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Drug-Coated Balloons: How Should We Incorporate Into Our Practice in Treating Superficial Femoral Artery Lesions?

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Opinion statement

Drug-coated balloons (DCBs) provide a novel method to locally deliver paclitaxel into the arterial wall without the need of a chronically implanted delivery system. Following the first positive pilot studies, two large pivotal trials have confirmed superiority of DCBs over plain old balloon angioplasty (POBA) in the treatment of TASC II A and B femoro-popliteal lesions. Even for more complex femoro-popliteal lesions such as long lesions and in-stent restenosis, single-center studies and small randomized studies have shown promising mid-term technical and clinical results. This review article summarizes the current knowledge about DCBs in femoro-popliteal interventions, supplements published guidelines with evidence-based recommendations, and discusses still unresolved needs.

Introduction

Despite an initial technical success rate of more than 95 % for percutaneous transluminal angioplasty to recanalize the femoro-popliteal artery using dedicated crossing and re-entry devices [1, 2], recanalization

procedures are limited by restenosis rates of 20 to 65 % of the treated segments after 6 to 12 months [3, 4]. Recently published and presented studies investigating drug-coated balloons (DCBs) have shown a substantial improvement of durability of endovascular treatment [5–10, 11••]. However, DCBs basically have the same limitations as plain old balloon angioplasty (POBA), specifically acute recoil including undilatable calcified lesions and severe dissections requiring provisional bare metal stenting [7, 12•, 13, 14•].

Moreover, current drug coatings are still imperfect with regard to drug persistence on top of the balloon catheter during DCB insertion into and through the sheath and target lesion as well as during balloon expansion. As a result, (1) the endovascular specialist is potentially exposed to the antiproliferative drug, currently exclusively paclitaxel, which potentially can be inhaled in an uncertain dose, and (2) there is a downstream drug distribution into tissue distal to the lesion location with uncertain consequences (e.g., effects on wounds in critical limb ischemia (CLI) [15••]). Currently, only 10 to 20 % of the active drug is transferred into the vessel wall [16, 17].

Appropriate drug coating of a balloon catheter surface is not trivial. On the one hand, due to its lipophilic nature, paclitaxel does not penetrate into the vessel wall sufficiently without a co-drug, a so called spacer or excipient. On the other hand, (1) both drugs have to be fixed effectively on top of the balloon surface in order to avoid significant drug loss prior to balloon expansion, and (2) sufficient drug release into the vessel wall during balloon expansion has to be guaranteed. In both terms, current DCB coatings are still imperfect. Whereas crystalline coatings result in a higher vessel wall persistence and, as a result, in a more effective suppression of neointima hyperproliferation, amorphous coatings are more stable on the surface of the balloon catheter with a significant lower loss of drug during balloon insertion into and through the sheath (Table 1).

Currently, researchers are investigating hundreds of potential exipients in order to optimize drug transfer into the vessel wall as well as drug persistence in the vessel wall in order to optimize the biological efficacy of DCBs and to potentially reduce the dose of the antiproliferative drug. Tests with alternative antiproliferative drugs besides paclitaxel such as limus substances (e.g., sirolimus and everolimus) did not yet result in a sufficient biological efficacy due to insufficient drug persistence in the vessel wall.

Nevertheless, two large pivotal randomized controlled trials (RCTs)—LEVANT 2 and INPACT SFA [11••]—have recently confirmed the initial positive results of pilot studies investigating different drug coatings in the treatment of femoro-popliteal artery lesions [5–10].

Treatment

DCBs for de novo and restenotic femoro-popliteal artery disease (TASC II A and B lesions)

Several first-in-man randomized trials and registries using first-generation DCBs in de novo and restenotic femoro-popliteal lesions excluding in-stent restenosis (ISR) have shown favorable technical outcomes in terms of late lumen loss (LLL), restenosis rate, and freedom from target lesion revascularization (TLR) as compared to POBA (Table 2) [5–10].

