Special Report

Interventional Cardiology

Drug-coated balloons in the treatment of femoro- and infra-popliteal lesions

Despite initially encouraging technical success after femoropopliteal percutaneous transluminal angioplasty (PTA), postprocedural restenosis remains the major challenge. Antiproliferative drugs applied via drug-coated balloons (DCBs) or drug-eluting stents suppress neointimal hyperplasia, the main cause of restenosis. The present article summarizes results of DCB treatments of femoropopliteal and infrapopliteal lesions and points out open questions. Major advantage of the DCB technology is leaving no stent scaffold behind and an immediate release of high drug concentrations. The superiority of DCB versus PTA was shown in several randomized clinical trials. Moreover, calcified lesions seem to impair the efficacy of DCB. Although mechanical abrasions have shown favorable periprocedural results, short and long-term impact is still controversial. Combinations of preceding debulking methods (atherectomy) with DCBs have shown promising results.

Keywords: atherectomy (AR) • critical limb ischemia • drug-coated balloon • femoropopliteal • paclitaxel • PAD • restenosis

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Characteristics of femoropopliteal lesions: limitations of established therapy options percutaneous transluminal angioplasty/stent

The treatment of femoropopliteal lesions displays a huge anatomic challenge since this segment serves various biomechanical functions. The superficial femoral artery (SFA) is beside to the aorta the longest artery in the human body with up to 30 cm length and underlies various biomechanical forces such as torsion, compression, flexion and extension by large muscular groups as well as shearing forces. These factors contribute to make endovascular treatment of femoropopliteal lesions especially challenging.

Despite high technical success rates, percutaneous transluminal angioplasty (PTA) for treatment of femoropopliteal stenosis results in restenosis rates of up to 58% in the first 6–12 months [1,2]. The expansion of the inflated balloon creates an injury in the vascular wall, which entails different biological processes. These can include immediate elastic recoil of the vessel wall and extensive intimal dissection as well as negative vascular remodeling and/or neointimal hyperplasia in the long term. Elastic recoil, dissection and, hence, the risk of early occlusion can be prevented by stenting. Stenting does not inhibit neointimal proliferation, which is supposed to be even stimulated by the stent struts. Neointimal hyperplasia arises from excessive extracellular matrix material synthesized by activated smooth muscle cells (SMC) in the media of the arteries [3]. Histologically, restenosis is an overshooting biological response resulting in loss of primary patency, late lumen loss (LLL), occlusion and/or the need for target lesion revascularization (TLR).

Besides balloon angioplasty (PTA), potential alternative treatment options of restenosis and in-stent restenosis (ISR) are atherectomy, laser-assisted PTA, brachytherapy, cutting or scoring balloon technique, cryoplasty and drug-eluting stents (DES) [4].

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Drug-coated balloon: principle of antiproliferation, different drug-coated balloon systems

Drug-coated balloons (DCBs) address the neointimal hyperplasia, the biological mechanism of restenosis formation, by local application of cytostatic agents in a local therapeutic concentration. Although various cytostatic substances are tried and tested, the antiproliferative taxane paclitaxel (PTX) seems to be right up to now the most effective therapeutic agent for DCBs due to local retention in the vascular wall resulting from its high lipophilic potential and a strong binding to hydrophobic cell constituents [5,6]. After a single application, PTX can still be detected with 3–5 ng/mg in swine SFA tissue at 28 days [7]. The underlying mechanism of PTX is the blocking of microtubule disassembly and therefore inhibition of cell division and, subsequently, inhibition of cell proliferation, cell migration and cellular ingrowth after angioplasty [8].

In vitro experiments displayed that human arterial SMC were more sensitive toward PTX than human arterial endothelial cells (EC) and up to 50-fold more sensitive than tumor cell lines. Therefore, low concentrations of PTX (<0.1 μmol/l) inhibited cell proliferation more in SMC than in EC while high concentrations of PTX displayed comparable effects on both cell types [8]. A single application of PTX (0.1–10 μmol/l) resulted in a complete inhibition of SMC proliferation and migration for more than 2 weeks, independent of the duration of application (continuous 24 h or bolus application for 20 min) [8]. PTX depositions at the vascular wall were associated with fibrin deposition, whereas rates of healing were dependent on drug concentration and particle size. This allowed faster re-endothelialization, while the active drug was still capable of preventing SMC proliferation [9].

The ability of PTX transfer from the balloon surface to the vessel tissue could be increased by hydrophilic carriers. Iopromide as a pharmacologically inert matrix enhanced release, dissolution and adherence of the lipophilic PTX to the vessel wall [10]. A single balloon inflation with a contact time of less than 1 min was sufficient to provide a sufficient PTX uptake into the vessel wall [11]. Animal experiments with overlapping DCBs showed that the minimal neointima formation was reached with a PTX dosage of 1–3 μg/mm^2 and could not be further reduced by increasing the PTX concentration [5]. From a standard PTX dosage (3 μg/mm^2), up to 20–30% permeated into the vessel wall, 10% remained at the balloon catheter and about 60% was lost into the blood stream. DCB use in swine coronary arteries revealed that maximum 200 μg of PTX was transferred into the vessel wall resulting in a concentration of 500 ng/mg arterial tis-

Table 1. Actual drug-coated balloon systems with CE mark for femoropopliteal lesions.

Name	CE mark	FDA approval	Company	PTX conc.	Excipient/coating
Advance®18 PTX	√		Cook Medical, IN, USA	3 μg/mm^2	None/COOK-specific coating
Cotavance®	√		Medrad, Bayer Healthcare, Berlin, Germany	3 μg/mm^2	Iopromide/Paccopath® technology
Elutax SV	√		Aachen Resonance, Aachen, Germany	2 μg/mm^2	Dextran/Snow&Ice&Sealing technology
Freeway™	√		Eurocor, Bonn, Germany	3 μg/mm^2	Shellac/Bioshell coating matrix
IN.PACT™ Admiral	√	√	Medtronic, Meerbusch, Germany	3.5 μg/mm^2	Urea/FreePac™ coating
IN.PACT™ Pacific	√		Medtronic, Meerbusch, Germany	3 μg/mm^2	Urea/FreePac™ coating
Legflow RX®/OTW®	√		Cardionovum, Bonn, Germany	3 μg/mm^2	Shellac/Cardionovum-specific coating
Lutonix™ DCB	√	√	C.R. BARD, NJ, USA	2 μg/mm^2	Polysorbate and sorbitol/Bard-specific coating
Ranger™	√		Boston Scientific, MA, USA	2 μg/mm^2	Citric acid ester/TransPax™ coating technology
Passeo-18 Lux	√		Biotronik SE, Berlin, Germany	3 μg/mm^2	Butyryl-tri-hexyl citrate (BTHC)/Biotronik-specific coating
Stellarex™ DCB	√		Spectranectrics, CO, USA	2 μg/mm^2	Polyethylene glycol/EnduraCoat™ technology

PTX: Paclitaxel.

sue at 40 min after intervention. Animal experiments in swine demonstrated that the biological half-life of PTX was 1–2 h. After 24 h, plasma concentration of PTX was out of measurement [10]. In porcine arterial tissue however, PTX concentration was 60 ng/mg at 1 h and 0.3 ng/mg at 30 days [9]. In DCB treatment of peripheral arteries, the maximum dosage per patient is 11.5 mg (11–17 mg) PTX per treated lesion [12]. In comparison, the recommended PTX dosage for tumor therapy is about 175 mg/m^2 body surface; systemic reactions to PTX (myelosuppression, peripheral neuropathy) are not expected at PTX concentrations less than 20 mg/m^2 [12].

