



Drug-coated balloon treatment for lower extremity vascular disease intervention: an international positioning document[†]

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The need for a drug-coated balloon consensus document in the peripheral field

The advent of drug-coated balloons (DCBs) provides a novel means to locally deliver paclitaxel into the arterial wall without the need of a chronically implanted delivery system. The widespread use of these devices in the clinical arena is contemporary with the introduction and adoption of paclitaxel eluting stents for peripheral vascular intervention. However, DCB remain highly attractive approach as the long-term consequences of permanent metallic implants in peripheral applications are still unknown. Notably, the clinical value of DCB is supported by robust pre-clinical evidence regarding safety and efficacy. Likewise, the clinical value of DCB in patients has also been demonstrated by multiple randomized clinical trials in the superficial femoral artery (SFA) and proximal popliteal artery territory. However, the widespread clinical adoption of DCB into routine clinical practice remains elusive. The evidence on the value of DCB has been summarized in consensus documents and in clinical practice guidelines. In the coronary field, currently available information has been summarized in two comprehensive Experts' Consensus Documents and the European Society of Cardiology (ESC) guidelines on coronary revascularization.^{1–3} These documents emphasized that not all DCB are created equal and that a 'class effect' cannot be anticipated as the results obtained with different DCB are not uniform. This remains a major challenge

since many CE marked devices are currently available yet many of these have not been supported by robust clinical results.

In the peripheral territory, the information regarding the clinical use of DCB is scarce. Moreover, no previous consensus document exists describing the clinical applications and indications for the use of this technology on this vascular territory. Likewise, specific guidelines have not been issued. Accordingly, the present document addresses this gap in knowledge by providing an evidence-based recommendation for the use of DCB technology in the peripheral vascular territory.

Methodological approach for the recommendations

This positioning document is the result of multiple discussions between experts in the field of DCB angioplasty and/or peripheral interventions. Experts on the field critically reviewed relevant literature on this dynamic field with the goal to provide a comprehensive framework to guide clinical practice and to discuss challenges and future perspectives supplementing the ESC guideline document.⁴

In the peripheral field, there are several territories where a gold standard treatment is currently not available and current treatments are of limited efficacy: here DCB may exert an important role. However, a rigid interpretation of our indications should not be pursued, and we believe that it is the responsibility of each physician to find the most appropriate treatment for the specific clinical circumstance.

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Rationale for the use of drug-coated balloons

In sharp contrast to percutaneous coronary interventions, peripheral vascular interventions are less dependent on the use of stents. In general, stenting long femoro-popliteal segments with tubular nitinol stents have demonstrated a significant risk of stent fracture due to physiological torsion of the femoral artery potentially resulting in either restenosis or vessel wall damage.⁵ In the below-the-knee (BTK) arterial distribution, long dedicated stents are not available. In-stent restenosis (ISR) is a major problem and complications related to lower extremity stents do not have clear cut solutions. Clinically available DCBs deliver paclitaxel via conventional angioplasty balloons, trying to overcome the need for scaffolding. The intended effect of the medication is to improve the long-term patency of the revascularization procedure. The only clinically studied drug at this juncture is paclitaxel, which has shown to inhibit cell proliferation and migration due to an irreversible stabilization of intracellular microtubules.⁶ This results in blocking cell replication during metaphase and anaphase of mitosis. Currently most available DCB use specific carriers to keep paclitaxel on the balloon surface until delivery and to favour its release and maintenance on the vessel wall.⁷ Currently, there are several DCB in the European market (Table 1) and are being introduced into the US market.

Mechanism of action and impact of coating on tissue peak concentration and vascular effects

Drug-coated balloons achieve the short-term transfer and long-term retention of paclitaxel to the arterial wall by different biological mechanisms.⁸ Experimental data have shown that paclitaxel transfer and retention are not necessarily inter-related phenomena and they largely depend on drug morphology and resulting solubility attained during the coating process.^{9,10} At the present time, a potential mechanism of action explaining long-term drug retention yielding sustained biological efficacy following single-time drug delivery is still matter of controversy. Early experimental data confirmed that paclitaxel transfer into the vessel wall occurs rapidly following balloon inflation.¹¹ In addition, tissue pharmacokinetic studies showed that short-term tissue levels of paclitaxel following balloon delivery were higher compared with drug-eluting stents (DESs)¹² and that therapeutic concentrations of paclitaxel were found beyond 28 days in the vessel wall. Also, several publications demonstrated that in combination with bare-metal stents the long-term vessel healing profile appears to be similar to first-generation DES.¹³ However, despite its documented clinical efficacy in selected clinical scenarios, a potential mechanism of action explaining long-term

