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CLINICAL INVESTIGATION

Two-Year Clinical Outcomes of the CONSEQUENT Trial: Can Femoropopliteal Lesions be Treated with Sustainable Clinical Results that are Economically Sound?

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Abstract

Purpose The previously reported 6-month angiographic and 12-month clinical outcomes of the CONSEQUENT trial demonstrated the safety and efficacy of a novel paclitaxel–resveratrol-coated balloon for the treatment of lesions in the femoropopliteal segment. The purpose of this report is to present the 2-year results including a cost-benefit analysis for Germany.

Materials and Methods Patients with symptomatic peripheral artery occlusive disease in femoropopliteal lesions were randomized either to drug-coated balloon (DCB, $n = 78$) or plain old balloon angioplasty (POBA, $n = 75$). As secondary endpoints, the 2-year clinical results consisting of target lesion revascularization (TLR), patency and increase in walking distance were recorded. Based on the Kaplan–Meier analyses for TLR and other adverse events, a cost-benefit analysis was conducted for the German DRG system.

Results There were no additional TLRs in both groups between 14 and 24 months so that the corresponding rates remained significantly different between the treatment groups (DCB: 19.1 vs. POBA 40.6%, $p = 0.007$). At 2 years, the patency rate was significantly higher in the DCB group (72.3 vs. 48.4%, $p = 0.006$). The walking distance increase was also significantly higher after DCB angioplasty (172 ± 103 vs. 52 ± 136 m, $p = 0.001$). We estimated 2-year cost savings of € 1111.97 per patient treated with DCB instead of POBA.

Conclusions The use of paclitaxel–resveratrol matrix-coated peripheral balloons compared to POBA was associated with a significantly reduced TLR rate, superior patency and substantial cost savings at 2 years.

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Background

The previously published results of the CONSEQUENT trial [1] (Clinical Trial on Peripheral Arteries treated with SeQuent® Please OTW Paclitaxel-Coated Balloon Catheter) revealed that 6-month late lumen loss, target lesion revascularization (TLR) and patency rates at 12 months were significantly better in patients treated with resveratrol–paclitaxel-coated balloons as compared to those who underwent revascularization with plain old balloon angioplasty (POBA). Despite these encouraging results, longer-term data are necessary to evaluate the sustained anti-restenotic effect and its clinical benefits for the patient.

A critical aspect of the treatment of femoropopliteal lesions with drug-coated balloons (DCB) is the sustainability of clinical results over longer time spans and the expected benefits for the patients as evaluated by Herten et al. [2]. The IN.PACT superficial femoral artery (SFA) trial [3] demonstrated that a urea–paxlitaxel coating is effective to maintain a significantly lower TLR rate as compared to POBA treatment. It is noteworthy that between the 1- and 2-year follow-up the freedom from TLR Kaplan–Meier curves remained parallel indicating that the grand majority of TLRs occurs in the first post-procedural year.

Given these encouraging results of the IN.PACT SFA trial, a cost-effectiveness analysis was conducted by Salisbury et al. [4] for the US healthcare system. They concluded that despite the initially higher cost for DCB angioplasty, there were cost savings over a 24-month time span of $576 for this particular DCB over POBA. Pietzsch et al. [5] studied the accumulated costs also over a time span of 2 years following various revascularization strategies such as DCB, POBA, bare metal stents (BMS) and drug eluting stents (DES) for the US and German reimbursement systems. They concluded that DCB and DES are the most cost-effective treatment options for PAOD patients when treating femoropopliteal lesions. Two-year cost savings compared to POBA were $2900 in the USA and €671 in Germany.

The purpose of this study was to report the clinical effectiveness of the paclitaxel/resveratrol balloon technology and its cost effectiveness at 2 years.

Methods and Results

Study Design and Patients

As previously reported, the CONSEQUENT trial (Clinical Trial on Peripheral Arteries Treated With SeQuent® Please OTW Paclitaxel-Coated Balloon Catheter, ClinicalTrials.gov Identifier: NCT00520507) is a prospective multicenter, controlled two-armed, randomized (DCB vs. POBA 1:1) study conducted in Germany [1]. In addition to the primary angiographic endpoint late lumen loss at 6 months, clinical outcomes such as target lesion revascularization (TLR), patency, ankle brachial index and walking distance and changes in Rutherford classifications were recorded at 6, 12 and at 24 months.

