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# A Randomized, Multicenter, Single-Blinded Trial Comparing Paclitaxel-Coated Balloon Angioplasty With Plain Balloon Angioplasty in Drug-Eluting Stent Restenosis

## The PEPCAD-DES Study

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**Objectives** This study sought to define the impact of paclitaxel-coated balloon angioplasty for treatment of drug-eluting stent restenosis compared with uncoated balloon angioplasty alone.

**Background** Drug-coated balloon angioplasty is associated with favorable results for treatment of bare-metal stent restenosis.

**Methods** In this prospective, single-blind, multicenter, randomized trial, the authors randomly assigned 110 patients with drug-eluting stent restenoses located in a native coronary artery to paclitaxel-coated balloon angioplasty or uncoated balloon angioplasty. Dual antiplatelet therapy was prescribed for 6 months. Angiographic follow-up was scheduled at 6 months. The primary endpoint was late lumen loss. The secondary clinical endpoint was a composite of cardiac death, myocardial infarction attributed to the target vessel, or target lesion revascularization.

**Results** There was no difference in patient baseline characteristics or procedural results. Angiographic follow-up rate was 91%. Treatment with paclitaxel-coated balloon was superior to balloon angioplasty alone with a late loss of 0.43 ± 0.61 mm versus 1.03 ± 0.77 mm ($p < 0.001$), respectively. Restenosis rate was significantly reduced from 58.1% to 17.2% ($p < 0.001$), and the composite clinical endpoint was significantly reduced from 50.0% to 16.7% ($p < 0.001$), respectively.

**Conclusions** Paclitaxel-coated balloon angioplasty is superior to balloon angioplasty alone for treatment of drug-eluting stent restenosis. (PEPCAD DES–Treatment of DES-In-Stent Restenosis With SeQuent® Please Paclitaxel Eluting PTCA Catheter [PEPCAD-DES]; NCT00998439) (J Am Coll Cardiol 2012;59:1377–82) © 2012 by the American College of Cardiology Foundation

Drug-eluting stents (DES) significantly reduce the occurrence of restenosis and the subsequent need for repeat revascularization (1,2). Nevertheless, the incidence of DES restenosis remains high due to the continuous increase in DES implantation (3). With present DES, complex lesions with a high restenotic potential are sufficiently treated (4), limiting the use

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**Abbreviations and Acronyms**

**BMS** = bare-metal stent(s)
**DAPT** = dual antiplatelet therapy
**DCB** = drug-coated balloon
**DES** = drug-eluting stent(s)
**MI** = myocardial infarction
**MLD** = minimal lumen diameter
**PCB** = paclitaxel-coated balloon catheter
**PES** = paclitaxel-eluting stent(s)
**POBA** = plain old balloon angioplasty
**SES** = sirolimus-eluting stent(s)
**TLR** = target lesion revascularization

of bare-metal stents (BMS) to patients not eligible for dual antiplatelet therapy (DAPT).

Paclitaxel-coated balloon (PCB) angioplasty is superior to plain old balloon angioplasty (POBA) (5) and noninferior to paclitaxel-eluting stent (PES) implantation for BMS restenosis (6). Whether the use of PCB angioplasty is also effective in DES restenosis has not been studied so far.

We evaluated in a randomized, multicenter, single-blinded trial the efficacy of a PCB angioplasty compared with POBA for DES restenosis in native coronary arteries.

## Methods

**Patient population.** From November 2009 to April 2011, 110 patients were recruited in 6 centers in the PEPCAD-DES (PEPCAD DES–Treatment of DES-In-Stent Restenosis With SeQuent® Please Paclitaxel Eluting PTCA Catheter) study. Inclusion criteria were an in-stent restenosis in sirolimus-eluting Cypher (Cordis, Warren, New Jersey) or Yukon (Translumina, Hechingen, Germany) stents, everolimus-eluting Xience (Abbott, Abbott Park, Illinois) or paclitaxel-eluting Taxus (Boston Scientific, Natick, Massachusetts) stents, reference vessel diameter of 2.5 to 3.5 mm, and lesion length of <22 mm. Exclusion criteria were thrombus within the target vessel, bifurcation lesion, multiple lesions in the target vessel, lesions in bypass grafts, total coronary artery occlusion, ostial or left main lesions, planned surgery within 6 months, and contraindication to DAPT. The protocol was approved by the ethics committee. All patients gave written informed consent (Clinical Trials ID: NCT00998439).