Table 1 Peripheral drug-coated balloons available in the European market

Brand name	Manufacturer	Excipient	Paclitaxel concentration ($\mu\text{g}/\text{mm}^2$)	Catheter type	Guidewire compatibility	Clinical trials published or presented
IN.PACT	Medtronic	Urea	3.5	OTW	0.014", 0.018", 0.035"	IN.PACT SFA; Pacifier; Italian SFA registry; FAIR ^a ; DEBELLUM ⁵⁴ ; DCB vs. DES in Long SFA ⁵⁵ ; Debate SFA; IN.PACT Deep ⁴¹ ; Debate BTK; Leipzig BTK Registry
Lutonix 14 Lutonix 35	Lutonix-Bard	Polysorbate/ sorbitol	2	OTW	0.014", 0.035"	Levant I ¹⁹ ; Levant II (VIVA 2014)
Biopath (prev. Freeway)	Eurocor/ Biosensors	Shellac	3	OTW	0.014", 0.035"	PACUBA I; FREEWAY STENT ^c
Passeo Lux	Biotronik	BTHC	3	OTW	0.018"	Biolux P- I ²¹ and P II
Stellarex	Spectranetics	Unknown	2	OTW	0.035"	ILLUMINATE FIH ^d
Elutax SV	Aachen Resonance	None	2.2	RX	0.014"	n/a
Legflow	Cardionovum	shellac	3	OTW-RX	0.014", 0.035"	n/a
Advance 18 PTX	Cook	None	3	OTW	0.018"	ADVANCE PTX trial ^b
Cotavance	Medtronic	Iopromide	3	OTW-RX	0.014", 0.035"	Copa Cabana; THUNDER ¹⁷ ; FemPAC ¹⁸ ; Definitive AR ^e (VIVA 2014)

In the US the FDA has currently only approved the Lutonix 35 and IN.PACT Admiral devices for human use outside clinical research.

FDA, Food and Drug Administration; OTW, over-the-wire; SFA, superficial femoral artery; DCB, drug-coated balloon; DES, drug-eluting stent; RX, rapid exchange.

^aT. Zeller—VIVA 2014 oral presentation.

^bD. Scheinert—LINC 2013 oral presentation.

^cK.L. Schulte—LINC 2014 oral presentation.

^dS. Duda—EuroPCR 2014 oral presentation.

^eT. Zeller—VIVA 2014 oral presentation.

drug retention and sustained biological effect has not been elucidated for DCB technologies.

Several studies have reported the importance of paclitaxel deposits on the vessel surface and long-term tissue retention. A recent publication demonstrated that following DCB dilatation, a proportion of the paclitaxel is retained on the vessel surface and is not acutely dissolved into the tissue. It seemed apparent that arterial wall levels of paclitaxel were driven by the sustained retention of drug on the surface of the vessel wall, thereby maintaining a positive concentration gradient from the vessel surface into the arterial wall. Interestingly, at 7 days tissue concentrations began to equalize the vessel surface levels, providing an explanation about the lack of tissue toxic effects.⁸ These results largely depended on coating crystallinity and seemed to be consistent with previous reports showing that specific binding to intracellular proteins occurs primarily in the subintimal space and determines arterial transport properties and microtubule binding of paclitaxel.¹⁴ As a consequence, the observed tissue half-life of paclitaxel delivered by DCB relates to the slow dissolution of paclitaxel deposits from the vessel surface into arterial tissue in a time-dependent fashion.¹⁵ In any case, the resulting tissue levels of paclitaxel at 28 days are above the reported inhibiting concentration (IC) 50 values for human smooth muscle cells (1.4–2 ng/g) and endothelial cell proliferation (1.7–6.8 ng/g).¹⁶ Thus, the proposed mechanism of action reconciles the apparent contradiction between the observed short-term supra-therapeutic tissue levels seen right after balloon delivery and the resulting vessel healing profiles seen at the experimental level.

The mechanism of action of DCB is an area of intense investigation and likely will unveil several mechanistic pathways that will help the future development of DCB technologies.

