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Impact of Patient and Lesion Characteristics on Drug-Coated Balloon Angioplasty in the Femoropopliteal Artery: A Pooled Analysis of Four Randomized Controlled Multicenter Trials

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Abstract

Objectives The principal objective of this pooled analysis was to investigate various patient and lesion characteristics on late lumen loss (LLL) after drug-coated balloon (DCB) angioplasty.

Background Four randomized controlled trials (THUNDER, FEMPAC, PACIFIER, CONSEQUENT) were pooled to investigate the influence of various patient and lesion characteristics on DCB angioplasty and on plain old balloon angioplasty (POBA) in patients with femoropopliteal artery disease.

Methods Angiographic data from 355 patients were pooled to assess the impact of patient (demographics, cardiovascular risk factors, cardiovascular co-morbidities, Rutherford stages) and lesion-/procedure-related (location, occlusion, length, restenosis, calcification, subintimal crossing, post-dilatation, dissection, stenting) characteristics on LLL. Linear regression models were utilized with LLL as the dependent variable to determine the predictive value of cardiovascular and lesion-/procedure-related factors.

Results Observational statistics revealed that LLL was lower in the DCB group as compared to POBA independent of all tested patient variables. LLL after DCB was also independent of most lesion and procedural characteristics except for lesion length and bailout stenting. LLL increased with lesion length in both treatment groups. Bailout stenting did not improve LLL in the DCB group but did so in the POBA group (0.74 ± 1.07 mm vs. 1.22 ± 1.36 mm, $p = 0.043$).

Conclusions DCB was superior to POBA for all tested patient subgroups and lesion subgroups. Our results suggest that all patients and lesions benefit to a similar degree from the use of DCB. DCB-PTA should therefore be preferred to POBA in all patients with steno-occlusive femoropopliteal lesions.

Keywords Drug-coated balloon angioplasty · Femoropopliteal lesions · Late lumen loss · Pooled data analyses

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Introduction

In recent years, several studies have demonstrated significant benefits of DCBs over POBA in femoropopliteal lesions with regards to reduced restenosis rates and improved patency [1–3], which have been confirmed in recent meta-analyses [4, 5]. Angiographic late lumen loss (LLL) and binary restenosis rates (both quantitative measures of restenosis) were significantly reduced [6–9]. Clinically driven TLR, i.e., the clinical need for re-intervention, which represents an important clinical endpoint, was also substantially reduced in the DCB groups [2, 3]. Furthermore, the routine use of POBA, DCB and primary stenting was compared in terms of their different re-intervention rates and associated costs which revealed that primary DCB use was the most cost-effective choice [10, 11].

Nevertheless, the use of DCBs entails a higher initial cost [10, 11]. It is therefore an important question, whether the use of DCBs is advantageous for all patients and all lesion types, or whether certain patient or lesion characteristics could also be treated with POBA.

Since LLL was chosen as the primary endpoint for most landmark DCB trials, relatively small-sized study populations were needed to demonstrate angiographic superiority over POBA. For dedicated subgroup analyses, patient populations were too small in most of the published series. This led to the concept of the current study to pool original data from several previous studies to reach a higher total number of subjects, thus enabling more meaningful analyses of clinically relevant subgroups. The 6-month angiographic data of the THUNDER [6], FEMPAC [7], PACIFIER [8] and CONSEQUENT [9, 12] trials were pooled and used for dedicated linear regression analyses of patient, lesion and procedural characteristics. The purpose of these analyses was to elucidate and to quantify the improvements in terms of the 6-month LLL in the superficial femoral artery (SFA) and the popliteal artery (PA) after the use of DCBs as compared to POBA.

Methods

Study Design and Patients

Data from the prospective THUNDER, FEMPAC, PACIFIER and CONSEQUENT randomized controlled studies were pooled and analyzed. All four studies were designed, organized and analyzed by the same core research group and recruited patients between 2006 and 2016 in several German centers. Some of the centers participated in more than one of these studies. The study designs of FEMPAC, PACIFIER and CONSEQUENT were almost identical with a treatment arm and a single control arm (randomisation 1:1). In THUNDER, there was a third arm (randomization 1:1:1) which was treated with an intra-arterial administration of paclitaxel. This treatment group was not included in this analysis. Table 1 provides an overview of the key protocol and procedural details of the four studies. Inclusion criteria of the studies were very similar (Table 1, bottom part).