In- and exclusion criteria were previously published in detail [1]. Briefly, symptomatic PAOD patients (Rutherford classes 2–4) could be treated in more than one femoropopliteal lesion with a diameter stenosis $\geq$ 70% and 4–27 cm in length. Heavily calcified lesions, occlusions, de novo or restenotic lesions after failed POBA were also allowed. In-stent restenoses were excluded and flow-limiting dissections or unacceptable recoil (> 30%) could be treated with additional bare metal stents. Longer lesions were treated with at least two DCBs and 1-cm overlap. Only occlusions had to be pre-dilated.

An independent critical event committee was installed to adjudicate adverse events and their relationship with the device.

Study Devices

A matrix-coated DCB (SeQuent® Please OTW, B.Braun Melsungen AG) or uncoated balloons of identical catheter design and balloon dimensions were used. The coating technology with a dose 3-µg paclitaxel/mm^2 balloon surface was described elsewhere [1]. One development target for this coating was to enhance the mechanical stability and coating integrity to allow challenging lesion crossing without significant drug loss before balloon inflation.

Comedication

Heparin at a dose 50–100 U i.a. per kg body weight was administered prior to the intervention. In addition, a 600 mg loading dose of clopidogrel was given unless the patient was already on long-term thienopyridines. Acetylsalicylic acid at a dose of $\geq$ 100 mg/d was recommended life long. A clopidogrel maintenance dose of 75 mg/day for 12 weeks was mandatory in both groups.

Ethics

The Federal Institute for Drugs and Medical Devices (Ref. 95.05-5660-8211), the Federal Agency for Radiation Protection (Ref. Z5-22462/2) and all relevant ethics committees of participating centers approved the study. Written informed consent prior to inclusion was obtained by all patients. Furthermore, an independent clinical event committee adjudicated all adverse and serious adverse events. This trial was registered with the US National Institutes of Health (clinicaltrials.gov NCT01970579) and conducted in accordance with the most recent Declaration of Helsinki at the time of patient recruitment.

Statistical Analysis

The number of patients per group was estimated based on the angiographic endpoint late lumen loss [1]. Whenever applicable, the two-sided Fisher's exact test or the Chi^2 were used to analyze dichotomous variables. In case the Shapiro–Wilk test revealed a strong deviation from normal distribution within each treatment group, the Mann–Whitney *U* test was used to analyze continuous variables. Otherwise the unpaired *t* test was utilized.

In addition, a retrospective cost-effectiveness analysis was undertaken using a Markov analytic decision model which had inputs from the 24-month clinical data and the direct medical costs (Table 1) obtained from the German DRG system [6]. To calculate to most realistic initial cost penalty when using DCBs a weighted additional cost was estimated based on the number of DCBs used per target lesion. For simplicity reasons, however, we assumed an average of two DCBs per patient and target lesion based on the actual 1.56 DCBs per patient and lesion in the study population. Figure 1 depicts the Markov model and the health states that the patient can pass through post-angioplasty such as no event, target lesion revascularization (TLR) which includes all-cause TLR with or without complications, major and minor amputations of the target limb and the final absorbing health state of death.

The primary health outcome considered was the time free of revascularization in months. The clinical data are reported at different time intervals than those in the Markov model. Therefore, the rates were converted to reflect the monthly cycle of the model using the following equation: rate $n = 1 - (1 - \text{Overall rate}) * (\text{Time n/Overall time})$. In addition, the model will be developed to analyze the costs following a cohort of 1000 patients throughout 20 years [7].

Results

Patient, Lesion and Procedural Characteristics

A total of 153 patients (DCB: 78 patients, POBA: 75 patients) were recruited from November 2013 to April 2015. Their demographics, cardiovascular risks and lesion morphological baseline data were equally balanced between the treatment groups as previously reported [1]. Noteworthy is that the complexity of the lesions was higher that in most previous DCB studies with a mean lesion length of 13.2 ± 10.4 cm and an occlusion rate of 26.1% (40/153, Table 2).

Since pre-dilatation was only mandatory in occlusions, 55.6% (85/153) of the patients were pre-dilated without differences between both treatment groups ($p = 0.448$).

Clinical Results at 24 Months

The actual follow-up intervals were 24.6 ± 1.8 months in the DCB group and 24.4 ± 3.0 in the POBA group ($p = 0.557$). The 24-month TLR rates (Table 2) were 19.1% (13/68) in the DCB group and 40.6% (26/64) in the POBA group ($p = 0.007$). The corresponding patency rates (presence of angiographic binary restenosis, i.e., > 50% or peak systolic velocity ratio > 2.4) were 72.3% (49/66) in patients treated with DCB and 48.4% (31/64) in the POBA group ($p = 0.006$). At 24 months, the accumulated all-cause mortality rates were 2.9% (2/70) and 1.5% (1/65) in DCB and POBA patients, respectively.