A meta-analysis relying on data available from some of these trials had TLR as primary endpoint, whereas secondary endpoints were angiographic binary restenosis, LLL, and all-cause mortality. A total of 381 patients were included (DCBs, n=186, vs. POBA, n=195) with a median follow-up of 10.3 months. DCB angioplasty reduced TLR rate (12.2 vs. 27.7 %; p<0.00001), angiographic restenosis rate (18.7 vs. 45.5 %; p<0.0001), and 6-month LLL (–0.05 to 0.50 mm vs. 0.61–1.7 mm; mean difference –0.75 mm; p<0.00001). No mortality difference was observed between DCBs and POBA [18].

In a recent subgroup analysis of the THUNDER trial, dissections did not negatively impact the benefit of DCB angioplasty if left alone without stent placement. At the 6-month follow-up, patients with dissection of any grade

Table 1. Differences in coating properties between crystalline and amorphous DCB coatings (according to J. Granada, TCT Washington 2012)

	Crystalline	Amorphous
Particles released	+++	++
Uniform coating	++	+++
Drug transfer to vessel	+++	++
Drug retention versus time	+++	+
Biological effectiveness	+++	++

after treatment with DCBs had significantly lower LLL than patients with dissection after POBA. In particular, patients with severe dissections (grade C–E) seemed to benefit from DCB treatment. Up to the 2-year follow-up TLR was performed in 56 % of patients in the control group compared to 10 % of patients in the DCB group (p=0.002) [19]. Patients of the THUNDER study were followed for 5 years. Over this study period, the cumulative number of patients with TLR was distinctly lower in the DCB group (21 vs. 56 %, p=0.0005) excluding a clinically significant late catch-up phenomenon after DCB angioplasty [20].

Currently, two large-scale international US IDE trials are still ongoing in their long-term follow-up phase up to 5 years; however, 1-year data had been published [11••] or presented during 2014 (LEVANT 2, K. Rosenfield, TCT 2014). Both studies enrolled patients with de novo femoro-popliteal TASC II A and B lesions with a 2:1 randomization between DCB and POBA, the IN.PACT SFA II trial enrolled a total of 331 patients, and the LEVANT 2 trial—the largest DCB trial to date—enrolled a total of 543 patients. Both RCTs are supplemented by large-scale single-arm registries enrolling respectively 1500 (INPACT global) and 650 patients (LEVANT registry).

The pooled randomized multicenter IN.PACT SFA I and II trials [11••] revealed that clinically driven TLR rates were significantly lower with the DCBs as compared to those achieved with angioplasty (2.4 vs. 20.6 %, p<0.001). Similarly, the primary patency rate achieved with IN.PACT Admiral balloons was 82.2 %, while the primary patency achieved with POBA was 52.5 % (p<0.001). Primary patency at 360 days calculated by Kaplan-Meier survival estimates was 89.8 % for the DCB group and 66.8 % for the POBA group.

In the LEVANT 2 trial which incorporated a “blinded follow-up” in contrast to previous trials, the primary patency at 1 year was 65.2 % for the DCB which was superior to that for POBA (52.6 %, p=0.015). Freedom from clinically driven TLR in the DCB group was 87.7 % compared to 83.2 % in the control group (p=0.208). It is uncertain why the difference in clinically driven TLR rate was smaller as compared to the patency rate; one potential explanation is that not each 50 % restenosis is resulting in clinically significant symptoms.

In both studies, no device-specific side effects were reported, and no major amputation occurred. Thus, there was no safety concern regarding wash off of a part of the antiproliferative drug into the distal vasculature. However, are both of the studies comparable? In brief, both studies enrolled only claudicants with femoro-popliteal lesions; lesions in the LEVANT 2 trial were slightly less challenging as compared to the IN.PACT SFA trial. Unlike to prior femoro-popliteal

Table 2. Currently published or presented femoro-popliteal DCB trials with their main baseline characteristics and primary endpoints [6-month late lumen loss (LLL), 1-year target lesion revascularization (TLR rate), 1-year primary patency (PP) rate]