The primary endpoint of all studies was core laboratory-analyzed late lumen loss (LLL) on the basis of digital subtraction angiography (DSA) conducted at 6 months. LLL was defined as the difference between the minimal luminal diameter after the procedure and at 6 months. Core laboratories were blinded to procedural details including the used DCB or uncoated balloon catheters.

Study Devices

In THUNDER and FEMPAC, the same DCB with Paccocath® coating, i.e., a prototype catheter of Cotavance® (Bayer Schering/Medtronic), was used. In PACIFIER, the InPact® Pacific (Medtronic) was studied, whereas in the CONSEQUENT trial, the SeQuent® Please OTW (B. Braun Melsungen AG) was investigated (Table 1). All balloons were coated with the same dose of paclitaxel (3 μg/mm^2) with similar release properties despite different excipients.

Statistical Analysis

Correlation models for LLL and lesion length were assumed to be linear for simplicity reasons. For the overall population and for the two treatment groups, linear regression models with LLL, as the dependent variable, were defined to investigate the predictive value of cardiovascular factors, lesion morphological and procedural characteristics. A backward elimination algorithm with a criterion of $p > 0.1$ was used to find the most predictive variables per treatment group. With the background elimination algorithm, all factors which may have an explanatory value are considered before only non-relevant factors can be eliminated from the regression analysis.

To illustrate LLL in subgroups, box-and-whisker plots were preferred to reveal the median, quartiles, mild and extreme outliers. The standard conventions for the two types of outliers were used based on 0.5 and 3.0 times the interquartile ranges, respectively.

For selected subgroups, explorative two-factorial analysis of variance (ANOVA) and unpaired t tests or in the case of a non-Gaussian distribution parametric tests were conducted. SPSS version 24.0 (IBM, Munich, Germany) was used for all statistical analyses.

Table 1 Key protocol details and inclusion criteria of the pooled DCB studies

Main study	THUNDER	FEMPAC	PACIFIER	CONSEQUENT
Groups	DCB, POBA + intra-arterial paclitaxel	DCB, POBA	DCB, POBA	DCB, POBA
Patients in original study	154	87	85	153
Angiographic follow-up	57.7% (89/154)	74.7% (65/87)	81.2% (69/85)	73.2% (112/153)
Device name	Cotavance®	Cotavance®	In.Pact Pacific®	SeQuent® Please OTW
Drug	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel
Excipient	Iopromide	Iopromide	Urea	Resveratrol
Pre-dilatation	Mandatory only for occlusions	Mandatory only for occlusions	Mandatory only for occlusions	Mandatory only for occlusions
Stenting	Bailout only after prolonged post-dilatation	Bailout only after prolonged post-dilatation	Bailout only after prolonged post-dilatation	Bailout only after prolonged post-dilatation
Primary endpoint	Angiographic LLL at 6 months	Angiographic LLL at 6 months	Angiographic LLL at 6 months	Angiographic LLL at 6 months
Rutherford stage	1–5	1–5	1–5	2–4
Lesion localization	SFA and popliteal artery	SFA and popliteal artery	SFA and popliteal artery	SFA and popliteal artery
Degree of stenosis	≥ 70%	≥ 70%	≥ 70%	≥ 70%
Lesion length	> 2 cm	NA	3–30 cm	4–27 cm
Below knee runoff artery	≥ 1	≥ 1	≥ 1	≥ 1

Results

Baseline Data

Inter-study patient demographics for all four studies, including risk factors, co-morbidities and claudicant/critical limb ischemia (CLI) status are detailed in Table 2 along with lesion characteristics and procedural details. As previously reported, intra-study comparisons did not reveal significant differences of baseline data between the POBA and the DCB groups [6–9].

Linear Regression Model for LLL in All Patients

All patient, lesion and procedural characteristics (Figs. 1 and 2) were used for the initial regression model to study their predictive values. Due to the highly significant impact of DCB angioplasty, i.e., the effect of the treatment group to reduce LLL, the linear regression models were then refined and applied per treatment group following the backward elimination (p value > 0.1) routine.

This decision to separate the linear regression models in treatment groups reflects clinical decision paths to choose DCB angioplasty over POBA.

Linear Regression Model for LLL in Treatment Groups

In POBA patients, only four independent variables remained in the analysis after backward elimination (see Table 3, top half). Besides lesion length ($p = 0.004$), CLI status ($p = 0.040$), presence of calcification ($p = 0.034$) and bailout stenting ($p = 0.042$) were significant predictors for LLL in the POBA group. All other patient and lesion variables had no effect on LLL.

