Drug-Coated Balloon Versus Standard Balloon for Superficial Femoral Artery In-Stent Restenosis: The Randomized Femoral Artery In-Stent Restenosis (FAIR) Trial

Running title: Krankenberg et al.; DCBA versus POBA for SFA in-stent restenosis

Hans Krankenberg, MD1*; Thilo Tübler, MD2*; Maja Ingwersen, DVM1; Michael Schlüter, PhD3; Dierk Scheinert, MD4; Erwin Blessing, MD5; Sebastian Sixt, MD6; Arne Kieback, MD7; Thomas Zeller, MD8

1Dept of Angiology, Cardiovascular Center (HGZ) Bad Bevensen, Bad Bevensen, Germany; 2Medtronic, Meerbusch, Germany; 3Asklepios proresearch, Hamburg, Germany; 4University of Leipzig Heart Center, Leipzig, Germany; 5Dept of Internal Medicine, SHR Clinic Karlsbad-Langensteinbach, Karlsbad-Langensteinbach, Germany; 6Hamburg University Cardiovascular Center, Hamburg, Germany; 7Dept of Angiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 8Dept of Angiology, Heart Center Bad Krozingen, Bad Krozingen, Germany

*shared first authorship

Address for Correspondence:
Hans Krankenberg, MD
Department of Angiology, Cardiovascular Center (HGZ) Bad Bevensen
Römstedter Str. 25
29549 Bad Bevensen, Germany
Tel: +49 5821 82 1157
Fax: +49 5821 82 3816
E-mail: h.krankenberg@hgz-bb.de

Journal Subject Terms: Peripheral Vascular Disease; Restenosis
Abstract

Background—Drug-coated balloon angioplasty (DCBA) was shown to be superior to standard balloon angioplasty (POBA) with regard to restenosis prevention for de-novo superficial femoral artery (SFA) disease. For in-stent restenosis (ISR), the benefit of DCBA over POBA remains uncertain.

Methods and Results—One-hundred-nineteen patients with SFA ISR and chronic limb ischemia were recruited over 34 months at 5 German clinical sites and prospectively randomized to either DCBA (n = 62) or POBA (n = 57). Mean lesion length was 82.2 ± 68.4 mm. Thirty-four (28.6%) lesions were totally occluded, 30 (25.2%) were moderately or heavily calcified. Clinical and duplex ultrasound follow-up was conducted at 6 and 12 months. The primary endpoint of recurrent ISR assessed by ultrasound at 6 months was 15.4% (8/52) in the DCBA and 44.7% (21/47) in the POBA group (P < 0.002). Freedom from target lesion revascularization (TLR) was 96.4% vs. 81.0% (P = 0.0117) at 6 months and 90.8% vs. 52.6% (P < 0.0001) at 12 months, respectively. At 12 months, clinical improvement by ≥ 1 Rutherford category without the need of TLR was observed in 35/45 DCBA patients (77.8%) and 23/44 POBA patients (52.3%, P = 0.015). No major amputation was needed. Two patients in the DCBA and 3 patients in the POBA group died. No death was procedure-related.

Conclusions—DCBA for SFA ISR is associated with less recurrent restenosis and a better clinical outcome than POBA, without an apparent difference in safety.

Clinical Trial Registration Information—www.clinicaltrials.gov. Identifier: NCT01305070.

Key words: in-stent restenosis; angioplasty; drug-eluting balloon; peripheral artery disease; randomized controlled trial; superficial femoral artery
Introduction

In the majority of patients with peripheral arterial disease the femoropopliteal segment is involved. Due to guideline recommendations mainly encouraging an endovascular first-line approach\textsuperscript{1,2} and due to the development of new generation nitinol stents, stenting of femoropopliteal lesions has become mainstream in recent years. However, mid- and long-term primary patency rates are suboptimal, with 1-year primary patency of 65-81\%\textsuperscript{3-6} for slotted tube nitinol stents, 83-86\% for interwoven-wire nitinol stents\textsuperscript{7,8}, and 83\%\textsuperscript{9} for drug-eluting stents. Five-year primary patency after endovascular therapy is reported to be 50\% for Trans Atlantic Inter-Society Consensus (TASC) A-C and 34\% for TASC D lesions\textsuperscript{10}. As a result, the treatment of in-stent restenosis (ISR) has become increasingly important.