	THUNDER [5]	FEMPAC [6]	LEVANT 1 [8]	PACIFIER [7]	BIOLUX P I [9]	ADVANCE PTX[a]	ILLUMINATE FIH[b]	IN.PACT SFA [11••]	LEVANT 2[c]
Balloon	Paccocath	Paccocath	Lutonix 35	In.Pact Pacific	Passeo 18 Lux	Advance 18 PTX	Stellarex	In.Pact Admiral	Lutonix 35
PTX dose ($\mu g/mm^2$)	3	3	2	3	3	3	2	3	2
Coating spacer	Ultravist	Ultravist	Polysorbate and sorbitol	Urea	BTHC (Butyryl-tri-hexyl Citrate)	None	unknown	Urea	Polysorbate and sorbitol
No. of patients	154	87	101	91	68	150	50	331	543
Lesion length (cm)	7.5	6.0	8.1	6.8	6.1	10.0	7.2	8.9	6.3
Occlusions (%)	27	15	40	30.8	38	37	12.1	25.8	21
Stent rate PTX versus control (%)	4/22	9/14	25/27	21/34	7/27	28/30	5.2/n.a.	7.3/12.6	2.5/6.9
LLL PTX (mm)	0.40	0.50	0.46	–0.01	0.50	0.90	0.54	na	na
LLL control (mm)	1.70	1.00	1.09	0.65	1.00	1.30	na	na	na
p value	<0.001	0.031	0.016	0.001	0.033	0.12	na	na	na
PP PTX (%)	na	na	na	na	na	na	na	82.2	65.2
PP control (%)	na	na	na	na	na	na	na	52.4	52.6
p value	na	na	na	na	na	na	na	<0.001	0.015
TLR PTX (%)	10	6.7	29	7.1	15.4	na	12.1	2.4	12.3
TLR control (%)	48	33.3	33	27.9	41.2	na	na	20.6	16.8
p value	<0.001	0.002	n.s.	0.02	0.064	na	na	<0.001	0.208

[a]D. Scheinert – LINC 2013 oral presentation
[b]S. Duda – EuroPCR 2014 oral presentation
[c]K. Rosenfield, TCT 2014 oral presentation
na not available, *n.s.* not significant

premarket approval studies, bailout stenting was not counted as a failure in both trials. Table 3 compares the main lesion criteria and outcomes.

Whether blinding did affect the indication for a redo procedure with regard to driving the TLR rate in the control group is still a matter of debate. On the first glance, differences in DCB performance regarding primary patency and freedom from clinically driven TLR seem to be attributed to the different coating technologies even if recent post hoc analyses seem to link inferior DCB outcomes in the LEVANT 2 study to undersizing of the DCB. Already, preclinical animal studies have shown that not each coating technique is equally effective. However, only a direct comparison of both DCB technologies could finally answer this question.

The major message of the both peripheral interventional landmark trials is that a DCB-based treatment approach for TASC II A and B femoro-popliteal lesions achieves superior technical and clinical 1-year outcomes compared to POBA, which is still considered the primary approach to treat easy de novo femoro-popliteal lesions in the international guidelines. DCBs are not yet classified in international guidelines because relevant data had not yet been published when literature research was performed for currenly available guidelines [21•].

According to usual international definitions, the use of DCB in femoro-popliteal TASC IIA and B de novo and restenotic lesions would qualify as a level of recommendation class I and a level of evidence class A. However, when comparing different drug-based technologies such as drug eluting stent (DES), longer-term follow-up will be needed. The recent presentation by Dr. Michael Dake (VIVA 2014, Las Vegas) of the 5-year drug eluting stent results demonstrated significant stability of patency and that DCBs will need to meet a similar benchmark. Also, of note, not every DCB is alike; each single DCB deserves its own clinical efficacy and safety studies.

DCB for long femoro-popliteal artery disease (TASC II C and D lesions)

Two single-center registries evaluating the performance of IN.PACT Admiral DCBs in the treatment of long femoro-popliteal lesions were either published [22] or presented (Schmidt LINC 2014, Leipzig). In the Leipzig registry, 260 patients treated with femoro-popliteal lesions and a mean lesion length of 24 cm were followed for 1 year. Provisional stent rate was 23.3 % and 1-year duplex-based primary patency rate for the entire cohort was 77.6 % (SFA only 82.4 % and ISR 85.2 %). The Bad Krozingen study enrolled 228 patients with femoro-popliteal lesions longer than 10 cm (mean lesion length of 19 cm).

