

## ORIGINAL ARTICLE

# Local Delivery of Paclitaxel to Inhibit Restenosis during Angioplasty of the Leg

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## ABSTRACT

**BACKGROUND**

Drug-eluting stents reduce restenosis in coronary arteries, but clinical trials have failed to prove their efficacy in peripheral arteries. We investigated the use of paclitaxel-coated angioplasty balloons and paclitaxel dissolved in the angiographic contrast medium during angioplasty of the leg.

**METHODS**

In a small, multicenter trial, we randomly assigned 154 patients with stenosis or occlusion of a femoropopliteal artery to treatment with standard balloon catheters coated with paclitaxel, uncoated balloons with paclitaxel dissolved in the contrast medium, or uncoated balloons without paclitaxel (control). The primary end point was late lumen loss at 6 months.

**RESULTS**

The mean ( $\pm$ SD) age of the patients was  $68\pm 8$  years, 24% were smokers, and 49% had diabetes. Twenty-seven percent of the lesions were total occlusions, and 36% were restenotic lesions. The mean lesion length was  $7.4\pm 6.5$  cm. There were no significant differences in baseline characteristics between the groups. There were no adverse events attributable to the paclitaxel-coated balloons. At 6 months, the mean late lumen loss was  $1.7\pm 1.8$  mm in the control group, as compared with  $0.4\pm 1.2$  mm ( $P<0.001$ ) in the group treated with paclitaxel-coated balloons and  $2.2\pm 1.6$  mm ( $P=0.11$ ) in the group treated with paclitaxel in the contrast medium. The rate of revascularization of target lesions at 6 months was 20 of 54 (37%) in the control group, 2 of 48 (4%) in the group treated with paclitaxel-coated balloons ( $P<0.001$  vs. control), and 15 of 52 (29%) in the group treated with paclitaxel in the contrast medium ( $P=0.41$  vs. control); at 24 months, the rates increased to 28 of 54 (52%), 7 of 48 (15%), and 21 of 52 (40%), respectively.

**CONCLUSIONS**

Use of paclitaxel-coated angioplasty balloons during percutaneous treatment of femoropopliteal disease is associated with significant reductions in late lumen loss and target-lesion revascularization. No significant benefit is seen with the use of a paclitaxel-containing contrast medium. (ClinicalTrials.gov number, NCT00156624.)

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**P**ERCUTANEOUS TRANSLUMINAL ANGIOPLASTY for revascularization of the superficial femoral artery has an initial technical success rate of more than 95%.<sup>1</sup> However, restenosis occurs in 40 to 60% of the treated segments after 6 to 12 months<sup>2-4</sup>; these rates are much higher than restenosis rates in other vascular beds, such as the coronary and renal arteries.<sup>5</sup> Stenting is more effective than balloon angioplasty for preventing restenosis in the coronary circulation, but a benefit of stenting in the vessels of the lower extremities remains to be confirmed.<sup>6-9</sup> Several other attempts to increase long-term patency in peripheral vascular disease have failed. One study of local drug delivery during angioplasty of the superficial femoral artery is the Sirolimus-Coated Cordis Self-Expandable Stent (SIROCCO) trial (NCT00232869), which reported that sirolimus-coated stents were not superior to uncoated stents.<sup>10-12</sup>

Several studies in cell culture and in swine<sup>13-18</sup> have demonstrated sustained inhibition of the proliferation of vascular smooth-muscle cells after the exposure of cells or tissues to paclitaxel, a highly lipophilic antineoplastic drug, for just a few seconds to a few minutes. This inhibitory effect was seen in animals both when paclitaxel was added to the contrast medium used to visualize the arteries during the intervention and when it was coated onto angioplasty balloons. A recent clinical trial suggested significant inhibition of re-restenosis after treatment of restenosis in coronary stents by paclitaxel-coated angioplasty balloons.<sup>19</sup> Acceptable adverse-event rates for paclitaxel dissolved in a contrast medium were confirmed in a dose-escalating phase 1 study in patients who were undergoing coronary angiography (unpublished data). The purpose of the current trial was to investigate the effect of paclitaxel on restenosis after angioplasty of stenotic or occluded superficial femoral or popliteal arteries.

## METHODS

### STUDY DESIGN

The THUNDER (Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries) trial was a prospective, randomized, multicenter trial performed at the universities of Tübingen and Berlin and at the Herz-Zentrum Bad Krozingen in Germany. We developed the protocol in accordance with the Declaration of Helsinki, and it was approved by the local ethics committees.