Randomized trials have shown that drug-coated balloon angioplasty (DCBA) for femoropopliteal de-novo disease is associated with less restenosis and target lesion revascularization than standard ("plain old") balloon angioplasty (POBA)\textsuperscript{11}. However, for superficial femoral artery (SFA) ISR currently available data are poor. In a small prospective registry of DCBA for SFA ISR\textsuperscript{12,13}, recurrent restenosis rates were 7.9\% (4/39) and 29.7\% (11/37) at 12 and 24 months, respectively. For diabetic patients, Liistro et al.\textsuperscript{14} reported significantly lower recurrent ISR rates at 12 months after DCBA as compared to a historical POBA group (19.5\% [8/41] vs.71.8\% [28/39], \( P<0.001 \)).

A direct comparison of DCBA and POBA for the treatment of SFA ISR has not been performed to date. Therefore, we initiated the randomized controlled Femoral Artery In-Stent Restenosis (FAIR) trial to assess the mid-term efficacy and safety of DCBA compared to POBA for SFA ISR.
Methods

Study design

The FAIR trial had a prospective, multicenter, block-randomized, non-blinded design and was conducted at 5 experienced vascular centers in Germany. Patients with SFA ISR were allocated 1:1 to either DCBA or POBA treatment.

Patients

Patients were eligible for enrollment if they had a SFA ISR of up to 20 cm in length. Diameter stenosis had to be at least 70% by duplex ultrasound. At baseline the popliteal artery as well as one of the infrapopliteal (below-the-knee) vessels had to be patent (≤ 50% stenosis) for sustained distal run-off. Clinically, the patients had to suffer from chronic limb ischemia of Rutherford category2 to 4. Major exclusion criteria were an untreated ipsilateral iliac artery stenosis; ongoing dialysis treatment; and treatment with oral anticoagulants other than antiplatelet agents. The FAIR trial was approved by the Freiburg Ethics Commission International (FEKI). All patients provided written informed consent.

Interventions

Patients were premedicated with acetylsalicylic acid (100 mg/d) and clopidogrel (75 mg/d) for at least 10 days. Patients not on this regimen were given an intravenous bolus of 500 mg of aspirin before the intervention and a loading dose of 600 mg clopidogrel orally before or immediately after the intervention. Following the procedure, patients received aspirin 100 mg/d indefinitely plus clopidogrel 75mg/d for at least 6 months.

Access to the SFA ISR was achieved at the investigator’s discretion either by way of a retrograde approach from the contralateral femoral artery using a dedicated 6F “cross-over” sheath or via an ipsilateral approach with a standard 6F sheath. After sheath placement, a body
weight-adjusted intravenous bolus of 5,000 to 10,000 units of heparin was administered to
achieve an activated clotting (ACT) time of >250 seconds.

Digital subtraction angiography (DSA) was subsequently performed to assess the
following variables: the type of lesion (restenosis or reocclusion), its location, pattern, length
(determined by means of a radiopaque ruler placed under the patient’s upper thigh), and degree
of calcification (by visual estimate). Furthermore, the patency status of the ipsilateral iliac
arteries, the popliteal artery, and the infrapopliteal arteries was documented. Protocol-mandated
angioplasty of a significant ipsilateral iliac-artery stenosis was performed, if needed, prior to
treatment of the SFA ISR.

Following successful passage of the target lesion with a hydrophilic 0.018-in. or 0.035-in.
guide wire, patients were randomly assigned either to POBA or to DCBA.

**POBA**

In patients randomized to POBA, an over-the-wire PTA balloon (Admiral Xtreme™, Medtronic,
Minneapolis, MN) was advanced into the lesion. Its nominal diameter had to be about the same
as the reference vessel diameter (RVD) and its length had to match the lesion length, with a
maximum balloon overhang of 10 mm at both edges. The balloon was gradually inflated until the
lesion diameter appeared to be visually identical to the RVD. Angioplasty was continued for at
least 60 seconds.