In contrast, the linear regression model for patients treated with DCBs (Table 3, bottom half), only lesion length ($p = 0.006$) and cigarette smoking ($p = 0.027$) were significant predictors, while all other patient and lesion variables had no effect on LLL.

To further elucidate the above findings, ANOVA was performed for the significant predictors in both groups. These were CLI status, calcium burden, bailout stenting and lesion length (Table 4).

Smoking Status

Smokers treated with DCB had a lower LLL as compared to non-smokers (0.10 ± 1.07 mm vs. 0.51 ± 1.05 mm, $p = 0.02$). However, in both smokers and non-smokers,

Table 2 Patient characteristics, lesion and procedural details of pooled DCB studies

Study name	THUNDER		FEMPAC		PACIFIER		CONSEQUENT	
Study group	POBA	DCB	POBA	DCB	POBA	DCB	POBA	DCB
Patients (N)	54	48	42	45	47	44	78	75
Age (years)	68 ± 9	69 ± 8	70	67	71 ± 7	71 ± 9	68 ± 9	68 ± 9
Female gender	37%	35%	40%	40%	36%	41%	24%	40%
Diabetes	46%	50%	55%	40%	28%	43%	39%	35%
Hypertension	83%	79%	81%	78%	66%	66%	80%	77%
Hypercholesteremia	63%	69%	59%	58%	47%	50%	52%	56%
History of smoking	22%	23%	36%	40%	60%	49%	49%	46%
Coronary artery disease	35%	31%	41%	38%	32%	32%	40%	42%
Cerebro-vascular disease	35%	31%	41%	38%	11%	32%	5%	4%
Claudicants	98%	90%	98%	96%	96%	100%	100%	100%
Critical limb ischemia	2%	10%	7%	4%	4%	0%	0%	0%
Mean lesion length (cm)	7.4	7.5	4.7	4.0	6.6	7.0	12.6	13.7
Occlusions	26%	27%	19%	13%	23%	38%	29%	23%
Mean diameter stenosis	91%	98%	84%	84%	80%	73%	77%	76%
Restenotic lesions treated	30%	38%	33%	36%	17%	32%	5%	8%
Lesion Calcification	52%	50%	52%	53%	66%	64%	68%	53%
Subintimal crossing	9%	4%	NA	NA	6%	2%	15%	13%
Post-dilatation	29%	43%	10%	16%	36%	51%	44%	40%
Dissections	47%	74%	52%	53%	53%	41%	46%	44%
Bailout stenting	22%	4%	14%	9%	34%	21%	19%	14%

LLL was significantly lower after DCB ($p < 0.001$ for both subgroups, Table 4).

Critical Limb Ischemia (CLI)

CLI patients had higher LLL than claudicants in the POBA group (1.85 ± 1.42 mm vs. 1.06 ± 1.3 mm, $p = 0.052$), but not in the DCB group. Both CLI patients and claudicants had significantly lower LLL after DCB ($p < 0.01$ for both subgroups, Table 4).

Lesion Length

Assuming a linear correlation function for LLL and lesion length, there was a significant albeit weak positive correlation between these two variables (DCB: $R^2 = 0.055$, POBA: $R^2 = 0.041$). Both treatment groups had identical inclines, i.e., a LLL increase of 0.03 mm per cm lesion length (Fig. 3). The only difference between treatments is the higher positive offset in the POBA group which amounts to a mean LLL increase of 0.77 mm as compared to DCB (Fig. 1). ANOVA in lesion length categories (< 5 cm/5–10 cm/> 10 cm) also revealed that LLL increased with lesion length and that in any lesion length category DCB outperformed POBA (Table 4).

Calcium Burden

Calcified lesions had higher LLL than non-calcified lesions in the POBA group (1.35 ± 1.46 mm vs. 0.95 ± 1.19 mm, $p = 0.051$), but not in the DCB group. Both calcified and non-calcified lesions had significantly lower LLL after DCB ($p < 0.001$ for both subgroups, Table 4).

Bailout Stenting

In patients who had to undergo bailout stenting, the LLL in the DCB group was 0.43 ± 1.25 mm ($n = 18$) and in POBA patients 0.74 ± 1.07 mm ($n = 39$) which failed statistical significance ($p = 0.348$). In contrast, if no bailout stenting was done, DCBs outperformed POBA (0.34 ± 1.05 mm vs. 1.22 ± 1.36 mm, $p < 0.001$). In the POBA group, bailout stenting significantly reduced LLL (0.74 ± 1.07 mm vs. 1.22 ± 1.36 mm, $p = 0.043$), but this was not the case in the DCB group (Table 4).

