A MONOCENTER RANDOMIZED CLINICAL TRIAL OF PACLITAXEL DRUGELUTING BALLOON VERSUS STANDARD PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY TO REDUCE RESTENOSIS IN PATIENTS WITH INSTENT STENOSES IN THE SUPERFICIAL FEMORAL AND PROXIMAL POPLITEAL ARTERY (PACUBA I TRIAL).

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All authors disclose potential conflicts of interest.

Purpose

- Endovascular treatment of peripheral arterial disease (PAD) of the superficial femoral artery (SFA) with bare metal stents has its limitations when it comes to intermediate- and long-term patency. **Restenosis after treatment with nitinol stents occurs in up to 30% of the patients at 12 months** and **up to 50% at 24 months** (1-3). In long lesions the restenosis rate may be even higher (4,5). The **rate of recurrent restenosis** after percutaneous transluminal angioplasty (PTA) of an in-stent restenosis (ISR) within the SFA **ranges up to 70% at 6 months** (4).

- **Paclitaxel eluting balloons** have shown to **reduce the late lumen loss** after angioplasty of the SFA within the first 6 to 12 months (6-10).

- A recent clinical trial suggested significant inhibition of restenosis after treatment of in-stent restenosis in peripheral arteries by Paclitaxel-coated angioplasty balloons(11).

- The purpose of our study was to test the **hypothesis** that **Paclitaxel eluting balloon angioplasty (DEB) yields superior results compared to standard PTA.**

Methods and Materials

Study Design

- The study was conducted as **a prospective dual-center single-blind randomized** (1:1**) investigator sponsored clinical trial**. Consecutive patients **with symptomatic in-stent restenoses of the SFA and P1 segment** of the popliteal artery were assigned to either Paclitaxel eluting balloon angioplasty (DEB) or standard PTA. The objective was to test the hypothesis that **Paclitaxel eluting balloon angioplasty (DEB)** yields superior **results compared to standard PTA when treating ISR** of femoropopliteal arteries.

Primary Endpoint

- was **the primary patency at 12-months** follow-up, defined as <50% diameter stenosis as demonstrated by CDUS and CTA in the absence of clinically driven TLR (Target Lesion Revascularization) during follow-up.

Secondary Endpoints

- were **technical success** (achievement of a <30% residual diameter stenosis by visual estimate), complication rate through 30 days post index procedure**, clinical success** (improvement in clinical Rutherford-Becker category after the index procedure), **change in ankle brachial index (ABI)**, and clinically driven **Target Lesion Revascularization (TLR) at 6-months, and 12-months** post index procedure.

Follow-up Schedule

- **Clinical evaluation and ABI** were assessed pre-study, at **1-month post-study, and at 6-months, and 12-months** after the index procedure. Colour Doppler duplex ultrasound (**CDUS)** was performed at 24 hours post-study, and at 6-months, and 12-months; computed tomography angiography **(CTA)** was obtained at 12-months after the index procedure.

Inclusion Criteria	Exclusion Criteria
• Age> 50 a	• Patients unable to give written informed consent
• Symptomatic PAD Rutherford-Becker 2-3	• Any known allergy,hypersensibility or intolerance to radiologic contrast media, ASA, clopidogrel, ticlopidine or paclitaxel
• In-stent restenosis > 50% in die SFA or P1-segment	• Serum creatinine levels > 2.5 mg/dl
• A distal run-off of at least 1 artery	

Methods and Materials

Intervention

All interventions were performed from an antegrade or a contralateral cross-over approach. Patients were **randomly assigned** to either **Paclitaxel eluting balloon angioplasty (DEB)** or **standard percutaneous balloon angioplasty (PTA)**. In the DEB arm **predilatation with a standard balloon for one minute** was followed by **paclitaxel balloon angioplasty for two minutes**. The study device was **the FREEWAY™ balloon 0.035** (Eurocor/Germany; Opto Eurocor Healthcare Ltd./India) with a shellac coating as spacer and paclitaxel in a concentration of 3 µg/mm^2. In the PTA arm balloon angioplasty was performed for 2 minutes with a standard balloon.

