

Angioplasty of Femoral-Popliteal Arteries With Drug-Coated Balloons



5-Year Follow-Up of the THUNDER Trial

Gunnar Tepe, MD,* Beatrix Schnorr, DVM,† Thomas Albrecht, MD,‡ Klaus Brechtel, MD,§ Claus D. Claussen, MD,§ Bruno Scheller, MD,|| Ulrich Speck, PhD,† Thomas Zeller, MD¶

ABSTRACT

OBJECTIVES The purpose of this study was to evaluate the 5-year follow-up (FU) data of the THUNDER (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries).

BACKGROUND The THUNDER trial was the first study to investigate the treatment of femoropopliteal arteries with a paclitaxel-coated balloon (PCB).

METHODS In 154 patients, femoropopliteal arteries were treated with PCB, with angioplasty with paclitaxel in contrast medium, or no paclitaxel (control). The primary endpoint was 6-month late lumen loss (LLL). Secondary endpoints included freedom from target lesion revascularization (TLR), binary restenosis rate, and amputation. The 5-year FU compares outcomes in patients treated with PCB and control subjects. Additionally, LLL at 6 months and TLR up to 5-year FU were analyzed in terms of sex and lesion length.

RESULTS Over the 5-year period, the cumulative number of patients with TLR remained significantly lower in the PCB group (21%) than in the control group (56%, $p = 0.0005$). In the small group of patients with angiographic and duplex sonographic follow-up, PCB was associated with a lower rate of binary restenosis (17% vs. 54%; $p = 0.04$). No signs of aneurysm formation or constrictive fibrosis were detected. Whereas LLL at 6-month FU did not differ between men and women in the PCB group, the TLR rate was lower in men than in women at 5-year FU. A benefit of PCB treatment in terms of LLL and TLR was seen independent of lesion length.

CONCLUSIONS The reduced TLR rate following PCB treatment was maintained over the 5-year FU period. No signs of drug-related local vessel abnormalities were detected. (Thunder Trial—Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries [THUNDER]; [NCT00156624](https://doi.org/10.1016/j.jcin.2014.07.023)) (J Am Coll Cardiol Intv 2015;8:102-8) © 2015 by the American College of Cardiology Foundation.

Long-term follow-up was requested following the surprising finding that a single treatment with paclitaxel-coated balloons (PCB) reduced restenosis rates for 6 to 24 months in the femoropopliteal arteries both in randomized studies (1-5) and in single-arm studies (6-8). Meanwhile 5-year follow-up of patients suffering from coronary in-stent restenosis treated with PCB is available (9). Follow-up data on the use of PCB in peripheral arteries have so far only been published for a maximum period

From the *RoMed Clinic Rosenheim, Rosenheim, Germany; †Department of Radiology, Experimental Radiology, Charité, University Hospital, Berlin, Germany; ‡Institute of Radiology and Interventional Therapy, Vivantes Klinikum Neukölln, Berlin, Germany; §Department of Diagnostic and Interventional Radiology, University Hospital, Tuebingen, Germany; ||Department of Internal Medicine III, University of Saarland, Homburg/Saar, Germany; and the ¶Department of Angiology, Klinik für Kardiologie und Angiologie II, Universitäts-Herzzentrum Freiburg-Bad Krozingen, Bad Krozingen, Germany. This work was supported by Medrad, Inc. Prof. Tepe receives study support from and serves on the advisory board of Medtronic; and has received speaking fees and research grants from Medrad. Prof. Albrecht has received lecture fees from Medtronic. Dr. Brechtel has received lecture fees and research grants from Medrad. Profs. Scheller and Speck are coinventors of a patent by Charité University Hospital, Berlin, for various methods of inhibiting restenosis including the formulation used in this trial. Prof. Zeller has lectured and received research grants from Medrad; and has served as a medical advisor to Medtronic and Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received June 5, 2014; revised manuscript received July 18, 2014, accepted July 31, 2014.

of 24 months (1,2,5,8). The patients of the THUNDER Trial (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries), a randomized study investigating the efficacy of PCB for restenosis prevention in the femoropopliteal arteries, have now been followed up for 5 years. The aim of this follow-up (FU) was to evaluate the long-term efficacy and safety of local paclitaxel administration in terms of potential complications such as development of aneurysms or occurrences of thrombotic occlusion.