Drug-coated balloons for *de novo* and restenotic femoro-popliteal artery disease

Several first-in-man randomized trials^{17–21} and a registry²² using first-generation DCB in femoro-popliteal lesions have shown favourable technical outcomes in terms of late lumen loss (LLL), restenosis rate, and freedom from target lesion revascularization (TLR) when compared with plain old balloon angioplasty (POBA) (Table 2).

A meta-analysis of these trials²³ had TLR as primary endpoint, whereas secondary endpoints were angiographic binary restenosis, LLL, and all-cause mortality. A total of 381 patients were included (DCB, $n = 186$ vs. POBA, $n = 195$). The median follow-up was 10.3 months. Angioplasty with DCB vs. POBA reduced TLR (12.2 vs. 27.7%; OR 0.22; 95% CI, 0.13–0.38; $P < 0.00001$), angiographic restenosis (18.7 vs. 45.5%; OR 0.26; 95% CI, 0.14–0.48; $P < 0.0001$), and 6-month LLL (–0.05 to 0.50 mm vs. 0.61–1.7 mm; mean difference –0.75 mm; 95% CI, –1.06 to –0.45; $P < 0.00001$). No mortality difference was observed between DCB and POBA (2.1 vs. 3.2%; OR, 0.99; 95% CI, 0.39–2.49; $P = 0.98$).

Table 2 Currently published or presented pilot multi-centre drug-coated balloon trials with their primary technical endpoint, 6-month late lumen loss and 12-month target lesion revascularization rate

	THUNDER ¹⁷	FemPAC ¹⁸	LEVANT I ¹⁹	PACIFIER ²⁰	BIOLUX P I ²¹	ADVANCE PTX ^a	ILLUMINATE FIH ^b
Balloon	Paccocath	Paccocath	Lutonix 35	IN.PACT Pacific	Passeo 18 Lux	Advance 18 PTX	Stellarex
PTX coating ($\mu\text{g}/\text{mm}^2$)	3	3	2	3	3	3	2
Coating spacer	Ultravist	Ultravist	Polysorbate and sorbitol	Urea	BTHC (butyryl-tri-hexyl citrate)	None	Unknown
No. of patients	154	87	101	91	68	150	50
Lesion length (cm)	7.5	6.0	8.1	6.8	6.1	10.0	7.2
Occlusions (%)	27	15	40	30.8	38	37	12.1
Stentrate PTX vs. control (%)	4/22	9/14	25/27	21/34	7/27	28/30	5.2/n.a.
LLL PTX (mm)	0.40	0.50	0.46	–0.01	0.50	0.90	0.54
LLL control (mm)	1.70	1.00	1.09	0.65	1.00	1.30	n.a.
<i>P</i> -value LLL	<0.001	0.031	0.016	0.001	0.033	0.12	n.a.
TLR PTX (%)	10	6.7	29	7.1	15.4	n.a.	12.1
TLR control (%)	48	33.3	33	27.9	41.2	n.a.	n.a.
<i>P</i> -value TLR	<0.001	0.002	n.s.	0.02	0.064	n.a.	n.a.

^aD. Scheinert—LINC 2013 oral presentation.

^bS. Duda—EuroPCR 2014 oral presentation.

In a recent subgroup analysis of the THUNDER trial,²⁴ 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 after treatment with coated balloons ($n = 43$) had significantly lower LLL than patients with dissection after POBA ($n = 43$, 0.4 vs. 1.9 mm, $P = 0.001$). Interestingly, especially patients with severe dissections (grade C–E) seemed to benefit from DCB in terms of LLL (0.4 vs. 2.4 mm, $P = 0.05$). Up to the 2-year follow-up, TLR was performed in 56% of patients in the control group compared with 10% of patients in the DCB group ($P = 0.002$). Patients of the THUNDER study were followed for 5 years.²⁵ Over this study period, the cumulative number of patients with TLR was distinctly lower in the DCB group (21 vs. 56%, $P = 0.0005$).

Currently, two large-scale international US IDE (*investigational device exemption*) trials are still ongoing in their 2-year follow-up phase; however, 1-year data had been presented or published during 2014. The IN.PACT SFA trial²⁶ which enrolled a total of 331 patients with a 2:1 randomization between DCB and POBA, and the Levant II trial (K. Rosenfield, TCT 2014, Washington DC, USA) which enrolled a total of 543 patients in a 2:1 randomization. Both RCTs are supplemented by large-scale registries enrolling, respectively, 1500 and 650 patients.