**DCBA**

In patients randomized to DCBA, predilation of the target lesion with a standard balloon was
mandatory to ensure that the DCB coating remains intact during lesion passage. The nominal
diameter of the predilation balloon had to be at least 1 mm less than the RVD. The drug-coated
balloon (IN.PACT™ Admiral paclitaxel-eluting balloon, Medtronic, Minneapolis, MN) is
mounted on an over-the-wire catheter and coated with a mixture consisting of urea and paclitaxel (FreePac™ coating, paclitaxel dose 3.5 μg/mm²). It was available in nominal diameters of 4, 5, 6, and 7 mm and nominal lengths of 40, 60, 80, and 120 mm at study inception. The duration of dilatation had to be at least 60 seconds. The nominal balloon diameter had to match the RVD. The DCBA-treated segment should at least have covered the lesion to avoid geographic miss but not exceeded it by more than 10 mm.

Both treatment groups

In lesions with >50% diameter residual stenosis, balloon inflation was repeated once for at least 3 minutes with the balloon already used. In case of a flow-limiting dissection or residual stenosis, “bailout” nitinol stent implantation was allowed.

Outcome assessment

Clinical evaluation

The patient’s clinical status was evaluated before the intervention as well as during outpatient hospital visits at 6 and 12 months. The evaluations included assessment of the Rutherford category, the ankle-brachial pressure index (ABI) at rest, and a treadmill test at 2 mph on a 12% incline to determine the patient’s relative and absolute claudication distance.

Ultrasound evaluation

Color duplex ultrasound (DUS) examination of the target SFA was performed within 1 week before the intervention and at 6- and 12-month follow-up. Each examination comprised measurements of the maximum peak systolic velocity 2 cm proximal to the culprit lesion (“prestenotic”), within the lesion (“intrastenotic”), and up to 4 cm distal to the lesion (“poststenotic”). In order to examine the correct lesion segments at DUS follow-up, the distance from the groin and the tibia plateau was noted in the patient chart with the help of a ruler placed
under the patient’s leg at the time of intervention. The ratio of the maximum intrastenotic and the maximum prestenotic peak systolic velocity (PVR) determined the degree of percent diameter stenosis (DS) by means of a validated reference table16 (PVR ≥2.4 corresponds to DS ≥50%).

End points

The primary study end point was the cumulative incidence of binary recurrent in-stent restenosis at 6 months. Restenosis was assessed by duplex ultrasound (PVR ≥ 2.4) at the study sites and confirmed by an independent and blinded core laboratory (coreLAB Bad Krozingen, Germany).

Secondary procedural end points were primary angiographic success (successful access and deployment of the device with ≤ 50% diameter residual stenosis without bailout procedures), cumulative incidence of binary recurrent restenosis at 12 months, and Kaplan-Meier estimate of freedom from TLR on grounds of recurrent restenosis ≥ 50%/reocclusion and based on clinical signs through 6- and 12-month follow-up (not including procedural bailout). Secondary hemodynamic end points were ABI at 6 and 12 months as well as immediate and sustained hemodynamic success (ABI improvement of ≥ 0.15 from baseline to discharge and to 6 and 12 months without the need for TLR). Secondary clinical end points were sustained clinical improvement by ≥ 1 Rutherford category, relative and absolute claudication distance at 6 and 12 months, and major adverse vascular events (MAVE), defined as all-cause death, myocardial infarction, major amputation, major bleeding, and thrombosis or surgical intervention related to the target limb.

Statistics

Based on an expected 6-month binary recurrent restenosis rate of 60% after POBA17 and postulating a reduction of the recurrent restenosis rate by half to 30% after DCBA, we calculated a sample size of 59 patients per group to give 80% power to detect a significant difference with a
two-sided α error of 5%. An anticipated dropout rate of 20% was taken into account.

Following a parallel-group, block randomization with a block size of 10 and an allocation ratio of 1:1, patients were assigned either DCBA or POBA. Allocation sequence was concealed from the investigators by sequentially numbered, opaque, and sealed envelopes.

Continuous variables are presented by means ± standard deviations, categorical variables by percent and counts. Differences between continuous variables were assessed using Student’s t test or Kolmogorov-Smirnov’s test. Differences between categorical variables were assessed using Fisher’s exact test, chi-square test and Kruskal-Wallis’ test. Kaplan-Meier analysis was performed to estimate freedom from TLR. The Mantel-Cox log-rank test was run to test whether the survival functions differ. A P-value < 0.05 indicated statistical significance. Statistical analyses were performed using SPSS 16.0.

