaches, including popliteal, tibial, or brachial access. All patients received 5000 IU of heparin. A diagnostic angiography was performed of the entire limb to determine the length and degree of the stenosis (stenosis of >50% were considered significant and met the inclusion criteria as well as occlusions) and outflow.

If there was any doubt whether a stenosis was significant, the intra-arterial translesional systolic blood pressure gradient was measured. A stenosis was considered hemodynamically significant when an intra-arterial translesional systolic blood pressure gradient of >10 mm Hg was measured. The presence of calcium was reported as moderate if eccentric calcium deposits were present and severe if concentric calcium deposits were present.

The lesion was predilated with an uncoated balloon that was 1-mm smaller in diameter than the reference diameter. To avoid geographic miss, treatment with the DEB started 10 mm proximal to the lesion and ended 10 mm distal to the lesion. The diameter of the DEB was at least the reference diameter or up to 1 mm oversized. The DEB used was the Passeo-18 Lux DEB (Biotronik AG, Bulach, Switzerland), which is coated with 3.0 µg/mm2 Paclitaxel and uses an excipient of butyryl-tri-hexyl citrate (BTHC).

Every DEB was inflated for at least 3 minutes. If the lesion length exceeded the length of the longest balloon, multiple DEBs were used to cover the entire lesion. If more than one DEB was used, the balloons overlapped at least 10 mm. Additional, prolonged inflation with an uncoated balloon was performed if a residual stenosis >30% or a flow-limiting dissection occurred. The duration of prolonged inflation was at least 5 minutes.

Provisional stenting was allowed if a stenosis >30% or a flow-limiting dissection persisted. Only the stenosis >30% or a flow-limiting dissection was treated with a stent (spot stenting). All commercially available self-expandable stents were allowed and were

oversized up to a diameter of 1 mm larger than the reference diameter. No drug-eluting stents or atherectomy devices were used in this series.

All patients were treated with aspirin (100 mg daily) and a statin daily at least 24 hours before the therapy, and both were continued lifelong. Clopidogrel (75 mg daily), starting before the therapy or after a procedural loading dose of 300 mg, was administered for 3 months. If patients were already being treated with a coumarin, clopidogrel (75 mg daily) was added for 3 months.

Follow-up

Patients were seen at the outpatient clinic 1, 6, and 12 months after the procedure for clinical evaluation. After 6 and 12 months, an ABI or treadmill test and duplex ultrasound imaging were performed. Patients without complications were discharged after 12 months. Only patients with symptomatic repeat stenoses or occlusions were scheduled for angiography and were treated accordingly.

Definitions and end points

Primary outcome of this study was primary patency after 1 year. Primary-patency was defined as freedom from binary restenosis or clinically driven target lesion revascularization (cd-TLR).

Secondary outcomes were technical success, defined as a procedure without complications or residual stenosis >30% by visual estimate after treatment with prolonged balloon expansion or provisional stent placement; freedom from binary restenosis, assessed by duplex ultrasound imaging performed by ultrasound technicians from an accredited vascular laboratory (peak systolic velocity ratio >2.5) or computed tomography angiography or magnetic resonance angiography (<50% reduction of lumen diameter); cd-TLR, defined as any repeat intervention of the target lesion for restenosis or other complications involving the target lesion; major amputation, defined as amputation above the ankle; all-cause mortality; change in the Rutherford-Baker class and change in ABI.

Statistical analysis

Data were collected and stored in an online electronic case report form (Castor edc, Ciwit BV, Amsterdam, The Netherlands). SPSS 24 software (IBM, Armonk, NY) was used for data analysis. Descriptive statistics, reported as frequency (%) for categoric variables and as mean ± standard deviation for continuous variables, were used to present baseline and follow-up variables. Primary and secondary endpoints were analyzed per patient or per treatment. Sensitivity analysis was performed in patients with intermittent claudication vs CLI, lesion length <150 mm vs >150 mm, and stenosis vs CTO. Kaplan-Meier survival analysis was used to estimate patency rates. Statistical significance was set at the two-tailed 0.05 level, and P values unadjusted for multiplicity are reported throughout. The one-sample t-test was used to compare means.

RESULTS

Patients

Between April 1, 2014, and March 10, 2016, 100 limbs in 98 patients were included in this study, and 100 femoropopliteal lesions were treated with DEB angioplasty. Baseline characteristics can be found in Table I. Treatment in 63% of patients was for intermittent claudication, and for CLI in 37%. Lesion characteristics are reported in Table II. Eighty-three percent were de-novo lesions. The mean lesion length was 105.7 ± 94.3 mm. Forty-one percent of the treated lesions were chronic total occlusions (CTOs). Half of the lesions were at least moderately (eccentric) calcified.