The randomized multi-centre IN.PACT SFA trial revealed that clinically driven TLR rates were significantly lower with the DCB when compared with those achieved with angioplasty (2.4 vs. 20.6%, $P < 0.001$). Similarly, the primary patency rate achieved with IN.PACT Admiral balloon was 82.2%, while the primary patency achieved with POBA was 52.45% ($P < 0.001$). 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 II trial which incorporated a 'blinded follow-up' in contrast to previous trials, the primary patency at 12 months defined as freedom from both restenosis and TLR was 65.2% for the DCB and 52.6% for control angioplasty demonstrating superior efficacy ($P = 0.015$). At 12 months, the freedom from clinically driven TLR in the DCB group was attenuated and similar to the control group (87.7 vs. 83.2%, $P = 0.208$). In this study, both the safety (freedom from death, amputation, reintervention) and efficacy primary endpoints were met; however, the lack of a clinical efficacy of DCB expressed by a TLR rate similar to the control group at 12 months is of concern.

In both studies, no device-specific side-effects were reported, no major amputation occurred. Thus, there was no safety concern regarding wash off of a part of the antiproliferative drug into the distal vasculature.

In-stent restenosis has been reported to occur in up to 40% of femoro-popliteal lesions treated with BMS within 1 year.^{27,28} Moreover, the risk of ISR increases with increasing lesion length. As the population with femoro-popliteal stenting continues to increase, occurrence of ISR has become a clinically relevant problem. The treatment of ISR in the femoro-popliteal artery is one of the major remaining challenges of endovascular therapy because treatment modalities such as PTA and cutting balloon angioplasty have failed to provide durable results.²⁹ A single-centre prospective registry, including 39 patients, reported an impressive 1-year primary patency rate of 92.1%³⁰ and a 2-year primary patency of 70.3%.³¹

Just recently, the data of the randomized, controlled FAIR (drug-eluting-balloon vs. PTA for superficial Femoral Artery In-stent Restenosis) trial was presented (T. Zeller, TCT 2014, Washington DC, USA) including 119 patients with ISR 1–20 cm in length and a mean lesion length of 8.2 cm in both study cohorts. The primary endpoint was the 6-month restenosis rate which was in favour for the DCB when compared with 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 ($P = 0.0001$).

Technical considerations for drug-coated balloon use in femoro-popliteal lesions

In order to optimize patency, it is essential to cover the entire lesion with DCBs, placing the balloon ends from *healthy-to-healthy* vessel segments and to avoid geographical miss and to cover every injured vessel segment after pre-dilatation with uncoated balloon. The same holds true for the treatment of in-stent restenotic lesions or bail-out stent placement, the DCB should cover either the entire stented segment (*Figure 1*) or the bail-out stent should be placed within the area which was dilated with the DCB. The balloon itself should not be wiped and care must be taken to avoid disturbing the medication prior to or during insertion of the DCB catheter into the sheath. At the present time, lesion pre-dilatation is always recommended to decrease the risk of drug loss related to potential coating scratching and dislodgement during lesion crossing.

Final recommendations

Drug-coated balloons are not yet classified in international guidelines because relevant data had not yet been published when literature research was performed for the guidelines. For example the 2011 ESC guidelines on peripheral artery diseases included only one single sentence about femoro-popliteal lesions: 'Early studies with drug-eluting balloons in the femoro-popliteal arteries showed improved short-term patency rates compared with plain balloon angioplasty'.⁴

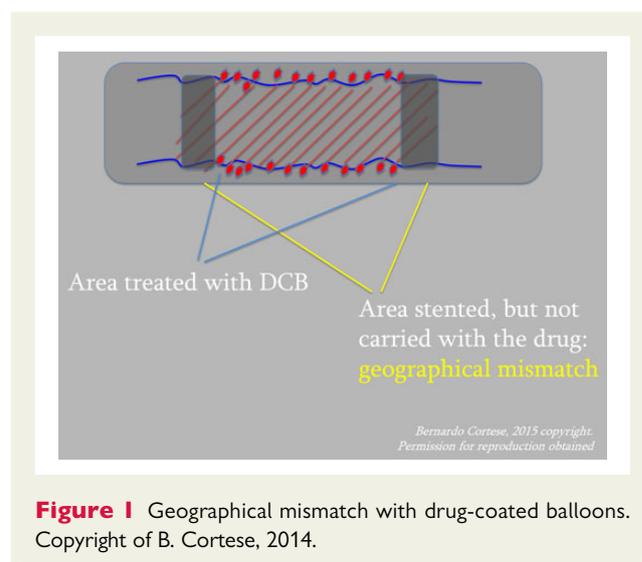


Figure 1 Geographical mismatch with drug-coated balloons. Copyright of B. Cortese, 2014.