Meanwhile, various PTX-DCBs with and without excipients (iopromide, urea, shellac, dextran, polysorbate and sorbitol, butyryl trihexyl citrate, citric acid ester, polyethylene glycol) and different coating technologies are available in Europe (CE marked) and recently with the US FDA approval in USA after providing level I scientific evidence (Table 1).

All actual DCBs with CE mark contain similar PTX concentrations of 2–3.5 µg PTX/mm^2. They differ in regard to drug homogeneity (PTX in crystalline aggregates, as hybrid crystalline or amorphous) and type of drug adherence to the balloon material. While a significant amount of drug coating will be lost during handling, insertion and delivery of the device, a minimal amount of particulate formation of PTX is desirable in order to avoid any downstream embolism. New technologies have been developed with the potential to reduce drug loss significantly while optimizing both deliverability and absorption of the drug in the targeted tissue. The complexities of the DCBs lie in their physical structural elements. The type of construct of the balloon and its material properties have significant effects upon how PTX and the excipient interact with the balloon and how well they transfer into the vessel wall. Also the excipient characteristics and the mixture of PTX and excipient are important for the drug retention at the wall. Finally, coating and unfolding principle of the balloon are important, whether it is open, closed, folded, not folded and whether it is inserted with a special loading tool or other features. All these aspects almost certainly make a difference of the available DCBs in performance and clinical characteristics [13].

Therefore not all DCBs are equal and their efficacy in inhibition of neointimal proliferation is different as demonstrated in various animal studies [10,14] and in an observational study from a large real-world population of 1129 patients treated with PTX-DCBs (Swedish Coronary and Angioplasty Registry [SCAAR/Swedeheart]) [15]. Most, but not all of the DCBs available in Europe are supported by solid data from prospective randomized trials. Long-term follow-up (FU), in the order of years, must be scrutinized in order to get a real sense of a device's efficacy. Comparing every DCB against all others would require thousands of patients for a sufficiently powerful study [16].

DCB in SFA: randomized clinical trials & registry reports

Early randomized clinical trials (RCTs) in the peripheral arteries showed that PTX-DCB angioplasty of femoropopliteal lesions was superior compared with standard uncoated PTA managing TASC IIA and IIB lesions (Table 2). The proportion of diabetic patients was less than 50% and the proportion of critical limb ischemia (CLI) mostly less than 10% apart from the drug-eluting balloon in peripheral intervention for in-stent restenosis (DEBATE ISR) study. Most of the lesions were *de novo* lesions (64–95%) with a mean lesion length of 57–89 mm.

In general, it is difficult to compare across trials because the patient populations may be materially different. In the RCTs, the demographic, peripheral vascular disease (PAD) and lesion characteristics were matched, but it can be argued of whether or not there are clinical differences in trial versus trial evaluation.

The first-generation PTX-DCB were coated with the Paccocath® technology and evaluated in the THUNDER RCT, in which 49 patients were treated with DCB system and compared with 54 patients treated by standard PTA (Table 2). The results for the DCB group were significantly superior: at 6 months, LLL (defined as the difference between the minimal luminal diameter after the procedure and at 6 months by quantitative angiography) was 0.4 mm in DCB versus 1.7 mm in PTA, restenosis rate (RR) was 17 versus 44% (defined as incidence of stenosis grade ≥50%) and TLR rate (defined as the need for repeated surgical or endovascular procedures at site of the previously treated lesion) was 10 versus 48% at 12 months and 15 versus 56% at 24 months, respectively [17]. In an additional analysis, it could be shown that high-grade, nonflow-limiting dissections did not negatively impact long-term outcome after PTX-coated balloon angioplasty [18]. Although the sample size was small for analysis of end points at 5-year FU (n = 22 vs 25), actual long-term result showed significant technical benefit regarding LLL of the DCB versus uncoated balloons persists over 5 years, resulting in a significantly lower TLR rate and a longer interval to reintervention in the PTX-DCB cohort. Additionally, this analysis has identified no signs of drug-related local vessel abnormality [19].

In the FemPac RCT, 45 patients were assigned for DCB group (Paccocath® technology) versus 42 patients for PTA group. At 6-month FU, angiography

Table 2. Femoropopliteal lesions – part I: clinical trials and registries of drug-coated balloon versus percutaneous transluminal angioplasty.

Femoropopliteal RCTs and registries I	**THUNDER Tepe *et al.* 2008 [17–19]**			**FemPac Werk *et al.* 2008 [20]**			**PACIFIER Werk *et al.* 2012 [21]**			**Advance PTX Scheinert *et al.* 2013 [22]**			**Italian Registry Micari 2013 [23,24]**	**IN.PACT long lesions Schmidt 2013 [25]**
DCB system	*Cotavance/ Paccocath®*			*Cotavance/ Paccocath®*			*IN.PACT™ Pacific*			*Advance® PTX®*			*IN.PACT™*	*IN.PACT™*
	DCB	**PTA**	**p-value**	**DCB**	**PTA**	**p-value**	**DCB**	**PTA**	**p-value**	**DCB**	**PTA**	**p-value**	**DCB**	**DCB**
Number of patients/ lesions	48	54		45	42		41	44		50	50		105	/288
Lesion lengths (mm)	75 ± 62	74 ± 65		57	61		70 ± 53	66 ± 55		102 ± 51	105 ± 50		76 ± 38	240 ± 101
de novo lesion type (%)	63	83		64	67		67	64		65	42		96	48
Total occlusions (%)	27	26		13	19		23	38					30	53
Calcified lesions (%)	50	52		53	52		64	66		37	37		67	
Severe calcification (%)													17	
Diabetic patients (%)	50	46		40	55		43	28					49	
PAD CLI patients (%)				4	7		4	4					8	
Bailout stenting (%)	4	22		9	14		21	34		28	30		12	23
FU 6 months														
LLL (mm)	0.4 ± 1.2	1.7 ± 1.8	<0.001	0.5 ± 1.1	1.0 ± 1.1	0.031	-0.01	0.65	01	0.9 ± 1.1	1.3 ± 1.2	0.12	0.6	
TLR (%)	4	37	<0.001	6.7	33	0.002	7.1	21.4	0.019					
Restenosis rate (%)	17	44	0.01				8.6	32.4	0.01					
Improvement in clinical outcome /RU			n.s.			0.045			n.s.					
Improvement in ABI			n.s.			n.s.								
FU ≥12 months														
TLR (%)	10	48	<0.001	7	17	n.s.	7.1	27.9	0.02				7.6	
PP (%)													84	77.6 (fem-pop) 82.4 SFA only
Restenosis rate (%)				17	40	n.s.								
Improvement in clinical outcome/RU (%)						n.s.								
Improvement in ABI														
FU ≥24 months														
TLR (%)	15	56	0.002				5.3	31.3	0.07				14.3	
PP													71	

ABI: Ancle brachial index; ADVANCE PTX: Advance® 18PTX® balloon catheter study: treatment of lesions in superficial femoral artery/popliteal artery with a paclitaxel-coated balloon; DCB: Drug-coated balloon; FemPac: Femoral paclitaxel-randomized pilot trial – inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated vs uncoated balloon; FU: Follow-up; LLL: Late lumen loss; mo: Months; n.s.: Not significant; PACIFIER: Paclitaxel-coated balloons reduce restenosis after femoropopliteal angioplasty trial; PAD CLI: Peripheral artery disease critical limb ischemia; PP: Primary patency rate; PTA: Percutaneous transluminal angioplasty; RU: Rutherford classification; SFA: Superficial femoral artery; THUNDER: Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg trial; TLR: Target lesion revascularization.

showed significantly less LLL and less clinical-driven TLR was necessary in DCB than in PTA group with 0.5 versus 1.0 mm and 6.7 versus 33%, respectively. Improvement in Rutherford classification (RU; defined as shift of ≥1) was significantly higher in DCB group [20] (Table 2).