Results
Between January 2010 and November 2012, 119 patients were enrolled at 5 German centers and randomized to undergo either DCBA or POBA for SFA ISR (Figure 1).

Patient cohorts were well matched with respect to risk factors and lesion characteristics. The majority of patients presented with hypertension or hyperlipidemia and more than a third had diabetes. The difference in diabetes prevalence between both groups was not significant (p = 0.085). Most patients (92.4%) had moderate (Rutherford 2) or severe (Rutherford 3) claudication (Table 1). Treated ISR lesion lengths in the DCBA and POBA group were 82.3 ± 70.9 mm and 81.1 ± 66.2 mm, respectively (median lesion length 60 [IQR 20-133] mm). Almost one third of the lesions were totally occluded and one fourth were moderately or heavily calcified (Table 2).

Primary end point outcome
The primary end point of binary recurrent restenosis assessed by DUS and adjudicated by core
laboratory was 15.4% (8/52) in the DCBA group and 44.7% (21/47) in the POBA group (P = 0.002; Figure 2). The DUS-dropout at 6 months for DCBA and POBA was 16.1% and 17.5%, respectively (Figure 1). Therefore, it was within the anticipated rate of 20% for sample size calculation.

Secondary procedural, clinical, and hemodynamical outcomes

Primary angiographic success was achieved in 95.1% (58/61) of patients in the DCBA group and in 78.9% (45/57) of patients in the POBA group (P = 0.102). However, due to repeated and prolonged inflations or provisional/bailout stenting (Table 2), there was no difference in the residual stenosis rate between both groups (median 0% [IQR 0-30%] versus 0% [IQR 0-20%] P = 0.630).

At 12 months, incidences of recurrent restenosis assessed by DUS were 29.5% (13/44 patients) in the DCBA and 62.5% (25/40 patients) in the POBA group (P = 0.004). Accordingly, freedom from TLR was significantly higher in the DCBA than the POBA group (96.4% vs. 81.0% at 6 months, P = 0.0117; 90.8% vs. 52.6% at 12 months, P < 0.0001, Figure 3).

From baseline to discharge, ABI increased from 0.63 ± 0.27 to 0.94 ± 0.30 in the DCBA group and from 0.64 ± 0.25 to 0.81 ± 0.22 in the POBA group. Rutherford category 0 or 1 was achieved in 64.7% (33/51) of DCBA and 53.2% (25/47) of POBA patients at 6 months (P = 0.413) and in 66.7% (30/45) of DCBA and 70.5% (31/44) of POBA patients at 12 months (P = 0.820). At 12 months, clinical improvement by ≥1 Rutherford category without the need of TLR was observed in 35/45 DCBA patients (77.8%) and 23/44) POBA patients (52.3%, P = 0.015, Table 3, Figure 4).

Safety outcomes

Two patients from the DCBA group (3.2%) and 3 patients from the POBA group (5.3%, P =
0.67) died within 12 months. None of these deaths was procedure-related. Procedure-related complications were one late stent thrombosis in a DCBA group patient and one subacute stent thrombosis after TLR with DCB in a POBA group patient. In another POBA group patient the tibioperoneal trunk occluded at 294 days. In two DCBA group patients a transient cerebral ischemic attack not related to the procedure occurred. Two distal embolizations in DCBA group patients were resolved without the need for intervention. Neither myocardial infarction nor major bleeding occurred and no major amputation was necessary (Table 3).

Discussion

This study represents the first randomized comparison of DCBA vs. POBA for SFA ISR. The treatment groups did not differ significantly with respect to patient or lesion characteristics.

There were four main findings in this trial: DCBA reduced the 6-month recurrent restenosis rate by two thirds as compared to POBA, thus demonstrating superiority. TLR was needed significantly less frequent with DCBA than with POBA. There was a positive and sustained clinical impact for patients treated with DCBA in terms of Rutherford category improvement. DCBA treatment of ISR was safe.

After stent implantation in the SFA, ISR is known to be associated with a high risk of recurrence in the mid-term. This applies in particular to femoropopliteal lesions, possibly due to a continued restenosis process and neointimal hyperplasia.

