Inhibition of Restenosis in Femoropopliteal Arteries

Paclitaxel-Coated Versus Uncoated Balloon: Femoral Paclitaxel Randomized Pilot Trial

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Background—The success of percutaneous intervention in peripheral arterial disease is limited by restenosis. The aim of the present pilot study was to evaluate a novel method of local drug delivery.

Methods and Results—This randomized multicenter study with blinded reading enrolled 87 patients in Rutherford class 1 to 4 with occlusion or hemodynamically relevant stenosis, restenosis, or in-stent restenosis of femoropopliteal arteries. Treatment was performed by either conventional uncoated or paclitaxel-coated balloon catheters. The primary end point was late lumen loss at 6 months. Secondary end points included restenosis rate, ankle brachial index, Rutherford class, target lesion revascularization, and tolerance up to >18 months. Before intervention, there were no significant differences in lesion characteristics such as reference diameter (5.3±1.1 versus 5.2±1.0 mm), degree of stenosis (84±11% versus 84±16%), proportion of restenotic lesions (36% versus 33%), and mean lesion length (5.7 cm [0.8 to 22.6 cm] versus 6.1 cm [0.9 to 19.3 cm]) between treatment groups. The 6-month follow-up angiography performed in 31 of 45 and 34 of 42 patients showed less late lumen loss in the coated balloon group (0.5±1.1 versus 1.0±1.1 mm; $P=0.031$). The number of target lesion revascularizations was lower in the paclitaxel-coated balloon group than in control subjects (3 of 45 versus 14 of 42 patients; $P=0.002$). Improvement in Rutherford class was greater in the coated balloon group ($P=0.045$), whereas the improvement in ankle brachial index was not different. The difference in target lesion revascularizations between treatment groups was maintained up to >18 months. No adverse events were assessed as related to balloon coating.

Conclusions—In this pilot trial, paclitaxel balloon coating caused no obvious adverse events and reduced restenosis in patients undergoing angioplasty of femoropopliteal arteries. **(*Circulation*. 2008;118:1358-1365.)**

Key Words: angioplasty ■ balloon ■ catheters ■ claudication ■ restenosis

Despite the substantial improvements in endovascular techniques in the last 20 years, the success of percutaneous intervention is still limited. Especially in patients with stenosis or occlusions of femoropopliteal arteries, the rate of restenosis after angioplasty or stent implantation remains high compared with other vascular beds. After 1 year, restenosis occurs in 40% to 60% of treated vessels,[1–3] with patency rates in the superficial femoral artery ranging between 22% and 61% after bare metal stent implantation.[4] Neointimal hyperplasia leading to restenosis develops slowly. Therefore, current concepts of the prevention and therapy of restenosis after angioplasty or vascular stenting are based on sustained antiproliferative drug release into the vessel wall. Despite efficacy in coronary arteries, initial clinical trials of drug-eluting stents failed to indicate restenosis inhibition in the superficial femoral artery.[5–7]

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Cell culture experiments showed that a brief contact between vascular smooth cells and lipophilic taxane compounds is sufficient to inhibit proliferation of the cells for a long period.[8–10] A preclinical study with paclitaxel-coated balloons in coronary and peripheral arteries in swine indicated that a high concentration of the drug significantly reduces neointimal proliferation even when there is only short exposure of the vessel wall to the drug.[11–13] The recently published Treatment of In-Stent Restenosis by Paclitaxel

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Received August 23, 2007; accepted June 10, 2008.

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Clinical trial registration information—URL: http://clinicaltrials.gov. Unique identifier: NCT 00472472.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.107.735985**

Coated PTCA Balloons study presented the first results of paclitaxel-coated balloons for treatment of coronary in-stent restenosis in humans.[14] Angiographic in-segment late lumen loss (LLL) and restenosis rate after 6 months were significantly reduced in the coated balloon group compared with the uncoated balloon group. However, differences in the anatomy and physiology of peripheral and coronary arteries and the disappointing results of a clinical trial in femoropopliteal arteries with stents coated in a manner similar to coronary drug-eluting stents[7] raise serious doubts about the predictive value of results obtained in coronary arteries for peripheral vessels.

The aim of the Femoral Paclitaxel (FemPac) trial was to investigate the efficacy and safety of percutaneous transluminal angioplasty (PTA) balloons coated with paclitaxel compared with conventional uncoated balloon catheters in a patient population with short femoropopliteal artery occlusion or stenosis.

Methods

Study Design

The efficacy, safety, and tolerance of paclitaxel on balloon catheters compared with identical uncoated balloon catheters in inhibiting restenosis of femoropopliteal arteries after PTA were investigated in 2 treatment arms. The randomized study was performed at the radiology departments of the medical schools of the universities of Berlin (Virchow Klinikum, Charité; 71 patients) and Greifswald (16 patients). Blinding of the investigators was attempted but not guaranteed because of differences in the appearance of coated and uncoated balloons. Quantitative evaluation of 6-month angiographic control was performed by an independent core laboratory blinded to the type of treatment. The protocol was written in conformance with the Declaration of Helsinki (World Medical Assembly, 1996) and approved by the local institutional ethics committees. The study was conducted in compliance with the requirements of the German medical devices law. All patients provided written informed consent.

