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Femoropopliteal In-stent Restenosis Repair: Midterm Outcomes After Paclitaxel Eluting Balloon Use (PLAISIR Trial)

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WHAT THIS PAPER ADDS

This study confirms the good results of the paclitaxel eluting balloon (PEB) in the treatment of femoropopliteal (FP) in-stent restenosis (ISR). It will help to define PEB angioplasty as the Gold Standard for the treatment of FP ISR.

Objective: The aim was to assess 18 month outcomes of the paclitaxel eluting balloon (PEB) in patients with femoropopliteal (FP) in-stent restenosis (ISR).

Methods: In a national prospective and multicentre cohort study, symptomatic patients with femoropopliteal in-stent restenosis were included from January 2012 to June 2013. Patients were treated by paclitaxel eluting balloon angioplasty (In Pact Admiral, Medtronic, Santa Rosa, CA, USA). Clinical and duplex scan follow-up evaluations were performed at 1, 3, 6, 9, 12, and 18 months. The primary endpoint was freedom from target lesion revascularisation (TLR) at 12 months. Secondary endpoints were major adverse cardiovascular events (MACE), Target extremity revascularisation (TER), primary and secondary sustained clinical improvement, recurrent restenosis rate, primary and secondary patency, quality of life assessed by EQ-5D questionnaire, technical success, clinical success, and length of stay

Results: A total of 53 patients were enrolled. After a blinded review, 10 patients were defined as protocol violation because restenosis occurred more than 2 years after stent implantation. Procedures were performed in 55 limbs, 48 (87%) for claudication and 7 (13%) for critical limb ischaemia. The mean diameter and length of PEB were 6 $\pm$ 0.57 mm and 86 mm $\pm$ 32 mm, follow-up was 17 months (range 1–19). At 1 year, the survival rate was 96 $\pm$ 2.7% and freedom from TLR and TER were 90.2 $\pm$ 4.2% and 85 $\pm$ 5%, respectively. Sustained primary and secondary clinical improvements were 78.6 $\pm$ 5.7% and 92.0 $\pm$ 3.8%, respectively. At 1 year, the primary patency rate was 83.7 $\pm$ 5.0%. Prior to the procedure, the mean EQ-5D score was 66 $\pm$ 14 and 74 $\pm$ 16 at 1 year ($p = .10$). Two patients died during follow-up; one patient died 33 days after the procedure because of limb ischaemia.

Conclusion: PEB for the treatment of FP ISR is associated with a low rate of re-interventions and restenosis. Clinical improvement is maintained at 18 months.

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INTRODUCTION

Over the last 20 years endovascular therapy has become the standard of care for revascularisation of the femoropopliteal (FP) arteries for Trans-Atlantic Inter-Society Consensus (TASC) A and B lesions, and could also be an option for TASC C and D lesions, although bypass is still the

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standard of care for the long FP lesion. However, the Achilles heel of this technique remains restenosis. Restenosis is a local process associated with elastic recoil, intimal hyperplasia, and constrictive remodelling. The overall vessel diameter reduction that occurs in constrictive remodelling is not well defined, but likely involved matrix turnover under the control of proteinases, particularly metalloproteinases. Intimal hyperplasia includes inflammatory phenomena, migration, and proliferation of smooth muscle cells (SMCs) and also extracellular matrix (ECM) deposition.[1] Prevention of restenosis was first focused on elastic recoil and constrictive remodelling by developing stents. Therefore, in-stent restenosis (ISR) is primarily due to intimal hyperplasia. The failure of plain balloon angioplasty to treat ISR prompted the development of other therapies to treat ISR.[2] However, most of them did not show promising results. Indeed directional atherectomy[3–5] shows a primary patency rate and freedom from target lesion revascularisation (TLR) at 1 year ranging from 25% to 54% and from 53% to 56%, respectively. Cutting balloon angioplasty failed to prove superiority when compared with conventional percutaneous transluminal angioplasty (PTA).[6] Indeed, the primary patency rate at 1 year was 35% and freedom from TLR was 59%. With laser atherectomy and PTA, the primary patency rate was 48%, and freedom from TLR rates ranged from 49% to 77%.[5] Other devices have limitations with regards to ease of use, technical limitations, or cost such as brachytherapy,[7] or laser atherectomy.[8–11] A covered stent[12] or paclitaxel eluting stent[13] showed promising results but stent superposition could result in the lumen loss.