Table 3. Key lesion characteristics and 1-year outcomes of the IN.PACT SFA and Levant 2 studies

	IN.PACT SFA	Levant 2
Mean lesion length	89 mm	63 mm
Total occlusions	25.8 %	21 %
1-year primary patency control group	52.45 %	52.6 %
1-year primary patency DCB group	82.2 %	65.2 %
1-year freedom from TLR	79.4 %	83.2 %

DCB drug-coated balloon, *TLR* target lesion revascularization

Patients were treated with either DCB or Zilver PTX DES (Cook Medical, Bloomington, IN, USA), and outcomes were compared with use of a propensity score based statistical analysis. Provisional stent rate in the DCB cohort was 18.3 %. At 1 year, there was no significant difference between IN.PACT DCB and Zilver PTX DES in terms of primary patency (76.1 vs. 69.9 %) and freedom from TLR [22].

According to the international definitions, the use of DCB in femoropopliteal TASC II C and D lesions would qualify as a level of recommendation class III and a level of evidence class C. Larger-scale international RCTs will be needed.

DCBs for *in-stent restenotic* femoro-popliteal artery disease

In-stent restenosis (ISR) has been reported to occur in up to 40 % of femoropopliteal lesions treated with BMS within 1 year [23, 24]. Moreover, the risk of ISR increases with increasing lesion length. The treatment of ISR in the femoropopliteal artery is one of the major remaining challenges of endovascular therapy because treatment modalities such as POBA and cutting balloon angioplasty have failed to provide durable results [25]. A single-center prospective registry, including 39 patients, reported a 1- and 2-year primary patency rate of 92.1 % [26] and 70.3 % [27] following DCB angioplasty of ISR, respectively.

Just recently, the data of the randomized controlled multicenter FAIR (DCB vs. PTA for superficial Femoral Artery In-stent Restenosis) trial was presented (Krankenberg, LINC 2014, Leipzig). This study included 119 patients with ISR 1–20 cm in length and a mean lesion length of 8.2 cm in both study cohorts. The 6-month restenosis rate, which was the primary endpoint, was in favor for the DCBs as compared to POBA (15.4 vs. 44.7 %, p=0.002). At 1-year, restenosis rates were 29.5 and 62.5 %, respectively (p=0.004), and freedom from clinically driven TLR at 390 days was 90.8 and 52.6 %, respectively (p=0.0001).

According to the international definitions, the use of DCB in femoropopliteal ISR lesions would qualify as a level of recommendation class II and a level of evidence class B. Larger-scale international RCTs and, as for TASC II A and B lesions, longer-term follow-up will be needed.

DCBs in failed surgical bypass

To date, there is only one study evaluating the use of DCBs in failing venous and prosthetic surgical bypass. Kitro et al. reported on 32 patients utilizing a comparison of historic controls at 7 months. No patency or revascularization improvement was suggested in this small study for DCBs [28]. This seems somewhat unexpected since early reports of DCBs in stent-related intimal hyperplasia appears to be very promising [25–27].

According to the international definitions, the use of DCBs in failed femoropopliteal bypass graft lesions would qualify as a level of recommendation class IV and a level of evidence class C. Larger-scale RCTs are mandatory to evaluate the role of DCB in this particular indication.

Use of DCBs Following Atherectomy

The combination of debulking followed by drug-coated technology seems an attractive collaboration between these technologies. The DEFINITIVE LE trial provided scientific data for procedural success, safety, and importantly 12-

month outcomes with regards to patency for patient with claudication and CLI using directional atherectomy (DA [29•]). In this 800-patient registry, lesions up to 20 cm were treated with DA using the SilverHawk device (Covidien, Minneapolis, MN, USA) as a planned stand-alone therapy in all anatomic territories of the lower limb. Bailout stenting was needed in only 3.1 %. In the claudicant group, primary patency was 78 % overall across all anatomic levels and was 75 and 90 % in the femoro-popliteal and infrapopliteal locations, respectively.