The majority of previously assessed data on SFA ISR treatment have not been convincing. Results derived from single-arm observations (DCBA\textsuperscript{12, 13}), historical comparisons (DCBA vs. POBA\textsuperscript{14}), subgroup analyses (drug-eluting stent\textsuperscript{18}), studies on specific lesions (chronic total occluded ISR\textsuperscript{19}), and initial experiments (cutting balloon vs. POBA\textsuperscript{17}). In some
cases, high rates of bailout stenting (10%13, 15.9%14) or additional laser mediated debulking (10%13) weaken the significance of findings.

Two prospective, randomized, controlled studies showed promising results for long SFA ISR lesions. The trial on covered stents20 (mean lesion length 173 mm) showed a significantly higher 12-month primary patency than POBA. However, duration and dosage of dual antiplatelet therapy with covered stents need further evaluation. Even the long-term benefit of a “stent-sandwich” remains to be proven. The trial on excimer laser atherectomy with adjunctive POBA21 (mean lesion length 196 mm) showed superiority to stand alone POBA alone with respect to 6-month freedom from TLR and 30-day major adverse events. The comparably higher rate of 6-month freedom from TLR after DCBA in FAIR may be attributable to shorter lesions. Therefore, efficacy and safety of the less invasive treatment of DCBA for long ISR lesions is worth to be assessed.

After all, the question of whether DCBA is working in ISR as opposed to de novo SFA lesions can now be answered: based on the clinical results of the present study, paclitaxel-coated balloons are as effective in restenotic lesions as in native vessels.

Limitations
This study was designed to assess the safety and efficacy of DCBA in comparison to POBA for SFA ISR treatment. At this stage, we did not focus on the assessment of predictive risk factors (e.g. subgroup analysis) for restenosis recurrence. The DUS-dropout rate for DCBA and POBA at 12 months was 29.0% and 29.8%, respectively (Figure 1). Therefore, the significance of the secondary outcome of 12-month restenosis rate is of minor weight.

Implications for future research
The recent results should be verified for longer follow-up periods. In addition, with a larger
number of patients, a multivariable analysis could provide information on predictive risk factors, such as lesion length and complexity (TOSACA classification\textsuperscript{22}), vessel morphology, comorbidities and gender. Moreover, the mode of stenting (intraluminal vs. subintimal) or the type of stent may be associated with the success of ISR treatment. Furthermore, it would be valuable to directly compare the efficacy of DCBA and DES implantation. In the next step, the treatment of recurrent ISR could be investigated.

**Conclusions**

This multicenter, randomized controlled study demonstrates for the first time that the treatment of SFA ISR of medium length with DCBA is associated with lower recurrent restenosis rates and TLRs at 6 and 12 months than POBA. Clinical improvement of $\geq 1$ Rutherford category at 12 months without the need of TLR was more frequent after DCBA in comparison to POBA. Safety profiles were equivalent between both treatment groups. Therefore, from the FAIR trial, a clear treatment recommendation can be made for DCBA in SFA ISR lesions up to 150 mm in length.

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**Conflict of Interest Disclosures:** T. Tübler served as a consultant for Medtronic in 2012. The other authors report no conflicts of interest.

**References:**


10. Iida O, Takahara M, Soga Y, Suzuki K, Hirano K, Kawasaki D, Shintani Y, Suematsu N, Yamaoka T, Nanto S, Uematsu M. Shared and differential factors influencing restenosis following endovascular therapy between TASC (Trans-Atlantic Inter-Society Consensus) II class