According to the international definitions, the use of DCB in femoro-popliteal TASC IIA and B *de novo* and restenotic lesions would be highly recommended because the given treatment is beneficial, useful, and effective and the data are derived from multiple randomized clinical trials.

However, longer-term follow-up data are still lacking for DCB as the recently presented for DES. The 5-year Zilver PTX RCT results demonstrated significant stability of patency (Duke M. VIVA 2014, Las Vegas, USA) and DCB will need to meet a similar benchmark.

Drug-coated balloon for below-the-knee artery disease

The long-term success of BTK endovascular procedures has been improving but remains inadequate for today's clinical requirements.³² The potential benefits and risks of DCBs are manifested in a variety of ways for different anatomical locations and clinical conditions.³³ The clinical and technical aspects of managing BTK occlusive disease and the critical limb ischaemia (CLI) syndrome are complex. For example, prolonged tibial artery patency would be of particular benefit in promoting the healing of foot wounds. However, the potential for interaction between an anti-mitotic medication and a non-healed but recently revascularized wound is not fully understood. Many issues must be resolved before DCB can significantly impact the care of BTK disease.

Restenosis after POBA ranges from 42% at 12 months for lesions <3 to 69% at 3 months for lesion length of 18.4 cm.^{34–37} A meta-analysis of BTK angioplasty performed upon studies published from 1990 to 2006 indicated that the 1-year patency of POBA was $58.1 \pm 4.6\%$ and the limb salvage rate was $86.0 \pm 2.7\%$.³⁸

Despite the number of approved DCB catheters in the EU, there is a paucity of well-controlled data on the use of this tool in the BTK vasculature. Early signals suggested that restenosis is less common than after POBA and tends to be more focal and with fewer reocclusions if treatment failure occurs.^{39,40} Schmidt *et al.*³⁹ treated long lesions (mean 17.3 cm) and 3-month angiographic restenosis was 27.4%. Most of the restenoses (61%) were focal and only 8% of BTK-DCB failures presented with occlusion. In the DEBATE BTK trial,⁴⁰ a randomized, controlled trial of DCB vs. POBA, both restenosis (27 vs. 74%, $P = 0.001$), and TLR (18 vs. 43%, $P = 0.003$), were reduced at 1 year. Moreover, vessel occlusion was 17 and 55% ($P < 0.001$), complete wound healing occurred in 86 vs. 67% ($P = 0.01$), and there were no significant differences in terms of major limb amputation.

However, the IN.PACT DEEP multi-centre, randomized, controlled trial that tested the same device could not confirm the initial single-centre study findings regarding either efficacy or clinical safety.⁴¹ The IN.PACT DEEP trial compared the performance of the IN.PACT Amphirion DCB with POBA in a 2 to 1 randomization protocol in 358 patients with pre-specified primary endpoints for efficacy (TLR and LLL) and safety (all-cause death, major amputations, or TLR). All patients were analysed at 1-year follow-up for their clinical endpoints whereas a subcohort of patients with lesions ≤ 10 cm in length underwent an angiographic control for assessment of the technical endpoints. Significant baseline differences between the DCB and POBA cohorts included mean lesion length

(10.2 vs. 12.9 cm; $P = 0.002$), impaired inflow (40.7 vs. 28.8%; $P = 0.035$), and previous target limb revascularization (32.2 vs. 21.8%; $P = 0.047$). Primary efficacy results of DCB vs. POBA were clinically driven TLR (CD-TLR) of 9.2 vs. 13.1% ($P = 0.291$) and LLL of 0.61 ± 0.78 vs. 0.62 ± 0.78 mm ($P = 0.950$). Primary composite safety endpoint was 17.7 vs. 15.8% ($P = 0.021$) and met the non-inferiority hypothesis. A safety signal driven by major amputations through 1 year was observed in the DCB vs. POBA arm (8.8 vs. 3.6%; $P = 0.080$) (Figures 2 and 3). As a consequence the IN.PACT Amphirion DCB product was withdrawn from the market.

