Percutaneous revascularization is an established treatment for femoro-popliteal artery disease. Yet, restenosis, reocclusion, and ensuing symptom recurrence can occur in as many as 50% of patients undergoing percutaneous transluminal angioplasty (PTA), often requiring repeat percutaneous or surgical intervention. The superficial femoral artery represents a unique challenging vessel. Bare-metal stents reduce restenosis versus PTA and have gained widespread adoption. Alternative therapies, such as drug-eluting balloon (DEB), may be valuable and worthwhile considering their promise and evidence to achieve patency outcomes at least similar to stents but with nothing left behind.

Several studies in coronary artery disease indicate effective restenosis inhibition by DEB in the treatment of in-stent restenosis whereas drug-eluting stent are the preferred medicated devices in most coronary de novo lesions. Two published randomized trials have so far provided favorable data on the usage of DEB versus PTA for the treatment of femoro-popliteal arterial disease. More recently, the effect of a novel paclitaxel coating formulation with urea excipient, a naturally occurring highly biocompatible hydrophilic component (FreePac, Medtronic, Santa Rosa, CA) was investigated within a multicenter registry in patients affected by femoral-popliteal arterial disease. To reach a more in-depth understanding on

Background—Peripheral percutaneous transluminal angioplasty is fraught with a substantial risk of restenosis and reintervention. A drug-eluting balloon (DEB) based on a novel coating was compared with uncoated balloons in patients undergoing femoro-popliteal percutaneous transluminal angioplasty.

Methods and Results—Patients with symptomatic femoro-popliteal atherosclerotic disease undergoing percutaneous transluminal angioplasty were randomized to paclitaxel-coated IN.PACT Pacific or uncoated Pacific balloons. The primary end point was late lumen loss at 6 months assessed by blinded angiographic corelab quantitative analyses. Secondary end points were binary restenosis and Rutherford class change at 6 months, and target lesion revascularization plus major adverse clinical events (major adverse events=death, target limb amputation, or target lesion revascularization) at 6 and 12 months. Eighty-five patients (91 cases=interventional procedures) were randomized in 3 hospitals (44 to DEB and 47 to uncoated balloons). Average lesion length was 7.0±5.3 and 6.6±5.5cm for DEB and control arm, respectively. Procedural success was obtained in all cases. Six-month quantitative angiography showed that DEB were associated with significantly lower late lumen loss (−0.01mm [95% CI, −0.29; 0.26] versus 0.65mm [0.37; 0.93], P=0.001) and fewer binary restenoses (3 [8.6%] versus 11 [32.4%], P=0.01). This translated into a clinically relevant benefit with significantly fewer major adverse events for DEB versus uncoated balloons up to 12 months (3 [7.1%] versus 15 [34.9%], P<0.01) as well as target lesion revascularizations (3 [7.1%] versus 12 [27.9%], P=0.02).

Conclusions—Use of IN.PACT Pacific DEB is associated with significant reductions in late lumen loss and restenoses at 6 months, and reinterventions after femoro-popliteal percutaneous transluminal angioplasty up to 1 year of follow-up.

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT01083030. (Circ Cardiovasc Interv. 2012;5:00-00.)

Key Words: angioplasty ☻ claudication ☻ drug-eluting balloon ☻ peripheral vascular disease ☻ restenosis ☻ revascularization

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Circ Cardiovasc Interv is available at http://circinterventions.ahajournals.org
DOI: 10.1161/CIRCINTERVENTIONS.112.971630
what is known

• Paclitaxel released from balloon catheters during the short period of inflation inhibits restenosis in animal models; however, restenosis inhibition does not persist beyond a few months.
• Two randomized trials have already shown significant and persistent reduction of late lumen loss and clinical endpoints in femoropopliteal arteries after treatment with a prototype drug-eluting balloon compared with standard balloons.

what the study adds

• This randomized clinical study of a paclitaxel-coated balloon catheter in femoropopliteal arteries confirms potent inhibition of restenosis and a reduction in target lesion revascularization at 1 year.
• Data indicate paclitaxel-induced regression of residual plaque following incomplete dilatation and moderate recoil.
• In agreement with previous studies, no coating-related adverse events were observed.

the entity of the antirestenotic effect of this DEB technology in comparison with standard PTA we designed a multicenter randomized trial focusing on 6-month, angiographically assessed late lumen loss (LLL) as primary end point to be consistent with the above-mentioned DEB trials.