Table I. Demographic characteristics

Variable*	Result
	(N = 98)
Age, y	67.5 (43.8-94.8)
Male sex	52 (53.1)
Diabetes mellitus	37 (37.8)
Hypertension	62 (63.3)
Hyperlipedemia	45 (45.9)
Cardiac disease	25 (25.5)
Neurologic disease	18 (18.5)
Renal failure	13 (13.4)
Smoking	
Unknown	24 (24.5)
Current or former	61 (62.3)
No	13 (13.3)
Preoperative Rutherford	(N = 100)
0	0 (0)
1	7 (7.0)
2	28 (28.0)
3	28 (28.0)
4	13 (13.0)
5	24 (24.0)
6	0 (0)
ABI	0.59 ± 0.26

ABI, ankle-brachial index
*Categoric data as number (%) and continuous data are reported as the mean (range) or mean ± standard deviation

Table II. Lesion characteristics

Variable*	Result
	N=100
Lesion type	
De novo	83 (83.0)
Restenosis	10 (10.0)
In-stent restenosis	7 (7.0)
Left side	48 (48.0)
Calcification	
None or slight	49 (49.0)
Moderate (eccentric)	41 (41.0)
Severe (concentric)	10 (10.0)
Total lesion length, mm	105.7 ± 94.3
Oclusion length, mm	100.1 ± 98.9
Lesion length <150 mm	75 (75)
Lesion length >150 mm	25 (25)
Location	
Femoral	76 (76.0)
Popliteal	7 (7.0)
Femoropopliteal	17 (17.0)
Stenosis	59 (59.0)
Occlusion	41 (41.0)
Concommitantly treated lesions	
Inflow	17 (17.0)
Outflow	13 (13.0)

*Categoric data are reported as number (%) and continuous data are reported as the mean ± standard deviation.

Procedural characteristics

Procedural characteristics are summarized in Table III. Technical success was achieved in 100%. After DEB inflation, residual stenosis occurred in 23 limbs (23%). This stenosis persisted after prolonged inflation in 18 limbs (18%), and additional stent placement was needed. Dissection occurred in 12 limbs (12%). This was successfully treated with prolonged balloon inflation in one limb, and additional stent placement was performed in the other 11 limbs (11%). Provisional stenting was required in 29 limbs (29%).

Five periprocedural complications (5%) occurred. One closure device (Angioseal, Terumo, Somerset, NJ) occluded the common femoral artery, and additional open surgical exploration with desobstruction of the common femoral artery was needed. One patient required

Table III. Procedural characteristics

Variable*	Result
	N=100
General anesthesia	16 (16.0)
Regional/local anesthesia	84 (84.0)
Acces	
Ipsilateral CFA	20 (20.0)
Contralateral CFA	79 (79.0)
Upper extremity	1 (1.0)
Closure	
Manual compression	35 (35.0)
Closure device	65 (65.0)
Technical succes	100 (100.0)
Prolonged balloon inflation	
Dissection	12 (12.0)
Residual stenosis	23 (23.0)
Additional stent placement	
Dissection	11 (11.0)
Residual stenosis	18 (18.0)
Stent length, mm	75.9 ± 36.5

CFA, Common femoral artery.
*Categoric data are reported as number (%) and continuous data are reported as the mean ± standard deviation.

surgical treatment for bleeding of the puncture site on postoperative day 1. One patient underwent conservative treatment for an infection at the puncture site. The completion angiography showed thromboembolic complications in the tibial arteries in two patients. One patient was treated successfully with thrombolytic therapy. The other patient was treated conservatively while showing no clinical symptoms and having uncompromised outflow through another tibial artery.

Follow-up

Follow-up data were available in 90 patients (90%). Ten patients were lost to follow-up: two patients returned to their referring hospital for follow-up, four were discharged without postoperative imaging, and four died during the follow-up period. One patient died of pneumonia, in another patient dialysis was discontinued when pancreatic cancer was diagnosed, and the cause of death in the other two patients was unknown.

