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ORIGINAL ARTICLE

Treatment of femoro-popliteal lesions with scoring and drug-coated balloon angioplasty: 12-month results of the DCB-Trak registry

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PURPOSE
Debulking strategies prior to drug-coated balloon (DCB) angioplasty were suggested to improve clinical results in femoro-popliteal lesions. Currently, there are no data regarding plaque modification with a scoring balloon with subsequent DCB-angioplasty. Recently published 6-month results of the DCB-Trak registry in patients treated with scoring-balloon angioplasty and DCB-angioplasty were promising without any safety concerns. Herein, we report the 12-month follow-up data.

METHODS
In a single center registry, 29 consecutive patients with 32 femoro-popliteal lesions were treated with a scoring-balloon (VascuTrak®) and a DCB subsequently. The primary endpoint was the clinically driven target lesion revascularization (TLR). Secondary endpoints were clinically driven target vessel revascularization (TVR), binary restenosis (peak systolic velocity ratio >2.4), change in Rutherford classification and ankle-brachial-index (ABI). Safety endpoints were major cardiovascular events (cardiovascular death, myocardial infarction, stroke, death) and need for amputation.

RESULTS
The procedure was successful in 29 lesions. There were no clinically driven TLRs after 12 months. Two patients required clinically driven TVR and one patient had a binary restenosis. ABI significantly increased after the procedure (0.87±0.24 to 1.04±0.18, $P < 0.01$) without a relevant change after 6 months (1.01±0.15, $P < 0.05$) or 12 months (1.01±0.20, $P < 0.05$). Rutherford classification improved in more than 90% of patients after 6 and 12 months. There was one major cardiovascular event at 6-month follow-up, but no amputations at 6- or 12-month follow-up.

CONCLUSION
Vessel preparation with a scoring-balloon and subsequent DCB-angioplasty was safe and effective in patients with femoro-popliteal lesions. Further multicenter trials have to validate these results.

Peripheral artery disease (PAD) significantly contributes to morbidity and mortality in the western industrial countries due to a high prevalence, especially in adults >80 years of age (1, 2). In symptomatic PAD, peripheral interventional procedures are suggested to be first-line treatment in most vascular centers, but significant restenosis remains a major problem, especially in femoro-popliteal lesions (3). The use of drug-coated balloons (DCB) was supposed to reduce rates of restenosis due to an effective delivery of paclitaxel, as the antiproliferative agent, to the vessel wall without a permanent implant (4). In femoro-popliteal lesions, the use of a DCB was demonstrated to be safe and effective in numerous clinical trials (5–8). Nevertheless, bail-out stenting rates vary in different trials with higher rates in those trials treating longer lesions. In the LEVANT-II-trial stenting rates were about 3% in the DCB-treatment arm (lesion length of 6 cm), whereas in InPact-SFA lesion length was about 9 cm with a bail-out stenting rate of 7.3% (6–8). In some trials and registries, stenting rates were as high as 20%, which might additionally be dependent on plain-balloon predilatation (9, 10). Moreover, recent data demonstrated an association of the amount of calcium with the formation of restenosis (11). Thus, heavily calcified lesions seem to be a predictor of decreased efficacy of the antiproliferative drug. Interestingly, a circumferential calcium deposition had a

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greater impact on DCB-outcome compared with a longitudinal distribution (11). Therefore, plaque modification or debulking strategies prior to antiproliferative treatment with a DCB might reduce rates of restenosis and further improve clinical outcome of the patients.

A feasible strategy for vessel- and plaque-preparation and modification is the use of scoring-balloon angioplasty (SBA), which is safe and seems to be superior to plain-balloon-angioplasty (PBA) in superficial femoral artery (SFA) (12). The beneficial effects of the SBA are most likely related to controlled dissection of the intimal layer with only a slight trauma to the vessel wall (12). This might further reduce the inflammatory response and the amount of neo-intima formation in the target lesion.

Thus, plaque modification with SBA might improve beneficial effects of subsequent DCB-angioplasty. Recently published 6-month results of 20 patients with femoro-popliteal lesions of the DCB-Trak registry treated with SBA and DCB-angioplasty were promising without any safety concerns (13). Herein we present the final data of the DCB-Trak registry at 12-month follow-up.