Adverse Events

The rates for all-cause death, TLR and amputations were available at 24 months. Except for the TLR rates (POBA: 40.4% vs. DCB: 16.3%, $p < 0.001$), there were no significant differences. All-cause death rates at 24 months were 5.5% in the POBA and 7.9% in the DCB group

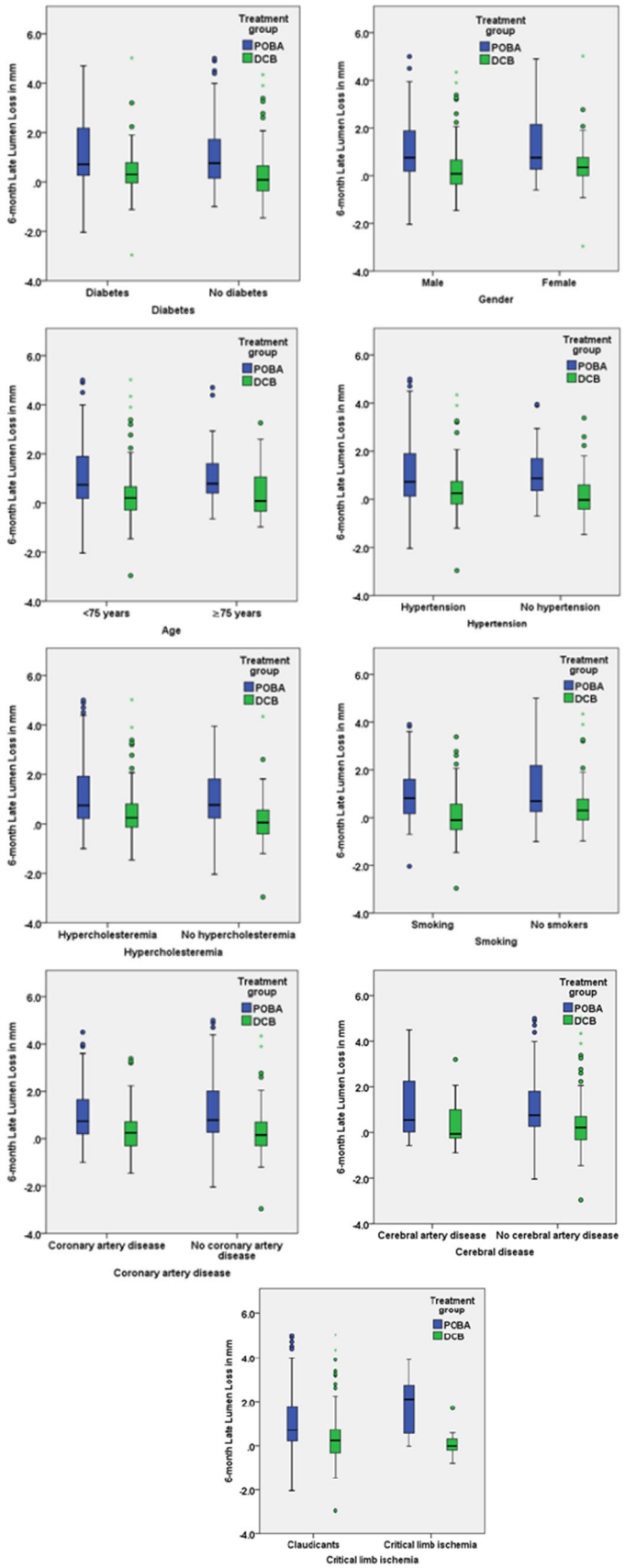

Fig. 1 Late lumen loss in demographic and risk factor subgroups

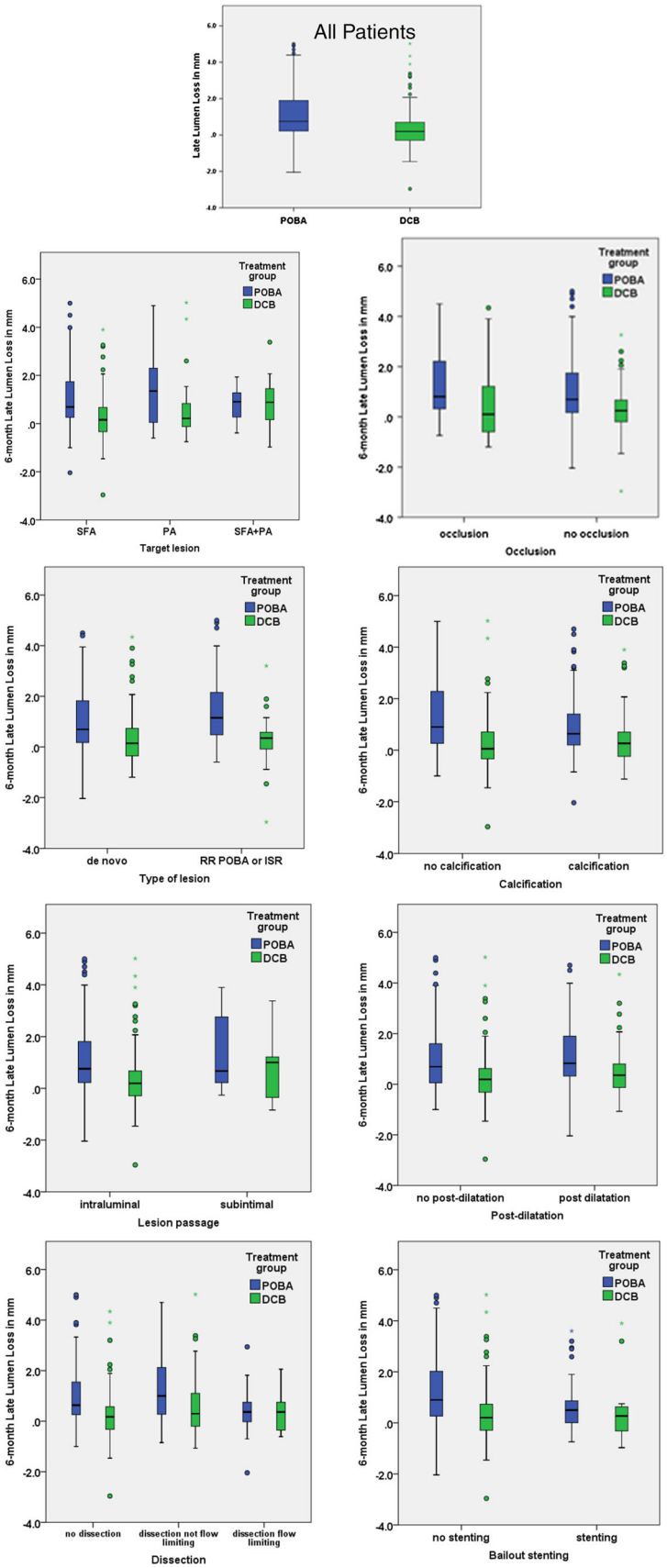

Fig. 2 Late lumen loss in lesion morphological and procedural subgroups

Table 3 Linear regression model results with LLL as the dependent variable and various predictive variables overall and their p values before and after backward elimination

Treatment group	Predictive variable	p value
POBA before backward elimination	Diabetes	0.358
	Gender	0.770
	Age	0.560
	Hypertension	0.346
	Hypercholesteremia	0.364
	Cigarette smoking	0.538
	Critical limb ischemia	0.021
	Bailout stenting	0.067
	Dissection	0.791
	Lesion passage (intraluminal, subintimal)	0.723
	Post-dilatation	0.362
	Occlusion	0.138
	Calcification	0.025
	Lesion length	0.005
POBA after backward elimination	Critical limb ischemia	0.040
	Bailout stenting	0.042
	Calcification	0.034
	Lesion length	0.004
DCB before backward elimination	Diabetes	0.700
	Gender	0.302
	Age	0.767
	Hypertension	0.675
	Hypercholesteremia	0.207
	Cigarette smoking	0.051
	Critical limb ischemia	0.246
	Bailout stenting	0.949
	Dissection	0.500
	Lesion passage (intraluminal, subintimal)	0.723
	Post-dilatation	0.264
	Occlusion	0.488
	Calcification	0.972
	Lesion length	0.019
DCB after backward elimination	Hypercholesteremia	0.088
	Cigarette smoking	0.027
	Lesion length	0.006

($p = 0.317$). The corresponding amputation rates were 2.3% vs. 2.8% ($p = 0.742$).

Discussion

Mean LLL was highly dependent on the treatment used, i.e., significantly lower after DCB as previously published. Importantly, LLL in the DCB group was independent of all tested patient variables, cardiovascular risk factors, cardiovascular co-morbidities and disease stage (claudication versus critical limb ischemia). These findings are consistent with the results of Laird et al. [2] who also did not find a significant impact of patient gender, age, diabetes or Rutherford stages on primary patency in their subgroup analysis of the INPACT SFA study.