Primary end point

After 6 and 12 months, the primary patency rate was 94.3% and 72.6% (Figure 1)

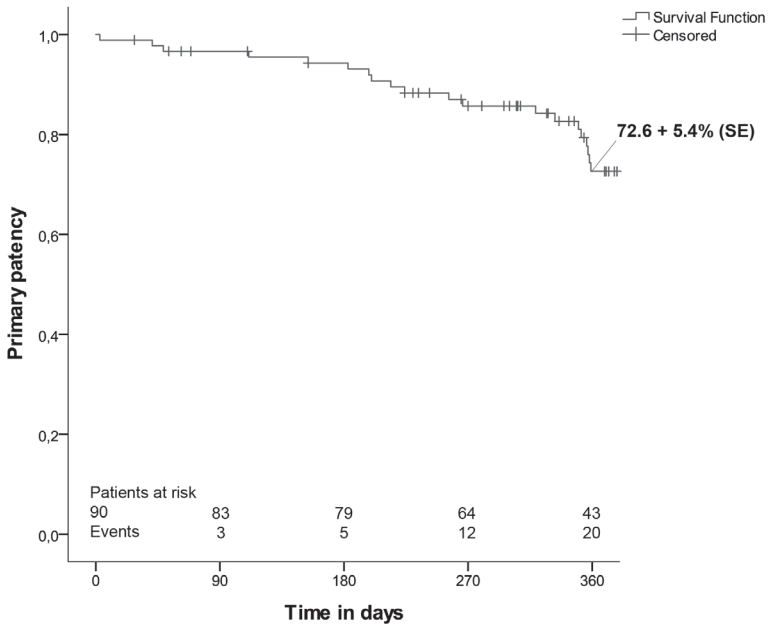

Figure 1. Primary patency (freedom from binary restenosis or cd-TLR)
Kaplan-meier curve depicting the incidence of the composite endpoint of freedom from binary restenosis and clinically driven TLR over a 12 month follow up period. Cd-TLR = clinically driven target lesion revascularization; SE = standard error.

Secondary end points

After 6 and 12 months, freedom from binary restenosis was 97.9% and 78.8% (Figure 2), freedom from cd-TLR was 96.8% and 91.7%, respectively (Figure 3).

Femoropopliteal artery thrombosis occurred in three limbs in the first year. Two patients were treated successfully with thrombolytic therapy at 2 and 12 months, respectively. One patient underwent surgical embolectomy with four-compartment fasciotomy. Multiple debridements were performed during the next 2 months; however the leg could not be salvaged and an above-the-knee amputation was performed 8 months after the primary intervention.

Two other major amputations were performed during the first year, resulting in a major amputation rate of 2.0%. One below-the-knee amputation was performed in a Rutherford class 5 patient 10 days after the primary intervention because of progression of the disease. Another below-the-knee amputation was performed in a Rutherford class 5 patient 20 days after the primary intervention due to progression of osteomyelitis.

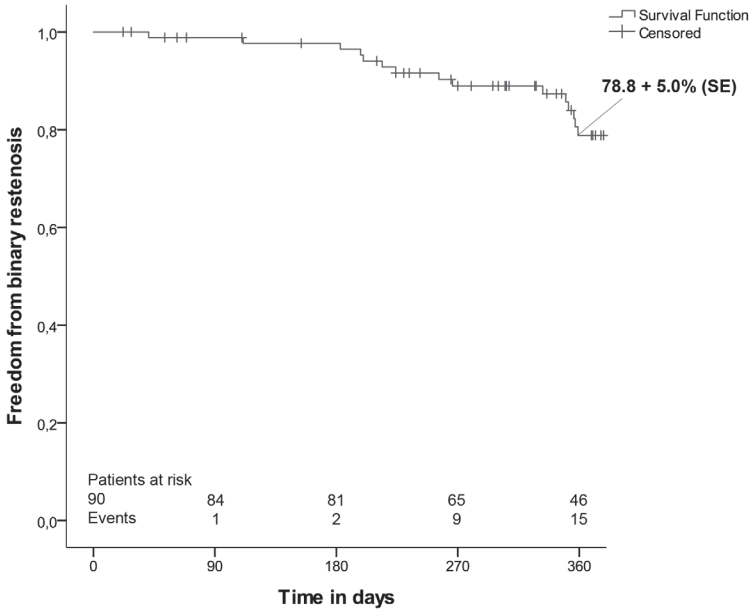

Figure 2. Freedom from binary restenosis
Kaplan-meier curve depicting freedom from binary restenosis over a 12 month follow up period. SE = standard error.