Methods

Design

PACIFIER was an investigator-initiated multicenter randomized trial conducted in 3 German institutions. The study was approved by local ethics committees. All patients provided written informed consent. Investigators had primary access to data and independently performed analyses. The study was registered on clinicaltrials.gov: NCT01083030.

Patients

Patients candidate to femoro-popliteal PTA were appraised for study participation. Key inclusion criteria were: (1) claudication or critical limb ischemia (Rutherford 2, 3, 4, or 5); (2) atherosclerotic disease involving the superficial femoral artery or the popliteal artery; (3) lesion length between 3 and 30 cm; (4) an occlusion or a grade of stenosis ≥50% residual plaque following incomplete dilatation and moderate recoil; (5) absence of contraindications to dual antithrombotic therapy; and (6) written informed consent. Key exclusion criteria were: (1) acute thrombus or aneurysm in the target vessel; (2) failure to cross the target lesion with a guidewire; (3) inflow lesions that cannot be successfully pretreated; (4) significant disease of all 3 infrapopliteal vessels; (4) renal failure (serum creatinine ≥2.0 mg/dL); (5) known intolerance or allergy to study medications; and (6) life expectancy <2 years.

Procedures

After noninvasive imaging suggestive of significant femoro-popliteal disease, patients underwent lower limb arteriography by means of ipsilateral or contralateral femoral access. After diagnostic angiography and confirmation that the patient fulfilled inclusion/exclusion criteria, including successful crossing of the lesion with the guidewire, patients were randomized 1:1 to use of the IN.PACT Pacific paclitaxel-eluting balloon versus an uncoated Pacific Xtreme balloon, both 0.018” compatible over-the-wire balloons (Medtronic, Santa Rosa, CA). Notably, IN.PACT Pacific is a DEB based on the Pacific Xtreme PTA balloon platform coated with the FreePac, Medtronic proprietary coating formulation made of Paclitaxel (3 µg/mm² balloon surface) and urea as hydrophilic natural spacer.

The randomization sequence was computer generated, in blocks of 10 patients each, and allocation concealment was guaranteed by the use of numbered, opaque, sealed envelopes, which were only opened after the decision was made that the patient had to be treated according to the protocol.

After randomization, vessels were predilated at the operator’s discretion and further dilated with either the study balloon (IN.PACT Pacific) or uncoated balloon (Pacific Xtreme) based on the randomization sequence. A 1.0 balloon-to-artery diameter ratio was used and balloon lengths were chosen to achieve complete lesion coverage with 1 cm coverage beyond both lesion edges. In case of long lesion requiring multiple DEB, an overlap of 1 cm was secured for adjacent DEB. DEB were inflated for ≥60 seconds at a pressure of 8 to 12 ATM. Procedural protocol limited nitinol stent use only for provisional or bail-out situations such as significant (>50%) residual stenoses or flow limiting dissections. The treatment of multiple lesions was allowed but all lesions had to be treated with the same type of balloon catheter, either coated or uncoated. The lesion presenting with worst attributes (length and stenosis degree) was chosen as target lesion.

Unfractioned heparin (40–70 IU/kg, with subsequent boluses adjusted according to activated clotting time) was administered during procedures. All patients were pretreated with aspirin and thienopyridines, which were continued for >2 months after PTA.

Before, immediately after the intervention, and 6 months later, angiography of the target vessel was performed in identical projections (2 orthogonal planes for each treated lesion). The target lesion as well as the other per protocol treated lesions were identified by an image of the vascular anatomy and specific landmarks (collaterals, bone landmarks) and a second image showing the inflated balloon(s). These images were compared with follow-up angiograms. Patients were followed clinically with direct patient visits at 24 hours, 6, and 12 months. In those refusing 6-month angiographic control, magnetic resonance angiography or duplex ultrasound were recommended to document vessel patency.

End Points and Definitions

The primary study end point was LLL, defined as the difference in minimum lumen diameter of the target lesion between the time points immediately postintervention and the 6-month follow-up angiography or at the time of a clinically driven target lesion revascularization (TLR). Secondary end points were binary angiographic restenosis and change in Rutherford class at 6 months, and TLR plus major adverse events (MAE, defined as death, target limb amputation, or TLR), at 6 and 12 months. Notably, TLR was performed if clinically indicated (recurrence of peripheral artery disease symptoms) and a target lesion diameter stenosis of ≥70%. Angiographic analyses were performed by an independent corelab blinded to treatment assignment, as all balloon catheters, coated and uncoated, were provided in equal numbers and sizes to the investigators. The core lab had no information on the treatment arms. In addition, balloon lengths were the same in the DEB and non-DEB group. Finally, procedural success was defined as final satisfactory angiographic result (residual diameter stenosis ≤30% as assessed by the investigators) in the absence of perioperative complications.