Recently, the paclitaxel eluting balloon (PEB) has shown promising results in preventing FP restenosis.[14,15] Drug-eluting balloons share three common components: a platform, an antiproliferative drug, and a drug carrier or an excipient. The aim of the drug is to reduce SMC proliferation, migration and ECM synthesis by interrupting the cell cycle. Currently the main drug used for a drug-eluting balloon for peripheral arterial disease (PAD) is paclitaxel, which is a cytotoxic drug.[16] Since ISR is mainly due to intimal hyperplasia, PEB use could improve endovascular treatment outcomes for FP ISR treatment. Currently, few studies are available regarding PEB use for ISR FP treatment.[17–19] In a prospective national multicentre cohort, the outcomes after PEB repair for patients with FP ISR have been investigated.

METHODS

Experimental design

PLAISIR was a multicentre, French, prospective cohort study in which patients referred for PAD and presenting with FP ISR lesions were included from January 2012 to June 2013. Patients were enrolled in 10 centres. This registry was established to determine the safety and the feasibility of PEB for treating ISR FP lesions. Inclusion and exclusion criteria are summarised in Table 1. Patients had either one or two limbs treated. The local ethics committee approved the protocol and all patients gave their informed consent.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Age $\geq$ 18 years old	No atheromatous disease
Symptomatic patient according to Rutherford Class 1, 2, 3, 4 or 5	Asymptomatic lesion
Clinical degradation by at least 1 Rutherford stage or absence of healing of all skin lesions	Known allergies to heparin, aspirin, other anti-coagulant/ antiplatelet therapies, and/or paclitaxel
Symptoms related to SFA ISR defined by PSVR $>$ 2.4 within 3 $-$24 months after SFA stenting of de novo atherosclerotic lesions. Each patient may have either one or both limbs treated in the study	Acute limb ischaemia
	Patient on oral anticoagulation therapy
	Target lesion requires/has been pretreated with alternative therapy such as: DES, laser, atherectomy, cryoplasty, cutting/scoring balloon, etc.
The target ISR lesion is fully contained between the origin of the SFA and distally the femoropopliteal crossover (crossing by SFA of medial rim of femur in the PA projection)	Life expectancy $<$ 1 year
	Patient involved in another trial
Adequate SFA inflow and outflow either pre-existing or successfully re-established (outflow defined as patency of at least one infragenicular artery)	Refusing patient
	Pregnancy
	Patients receiving anticoagulation
The target lesion must not extend beyond the stent margin	
Successful crossing of the target lesion, inflow and outflow lesions with a guidewire	
Patient belongs to the French health care system	
Written informed consent	

ISR = in-stent restenosis; PSVR = peak systolic velocity ratio; SFA = superficial femoral artery.

The PLAISIR trial was declared to clinical.gov.trial (NCT01587482).

Procedures

Briefly, the procedure was performed under local, locoregional, or general anaesthesia. After a percutaneous femoral (ipsilateral or contralateral) or brachial approach, an arteriogram was performed. The lesion was catheterised. Predilatation was performed using a standard balloon. The standard balloon dimensions were chosen so that the nominal diameter was less than the nominal vessel diameter by 1 mm and the length did not exceed the ISR length. For a residual restenosis $>$ 50%, a high pressure balloon could be used. In case of predilatation failure, the procedure was considered as a technical failure and recorded. Following a successful predilatation, a PEB (IN.PACT Admiral, Medtronic, Santa Rosa, CA, USA) was used. The PEB dimensions were chosen so that the nominal diameter was equal to the nominal vessel diameter and the length did not exceed the ISR length by more than 5–10 mm at each edge. In case of the use of two or more PEBs, a 1 cm PEB overlap was required. According to the Medtronic

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