Technical considerations for drug-coated balloon use in the below-the-knee lesions

Multiple aspects of BTK disease may influence the technical use of DCB. The management of long, calcified lesions in multiple small calibre, low-flow arteries with a high-resistance outflow bed may influence the technical aspects of medication delivery.

Below-the-knee arteries represent a tapering system with smaller arteries at the ankle and foot. If the artery is significantly tapered along the length of a single device, drug application may not be uniform. Avoidance of geographic miss is also an essential feature of DCB use in the BTK arteries. Multiple lesions in different arteries with few anatomic landmarks may promote the opportunity for geographic miss to occur. Because of the greater distance from the access site to the target lesion and the smaller calibre of the artery and lesion length, it may be possible that proportionally more of the drug is lost from the balloon surface during the advancement and placement of the balloon in the BTK arteries.

Medial calcification is a common finding among diabetics with BTK lesions. It is not clear whether this will enhance drug uptake, due to the less likely presence of bulky, inert, calcified lesions, or hinder it, due to the poor health of the medial layer. The less common need for provisional after BTK angioplasty with POBA is likely to favour DCB, since the need for provisional stenting is a potential confounding variable. Critical limb ischaemia patients very often have multilevel lower extremity occlusive disease. If DCB is required for above-the-knee lesions, as well as BTK, there is a potential for oversaturation of the distal tissues with excess drug released.

Drug-coated balloons at ankle and foot seem to have lower patency than DCB for the proximal and mid-tibial arteries.³⁹ This may be due to the small calibre of the arteries, in which case manipulation of the DCB is limited by increasing friction due to the drug coating with decreasing lumen diameters. This may result in an insufficient drug coverage of the pre-dilated lesion or a significant drug loss upstream due to the friction between vessel wall and balloon surface. However, the low patency of these very distal arteries may also be due to a mechanical effect (external forces, impingement, and constant movement) that cannot be solved by DCB. In these cases, DCB may not enhance much the results of POBA.

Final recommendations

There is currently widespread opinion to suggest that DCB is likely to substantially improve the success of endovascular procedures for BTK disease. However, the recent results of the IN.PACT DEEP study that alarmed in terms of safety and lack of efficacy suggest that an abundance of caution is reasonable.

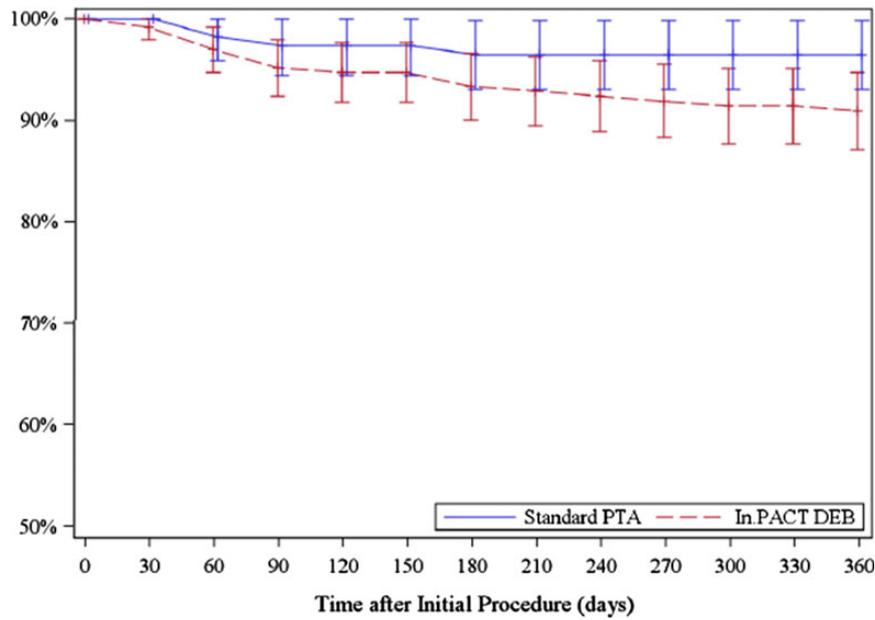


Figure 2 12-Month freedom from major amputations in the drug-coated balloon and plain old balloon angioplasty groups, from the In.PACT DEEP trial.