Analysis

Analyses were performed for all enrolled cases, including 5 patients who were a second time enrolled with the contralateral limb and 1
Continuous values are reported as means with SD for nonrepeated measurements. For repeated measurements of continuous variables, results were estimated in mixed linear models and shown as means with 95% CI. For nonrepeated continuous data, t tests or Wilcoxon rank sum tests were used for treatment group comparisons as appropriate. Categorical data are shown as relative and absolute frequencies. For categorical data, a Fisher exact test or a χ² test was used for treatment group comparisons for nonrepeated measurements. For analyses of multiple observations per patient (ie, multiple lesions), mixed models were used for continuous data, multinomial regression analysis based on generalized estimation equations for categorical data, and logistic regression analysis based on generalized estimation equations for binary data. Independence was used as working correlation matrix to account for the correlation of multiple observations per patient (the correlation applies for all lesions only). The P values for the categorical and binary data are drawn from the Type3 likelihood ratio test for the factor treatment when using PROC GENMOD in SAS. For the end points, MAE and TLR, survival analysis was performed on the days from randomization to first event using proportional hazard Cox regression and log-rank tests. Data were displayed by Kaplan-Meier curves. If no event was reported, the days to event were censored at the last visit with reports on the end point of interest.

Correlations between continuous variables were computed with Spearman rho correlation coefficient. Statistical significance was set at the 2-tailed 0.05 level. Computations were performed with SAS 9.2 (SAS Institute, Cary, NC).

Results

Patients and Procedures

A total of 85 mainly white patients were randomized (41 to the IN.PACT Pacific DEB and 44 to the uncoated Pacific Xtreme balloon; Figure 1). Five patients were included twice in the study with a new femoro-popliteal stenosis of the contralateral leg. Another patient had a restenosis of the target lesion 6 months after the first randomized intervention. At the 6-month follow-up the case report form for this lesion was formally closed because according to the protocol the primary end point was reached and the patient was included for the second time with the identical target lesion. All these 6 patients were re-randomized according to the randomization list resulting in a total of 91 randomized cases.

Baseline patient, lesion, and procedural features are reported in Tables 1, 2, and 3. No clinically relevant differences were found comparing the 2 groups in the prognostically relevant variables; treatment groups differed slightly in respect of mean baseline diameter stenosis (DEB: 73.3%...
### Table 1. Patient Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Drug-Eluting Balloon</th>
<th>Uncoated Balloon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized cases (including 6 patients who were treated twice)</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Patients</td>
<td>41</td>
<td>44</td>
</tr>
<tr>
<td>Lesions</td>
<td>62</td>
<td>55</td>
</tr>
<tr>
<td>Lesions per case</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>29 (65.9%)</td>
<td>39 (82.9%)</td>
</tr>
<tr>
<td>2</td>
<td>12 (27.2%)</td>
<td>8 (17.0%)</td>
</tr>
<tr>
<td>3</td>
<td>3 (6.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Age, y</td>
<td>71±7</td>
<td>71±9</td>
</tr>
<tr>
<td>Female sex</td>
<td>18/44 (41.0%)</td>
<td>17/47 (36.0%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19/44 (43.2%)</td>
<td>13/47 (27.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29/44 (65.9%)</td>
<td>31/47 (66.0%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>22/44 (50.0%)</td>
<td>22/47 (46.8%)</td>
</tr>
<tr>
<td>Current or prior smoker</td>
<td>21/44 (46.8%)</td>
<td>28/47 (59.6%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>14/44 (31.8%)</td>
<td>15/47 (31.9%)</td>
</tr>
<tr>
<td>History of stroke or transient ischemic attack</td>
<td>2/44 (4.5%)</td>
<td>5/47 (10.6%)</td>
</tr>
<tr>
<td>Family history of peripheral artery disease</td>
<td>11/44 (28.9%)</td>
<td>8/47 (19.0%)</td>
</tr>
<tr>
<td>Ankle brachial index</td>
<td>0.73±0.30</td>
<td>0.65±0.26</td>
</tr>
<tr>
<td>Rutherford stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4/44 (9.1%)</td>
<td>6/47 (12.8%)</td>
</tr>
<tr>
<td>3</td>
<td>38/44 (86.4%)</td>
<td>39/47 (83.0%)</td>
</tr>
<tr>
<td>4</td>
<td>0/44</td>
<td>2/47 (4.3%)</td>
</tr>
<tr>
<td>5</td>
<td>2/44 (4.5%)</td>
<td>0/47</td>
</tr>
</tbody>
</table>