SEE PAGE 109

METHODS

OUTLINE OF THUNDER STUDY: DESIGN, STUDY PATIENTS, AND 6- TO 24-MONTH FOLLOW-UP. The THUNDER study was designed to investigate the effect of local paclitaxel administration using a PCB on the restenosis rate after peripheral arterial interventions. A total of 154 patients were recruited and randomized in a multicenter trial. The target lesions had a mean pre-dilation degree of stenosis of $90 \pm 9\%$ and a mean length of 7.4 ± 6.5 cm. One group was treated with PCB and standard nonionic contrast medium (CM) (PCB group), a second group was treated with plain old balloon angioplasty and paclitaxel added to the CM (paclitaxel-in-CM group), and a third group was treated with plain old balloon angioplasty and standard nonionic CM (control group).

The PCB were coated with paclitaxel at a dose of $3 \mu\text{g}/\text{mm}^2$ of balloon surface embedded in a matrix consisting of a small amount of the nonionic contrast agent iopromide (10), referred to in the literature as Paccocath coating (B. Braun Melsungen AG, Berlin, Germany). The total paclitaxel dose administered per patient ranged from 1 to 17 mg (mean: 5 mg).

Details of the methods and 6-month and 2-year FU results have been previously published (1).

DESIGN, PATIENTS, AND ENDPOINTS AT 5-YEAR FOLLOW-UP. The outcome in the paclitaxel-in-CM group did not differ significantly from that in the control group at 6- and 24-month FU (late lumen loss [LLL]: 2.2 ± 1.6 mm, $p = 0.14$; target lesion revascularization [TLR]: 40%, $p = 0.25$). Therefore, only control patients and those treated with PCB were invited to a 5-year FU visit. No 5-year FU was conducted in patients with >1 TLR, with femoropopliteal bypass graft involving the target lesion, and with amputations of the study leg up to 24-month FU. **Figure 1** presents a chart of the 5-year FU disposition of the original THUNDER population.

Patients underwent 5-year FU by clinical observation. This was done during a visit to the study center or, if patients could not come to the study center, by telephone interview. All patients were asked to complete a questionnaire on their current health status and on clinical events having occurred since their last FU. If the patients consented, any angiographies or duplex ultrasound examinations conducted after the 24-month follow-up, which included the target lesion and allowed its evaluation, were included in the 5-year FU analysis.

Clinical endpoints at 5-year FU included TLR, major amputation of the treated leg as well as death. Available angiography and duplex sonography data were used to determine the binary restenosis rate. Angiograms were also evaluated for LLL and for the presence of aneurysms or other abnormalities of the treated arteries.

The conduct of the THUNDER trial and the 5-year FU evaluation met all local legal and regulatory requirements and were approved by the local ethics committee at each study site. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guideline. Furthermore, study conduct was in accordance with sections 40/41 of the German Drug Act and sections 20 to 22 of the Medical Devices Act. All patients gave written informed consent.

SEX COMPARISON AND ANALYSIS OF LESION LENGTH.

Angiographic LLL (difference between the post-procedural and 6-month FU minimal lumen diameter, evaluated by quantitative angiography) was the primary endpoint. Data referring to the intervention and 6-month FU were taken from the analysis provided by the blinded core lab. Analysis of TLR was performed up to 5-year FU.

STATISTICAL ANALYSIS. Statistical analysis was performed using SAS (version 9.2, SAS Institute Inc., Cary, North Carolina). In the patients available for 5-year FU, the incidence of first TLR overall and the incidence, intensity, and relationship to study treatment of serious adverse events (SAE) were analyzed as categorical or binary data. Data are presented as relative and absolute frequencies and were tested for group differences using the Fisher exact test.

Continuous data are presented as mean \pm SD and were tested for group differences using a Wilcoxon rank sum test.