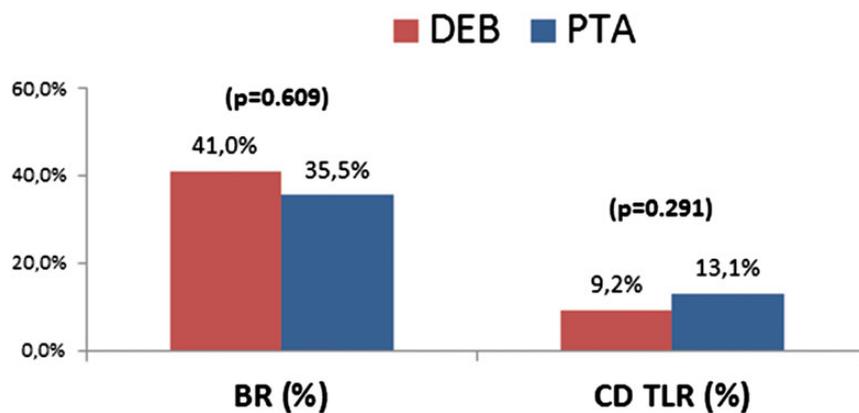


Figure 3 12-month binary restenosis and clinically driven target lesion revascularization, from the In.PACT DEEP trial.

Among patients with BTK arterial disease, there are multiple subgroups that require attention but for whom no specific recommendation can be made at this time, including patients with the following: tissue loss, arterial disease of the ankle and foot requiring treatment, recurrent stenosis following POBA, BTK ISR, and failing bypasses. Patients with limb-threatening wounds of category 5 or 6 face unique challenges. Longer term patency is desirable in these patients, but ultimately wound healing and limb salvage are the desired outcome and it is not yet clear that DCB will positively influence these

endpoints. There exists vital need for further investigation of DCB in a variety of BTK lesion subsets and clinical conditions.

Use of ancillary devices including atherectomy and stents

The combination of debulking followed by drug-coated technology to afford the ‘best’ outcome for both acute and long-term success

seems an attractive parallel use of these technologies. The DEFINITIVE LE trial,⁴² a 800-patient registry including patients with claudication and CLI using directional atherectomy (DA) resulted in a fair 1-year primary patency rate of 68 and 75% in the femoro-popliteal location for CLI patients and claudicants, respectively. The stent rate was as low as 3%.

Early small single-centre reports of the combination of DA and DCB has shown some promise in this approach for patients with lower limb arterial disease. In one protocol, the combination of DA and DCB (60 patients) was compared with DA and POBA (29 patients). The outcomes were primary patency of 84.7% in the DCB group compared with 43.8% in the POBA group.⁴³ Also, in heavily calcified lesions the combination of DCB provided a 90% freedom from clinically driven TLR in 30 patients studied from a single centre.⁴⁴ Thus, the combination of DA and DCB seems to be a logical treatment to continue with a *leave nothing behind* approach for arterial obstructive disease. Clearly, the scientific data are in its infancy and the further cost-analysis will need to be conducted. Just recently the DEFINITIVE AR trial was presented (T. Zeller, VIVA Las Vegas, 2014). DEFINITIVE AR is a prospective, multi-centre, 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. One hundred and twenty-one 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. The mean lesion length ranged from 9.7 to 11.9 cm. In the randomized groups, the primary endpoint, the per cent stenosis at 12 months, was similar in both cohorts angiographic patency ($\leq 50\%$ stenosis and without TLR) was 82.4% in the DA + DCB arm and 71.8% in the DCB arm. Major adverse event rate, defined as a composite of clinically driven TLR, death, and major amputation, was 11.6% for the randomized DA + DCB arm, 9.8% for the randomized DCB arm, and 5.9% for the severely calcified lesion registry arm ($P = \text{ns}$). This pilot study suggests trends to an added benefit for combination therapy (DA + DCB) in long and calcified lesions which was not observed in the DCB subgroup alone. Further investigation in larger, prospective, statistically powered randomized trials is warranted.

Additionally, the use of DCB combined with bare-metal nitinol stent on bail-out indication has been tested. Bail-out stents were used in 26 patients in the LEVANT I study. There were 14 DCB patients and 12 POBA patients who received stents. The LLL for the DCB alone and DCB stented group was 0.45 and 0.49 mm, respectively, whereas in the POBA alone and POBA/stent groups LLL was 1.19 and 0.90 mm, respectively (P -values not significant for both comparisons). In the IN.PACT SFA trial, there were fewer reported stents used and the outcomes of these small numbers would become difficult. In the DEBATE SFA trial lesions were pre-dilated before bare-metal stent placement with either DCB or POBA resulting in significant better 1-year outcomes for the DCB cohort (17 vs. 47.3%, $P = 0.008$ and TLR rate 17 vs. 32.7%, $P < 0.05$).⁴⁵

The additional potential for focal stenting for persistent dissections and acute vessel recoil seems attractive though, at this early stage, the indications or guidelines for use remain unclear.