Methods

Study population

A total of 29 consecutive patients with symptomatic PAD (Rutherford classification 2–6) with 32 femoro-popliteal lesions (>70% diameter stenosis or occlusion, reference vessel diameter 4–6 mm) were included. In three patients, both legs were treated within two deferred procedures. The DCB-Trak-registry is a single-center, non-blinded, prospective study. Exclusion criteria were patients with stenosis >70% proximal to the target lesion or the absence of a run-off-vessel below the knee. Inflow treatment of proximal stenosis was allowed, but not necessary in all patients. Informed consent was obtained from all patients, the study protocol of the DCB-Trak registry was approved by the local ethics committee. The study was registered at clinical-trials.gov: NCT02198105.

Main points

- Lesion preparation in femoro-popliteal stenosis might further improve outcome of patients with peripheral artery disease, particularly in calcified lesions.
- Combined treatment with a scoring- and a drug-coated-balloon is safe and suggested to be superior to a drug-coated-balloon angioplasty alone, in short and mid-length lesions.
- Randomized trials are needed to verify these promising results, especially in longer lesions.

Procedure

At first, the target lesion was prepared with a scoring-balloon (VascuTrak®, 5 mm diameter, BARD GmbH) for 60–120 seconds. Subsequently, DCB-angioplasty with an inflation time of 60 seconds was performed. Technical success was defined as absence of any recoil >50% of the reference vessel diameter, absence of any flow limiting dissection >type B and absence of stent implantation, despite spot stenting of <1/3 of the initial target lesion length. After a loading dose of 600 mg clopidogrel during the interventional procedure, all patients were treated with aspirin (100 mg) and clopidogrel (75 mg) for 4 weeks, followed by lifelong treatment with either aspirin or clopidogrel.

Calcification analysis

Lesion calcification was analyzed using two different fluoroscopy/digital subtraction angiography based scoring systems, assessed in anterior-posterior projection (14, 15). Both, the peripheral arterial calcium scoring system (PACSS) and the Compliance 360°-score distinguish five different grades of calcification with regard to the length and circumferential distribution of the calcium deposit.

Study endpoints

Follow-up was conducted at 6 and 12 months. The primary endpoint was the clinically driven TLR. Secondary endpoints were clinically driven TVR, binary restenosis (peak systolic velocity ratio, PSVR>2.4), change in ankle-brachial-index (ABI) and Rutherford-classification. ABI was determined with a mercury sphygmomanometer (WelchAllyn) and a portable Doppler-ultrasound (handydop, ELCAT) after the patient had rested in a supine position for at least five minutes. ABI was measured as the ratio of the ankle systolic blood pressure divided by the brachial systolic blood pressure with the use of the higher of the two ABI-values and the higher brachial value. In diabetic patients with an ABI higher than 1.30, further analysis was performed with 1.30 to account for the test-related intraindividual variability of the ABI in those patients with severe media sclerosis. Safety endpoints were major cardiovascular events (myocardial infarction, stroke, death, cardiovascular death) and freedom from amputation.

Statistical analysis

All data are expressed as mean±standard deviation (SD). Statistical significance was accepted as $P < 0.05$. Data were tested for normal distribution with the Kolmogorov-Smirnov-test. Except Rutherford classification and grade of calcification scores, values followed a normal distribution. Analyses were performed with the Student t-test, except calculations related to calcification scores. Therefore, the Kruskal-Wallis-test comparing the median of the calcification scores was used due to the small sample size of the comparator groups (technical failure n=3, need for spot-stenting n=5). PSPP® for Mac-OS was used for statistical analysis.

Results

A total of 29 patients (21 male patients, 72%) with 32 femoro-popliteal lesions were included in the DCB-Trak registry. Baseline characteristics are demonstrated in Table 1, lesion- and procedural characteristics in Ta-

Table 1. Patient baseline characteristics

Total, n (%)	29 (100)
Male gender, n (%)	21 (72)
Age (yrs), mean (range)	68 (48–81)
HLP, n (%)	28 (97)
Diabetes, n (%)	18 (59)
Hypertension, n (%)	28 (97)
Current smoking, n (%)	20 (69)
Rutherford classification, n (%)	
2	1 (3)
3	21 (73)
4	2 (7)
5	3 (10)
6	2 (7)
Median	3
ABI, mean±SD	0.87±0.24
ABI (diabetics)	0.93±0.27
ABI (nondiabetics)	0.79±0.18

There was no significant difference between ABI of diabetic and nondiabetic patients ($P = 0.126$).
HLP, hyperlipoproteinemia; ABI, ankle brachial index; SD, standard deviation.