Medical Therapy

Aspirin and clopidogrel were given at least 1 day prior to the intervention; otherwise a loading dose of 300 mg clopidogrel was given during the intervention. All patients received aspirin 100mg daily indefinitely and clopidogrel 75 mg daily for 3 months post intervention.

Control imaging

A colour Doppler duplex ultrasound **(CDUS)** was performed pre-study, at **24 hours, 6 and 12 months post index procedure**. Angiographic evaluation of restenosis **at 12 months** was performed using contrast enhanced **CTA** on a "Somatom Flash" 128-row, multi-slice CT scanner (Siemens Medical Systems, Erlangen, Germany). The evaluation of the angiograms was performed from the **CTA core laboratory** at the Medical University of Vienna(MUW), which was blinded with regard to the treatment arm.

Statistics

Assuming a 70% patency rate in the study arm compared to a 30% primary patency in the control arm, the sample size required for the superiority hypothesis on the 12-months primary patency endpoint was 33 subjects in each arm and 75 patients to compensate losses in follow-up. This endpoint was evaluated by the **Kaplan-Meier method of time-to-event analysis**, using the **log rank test** to evaluate statistically significant differences between treatment groups. Data analysis for primary and secondary study end points was performed according to the intention-to-treat principle. Descriptive data are given as means ± SD, proportions were compared by Chi-square statistics. Calculations were performed using Stata release 8.0 (Stata Inc. College Station, TX, U.S.).

Results – Descriptive Statistics

Table 1: Patient Demographics and Cardiovavascular Risk Factors

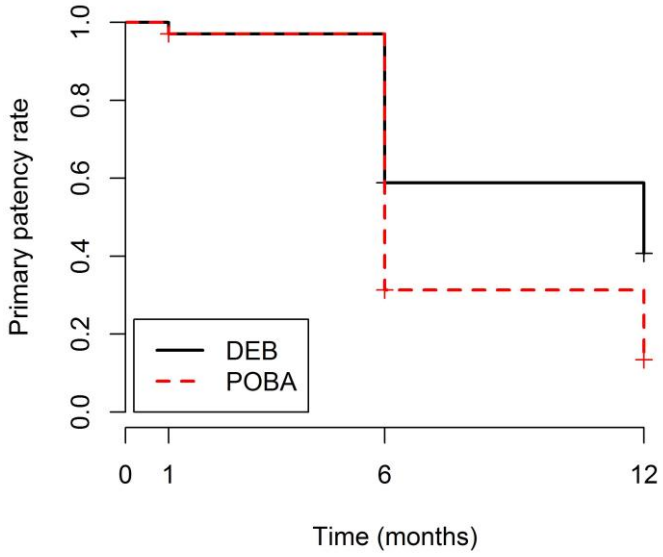
	DEB	***PTA***
n	35	39
Age (years) mean ± SD	68.1 ± 9.2	68.3 ± 0.4
Gender (male) (n / %)	20/57	23/59
Smoker (n / %)	17/52	18/53
CHD (n / %)	12/36	14/41
Hypertension (n / %)	26/79	27/79
Diabetes (n / %)	17/52	13/38
Hyperlipidemia (n / %)	18/55	25/74
Renal Failure (n / %)	6/19	6/16
Creatinine (mg/dl) mean ± SD	1.03 ± 0.28	0.98 ± 0.25
Obesity (n / %)	7/22	7/21
Family history of PAD (n / %)	7/29	8/28

Table 2: Baseline Lesions Characteristics

	DEB	***PTA***
Length (cm) mean ± SD	17.3 ± 11.3	18.4 ± 8.8
Occlusions (n / %)	11/31	11/28
Reference vessel diameter (mm)	5.7 ± 1.1	5.4 ± 0.9
TASC Classification		
• TASC A (n / %)	8/23	2/5
• TASC B (n / %)	8/23	14/36
• TASC C (n / %)	5/14	10/26
• TASC D (n / %)	14/40	13/33
TOSAKA Classification		
• Class I (n / %)	8/23	2/5
• Class II (n / %)	16/46	26/67
• Class III (n / %)	11/31	11/28