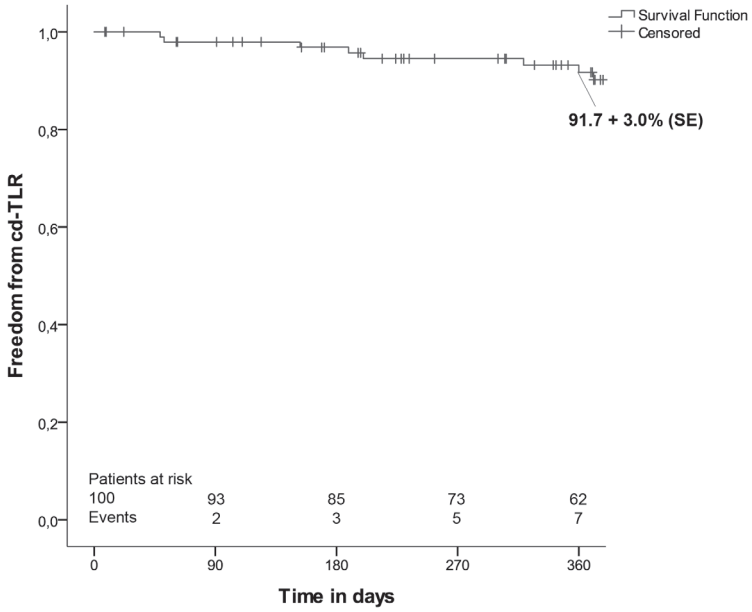

Figure 3. Freedom from clinically driven TLR
Kaplan-meier curve depicting freedom from clinically driven TLR over a 12 month follow up period. Cd-TLR = clinically driven target lesion revascularization; SE = standard error.

Clinical improvements

Improvement of at least one Rutherford-Baker category was found in 73 of 90 limbs (81.1%), but the Rutherford-Baker category did not improve in 12 of 90 limbs (13.0%). Eleven of these patients were treated conservatively, and one patient received a polytetrafluoroethylene infrageniculate femoropopliteal bypass (Propaten). Five limbs deteriorated at least one Rutherford-Baker category after DEB angioplasty. Three of these patients underwent a major amputation, and the other two received venous suprageniculate femoropopliteal bypasses. The mean ABI in all patients at discharge was significantly higher compared with the preoperative value (0.83 ± 0.21 vs 0.58 ± 0.26; $P < 0.05$).

Sensitivity analysis

The primary and secondary end points were also evaluated in patients with intermittent claudication vs CLI, lesion length <150 mm vs >150 mm, and stenosis vs CTO. Results can be found in Table IV. Lesions >150 mm had a significantly higher chance of binary restenosis and consequently lower primary patency. However, this did not lead to increased cd-TLR.

Table IV. Sensitivity analysis after 12 months

Outcome	IC - CLI	P value	<15 cm - >15 cm	P value	Stenosis – CTO	P value
Primary patency, %	74.3 ± 6.9 vs 68.2 ± 8.8	.535	80.2 ± 5.5 vs 48.1 ± 12.5	.011	72.2 ± 7.4 vs 72.8 ± 7.9	.595
Freedom from binary restenosis	76.7 ± 6.6 vs 81.8 ± 7.4	.269	87.4 ± 4.5 vs 50.7 ± 12.9	.003	75.9 ± 7.2 vs 82.3 ± 6.7	.863
Freedom from cd-TLR	98.4 ± 1.6 vs 83.3 ± 6.9	.538	92.5 ± 3.3 vs 94.4 ± 5.4	.133	96.1 ± 2.7 vs 88.7 ± 5.4	.540

cd-TLR, Clinically driven target lesion revascularization; *CLI,* critical limb ischemia; *CTO*, chronic total occlusion; *IC*, intermittent claudication.

DISCUSSION

This study represents the outcomes of daily practice use of DEB in the femoropopliteal arteries in a vascular referral center in the Netherlands. The clinical outcomes after 12 months were comparable with those found in large RCTs comparing DEBs with uncoated balloons, although the current series contains more patients with CLI (37%) and CTOs (41%).

The operating mechanism of DEBs is the transfer of cytostatic or cytotoxic agents into the vessel wall, inhibiting neo-intimal hyperplasia.[15] In femoropopliteal DEB angioplasty, this agent is paclitaxel. The paclitaxel dosage on the DEB, as well as the excipient used to transfer paclitaxel to the vessel wall, both influence the effect of the treatment.[16] The Passeo-18 Lux DEB that was used in our study has a paclitaxel dose of 3 μg/mm^2, and the excipient used is butyryl-tri-n-hexyl citrate (BTHC). Scheinert et al[17] published a study in 2015 using the Passeo-18 Lux DEB in the femoropopliteal stenosis and occlusions. This prospective, multicenter RCT randomized 60 patients to either angioplasty with the Passeo-18 Lux DEB or the Passeo-18 uncoated balloon. Baseline characteristics in the DEB group of 30 patients were fairly comparable to the present cohort; however, the mean lesion length in the current series was twice as long (51.4 mm vs 103.8 mm), and a larger portion of the patients had CLI (20% vs 37%). Despite the more complex patients in the current series, outcomes in the present series are comparable or even better than the outcomes published in the Biolux P1 trial. Binary restenosis at 6 months was 11.5% vs 2.1%, and clinically driven TLR at 12 months was 15.4% vs 8.3% in the current series.

