Drug-eluting balloons and uncoated balloons perform equally in autologous bypasses at risk.

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ABSTRACT

Objective

Endovascular treatment of a significant stenosis in an infrainguinal autologous bypass prevents bypass occlusion and improves bypass patency. Drug-eluting balloons (DEB) have been proven to possess antirestenotic features in the treatment of femoropopliteal stenoses and occlusions. This study evaluated the effects of DEB angioplasty vs uncoated angioplasty (UCB) to rescue infrainguinal autologous bypass grafts at risk (BAR).

Methods

All consecutive patients treated endovascularly for BAR from December 1, 2012, to July 31, 2015, were included in this study. As of April 1, 2014, primary treatment of BAR was changed from UCB to DEB. Patients treated with DEB were prospectively recorded in a database and retrospectively analyzed. Patients treated with UCB were retrospectively collected from a historical cohort with a similar inclusion period length as the DEB cohort. The follow-up scheme did not differ between the 2 groups. The primary end point was the combined endpoint of freedom from recurrent stenosis or bypass occlusion. Secondary end points were primary assisted patency, secondary patency, technical success, major amputation, and mortality.

Results

Twenty-one patients were treated in the DEB group and 18 were treated in the UCB group. The 2 groups were evenly distributed in demographics, bypass-, treatment-, and lesion characteristics. No statistically significant differences were found in the combined endpoint of freedom from recurrent stenosis and the occlusion rate after 1 year between the UCB group (77.8%) and the DEB group (80.0%) (P = .76). After 1 year, the primary assisted patency rate was 88.2% in the UCB group vs 95.2% in the DEB group (P = .47), and the secondary patency rate was 94.1% in the UCB group vs 95.2% in the DEB group (P = .91). During follow-up, restenosis developed in 4 patients (22.2%) in the UCB group and in 4 patients (19.0%) in the DEB group (P = .80). One bypass (5.6%) in the UCB group and 1 bypass (4.8%) in the DEB group occluded during follow-up (P = .884).

Conclusion

DEB and UCB perform equally in the treatment of significant stenosis in infrainguinal autologous bypasses with regard to freedom from restenosis or bypass occlusion, primary assisted patency, and secondary patency at 1 year. The authors suggest using a less expensive UCB in the treatment of BAR.

INTRODUCTION

Autologous infrainguinal bypasses are widely used for the treatment of extensive femoropopliteal arterial occlusive disease because they show excellent long-term patency, with reported 5-year patency rates of 60% to 80%.[1–3] One-third of patients will develop a significant stenosis in the autologous bypass, predominantly in the first year after surgery.[4,5] An autologous bypass with a significant stenosis is associated with an increased risk for bypass occlusion and is called a bypass at risk (BAR).[4,6,7] Duplex ultrasound surveillance is performed to identify autologous bypass stenoses.[8,9] Early endovascular intervention is the preferred technique to rescue infrainguinal BAR. Although the freedom from recurrent stenosis after percutaneous angioplasty with uncoated balloons (UCBs) is disappointing, repeated endovascular revascularization results in patency rates of >80%.[10,11]

In the past decade drug-eluting balloons (DEBs) have been introduced to improve patency rates. Antiproliferative medication (Paclitaxel) on the exterior of the balloon is transferred into the arterial wall using an excipient during inflation to reduce neointimal hyperplasia.[12,13] Recent meta-analyses of randomized controlled trials comparing treatment of atherosclerotic lesions in femoropopliteal arteries with DEBs and UCBs show a significant reduction of binary restenosis, decreased late lumen loss, and reduction of target lesion revascularization after DEB angioplasty.[14,15] However, whether endovascular treatment of autologous infrainguinal bypass stenoses with DEBs results in improved outcome compared with UCB angioplasty is still unclear. This study evaluated the effects of DEB angioplasty on significant stenosis in infrainguinal autologous bypass grafts compared with UCB angioplasty.

METHODS

The Institutional Review Board approved the study. The requirement for written patient consent was waived.

Study design

On April 1, 2014, primary treatment of infrainguinal autologous BAR changed from UCB angioplasty to DEB angioplasty in our institution. To obtain a minimal follow-up of 1 year, all consecutive patients with an autologous infrainguinal BAR treated with DEB angioplasty between April 1, 2014, and July 31, 2015 were included. Data on treatment with DEBs were prospectively collected and retrospectively analyzed. These results were compared with a historical cohort of patients with autologous infrainguinal BAR treated with UCB angioplasty, some of which have been published previously.[10] A similar inclusion period length as the DEB cohort of 16 months was chosen for the UCB angioplasty cohort.