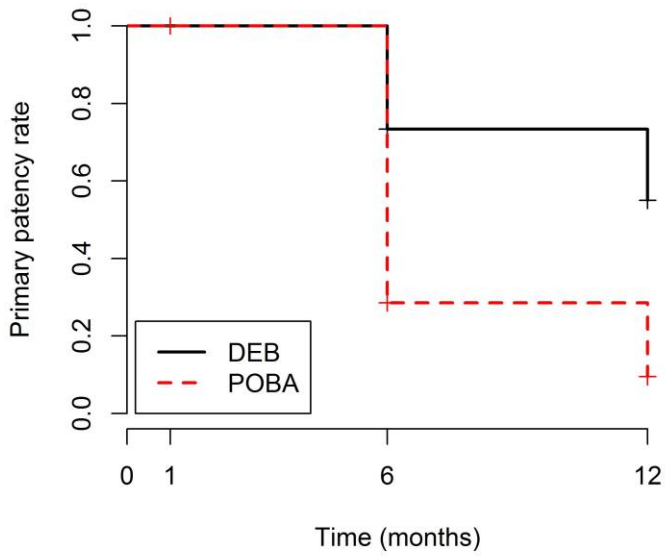
Results – Primary Patency

Figure 1: Kaplan-Meier estimation of the primary patency rate of patients treated with paclitaxel eluting balloon angioplasty (DEB) versus standard balloon angioplasty (PTA).
Patency rates at 6-months **and 12-months** are 58.8% versus 31.3% and **40.7 versus 13.4%** for **DEB versus PTA** (log-rank **p=0.02**).



DEB	1 (34)	13 (33)	4 (13)
POBA	1 (34)	21 (31)	4 (7)

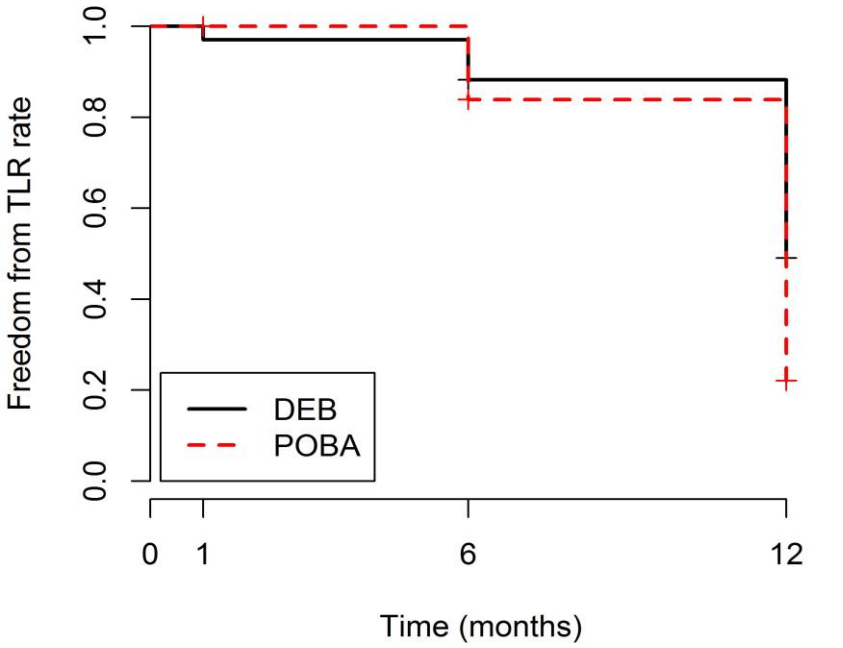
Figure 2: Kaplan-Meier estimation of the primary patency rate of lesions **TASC A and B** treated with paclitaxel eluting balloon angioplasty (DEB) versus standard balloon angioplasty (PTA).
Patency rates at 6-months and **12-months** are 73.3% versus 28.6% and **55.0% versus 9.5%** for **DEB versus PTA** (log-rank **p=0.008**).



DEB		4 (15)	2 (8)
POBA		10 (14)	2 (3)

Numbers at bottom are numbers of events, in parenthesis number of remaining patients at risk at 1-month, 6-months, and 12-months follow-up.

Results – Freedom from TLR



DEB	1 (34)	3 (33)	8 (18)
POBA		5 (31)	14 (19)

Numbers at bottom are numbers of events, in parenthesis number of remaining patients at risk at 1-month, 6-months, and 12-months follow-up.