Health-economic evaluation of drug-coated balloon 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.^{46,47} Its treatment represents a growing financial burden to healthcare systems.⁴⁸ Drug-coated balloon, as one of the most recent emerging revascularization strategies that holds the promise of reducing TLR in femoro-popliteal interventions further, are acutely more costly for healthcare providers and payers compared with standard endovascular strategies such as balloon angioplasty. Recent cost-effectiveness evaluations tried to analyse the impact of increased patency rates resulting in reduced TLR rates of DCB and DES on the long-term costs.^{49–51}

The most robust study summarized the clinical efficacy of four endovascular strategies (POBA, DCB, BMS, and DES) as index femoro-popliteal procedures.⁴⁹ 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. The drug-eluting strategies had a lower projected budget impact over 24 months compared with BMS and POBA in both the US Medicare and German healthcare 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, followed by POBA and DES, with DCB providing the lowest revenue. 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, followed by BMS, DES, and DCB.

Using base case clinical effectiveness assumptions and comparing the most effective therapy (DCB) to the least effective therapy (POBA), approximately for every four lesions treated with DCB as opposed to POBA, one TLR could be avoided over the 24-month horizon. For the US and German payer perspective, this increase in clinical efficacy could be obtained at overall cost savings of \$2870 per patient in the USA and €662 per patient in Germany over a 24-month period. Under a conservative assumption that 50% of the 175 000 reported 'lower extremity arterial angioplasty' cases in the US Medicare system and 75% of reported 61 400 'thigh artery balloon angioplasty' cases in Germany are currently treated with POBA, a change to a DCB strategy for the index procedure would lead to an annual cost reduction of \$250 million to US Medicare and of €30.5 million to payers in Germany.

A cost-effectiveness analysis based on the Swiss reimbursement system resulted in the following outcomes over a 1-year period:⁵⁰ POBA is ~90 000 Swiss francs more costly than DCB therapy due to repeat intervention costs, despite the greater DCB acquisition costs. However, POBA reimbursement is ~154 000 Swiss francs more than DCB from the physician/facility-provider perspective. The authors conclude that DCB may be cost-effective through prevention of TLR at 1-year follow-up. Financial incentives to improve DCB reimbursements may help to lower total healthcare costs.

Another analysis based on a discrete-event simulation model on cost-effectiveness from a health service perspective from England

including eight endovascular therapies (DES, DCB, BMS, brachytherapy, stent-grafts, cryoplasty) vs. standard of care concluded that DCB may be a cost-effective alternative to POBA with bail-out BMS.⁵¹

In conclusion, DES and DCB seem to offer clinical advantages over POBA and BMS. Drug-coated balloons 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.

The future of drug-coated balloon in the peripheral field

In the peripheral field, emerging data from randomized trials in the femoro-popliteal district^{17–20} including two pivotal studies (LEVANT II, data-on-file FDA 2014; IN.PACT SFA²⁶) created strong clinical evidence for the superiority of DCB over POBA. Market forecasts expect a billion dollar market in the 2020s for DCB in this district. However, conflicting data exist in the BTK area and lead to market withdrawal of a single device for the BTK indication. Furthermore, uncertainty about the combination of DCB with stents, atherectomy, or other treatment modalities exists.

The major limitation of DCB, especially in the coronary application, is dissections. To overcome this limitation, several attempts have been discussed like some kind of spot-stenting ('tack-it'), drug-coated scoring balloons,⁵² upfront atherectomy,⁴⁴ or the combination with fully bioabsorbable stents. Furthermore, the role of other drugs than paclitaxel, especially 'limus', remains unclear and has to be further investigated.^{7,53}

In conclusion, given the confusion generated by questionable clinical trials and the absence of clear evidence-based data, this experts' peripheral Positioning Document aims at defining the best indications for the use of this promising technology in peripheral artery disease management. The experts find a precise role of DCBs for the treatment of both native and restenotic femoro-popliteal lesions, whereas suggest a limited and tailored use DCBs for the treatment of BTK lesions, until future evidence will become available.

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