Therefore, all consecutive patients with an autologous infrainguinal BAR treated with UCB angioplasty from December 1, 2012, to April 1, 2014, were included. Patients that were treated previously with a PTA were all treated prior to December 1, 2012, ruling out crossover between the two groups.

Indication for endovascular treatment

Patients with peripheral arterial occlusive disease treated with an infrainguinal autologous bypass graft were monitored for at least 1 year according to the guidelines of the Dutch Vascular Society.[16] Duplex ultrasound surveillance was performed at 6 and 12 months after surgery by ultrasound technicians from an accredited vascular laboratory. Thereafter, duplex ultrasound imaging was performed if the patient became symptomatic. A stenosis of >70% was considered a significant stenosis and was defined as a peak systolic velocity (PSV) of >300 cm/s or a PSV ratio >3.0.

Treatment

Patients with BAR were scheduled for digital subtraction angiography. The stenosis or multiple stenoses in the BAR were identified and classified as anastomotic or nonanastomotic. The bypass diameter proximal and distal to the stenosis was measured, and before April 1, 2014, an UCB with a diameter similar to the bypass diameter was used for angioplasty. After April 1, 2014, a Passeo-18 Lux DEB (Biotronik AG, Buelach, Switzerland) was used. All patients received 5000 IU of heparin. In the DEB group all lesions were predilated with an angioplasty balloon 1 mm smaller than the target vessel and the inflation time was 3 minutes in all patients. In the UCB group no minimal balloon inflation time was indicated.

If a residual stenosis of >30% persisted, prolonged inflation with an UCB was performed. Treatment was considered a technical success if a residual stenosis of <30% was achieved after percutaneous transluminal angioplasty, with or without prolonged balloon inflation. In case of flow-limiting dissection or residual stenosis of >30%, a self-expanding bare-metal stent was placed. Obstructive lesions in other arterial segments (ie, iliac or tibial) were treated simultaneously with percutaneous transluminal angioplasty (PTA) and optional stenting, to obtain unimpeded runoff through at least one artery passing the ankle.

Patients received oral anticoagulation therapy for at least 2 years after bypass surgery.[17] Antiplatelet therapy (Aspirin) was prescribed for patients who were not eligible for anticoagulation therapy. All patients received a statin as primary cardiovascular protection.

Follow-up

The follow-up protocol was similar in both groups. After endovascular treatment of BAR, patients were routinely monitored in the outpatient clinic. Duplex ultrasound surveillance

was performed at 6 and 12 months. In patients with clinical deteriorating duplex ultrasound or direct angiography was performed.

Our institution has adopted an endovascular-first approach for primary and recurrent stenosis. Patients with recurrent significant stenosis in the bypass on duplex ultrasound were rescheduled for digital subtraction angiography, and if a stenosis of >70% was found during angiography, a PTA was performed. If a bypass occluded during follow-up, thrombolytic therapy or surgical embolectomy was performed. If thrombolytic therapy or surgical embolectomy was not successful or not performed, the bypass was considered failed.

Study end points

Comorbidities and outcomes were in accordance with those proposed by the Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease.[18] Because primary patency according to the reporting standards was already lost during the first endovascular treatment of BAR, the primary end point of this study was a combined endpoint of freedom from recurrent stenosis or occlusion after angioplasty of the stenosis in the autologous bypass with either an UCB or DEB. Secondary outcomes in this study were primary assisted patency, defined as freedom from any intervention to prevent bypass occlusion; secondary patency, defined as freedom from any intervention to maintain bypass patency after occlusion; major amputation, defined as an amputation above the ankle, and all-cause mortality.

Statistical methods

Data were collected and stored in on-line case report forms (Castor EDC, Ciwit BV, Amsterdam, the Netherlands). Data were analyzed with SPSS 24 software (IBM, Armonk, NY, USA). All results were analyzed on an as-treated basis. Continuous data are presented as means ± standard deviation, and categoric data are given as counts with percentages. Means were compared with the independent samples t-test. Differences between counts in groups were compared using the χ^2 test. Kaplan-Meier analysis was used to estimate freedom from recurrent stenosis or occlusion, primary assisted patency, and secondary patency. Statistical differences were calculated using log-rank (Mantel-Cox). A P value of <.05 was considered statistical significant.