Figure 3: Kaplan-Meier estimation of the freedom from clinical driven target lesion revascularization (TLR) rate of patients treated with paclitaxel eluting balloon angioplasty (DEB) versus standard balloon angioplasty (PTA).

Freedom from TLR rates at 6-months and **12-months** are 88.2% versus 83.8% and **49.0% versus 22.1% for DEB versus PTA** (log-rank **p=0.11**).

At 6-months 13 patients in the DEB group had a recurrent stenosis or occlusion; 3 were treated by TLR. In the PTA group 21 patients had a stenosis; 5 were treated by TLR. At 12-months in the DEB group 4 additional patients had a stenosis, 8 had a TLR; in the PTA group another 4 patients had a stenosis, 14 had a TLR

Results – Clinical Improvement

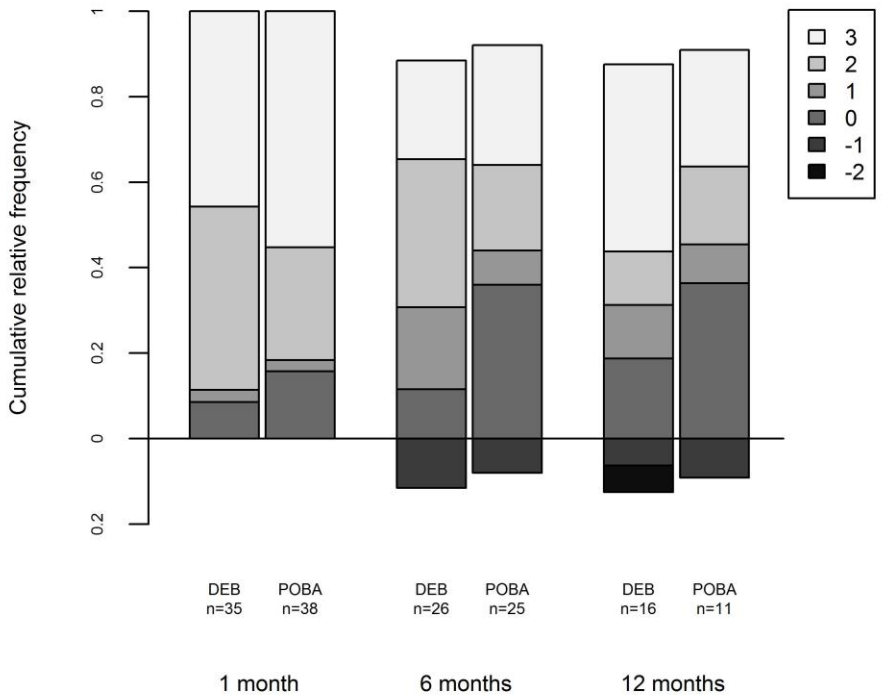


Figure 4: Distribution of the Rutherford-Becker score in the DEB and POBA groups at time-points 1, 6 and 12-months; n indicates the respective number of patients for which the score was observed.

At 1-month a clinical improvement by at least 1 Rutherford-Becker (RB) category was observed in 32/35 (91.4%) versus 32/38 (84.2%) patients (Fisher exact test p=0.46), at 6-months in 20/26 (76.9%) versus 14/25 (56.0%) patients (p=0.23), and at 12-month in 11/16 (68.8%) versus 6/11 (54.5%) patients (p=0.87) in the DEB versus PTA group, respectively.

Rutherford-Becker symptom grading corresponds to -2 moderate worsening, -1 minor worsening, 0 no change, +1 minor improvement, +2 moderate improvement, +3 major improvement.

Conclusions

Key Findings:

1. Patients treated with Paclitaxel eluting balloon (**DEB**) had a **significantly higher primary patency rate** of **40.7%** (95% CI 0.26-0.64) **versus standard PTA 13.4%** (95% CI 0.05-0.36) (log-rank p=0.02) **at 12-months**

2. this finding was **more evident in short TASC A and B lesions (**log-rank p=0.008) than in long TASC C and D lesions (p=0.4).

3. there was **no difference in clinical parameters** such as ABI, improvements in Rutherford category **and clinical driven TLR**.

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