ABBREVIATIONS AND ACRONYMS

CM	= contrast medium
CRF	= case report form
FU	= follow-up
LLL	= late lumen loss
PCB	= paclitaxel-coated balloon
SAE	= serious adverse event(s)
TLR	= target lesion revascularization

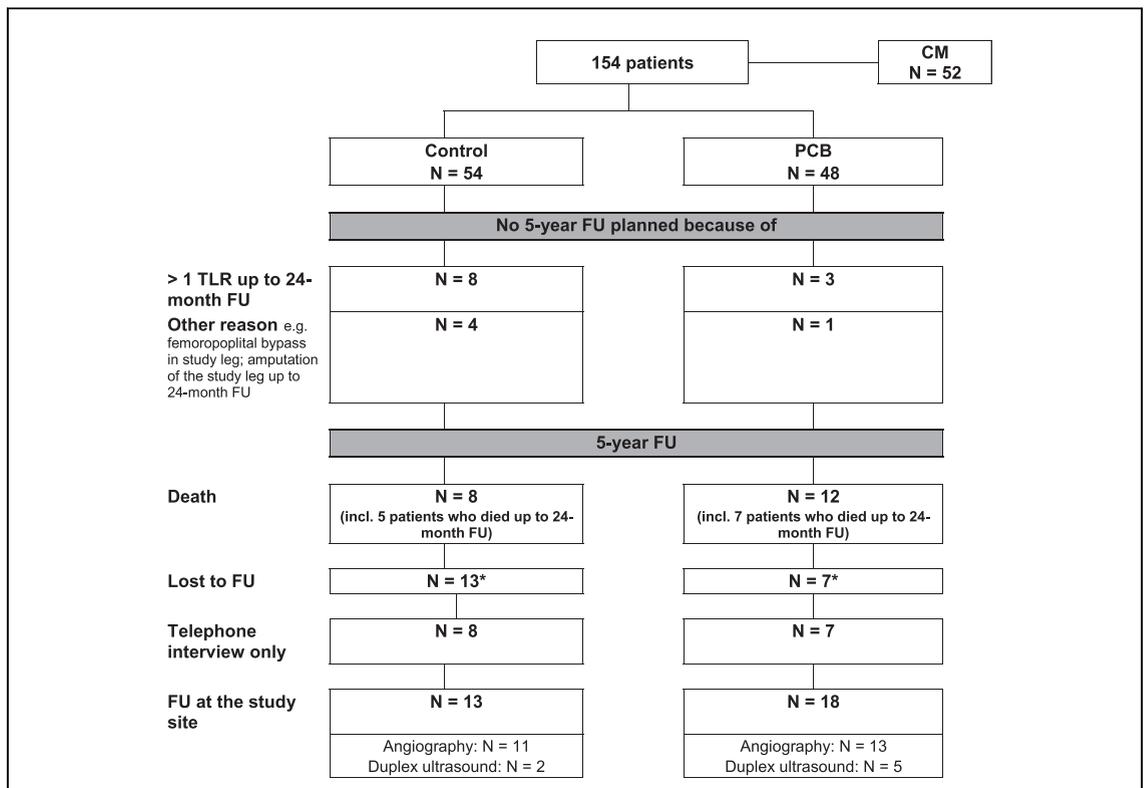


FIGURE 1 Disposition of Patients at 5-Year FU

Chart presents the original THUNDER (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries) population and the 5-year follow-up (FU) disposition. Only control patients and those treated with paclitaxel-coated balloon (PCB) were invited to a 5-year FU visit. Reasons for not performing the 5-year FU are listed. *1 study site dropped out (7 patients in the control group and 2 patients in the PCB group). CM = uncoated balloon plus paclitaxel in contrast medium; PCB = paclitaxel-coated balloon; TLR = target lesion revascularization.

In case of multiple measurements per patient, multinomial or logistic regression methods were used based on generalized estimation equations to account for correlations between observations within the same patient. Independence was used as the working correlation matrix.

For the endpoint TLR, survival analysis was performed for the period from randomization to first event using proportional hazard Cox regression and log-rank tests. Data are displayed as Kaplan-Meier curves.

All analyses of the 5-year follow up are descriptive or exploratory. The follow-up was not included in the original study protocol.

RESULTS

DISPOSITION OF PATIENTS AT 5-YEAR FU. Five-year FU was available after 56 months on average (control group: 56.4 ± 8.6 months; PCB group: 56.1 ± 10.1 months).