In contrast to the findings of Tepe and co-workers originating from a smaller retrospective analysis [13], we could not find an impact of diabetes or coronary artery disease on LLL in the DCB group. We detected a lower LLL in smokers within the DCB group (0.10 ± 1.07 mm vs. 0.51 ± 1.05, $p = 0.02$), which is counter-intuitive. Given the sufficiently balanced groups (smokers $n = 61$, non-smokers $n = 100$), this appears to be a finding to be explored further. Nonetheless, in both smokers and non-smokers, LLL was significantly lower after DCB.

Table 4 Late lumen loss in relevant subgroups

Late lumen loss in mm	DCB (n = 161)	POBA (n = 174)	p values
No smoking history	0.51 ± 1.05 (n = 100)	1.22 ± 1.46 (n = 71)	$p_{\text{non-smoker}} < 0.001$
Smoking history	0.10 ± 1.07 (n = 61)	0.97 ± 1.10 (n = 103)	$p_{\text{smoker}} < 0.001$
	$p_{\text{DCB}} = 0.020$	$p_{\text{POBA}} = 0.202$	
Claudicants	0.38 ± 1.10 (n = 148)	1.06 ± 1.30 (n = 163)	$p_{\text{claudicants}} < 0.001$
Critical limb ischemia	0.10 ± 0.60 (n = 13)	1.85 ± 1.42 (n = 11)	$p_{\text{CLI}} = 0.002$
	$p_{\text{DCB}} = 0.383$	$p_{\text{POBA}} = 0.052$	
Lesion length ≤ 5 cm	0.19 ± 0.81 (n = 70)	0.78 ± 1.16 (n = 79)	$p_{\leq 5\text{cm}} = 0.001$
Lesion length > 5–10 cm	0.31 ± 1.15 (n = 33)	1.40 ± 1.26 (n = 39)	$p_{> 5\text{–}10\text{cm}} < 0.001$
Lesion length > 10 cm	0.57 ± 1.27 (n = 58)	1.38 ± 1.46 (n = 56)	$p_{> 10\text{cm}} = 0.001$
	$p_{\text{DCB}} = 0.137$	$p_{\text{POBA}} = 0.009$	
No calcification	0.32 ± 1.21 (n = 71)	1.35 ± 1.46 (n = 69)	$p_{\text{no calcification}} < 0.001$
Calcification	0.38 ± 0.95 (n = 90)	0.95 ± 1.19 (n = 105)	$p_{\text{calcification}} < 0.001$
	$p_{\text{DCB}} = 0.759$	$p_{\text{POBA}} = 0.051$	
Bailout stenting	0.43 ± 1.25 (n = 18)	0.74 ± 1.07 (n = 39)	$p_{\text{stent}} = 0.348$
No bailout stenting	0.34 ± 1.05 (n = 143)	1.22 ± 1.36 (n = 135)	$p_{\text{no stent}} < 0.001$
	$p_{\text{DCB}} = 0.749$	$p_{\text{POBA}} = 0.043$	

Similarly, LLL in the DCB group was independent of most of the lesion and procedural characteristics tested, except for lesion length and bailout stenting.

As depicted in Fig. 3, the longer the lesion, the higher the LLL after DCB angioplasty or POBA. However, the advantage of DCB over POBA is preserved throughout all lengths as we found significantly lower LLL after DCB for all lesion length subgroups. This finding is consistent with the results of Laird et al. [2], who found significantly better 24-month primary patency after DCB as compared to POBA in all lesion length subgroups (up to 18 cm) in the INPACT SFA study. Similarly, in the AcoArt I Trial [14], LLL was significantly lower after DCB as compared to POBA in the overall population and in the lesion subgroup with a lesion length > 20 cm.

Bailout stenting did not improve LLL in the DCB group over non-stented lesions (0.43 ± 1.25 mm vs. 0.34 ± 1.05, $p = 0.749$); however, it did in the POBA group (0.74 ± 1.07 mm vs. 1.22 ± 1.36 mm, $p = 0.043$). Direct comparison of DCB and POBA in the bailout stenting subgroup showed lower LLL for DCB (0.43 ± 1.25 mm vs. 0.74 ± 1.07), but this was not statistically significant ($p = 0.348$) possibly due to the small sample size of only 18 stented lesions in the DCB group. In the AcoArt I trial, a statistically significant reduction of LLL by DCB as compared to POBA was found in the subgroup of provisional stenting, which was also small [14]. In the DEBATE-SFA study with 55 lesions in each group, there was a significant reduction in the restenosis rate in lesions treated with DCB followed by primary stenting versus conventional balloon angioplasty followed by primary stenting [15].