RESULTS

Patients

The study included 39 endovascularly treated autologous infrainguinal BARs between December 1, 2012, and July 31, 2015; of these, 18 patients were treated with UCB angioplasty and 21 were treated with DEB angioplasty. With the exception of neurologic comorbidity,

demographics were evenly distributed between the groups (Table I). As reported in Table II, bypass characteristics were evenly distributed between the groups.

Table I. Demographics

Variable	UCB	DEB	P-value
	(N=18)	(N=21)	
Age (years)	71.3 ± 6.8	69.6 ± 13.4	.64
Male sex (%)	7 (39)	13 (62)	.15
Diabetes mellitus (%)	5 (28)	6 (29)	.96
Hypertension (%)	15 (83)	12 (57)	.08
Hyperlipidemie (%)	14 (78)	11 (52)	.10
Cardiac disease (%)	7 (39)	10 (48)	.58
Neurologic disease (%)	7 (39)	2 (10)	.03
Renal failure (%)[1]	0 (0)	2 (10)	.18
Current or history of smoking (%)	14 (78)	17 (81)	.66

Continuous data are shown as mean ± standard deviation and categoric data as number (%)
[1] Glomerular filtration rate < 60

Procedure

Additional interventions to obtain unimpeded runoff through at least one artery passing the ankle, the location of the stenosis in the bypass and the number of lesions previously treated with UCB were evenly distributed between the UCB and DEB groups (Table II and III). General anesthesia was used to treat 2 patients (11%) in the UCB group and 4 (19%) in the DEB group (P = .53). All other patients were treated under local anesthesia.

Technical success was obtained in all but 1 patient in the UCB group (P = .27). In this patient, PTA with an UCB resulted in rupture of the bypass, which was successfully treated with a covered self-expandable stent. No other periprocedural complications were observed in the UCB group. One complication occurred in the DEB group (P = .35). A dysrhythmia developed in this patient that needed cardiologic evaluation, but no additional treatment was indicated. The procedure was performed afterwards, and the patient fully recovered.

Primary end point

Mean follow-up was 20.8 ± 9.7 months in the UCB group and 15.6 ± 8.6 months in the DEB group (P = .08). No patients were lost to follow-up. The estimated freedom from recurrent stenosis and the occlusion rate after 1 year was 77.8% ± 9.8 in the UCB group and 80.0% ± 9.0 in the DEB group (P = .76) (Figure 1).

Table II. Bypass characteristics

Variable	UCB	DEB	P-value
	(N=18)	(N=21)	
Bypass indication			
Intermittent claudication	9 (50)	10 (48)	.88
Critical limb ischemia	9 (50)	11 (52)	
Previous PTA (before December 1st 2012)	8 (44)	9 (43)	.92
Symptoms prior to PTA			
No symptoms	7 (39)	11 (52)	.65
Intermittent claudication	8 (44)	8 (38)	
Critical limb ischemia	3 (17)	2 (10)	
Bypass type			
Suprageniculate femoropopliteal	4 (22)	6 (29)	.61
Infrageniculate femoropopliteal	12 (67)	10 (48)	
Femoroanterior tibial	0 (0)	2 (9)	
Femoroposterior tibial	1 (6)	1 (5)	
Femoroperoneal	1 (6)	2 (9)	
Single segment greater sapheneous vein bypass	16 (89)	18 (86)	.77
Reversed	10 (63)	10 (56)	.62
Non-reversed	6 (37)	7 (39)	
In situ	0 (0)	1 (6)	
Spliced vein bypass			
Greater saphenous veins	2 (11)	3 (14)	.77
Arm veins	0 (0)	0 (0)	

Categoric data are shown as number (%)

Secondary end points

Primary assisted patency after 1 year was 88.2% ± 7.8 in the UCB group and 95.2% ± 4.6 in the DEB group (P = .47) (Figure 2). Secondary patency after 1 year was 94.1% ± 5.7 in the UCB group and 95.2% ± 4.6 in the DEB group (P = .91) (Figure 3).

Almost half of the patients were asymptomatic prior to the PTA (Table II). In the UCB group, all patients with intermittent claudication experienced improvement of at least 1 Rutherford classification. Two patients with critical limb ischemia improved to intermittent claudication and one patient became asymptomatic. In the DEB group, all of the 8 patients with intermittent claudication improved at least 1 Rutherford classification. One patient with critical limb ischemia became asymptomatic. In another patient with critical limb ischemia the bypass occluded before wound healing occurred.