The censored walking distance was higher in the DCB group (DCB: 172 ± 103 m, $n = 28$ vs. 52 ± 136 m, $n = 20$; $p = 0.001$). The Rutherford category shift was numerically higher in the DCB treatment arm but did not reach statistical significance (2.1 ± 1.3 vs. 1.7 ± 1.3, $p = 0.113$). There were no additional amputations since the 12-month follow-up. The Kaplan–Meier curve revealed no additional TLRs in both treatment groups between the already reported follow-up at 12 ± 2 months and the final clinical follow-up at 24 months (Fig. 2). Log-rank analysis ($p = 0.008$) confirmed the significantly reduced TLR rate in DCB patients.

Cost-Efficacy DCB vs. POBA

The patients entered the model in the DCB treatment or the POBA arm in the "TLR" stage and passed through the model accordingly. The results of the analysis are shown in Table 3.

The analysis showed that the DCB treatment arm incurs a higher initial cost (€4154.11, see Table 1: € 3193.80 + €860.31) compared to POBA (€3193.80) but

Table 1 Healthcare costs in the German DRG system [6]

Parameter	Value	Reimbursement reference code
Initial revascularization		
Initial intervention with POBA or DCB base case	€3193.80	G-DRG F59D
Cost penalty DCB versus POBA[a]	€860.31	ZE137.02
Repeat revascularization (TLR)		
DCB	€3451.17	G-DRG F59D + ZE137.01
POBA	€3193.80	G-DRG F59D
Amputation		
Minor	€4118.00	G-DRG F28C
Major	€5478.00	G-DRG 801D
Thrombectomy	€2704.00	G-DRG F59C
Blood loss anemia	€–	G-DRG F59D

[a]To account for multiple DCB use per patient, an average additional cost was based on €860.31 (ZE137.02) which corresponds to two DCBs per lesion and patient

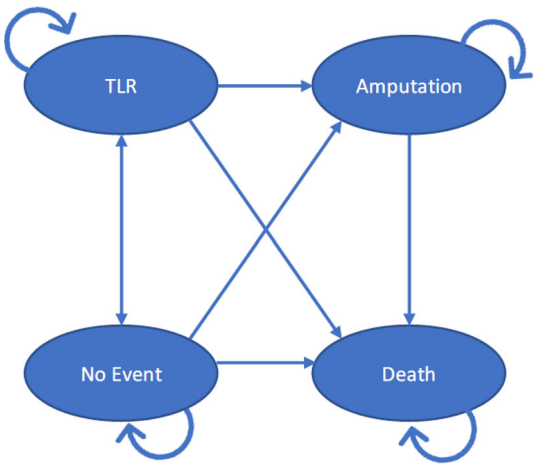

Fig. 1 Markov model [7]

the acquisition cost is offset by later cost savings from decreased revascularization events. The relatively higher incremental cost-effectiveness ratio (ICER) is due to the slight improvement in months free from TLR. Sensitivity analysis was also performed and the overall cost savings depended highly on the initial procedure and complications of the patient as well as the length of the lesion. However, DCB was still found to be the most cost-effective option approximately 70% of the time with a ceiling ratio of € 2000.00.

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Discussion

As pointed out by Byrne et al. [9], there is a plethora of commercially available DCBs to treat PAOD. All of them use paclitaxel as the active anti-restenotic agent and various excipients such as iopromide [10, 11], urea [3, 12], polysorbate and sorbitol [13, 14], polyethylene glycol [15, 16], butyryl-tri-n-hexyl citrate [17], magnesium stearate [18] and resveratrol [1].

Katsanos et al. [19] conducted a meta-analysis on some of the aforementioned DCB technologies and concluded that overall DCBs are effective to reduce 6-month TLRs by more than 50% in comparison with POBA, which is in agreement with our TLR rates of 19.1% (DCB) and 40.6% (POBA), however, at 24 months. As observed in the IN.PACT SFA trial [3], there were no new reported events between 14 and 24 months in our trial. This leads us to the conclusion that the efficacy of DCB angioplasty is primarily demonstrated in the first 14 months following the index intervention. One detail that should be mentioned is that some patients were lost to follow-up during this post-procedural time bracket (DCB: 73 patients at 1 year, 68 patients at 2 years, POBA: 69 patients vs. 64 patients). In the IN.PACT SFA study, the all-cause TLR rate at 24 months was 10.1%, which is lower than our corresponding 19.1% rate. However, in the IN.PACT SFA trial, the lesions were substantially shorter with 8.9 ± 4.9 cm than the 13.7 ± 12.2 cm in our trial. Also in the recently published 1-year results of the ILLUMINATE randomized controlled trial (RCT) which investigated a low-dose paclitaxel DCB with polyethylene glycol as the excipient the lesion lengths were quite short with 8.0 ± 4.5 cm [20]. This in turn makes an inter-study comparison of the all-cause TLR rate at 12 months (DCB: 9.5% vs. POBA 17.9%, $p = 0.043$) with our 12-month all-cause TLR rate of 17.8% in the DCB group difficult since by nature the lesion