The following generation PTX-DCB proved the encouraging results of the earlier RCTs. In the PACIFIER RCT, patients were assigned to IN.PACT™ Pacific or uncoated balloons (41 vs 44 patients). Angiographic results at 6 months displayed a significantly lower LLL in the DCB group (-0.01 vs 0.65 mm) and significantly

lower TLR and restenosis rate in DCB vs PTA of 7.1 versus 21.4% and of 8.6 versus 32.4%, respectively [21] (Table 2).

The Advance PTX RCT investigated the use of the Advance®PTX DCB versus standard PTA (50 vs 50 patients). At 6-month FU, there was no significant difference in LLL between the two groups [22].

The use of certain DCBs was documented in registries such as the Italian IN.PACT registry, where the data of 105 patients treated with IN.PACT DCB were exploited: at 6-month FU, an average LLL of 0.6 mm was registered, while TLR rate was 7.6 and 14.3% at 12 and 24 months and primary patency rate (PP) was 84 and 71%, respectively [23,24] (Table 2).

In the above-described trials and registries, mean lesions lengths were 57–89 mm. Looking at long lesions, there is not much evidence for DCB use up until now. In the IN.PACT Leipzig single-center registry for long lesions (240 ± 101 mm), 288 lesions (48% *de novo* lesions, 53% total occlusions) were treated with IN.PACT DCB resulting in a PP with of 77.6% at 12-month FU [25] (Table 2).

The superiority of DCB therapy in femoropopliteal arterial disease of the above-mentioned RCTs was shown in a meta-analysis. PTX-DCB therapy was associated with superior antirestenotic efficacy as compared with standard PTA with no evidence of a differential safety profile [26].

Meanwhile, data about the latest generation of DCB have been presented at international conferences, while results are going to be published (Table 3).

In the BIOLUX P1 RCT, 60 patients with femoropopliteal lesions were 1:1 randomly assigned to the Passeo-18 Lux DCB or to standard PTA. Angiographic results at 6 months displayed a significantly lower LL in the DCB group vs PTA (0.6 vs 1.1 mm) and significantly lower TLR rate of 11.5 versus 34.6% and of 27 versus 74% at 12 months, respectively. Improvement in RU and ABI was significantly higher after DCB use [27] (Table 3).

Also in the IN.PACT SFA I & II RCT, the superiority of the IN.PACT™Admiral DCB over standard PTA could be proven. In this trial, 220 patients were treated with DCB and 110 patients with PTA. At 12-month FU, TLR was significantly lower after DCB compared with PTA treatment (2.4 vs 20.6%). PP, defined as freedom from restenosis more than 50% of target lesion by duplex ultrasound based on peak systolic velocity ratio (PSVR) greater than 2.4 m/s at lesion site, was significantly better in DCB compared with PTA with 82.2 versus 52.4%. Clinical outcome and improvement in ABI at 12-month FU was significantly better in DCB than in PTA [28]. A subanalysis revealed that there was a difference in DCB effect on gender: females had less benefit from DCB than men (Table 3).

In the LEVANT I RCT, the Lutonix™DCB was used in 49 patients and compared with standard PTA in 44 patients. At 6 months, LLL was significantly lower for DCB than for PTA (0.46 vs 1.09 mm) [29].

In the LEVANT II RCT, 316 patients were treated with Lutonix™DCB and compared with 160 patients receiving PTA. At 12-month FU, PP was significantly better after DCB treatment with 65.2 versus 52.6%, while RU also improved significantly in the DCB group [30]. Concerning the DCB size recommended, a post hoc subgroup analysis suggested a minimum balloon–artery ratio of 1.04:1 for full wall apposition of the DCB facilitating drug delivery. Increased primary patency rates were reached in comparison to a balloon–artery ratio of 0.9 (Table 3) [30].

In the ILLUMENATE FIH RCT, the Stellarex™DCB was used in 50 patients with 58 *de novo* lesions (predilation subgroup). First results reported of a TLR rate of 10 and 14.2% and a PP rate of 89.5 and 80.3% at 12 and 24 months, respectively [31].

All data presented so far arouse from *de novo* lesions (64–100%). Special attention is given for the use of DCB in restenotic lesions and for ISR. The first two studies and one registry, which are dealing with DCB use in ISR, are listed in Table 4.

In the Italian ISR registry, 39 patients with femoropopliteal ISR were treated with IN.PACT DCB. Results for DCB treatment were impressive with PP of 92.1 and 70.3% at 12 and 24 months and TLR rate of 7.9 and 21.6% at 12 [32] and 24 months [33] compared to the results of uncoated balloons in the femoropopliteal ISR. In contrast, according to the severity of ISR before treatment (class I = focal, II = diffuse, III= totally occluded) standard PTA intervention revealed a TLR rate of 15.9, 18.8 and 64.4% at 24-month FU [34] (Table 4).

The DEBATE ISR RCT comprised diabetic patients (67–78% CLI) with femoropopliteal ISR (lesion length: 132 cm), who were treated either with IN.PACT DCB (n = 44) or PTA (n = 42). At 12-month FU, results were significantly superior for DCB: TLR rate was 13.6 versus 31% and restenosis rate 19.5 versus 71.8% [35,36].

Recently, data from FAIR RCT were presented at the LINC 2015. 119 patients with femoropopliteal ISR received either endovascular intervention with IN.PACT™Admiral DCB (n = 62) or with standard PTA (n = 57). Treatment of ISR with DCB was significantly superior to PTA at 6 months showing a PP of 44.7 versus 14.5% and, at 12 months, a TLR rate of 9.2 versus 47.2% and restenosis rate of 29.5 versus 62.5%, respectively [37] (Table 4).

Table 3. Femoropopliteal lesions – part II: clinical trials of drug-coated balloon versus percutaneous transluminal angioplasty and registries of drug-coated balloon use.

Femoropopliteal RCTs and registries II	**BIOLUX-PI Scheinert *et al.* 2015 [27]**			**IN.PACT SFA I & II Tepe *et al.* 2015 [28]**			**LEVANT I Scheinert *et al.* 2014 [29]**			**LEVANT II Rosenfield *et al.* 2015 [30]**			**ILLUMENATE FIH Schröder 2015 [31]**
DCB system	*Passeo-18 Lux*			*IN.PACT™ Admiral*			*Moxy/Lutonix®*			*Lutonix®*			*Stellarex™*
	DCB	**PTA**	**p-value**	**DCB**	**PTA**	**p-value**	**DCB**	**PTA**	**p-value**	**DCB**	**PTA**	**p-value**	**DCB**
Number of patients/ lesions	30	30		220	111		49	52		316	160		50/58
Lesion lengths (mm)	51 ± 47	68 ± 57	n.s.	89 ± 49	88 ± 51		81 ± 37	80 ± 37		63 ± 41	63 ± 40		72 ± 47
De novo lesion type (%)				95	95		90	88					100
Total occlusions (%)				26	20		41	42		21	22		12
Calcified lesions (%)										59.2	57.5		
Severe calcification (%)				8.1	6.2								
Diabetic patients (%)	37	30		41	49		45	50		43	42		34
PAD CLI patients (%)	20	13		5	5.4		6	7		7.9	8.1		2
Bailout stenting (%)	6.7	26.7	0.038	7.3	12.6		2.7	15.8		2.5	6.9		8.1
FU 6 months													
LLL (mm)	0.6 ± 0.7	1.1 ± 1.0	0.038				0.46	1.09	0.016				0.54
TLR (%)							13	22	n.s.				
Restenosis rate (%)	11.5	34.6	0.048										
Improvement in clinical outcome/RU							83	73					
Improvement in ABI			n.s.										
FU ≥ 12 months													
TLR (%)	16	52.9	0.020	2.4	20.6	<0.001	29	33		12.3	16.8		12.1
PP (%)				82.2	52.4					65.2	52.6	0.015	89.5
Restenosis rate (%)	27	74	<0.001										
Improvement in clinical outcome/RU (%)	Yes		0.06	85	69	<0.001	45	38		Yes		0.027	
Improvement in ABI	Yes		<0.001	Yes		0.002	42	38					
FU ≥ 24 months													
TLR (%)							36	51	0.23				14.2
PP													80.3