According to the exclusion criteria outlined (>1 TLR, femoropopliteal bypass graft involving the target lesion, and major amputation of the study leg up to 24-month FU), 16 of 102 patients were not invited to a 5-year FU visit: 12 of 54 patients (22%) in the control group and 4 of 48 patients (8%) in the PCB group. Because 1 study site did not participate in the 5-year FU, 9 patients were not available for evaluation at this time (7 patients from the control group, 2 patients from the PCB group).

Follow-up data at 5 years were obtained from 66 patients (29 patients in the control group and 37 patients in the PCB group), whereas no data on the status of the study leg and/or death were available for a total of 20 of 102 patients (20%) (Figure 1).

With the exception of Rutherford stages, demographic data, risk factors, and baseline characteristics were well balanced between the 2 groups. At baseline, 85% of patients in the control group had Rutherford stage ≥ 3 as opposed to a total of 96% of patients in the PCB group. However, at 5-year

FU, the results are similar in the both groups. About 57% of patients with available Rutherford assessment have Rutherford stages ≤ 2 (Table 1).

CLINICAL RESULTS. Up to the 24-month FU examination, TLR was performed in 28 of 54 patients in the control group (52%) versus 8 of 48 patients treated with PCB (17%, $p < 0.001$). Between 24-month and 5-year FU, 7 TLR were performed in 6 of 29 patients of the control group. In the PCB group, 5 TLR were necessary in 3 of 37 patients. Data from the entire study period show that the cumulative number of patients with at least 1 TLR was distinctly lower in the PCB group. In the control group, TLR was necessary in 30 of 54 of the patients (56%) compared with 10 of 48 (21%) in the PCB group ($p = 0.0005$). In patients with TLR, the time from the intervention to the TLR was 607 days in the PCB group versus 206 days in the control group ($p = 0.04$) (Figures 2 and 3); however, the patients without TLR were not included in this calculation. The Kaplan-Meier curves for TLR are shown in Figure 2.

Eight of 54 evaluable patients (15%) died in the period between the 24-month and 5-year FU: 3 of 24 (12.5%) in the control group and 5 of 35 (16.7%) in the PCB group.

Two patients with baseline Rutherford class 5 had major amputations below-the-knee 0.6 and

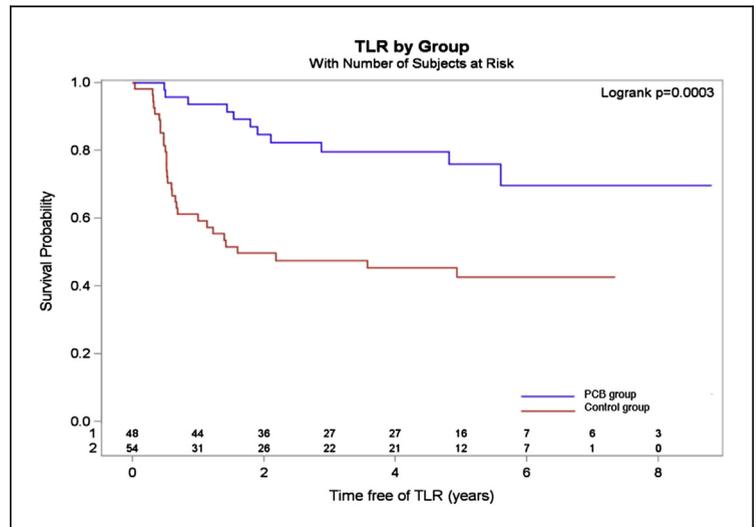


FIGURE 2 Time From the Intervention to the TLR in Patients With TLR

Histogram shows the distribution and the time from the intervention to the TLR in the PCB and control groups. Median values are presented. Abbreviations as in Figure 1.

2.4 months after treatment with a PCB. One additional patient (PCB group, baseline Rutherford class 3) had a major below-the-knee amputation 11 months after the study intervention (1). Between 24-month FU and 5-year FU, 1 above-the-knee amputation (28 months after the intervention) in a patient of the control group and 1 major below-the-knee amputation (45 months after the intervention) in the PCB group were reported. None of the events was classified as related to the study device by the investigator.