Early small single-center reports of the combination of DA and DCB have shown some promise in this approach for patients with lower limb arterial disease. In one retrospective analysis, the combination of DA and DCB (60 patients) was compared with DA with non-DCB angioplasty (29 patients). The primary patency was significantly higher in the DCB group (84.7 %) compared with 43.8 % in the non-DCB group [30]. Of note, in this analysis, the atherectomy outcome is inferior to other reports including the prospective independently controlled DEFI NITIVE LE study [29•]. Also, in heavily calcified lesions, the combination of DCB provided a 90 % 1-year freedom from clinically driven TLR in 30 patients studied from a single center [31]. Thus, the combination of DA with the added technology of DCBs seems to be a logical treatment to continue with a "leave nothing behind" approach for arterial obstructive disease. Just recently, the DEFINITIVE AR trial was presented (T. Zeller, VIVA Las Vegas, 2014) being a prospective, multicenter, pilot feasibility study designed to assess and estimate the effect of treating vessels with DA prior to a paclitaxel-coated balloon (DA+DCB) in order to facilitate the development of a pivotal study. Claudicants with 7–15-cm SFA and/or popliteal lesions were randomized 1:1 to either DA+DCB or to DCB alone. Subjects with severely calcified lesions were assigned to a non-randomized registry arm and were treated with DA+DCB. A total of 121 subjects were enrolled, 48 in the DA+DCB arm, 54 in the DCB arm, and 19 in the severely calcified lesion DA+DCB registry group. Lesion length ranged from 9.7 to 11.9 cm. In the randomized groups, the 1-year duplex patency estimated by Kaplan-Meier (KM) analysis was 93.4 % for the DA+DCB arm and 89.6 % for the DCB arm. Angiographic patency (≤50 % stenosis and without TLR) was 82.4 % in the DA+DCB arm and 71.8 % in the DCB arm. This pilot study suggests that there may be an added benefit for combination therapy (DA+DCB) in long and calcified lesions which was not observed in the DCB subgroup alone.

According to the international definitions, the combined use of atherectomy and DCB in femoro-popliteal lesions would qualify as a level of recommendation class II and a level of evidence class B. Further investigation in larger, prospective, statistically powered randomized trials is warranted.

Health economic evaluation of DCBs for femoro-popliteal artery disease

Peripheral artery disease is associated with reduced quality of life and increased mortality and affects more than 7 million patients in the USA and 1.2 million patients in Germany alone [32, 33]. Its treatment

represents a growing financial burden to health care systems [34•]. Recent cost-effectiveness evaluations tried to analyze the impact of increased patency rates resulting in reduced TLR rates of DCBs and DES on the mid-term costs up to 2 years [35•, 36, 37].

The most robust study summarized the clinical efficacy of four endovascular strategies (POBA, DCBs, BMS, and DES) as index procedures [35•]. Budget impacts on the current largest and most mature market for drug-eluting peripheral therapies (Germany) and the largest medical device market (USA) were compared. Both drug-eluting strategies, DES and DCBs, are associated with lower TLR probabilities than POBA. The 24-month probability of TLR for each treatment was weighted by sample size. Base cases were developed for US Medicare and the German statutory sickness fund perspectives using 2013 reimbursement rates.

The drug-eluting strategies had a lower projected budget impact over 24 months compared to BMS and POBA in both the US Medicare and German health care systems. The US facility provider perspective suggested that BMS would result in the greatest revenue (i.e., Medicare reimbursement minus device costs) to the hospital ($11,490), followed by POBA and DES, with DCBs providing the lowest revenue at $8120. The German facility-provider analysis showed that the non-drug-eluting therapies resulted in the highest operational margin for hospitals relative to the drug-eluting therapies: POBA led to the highest revenue at €3689, followed by BMS, DES, and DCB (€2533).