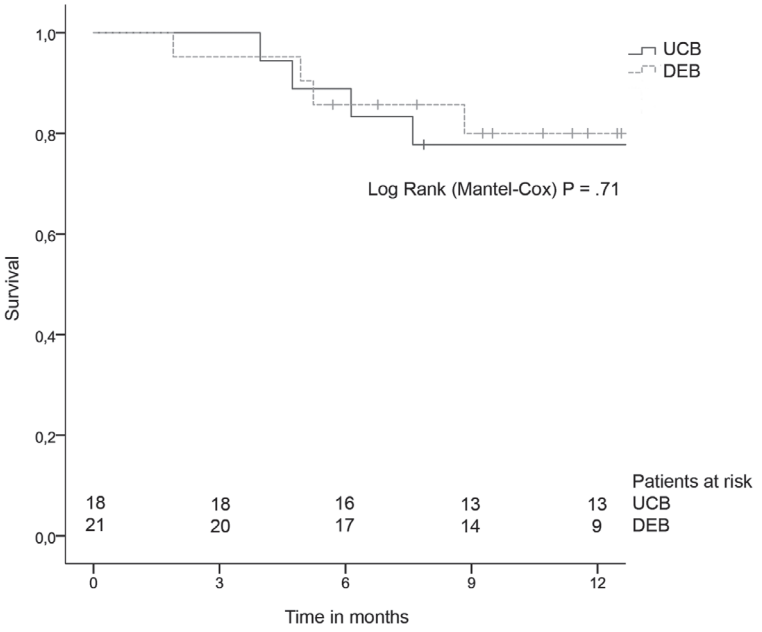

Figure 1. Freedom from recurrent stenosis or occlusion
UCB = Uncoated balloon, DEB = Drug-eluting balloon.

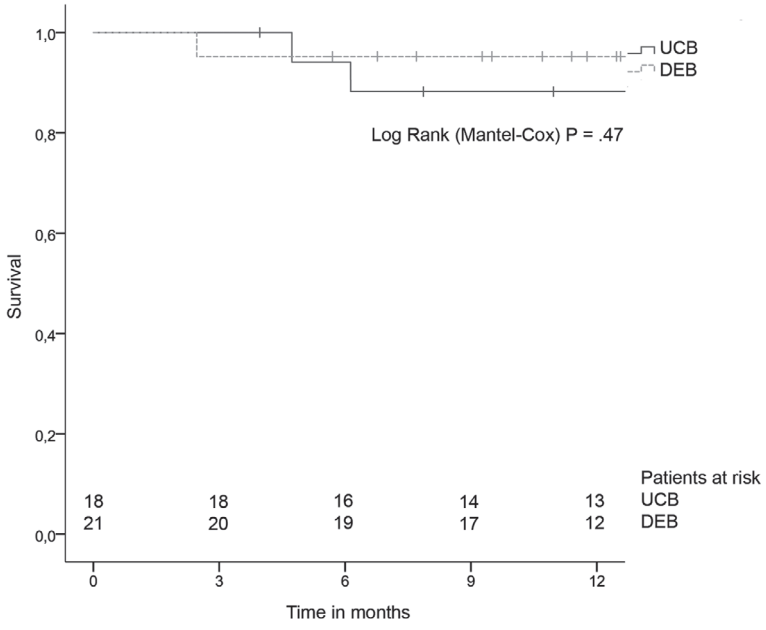

Figure 2. Primary-assisted patency
UCB = Uncoated balloon, DEB = Drug-eluting balloon.