ABI: Ancle brachial index; BIOLUX-PI: First in man study to assess the safety and performance of the Passeo-18 lux paclitaxel releasing PTA balloon catheter vs the uncoated Passeo-18 balloon catheter in patients with stenosis and occlusion of the femoropopliteal arteries; DCB: Drug-coated balloon; FU: Follow-up; ILLUMENATE FIH: Study to evaluate treatment of obstructive superficial femoral artery or popliteal lesions with a novel paclitaxel-coated percutaneous angioplasty balloon; In.PACT SFA I&II: Randomized trial of IN.PACT Admiral™ drug-eluting balloon vs standard PTA for the treatment of SFA and proximal popliteal arterial disease; LEVANT I: Trial comparing the Lutonix catheter vs standard balloon angioplasty for treatment of femoropopliteal arteries with and without stenting; LEVANT II: Continuation registry of the Moxy drug-coated balloon for treatment of femoropopliteal arteries; LLL: Late lumen loss; mo: Months; n.s.: Not significant; PAD CLI: Peripheral artery disease critical limb ischemia; PP: Primary patency rate; PTA: Percutaneous transluminal angioplasty; RU: Rutherford classification; TLR: Target lesion revascularization.

In the COPA CABANA RCT, 88 patients with femoropopliteal ISR were treated with Cotavance®DCB (n = 47) or with standard balloon angioplasty (n = 41). At 6 months, LLL was significantly lower in the DCB group (0.3 vs 1.6 mm) [38].

A direct comparison of efficacy of DCBs in restenotic (n = 46) versus *de novo* lesions (n = 65) revealed that DCB treatment for femoropopliteal lesions showed significantly better performance in *de novo* stenosis or occlusions than in restenosis (PP: 93 vs 81% at 6 months and 85 vs 68% at 12 months, respectively) [39].

In all the trials and registries mentioned above, predilation with standard PTA balloon was performed before DCB use. In the ILLUMENATE FIH study, a subgroup analysis investigated the effect of predilation versus direct use of DCB (58 vs 37 lesions) on DCB

outcome. There were more severe calcified lesions and more total occlusions in the predilation cohort (13.8 vs 2.7% and 12.1 vs 5.4%, respectively). While at 6 months, LLL was less for the direct cohort (0.08% vs 0.54 mm) indicating a good drug effect, at 12 months, PP was superior in the predilation cohort (89.5 vs 77.5%). There was one amputation in the direct and none in the predilation cohort. The authors suggested that direct use of the DCB without predilatation may be optional in simple lesions [40].

There has been a debate about bias in TLR rates and bailout stenting rates between the test and the control groups in the early trials since the operators performing the actual procedure could not be blinded and were involved in the TLR decision in most of the cases. However, as a consequence, in the actual RCTs LEVANT 2 and IN.PACT SFA II, the trial design excludes these bias: investigators performing the actual procedure would not be involved in clinical decision-making thereafter [41]. IN.PACT SFA II RCT, the TLR decision was performed by an independent blinded core laboratory and blinded clinical events committee creating a situation close to being double blinded.

Ultimately, there are many trials and superior results for DCB use versus PTA in femoropopliteal lesions. DCBs are different and efficacies are different – up to now all of them are safe. There were no significant differences in distal embolization or amputation rates reported.

There are many different studies, but they all vary in end points, inclusion and exclusion criteria. Currently, there are no trials comparing one DCB against another and not enough prospective long-term data to state superiority of one DCB technology. Regarding the degree of calcification, in most of the above-mentioned studies severe calcified stenosis has been excluded. The combination of debulking and DCB use is described in the section 'atherectomy and DCB' in more detail.

DCB in below the knee: study reports

There are both a poor life expectancy and a poor prognosis of limb salvage in those patients with stenosis or occlusions of the lower limb (TASC Consensus). While in the femoropopliteal region, results of endovascular therapy depend on lesion length, grade of calcification and quality of outflow; in the below the knee (BTK) region, additional issues like tissue damage (CLI patients), angiosomal perfusion, ongoing infection as well as co-morbidities such as diabetes and dependency on hemodialysis are also of importance. Limb salvage and RU are the key criteria to evaluate the benefit of innovative treatment modalities in the BTK region. Limitations of the studies in BTK region were nonstandardized wound therapy and that DCB efficacy was not considered in terms of wound healing as an end point.

Recent RCTs and registries in the peripheral arteries for the region BTK are listed in Table 5. Demographic, PAD and lesion characteristics were matched. Nearly, all lesions (93–100%) were *de novo* lesions, while almost more than half or up to 100% of the patients were diabetics. In contrast to the femoropopliteal studies listed in the section 'DCB in SFA' (Tables 2, 3 & 4), the proportion of CLI patients was more than half or even 100%.

In the DEBELLUM RCT, 50 patients (≈36–52% diabetic, 36–40% CLI) with 75% femoropopliteal and 25% BTK lesions of 75 mm were 1:1 randomly assigned to be treated either with the IN.PACT™Amphirion DCB or with standard PTA. At 6-month FU, DCB treatment showed significantly superior data for LLL (0.5 vs 1.6 mm), for TLR (6.1 vs 23.6%) and for restenosis rate (9.1 vs 28.9%), respectively. At 12-month FU, TLR rate for DCB was significantly lower compared with PTA (10 vs 48%) [42] (Table 5).

In the DEBATE-BTK RCT, 65 versus 67 patients with long BTK lesions (130 mm) received treatment with the IN.PACT™Amphirion DCB or standard PTA. The occlusion rate was 77–82% with 100% diabetic and CLI patients. At 12-month FU, DCB treatment showed significantly superior data for TLR and restenose rates with 18 versus 43% and 27 versus 74%, respectively. Improvement in clinical outcome/RU and ABI was significant after DCB use [43] (Table 5).

The most recent study investigation for DCB in the BTK region was the IN.PACT DEEP RCT, in which 239 patients were treated with IN.PACT™Amphirion DCB and 119 patients with standard PTA. Most patients were diabetic (69–76%) and suffered from PAD with RU ≥ 4 (CLI stage). Clinical characteristics were similar between the two groups. Significant baseline differences between the DCB and PTA arms included mean lesion length, impaired inflow and previous target limb revascularization. Primary, nonsignificant efficacy results of DCB versus PTA were TLR of 9.2 versus 13.1% and LLL of 0.61 versus 0.62 mm. In patients with CLI, DCB had comparable efficacy to PTA. A safety parameter driven by major amputation rate at 12 months was observed in the DCB arm versus the PTA arm (8.8 vs 3.6%). While primary safety was met, there was a trend toward an increased major amputation rate at 12 months compared with PTA [44] (Table 5).

In summary, there are three RCTs using the IN.PACT™Amphirion DCB in BTK lesions displaying controversial results. The DEBELLUM and the DEBATE-BTK trial with 50 and 132 patients in a 1:1 design could show superior performance of the DCB.

Table 4. In-stent restenosis in femoropopliteal lesions: clinical trials of drug-coated balloon versus percutaneous transluminal angioplasty.

