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Angioplasty of Femoral-Popliteal Arteries With Drug-Coated Balloons

5-Year Follow-Up of the THUNDER Trial

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ABSTRACT

OBJECTIVES The purpose of this study was to evaluate the 5-year follow-up (FU) data of the THUNDER (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries).

BACKGROUND The THUNDER trial was the first study to investigate the treatment of femoropopliteal arteries with a paclitaxel-coated balloon (PCB).

METHODS In 154 patients, femoropopliteal arteries were treated with PCB, with angioplasty with paclitaxel in contrast medium, or no paclitaxel (control). The primary endpoint was 6-month late lumen loss (LLL). Secondary endpoints included freedom from target lesion revascularization (TLR), binary restenosis rate, and amputation. The 5-year FU compares outcomes in patients treated with PCB and control subjects. Additionally, LLL at 6 months and TLR up to 5-year FU were analyzed in terms of sex and lesion length.

RESULTS Over the 5-year period, the cumulative number of patients with TLR remained significantly lower in the PCB group (21%) than in the control group (56%, $p = 0.0005$). In the small group of patients with angiographic and duplex sonographic follow-up, PCB was associated with a lower rate of binary restenosis (17% vs. 54%; $p = 0.04$). No signs of aneurysm formation or constrictive fibrosis were detected. Whereas LLL at 6-month FU did not differ between men and women in the PCB group, the TLR rate was lower in men than in women at 5-year FU. A benefit of PCB treatment in terms of LLL and TLR was seen independent of lesion length.

CONCLUSIONS The reduced TLR rate following PCB treatment was maintained over the 5-year FU period. No signs of drug-related local vessel abnormalities were detected. (Thunder Trial—Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries [THUNDER]; NCT00156624) (J Am Coll Cardiol Intv 2015;8:102–8) © 2015 by the American College of Cardiology Foundation.

Long-term follow-up was requested following the surprising finding that a single treatment with paclitaxel-coated balloons (PCB) reduced restenosis rates for 6 to 24 months in the femoropopliteal arteries both in randomized studies (1–5) and in single-arm studies (6–8). Meanwhile 5-year follow-up of patients suffering from coronary in-stent restenosis treated with PCB is available (9). Follow-up data on the use of PCB in peripheral arteries have so far only been published for a maximum period

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of 24 months (1,2,5,8). The patients of the THUNDER Trial (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries), a randomized study investigating the efficacy of PCB for restenosis prevention in the femoropopliteal arteries, have now been followed up for 5 years. The aim of this follow-up (FU) was to evaluate the long-term efficacy and safety of local paclitaxel administration in terms of potential complications such as development of aneurysms or occurrences of thrombotic occlusion.

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METHODS

OUTLINE OF THUNDER STUDY: DESIGN, STUDY PATIENTS, AND 6- TO 24-MONTH FOLLOW-UP. The THUNDER study was designed to investigate the effect of local paclitaxel administration using a PCB on the restenosis rate after peripheral arterial interventions. A total of 154 patients were recruited and randomized in a multicenter trial. The target lesions had a mean pre-dilation degree of stenosis of 90 ± 9% and a mean length of 7.4 ± 6.5 cm. One group was treated with PCB and standard nonionic contrast medium (CM) (PCB group), a second group was treated with plain old balloon angioplasty and paclitaxel added to the CM (paclitaxel-in-CM group), and a third group was treated with plain old balloon angioplasty and standard nonionic CM (control group).

The PCB were coated with paclitaxel at a dose of 3 μg/mm^2 of balloon surface embedded in a matrix consisting of a small amount of the nonionic contrast agent iopromide (10), referred to in the literature as Paccocath coating (B. Braun Melsungen AG, Berlin, Germany). The total paclitaxel dose administered per patient ranged from 1 to 17 mg (mean: 5 mg).

Details of the methods and 6-month and 2-year FU results have been previously published (1).

DESIGN, PATIENTS, AND ENDPOINTS AT 5-YEAR FOLLOW-UP. The outcome in the paclitaxel-in-CM group did not differ significantly from that in the control group at 6- and 24-month FU (late lumen loss [LLL]: 2.2 ± 1.6 mm, p = 0.14; target lesion revascularization [TLR]: 40%, p = 0.25). Therefore, only control patients and those treated with PCB were invited to a 5-year FU visit. No 5-year FU was conducted in patients with >1 TLR, with femoropopliteal bypass graft involving the target lesion, and with amputations of the study leg up to 24-month FU. **Figure 1** presents a chart of the 5-year FU disposition of the original THUNDER population.

Patients underwent 5-year FU by clinical observation. This was done during a visit to the study center or, if patients could not come to the study center, by telephone interview. All patients were asked to complete a questionnaire on their current health status and on clinical events having occurred since their last FU. If the patients consented, any angiographies or duplex ultrasound examinations conducted after the 24-month follow-up, which included the target lesion and allowed its evaluation, were included in the 5-year FU analysis.

Clinical endpoints at 5-year FU included TLR, major amputation of the treated leg as well as death. Available angiography and duplex sonography data were used to determine the binary restenosis rate. Angiograms were also evaluated for LLL and for the presence of aneurysms or other abnormalities of the treated arteries.

The conduct of the THUNDER trial and the 5-year FU evaluation met all local legal and regulatory requirements and were approved by the local ethics committee at each study site. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guideline. Furthermore, study conduct was in accordance with sections 40/41 of the German Drug Act and sections 20 to 22 of the Medical Devices Act. All patients gave written informed consent.

SEX COMPARISON AND ANALYSIS OF LESION LENGTH. Angiographic LLL (difference between the post-procedural and 6-month FU minimal lumen diameter, evaluated by quantitative angiography) was the primary endpoint. Data referring to the intervention and 6-month FU were taken from the analysis provided by the blinded core lab. Analysis of TLR was performed up to 5-year FU.

STATISTICAL ANALYSIS. Statistical analysis was performed using SAS (version 9.2, SAS Institute Inc., Cary, North Carolina). In the patients available for 5-year FU, the incidence of first TLR overall and the incidence, intensity, and relationship to study treatment of serious adverse events (SAE) were analyzed as categorical or binary data. Data are presented as relative and absolute frequencies and were tested for group differences using the Fisher exact test.

Continuous data are presented as mean ± SD and were tested for group differences using a Wilcoxon rank sum test.

ABBREVIATIONS AND ACRONYMS

CM = contrast medium
CRF = case report form
FU = follow-up
LLL = late lumen loss
PCB = paclitaxel-coated balloon
SAE = serious adverse event(s)
TLR = target lesion revascularization