Patients

Eligible patients had an occlusion or stenosis ≥70% diameter of the superficial femoral artery and/or popliteal artery with clinical Rutherford stage 1 to 5. Study entry criteria also included adult age (18 to 90 years) and successful guidewire passage of the lesion. The main exclusion criteria were acute symptoms with an indication for thrombolytic therapy or operation, leg-threatening ischemia, distal outflow over <1 vessel, manifest hyperthyroidism, renal insufficiency (creatinine >2.0 mg/dL), and major gastrointestinal bleeding within the last 6 months. Patients with known intolerance to study medications or contrast agents and additional severe disease that might lead to noncompliance or was associated with reduced life expectancy <2 years also were excluded. Further exclusion criteria were conditions requiring different treatment, serious safety concerns regarding the procedure, or doubtful willingness or capability of patients to undergo the 6-month follow-up.

Balloon Catheters

Regular commercial PTA balloon catheters produced by Bavaria Medizin Technologie GmbH (Oberpfaffenhofen, Germany) were used. Balloons were either uncoated or coated with paclitaxel, produced under FDA-GMP by Indena (Milan, Italy) at a dose of 3 $\mu g/mm^2$ balloon surface. Every balloon catheter was collected postinterventionally, and quantitative analysis of paclitaxel residue on balloon was performed by high-performance liquid chromatography analysis[11] in the drug-eluting group.

Randomization

Randomization was done centrally in advance for all patients without any stratification. Portions of the random list (eg, numbers 1 to 30) were assigned to a center that enrolled the patients in the sequence of the randomization list. Patients were randomized if they fulfilled the inclusion criteria and had none of the exclusion criteria and if a suitable lesion was identified and successfully passed by the guidewire. Few patients considered candidates for the study who gave informed consent were not enrolled because, for example, the angiogram did not confirm the initial diagnosis, distal outflow was not sufficient, or the guidewire passage was not possible. One center was unable to enroll the assigned number of patients for organizational reasons.

Angioplasty and Follow-Up

Oral clopidogrel 75 mg/d and aspirin 100 mg/d were started as long-term medication on the day of angioplasty. After common femoral sheath placement, all patients received an initial bolus of 2500 to 5000 IU heparin. Further concomitant medication was documented by the investigator.

The intervention was performed according to the usual procedure, preferably with crossover catheter access into the superficial femoral or popliteal artery. After successful crossing of the lesion by the guidewire, patients were treated with ≥1 uncoated or paclitaxel-coated balloons mounted on standard angioplasty catheters according to a randomization list. The investigator could choose an inflation pressure up to 12 atm; balloon inflation time was standardized to 1 minute. Repeat dilatation and stent placement were allowed after acute failure of PTA in cases of dissection and recoil.

Before and immediately after the intervention and at the 6-month follow-up, angiography with quantitative analysis of the target vessel was performed in identical projections (2 planes of treated lesion). The target lesion was identified by an image of the vascular anatomy and a second image showing the inflated balloon(s). These images were compared with follow-up angiograms.

Ankle brachial index was measured before and after the intervention and after 6 months. Other follow-up investigations took place before hospital discharge and 6 and 18 to 24 months after the procedure.

End Points

The primary end point was LLL, defined as the difference between the minimal luminal diameter after the procedure and at 6 months by quantitative angiography. Secondary end points included the restenosis rate (defined as incidence of stenosis ≥50%) in the treated lesion at the 6-month follow-up angiography, target lesion revascularization (TLR), change in mean ankle brachial index, Rutherford class at baseline and 6-month visit, and amputation. Safety end points included thrombotic complications of the target vessel and clinical adverse events.

Statistical Analysis

A power analysis (nQuery Advisor, Statistical Solutions, Boston, Mass) was performed as part of the study protocol. The aim was to detect a 15% difference in LLL between the equally sized treatment groups, which is considered to be clinically meaningful, eg, 0.75 mm for a reference diameter of 5 mm at a level of $P<0.05$ with a power of 80%. An SD of ±1.0 mm for LLL was estimated to result in a raw total sample size of 58 patients. Assuming a loss to follow-up of 20%, at least 74 patients were to be enrolled. The ethics committee approved inclusion of up to 90 patients.