Fempop RCT/ registry	**Italian Registry Stabile *et al.* 2012 [32,33]**	**DEBATE ISR Liistro *et al.* 2014 [35,36]**			**FAIR Krankenberg 2015 [37]**			**COPA CABANA Tepe 2015 [38]**		
DCB system	*IN.PACT™*	*IN.PACT™ Admiral*			*IN.PACT™ Admiral*			*Cotavance®*		
	DCB	**DCB**	**PTA**	**p-value**	**DCB**	**PTA**	**p-value**	**DCB**	**PTA**	**p-value**
Number of patients	39	44	42		62	57		47	41	
Lesion lengths (mm)	83 ± 39	132 ± 86	137 ± 82		82 ± 71	82 ± 66		119 ± 96	109 ± 78	
Lesion type (%)	ISR	ISR	ISR		ISR	ISR		ISR	ISR	
Total occlusions (%)	20				24	33		18	35	
Diabetic patients (%)	49	100	100		45	30		43	46	
PAD CLI patients (%)		75	67		26	21		8	11	
Bailout stenting (%)	10.3	15.9	26.2							
FU 6 months										
LLL (mm)								0.3	1.6	<0.05
TLR (%)										
PP (%)										
Restenose rate (%)					15.4	44.7	0.002			
FU ≥ 12 months										
TLR (%)	7.9	13.6	31	0.045	9.2	47.4	<0.001			
PP (%)	92.1									
Restenosis rate (%)		19.5	71.8	<0.001	29.5	62.5	0.004			
Improvement in RU					Yes		n.s.			
Improvement in ABI					Yes		n.s.			
FU ≥ 24 months										
TLR (%)	21.6									
PP (%)	70.3									

ABI: Ancle brachial index; COBA CABANA trial: Cotavance™ paclitaxel-coated balloons vs uncoated balloon angioplasty for treatment of in-stent restenosis in SFA and the popliteal arteries; DCB: Drug-coated balloon; DEBATE ISR: Drug-eluting balloon in peripheral intervention for in-stent restenosis; FAIR: Drug-eluting balloon vs PTA for superficial femoral artery in-stent restenosis trial; FU: Follow-up; ISR: In-stent restenosis; mo: Months; n.s.: Not significant; PAD CLI: Peripheral artery disease critical limb ischemia; PP: Primary patency rate; PTA: Percutaneous transluminal angioplasty; RU: Rutherford classification; TLR: Target lesion revascularization.

In the INPACT DEEP trial 358 patients were enrolled in a DCB:PTA 2:1 design. Limb salvage was significantly better in the PTA control arm, which led to a withdrawal of the IN.PACT™Amphirion DCB from the market.

Recently, data from the Biolux P2 RCT were presented at the LINC 2014 [45]. 72 patients (61–72% diabetic) were assigned either to treatment with Passeo-18 Lux DCB or with PTA. PP and improvement of clinical outcome/RU were better after DCB treatment, but not significantly.

In the IN.PACT BTK registry, 104 patients (83% CLI) with a mean lesion length of 176 mm were prospectively collected. The early restenosis rate of long-segment infrapopliteal disease was significantly lower after treatment with DEB compared with historical data using uncoated balloons. At 12 months, clinical improvement was present in 91% and TLR was 17% [46] (Table 5).

There is an ongoing global trial on DCB in BKT looking at limb salvage and PP at 12-month FU (Lutonix BTK clinical trial) [47]. First single-center experience of the Lutonix™DCB in BTK was presented at the LINC 2015. 208 patients (69% diabetic, 82% CLI patients, 222 lesions) with mean lesion length of 242 ± 122 mm were treated (median FU time: 9 months). The rate for freedom from TLR was 89 and 77% and freedom from major amputations was 97 and 96% at 6 and 12 months, respectively [48].

At the moment, there seems to be a lack of level I evidence of DCB efficacy in BTK. Also drawbacks of pathological studies on DCBs are distal emboli, which is an important point for treating chronic limb ischemia patients [49]. Further research is needed here, also with new DCB-coating technologies with less drug loss, and necessarily, with defined wound care through wound managers and in cohorts that represent the real world.

Table 5. Lesions below the knee: clinical trials of drug-coated balloon versus percutaneous transluminal angioplasty and registries of drug-coated balloon use.

BTK RCTs/ registries	**DEBELLUM (75% ATK, 25% BTK) Fanelli *et al.* 2012 [42]**			**DEBATE-BTK Liistro *et al.* 2013 [43]**			**IN.PACT DEEP Zeller *et al.* 2014 [44]**			**BIOLUX-PII Brodmann 2015 [45]**			**IN.PACT BTK registry – Leipzig Schmidt *et al.* 2011 [46]**
DCB system	*IN.PACT™ Amphirion*			*IN.PACT™ Amphirion*			*IN.PACT™ Amphirion*			*Passeo-18 Lux*			*IN.PACT™*
	DCB	**PTA**	**p-value**	**DCB**	**PTA**	**p-value**	**DCB**	**PTA**	**p-value**	**DCB**	**PTA**	**p-value**	**DCB**
Number of patients	25	25		65	67		239	119		36	36		104
Lesion lengths (mm)	75 ± 35	74 ± 35		129 ± 83	131 ± 79		101 ± 91	129 ± 95	0.002	113 ± 88	115 ± 87		176 ± 88
De novo lesion type (%)	100	100		100	100		93	96					65
Total occlusions (%)	21	22		77	82		39	46					62
Calcified lesions (%)							75	78					
Severe calcification (%)							14	11					
Diabetic patients (%)	52	36		100	100		76	69		61	72		71
PAD CLI patients (%)	36	40		100	100		100	99					82
FU 6 months													
LLL (mm)	0.5 ± 1.4	1.6 ± 1.7	<0.01										
TLR (%)	6.1	23.6	0.02										
PP (%)										84.3	75.9	n.s.	
Restenosis rate (%)	9.1	28.9	0.03										
Improvement in clinical outcome/RU			0.04							59	47	n.s.	
Improvement in ABI			<0.05										
Major amputation rate (%)							8.8	3.6	0.080	3.3	5.7	n.s.	
FU ≥ 12 months													
LLL							0.6 ± 0.8	0.6 ± 0.8	n.s.				
TLR (%)	10	48	<0.001	18	43	0.002	9.2	13.1	n.s.				17
PP (%)													
Restenosis rate (%)				27	74	<0.001	41	36	n.s.				
Improvement in clinical outcome/RU (%)						0.06							Yes
Distal embolization (%)							2.8	0.6	n.s.				
Improvement in ABI				Yes		<0.001							
Major amputation rate (%)	4	12	n.s	0	1.5	n.s.	8.8	3.6	0.08				
FU ≥ 24 months													
TLR	15	52	<0.001										

ABI: Ancle brachial index; ATK: Above the knee; BIOLUX-PII: BIOTRONIK's – First in men study of the Passeo-18 Lux drug-releasing PTA balloon catheter vs the uncoated Passeo-18 Balloon catheter in subjects requiring revascularization of infrapopliteal arteries; BTK: Below the knee; DCB: Drug-coated balloon; DEBELLUM: Lower limb multilevel treatment with drug-eluting balloon trial; DEBATE-BTK: Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation trial; FU: Follow-up; LLL: Late lumen loss; INPACT-DEEP: Study of IN.PACT Amphirion™ drug-eluting balloon vs standard PTA for the treatment of below the knee critical limb ischemia; mo: Months; n.s.: Not significant; PAD CLI: Peripheral artery disease critical limb ischemia; PP: Primary patency rate; PTA: Percutaneous transluminal angioplasty; RU: Rutherford classification; TLR: Target lesion revascularization.