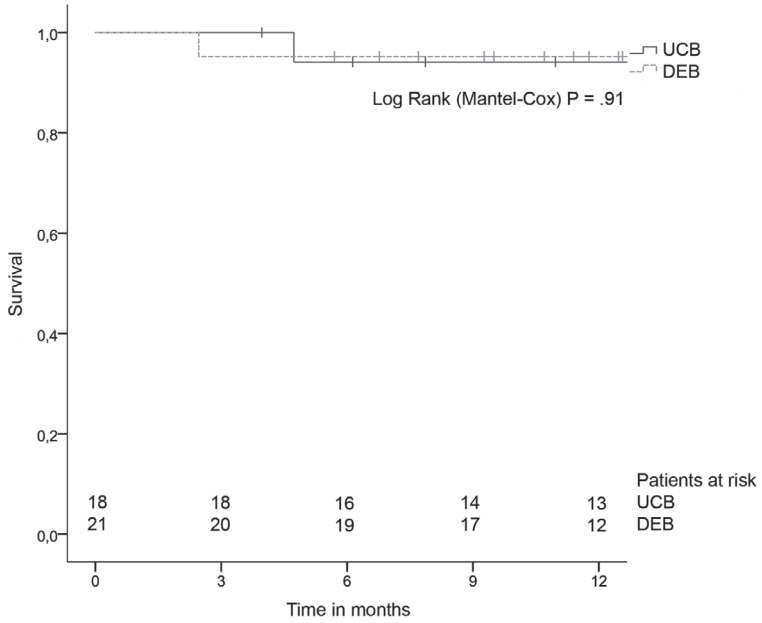

Figure 3. Secondary patency
UCB = Uncoated balloon, DEB = Drug-eluting balloon.

Recurrent stenosis was observed in 4 of the bypasses (22.2%) in the UCB group and in 4 of the bypasses (19.0%) in the DEB group during follow-up (P = .80). In the UCB group, 3 patients underwent a second PTA with a DEB, and 1 patient underwent a second PTA with UCB. The bypasses remained patent afterwards. In the DEB group, 2 patients underwent a second PTA with a DEB, and 1 patient underwent 3 additional PTAs with a DEB to remain patent. One patient underwent a second PTA with a DEB, and a self-expandable stent was placed because of residual stenosis. The stent occluded 3 days later. Thrombolytic therapy was not successful, and the bypass was considered failed, as mentioned previously.

Bypass occlusion was observed in 1 patient (5.6%) in the UCB group and in 1 patient (4.8%) in the DEB group (P = .88). The bypass occlusion in the UCB group occurred after 6 months and was successfully treated with thrombolytic therapy. The bypass occlusion in the DEB group occurred after 3 months and was treated unsuccessfully with thrombolytic therapy, as mentioned previously.

No amputations were required. Two patients in the DEB group died within the first year after PTA. One patient died of a malignancy of unknown origin after 6 months, and the other patient died of cardiac causes after 3 months. No patients in the UCB group died during the first year (P = .19).

DISCUSSION

This single-center series found DEB angioplasty does not improve freedom from recurrent stenosis or occlusion after 1 year in BARs compared with UCB. Primary assisted patency rates and secondary patency rates are also comparable between the 2 groups. Others have published similar results. Kitrou et al[19] reported outcomes of 32 patients with failing autologous or synthetic bypasses who underwent DEB angioplasty compared with a historical cohort of 24 patients who were treated with UCB. They concluded that DEB does not significantly inhibit restenosis or improve freedom from repeat angioplasty. In a retrospective analysis by Linni et al,[20] 42 vein bypasses treated with DEB were compared with 41 bypasses treated with UCB. They concluded that treatment of significant infrainguinal vein bypass stenoses with DEB and UCB performed equally with regard to clinical and hemodynamic improvement as well as primary and primary assisted patency rates. A single-arm series of 41 patients with 63 anastomotic or in-graft stenosis of vein or prosthetic bypasses reported cumulative target site primary and secondary patency rates of 70% and 90%, respectively, after 12 months.[21]

The freedom from binary restenosis rate (also defined as primary patency in some studies) after treatment with both UCB and DEB has a wide range from less than 40% up to 88% after 1 year.[10,19–21] This may be the result of the heterogeneity of the included lesions, different definitions of stenosis and the use of different balloons.

In contrast to others studies, the current series only included patients with autologous bypasses and the majority of patients had been treated for a stenosis at the distal anastomosis. Moreover, 17 of 39 patients had been treated previously with UCB angioplasty.

Different outcomes may also be the result of different definitions of a stenosis. In the current study we have defined a significant stenosis as a stenosis of >70%. In other studies a stenosis of >50% was already considered to be significant, potentially resulting in a decreased freedom from binary restenosis rate.[19,21]

In the above-mentioned studies the In.Pact Admiral, In.Pact Pacific and In.Pact Amphirion DEB (Medtronic, Minneapolis, Minnesota) have been used. In the current study the Passeo-18 Lux DEB (Biotronik AG, Buelach, Switzerland) has been used. All balloons are coated with Paclitaxel, however the excipient to transfer Paclitaxel into the vessel wall differs between the balloons. If a therapeutic effect of Paclitaxel exists in the treatment of autologous bypass stenosis, the different excipients may have an effect on the restenosis rate.[13,15]