Calcium burden may present a barrier of drug transfer after DCB angioplasty. Fanelli et al. [16] found less positive effects of DCB on the reduction in LLL with increasing calcium burden. A limitation of Fanelli's study is the use of ultrasound for LLL measurements. Similarly, Tepe et al. [17] observed an association between the severity of lesion calcification and LLL after treatment with DCB in a small retrospective study. However, there is no generally accepted scoring system for lesion calcification in peripheral arteries and the definition of calcifications across published studies is quite heterogeneous. We only had binary data, i.e., the presence or absence of any lesion calcification available for our analyses and found no differences in LLL between lesions with or without calcifications in the DCB group, while there was a difference after POBA with higher LLL in calcified lesions. A detailed analysis of the degree of calcifications, which was not possible based on our data, may have produced different results for the DCB group. Furthermore, post-dilatations did not improve LLL in both groups which was not reported elsewhere.

Limitations

Our study has several limitations. First, it is a post hoc subgroup analysis of prospectively collected data over a considerable time span which coincided with the overall learning curve to use DCBs. Second, different DCBs were used in three of the four pooled studies. However, each of the individual studies showed a significant reduction in LLL, irrespective of the DCB used. Third, only a binary scoring of lesion calcification was available. Fourth, since

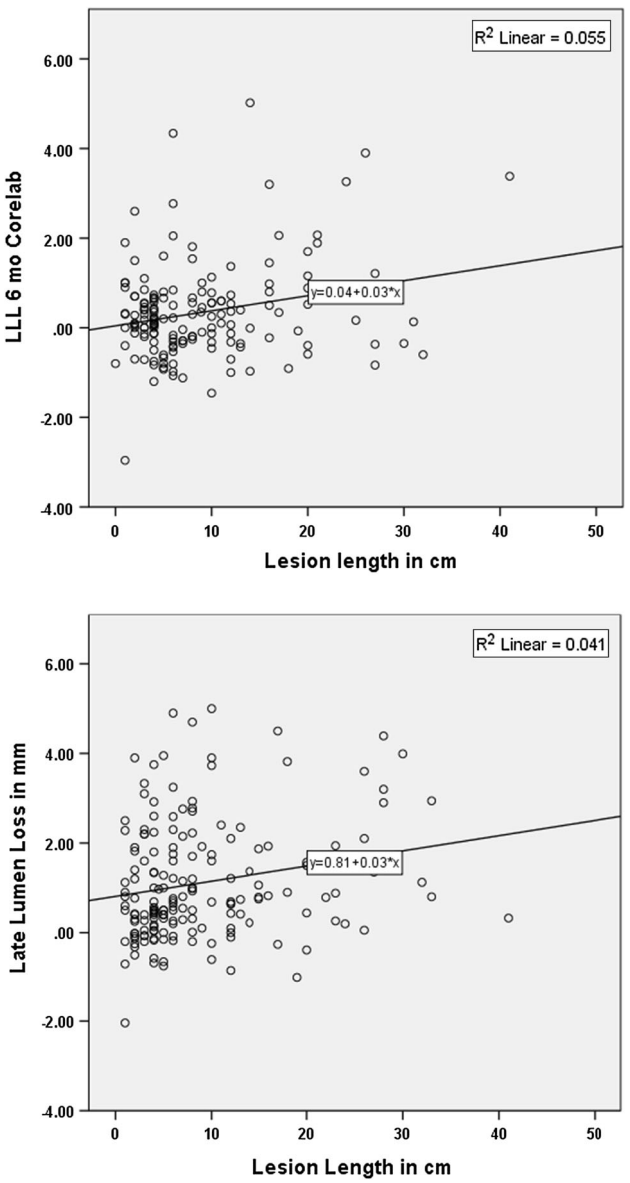

Fig. 3 Late lumen loss versus lesion length in the DCB group (top panel) and the POBA group (bottom panel), all available data, i.e., DCB/POBA with and without bailout stenting

we analyzed LLL our follow-up is limited to 6–8 months post-intervention.

Conclusions

The improved LLL outcome after DCB angioplasty as compared to POBA was independent of patient-related variables such as age, gender, cardiovascular risk factors and co-morbidities. Importantly and contrary to previous reports, there was no negative effect of diabetes or coronary artery disease on angiographic outcomes after DCB use. Most lesion variables also had no impact on LLL after treatment with DCB and POBA. Importantly, a clear benefit of DCB was found for all lesion length subgroups.