Table 2a. Lesion characteristics

Vessel diameter (mm), mean±SD (range)	5.56±0.70 (4.1–7.0)
Target lesion length (mm), mean±SD (range)	
Total (n=32)	60.34±59.67 (12–260)
Technical success (n=29)	52.76±48.07 (12–250)*
Technical failure (n=3)	133.76±118.11 (26–260)*
Grade of stenosis (%), mean±SD (range)	81.59±12.11
Total occlusion, n of patients (%)	7 (22)
Periprocedural dissection, n of patients (%)	
None	15 (47)
Type A	5 (16)
Type B	9 (28)
> Type B	3 (9)
Spot stenting <1/3 lesion length, n of patients (%)	5 (16)

*P = 0.023 for technical success vs. failure.

Table 2b. Lesion characteristics – grade of calcification

	Technical success (n=29)	Technical failure (n=3)	P	Spot stenting (n=5)	No spot stenting (n=27)	P
PACSS						
Mean rank, median (range)	16.34, 1 (0–4)	18.00, 2 (0–4)	0.471	22.70, 3 (0–4)	15.35, 1 (0–4)	0.106
Compliance 360°						
Mean rank, median (range)	16.47, 2 (0–4)	16.83, 2 (0–4)	0.702	20.70, 3 (0–4)	15.72, 1 (0–4)	0.075

Grade of calcification measured with the peripheral arterial calcium scoring system (PACSS) and the Compliance 360° score distinguishing five different grades of calcification with regard to the length and circumferential distribution of calcium deposit was not significantly increased in patients with technical failure or need for spot stenting.

Table 3. Primary and secondary endpoints at 6- and 12-month follow-up

Primary endpoint	6-month follow-up lesions, n (%)	12-month follow-up lesions, n (%)
Clinically driven TLR	0 (0)	0 (0)
Secondary endpoints		
Clinically driven TVR	0 (0)	2 (7)[a]
Binary restenosis (PSVR >2.4)	1 (4)[b]	1 (4)[b]
MACE	1 (3)	0 (0)
Any amputation	0 (0)	0 (0)

Change in Rutherford classification and change in ABI were demonstrated in Figs. 1 and 2.
TLR, target lesion revascularization; TVR, target vessel revascularization; PSVR, peak systolic velocity ratio; MACE, major adverse cardiovascular events (myocardial infarction, stroke, death, cardiovascular death).
[a]Both *de novo* lesions were located proximately to the initial lesion treated. The one MACE at 6-month follow-up was a myocardial infarction.
[b]PSVR assessed in 23 patients (25 lesions) at 6-month follow-up and 21 patients (23 lesions) at 12-month follow-up. Patients with PSVR >2.4 after 6 and 12 months were not identical. PSVR of the patient with binary restenosis at 6 months declined to 0.8 at 12 months.

ble 2a and 2b. The procedure was successful in 29 lesions (90.6%). Bail-out-stenting was necessary in three patients (9.4%, one patient with recoil >50%, one patient with type-c dissection, one patient with both). Successfully treated vessels had significantly shorter lesion length than the unsuccessful ones (P = 0.023, Table 2a). There was no association between the grade of calcification of the target lesion and the procedural success (Table 2b).

In five patients (16%) we performed spot stenting of <1/3 of lesion length. One patient was lost to follow-up between 6 and 12 months. Thus, 26 patients with 29 lesions were followed for 6 months and 25 patients with 28 lesions for 12 months. The primary endpoint (clinically driven TLR) was negative for all patients after 6 and 12 months. Secondary endpoints are demonstrated in Table 3. There was one major adverse cardiovascular event (myocardial infarction) at 6-month follow-up.

ABI and Rutherford classification improved at 6 months and 12 months (Figs. 1 and 2).

Discussion

For the first time, the results of the current study indicate a safe and effective use of the combined treatment of SBA and DCB angioplasty in patients with femoro-popliteal lesions.