The THUNDER trial was sponsored by the Bavaria Medizintechnologie and Schering, Germany. The sponsors had no involvement in the design of the trial, collection and analysis of the data, or writing of the report. The authors vouch for the accuracy and completeness of the data and the statistical analysis.

### STUDY PATIENTS

Eligible patients were between 18 and 95 years of age and had symptomatic peripheral-artery disease (Rutherford stages 1 to 5; the Rutherford scale ranges from 0 to 6, with higher numbers indicating worse disease).<sup>20</sup> All patients had one or more obstructive lesions, either new lesions or restenoses, at least 70% of vessel diameter and at least 2 cm in length, in the superficial femoral artery, the popliteal artery, or both. If more than one lesion required intervention, only one was treated as the study lesion. Exclusion criteria included poor inflow, absence of a patent crural artery, acute onset of symptoms, pregnancy, life expectancy of less than 1 year, and contraindications to required medication. All patients gave written informed consent.

All patients underwent initial diagnostic angiography of the leg with the use of a standard angiographic contrast medium (Ultravist 300, Schering) to confirm their candidacy for the trial. After the guidewire had been passed through the target lesion, patients were assigned to one of three treatment groups according to a lot-generated random list. One group was treated with paclitaxel-coated balloons and standard nonionic contrast medium, a second group was treated with standard uncoated balloons with paclitaxel added to the contrast medium, and the control group was treated with standard uncoated balloons and standard nonionic contrast medium.

The patients and investigators were not informed of the assigned intervention. However, the paclitaxel-coated balloons had a distinctive appearance that could be recognized by the investigators, who also performed some of the post-study evaluations.

### STUDY PROCEDURE

Treatment-group assignment was followed by balloon dilation of the target lesion, which was performed with balloon catheters provided by Bavaria Medizintechnologie. The balloons either were uncoated or were coated with paclitaxel at a dose of

3  $\mu\text{g}$  per square millimeter of balloon surface, as previously described.<sup>15,19</sup> To restore the reference diameter of the vessel, the balloons were inflated with a maximum of 12 atm for a standardized inflation time of 1 minute. All study balloons were inflated only once. Additional study balloons were used for lesions exceeding the length of the first balloon. If angiography after the procedure showed residual stenosis of more than 30%, inflation with a conventional nonstudy balloon was repeated for 5 minutes. Nitinol (nickel–titanium) stents were implanted in lesions that had persistent residual stenosis or as clinically needed.

Angiography during and after the angioplasty procedure was performed with the use of the study contrast medium — either the contrast medium alone (Ultravist 300) or the contrast medium mixed with paclitaxel. To prepare the mixture, 100 ml of contrast medium was added to 17.1 mg of paclitaxel in 1 ml of absolute ethanol immediately before use. If more than 100 ml of contrast medium was required during the course of the procedure, standard Ultravist 300 was used.

Patients not already taking aspirin and clopidogrel were administered loading doses of 300 mg of each drug 12 hours before the procedure. All patients received aspirin (100 mg daily) indefinitely and clopidogrel (75 mg daily) for 4 weeks after the intervention. In addition, patients were given an intraarterial bolus of heparin (3000 to 5000 U) at the time of the procedure. The amount of residual paclitaxel on the balloons after use and plasma paclitaxel concentration immediately after the intervention and 2 hours later were determined by high-performance liquid chromatography.<sup>15</sup>

#### FOLLOW-UP AND END POINTS

Clinical evaluations were performed at baseline, at 24 to 72 hours after intervention, and at 6 months after intervention. The evaluations included staging of peripheral arterial occlusive disease according to the Rutherford classification, measurement of the ankle–brachial index, clinical laboratory testing, and assessment of adverse events.

Angiographic evaluation of restenosis was performed at 6 months with the same projections as those used during intervention. All angiograms were assessed in a blinded fashion by an independent angiographic core laboratory (C2RM, Lille, France). The primary end point was late lumen

loss, defined as the difference between the minimum lumen diameters after dilation and at the 6-month follow-up. The secondary efficacy end points were the technical success of the intervention, the 6-month angiographic restenosis rate (i.e., the incidence of stenosis of  $\geq 50\%$  of the diameter of the reference-vessel segment), change in Rutherford stage, the ankle–brachial index, the patency rate, and the incidence of target-lesion revascularization. The safety of paclitaxel administration was assessed by monitoring biochemical and hematologic changes during the first 72 hours and clinically and angiographically apparent adverse events for 6 months.