Table 2 Selected baseline data and clinical results at 6, 12 and 24 months

	Drug-coated balloon	Uncoated balloon	*p* value
Patients	78	75	–
Age, years	68.2 ± 8.5	68.0 ± 9.0	0.884
Reference vessel diameter, mm	5.06 ± 0.77	5.38 ± 0.94	0.050
Lesion length, cm	13.7 ± 12.2	12.6 ± 8.2	0.540
Target lesion total occlusions	18 (23.1%)	22 (29.3%)	0.462
Pre-procedure			
Censored walking distance, m	149 ± 97	163 ± 77	0.528
Target leg ABI	0.83 ± 0.17	0.82 ± 0.14	0.749
6 months (range 6–8 months)			
Number of follow-ups angiographic, sonographic, clinical and phone	75 (96.2%)	74 (98.7%)	0.303
Target lesion revascularization	7 (9.3%)	23 (31.1%)	0.001
Patency[a]	54 (80.6%) (n = 67)	41 (60.3%) (n = 68)	0.010
Death all causes	2 (2.7%)	1 (1.4%)	0.568
Increase in censored[b] walking distance, m	137 ± 160 (*n* = 42)	71 ± 130 (*n* = 43)	0.039
Uncensored[c] target leg ABI	0.96 ± 0.14	0.89 ± 0.21	0.043
Rutherford category shift 12 months versus pre-interventional	1.6 ± 1.4 (*n* = 63)	1.1 ± 1.4 (*n* = 62)	0.086
1 year (range 9–15 months)			
Number of follow-ups including premature TLR	73 (93.6%)	69 (92.0%)	0.704
Target lesion revascularization	13 (17.8%)	26 (37.7%)	0.008
Patency[a]	49 (74.2%) (*n* = 66)	37 (54.4%) (*n* = 68)	0.017
Death all causes	2 (2.8%)	1 (1.4%)	0.585
Increase in censored[b] walking distance, m	165 ± 105 (*n* = 42)	94 ± 136 (*n* = 34)	0.012
Uncensored[c] target leg ABI	0.91 ± 0.20 (*n* = 53)	0.91 ± 0.25 (*n* = 42)	0.967
Rutherford category shift 12 months vs. pre-interventional	2.1 ± 1.3 (*n* = 70)	1.7 ± 1.3 (*n* = 65)	0.088
2 years (range 21–27 months)			
Number of follow-ups angiographic, sonographic, clinical and phone for TLR	68 (87.2%)	64 (85.3%)	0.740
Follow-up time, months	24.6 ± 1.8	24.4 ± 3.0	0.557
Target lesion revascularization	13 (19.1%)	26 (40.6%)	0.007
Patency[a]	47 (72.3%) (*n* = 65)	31 (48.4%) (*n* = 64)	0.006
Death all causes	2 (2.9%) (*n* = 70)	1 (1.5%) (*n* = 65)	0.604
Increase in censored[b] walking distance, m	172 ± 103 (*n* = 28)	52 ± 136 (*n* = 20)	0.001
Uncensored[c] target leg ABI	0.92 ± 0.19 (*n* = 56)	0.90 ± 0.20 (*n* = 56)	0.499
Rutherford category shift 24 months versus pre-interventional	2.1 ± 1.3 (*n* = 53)	1.7 ± 1.3 (*n* = 53)	0.113

All continuous variables are expressed as mean ± one standard deviation

[a]Patency defined as binary restenosis with diameter stenosis > 50% (angiographic) or PSVR > 2.4 (sonographic), definition by Diehm et al. [8]

[b]All patients with non-vascular walking limitations and/or TLR prior to the measurement of walking distance were excluded

[c]All available ankle brachial index (ABI) measurements were used

length will have an impact on TLR. Overall there is the impression that in most RCTs investigating DCB, the lesion lengths did not fully reflect those currently treated in clinical practice. Furthermore, we reported the rate of all-cause TLR in contrast to the commonly reported clinically driven TLRs [3, 20]. Overall, the 72.3% primary patency in our DCB group appears to be very favorable given that the lesions in our trial were substantially longer than in most studies.