Efficacy of endovascular treatment in patients with PAD increased within the last decades due to improvement and diversification of endovascular techniques. Especially in femoro-popliteal lesions, patency rates of long lesions increased with the usage of stents, with and without drug coating. Nevertheless, in-stent restenosis remains a major problem. Particularly in the femoro-popliteal region, restenosis might be related to stent fracture due to the high mechanical stress in this vascular region (6, 16). Therefore, avoidance of a permanent implant is supposed to be the best choice, preserving all treatment options for the patient in future (6). DCBs were demonstrated to further improve the outcome of patients and decrease the rate of restenosis without any scaffold (5–8). However, this concept is restricted by flow-limiting dissections or by a significant recoil of the target lesion. Current data indicate highly variable bail-out stenting rates in clinical trials and registries evaluating DCB-angioplasty (9, 10). High bail-out-stenting rates are supposed to be dependent on lesion length and pre-dilata-

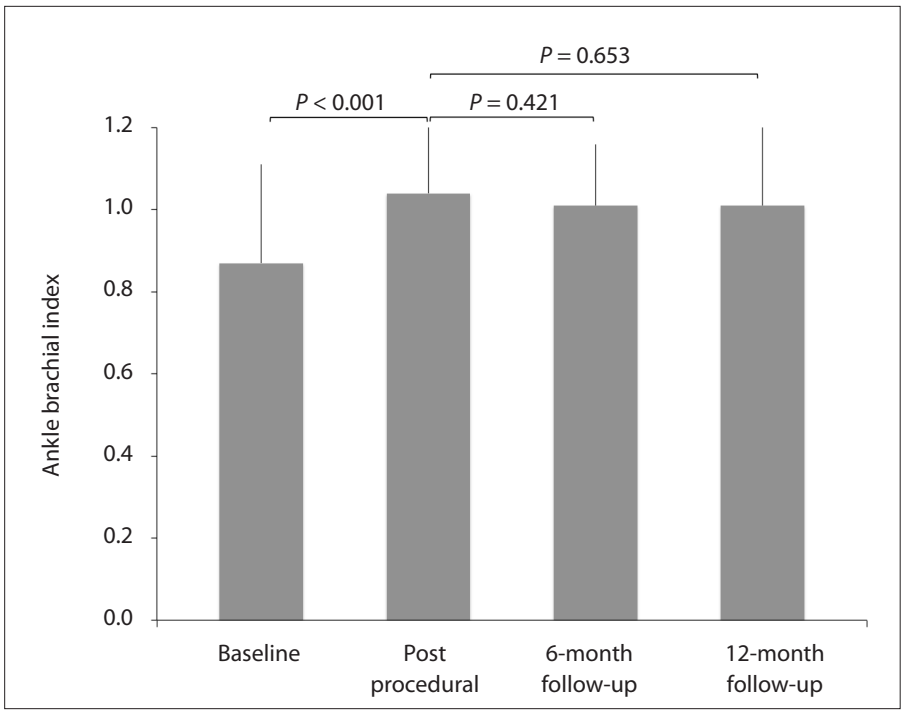

Figure 1. Change of ankle brachial index: 6- and 12-month follow-up versus pre- and postprocedural baseline data (±SD). ABI significantly increased after the procedure without a relevant change after 6 months or 12 months. In diabetic patients with an ABI higher than 1.30, analysis was performed with 1.30.