Additional follow-up after 1 and 2 years was planned if the 6-month follow-up indicated differences between treatment groups. On the basis of the results at 6 months, the ethics committees were asked to approve expansion of the observation period with additional follow-up examinations after 1 and 2 years. Twelve and 24 months after the original procedure, patients were asked to come to the hospital for examination; patients who were not able and willing to do so were interviewed by telephone.

#### STATISTICAL ANALYSIS

We estimated that 45 patients would have to be enrolled in each group to yield a statistical power of 80% for the detection of an absolute difference in late lumen loss of 15% of the reference diameter between study groups at a P value of less than 0.05. These calculations assumed a standard deviation for late lumen loss of 20% of the reference diameter and a 20% loss of patients to angiographic follow-up. Calculations were performed with nQuery software, version 4.0.

All data were analyzed according to the intention-to-treat principle. No patients were excluded until they reached one of the defined end points. For continuous variables, the arithmetic mean and standard deviation were calculated, and comparisons were performed by a two-sided Wilcoxon rank-sum test. For categorical variables, the absolute and relative frequencies were calculated, and comparisons were performed by Fisher's exact test. Ninety-five percent confidence intervals were calculated for the differences of means and relative frequencies. Statistical calculations were performed with SAS software, version 9.1.

## RESULTS

**PATIENT POPULATION**

Patient enrollment began in June 2004 and ended in June 2005. The three study centers enrolled 154 patients; 54 were assigned to the control group, 48 to treatment with paclitaxel-coated balloons, and 52 to treatment with paclitaxel in the contrast medium (Table 1). The patients had a mean ( $\pm$ SD) age of  $68\pm 8$  years, 66% were male, 24% were smokers, and 49% had diabetes. The majority of the patients had hypertension. The mean Rutherford stage before the intervention was  $3.3\pm 0.9$ , and the mean ankle-brachial index was  $0.5\pm 0.3$ .

The mean predilation degree of stenosis was  $90\pm 9\%$ , and the mean length of the target lesion (as reported by the investigators) was  $7.4\pm 6.5$  cm. Twenty-seven percent of treated lesions were total occlusions, and 30 to 42% were restenoses.

**INTERVENTION**

All patients were treated as assigned. Puncture of the contralateral common femoral artery was chosen for 30 to 44% of the patients in the three treatment groups (Table 2), followed by placement of a crossover sheath ending in the iliac artery of the treated leg. Procedural success — defined as completion of the procedure with less than 30% residual stenosis of the target lesion (after prolonged dilation and stenting, if necessary) — as estimated by the investigators was achieved in 151 of 154 cases. In the remaining three cases, a residual stenosis of 30 to 40% of the reference diameter was achieved. Nitinol stents were implanted in 17 patients because of vessel recoil or dissection; most of the patients receiving nitinol stents were in the control group. The average residual stenosis at the end of the intervention was 8 to 14% in the three treatment groups, with the best results in the control group.

The mean Rutherford stage improved after the intervention from  $3.1\pm 0.8$  to  $1.2\pm 1.5$  in the control group, from  $3.4\pm 0.8$  to  $1.1\pm 1.2$  in the group treated with paclitaxel-coated balloons, and from  $3.4\pm 1.0$  to  $1.7\pm 1.8$  in the group treated with paclitaxel in the contrast medium. The overall mean ankle-brachial index improved from  $0.5\pm 0.3$  to  $0.9\pm 0.3$ . The differences between treatment groups were not significant.

For patients treated with coated balloons, the average paclitaxel dose per patient was 5 mg (range, 1 to 17 mg); for those treated with pacli-

taxel added to the contrast medium, the average dose was 17 mg, with little variation among patients. In 40 of 42 patients treated with coated balloons, the maximum plasma paclitaxel concentration remained below the detection limit ( $<0.03$   $\mu$ g per milliliter), whereas the majority of patients receiving paclitaxel in the contrast medium had measureable plasma concentrations immediately after the procedure (Table 2).

**ANGIOGRAPHIC FOLLOW-UP**

Eighty-three percent of the patients (128 of 154) underwent angiography at the 6-month follow-up. The primary end point of mean late lumen loss was significantly lower in the group treated with paclitaxel-coated balloons than in the control group ( $0.4\pm 1.2$  mm vs.  $1.7\pm 1.8$  mm,  $P<0.001$ ). In contrast, late lumen loss in the group receiving paclitaxel in the contrast medium ( $2.2\pm 1.6$  mm) did not differ significantly from that in the control group ( $P=0.14$ ) (Table 2). The angiographic restenosis rate was significantly lower among patients treated with paclitaxel-coated balloons than among patients in the control group (17% vs. 44%,  $P=0.01$ ). However, the rate among patients receiving paclitaxel in the contrast medium (55%) did not differ significantly from that among patients in the control group ( $P=0.39$ ). There were no significant differences in the primary patency rate at 6 months between either of the paclitaxel groups and the control group. Figure 1 shows angiograms of a control patient and a patient treated with a paclitaxel-coated balloon.