Table 6. Atherectomy in femoropopliteal regions: registries and clinical trials.

Name	PI	Design	AR device used	Patients/ lesions	Lesion type	Lesion length (mm)
	Zeller et al. 2006 [57]	DA	SilverHawk™	/43	100% *de novo*	131 ± 111
	Zeller et al. 2006 [57]	DA	SilverHawk™	/43	100% restenosis	131 ± 111
	Zeller et al. 2006 [57]	DA	SilverHawk™	/43	100% ISR	131 ± 111
TALON registry	*Ramaiah et al. 2006* [58]	DA ± PTA	SilverHawk™	601/	87% *de novo*	
	McKinsey et al. 2008 [59]	DA	SilverHawk™	275/		
	Trentmann et al. 2010 [60]	DA	SilverHawk™	33/	100% ISR	141 ± 81
	Sixt et al. 2010 [61]	DA + PTA	SilverHawk™	161/164	36% ISR	127 ± 126
	Minko et al. 2011 [62]	DA	SilverHawk™	38/42		75 ± 35
	Shammas et al. 2012 [63]	DA + PTA, 56% filter	SilverHawk™	41	100% ISR	126 ± 79
	Shammas et al. 2011 [64]	DA + PTA	SilverHawk™	29/		
	Shammas et al. 2011 [64]	PTA	-	29/		
DEFINITIVE-Ca	*Roberts et al. 2014* [65]	DA	SilverHawk™ TurboHawk™ SpiderFX	133/168	88% *de novo*	43 ± 31
DEFINITIVE-LE	*McKinsey et al. 2014* [66]	DA	SilverHawk™+22% SpiderFX	799/	92% *de novo*	74 ± 53
PATHWAY PVD	*Zeller et al. 2009* [67]	RA + PTA	Jetstream™	172/210	No ISR	274 ± 24
	Silingardi et al. 2010 [68]	RA + PTA	Rotarex®	32	100% ISR	160
	Sixt et al. 2011 [69]	RA	Jetstream™	172		
	Beschorner et al. 2013 [70]	RA ± PTA	Pathway PV™	33/44	100% ISR	86
LACI	*Laird et al. 2006* [71]	LA + PTA	Excimer Laser	145/155		110
	Stoner et al. 2007 [72]	LA + PTA	Excimer Laser	40/47		
CELLO	*Dave et al. 2009* [73]	LA + PTA	TURBO-Elite laser + TURBO-Booster®	65	100% *de novo*	56 ± 54
SALVAGE	*Laird et al. 2012* [74]	LA, PTA or coated stent	Excimer Laser	27	100% ISR	207 ± 103
PATENT	*Schmidt et al. 2014* [75]	LA + PTA	TURBO-Elite laser + TURBO-Booster®	90	100% ISR	123 ± 96
EXCITE ISR	*Dippel et al. 2014* [76]	LA + PTA	Excimer Laser 40% filter	169	100% ISR	196 ± 120
	Dippel et al. 2014 [76]	vs PTA	-	81	100% ISR	193 ± 119
CALCIUM 360	*Shammas et al. 2012* [77]	OA+PTA	DiamondBack 360®	27/29		
	Shammas et al. 2012 [77]	vs PTA	-	28/34		
OASIS	*Safian et al. 2009* [78]	OA ± PTA	DiamondBack 360®	124		
CONFIRM I & II	*Das et al. 2014* [79]	OA	DiamondBack 360®/Predator Stealth	733/1127/1275		72 ± 72
COMPLIANCE 360	*Dattilo et al. 2014* [80]	OA	DiamondBack 360®	/38	100% *de novo*	56 ± 54
	Dattilo et al. 2014 [80]	vs PTA	-	/27	100% *de novo*	87 ± 86
	Korabathina et al. 2010 [81]	OA ± PTA	DiamondBack 360®	98/118	81% *de novo*	
	Makam et al. 2013 [82]	OA + PTA	DiamondBack 360®	46/57		

AR: Atherectomy; ATK: Above the knee; BTK: Below the knee; CALCIUM 360: Comparison of orbital atherectomy plus balloon angioplasty vs balloon angioplasty alone in patients with critical limb ischemia trial; CELLO: CliRpath® excimer laser system to enlarge lumen openings trial; CLI: Critical limb ischemia, RU ≥ 4; COMPLIANCE 360: Comparing balloon angioplasty to Diamondback 360® orbital atherectomy system in calcified femoropopliteal disease trial; CONFIRM: Technique optimization of orbital atherectomy in calcified peripheral lesions of the lower extremities trial; DA: Directional atherectomy; DEFINITIVE-Ca: Study of the SilverHawk/TurboHawk plaque excision systems used with SpiderFX to treat calcified peripheral arterial disease; DEFINITIVE-LE: Determination of effectiveness of the SilverHawk peripheral plaque excision system (SilverHawk™ Device) for the treatment of infrainguinal vessels/lower extremities trial; EXCITE ISR: Excimer Laser randomized controlled study for treatment of femoropopliteal in-stent restenosis; Fempop: Femoropopliteal; ISR: In-stent restenosis; LA: Laser atherectomy; LACI: Limb salvage following laser-assisted angioplasty for critical limb ischemia trail; mo: Months; OA: Orbital atherectomy; OASIS: Orbital atherectomy system for the treatment of peripheral vascular stenosis; PATENT: Photoablation using the TURBO-booster and excimer laser for in-stent restenosis treatment trial; PATHWAY PVD: Percutaneous rotational atherectomy with aspiration in infringuinal peripheral arterial occlusive disease trail; PI: Principle investigator; PP: Primary patency rate; PTA: Percutaneous transluminal angioplasty; RA: Rotational atherectomy; RU: Rutherford classification; SALVAGE: Eximer Laser with adjunctive balloon angioplasty and heparin-coated self-expanding stent grafts for the treatment of femoropopliteal artery in-stent restenosis trial; TALON: Treating peripherals with SilverHawk: outcomes collection registry; TLR: Target lesion revascularization.

Region	CLI (%)	Total occl. (%)	Calcification (%)	Bailout stenting (%)	Embolization (%)	TLR 6 mo (%)	TLR 12 mo (%)	TLR 18 mo (%)	PP 6 mo (%)	PP 12 mo (%)	PP 24 mo (%)	Amputation (%)
Fempop							16	22		84		0
Fempop							44	56		54		2.3
Fempop							47	49		54		4.6
ATK & BTK	31	27	65	6.3	0.5		20					1.8
Fempop	27	21	37		3.8		5		95	78 (71)		
Fempop					11				68	25		
Fempop				6.8			38			61		
Fempop	63				7.8					69		13.2
Fempop	12.5			24.4	7.3		32					0
Fempop				27.6			11.7					
Fempop				62.1			16.7					
Fempop	16	10	52		2.3							
ATK + BTK	27	21	37		3.8		5		95	78 (71)		
Fempop		31	51		9.9	14.5	26					1.2
Fempop, iliacal	69				0				75	58		3.1
ATK + BTK				9.9			14.5					1.2
Fempop		20			6.1					33	25	
Fempop	100	92		45	3.2							6
Fempop	65			28			23			44		
Fempop	0	20	62	23					59	54		0
Fempop	74						17			48		
Fempop	7	34	39	2.2	10	12.2	35.5		64.1	37.8		0
Fempop	16		29	4.1	8.3	26.5						0
Fempop	12		9	11.1	4.9	48.2						2.3
ATK + BTK	100			6.9			6.7					
ATK + BTK	100			14.3			20					
BTK infrapop	32	12	55	2.5	0.8	5.6						0
ATK + BTK				5.7	2.2							
Fempop		21		5.3			18.8					
Fempop		18.5		77.8			21.7					
ATK + BTK	46			14.5	1							0
ATK + BTK					0		10.9					0