Continuous data are expressed as mean±SD in the text but as median and 25th to 75th percentiles in the tables because comparisons were performed by a parameter-free Wilcoxon rank-sum test. Categorical variables (given as number and percent) were compared by use of Fisher's exact test. For Rutherford stage, the change in the class number between baseline and the 6-month control was calculated for individual patients. Significance between the treatment groups was tested by Cochran-Mantel-Haenszel statistics, which also was applied to TransAtlantic Inter-Society Consensus (TASC) II classification. A 2-sided value of $P=0.05$ was considered significant. No adjustment was made for multiple testing. Probability values for secondary outcomes are considered descriptive. With regard to the

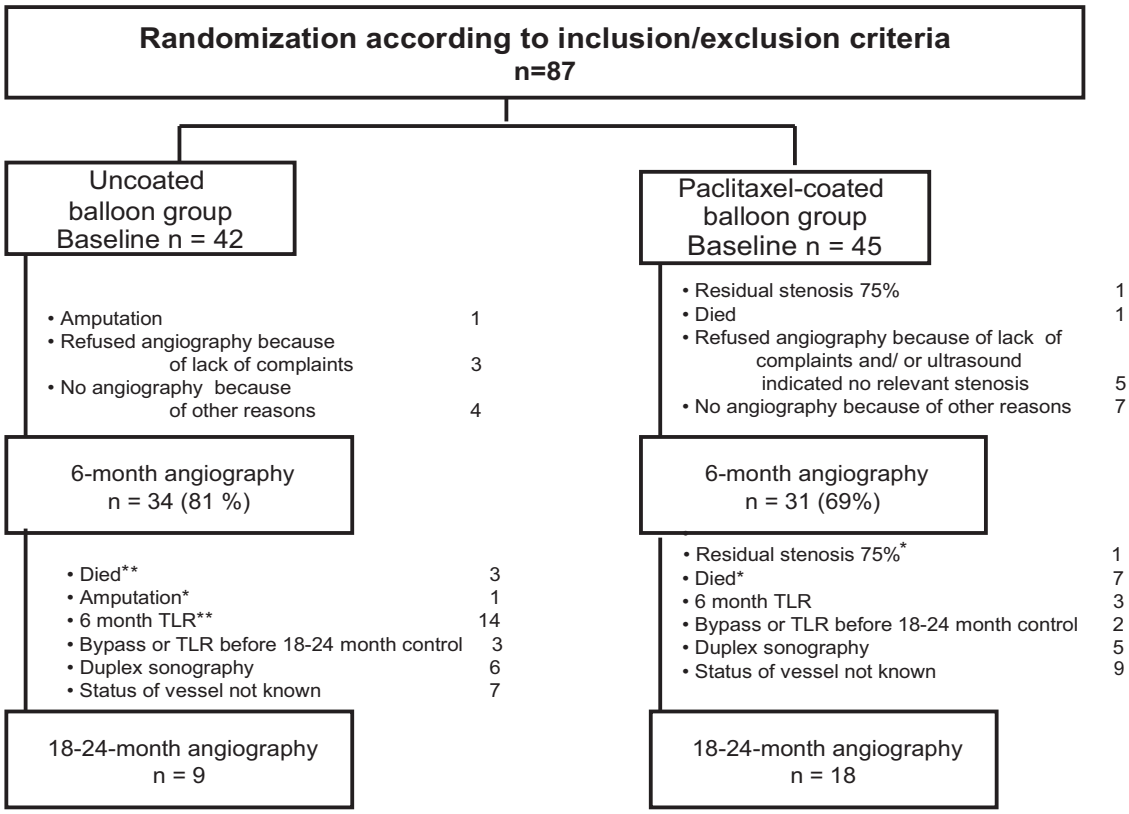

Figure 1. Flow diagram of patients. Patients who reached the primary end point of TLR during the first 6-month period were not included in the 18- to 24-month evaluation. *The patient with major amputation, residual stenosis, and a patient who died during the first 6 months are identical to those listed between the boxes for baseline and 6-month angiography. **One patient had a TLR more than a year before she died. She is mentioned twice.

primary end point, center effects are not significant ($P=0.92$, ANOVA), and no adjustment was made.

TLR and amputation are presented as Kaplan–Meier analysis with the Mantel-Cox log-rank test. Analysis was performed with the SAS 9.1 program (SAS Institute, Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patients and Lesions

A total of 87 patients were enrolled in the study from July 2004 to January 2006 and followed up for up to 2 years (Figure 1). Forty-five patients were randomly assigned to treatment with paclitaxel-coated balloons; 42 patients were included in the uncoated balloon group. Baseline characteristics of the patients are compiled in Tables 1 and 2. Slight differences were present in the following characteristics: 15 of 42 patients (36%) in the control group versus 21 of 45 (47%) in the coated balloon group were smokers; diabetes was slightly more frequent in the control group (23 of 42, 55%) than in the coated balloon group (18 of 45, 40%); and a family history of vascular disease was reported more often in the coated balloon group (56% versus 36%). All other basic patient and vessel data, ie, incidence of hypertension, restenotic lesions, occluded vessels, lesion length, vessel diameter, and calcification, were almost identical in the 2 treatment arms.