During the original intervention, significantly more patients in the control group than in either of the paclitaxel groups required stent implantation in the target lesion. Therefore, we also calculated late lumen loss for the patients who received no stents. Late lumen loss reached  $1.9\pm 1.8$  mm in the control group (39 patients),  $0.3\pm 1.1$  mm in the group treated with paclitaxel-coated balloons (39 patients,  $P<0.001$  vs. the control group), and  $2.1\pm 1.6$  mm in the group treated with paclitaxel in the contrast medium (38 patients,  $P=0.58$  vs. the control group).

**CLINICAL FOLLOW-UP**

All but eight patients (one in the control group, two in the group treated with paclitaxel-coated balloons, and five in the group treated with paclitaxel in the contrast medium) underwent a timely clinical follow-up assessment at 6 months, in-

**Table 1. Patients and Treated Lesions.\***

Characteristic	Control Patients (N=54)	Patients with Paclitaxel-Coated Balloons (N=48)	Patients with Paclitaxel in the Contrast Medium (N=52)	Percent Difference between Control and Paclitaxel-Coated Balloon Groups (95% CI)	P Value	Percent Difference between Control and Paclitaxel-Contrast-Medium Groups (95% CI)	P Value
Age — yr	68±9	69±8	68±8	-1.6 (-4.9 to 1.7)	0.35	-0.2 (-3.5 to 3.0)	0.76
Male sex — no. (%)	34 (63)	31 (65)	36 (69)	-2 (-20 to 17)	1.00	-6 (-24 to 12)	0.54
Smoker — no./total no. (%)	12/54 (22)	11/48 (23)	14/51 (27)	-1 (-17 to 16)	1.00	-5 (-22 to 11)	0.65
Diabetes mellitus — no. (%)	25 (46)	24 (50)	27 (52)	-4 (-23 to 16)	0.84	-6 (-25 to 13)	0.70
Type 1 diabetes mellitus — no. (%)	14 (26)	18 (38)	14 (27)	-12 (-30 to 6)	0.29	-1 (-18 to 16)	1.00
Hyperlipidemia — no./total no. (%)	34/54 (63)	33/48 (69)	33/51 (65)	-6 (-24 to 13)	0.68	-2 (-20 to 17)	1.00
Hypertension — no. (%)	45 (83)	38 (79)	45 (87)	4 (-11 to 19)	0.62	-3 (-17 to 10)	0.79
Baseline Rutherford stage of peripheral-artery disease†	3.1±0.8	3.4±0.8	3.4±1.0	-0.30 (-0.62 to 0.02)	0.03	-0.33 (-0.69 to 0.03)	0.05
Baseline ankle-brachial index‡	0.5±0.3	0.5±0.3	0.5±0.3	0.01 (-0.12 to 0.14)	0.71	-0.01 (-0.13 to 0.11)	0.96
Target vessel — no. (%)							
Superficial femoral artery only	35 (65)	33 (69)	35 (67)	-4 (-22 to 14)	0.83	-2 (-21 to 16)	0.84
Popliteal artery with or without superficial femoral artery	19 (35)	15 (31)	17 (33)	4 (-14 to 22)	0.83	2 (-16 to 21)	0.84
Degree of stenosis — % of target-vessel diameter	91±7	89±8	89±7	1.5 (-1.5 to 4.4)	0.45	2.1 (-0.6 to 4.7)	0.09
Length of target lesion — cm§	7.4±6.7	7.5±6.2	7.4±6.5	-0.1 (-2.7 to 2.5)	0.73	0.0 (-2.6 to 2.6)	0.93
Reference diameter of target lesion before intervention — mm	4.7±0.6	5.0±0.7	4.8±0.5	-0.2 (-0.5 to 0.0)	0.07	-0.1 (-0.3 to 0.2)	0.95
Calcified lesion — no. (%)¶	28 (52)	24 (50)	21 (40)	2 (-18 to 21)	1.00	11 (-7 to 30)	0.25
Occlusion with or without stenosis — no. (%)	14 (26)	13 (27)	14 (27)	-1 (-18 to 16)	1.00	-1 (-18 to 16)	1.00
Restenotic lesion — no. (%)							
After PTA without stenting	10 (19)	10 (21)	14 (27)	-2 (-18 to 13)	0.81	-8 (-24 to 7)	0.36
After PTA with stenting	6 (11)	8 (17)	8 (15)	-6 (-19 to 8)	0.57	-4 (-17 to 9)	0.58
No. of lesions treated	1.6±0.7	1.8±0.8	1.7±0.9	-0.2 (-0.5 to 0.1)	0.24	-0.2 (-0.5 to 0.2)	0.45
No. of runoff vessels	2.1±0.8	1.8±0.8	1.9±0.7	0.3 (0.0 to 0.6)	0.08	0.2 (-0.1 to 0.5)	0.21

\* Plus-minus values are means ±SD. PTA denotes percutaneous transluminal angioplasty.