AR: Atherectomy; ATK: Above the knee; BTK: Below the knee; CALCIUM 360: Comparison of orbital atherectomy plus balloon angioplasty vs balloon angioplasty alone in patients with critical limb ischemia trial; CELLO: CliRpath® excimer laser system to enlarge lumen openings trial; CLI: Critical limb ischemia, RU ≥ 4; COMPLIANCE 360: Comparing balloon angioplasty to Diamondback 360® orbital atherectomy system in calcified femoropopliteal disease trial; CONFIRM: Technique optimization of orbital atherectomy in calcified peripheral lesions of the lower extremities trial; DA: Directional atherectomy; DEFINITIVE-Ca: Study of the SilverHawk/TurboHawk plaque excision systems used with SpiderFX to treat calcified peripheral arterial disease; DEFINITIVE-LE: Determination of effectiveness of the SilverHawk peripheral plaque excision system (SilverHawk™ Device) for the treatment of infrainguinal vessels/lower extremities trial; EXCITE ISR: Excimer Laser randomized controlled study for treatment of femoropopliteal in-stent restenosis; Fempop: Femoropopliteal; ISR: In-stent restenosis; LA: Laser atherectomy; LACI: Limb salvage following laser-assisted angioplasty for critical limb ischemia trail; mo: Months; OA: Orbital atherectomy; OASIS: Orbital atherectomy system for the treatment of peripheral vascular stenosis; PATENT: Photoablation using the TURBO-booster and excimer laser for in-stent restenosis treatment trial; PATHWAY PVD: Percutaneous rotational atherectomy with aspiration in infringuinal peripheral arterial occlusive disease trail; PI: Principle investigator; PP: Primary patency rate; PTA: Percutaneous transluminal angioplasty; RA: Rotational atherectomy; RU: Rutherford classification; SALVAGE: Eximer Laser with adjunctive balloon angioplasty and heparin-coated self-expanding stent grafts for the treatment of femoropopliteal artery in-stent restenosis trial; TALON: Treating peripherals with SilverHawk: outcomes collection registry; TLR: Target lesion revascularization.

However, the DCB concept for SFA may not be transferred as it is into the challenging BTK region – here other concepts of treatment might be necessary. Especially in this region, proper wound bed preparation seems to be important for DCB efficacy. A possible loss of balloon coating during insertion in sense of distal embolization might have a negative impact on amputation rates, a point, which is debated controversially.

De novo versus restenosis: different pathology?

While the role of DEBs in the treatment of PAD is well established in Europe, most lesions treated within the published studies and registries have been *de novo* stenosis, ranging from 63 to 100% in ATK and 65 to 100% in BTK studies (Table 2–5). Results demonstrated the effectiveness of DCBs in above the knee (ATK) lesions, whereas contradictory outcomes in safety and efficacy have been reported for BTK lesions.

Assessments of the efficacy of PTX-DEB in restenotic (stented and nonstented) versus *de novo* stenotic femoropopliteal arteries revealed that the results for DCB are significantly better after treatment of *de novo* compared with restenotic lesions [39]. The different results between *de novo* and restenotic lesions could be due to different efficacies of PTX distribution. Several animal studies demonstrated that PTX reaches the target, the SMC layer despite intimal plaque in *de novo* stenotic vessels [8,50]. In restenotic lesions, a vascular injury is seen following vessel dilation and/or after stenting that creates a stimulus for subsequent repair mechanism and stimulates the mitotic cell cycle. SMC convert from the contractile phenotype to a dedifferentiated synthetic phenotype starting to secrete extracellular matrix components. Restenosis occurs when this proinflammatory regenerative process is not counterbalanced by appropriate stimuli for matrix-degrading enzymes. The composition of the extracellular matrix components changes from a provisional fibrin-rich to a permanent matrix. These changes are accompanied by a reduced SMC density [51]. The innermost vessel layer forming the restenosis consists mainly of noncellular material. The cytotoxic effect of the PTX may not be able to reach the cellular layer [52]. Atherectomy can remove these inner layers enabling the PTX to reach the target cells.

Debulking: different principles used & study reports

While PTA modifies the obstruction in the lesions by a disruptive stretching process, atherectomy has the potential to remove the lesion material. Different principles are used for the percutaneous excision. Directional atherectomy (DA) the excision of atherosclerotic plaque with a cutting device in the longitudinal plane. Tiny rotation blades shave the plaque from the insight of the vessel lumen, while excised tissue is captured in the tip of the device (SilverHawk™ and TurboHawk™, Covidien, Dublin, Ireland) [53,54]. The combination of optical coherence tomography (OCT) imaging with a directional atherectomy system (Pantheris System, Avinger, CA, USA) for use in the peripheral vasculature is currently investigated in a prospective, global clinical trial (VISION).

Rotational aspiration/atherectomy (RA) devices work with a high-speed-rotating cutting blade covered with abrasive material, which is cutting differentially upon the atheroma layers. While saline solution can be injected, the atherosclerotic material is aspirated into the tip and removed through ports into the lumen of the catheter (Jetstream; Bayer Pathway PV system, Pathway Medical Technologies, WA, USA; Phoenix atherectomy catheter, AtheroMed, CA, USA) [53,54]. Orbital atherectomy (OA) employs a rotational device with an eccentric, diamond-grit-coated abrasive crown to remove circumferential plaque within the vessel outline [55]. Available orbital atherectomy device is the CSI Diamondback Orbital atherectomy system (OAS, Cardiovascular Systems, Inc., MN, USA) [54]. Excimer laser atherectomy (LA) removes atherosclerotic plaque by photoablation (atheroablation) with a laser. The device consists of a fiber-optic catheter (in various sizes) attached to a console (Turbo-Booster/Turbo-Elite laser catheter, Spectranetics, CO, USA) [53,54].

Various debulking devices are available with good procedural results. While data from randomized clinical trials are lacking, the evidences from multicenter prospective registries of debulking with/without PTA are summarized in Table 6.

Mechanical atherectomy may be associated with a risk of peripheral embolization. Embolic protection devices have been used successfully and their use is considered as reasonable strategy to avoid distal thromboembolism.

None of the so far published trials evaluated any remarkable safety issue; however, it has to be stated that for the ultimate application in ISR, the application of DA and RA is off-label use and not approved for ISR treatment [83].

Currently, there are four FDA-approved atherectomy devices on the market; however, there are no RCT data regarding their comparative efficacy and safety. Most of the published evidence supporting their use consists of single-arm observational studies or case series. As a result, the available data do not support the use of atherectomy alone. Registry data of CLI patients undergoing endovascular tibial interventions revealed that the adjunctive use of different

atherectomy measures (n = 68) offered no improvement in primary outcomes over PTA alone (n = 333) at 12 and 36 months [84].

However, despite favorable acute periprocedural results, mechanical atherectomy seems to be limited by low patency rate and the long-term benefit in relation to restenosis and clinical outcomes is still controversial. Additional randomized controlled studies are warranted to establish the efficacy and cost–effectiveness of the various atherectomy techniques, and to define their role in contemporary endovascular practice.

Since debulking is traumatic to the vessel wall, an inflammatory response will occur triggered by an eruption of the elastic lamina, which has to be avoided. Therefore, atherectomy as a stand-alone therapy does not appear to be sufficient – a combination with DCBs seems to be promising.

Atherectomy & DCB: study reports

The rationale behind combining atherectomy and DCB is that removal of plaque facilitates the local delivery of the antiproliferative drug and might therefore optimize the drug delivery to the vessel wall.