Clinical Perspective

Due to an increasing tendency to stent superficial femoral artery (SFA) lesions, which is, however, associated with not entirely satisfying primary patency rates, the treatment of SFA in-stent restenosis (ISR) has become increasingly important. Drug-coated balloon angioplasty (DCBA), when compared with standard balloon angioplasty (POBA), had shown superior efficacy for de-novo lesions. Therefore, DCBA seemed to be the obvious approach to minimally invasive treatment of SFA ISR. However, available data were poor and did not allow for therapeutic decisions. The multicenter, randomized controlled FAIR trial demonstrates for the first time that the treatment of SFA ISR with DCBA is associated with lower recurrent restenosis rates and target lesion revascularizations (TLRs) than POBA at 6 and 12 months. Moreover, clinical improvement of ≥1 Rutherford category at 12 months without the need of TLR was observed more often after DCBA. Safety profiles were equivalent between both treatment groups. Therefore, the question of whether DCBA is working in an SFA ISR as opposed to de-novo SFA lesions can now be answered: Based on the clinical results of the FAIR trial, paclitaxel-coated balloons are as effective in restenotic lesions as in native vessels. A clear treatment recommendation can be made for DCBA in SFA ISR up to 150 mm in length.
Table 1. Baseline Patient Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>DCBA (n = 62)</th>
<th>POBA (n = 57)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69 ± 8</td>
<td>67 ± 9</td>
<td>0.296</td>
</tr>
<tr>
<td>Male</td>
<td>53.2% (33)</td>
<td>70.2% (49)</td>
<td>0.058</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 30)</td>
<td>19.4% (12)</td>
<td>21.1% (12)</td>
<td>0.316</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>45.2% (28)</td>
<td>29.8% (17)</td>
<td>0.085</td>
</tr>
<tr>
<td>Insulin-dependent</td>
<td>42.9% (12/28)</td>
<td>35.3% (12/17)</td>
<td>0.616</td>
</tr>
<tr>
<td>Hypertension</td>
<td>83.9% (52)</td>
<td>93.0% (53)</td>
<td>0.123</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>77.4% (48)</td>
<td>78.9% (45)</td>
<td>0.840</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>12.9% (8)</td>
<td>17.5% (10)</td>
<td>0.480</td>
</tr>
<tr>
<td>Dialysis</td>
<td>0.0% (0/8)</td>
<td>10.0% (1/10)</td>
<td>1.000</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td>0.635</td>
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<tr>
<td>Active</td>
<td>29.0% (18)</td>
<td>35.1% (20)</td>
<td></td>
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<tr>
<td>Previous</td>
<td>41.9% (26)</td>
<td>45.6% (26)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>41.9% (26)</td>
<td>38.6% (22)</td>
<td>0.681</td>
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<tr>
<td>Carotid vascular disease</td>
<td>22.6% (14)</td>
<td>17.5% (10)</td>
<td>0.791</td>
</tr>
<tr>
<td>Infrapopliteal vascular disease</td>
<td>25.8% (16)</td>
<td>21.1% (12)</td>
<td>0.495</td>
</tr>
<tr>
<td>Ankle-brachial index</td>
<td>0.63 ± 0.27</td>
<td>0.64 ± 0.25</td>
<td>0.872</td>
</tr>
<tr>
<td>Relative claudication distance, m</td>
<td>79.2 ± 52.0</td>
<td>102.9 ± 70.9</td>
<td>0.527</td>
</tr>
<tr>
<td>Absolute claudication distance, m</td>
<td>131.4 ± 87.1</td>
<td>145.9 ± 93.7</td>
<td>0.849</td>
</tr>
<tr>
<td>Leg treated</td>
<td></td>
<td></td>
<td>0.582</td>
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<tr>
<td>Left</td>
<td>50.0% (31)</td>
<td>56.1% (32)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>50.0% (31)</td>
<td>43.9% (25)</td>
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<tr>
<td>Rutherford category</td>
<td></td>
<td></td>
<td>0.927</td>
</tr>
<tr>
<td>0 – asymptomatic</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td></td>
</tr>
<tr>
<td>1 – mild claudication</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td></td>
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<tr>
<td>2 – moderate claudication</td>
<td>43.5% (27)</td>
<td>47.4% (27)</td>
<td></td>
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<tr>
<td>3 – severe claudication</td>
<td>51.6% (32)</td>
<td>42.1% (24)</td>
<td></td>
</tr>
<tr>
<td>4 – ischemic pain at rest</td>
<td>1.6% (1)</td>
<td>10.5% (6)</td>
<td></td>
</tr>
<tr>
<td>5 – minor tissue damage</td>
<td>3.2% (2)</td>
<td>0.0% (0)</td>
<td></td>
</tr>
<tr>
<td>6 – major tissue damage</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td></td>
</tr>
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</table>

Data are means ± SD or percent (number).
**Table 2.** Baseline Lesion and Procedural Characteristics.