† The Rutherford scale ranges from 0 to 6, with higher numbers indicating worse disease.

‡ Fifty-two patients were assessed in the control group, 42 in the paclitaxel-coated-balloon group, and 47 in the paclitaxel-contrast-medium group.

§ The length of the target lesions was assessed by the investigator.

¶ Calcification was assessed by the investigator.

|| Forty-seven patients each were assessed in the control group and the paclitaxel-contrast-medium group, and 46 were assessed in the paclitaxel-coated-balloon group.

**Table 2. Target-Lesion Intervention and Follow-up.\***

Variable	Control Patients (N = 54)	Patients with Paclitaxel-Coated Balloons (N = 48)	Patients with Paclitaxel in the Contrast Medium (N = 52)	Percent Difference between Control and Paclitaxel-Coated Balloon Groups (95% CI)	P Value	Percent Difference between Control and Paclitaxel-Contrast-Medium Groups (95% CI)	P Value
<b>Procedural data</b>							
Crossover access — no. (%)†	16 (30)	21 (44)	19 (37)	-14 (-33 to 4)	0.15	-7 (-25 to 11)	0.54
Degree of stenosis — % of target-vessel diameter							
Before dilation	91±7	89±8	89±7	1.5 (-1.5 to 4.4)	0.45	2.1 (-0.6 to 4.7)	0.09
After dilation	8±9	14±14	13±12	-5.7 (-10.2 to -1.2)	0.05	-4.9 (-9.0 to -0.8)	0.04
Patients with additional stents in target lesion — no. (%)	12 (22)	2 (4)	3 (6)	18 (6 to 31)	0.009	16 (4 to 29)	0.02
Total paclitaxel dose — mg		4.7±3.5	16.8±1.9				
Paclitaxel residue on balloon after intervention — % of dose		6.6±4.5					
Plasma concentration of paclitaxel after intervention — mg/ml		<0.01±0.02	0.31±0.42				
Rutherford stage of peripheral-artery disease at 72 hr after intervention‡§	1.2±1.5	1.1±1.2	1.7±1.8	0.15 (-0.43 to 0.73)	0.92	-0.51 (-1.21 to 0.19)	0.15
Ankle-brachial index at 72 hr after intervention	0.9±0.3	0.9±0.3	0.9±0.2	-0.03 (-0.14 to 0.08)	0.79	0.02 (-0.08 to 0.13)	0.79
<b>Angiographic findings at 6 mo</b>							
Months between intervention and repeat angiography¶	6.0±0.9	6.1±0.9	6.0±0.6	-0.08 (-0.46 to 0.31)	0.29	-0.02 (-0.37 to 0.33)	0.44
Reference diameter — mm¶	4.9±0.6	5.1±0.6	4.9±0.5	-0.24 (-0.49 to 0.01)	0.05	-0.07 (-0.31 to 0.17)	0.73
Minimum lumen diameter — mm¶	2.8±1.9	4.1±1.4	2.1±1.4	-1.32 (-2.04 to -0.59)	0.001	0.64 (-0.09 to 1.37)	0.14
Late lumen loss — mm¶	1.7±1.8	0.4±1.2	2.2±1.6	1.30 (0.65 to 1.95)	<0.001	-0.48 (-1.20 to 0.24)	0.11
Angiographic restenosis — no./total no. (%)	21/48 (44)	7/41 (17)	21/39 (54)	27 (9 to 45)	0.01	-10 (-31 to 11)	0.39
Total occlusion — no./total no. (%)	4/48 (8)	1/41 (2)	2/40 (5)	6 (-3 to 15)	0.37	3 (-7 to 14)	0.68