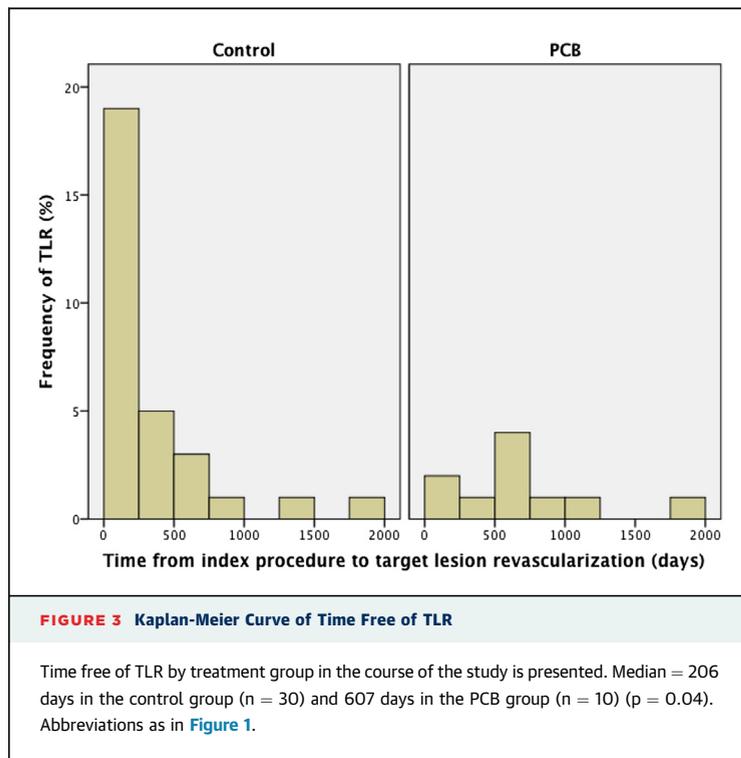
ANGIOGRAPHY/DUPLEX ULTRASOUND. The primary endpoint of LLL 6 months after angioplasty was significantly lower in the group treated with PCB than in the control group (0.4 ± 1.2 mm vs. 1.7 ± 1.8 mm, $p < 0.001$) (1). At 12-month FU, mean LLL was determined in 33 of 48 patients (69%) in the PCB group and in 36 of 54 patients (67%) in the control group. In 2 patients of the PCB group and in 14 patients of the control group, TLR was performed prior to 12-month reangiography. Nevertheless, the statistical comparison of the treatment groups resulted in a significant difference in favor of the PCB group versus the control group (LLL: 0.7 ± 1.5 mm vs. 1.9 ± 1.9 mm, $p = 0.01$). Significantly better results ($p < 0.05$) for the PCB versus the control group were observed for the binary restenosis rate at the 6-month (17% vs. 44%) and 12-month FU (24% vs. 50%).

At 5-year FU, 31 patients consented to an angiographic or duplex ultrasound evaluation of the target lesion (13 patients in the control group and 18

TABLE 1 Rutherford Stage - CRF Data

	Control Group	PCB Group
Whole study population, N = 102	54	48
Baseline		
1	1 (1.9)	-
2	7 (13.0)	2 (4.2)
3	39 (72.2)	33 (68.8)
4	1 (1.9)	6 (12.5)
5	6 (11.1)	7 (14.6)
5-year FU population, n = 30	14	16
Baseline		
2	1 (7.1)	-
3	12 (85.7)	11 (68.8)
4	-	2 (12.5)
5	1 (7.1)	3 (18.8)
5-year FU*		
0	4 (28.6)	2 (12.5)
1	3 (21.4)	7 (43.8)
2	1 (7.1)	-
3	4 (28.6)	5 (31.3)
4	2 (14.3)	-
5	-	1 (6.3)
6	-	1 (6.3)

Values are n or n (%). Dashes indicate no patients in this Rutherford stage.
 *Data include 3 patients each with previous TLR.
 CRF = case report form; FU = follow-up; PCB = paclitaxel-coated balloon.



patients in the PCB group). The control group included 5 patients who had undergone TLR prior to reangiography or duplex ultrasound, whereas the PCB group included only 3 patients after TLR. In this small group of 31 patients, PCB was associated with a lower rate of binary restenosis at 5-year FU (3 of 18 [17%

vs. 7 of 13 [54%], p = 0.04). In the patients with angiography, there was a statistically not significant difference in LLL (1.5 mm in the control group vs. 0.7 mm in the PCB group, p = 0.54) (Table 2).