*Reported as mean±SD, or n/N (%), no P values reported (Consort-guidelines).11

[95% CI 68.7%; 77.9%] versus uncoated group:80.2% [75.7%; 84.7%] and a lower rate of postprocedural dissections (DEB: 18/38 [47.4% of patients for whom the information was available] versus 25/34 [73.5%], P=0.03) in the uncoated group. The larger number of devices per case used in the DEB group (1.6±0.9 versus 1.1±0.4, P<0.001) is explained by the fact that lesions in excess of the length of a single balloon had to be treated with >1 DEB because DEB can only be used once for the scope of drug delivery whereas the uncoated balloons could be repeatedly inflated. Predilatation was performed in 6 cases (13.6%) in the DEB arm and in 3 cases (6.4%, P=0.31) in the control arm and stents were provisionally implanted in 9 (20.5%) and 16 cases (34.0%, P=0.17), respectively.

### Table 2. Target Lesion Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Drug-Eluting Balloon</th>
<th>Uncoated Balloon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized cases, one target lesion each</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Restenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-angioplasty</td>
<td>7/44 (15.9%)</td>
<td>2/47 (4.3%)</td>
</tr>
<tr>
<td>In-stent</td>
<td>7/44 (15.9%)</td>
<td>6/47 (12.8%)</td>
</tr>
<tr>
<td>Reference vessel diameter, mm</td>
<td>4.92 (4.66; 5.17)</td>
<td>4.90 (4.64; 5.17)</td>
</tr>
<tr>
<td>Minimum lumen diameter, mm</td>
<td>1.32 (1.08; 1.56)</td>
<td>1.00 (0.76; 1.24)</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>73.3% (68.7%; 77.9%)</td>
<td>80.2% (75.7%; 84.7%)</td>
</tr>
<tr>
<td>Lesion length, cm</td>
<td>7.0±5.3</td>
<td>6.6±5.5</td>
</tr>
<tr>
<td>Lesions ≥10 cm long</td>
<td>13/44 (29.5%)</td>
<td>9/47 (19.1%)</td>
</tr>
<tr>
<td>Total occlusion</td>
<td>10/44 (22.7%)</td>
<td>18/47 (38.3%)</td>
</tr>
<tr>
<td>Calcification</td>
<td>28/44 (63.6%)</td>
<td>31/47 (66.0%)</td>
</tr>
<tr>
<td>Infracpopliteal patent vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12/44 (27%)</td>
<td>17/47 (36%)</td>
</tr>
<tr>
<td>2</td>
<td>16/44 (36%)</td>
<td>10/47 (21%)</td>
</tr>
<tr>
<td>3</td>
<td>16/44 (36%)</td>
<td>20/47 (43%)</td>
</tr>
</tbody>
</table>

*Reported as mean±SD, mean (95% CI), or n/N (%), no P values reported (Consort-guidelines).11
Procedural data are provided in Table 3. Procedural success was obtained in all cases. The total dose of paclitaxel in the coated balloon patient group ranged from 1.5 to 21.0 mg per intervention, depending on the size and number of balloons used. On the basis of the analysis of residual paclitaxel on the balloon surface after retrieval, 86±12% of the dose was released from the balloons during the procedure.

### Angiographic Findings

Control angiograms at 6 months were available for comparison with postprocedural results in 35 (79.5%) of cases from the DEB group and 34 (72.7%) from the uncoated balloon group (Table 4). Quantitative angiographic analysis for the primary study end point showed that DEB was associated with a significantly lower late loss (−0.01 mm [−0.29; 0.26] versus 0.65 mm [0.37; 0.93] for uncoated balloons, P=0.001). Accordingly, DEB was associated with a lower rate of binary restenosis (3 [8.6%] versus 11 [32.4%], P=0.01). Subgroup analyses for the primary end point confirmed the significant superiority of DEB in the following lesion subtypes: de novo versus restenotic, non-occlusive versus occlusive, relatively short versus long lesions (Figures 2 and 3).