Clinical and laboratory follow-up							
Rutherford stage at 6 mo <sup>§</sup>	1.6±1.6	1.2±1.7	2.0±1.8	0.42 (-0.27 to 1.11)	0.15	-0.43 (-1.13 to 0.27)	0.26
Change in Rutherford stage from 72 hr to 6 mo <sup>§</sup>	0.3±1.8	0.1±1.7	0.4±1.5	0.22 (-0.55 to 0.99)	0.48	-0.11 (-0.87 to 0.65)	0.96
Ankle-brachial index at 6 mo <sup>§</sup>	0.8±0.3	0.9±0.3	0.8±0.3	-0.10 (-0.24 to 0.05)	0.09	-0.01 (-0.15 to 0.14)	0.79
Change in ankle-brachial index from 72 hr to 6 mo <sup>§</sup>	-0.1±0.2	-0.1±0.3	-0.1±0.3	-0.03 (-0.16 to 0.09)	0.37	0.03 (-0.10 to 0.15)	0.93
Target-lesion revascularization at 6 mo — no. (%)	20 (37)	2 (4)	15 (29)	33 (19 to 47)	<0.001	0.08 (-0.10 to 0.26)	0.41
Amputation of target leg above the foot at 6 mo — no. (%)	0	2 (4)	2 (4)	-4 (-10 to 1)	0.22	-4 (-9 to 1)	0.24
Death at 6 mo — no. (%)	1 (2)	2 (4)	2 (4)	-2 (-9 to 4)	0.59	-2 (-8 to 4)	0.61
Target-lesion revascularization at 12 mo — no. (%)	26 (48)	5 (10)	18 (35)	38 (22 to 54)	<0.001	14 (-5 to 32)	0.17
Target-lesion revascularization at 24 mo — no. (%)	28 (52)	7 (15)	21 (40)	37 (21 to 54)	<0.001	11 (<1 to 30)	0.25

\* Plus-minus values are means ±SD.  
 † Crossover access indicates insertion of a crossover sheath into a common femoral artery in the cranial direction to reach the contralateral femoral artery.  
 ‡ The Rutherford scale ranges from 0 to 6, with higher numbers indicating worse disease.  
 § Most, but not all, patients were assessed for this variable.

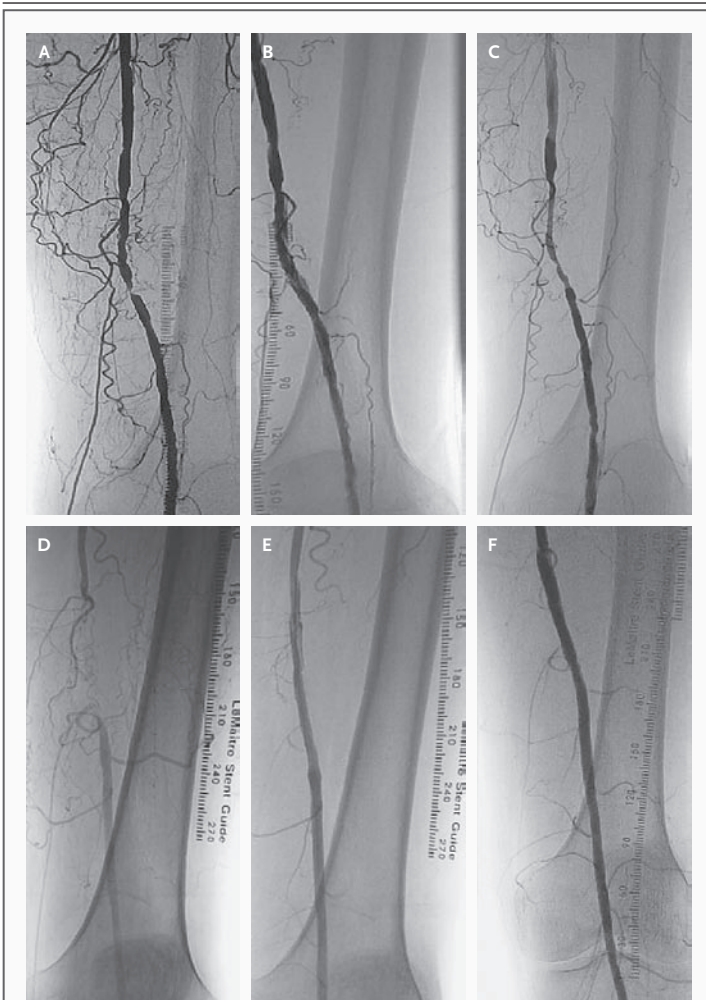
cluding those who refused follow-up angiography (Table 2). The mean Rutherford stage increased slightly in all three groups, but the increase tended to be less pronounced in the group treated with paclitaxel-coated balloons. The ankle-brachial index remained almost unchanged. Target-lesion revascularization was performed in 20 of 54 patients in the control group (37%), as compared with 15 of 52 patients in the group treated with paclitaxel in the contrast medium (29%, P=0.41) and 2 of 48 patients in the group treated with paclitaxel-coated balloons (4%, P<0.001).