The walking distance increase was significantly higher in the DCB group as compared to the POBA group (172 ± 103 m vs. 52 ± 136 m, $p = 0.001$). However, relatively few patients were available for this comparison, mainly due to non-peripheral arterial comorbidities such as dyspnea. This is not surprising given the 41.2% incidence of coronary artery disease in the overall CONSEQUENT population [1].

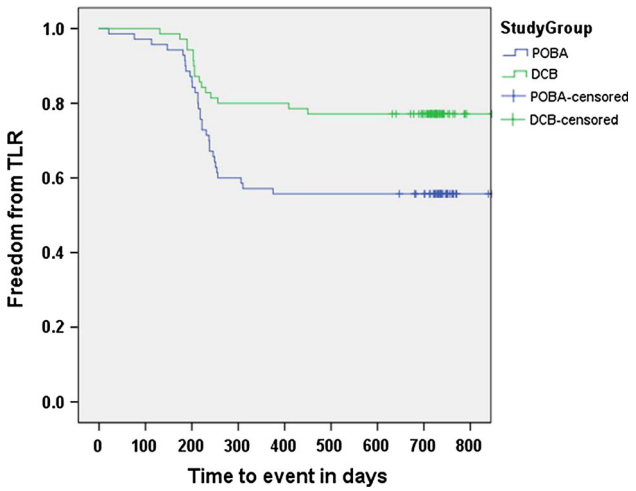

Fig. 2 Kaplan–Meier curve freedom from TLR (log-rank $p = 0.008$)

Table 3 Cost-effectiveness analysis: base case (2 DCBs per lesion and patient [7])

	DCB	POBA	Incremental
Total cost	€6086.31	€7198.28	€1111.97
Time free of TLR[a] in months	21.02	20.30	− 0.72
ICER (€/time free of TLRs in months)			Cost saving − €1.553.05
Accumulated costs for 24 months per patient	€6086.31	€7198.28	€1111.97

[a]*TLR* target lesion revascularization, *ICER* incremental cost-effectiveness ratio

In terms of cost efficacy, our analytic Markov decision model revealed costs of €7198.28 per POBA patient and €6086.31 per patient treated with DCB. The net financial benefit was €1111.97 per patient treated with DCB instead of POBA over 24 months. These were primarily driven by the difference in TLR. The cost savings of €1111.97 per patient are quite high compared to the cost analysis for the German market by Pietzsch et al. [5] published in 2014. This may be explained in part by the fact that Pietzsch and co-workers assumed a DCB market price of €817 for one DCB device or a cost premium of €637 over an uncoated balloon; however, DCB prices have since fallen. The cost premium in our study was €860.31 (based on the 2017 DRG catalog) for two devices to cover the relatively long lesions in our study. The TLR rates are considered the primary outcome measure in the cost-effectiveness analysis not only because TLR tends to be the cost driver and as such is relevant from a reimbursement perspective but also because it is a valuable clinical outcome. As mentioned in the results section, the higher initial costs of the DCB strategy compared to POBA are offset by later cost savings from decreased revascularization events.

Study Limitations

The patient population was calculated on the basis of an angiographic endpoint at 6 months and not for differences in clinical event rates. Moreover, it would have been desirable to have more patients per group with usable walking distance data. A walking impairment questionnaire could have been used instead to obtain a more clinically relevant analysis. The presented cost-efficacy data are only valid for the German DRG system.

Conclusions

The use of paclitaxel–resveratrol matrix-coated peripheral balloons as compared to POBA was associated with half the TLR rate, a 23.9% higher patency rate, a higher increase in walking distance and cost savings of € 1111.97.

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Funding Based on a milestone system, all study participants received funding from B.Braun per included patient.

Compliance with Ethical Standards

Conflict of interest TA and GT have received lecturer honoraria and research grants from B.Braun to conduct this trial. MW is a full-time employee in the Medical Scientific Affairs department of B.Braun Melsungen AG, Vascular Systems, Berlin/Germany. SMH received lecturer honoraria and travel grants from Terumo and Boston Scientific. TZ received honoraria from Abbott Vascular, Bard Peripheral Vascular, Veryan, Biotronik, Boston Scientific Corp., Cook Medical, Gore & Associates, Medtronic, Philips-Spectranetics, TriReme, Veryan, Shockwave, Biotronik, QT Medical and consulted for Boston Scientific Corp., Cook Medical, Gore & Associates, Medtronic, Spectranetics, B.Braun.

Ethical Approval The study was approved by the Federal Institute for Drugs and Medical Devices (Ref. 95.05-5660-8211), by the Federal Agency for Radiation Protection (Ref. Z5-22462/2) 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 laboratory. This trial was registered with the US National Institutes of Health (clinicaltrials.gov NCT01970579) 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.

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