<table>
<thead>
<tr>
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<th>DCBA (n = 62)</th>
<th>POBA (n = 57)</th>
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<tr>
<td>Target lesion</td>
<td></td>
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<td>0.184</td>
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<tr>
<td>Proximal SFA</td>
<td>48.8% (30)</td>
<td>43.9% (25)</td>
<td></td>
</tr>
<tr>
<td>Mid SFA</td>
<td>38.7% (24)</td>
<td>45.6% (26)</td>
<td></td>
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<tr>
<td>Distal SFA</td>
<td>38.7% (24)</td>
<td>29.8% (17)</td>
<td></td>
</tr>
<tr>
<td>Adjacent to 1&lt;sup&gt;st&lt;/sup&gt; segm. popliteal artery</td>
<td>11.3% (7)</td>
<td>8.8% (5)</td>
<td></td>
</tr>
<tr>
<td>Reference vessel diameter, mm</td>
<td>5.1 ± 0.9</td>
<td>5.4 ± 0.5</td>
<td>0.062</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>82.3 ± 70.9</td>
<td>81.1 ± 66.2</td>
<td>0.991</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>89.0 ± 8.9</td>
<td>89.9 ± 9.6</td>
<td>0.627</td>
</tr>
<tr>
<td>Total occlusions, %</td>
<td>24.2% (15)</td>
<td>33.3% (19)</td>
<td>0.313</td>
</tr>
<tr>
<td>Ulceration</td>
<td>6.2% (2)</td>
<td>1.8% (1)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Thrombus</td>
<td>4.8% (4)</td>
<td>5.3% (3)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Calcification</td>
<td></td>
<td></td>
<td>0.327</td>
</tr>
<tr>
<td>Mild</td>
<td>17.7% (11)</td>
<td>14.0% (8)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>21.0% (13)</td>
<td>10.5% (6)</td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>9.7% (6)</td>
<td>8.8% (5)</td>
<td></td>
</tr>
<tr>
<td>ISR pattern</td>
<td></td>
<td></td>
<td>0.952</td>
</tr>
<tr>
<td>Focal</td>
<td>25.8% (16)</td>
<td>28.1% (16)</td>
<td></td>
</tr>
<tr>
<td>Diffuse</td>
<td>51.6% (32)</td>
<td>52.6% (30)</td>
<td></td>
</tr>
<tr>
<td>Multifocal</td>
<td>22.6% (14)</td>
<td>19.3% (11)</td>
<td></td>
</tr>
<tr>
<td>Patency of distal run-off vessels</td>
<td></td>
<td></td>
<td>0.854</td>
</tr>
<tr>
<td>All vessels patent</td>
<td>54.8% (34)</td>
<td>57.9% (33)</td>
<td></td>
</tr>
<tr>
<td>≥1 vessel occluded</td>
<td>43.5% (27)</td>
<td>42.1% (24)</td>
<td></td>
</tr>
<tr>
<td>Predilation</td>
<td>90.3% (56)</td>
<td>12.3% (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inflation time, sec</td>
<td>131.1 ± 46</td>
<td>153 ± 63</td>
<td>0.021</td>
</tr>
<tr>
<td>Postdilation</td>
<td>9.7% (6)</td>
<td>22.8% (13)</td>
<td>0.113</td>
</tr>
<tr>
<td>Stenting</td>
<td>1.6% (1)*</td>
<td>7.0% (4)†</td>
<td>0.199</td>
</tr>
</tbody>
</table>

SFA = superficial femoral artery

*Stenting for persistent stenosis; †Stenting for persistent stenosis (3.5%), occlusive complication (1.8%), or dissection (1.8%)

DOI: 10.1161/CIRCULATIONAHA.115.017364
Table 3. Hemodynamic, Clinical and Safety Outcomes.