The assessment of the calcium burden and its impact on drug-eluting balloons was investigated in a study with 60 patients and calcified lesions. Results showed that calcium had a proportional impact on restenosis formation: DCB effect was lower in patients with higher degree of calcium. Calcium seems to be a predictor of decreased efficacy of DCB. While the length of the calcified stenosis was less relevant, localization of the calcium was of major importance: a greater impact could be observed in circumferential versus longitudinal distribution [85].

Table 7 shows the outcomes of several registries and studies combining AR with DCB.

Table 7. Atherectomy and drug-coated balloon in femoropopliteal lesions: clinical trials and registries of atherectomy + drug-coated balloon versus drug-coated balloon alone or versus atherectomy + percutaneous transluminal angioplasty.

AR + DCB registries/RCTs	**van den Berg *et al.* 2012 [85]**	**Cioppa *et al.* 2012 [86]**	**Sixt *et al.* 2013 [87]**			**Gandindi *et al.* 2013 [88]**			**DEFINITIVE-AR Tepe 2015 [89]**		
Study design, AR/DCB devices used	*LA + DCB, Excimer laser + IN.PACT™ Amphirion*	*DA + DCB*	*DA + DCB vs DA + PTA, SilverHawk™*			*LA + DCB vs DCB alone, TurboElite Laser, Freeway DCB®*			*DA + DCB vs DCB alone SilverHawk™/TurboHawk™ Cotavance® DCB*		
Parameter	**LA + DCB**	**DA + DCB**	**DA + DCB**	**DA + PTA**	**p-value**	**LA + DCB**	**DCB**	**p-value**	**DA + DCB**	**DCB**	**p-value**
Number of patients	10	30	29	60		24	24		48	54	
Lesion lengths (mm)	115	115 ± 35	153 ± 93	180 ± 136		200 ± 101	233 ± 91		113	97	0.05
Lesion type (%)	100% ISR	100% *de novo*	93% ISR	60% ISR		100% ISR	100% ISR				
Total occlusions (%)		13									
Severe calcified SFA (%)						25	42		25	19	
PAD CLI patients (%)	50	94	42	17		100	100				
FU 6 months											
TLR (%)	0										
PP (%)	70					91.7	58.3	0.01			
FU ≥ 12 months											
TLR (%)		10				16.7	50.0		7.0	7.8	n.s.
PP (%)	50		84.7	43.8		66.7	37.5	0.01	82.4	71.8	n.s.
Restenosis rate (%)			15.3	56.2	0.004				33.6	36.4	n.s.
Distal embolization			5	7		1	2		3	0	n.s.
Limb salvage rate (%)		100				92	54	0.001	100	100	
Ulcer healing (%)						87	62	0.03			
Amputation rate (%)		0				8	47	0.001	0	0	

AR: Atherectomy; DA: Directional atherectomy; DCB: Drug-coated balloon; DEFINITIVE-AR: Study of the SilverHawk/TurboHawk plaque excision systems used with SpiderFX to treat calcified peripheral arterial disease; ISR: In-stent restenosis; LA: Laser atherectomy; mo: Months; PAD CLI: Peripheral artery disease critical limb ischemia; PP: Primary patency rate; PTA: Percutaneous transluminal angioplasty; RCT: Randomized controlled trial; TLR: Target lesion revascularization.

Earlier registries using AR and DCB reported about primary patency rates of 90% with LA + DCB in 10 patients [86] or TLR rate of 10% with DA + DCB at 1-year FU in 30 patients [87]. The first comparison of DA + DCB versus DA standard balloon (29 vs 60 patients) revealed a significant superior restenosis rate for DA + DCB (15.3 vs 56.2%) at 1 year [88]. Also in femoropopliteal ISR lesions, the use of laser atherectomy plus DCB (n = 24) versus DCB alone (n = 24) showed convincing TLR results (16.7 vs 50%) at 1-year FU [89].

In the DEFINITIVE-AR RCT, 102 patients with moderate calcified lesions were treated with DA + DCB (n = 48, directional atherectomy + antirestenotic therapy = DAART group) and compared with 54 patients with DCB treatment only. In the DAART group, technical success was higher and the incidence of flow-limiting dissection lower than in the DCB only group. At 12 months, PP and restenosis rates were better in the DAART group, but without statistical significance. The DAART resulted in a significant larger minimum lumen diameter compared with the DCB only group (4.37 vs 3.8 mm). Additionally, a group of patients with severely calcified lesions (n = 19) were also treated with DAART. Results suggested trends favoring DAART in lesions ≥10 cm and in severely calcified lesions [90].

Other trials like the ADCAT [91] are currently investigating the performance of atherectomy followed by a DCB angioplasty over DCB angioplasty alone will be compared in long *de novo* lesions.

Conclusion & future perspective

A novel concept for drug delivery was exhibited recently in form of the Bullfrog® Micro-Infusion device (Mercator Medsystems, CA, USA), a catheter-guided system designed to infuse directly and nonsystemically therapeutic agents through the blood vessel wall into deep tissues. Currently, clinical trials (DANCE trial [92], LIMBO trial [93]) investigate the infusion of anti-inflammatory drugs like dexamethasone to the adventitia to enhance clinical efficacy after femoropopliteal revascularization and to intervene with the vessel response at an earlier stage.

An alternative method, the treatment of calcified lesions, was presented lately at the LINK [94]. The Shockwave Lithoplasty™ concept is based on lithotripsy shock waves which travel outside a low-pressure balloon and disrupt deep, superficial calcium prior to low-pressure dilation to reference vessel diameter. In the DISRUPT PAD safety and performance study, 35 patients (39 lesions) with RU 2–3 (97%) and moderate (36%) to severe (64%) calcified lesions (mean length: 80 ± 38 mm) of infrainguinal peripheral arteries were treated. Primary end point was defined as residual diameter stenosis of less than 50%. Preliminary results showed that it was reached in all lesions, while the average residual diameter of stenosis was 23%. At 30 days, patency was 100% and the average peak velocity ratios (PSVR) decreased from 1.40 to 1.21, which might hint at a positive remodeling effect [94].

Although improved stent designs are beginning to have an impact on PAD, interventional treatments designed for femoropopliteal PAD are required to withstand certain biomechanical factors that are currently only met by DCBs. Unlike DES, the local delivery of PTX loaded on a balloon has the advantage, of not having a permanent implant left behind that can provoke inflammation resulting in overshooting neointimal proliferation, late catch-up, and restenosis [49].

Looking at the cost economic value of DCB on the basis of the IN.PACT SFA RCT, the clinically driven TLR at 12 months was significantly lower in the DCB group versus PTA (2.4 vs 20.6%). Interim cost analysis stated that the index hospitalization cost was approximately $1000 per patient higher in patients treated with DCB – driven primarily by the costs of the DCB itself. The incremental cost–effectiveness ratio for the DCB was apprapproximately $2.910 per repeat revascularization avoided [95]. Analysis of a simplified decision-analytic model also revealed that use of DEBs may be cost-effective through prevention of TLR at 1 year of FU [96].

Executive summary

- In conclusion, drug-coated balloons (DCB) stand-alone therapy gives excellent results in TASC IIA and IIB lesions. However, the drug-eluting balloon concept does not overcome the early failure modes of percutaneous transluminal angioplasty, such as recoil and dissection.
- Since calcium seems to be a predictor of decreased efficacy of DCB, modern recanalization tools and techniques make endovascular therapy feasible for TASC IIC and IID lesions [56].
- Highly complex superficial femoral artery lesions need lesion and patient-tailored approaches that take into account the RU, lesion location, lesion length, grade of calcification and patients co-morbidities and renal function. These tailored approaches will for certain include plaque modulation and debulking techniques such as laser or atherectomy, DCBs and nitinol stents as part of the treatment concept.

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