Our results suggest that all patients and lesions benefit to a similar degree from the use of DCB. DCB-PTA should therefore be preferred to POBA in all patients with stenoocclusive lesions of the SFA and popliteal artery, irrespective of lesion types and patient risk factors or co-morbidities.

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Compliance with Ethical Standards

Conflict of interest In the previously conducted randomized controlled trials that provided the raw data for this analysis, TA, MW, TZ and GT received research grants from Medtronic, whereas TA, TZ and GT obtained research funding from B.Braun. MWW is a full-time employee of the Medical Scientific Affairs department of B.Braun Melsungen AG.

Ethical Approval All studies were approved by the Federal Institute for Drugs and Medical Devices, by the Federal Agency for Radiation Protection and by all relevant ethics committees of participating centers. Patients gave written informed consent prior to inclusion. An independent critical event committee was installed to adjudicate event rates. Blinded quantitative angiographic analysis was conducted by an independent core lab. All trials were registered with the US National Institutes of Health prior to recruitment. This trial was conducted in accordance with the updated Declaration of Helsinki and other relevant guidance.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Rosenfield K, Jaff MR, White CJ, LEVANT 2 Investigators, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. N Engl J Med. 2015;373:145–53.
2. Laird JR, Schneider PA, Tepe G, IN.PACT SFA Trial Investigators, et al. Durability of treatment effect using a drug-coated balloon for femoropopliteal lesions: 24-month results of IN.PACT SFA. J Am Coll Cardiol. 2015;66:2329–38.
3. Schroeder H, Werner M, Meyer, ILLUMENATE EU RCT Investigators, et al. Low-dose paclitaxel-coated versus uncoated percutaneous transluminal balloon angioplasty for femoropopliteal peripheral artery disease: one-year results of the ILLUMENATE European randomized clinical trial (randomized trial of a novel paclitaxel-coated percutaneous angioplasty balloon). Circulation. 2017;135:2227–36.
4. Katsanos K, Spiliopoulos S, Paraskevopoulos I, et al. Systematic review and meta-analysis of randomized controlled trials of paclitaxel-coated balloon angioplasty in the femoropopliteal arteries: role of paclitaxel dose and bioavailability. J Endovasc Ther. 2016;23:356–70.
5. Giacoppo D, Cassese S, Harada Y, et al. Drug-coated balloon versus plain balloon angioplasty for the treatment of femoropopliteal artery disease: an updated systematic review and meta-

analysis of randomized clinical trials. JACC Cardiovasc Interv. 2016;9:1731–42.
6. 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.
7. 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.
8. 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.
9. Tepe G, Gögebakan Ö, Redlich R, et al. Angiographic and clinical outcomes after treatment of femoro-popliteal lesions with a novel paclitaxel-matrix coated balloon catheter. Cardiovasc Intervent Radiol. 2017;40:1535–44.
10. Pietzsch JB, Geisler BP, Garner AM, et al. 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.
11. Salisbury AC, Li H, Vilain KR, et al. Cost-effectiveness of endovascular femoropopliteal intervention using drug-coated balloons versus standard percutaneous transluminal angioplasty: results from the IN.PACT SFA II trial. JACC Cardiovasc Interv. 2016;9:2343–52.
12. Albrecht T, Waliszewski M, Roca C, et al. Two-Year clinical outcomes of the CONSEQUENT trial: Can femoropopliteal lesions be treated with sustainable clinical results that are economically sound? Cardiovasc Intervent Radiol. 2018;41:1008–14.
13. Tepe G, Zeller T, Schnorr B, 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.
14. Jia X, Zhang J, Zhuang B, et al. Acotec drug-coated balloon catheter: randomized, multicenter, controlled clinical study in femoropopliteal arteries: evidence from the AcoArt I trial. JACC Cardiovasc Interv. 2016;9(18):1941–9.
15. Liistro F, Grotti S, Porto I, et al. Drug-eluting balloon in peripheral intervention for the superficial femoral artery: the DEBATE-SFA randomized trial (drug eluting balloon in peripheral intervention for the superficial femoral artery). JACC Cardiovasc Interv. 2013;6:1295–302.
16. Fanelli F, Cannavale A, Gazzetti M, et al. Calcium burden assessment and impact on drug-eluting balloons in peripheral arterial disease. Cardiovasc Intervent Radiol. 2014;37:898–907.
17. Tepe G, Beschorner U, Ruether C, et al. Drug-eluting balloon therapy for femoropopliteal occlusive disease: predictors of outcome with a special emphasis on calcium. J Endovasc Ther. 2015;22:727–33.