Further exploration of the association between postprocedural angiographic features and LLL showed that lesions with higher postprocedural residual stenosis were more likely to exhibit lower LLL values or even late lumen gain (Figure 4), which constitutes an expression of plaque regression. Finally, angiographic analysis for safety up to 6 months showed freedom from aneurismal changes, ectasia, persistent dissection or thrombosis in all cases. Results remained largely unchanged if the repeat enrolments were left out. Because of the lower number of cases the level of statistical significance was missed if the second enrollments are omitted from the analysis (P=0.065) and the difference in TLR was reduced. After 12 months, 3 of 39 DEB-treated patients (7.7%) experienced a TLR or MAE, whereas the number increased to 10 of 40 patients with TLR (25%) and 13 patients with MAE (32.6%) in the uncoated group. In spite of the slightly lower number of cases, the differences between the groups are for both parameters statistically significant (P=0.02 and 0.01, respectively). The Kaplan-Meier survival analysis confirms these findings (Figure 5A and 5B).

### Clinical Follow-Up

**Randomized Cases Including 6 Patients Who Were Treated Twice**

Clinical outcomes were appraised at 6 and 12 months after PTA (Table 4). At 6-month follow-up 10 TLR were recorded in 9 (21.4%) cases in the uncoated group, as compared with 3 TLR in 3 cases (7.1%) in the DEB group (P=0.12, referring to the number of cases with TLR). The total rate of TLR at 12 months remained unchanged in the group treated with DEB. In this group, no additional TLR were performed, as compared with 5 additional TLR in the group treated with uncoated balloons resulting in 15 TLR in 12 (27.9%) cases in the control group (P=0.02, again referring to the number of cases with TLR). The superior efficacy of DEB was confirmed when analyzing such secondary end points, as the risk of MAE was significantly lower in the DEB group in comparison with the uncoated balloon group at 6 months (3 [7.1%] versus 11 [26.2%], P=0.040), as well as at 12 month (3 [7.1%] versus 15 [34.9%], P<0.01). In both treatment groups, female patients showed a trend toward a higher rate of TLR.

### Data Referring to First Enrolment

Six months after treatment, the incidence of both TLR and MAE was higher in the uncoated than in the DEB group, however, in the case of MAE the level of statistical significance reached with the full number of cases (P=0.04) after 6 months is missed if the second enrollments are omitted from the analysis (P=0.065) and the difference in TLR was reduced. After 12 month, 3 of 39 DEB-treated patients (7.7%) experienced a TLR or MAE, whereas the number increased to 10 of 40 patients with TLR (25%) and 13 patients with MAE (32.6%) in the uncoated group. In spite of the slightly lower number of cases, the differences between the groups are for both parameters statistically significant (P=0.02 and 0.01, respectively). The Kaplan-Meier survival analysis confirms these findings (Figure 5A and 5B).
Comparing female and male subgroups, no statistical significant difference was found in women for late loss (0.36 mm [−0.10; 0.82] for DEB versus 0.85 mm [0.39; 1.30] for uncoated balloons, \(P=0.13\)) or 12-month TLR rates (3 [16.7%] versus 5 [35.7%], \(P=0.252\)), whereas both comparisons were significant in men (respectively, −0.23 mm [−0.58; 0.12] versus 0.53 mm [0.18; 0.89], \(P=0.003\), and 0 versus 7 [24.1%], \(P=0.012\)).

### Discussion

This randomized trial, appraising the safety and efficacy of IN.PACT Pacific DEB for infra-inguinal revascularization, indicates the following implications: (1) its use for femoropopliteal PTA is feasible and safe, even without extensive predilation; (2) it significantly reduces restenosis entity and rates (ie, angiographic LLL and binary restenosis) in comparison with current state-of-the-art uncoated balloons;
(3) such angiographic superiority translates into significant clinical benefits (albeit largely driven by fewer TLR); (4) notably, this DEB paclitaxel-urea based technology may exert a more pronounced biologic effect in lesions with higher plaque burden (as appraised by postprocedural residual stenosis).

Whereas stents, bare-metal or drug-eluting, have provided superior results to standard PTA for femoro-popliteal disease, they permanently change the structure of the vessel and in-stent restenosis is more difficult to treat than restenosis in nonstented segments. The introduction of DEB in coronary and peripheral artery disease offers supplementary or alternative treatment options. Drug-coated balloons combine the advantages of local drug delivery (with ensuing inhibition of restenotic processes), but lacking any permanent implant typical of balloons. They are very flexible, versatile, and may also be safely envisioned in lesion locations where stenting could be considered undesirable or impractical, or with anatomically challenging features. As done in this study, significant dissections after PTA may be stented without recognizable disadvantage for the outcome.