Angioplasty

All procedural data, including balloon size and required additional stents, were similar in both treatment groups (Tables 2 and 3). Crossover access was chosen in 31 of 42 control patients (74%) and 37 of 45 patients (82%) treated with the coated balloon. Stenosis of treated lesions as assessed by the investigators was 84±16% in the control group and 84±11% in the coated balloon group. The interventions with coated balloons were performed exactly the same way as those with uncoated balloons. No technical problems or adverse events assessed as at least possibly related to the drug coating were observed. The total dose of paclitaxel in the coated balloon patient group ranged from 1.3 to 12.2 mg, depending on the size and number of balloons used. During the procedure, >90% of the dose was released from the balloons. As a result of recoil or dissection, nitinol stents (Luminex stents, Bard, Tempe, Ariz, in all but 2 patients) were implanted in 6 of 42 and 4 of 45 patients. Residual stenosis after treatment assessed by the core laboratory was 27±14% and 23±13% in the control and coated balloon groups, respectively, which were somewhat different from the investigators' estimates—12.4±9.5% and 16.1±13.9%—in these groups.

Follow-Up at 6 Months

Details of the follow-up are given in Table 4. About equal numbers of patients in both treatment groups withdrew consent or were not available for other reasons for the

Table 1. Baseline Patient Data

Characteristic	Uncoated Balloon Group	Paclitaxel-Coated Balloon Group	P
Age, y	70.2/66.2–77.6 (42)	67.3/63.5–76.4 (45)	0.28
Male, n (%)	25/42 (60)	27/45 (60)	1.00
Other conditions, n (%)			
Diabetes mellitus	23/42 (55)	18/45 (40)	0.20
Current smokers	15/42 (36)	21/45 (47)	0.38
Hypertension	34/42 (81)	35/45 (78)	0.79
Hypercholesterolemia	24/41 (59)	26/45 (58)	1.00
Family history of vascular disease	15/42 (36)	24/43 (56)	0.08
TASC II classification, n (%)			0.52*
Type A	21/42 (50)	14/45 (31)	
Type B	4/42 (10)	11/45 (24)	
Type C	10/42 (24)	16/45 (36)	
Type D	7/42 (17)	4/45 (9)	
Vessels affected, n (%)			
Popliteal involvement	8/42 (19)	6/45 (13)	0.56
Thereof PII segment	4/42 (10)	4/45 (9)	1.00
Type of stenosis, n (%)			
De novo	28/42 (67)	29/45 (64)	1.00
Restenosis	14/42 (33)	16/45 (36)	1.00
Restenosis after, n (%)			
PTA	10/42 (24)	14/45 (31)	0.48
In stent	4/42 (10)	2/45 (4)	0.67
Rutherford stage			0.33*
Class 1	1/42 (2)	2/45 (4)	
Class 2	7/42 (17)	10/45 (22)	
Class 3	31/42 (74)	31/45 (69)	
Class 4	3/42 (7)	2/45 (4)	
Ankle brachial index	0.7/0.5–0.8 (39)	0.7/0.6–0.8 (36)	0.33
Median lesion length, cm	4.7/2.7–8.5 (42)	4.0/2.1–6.1 (44)	0.45
Calcified lesion, n (%)	22/42 (52)	24/45 (53)	1.00
Total occlusion, n (%)	8/42 (19)	6/45 (13)	0.56
Patent vessels, lower leg, n			0.18
1	7/42 (17)	14/45 (31)	
2	15/42 (36)	14/45 (31)	
3	20/42 (48)	17/45 (38)	

Values are median/25th to 75th percentiles (n) or number of patients/total number of patients for whom the information is available (%).

*Cochran-Mantel-Haenszel test.

6-month reangiography. Thirty-four patients in the control group and 31 patients in the coated balloon group underwent angiographic 6-month follow-up. Follow-up angiography was performed after 7.2±1.8 months in 31 patients in the paclitaxel-coated balloon group and after 6.9±2.0 months in 34 patients in the uncoated balloon group. The primary end point of LLL was 0.5±1.1 mm in the paclitaxel-coated balloon group and 1.0±1.1 mm in the control group (P=0.031). A subgroup analysis yielded an LLL of 0.9±1.2 mm (n=22) in de novo lesions of control patients versus 0.4±1.2 mm (n=22) in de novo lesions in the coated balloon group (P=0.12) and 1.1±0.9 mm (n=12) and 0.6±0.5 mm (n=9) in restenotic lesions (P=0.095), respectively.

Table 2. Preinterventional Lesion Characteristics

Preinterventional Angiographic Findings	Uncoated Balloon Group	Paclitaxel-Coated Balloon Group	P
Reference diameter, mm	5.0/4.7–5.6 (41)	5.2/4.9–6.2 (43)	0.23
Total occlusion, n (%)	8/42 (19)	6/45 (13)	0.56
Degree of stenosis, %	85/80–90 (42)	85/75–90 (45)	0.55

Values are median/25th to 75th percentiles (n) or number of patients/total number of patients for whom the information is available (%).

Restenosis developed in 16 of 34 patients (47%) in the control group and 6 of 31 patients (19%) in the paclitaxel-coated group (P=0.035). Compared with before the intervention, Rutherford class improved in both treatment groups, but the improvement was larger in the patients treated with the coated balloons (P=0.045). No statistically significant difference between treatment groups was seen in the change in ankle brachial index during the period from shortly after PTA to 6 months.