Analysis of angiography and ultrasound findings as well as SAE revealed no evidence of aneurysm formation or other vascular abnormalities.

SEX ANALYSIS. In the explorative analysis of these data there was no difference in LLL at 6-month FU between women and men in the control (1.61 mm vs. 1.76 mm) and PCB groups (0.37 mm vs. 0.42 mm) (Figure 4). In contrast, 5 years after treatment with a PCB, the cumulative TLR rate was lower in men than in women (4 of 24 patients [17%] vs. 6 of 16 patients [38%]) (Table 3). The cumulative 5-year TLR rate in the control group was instead slightly higher for men (20 of 28 patients [71%] vs. 10 of 19 patients [52%]) (Table 3).

LESION LENGTH ANALYSIS. There were 18 patients with target lesion lengths >10 cm (9 patients in the control group [average lesion length: 19.9 cm] and 9 patients in the PCB group [average lesion length: 17.2 cm]), and 84 patients with a lesion length ≤10 cm (39 in the PCB group and 45 in the control group). The positive effect of the PCB was also observed for lesions with >10 cm in length: LLL at 6-month FU as well as the cumulative 5-year TLR rate were in favor of the PCB (LLL: 1.3 mm and TLR rate: 33% vs. LLL: 2.6 mm and TLR rate: 75% in the control group) (Figure 5).

TABLE 2 LLL, Binary Restenosis, and Cumulative TLR Over the Study Period

LLL (mm)	Control Group (n = 54)		PCB Group (n = 48)		p Value
	Mean ± SD	Patients With Data, n	Mean ± SD	Patients With Data, n	
6-month FU	1.7 ± 1.8	48	0.4 ± 1.2	41	0.0007
12-month FU	1.9 ± 1.9	36	0.7 ± 1.5	33	0.01
5-year FU	1.5 ± 1.3	11	0.7 ± 1.9	13	0.54
		14 with previous TLR		2 with previous TLR	
		4 with previous TLR		1 with previous TLR	
Binary Restenosis (%)	n	% Related to Patients With Data	n	% Related to Patients With Data	p Value
6-month FU	21	43.8	7	17.1	0.01
12-month FU	17	50.0	8	24.2	<0.05
5-year FU	7	54	3	17	0.04
First TLR (cumulative)	n	Treated Patients, % (n = 54)	n	Treated Patients, % (n = 48)	p-value
6-month FU	20	37.0	2	4.2	<0.0001
12-month FU	26	48.1	5	10.4	<0.0001
24-month FU	28	51.9	8	16.7	0.0003
5-year FU	30	55.6	10	20.8	0.0005

LLL = late lumen loss; TLR = target vessel revascularization; other abbreviations as in Table 1.

DISCUSSION

The aim of the long-term FU of the THUNDER study was to assess the clinical efficacy of the PCB compared with that of the uncoated balloon based on the number of TLR. In addition, safety was assessed by analyzing SAE reported in the total patient cohort. The intention of the angiographic or duplex ultrasound FU after 5 years was to detect possible side effects of PCB, which might not be reflected by the TLR rate (e.g., aneurysms). Because patients with >1 TLR already had several interventions prior to the 5-year FU, they were excluded from this additional analysis.

The present study was designed to measure angiographic LLL at 6-month FU and was not powered to assess angiographic and clinical outcomes up to 5 years after study intervention. However, the use of PCB resulted in reduced LLL, binary restenosis, and TLR rate at 5-year FU. Over this period, the cumulative number of patients with first TLR was distinctly lower in the PCB group than in the