Another cost-effectiveness analysis based on a discrete-event simulation model from a health service perspective in England included eight endovascular therapies (DES, DCBs, BMS, brachytherapy, stent-grafts, cryoplasty) versus standard of care and concluded that DCBs may be a cost-effective alternative to POBA with bailout BMS [37].

In conclusion, DES and DCBs seem to offer clinical advantages over POBA and BMS. DCBs and DES offer the lowest budget impact and therefore the greatest economic value to payers. The current analyses highlight the importance of promoting a shift from low- to high-value treatments and balancing payers' savings with providers' financial viability.

In summary, DCBs have proven to be effective in broad spectrum of femoro-popliteal lesions in a claudicant population. Thus, also considering their cost-effectiveness in this indication (TASC II A and B lesions), DCBs should become first-line strategy for the treatment of femoro-popliteal disease. Based on the most recent study outcomes, there seems to remain no indication for stand-alone POBA. For more complex lesions such as long or calcified lesions, the combination of DCBs and bare metal stents, DES, or the combination of DA and DCBs might be indicated. One considerable benefit of stent less treatment strategies is the short duration of dual antiplatelet therapy of only 4 weeks whereas it is recommended up to 3 months for DES and the combination of DCBs and BMS. However, there is a need for further optimization of the drug coatings in terms of reducing drug loss during balloon insertion to almost zero percent and to increase drug penetration and persistence in the vessel wall with the goal of further optimization of biological drug efficacy despite reducing the

effective drug dose on the balloon surface. Of note, every new drug formulation has to be tested in individual clinical trials.

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Thomas Zeller is a paid member of the advisory board of Medtronic, Boston Scientific, Cook, W.L. Gore, Covidien, Spectranetics, Volcano, Bard, and Veryan. Dr. Zeller reports grants from Biotronik, B. Braun, Medtronic, Covidien, Volcano, Bard, Cook, Gore, Boston Scientific, Veryan, and Spectranetics. Dr. Aljoscha Rastan, Dr. Roland Macharzina, Dr. Ulrich Beschorner, and Dr. Elias Noory each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease. Int Angiol. 2007;26:81–157.
2. Beschorner U, Sixt S, Schwarzwälder U, et al. Recanalization of chronic occlusions of the superficial femoral artery using the outback™ re-entry catheter: a single centre experience. Catheter Cardiovasc Interv. 2009;74:934–8.
3. Johnston KW. Femoral and popliteal arteries: reanalysis of results of balloon angioplasty. Radiology. 1992;183:767–71.
4. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. N Engl J Med. 2006;354:1879–88.
5. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. N Engl J Med. 2008;358:689–99.
6. Werk M, Langner S, Reinkensmeier B, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. Circulation. 2008;118:1358–65.
7. Werk M, Albrecht T, Meyer DR, et al. Paclitaxel-coated balloons reduce restenosis after femoro-popliteal angioplasty: evidence from the randomized PACIFIER trial. Circ Cardiovasc Interv. 2012;5:831–40.
8. Scheinert D, Duda S, Zeller T, et al. The LEVANT I (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) trial for femoropopliteal revascularization: first-in-human randomized trial of low-dose drug-coated balloon versus uncoated balloon angioplasty. JACC Cardiovasc Interv. 2014;7:10–9.
9. Scheinert D, Schulte KL, Zeller T, Lammer J, Tepe G. Novel paclitaxel releasing balloon in femoropopliteal lesions: 12-month evidence from the BIOLUX P-I randomized trial. JEVT 2014, in press.
10. Micari A, Cioppa A, Vadalà G, Castriota F, Liso A, Marchese A, et al. Clinical evaluation of a paclitaxel-eluting balloon for treatment of femoropopliteal arterial disease: 12-month results from a multicenter Italian registry. JACC Cardiovasc Interv. 2012;5:331–8.
11. •• Tepe G, Laird J, Schneider P, Brodmann M, Krishnan P, Micari A, Metzger C, Scheinert D, Zeller T Cohen DJ, Snead DB, Alexander B, Landini M, Jaff MR for the IN.PACT SFA Trial Investigators. Drug-Coated Balloon versus Standard Percutaneous Transluminal Angioplasty for the Treatment of Superficial Femoral and/or Popliteal Peripheral Artery Disease: 12-month Results from the IN.PACT SFA Randomized Trial. Circulation 2015;131(5):495-502.