Multiple DEBs from various manufacturers are currently available with differences in paclitaxel dosages and excipients used. To date no studies have directly compared different DEBs. An indirect comparison of standard-dose DEBs (3-3.5 μg/mm^2) with low-dose DEBs (2 μg/mm^2) suggested a significantly worse treatment effect of the low-dose DEBs[13]; However recent studies report promising results with low-dose DEBs.[18–20] The efficacy and importance of the different excipients is still unclear.

DEBs may limit the need and use for femoropopliteal stenting. Negative consequences such as stent fracture or stent occlusion may be averted. However, excellent outcomes of femoropopliteal stenting have been reported, especially in long calcified lesion. Published data on the outcomes of DEBs in long superficial femoral artery lesions are scarce, but show promising 1-year results.[21,22] The primary patency rate of long lesions (>15 cm) in our series was only 48.1% compared with 83.2% published by Micari et al. and 79.2% by Schmidt et al. However, in the current series the cd-TLR rate of long lesions was 94.4%, which is comparable to the cd-TLR rates of 85.1% and 96.0% found by Schmidt and Micari respectively.[21,22]

Our treatment strategy consisted of DEB angioplasty and provisional stenting with a self-expanding stent if residual stenosis or flow-limiting dissection persisted after prolonged inflation. Twenty-nine percent of our patients required provisional stenting. Another strategy in endovascular treatment is primary stenting (PS). Recent studies comparing DEB angioplasty with PS and UCB angioplasty with PS report improved outcomes after use of DEB. In 2013 the DEBATE-SFA trial randomized 104 patients to treatment of femoropopliteal lesions with either DEB + PS or UCB + PS with a bare metal stent. The use of DEB before stent placement significantly reduced both binary restenosis and cd-TLR rate.[23] The same conclusion was found in the more recent ISAR-STATH trial, comparing 150 patients with femoropopliteal lesions. The cohort was randomized to treatment with UCB followed by DEB angioplasty + PS with a bare metal stent (n=48), UCB and stenting (n=52), or directional atherectomy with distal protection and bailout stenting (n=55). The DEB group showed a significant lower late lumen loss at 6 months and significant reduction of binary restenosis and cd-TLR rate compared to UCB + PS or directional atherectomy.[24] In 2017, Mwipatayi et al[25] published a single-arm series of 51 stent placements, inflated by a DEB, with an 88% rate of freedom from clinically driven TLR rate after 2 years. Of note, cumulative stent fractures were observed in 10% of the patients in their series. PS + DEB demonstrates high technical success percentages and favorable short term results, especially in long lesion. However, these results may be obtained at expense of long-term complications of intra-arterial stenting such as in-stent stenosis, stent thrombosis and stent fracture.[8–10]

Drug-eluting stents (DES) are stents coated with antiproliferative drugs and provide a depot, slowly releasing the drug into the vessel wall.[16] Like DEB, DES has demonstrated decreased reintervention and restenosis rates in treatment of femoropopliteal lesions, with follow-up available up to 5 years.[26,27] Comparing the two strategies of DEB angioplasty with provisional stenting and primary stenting with DES may benefit the ongoing search of minimally invasive but durable treatments of femoropopliteal arterial occlusive disease. Multiple research groups are currently conducting such a trial (REAL PTX[28], DRASTICO[29], FOREST[30])

This study was a single-center, retrospective analysis of a prospectively maintained database. Limitations include small sample size, short time of follow-up, and the nonrandomized and noncomparative nature of the study. Some of the patients were lost to follow-up, increasing the risk of attrition bias.

CONCLUSIONS

In a real-world vascular population in the Netherlands, DEB angioplasty with provisional bail-out stenting was a feasible technique for endovascular treatment of femoropopliteal arterial stenoses and occlusions. Lesions >150 mm have a significantly higher chance of binary restenosis; however, this does not affect the freedom from TLR rate.

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