**Study design and study procedures.** Patients were randomly assigned to treatment of DES restenosis with PCB (SeQuent Please, B. Braun, Melsungen, Germany) or POBA alone. Pre-dilation with POBA according to the size of the restenotic stent was mandatory. The length of the PCB was chosen to overlap the lesion for at least 1 to 2 mm at the proximal and distal margin. Study balloons were inflated for 60 s at 10 bar. Patients received heparin to an activated clotting time of 200 to 250 s. The diameter of the study balloon had to be at least the diameter of the pre-dilation balloon and was left to the discretion of the operator. DAPT with acetylsalicylic acid 100 mg per day and clopidogrel 75 mg per day was prescribed for 6 months in both groups. Patients were followed by telephone or hospital visit at 30 days. Angiographic and clinical follow-up was scheduled at 6 months.

**Quantitative coronary angiography.** Angiographic measurements were done with the CAAS version 5.7 software (Pie Medical Imaging, Maastricht, the Netherlands) in the core lab of the University of Ulm, Ulm, Germany (4,7). The core lab was blinded to the randomized treatment strategy. Angiographic measurements were done separately at the target lesion treated by study balloon, within 5 mm proximal and distal to the target lesion, and over the total segment. Pattern of restenosis was classified according to Mehran et al. (8).

**Statistical analysis and primary and secondary endpoints.** To estimate the number of patients per group based on a 2:1 randomization, the 2-group Satterthwaite *t* test was used. Primary endpoint was late lumen loss at the target lesion at 6 months angiographic follow-up. With an assumed late lumen loss of 0.20 ± 0.30 mm in the drug-coated balloon (DCB) group and 0.80 ± 0.80 mm in the POBA group (6), the calculated number of patients were 64 in the PCB and 34 in the POBA groups to achieve 90% power. With an assumed dropout rate of 10%, the patient numbers to be recruited were 71 in the PCB and 38 in the POBA group. Categorical variables were compared using Pearson's chi-square test or Fisher exact test, when appropriate. All continuous variables are described with mean ± SD. Differences between proportions and *t* tests were computed with SPSS version 18.0 (IBM, Armonk, New York), whereas sample sizes were estimated with nQuery Advisor version 7.0 (Statistical Solutions, Saugus, Massachusetts).

Secondary angiographic endpoints were binary restenosis, minimal lumen diameter (MLD), and diameter stenosis at the target lesion and in the total segment. Secondary clinical endpoints were target lesion revascularization (TLR), myocardial infarction (MI), cardiac death, and stent thrombosis, defined according to the Academic Research Consortium criteria (9). Major adverse cardiac event was defined as a composite of cardiac death, MI attributed to the target vessel, and TLR.

## Results

A total of 110 patients with DES restenosis were randomized: 72 patients to treatment with PCB and 38 patients to POBA. Baseline clinical and angiographic characteristics were similar in the 2 groups (Table 1). There was a high frequency of patients with diabetes mellitus, with 36.1% in the PCB group and 34.2% in the POBA group ($p = 0.84$). Length (PCB: 19.8 ± 7.7 mm, POBA: 21.0 ± 7.7 mm; $p = 0.41$) and size (PCB: 2.75 ± 0.34 mm, POBA: 2.83 ± 0.39 mm; $p = 0.29$) of the restenosed DES were not different. First DES restenosis occurred in 46.4% of patients, and at least a second restenotic lesion in 53.6%.

Procedural success was 100% in both groups. All PCB catheters were successfully applied. Bailout stenting with a BMS was performed in 1 patient in each group due to unsatisfying balloon result or edge dissection.

**Quantitative coronary angiography.** Prior to percutaneous coronary intervention, lesion length, reference vessel diameter, diameter stenosis, and MLD did not differ between groups (Table 2). At baseline, the type of restenosis was focal in about two-thirds of patients in both treatment