IN.PACT SFA is the to date largest and most robust published trial demonstrating a clear technical and clinical benefit up to 1 year for the treatment of femoro-popliteal artery disease using DCB.

12. • Fanelli F, Cannavale A, Gazzetti M, Lucatelli P, Wlderk A, Cirelli C, et al. Calcium burden assessment and

impact on drug-eluting balloons in peripheral arterial disease. Cardiovasc Intervent Radiol. 2014;37(4):898–907.

An important study about the main limitation of DCB use in femoro-popliteal lesions.

13. Rocha-Singh KJ, Zeller T, Jaff MR. Peripheral arterial calcification: prevalence, detection and clinical implications. Catheter Cardiovasc Interv. 2014;83:E212–220.

14.• Lanzer P, Böhm M, Sorribas V, Thiriet M, Janzen J, Zeller T, et al. Mönckeberg's media sclerosis; a non-inflammatory vascular calcification disorder. EHJ. 2014;35:1515–25.

The most comprehensive review of current data concerning mediacacinosis, one potential limitation of DCB use.

15.•• Zeller T, Baumgartner I, Scheinert D, Brodmann M, Bosiers M, Micari A, et al. IN.PACT DEEP trial investigators. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. J Am Coll Cardiol. 2014;64:1568–76.

IN.PACT deep is to date the largest DCB trial evaluating the performance of DCB in infra-popliteal intervention in a CLI population.

16. Schnorr B, Kelsch B, Cremers B, Clever YP, Speck U, Scheller B. Paclitaxel-coated balloons - Survey of preclinical data. Minerva Cardioangiol. 2010;58(5):567–82.

17. Schnorr B, Albrecht T. Drug-coated balloons and their place in treating peripheral arterial disease. Expert Rev Med Devices. 2013;10(1):105–14.

18. Cassese S, Byrne RA, Ott I, Ndrepepa G, Nerad M, Kastrati A, et al. Paclitaxel-coated versus uncoated balloon angioplasty reduces target lesion revascularization in patients with femoropopliteal arterial disease: a meta-analysis of randomized trials. Circ Cardiovasc Interv. 2012;5:582–9.

19. Tepe G, Zeller T, Schnorr B, Claussen CD, Beschorner U, Brechtel K, et al. High-grade, non-flow-limiting dissections do not negatively impact long-term outcome after paclitaxel-coated balloon angioplasty: an additional analysis from the THUNDER study. J Endovasc Ther. 2013;20:792–800.

20. Tepe G; Schnorr B; Albrecht T; Brechtel K; Claussen CD; Scheller B; Speck U; Zeller T. Five-year follow-up data of the Thunder trial: angioplasty of femoro-popliteal arteries with drug-coated balloons. JACC Cardiovasc Interv 2014, in press.

21.• Endorsed by: the European Stroke Organisation (ESO), Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clément D, Collet JP, Cremonesi A, De Carlo M, Erbel R, Fowkes FG, Heras M, Kownator S, Minar E, Ostergren J, Poldermans D, Riambau V, Roffi M, Röther J, Sievert H, van Sambeek M, Zeller T; ESC Committee for Practice Guidelines. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries * The Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). European Heart Journal 2011;32:2851–2906.

The ESC guidelines on the treatment of peripheral artery disease are the most recent by a cardiovascular society published international guidelines.

22. Zeller T, Rastan A, Macharzina R, Tepe G, Kaspar M, Chavarria J, et al. Drug eluting balloons vs. drug eluting stents in long femoropopliteal lesions – a retrospective propensity score analysis. J Endovasc Ther. 2014;21:359–68.

23. Bosiers M, Torsello G, Gissler H-M, Ruef J, Müller-Hülsbeck S, Jahnke T, et al. Nitinol stent implantation in long superficial femoral artery lesions: 12-month results of the DURABILITY I study. J Endovasc Ther. 2009;16:261–9.