Adverse Events

During and shortly after the intervention, 4 adverse events were reported: 2 events in the paclitaxel-coated balloon group (peripheral embolism, skin rash) and 2 in the control group (allergoid reaction, temporary serum creatinine increase).

During the 6-month follow-up period, 1 patient in the paclitaxel-coated balloon group died as a result of multiple organ failure, which was not related to the study medication or PTA. In 1 patient in the uncoated balloon group, bilateral

Table 3. Procedural Data

Intervention	Uncoated Balloon Group	Paclitaxel-Coated Balloon Group	P
Balloons for target lesion			
Balloons per patient, n	1/1–1 (42)	1/1–1 (45)	0.29
Maximum length, cm*	4/4–6 (42)	5/4–6 (45)	0.89
Maximum diameter, mm*	5/5–5 (42)	5/5–6 (45)	0.07
Paclitaxel			
mg/balloon, mean±SD (n)		2.8±0.9 (54)	
mg/patient, mean±SD (n)		3.7±2.5 (44)	
Paclitaxel residue on balloon after angioplasty, mean±SD, % (n)		6.4±2.9 (54)	
Postdilatation, n (%)	4/42 (10)	7/45 (16)	0.52
Stent implantation, n (%)	6/42 (14)	4/45 (9)	0.51
Treated lesions, n	1/1–2 (41)	1/1–2 (45)	0.99
Duration of intervention, min	83/60–90 (42)	60/50–90 (45)	0.13
Ankle brachial index	0.9/0.8–1.0 (25)	0.8/0.7–1.0 (27)	0.16

Values are median/25th to 75th percentiles (n), mean±SD (n), or number of patients/total number of patients or balloons for whom the information is available (%).

*Sizes refer only to the largest balloon used in a target lesion; multiple balloons were applied in some patients with long lesions.

Table 4. Stenosis and Restenosis

	Uncoated Balloon	Paclitaxel-Coated Balloon	*P*
Follow-up angiography at 6 mo			
Time between intervention and reangiography, mo	6.4/5.9–7.6 (34)	6.6/6.1–7.8 (31)	0.44
Reference diameter, mm	5.1/4.9–5.7 (33)	5.2/4.9–5.6 (30)	0.62
Minimal lumen diameter, mm	2.7/1.6–3.8 (34)	3.6/2.9–4.2 (31)	0.037
LLL			0.031
All patients, mm	0.8/0.4–1.6 (34)	0.3/0.0–0.8 (31)	0.031
De novo lesions only, mm	0.5/0.3–1.6 (22)	0.2/−0.5–0.9 (22)	0.121
Restenotic lesions, mm	1.1/0.5–1.9 (12)	0.5/0.2–0.8 (9)	0.095
Binary restenosis, n (%)	16/34 (47)	6/31 (19)	0.035
Primary patency, n (%)	32/34 (94)	29/31 (94)	1.00
Follow-up clinical results at 6 mo			
Rutherford stage, related to baseline, n (%)			
Worsened	2/42 (5)	0/45 (0)	
Equal	15/42 (36)	8/45 (18)	
Improved	15/42 (36)	26/45 (58)	
Missing	10/42 (23)	11/45 (24)	
Difference, uncoated vs coated balloon group			0.045*
Ankle brachial index	0.8/0.7–0.9 (24)	0.8/0.7–0.9 (26)	0.90
Mean difference in ankle brachial index, after PTA to 6 mo	−0.1/−0.1–0.0 (12)	0.1/−0.1–0.2 (15)	0.1
TLR, n (%)	14/42 (33)	3/45 (7)	0.0024
Major amputations of target leg/excluding toes, n (%)	1/42 (2)	0/45 (0)	0.48
Death, n (%)	0/42 (0)	1/45 (2)	1.00
Follow-up at 18–24 mo			
First TLR during, n (%)			
6–24 mo	7/42 (17)	3/45 (7)	0.19
0–24 mo	21/42 (50)	6/45 (13)	0.001
Stenosis as estimated by the investigators in patients without prior TLR, %	30/10–75 (15)	10/10–30 (23)	0.12
Binary restenosis in patients without prior TLR, n (%)	6/15 (40)	4/23 (17)	0.15
Rutherford stage, related to baseline, n (%)			
Worsened	3/42 (7)	5/45 (11)	
Equal	6/42 (14)	5/45 (11)	
Improved	15/42 (36)	16/45 (35)	
Missing	18/42 (43)	19/45 (43)	
Difference, uncoated vs coated balloon group			0.98*
Major amputations, n (%)	0/42 (2)	0/45 (0)	1.00
Death, n (%)	3/42 (7)	6/45 (13)	0.49

Values are median/25th to 75th percentiles (n) or number of patients/total number of patients for whom the information is available (%).
*Cochran-Mantel-Haenszel test.

below-knee amputation had to be performed within this time period. A comparable number of serious adverse events, including any hospitalization or prolongation of hospitalization according to the common definition (serious adverse events), were reported in both treatment groups: 22 patients (48.9%) in the paclitaxel-coated balloon group and 22 patients (52.4%) in the uncoated balloon group. Most of these serious adverse events were due to vascular disorders, including TLR, which was significantly more frequent in the control group (14 of 42, 33%) than in the coated balloon group (3 of 45, 7%) ($P=0.002$). The majority of TLRs (10 of 14 in the control group and 2 of 3 in the coated balloon group) were stimulated by documented complaints the patients had before control angiography was performed; in the remaining cases, the decision was based on the angiographic result.