In multiple randomized controlled trials, DEBs have proven to possess antirestenotic features at short-term and midterm follow-up compared with UCB in femoropopliteal arterial occlusive disease.[14] These effects seem to be absent in the treatment of BAR. This

may be explained by a different etiology for atherosclerotic stenosis in a native artery and stenosis in an autologous bypass. A stenosis in an autologous bypass is the result of intrinsic tissue changes, such as subendothelial hypertrophy, layering of intimal thrombi, fibrosis of venous valves, and atherosclerosis, and also technical reasons such as improper suturing and instrumental trauma.[5]

The optimal treatment for autologous bypass restenosis has yet to be found. The use of cutting balloons is controversial. In a study reporting 161 stenosis in infrainguinal bypasses treated with open surgery (n = 42), PTA (n = 57), or cutting balloons (n = 62), cutting balloon angioplasty was considered a reasonable, safe, and minimally invasive initial treatment for infrainguinal vein graft stenosis in most patients. The authors report patency rates after treatment with cutting balloons that are comparable to open surgery and superior to PTA.[22] However, in another study reporting 109 cutting balloon angioplasties of infrainguinal vein bypass graft stenoses, the authors stated that cutting balloon angioplasty is technically feasible but associated with a relatively high complication rate and a relatively low short-term patency rate.[23]

The effects of drug-eluting stents for the treatment of stenosis in bypasses have only been evaluated in a small series of 11 patients.[24] Expanded polytetrafluoroethylene arteriovenous grafts were created in a porcine model, and drug-eluting stents were implanted over the anastomosis. Intimal hyperplasia was almost completely abolished in this group compared with the unstented and bare-metal stented group.[25]

Limitations

The current study has several limitations. Our treatment regimen of BAR changed from UCBs to DEBs as of April 1, 2014. Since then, we have prospectively kept a database on these patients. To compare our results, we retrospectively collected a historical cohort treated with UCBs with the exact length of the cohort treated with DEBs. Although our follow-up regimen did not change between the 2 groups, the collected data are at risk for missing data and selection bias.

Almost half the patients in both groups had been treated previously (Table II). Although evenly distributed between both groups, in a substantial percentage of the patient analysis was performed for endovascular treatment of a recurrent stenosis. The small study population is also a limitation and probably responsible for the difference in neurologic comorbidity between the groups. Larger, prospectively managed randomized trials should be performed to fully demonstrate the role of DEBs in the treatment of BAR.

Table III. Treatment and lesion characteristics

Variable	UCB	DEB	P-value
	(N=18)	(N=21)	
Acces			
Common femoral artery (ipsilateral)	5 (28)	8 (38)	.93
Cross over procedure	10 (56)	10 (48)	
Upper extremity	2 (11)	1 (5)	
Bypass	1 (6)	2 (9)	
Concommitantly treated lesion			
Inflow	3 (17)	0 (0)	.06
Outflow	5 (28)	4 (19)	.52
Distribution			
Solitary	14 (78)	16 (76)	.91
Multiple	4 (22)	5 (24)	
Location			
Proximal anastomosis	6 (33)	6 (29)	.75
Proximal third in graft [1]	4 (22)	2 (10)	.27
Middle third in graft	1 (6)	1 (5)	.91
Distal third in graft [1]	3 (17)	2 (10)	.51
Distal anastomosis	9 (50)	15 (71)	.17
Degree of stenosis on angiography, %	81.1 ± 12.6	80.9 ± 11.2	.98
Balloon diameter, mm	5.3 ± 1.4	4.9 ± 1.0	.36
Technical succes	17 (94)	21 (100)	.27
Postoperative complication	0 (0)	1 (5)	.35

Continuous data are shown as mean ± standard deviation and categoric data as number (%)
[1] Excluding anastomosis

CONCLUSION

DEB and UCB perform equally in the treatment of significant stenosis in infrainguinal autologous bypasses with regard to freedom from restenosis or bypass occlusion, primary assisted patency, and secondary patency at 1 year. The authors suggest using a less expensive UCB in the treatment of BAR.

AUTHOR CONTRIBUTION

Conception and design: HJ, BF
Analysis and interpretation: HJ, GA, AS, DV, JV, BF
Data collection: HJ
Writing of the manuscript: HJ
Critical revision of the manuscript: HJ, GA, AS, DV, JV, BF
Final approval of the manuscript: HJ, GA, AS, DV, JV, BF
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Overall responsibility: BF

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