24. Krankenberg H, Schlüter M, Steinkamp HJ, Bürgelin K, Scheinert D, Schulte KL, et al. Nitinol stent implantation versus percutaneous transluminal angioplasty in superficial femoral artery lesions up to 10 cm in length: the femoral artery stenting trial (FAST). Circulation. 2007;116:285–92.

25. Dick P, Sabeti S, Mlekusch W, Schlager O, Amighi J, Haumer M, et al. Conventional balloon angioplasty versus peripheral cutting balloon angioplasty for treatment of femoropopliteal artery in-stent restenosis: initial experience. Radiology. 2008;248:297–302.

26. Stabile E, Virga V, Salemme L, Cioppa A, Ambrosini V, Sorropago G, et al. Drug-eluting balloon for treatment of superficial femoral artery in-stent restenosis. J Am Coll Cardiol. 2012;60:1739–42.

27. Virga V, Stabile E, Biamino G, Salemme L, Cioppa A, Giugliano G, et al. Drug-eluting balloons for the treatment of the superficial femoral artery in-stent restenosis: 2-year follow-up. JACC Cardiovasc Interv. 2014;7:411–5.

28. Kitrou P, Parthipun A, Diamantopoulos A, Padayachee S, Karunanithy N, Ahmed I, et al. Paclitaxel-coated balloons for failing peripheral bypass grafts: the BYPACS study. J Cardiovasc Surg (Torino). 2014;55:217–24.

29.• McKinsey JF, Zeller T, Rocha-Singh KJ, Jaff MR, Garcia LA, DEFINITIVE LE Investigators. Lower extremity revascularization using directional atherectomy: 12-month prospective results of the DEFINITIVE LE study. JACC Cardiovasc Interv. 2014;7:923–33.

DEFINITIVE LE ist to date the largest independently controlled trial investigating the performance of atherectomy in the entire infra-inguinal vessel territory.

30. Sixt S, Carpio Cancino OG, Treszl A, Beschorner U, Macharzina R, Rastan A, et al. Drug-coated balloon angioplasty after directional atherectomy improves outcome in restenotic femoropopliteal arteries. J Vasc Surg. 2013;58:682–6.

31. Cioppa A, Stabile E, Popusoi G, Salemme L, Cota L, Pucciarelli A, et al. Combined treatment of heavy calcified femoro-popliteal lesions using directional atherectomy and a paclitaxel coated balloon: one-year single centre clinical results. Cardiovasc Revasc Med. 2012;13:219–23.

32. Pande RL, Perlstein TS, Beckman JA, Creager MA. Secondary prevention and mortality in peripheral artery disease: National Health and Nutrition Examination Study, 1999 to 2004. Circulation. 2011;124:17–23.
33. Inglis SC, Lewsey JD, Lowe GDO, Jhund P, Gillies M, Stewart S, et al. Angina and intermittent claudication in 7403 participants of the 2003 Scottish Health Survey: impact on general and mental health, quality of life and five-year mortality. Int J Cardiol. 2013;167:2149–55.
34.• Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013;382:1329–40.
The most recent overview about the epidemiology of PAD.
35.• Pietzsch JB, Geisler BP, Garner AM, Zeller T, Jaff MR. Economic analysis of endovascular interventions for femoropopliteal arterial disease: a systematic review and budget impact model for the United States and Germany. Catheter Cardiovasc Interv. 2014;84:546–54.
The most robust cost evaluation of the main stream peripheral interventional techniques in the most relevant global markets, the US and Germany.
36. Diehm N, Schneider H. Cost-effectiveness analysis of paclitaxel-coated balloons for endovascular therapy of femoropopliteal arterial obstructions. J Endovasc Ther. 2013;20:819–25.
37. Kearns BC, Michaels JA, Stevenson MD, Thomas SM. Cost-effectiveness analysis of enhancements to angioplasty for infrainguinal arterial disease. Br J Surg. 2013;100:1180–8.