Neither of the 2 treatment groups showed unexpected adverse events or an unusual frequency of adverse events.

Follow-Up at 18 to 24 Months

During the period of 6 to 24 months, 3 patients in the control group (1 patient after amputation of the foot of the target leg)

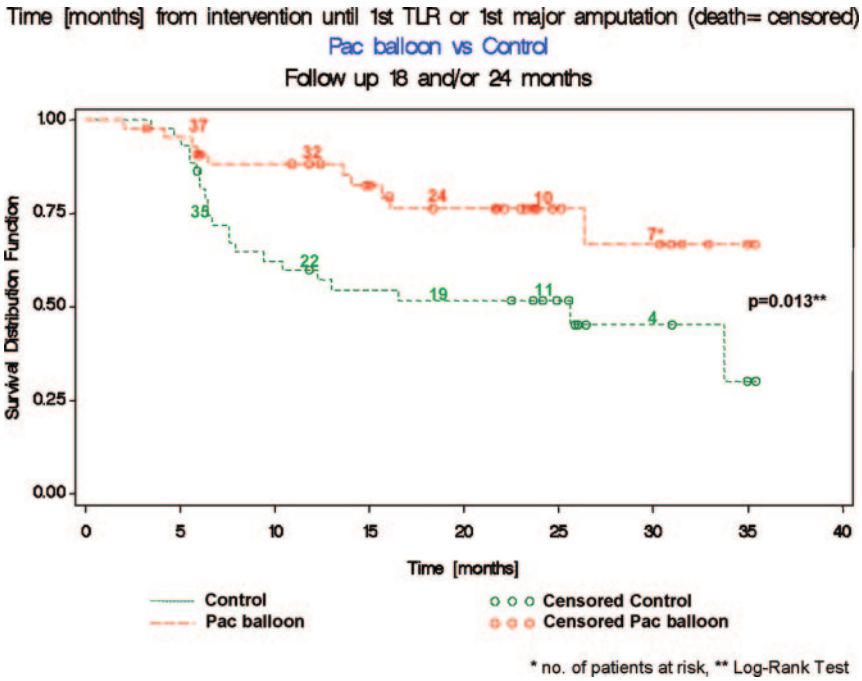

Figure 2. Kaplan–Meier presentation of patients up to ≈24 months. Pac indicates paclitaxel.

and 6 patients in the coated balloon group (unrelated) died. No additional amputation was recorded. Seven patients in the control group and 3 patients in the coated balloon group required TLR before or during the 18- to 24-month follow-up, of which 3 and 2, respectively, were clinically driven. Three of 14 patients in the control group who had a TLR within the first 6 months required bypass surgery of the target vessel segment; 1 patient of the coated balloon group underwent repeat PTA. Patients who did not require interventional or surgical treatment of the target lesion were asked to attend a follow-up examination 18 to 24 months after the initial procedure. Patients who reached a clinical end point that made further assessment of the effect of the initial treatment impossible or difficult (death, amputation, TLR) were excluded. No Doppler or angiographic information was obtained from 7 patients in the control and 9 patients in the coated balloon group; however, 1 of 7 patients (control) and 3 of 9 patients (coated balloon) stated that they did well with respect to the treated leg. Fifteen patients in the control and 23 patients in the coated balloon group underwent Doppler sonography or angiography. In these patients, percent stenosis as estimated by the investigators and binary restenosis rates were identical for the treatment groups (Table 4). The Kaplan–Meier presentation (Figure 2) of survival without TLR and amputation indicates a persistent benefit of the drug-coated balloons ($P=0.013$).

Discussion

A variety of methods, including brachytherapy, laser, atherectomy, cryotherapy, and stenting with bare metal and drug-eluting stents, have been tried to improve acute success and long-term patency in patients with femoropopliteal occlusions. Only rarely did controlled randomized trials indicate advantages of new methods over standard treatment.[15–17]

In the present study, the efficacy of a novel drug-coated balloon catheter for the prevention of restenosis after treatment of atherosclerotic femoropopliteal lesions was investigated. The study design included a control group treated with conventional balloon PTA, which is considered the standard therapy. Patients were randomized to 1 of 2 treatment arms. Stent implantation was permitted in both treatment groups if the primary result of PTA was not satisfactory and was performed in about equal numbers of patients in both treatment groups. Owing to slight differences in the appearance of the balloons caused by the coating, blinding of investigators was not perfect. Quantitative angiography was performed by a blinded independent core laboratory (U.D.), providing the data for the primary end point (LLL), restenosis rate, and other parameters. LLL was chosen as the primary end point because it was found to be the most sensitive parameter for recognizing restenosis caused by neointimal proliferation in cardiological studies.[18] Other radiographic and clinical measures indicative of target lesion restenosis also were observed. The initial follow-up was planned for 6 months, resulting in a mean follow-up of 7 months. A second follow-up was planned for 18 to 24 months after the intervention.