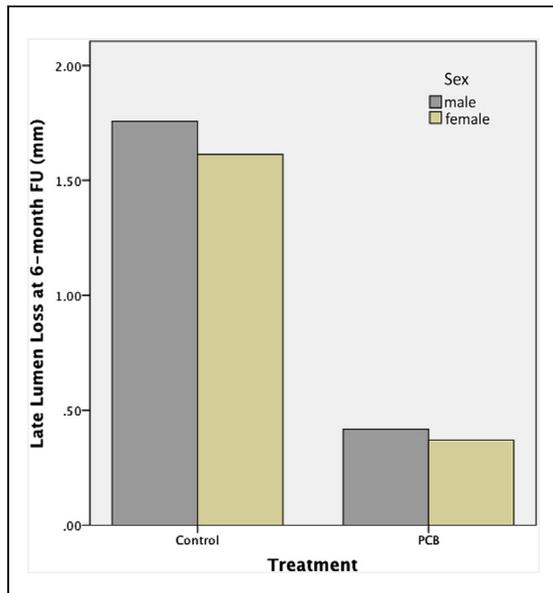


FIGURE 4 Sex Analysis: LLL at 6-Month FU

The histogram presents late lumen loss (LLL) at 6-month FU in female and male patients. Abbreviations as in Figure 1.

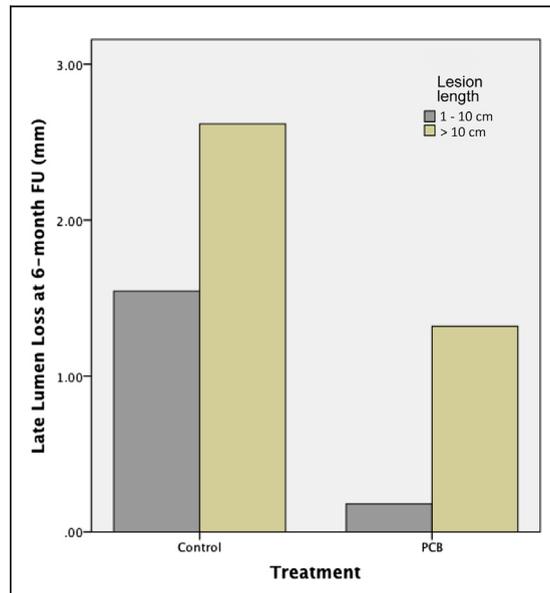


FIGURE 5 Lesion Length Analysis: LLL at 6-Month FU

The histogram presents LLL at 6-month FU in lesions with a length of 1 to 10 cm and >10 cm. Abbreviations as in Figures 1 and 4.

control group. The same applies to the total number of TLR in the respective treatment groups. Most of the first TLR in the control group were necessary within the first 6 to 8 months after the intervention (20 of 30 TLR = 67% of TLR), whereas treatment with a PCB resulted in only 2 of 10 TLR during this period. These results show that, despite the very short contact of the PCB with the vessel wall, paclitaxel inhibits restenosis due to neointimal proliferation in the first months after angioplasty. The benefit persists over the entire study period, which is reflected in the observation that the low TLR rate at 24-month FU (17% vs. 52%) is maintained over the 5-year FU period. There is no increase in the incidence of late TLR in the group treated with the PCB although treatment with the coated balloon cannot prevent progression of

atherosclerosis, which ultimately results in similar TLR rates in both groups.

Using multiple PCB for treating long lesions might lead to higher local and systemic paclitaxel exposure and to a higher incidence of adverse events several years after treatment. However, peak plasma concentrations of paclitaxel shortly after the intervention were found to be below those known to cause systemic side effects (11). No late thrombosis or formation of aneurysm was recorded in any patient up to 2 years after treatment (1). The incidence of SAE, major amputation rate, and death at the 5-year FU did not differ significantly between both groups. Driven by the fact that the patients of the control group received more frequently more than 1 TLR during the first 24 months after the intervention, which was a pre-defined exclusion criterion for long-term FU, only a positive selection of patients were invited for the 5-year FU examination. This selection process favored the control group over the PCB group (Figure 1). Furthermore, in the 5-year FU population of the control group, approximately 93% of patients had baseline Rutherford stages ≤ 3 (7% with Rutherford 5) compared with 70% of patients in the PCB group (30% with Rutherford 4 or 5) (Table 1). This might have affected outcomes and have impacts on the direct comparison of the 2 groups in terms of death and amputation rates up to 5-year FU. The

TABLE 3 Sex Analysis: Cumulative TLR Over the Study Period

Follow-Up	Control Group		PCB Group	
	Female (n = 20)	Male (n = 34)	Female (n = 17)	Male (n = 31)
6-month	7 (35)	13 (38)	1 (6)	1 (3)
12-month	9 (45)	17 (50)	3 (18)	2 (6)
24-month	9 (50)	19 (58)	6 (38)*	2 (7)*
5-year	10 (52)	20 (71)	6 (38)	4 (17)

Values are n (% related to available patients/patients with data). *Differences between sexes are significant.

results presented here are consistent with the 5-year FU results of the coronary Paccocath ISR study (9).