DEB have been associated with favorable clinical results in several studies. The present study exploiting IN.PACT Pacific DEB builds upon the currently available clinical experience and provides further evidence favoring the use of DEB for femoro-popliteal PTA. Indeed, angiographic results obtained with IN.PACT Pacific DEB are remarkable and obtained with a low stent rate, implanted in bail-out only indications, and homogeneously found in simple as well as complex and long lesions, without apparent coating-related adverse events. Despite the fact that all currently approved DEB share the same drug agent, differences in drug concentration and elution kinetics may impact on late loss and restenosis extent. Our results indicate that the response to the paclitaxel-coated balloons may depend on the gender. However, this has to be explored in larger trials or may be subject to meta-analysis of available data since the number of patients in our study was too small.

Negative late loss after balloon expandable stent implantation in the coronary experience has been associated with aneurysms, stent malapposition, and ultimately thrombotic events.}

**Figure 2.** (A-C) Subgroup analyses for the primary end point, that is, late lumen loss. DEB indicates drug-eluting balloon; L, length; and Occl, occlusion. *Indicates either after percutaneous transluminal angioplasty or stenting.
The slightly negative mean late loss observed in the present study without evidence of aneurismatic effects, seems to be an expression of luminal gain because of plaque regression from postprocedure to 6 months. Particularly, the occurrence of such negative late loss in cases with higher postprocedural residual stenosis seems significant in the DEB arm.

Regarding the safety of paclitaxel, the maximum exposure of patients to paclitaxel because of the use of 5 large balloons for the treatment of a 32-cm–long lesion was 21 mg, which is significantly below the limit known to cause systemic effects. Margolis et al\textsuperscript{14} reported no relevant side effects ≤50 mg/patient. A study reporting hematologic analyses after the use of multiple paclitaxel-coated balloon catheters in femoro-popliteal vessels up to a dose of ≈25 mg/patient did neither indicate paclitaxel plasma levels coming close to those known to cause systemic effects nor changes in cell counts which would indicate systemic toxicity.\textsuperscript{15} Therefore, no risk of relevant systemic effects of paclitaxel because of coated balloon catheters can be recognized as long as the total dose of paclitaxel on multiple catheters is limited to ≤50 mg/patient. However, embolization of plaque material or device components is an inherent risk of angioplasty which frequently induces plaque rupture. The potential additional risk because of drug-coating was assessed. Prior animal\textsuperscript{16} and human trials in a still limited number of patients\textsuperscript{9} did not detect such risk nor are any case reports known from the widespread use of drug-coated balloons in coronary arteries or selected applications in intracranial in-stent restenosis.\textsuperscript{17}

**Study Limitations**

This randomized trial was powered on a 6-month angiographic primary end point, thus resulting in a small sample size, normally insufficient to detect meaningful clinical differences. Therefore, results pertaining to secondary end points...
should be taken with caution. In addition, some imbalances between patient groups were found, which should not be seen as unexpected given the sample size. However, such differences did not confound the effect of DEB on outcomes, as overall the risks were balanced with more diabetics and more restenosis cases in the DEB group and more total occlusions in the uncoated group. The operators could not be blinded to the assigned treatment because of the different appearance of coated and uncoated balloons. Predetermined assignment of patients to treatments only after the decision to enroll avoided a
selection bias. Blinding was only possible for the angiographic parameters including the primary end point for which the study was powered, hence, the study design and the sample size are not adequate to draw conclusions beyond pure lesion specific considerations. Moreover, stenting in both arms was reserved to bail-out indications, thus no direct comparison with trials focusing on routine stenting can be envisioned. Although stenting was more common in the control group, in our small number of cases LLL was actually smaller in the stented controls than in the lesions which were not stented. Despite the willingness to treat even long lesions, referral patterns at participating centers made patients with lesions below 10 cm the most prevalent enrollment group. Systematic angiographic follow-up may have increased the TLR and event rate. Finally, follow-up of this and similar studies is required.

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Disclosures
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References
Paclitaxel-Coated Balloons Reduce Restenosis After Femoro-Popliteal Angioplasty: Evidence From the Randomized PACIFIER Trial

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