<table>
<thead>
<tr>
<th></th>
<th>At 6 months</th>
<th></th>
<th>P</th>
<th>At 12 months</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DCBA</td>
<td>POBA</td>
<td></td>
<td>DCBA</td>
<td>POBA</td>
<td></td>
</tr>
<tr>
<td>Hemodynamic outcome*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodynamic improvement†</td>
<td>67.5% (27/40)</td>
<td>58.3% (21/36)</td>
<td>0.408</td>
<td>61.1% (22/36)</td>
<td>50.0% (18/36)</td>
<td>0.343</td>
</tr>
<tr>
<td>Ankle-brachial index</td>
<td>0.90 ± 0.25</td>
<td>0.84 ± 0.33</td>
<td>0.379</td>
<td>0.86 ± 0.30</td>
<td>0.90 ± 0.17</td>
<td>0.502</td>
</tr>
<tr>
<td>Clinical outcome*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical improvement††</td>
<td>70.6% (36/51)</td>
<td>57.4% (27/47)</td>
<td>0.209</td>
<td>77.8% (35/45)</td>
<td>52.3% (23/44)</td>
<td>0.015</td>
</tr>
<tr>
<td>Relative claudication distance, m</td>
<td>115 ± 63</td>
<td>153 ± 107</td>
<td>0.118</td>
<td>126 ± 89</td>
<td>105 ± 82</td>
<td>0.431</td>
</tr>
<tr>
<td>Absolute claudication distance, m</td>
<td>200 ± 128</td>
<td>216 ± 128</td>
<td>0.610</td>
<td>218 ± 187</td>
<td>216 ± 136</td>
<td>0.968</td>
</tr>
<tr>
<td>Safety outcome (cumulative incidence)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause death§</td>
<td>0%</td>
<td>2.1% (1/47)</td>
<td>0.124</td>
<td>4.3% (2/47)</td>
<td>6.8% (3/44)</td>
<td>0.591</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Major amputation</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1.8 (1/55)</td>
<td>2.1% (1/47)</td>
<td>0.910</td>
<td>2.1% (1/47)</td>
<td>4.5% (2/44)</td>
<td>0.519</td>
</tr>
<tr>
<td>Surgical intervention††</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
<td>2.1% (1/47)</td>
<td>0%</td>
<td>0.331</td>
</tr>
</tbody>
</table>

* Without the need for TLR
† ABI improvement of ≥0.15
‡ Clinical improvement of ≥1 Rutherford category
§ No procedure related death
** DCBA group: one patient with target lesion occlusion at 199 days; POBA group: one patient with subacute stent-thrombosis following TLR with DCB at 84 days and one patient with occlusion of tibioperoneal trunk at 294 days
†† Femoropopliteal bypass at target limb
Figure Legends:

**Figure 1.** Patient flow chart. DCBA = drug-coated balloon angioplasty; POBA = standard balloon angioplasty.

**Figure 2.** Primary endpoint of binary recurrent in-stent restenosis at 6 months.

**Figure 3.** Cumulative freedom from, and Kaplan-Meier estimates of, target lesion revascularization (TLR) according to treatment modality. SE = standard error.

**Figure 4.** Change in Rutherford category at 6 and 12 months according to treatment modality. Negative changes denote clinical improvement. TLR = target lesion revascularization.
Assessed for eligibility
N=119

Randomized
N=119

DCBA
N=62

POBA
N=57

6-month follow-up

N=52 (DUS)
N=40 (ABI)
N=51 (Clinical)
N=55 (Safety)

N=47 (DUS)
N=36 (ABI)
N=47 (Clinical)
N=47 (Safety)

12-month follow-up

N=44 (DUS)
N=36 (ABI)
N=45 (Clinical)
N=47 (Safety)

N=40 (DUS)
N=36 (ABI)
N=44 (Clinical)
N=44 (Safety)
Figure 2
Figure 3

- **DCBA**
  - 6 months: 96.4 ± 3%
  - 12 months: 90.8 ± 6%
- **POBA**
  - 6 months: 81.0 ± 5%
  - 12 months: 52.6 ± 10%

Patients at risk:
- **DCBA**: 62, 62, 57
- **POBA**: 55, 53, 50

**P values**:
- **DCBA vs. POBA**
  - 6 months: P = 0.0117
  - 12 months: P < 0.0001
Figure 4
Drug-Coated Balloon Versus Standard Balloon for Superficial Femoral Artery In-Stent Restenosis: The Randomized Femoral Artery In-Stent Restenosis (FAIR) Trial
Hans Krankenberg, Thilo Tübler, Maja Ingwersen, Michael Schlüter, Dierk Scheinert, Erwin Blessing, Sebastian Sixt, Arne Kieback and Thomas Zeller

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