The rate of target-lesion revascularization at 12 months remained low in the group treated with paclitaxel-coated balloons. In this group, 5 of 48 patients (10%) underwent target-lesion revascularization during the first year, as compared with 26 of 54 (48%) in the control group and 18 of 52 (35%) in the group treated with paclitaxel in the contrast medium. Only a few additional target-lesion revascularizations were reported between 12 and 24 months, for a total of 28 of 54 in the control group (52%) and 21 of 52 in the group treated with paclitaxel in the contrast medium (40%, P=0.25), as compared with 7 of 48 in the group treated with paclitaxel-coated balloons (15%, P<0.001).

**ADVERSE EVENTS**

No adverse events occurred during the procedure that were attributed to the study medication (Table 3). Embolic complications during the procedure or thrombosis up to 2 weeks afterward occurred in three patients in the control group, two patients in the group treated with paclitaxel-coated balloons, and seven patients in the group treated with paclitaxel in the contrast medium (one patient had two events). No late thrombosis was recorded in any patient. No hematologic or biochemical results suggested systemic effects of paclitaxel.

During the period from 2 weeks after the intervention until follow-up angiography, 46 to 58% of patients in the three treatment groups had a serious adverse event (P>0.05); most events were related to progression of atherosclerosis or underlying disease. In 75 of 80 patients, these events were judged by the investigators to be unrelated to the study medication. By 6 months after the intervention, five patients had died and four had undergone major amputation (above the foot or higher) (Table 2). All four amputations were performed in obese patients who were 62 to 77 years



**Figure 1.** Angiograms of Two Patients Who Presented with Rutherford Stage 3 Peripheral Arterial Occlusive Disease.

Patient 1 was treated with an uncoated balloon; Panel A shows the initial angiogram, Panel B the postprocedure angiogram, and Panel C the 6-month follow-up angiogram showing restenosis. Patient 2 was treated with a paclitaxel-coated balloon; Panel D shows the initial angiogram, Panel E the postprocedure angiogram, and Panel F the 6-month follow-up angiogram showing no restenosis of the target vessel. The Rutherford scale ranges from 0 to 6, with higher numbers indicating worse disease.

of age, who had type 1 diabetes, and who entered the study at Rutherford stage 4 (one patient) or 5 (three patients).

## DISCUSSION

The THUNDER trial was designed for preliminary evaluation of the safety and efficacy of immediately bioavailable, local paclitaxel for the prevention of restenosis in the superficial femoral and

popliteal arteries after percutaneous transluminal angioplasty. The use of paclitaxel-coated angioplasty balloons was associated with a significant reduction in late lumen loss and in angiographic restenosis at 6 months after intervention. In contrast, the addition of paclitaxel to the angiographic contrast medium had no significant effect on these end points.

Late lumen loss and the rate of angiographic restenosis are common end points in clinical trials investigating new approaches to the reduction of restenosis. However, these angiographic end points may not reflect clinical efficacy. Therefore, it is important to note that treatment with paclitaxel-coated balloons was also found to be associated with reduced target-lesion revascularization at the 6-month to 24-month visits.

The paclitaxel-coated balloons used in this trial were standard angioplasty balloons. Paclitaxel adheres to the balloon until it is expanded. During inflation of the balloon, it is almost completely released. Experiments in animals show that 10 to 20% of the drug is taken up by the vessel wall.<sup>15</sup> The efficacy of paclitaxel-coated balloons in preventing restenosis of the superficial femoral and popliteal arteries in this trial is consistent with the results of previous studies of the coronary circulation.<sup>19</sup>

In contrast to the findings in animals, the addition of paclitaxel to the angiographic contrast medium failed to show a benefit up to 6 months after treatment. The contrast medium was chosen as the vehicle for paclitaxel because it significantly enhances the solubility of the drug.<sup>21</sup> There are several possible explanations for the lack of efficacy of paclitaxel in the contrast medium. Studies of this delivery approach in animals were performed in the coronary circulation, which differs from the peripheral circulation with regard to vessel diameter and capillary supply of the adjacent muscle. These differences influence local drug effects. Also, the patients in this study group were at a slight disadvantage as compared with those in the control group with regard to the number of treated restenoses and a somewhat higher Rutherford stage after the procedure.