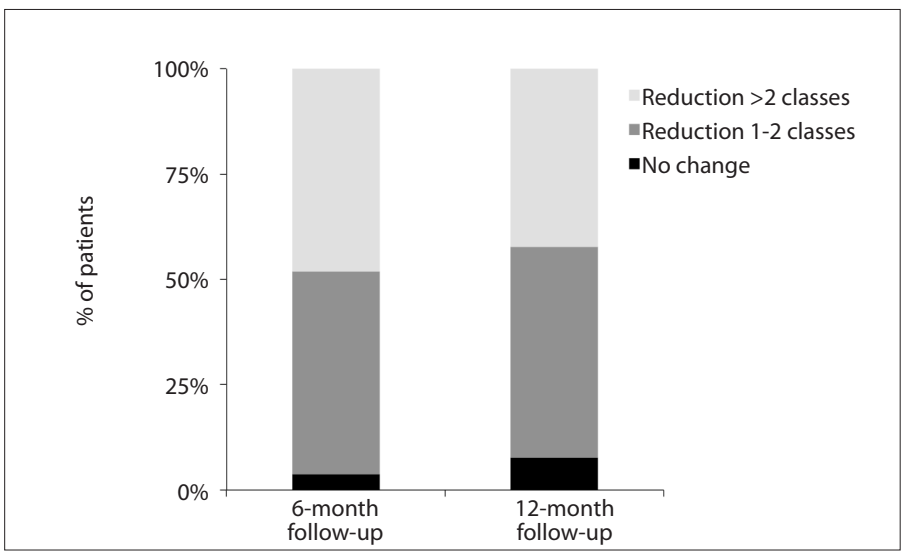

Figure 2. Change of Rutherford classification 6 months (n=26) and 12 months (n=25) after treatment. Rutherford classification did not improve in 3.7% of patients after 6 months and 7.7% of patients after 12 months. Improvement by 1-2 classes was detected in 48.2% and 50% of patients, by more than 2 classes in 48.1% and 42.3% of patients after 6 and 12 months, respectively. None of the patients showed worsening of Rutherford classification.

tion with plain-balloon angioplasty; however, lesion preparation might reduce rates of permanent implants.

Beneficial effects of DCB-angioplasty are highly related to the antiproliferative effects of paclitaxel and, therefore, to sufficient drug-delivery into the vascular lesion and the vascular wall, respectively. Correspondingly, effectiveness of DCB-angioplasty is suggested to be limited in highly calcified lesions. Thus, debulking strategies with directional atherectomy prior to DCB-treatment were demonstrated to further improve patency rates in recent trials (17). Irrespective of the high procedural costs with directional atherectomy, it is not clear whether beneficial effects are related to the decrease of plaque burden or increased efficacy of the DCB, or both. However, in an animal model, orbital atherectomy enhanced the vascular effects of paclitaxel in femoral artery stenosis (18). Moreover, severity of lesion calcification was significantly associated with the median late lumen loss after DCB-treatment in femoro-popliteal lesions, highlighting the importance of an adequate lesion preparation before using a DCB (19).

Plaque modification with a scoring-balloon was already demonstrated to be superior to PBA in short femoro-popliteal lesions and is suggested to be a sufficient technique in calcified lesions leading to a well-defined dissection of the intima without limiting blood flow (12, 20, 21). In our study, lesion preparation with the scoring-balloon was safe and efficient in short- and mid-stenosis. Moreover, calcification of the target lesion did not have an impact on technical success of the procedure. Subsequent DCB-treatment led to favorable results in those lesions without need for any target lesion revascularization after 6 or 12 months. These beneficial effects might be related to improved antiproliferative effect of the DCB following plaque modification with the scoring-balloon.

Our study had some limitations. First, the intention of the current trial was to evaluate safety and effectiveness of the combined treatment with a scoring-balloon and DCB in femoro-popliteal lesions. We did not include a control group as this was a proof of concept study. A DCB-angioplasty alone treatment arm might be the right comparator for the combination treatment, but a higher sample size is mandatory. Second, technical success rate was high with only three patients requiring bail-out-stenting. Nevertheless, spot-stenting was necessary in five patients, thus a total of eight patients underwent stenting for any purpose. However, in patients with flow-limiting dissections, spot stenting is an upcoming technique to fix the proximal entry of a dissection and to attach the dissection membrane. We think that those short stents preserve vascular and especially endothelial function within the target lesion. Third, lesion length in our study was about 60 mm, comparable to the LEVANT-II-trial, but shorter than the ones in the DEBATE-SFA or IN.PACT-SFA trials (5, 6, 8). Thus, interpretation of results from this pilot trial might be limited to shorter lesions and have to be confirmed in longer lesions, espe-

cially with regard to the longer lesion length in those patients with need for provisional stenting in our study.

In conclusion, in femoro-popliteal lesions, vessel preparation with a scoring-balloon prior to DCB-angioplasty was safe and effective in short and mid-lesions, with no influence of plaque calcification properties on technical success. This proof of concept might be the background for future multicenter trials.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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