Women account for a growing percentage of the elderly population presenting with peripheral arterial disease. The analysis presented here suggests that the response to treatment with PCB may be different in men and women, confirming a tendency observed in the PACIFIER (Reocclusion Prophylaxis with Paclitaxel-coated Angioplasty Balloon Catheters in Atherosclerotic Stenosis and Occlusion of Femoropopliteal Arteries) study (3). Although LLL at 6 months was similar in the PCB group in women and men, the long-term benefit of coated-balloon treatment appears to be greater in men than women, although absolute numbers of patients are small.

We found beneficial effects of PCB in the treatment of femoropopliteal arteries for lesions <10 cm and a tendency toward a benefit also for longer lesions compared with correspondingly long lesions in the control group. However, a statistically significant superiority could not be shown, which is probably attributable to the smaller number of patients with lesions >10 cm in length.

PCB used in the THUNDER study were provided by Bavaria Medizintechnologie, later on marketed by Bayer HealthCare's as Cotavance drug-eluting balloon with Paccocath coating. In 2013, Bayer discontinued offering the product on reasons unrelated to clinical performance. The Paccocath coating

formulation is successfully used in cardiology on SequentPlease balloons (B. Braun Melsungen).

STUDY LIMITATIONS. This randomized trial was powered on a 6-month angiographic primary endpoint. The 5-year FU was not prespecified in the study protocol. Therefore, the sample size is small for analysis of endpoints at 5-year FU and for subgroup analysis regarding sex and lesion length.

CONCLUSIONS

Our 5-year analysis shows that a significant technical benefit regarding LLL of the PCB versus uncoated balloons persists over 5 years, resulting in a significantly lower TLR rate and longer interval to reintervention in the PCB cohort. At the same time, this analysis has identified no signs of drug-related local vessel abnormality.

ACKNOWLEDGMENTS The authors thank Maren Kutschera and Carsten Schwenke for their contribution to the evaluation and statistical analysis of data.

REPRINT REQUESTS AND CORRESPONDENCE: Prof. Dr. Gunnar Tepe, Institute for Diagnostic and Interventional Radiology, RoMed Clinic Rosenheim, Pettenkoferstrasse 10, 83022 Rosenheim, Germany. E-mail: gunnar.tepe@ro-med.de.

REFERENCES

1. 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.
2. 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.
3. 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.
4. Fanelli F, Cannavale A, Boatta E, et al. Lower limb multilevel treatment with drug-eluting balloons: 6-month results from the DEBELLUM randomized trial. *J Endovasc Ther* 2012;19:571-80.
5. 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. *J Am Coll Cardiol Interv* 2014;7:10-9.
6. Micari A, Cioppa A, Vadalà G, et al. Clinical evaluation of a paclitaxel-eluting balloon for treatment of femoropopliteal arterial disease: 12-month results from a multicenter Italian registry. *J Am Coll Cardiol Interv* 2012;5:331-8.
7. Cioppa A, Stabile E, Popusoi G, 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.
8. Micari A, Cioppa A, Vadalà G, et al. 2-year results of paclitaxel-eluting balloons for femoropopliteal artery disease: evidence from a multicenter registry. *J Am Coll Cardiol Interv* 2013;6:282-9.
9. Scheller B, Clever YP, Kelsch B, et al. Long-term follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *J Am Coll Cardiol Interv* 2012;5:323-30.
10. Scheller B, Speck U, Abramjuk C, Bernhardt U, Böhm M, Nickenig G. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. *Circulation* 2004;110:810-4.
11. Freyhardt P, Zeller T, Kröncke TJ, et al. Plasma levels following application of paclitaxel-coated balloon catheters in patients with stenotic or occluded femoropopliteal arteries. *Rofo* 2011;183:448-55.

KEY WORDS angioplasty, drug-coated balloon, femoral artery, long-term outcome, paclitaxel, peripheral arterial disease