The development of thrombosis as a result of vessel injury or delayed endothelialization is a recognized risk of percutaneous intervention, especially when agents such as paclitaxel are used to prevent restenosis. In the present trial, clopidogrel was given for 4 weeks in all three groups to pre-

**Table 3. Complications and Adverse Events.**

Event	Control Patients (N = 54)	Patients with Paclitaxel-Coated Balloons (N = 48)	Patients with Paclitaxel in the Contrast Medium (N = 52)	Percent Difference between Control and Paclitaxel-Coated-Balloon Groups (95% CI)	P Value	Percent Difference between Control and Paclitaxel-Contrast-Medium Groups (95% CI)	P Value
<b>During or soon after intervention</b>							
Peripheral embolism — no. (%)	1 (2)	1 (2)	4 (8)	0 (-6 to 5)	1.00	-6 (-14 to 2)	0.20
Minor bleeding — no. (%)	1 (2)	1 (2)	4 (8)	0 (-6 to 5)	1.00	-6 (-14 to 2)	0.20
Acute thrombosis up to 2 days after intervention — no. (%) <sup>*</sup>	2 (4)	1 (2)	3 (6)	2 (-5 to 8)	1.00	-2 (-10 to 6)	0.68
Acute thrombosis up to 2 wk after intervention — no. (%)	—	—	1 (2)	—	—	-2 (-6 to 2)	0.49
Premature termination of intervention — no. (%)	—	—	—	—	—	—	—
Allergy-like reaction — no. (%)	—	—	1 (2)	—	—	-2 (-6 to 2)	0.49
Other events — no. (%) <sup>†</sup>	2 (4)	1 (2)	1 (2)	2 (-5 to 8)	1.00	2 (-4 to 8)	1.00
<b>Serious adverse events during intervention — no. (%)<sup>‡</sup></b>	2 (4)	3 (6)	4 (8)	-3 (-11 to 6)	0.66	-4 (-13 to 5)	0.43
<b>Serious adverse events from 2 wk to 6 mo after intervention</b>							
Patients with ≥1 events — no. (%)	28 (52)	22 (46)	30 (58)	6 (-13 to 25)	0.56	-6 (-25 to 13)	0.56
Patients with an event related to study medication — no./total no. (%) <sup>§</sup>	4/28 (14)	0/22	1/30 (3)	14 (1 to 27)	0.12	11 (-4 to 25)	0.19

\* Thrombosis may have already existed at the time of intervention.

† An increase in blood pressure occurred in one patient in the control group, a pseudoaneurysm of the left groin in one patient in the control group and one patient in the paclitaxel-contrast-medium group, and a swelling of the left forefoot in one patient in the paclitaxel-coated-balloon group.

‡ In the control group, left ventricular failure occurred in one patient and peripheral-artery occlusion in another patient. Among the patients with paclitaxel-coated balloons, toe amputation occurred in one patient, abrupt total occlusion in another patient, and cerebellar infarction in a third patient. Among the patients with paclitaxel in the contrast medium, hypertensive crisis occurred in one patient, puncture-site hemorrhage in one patient, catheter-related complication (peroneal-artery perforation) in one patient, and pseudoaneurysm in one patient.

§ The number of serious adverse events considered by study investigators to be possibly, probably, or very probably related to study medication is given. All five events were restenoses, treated 6 to 7 months after the study intervention, that were considered only possibly related to the study medication. Four of them occurred in the control group, indicating that probably no causal relationship existed.

vent thrombosis. No increase in thrombotic or embolic events was seen in the paclitaxel groups.

The mortality rate seen in our trial, and the inability of some patients to undergo follow-up investigation, are probably consequences of the severity of the underlying disease. Among the participants were 25 patients with critical limb ischemia (6 in the control group, 7 in the group treated with paclitaxel-coated balloons, and 12 in the group treated with paclitaxel in the contrast medium). Such patients are known to have a survival rate of only 75% per year.<sup>22</sup> None of the deaths or other severe adverse events in the patients treated with paclitaxel-coated balloons were classified as possibly related to the study drug by any of the participating physicians.

The THUNDER trial was a preliminary study that was limited in scope and observation period. Additional and larger trials will be necessary to provide definitive evidence of benefit.

In conclusion, we conducted an initial trial to evaluate the efficacy and safety of local delivery of paclitaxel during angioplasty of the superficial

femoral and popliteal arteries. Use of paclitaxel-coated balloon catheters significantly lowered the incidence of restenosis at 6 months and the rate of target-lesion revascularization at 6, 12, and 24 months. In contrast, the addition of paclitaxel to the angiographic contrast medium did not have a significant effect.

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