The patients' mean age was 69 years; the majority were male; almost half of the patients were diabetics and smokers; ≈80% were hypertensive; and almost 60% suffered from hypercholesterolemia. The proportion of type C and D lesions according to the TASC II classification was 43%; the incidence of restenotic lesions was high (≥33%); and the mean lesion length was 6 cm, which is not high but at the upper limit of comparable trials.[19] The incidence of risk factors is reflected in the high binary restenosis rate in the control group already 7 months after the intervention.

The primary end point, LLL, was significantly different between both treatment groups in favor of the coated balloon group (coated balloon, 0.5±1.1 mm [n=31]; control,

1.0±1.1 mm [n=34]; $P=0.031$) at the 6-month follow-up angiography with no large difference regardless of whether primary or restenotic lesions were treated. This result was confirmed by a significant difference in the secondary end point of binary restenosis (coated balloon group, n=6 of 31, 19%; control group, n=16 of 34, 47%; $P=0.035$) and the clinical end point improvement in Rutherford class at 6 months compared with pretreatment ($P=0.045$). No coating-associated serious adverse events were observed in this study.

The advantage with respect to TLR was maintained up to 18 to 24 months after treatment. Patients who did not require TLR did equally well in both treatment groups, whereas this proportion was significantly greater in the paclitaxel-coated balloon (87%) than in the control (50%; $P<0.001$) group.

Delivery of a drug by coated-balloon catheters differs substantially from delivery by drug-eluting stents. Whereas drug-eluting stents contain low doses of drugs that are released slowly from a polymer stent coating, the drug-eluting balloons used in our trial are coated with the free drug. A small amount of a radiographic contrast agent known to improve the solubility of paclitaxel added to the coating leads to enhanced dissolution of the drug.[9] The coated balloon releases most of the drug immediately during the first inflation when there is short contact with the vessel wall for 60 seconds.[11] The duration of inhibition of cell proliferation far exceeds the time during which the cells are actually exposed to the drug.[8–10] Postinterventionally, only about 6.4±2.9% of the original paclitaxel dose was found to be extractable from the surface of the balloons used in our trial. Although animal studies[11,20] indicate that as much as 70% to 80% of the drug dose might be lost in the bloodstream, the remaining dose and duration of drug exposure seem to be sufficient to prevent neointimal proliferation.[8,9,10,20]

The lack of efficacy of drug-eluting nitinol stents shown in a clinical trial[21] may be explained by the fact that no sufficient drug concentration was reached between the stent struts during elution. The distance between stent struts of nitinol stents for peripheral vessels is larger than in balloon-expandable coronary stents. The drug that is delivered by the coated balloon is distributed more evenly on the vessel surface than the drug bound to the struts of a drug-eluting stent.[22]

Schillinger et al[16,17] recently demonstrated that primary placement of bare metal stents in femoropopliteal lesions may improve patency compared with PTA. In our study, stent placement was performed after failure of PTA (control, n=6 of 42, 14%; paclitaxel, n=4 of 45, 9%; $P=0.51$); 2 of the patients in the control group and 1 patient in the coated balloon group required TLR, whereas the LLL in the other patients was below average.

Data comparing treatment with primary placement of bare metal stents with use of coated balloons are still missing. However, performing angioplasty with a coated balloon does not conflict with the placement of stents after PTA has failed.

The primary limitations of this study are the small patient number, the heterogeneity of the population, the small proportion of long lesions, and the less-than-optimal number of patients who agreed to undergo control angiography as part of their treatment plan. None of these limitations favors one of the treatments. Risk factors were balanced between treatment groups, with a slightly larger number of diabetics in the control group and a slightly higher number of current smokers and patients with a family history of vascular disease in the coated balloon group. The short duration of the follow-up is a further limitation of this study.

The results of the study presented here are in good agreement with those of the recently published Thunder study[23] (Local Paclitaxel Delivery to Inhibit Restenosis During Lower Extremity Angioplasty), which had a similar design. Both studies were initiated at about the same time by different clinical investigators in different hospitals. The Thunder study differed from the present study by including a third treatment group that received paclitaxel in the contrast agent. The patient populations were similar. In the present trial, a larger proportion of patients smoked; there were fewer patients in whom a popliteal segment was treated; and the proportion of total occlusions treated was somewhat lower. Mean lesion length was 7.4 cm in the Thunder trial and 6 cm in the present study (median length is shorter). The proportion of patients who required stent implantation was low in both studies and more balanced in the present study. In both studies, the primary end point, LLL after 6 months, was significantly lower in the patients treated with the paclitaxel-coated balloon; however, the mean LLL in the control group of this study was lower than in the Thunder trial (1.0±1.1 versus 1.7±1.8 mm). The difference between the control group and the coated-balloon group reached the level of statistical significance ($P<0.05$) also with respect to the secondary end points, binary restenosis rate and TLR at 6 months and after 1 and 2 years (Thunder) or at 18 to 24 months in this trial. These results indicate that short-term exposure of injured arteries to paclitaxel may be sufficient to inhibit restenosis during a critical period of time after angioplasty of femoropopliteal arteries.

Acknowledgment

We thank the Beratungsinstitut für Angewandte Statistik, Berlin, Germany, and C. Abramjuk for excellent support of documentation.

Sources of Funding

The authors received balloon catheters for the study from Bavaria Medizin Technologie, Oberpfaffenhofen, Germany, and financial support from Bayer-Schering-Pharma AG, Berlin, Germany.

Disclosures

Dr Tepe reports serving as a consultant to and receiving research grants from Abbott Vascular and Cordis and receiving research grants from Cook and InnoRa. Dr Speck has served as a consultant to Bayer Schering Pharma AG and is coinventor of a patent at the Charité University Hospital in Berlin on drug-coated balloons. Dr Ricke reports serving as consultant to and receiving research grants from Bayer Schering Pharma. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Although recent data indicate that primary stent implantation improves morphological and clinical outcome in treating sclerosed femoropopliteal vessels, the problem of restenosis associated with interventional treatment remains to be solved. Two competing procedures for restenosis prevention involve the use of coated stents and covered stent grafts. Stents not only serve to stabilize a lesion after dilatation but also are approved to serve as carriers for the local delivery of antiproliferative drugs. The Femoral Paclitaxel (FemPac) Randomized Pilot Trial introduces a new method of drug delivery using standard angioplasty catheters as carriers. Whereas stents have a number of drawbacks, including the risk of fracture, material fatigue, and induction of local inflammation in the long run, and are less desirable in the treatment of in-stent restenosis, the concept of balloon-mediated short-time contact offers the chance to combine drug administration for the prevention of restenosis and optional stent placement if needed for lesion stabilization. With the coated-balloon approach, the vessel can be left in its native state if effective dilatation can be achieved without stent implantation. This new concept is currently under further investigation with ongoing trials in below-knee infraglenoidal angioplasty and several indications in the coronary arteries.

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Inhibition of Restenosis in Femoropopliteal Arteries: Paclitaxel-Coated Versus Uncoated Balloon: Femoral Paclitaxel Randomized Pilot Trial

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Circulation. 2008;118:1358-1365; originally published online September 8, 2008;
doi: 10.1161/CIRCULATIONAHA.107.735985
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Correction

In the version of the article, "Inhibition of Restenosis in Femoropopliteal Arteries: Paclitaxel-Coated Versus Uncoated Balloon: Femoral Paclitaxel Randomized Pilot Trial," by Werk et al that was posted online on September 8, 2008 (DOI:10.1161/CIRCULATIONAHA.107.735985), several errors occurred.

In the Abstract, Methods and Results, line 11, the number of target lesion revascularizations in the paclitaxel-coated balloon group should be 3 of 45 rather than 4 of 45, and the *P* value compared to control subjects should be 0.002 rather than 0.007.

On the third page, first full paragraph, column 1, the information in parentheses, "(SPSS version 13.0.1, SPSS Inc, Chicago, Ill)" should be deleted.

In Table 4, left column, the units for "All patients" and "De novo lesions only" under LLL should be "mm" rather than "n (%)."

On the fifth page, final 2 lines in column 1 and top line of column 2, the number of target lesion revascularizations in the paclitaxel-coated balloon group should be 3 of 45 rather than 4 of 45, and the *P* value compared to control subjects should be 0.002 rather than 0.007. The number of TLRs in the control group should be 10 of 14 rather than 11 of 14, and the number of TLRs in the coated balloon group should be 2 of 3 rather than 3 of 4.

On the fifth page, last line of column 2, the number of patients in the coated balloon group who died should be 6 rather than 5.

On the sixth page, lines 1 through 4, column 1, the second sentence should read, "Seven patients in the control group and 3 patients in the coated balloon group required TLR before or during the 18- to 24-month follow-up, of which 3 and 2, respectively, were clinically driven."

On the sixth page, column 1, starting at line 15, the sentences should read, "No Doppler or angiographic information was obtained from 7 patients in the control and 9 patients in the coated balloon group; however, 1 of 7 patients (control) and 3 of 9 patients (coated balloon) stated that they did well with respect to the treated leg. Fifteen patients in the control and 23 patients in the coated balloon group underwent Doppler sonography or angiography."

On the seventh page, column 1, first full paragraph, line 5, the data 80%, 52%, and $P=0.012$ should be replaced by 87%, 50%, and $P<0.001$, respectively.

The errors have been corrected in the final print version of the article in the September 23, 2008, issue of the journal (*Circulation*. 2008:118:1358–1365) and in the current online version.

The publisher regrets the errors.

DOI: 10.1161/CIRCULATIONAHA.108.191023

(*Circulation.* 2008;118:e670.)

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