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Drug-Eluting Balloons for the Treatment of the Superficial Femoral Artery In-Stent Restenosis

2-Year Follow-Up

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Objectives The aim of this prospective registry was to evaluate the safety and efficacy at 2-year follow-up of the use of drug-eluting balloons (DEBs) for the treatment of superficial femoral artery (SFA) in-stent restenosis (ISR).

Background The use of DEBs for the treatment of SFA ISR is associated with a satisfactory primary patency rate at 1 year, but no data are available for longer follow-up. Unfortunately, when DEBs were used to treat SFA de novo lesions, the occurrence of restenosis increased by 50% between the first and the second years of follow-up.

Methods From December 2009 to December 2010, 39 consecutive patients underwent percutaneous transluminal angioplasty of SFA ISR at our institution (Clinica Montevergine, Mercogliano, Italy). All patients underwent conventional SFA percutaneous transluminal angioplasty and final post-dilation with paclitaxel-eluting balloons (IN.PACT, Medtronic Inc., Minneapolis, Minnesota). Patients were evaluated for up to 24 months.

Results During follow-up, 1 patient died of heart failure and another of sudden death, for a 2-years rate of cardiovascular mortality rate of 5.12 %. The primary patency rate at 2 years was 70.3% (11 of 37 patients experienced restenosis recurrence at 2-year follow-up). The treatment of complex ISR lesions (classes II and III) was associated with an increased rate of recurrent restenosis compared with class I (33.3 % and 36.3 % vs. 12.5%; $p = 0.05$).

Conclusions The data suggest that adjunctive use of DEBs for the treatment of SFA ISR is a safe and effective therapeutic strategy up to 2 years of follow-up. (J Am Coll Cardiol Intv 2014;7:411–5) © 2014 by the American College of Cardiology Foundation

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The use of self-expanding nitinol stents has improved the patency rate of percutaneous transluminal angioplasty (PTA) of the superficial femoral artery (SFA). Unfortunately, the occurrence of SFA in-stent restenosis (ISR) has been reported to occur within 1 year in at least one-fourth of the patients (1).

The use of drug-eluting balloons (DEBs) for the treatment of SFA ISR has shown promising results in terms of clinical benefit and primary patency over 1 year (2). When DEBs were used to treat SFA lesions, the occurrence of restenosis increased by 50% between the first and the second years of follow-up (3). No data are available on the SFA ISR long-term recurrence and late thrombosis occurrence.

The aim of this registry was to provide 2-year follow-up data on the use of DEBs for the treatment of SFA ISR.

Methods

Study population. From December 2009 to December 2010, 39 patients underwent PTA for the treatment of SFA ISR at our institution (of a total of 308 SFA interventions). Patients were treated in the standard manner of our practice and included in a prospective registry. The follow-up protocol was approved by the hospital institutional review board.

Abbreviations and Acronyms

DEB = drug-eluting balloon

ISR = in-stent restenosis

PTA = percutaneous transluminal angioplasty

PVR = proximal velocity ratio

SFA = superficial femoral artery

TLR = target lesion revascularization

Concomitant therapy. All patients received aspirin (75 to 160 mg/day) and should have been on ticlopidine (250 mg twice daily) for at least 7 days. Alternatively, patients received a clopidogrel pre-load (300 mg) 24 h before the procedure. After the procedure, thienopyridines were continued for 30 days, whereas aspirin continued for life. For anticoagulation, 70 to 100 IU/kg of unfractionated heparin was administered, with the intention to achieve an activated clotting time of >250 s.

PTA technique. All procedures were performed percutaneously as previously reported (2). All patients underwent standard balloon angioplasty for at least 60 s, sizing was 0.8:1 to the reference vessel diameter. Laser-mediated lesion debulking was used to substitute balloon pre-dilation at the operator's discretion. A final post-dilation, at least 180 s, was performed with DEBs (IN.PACT, Medtronic Inc., Minneapolis, Minnesota) and sizing was 1:1 to the reference vessel diameter. The IN.PACT balloon has a surface-specific matrix coating consisting of paclitaxel combined with an hydrophilic spacer (Freepac, Medtronic, Inc.) (4).

Nitinol stent implantation was allowed for bail-out stenting (residual stenosis >30% or flow-limiting dissections).

Patients follow-up. Patients were evaluated through hospital discharge, at 30 days, and at 3, 6, 12, 15, 18, 21, and 24 months post-procedure. Clinical follow-up was performed by clinical examinations and duplex ultrasonography scans. Repeat angiography was performed when proximal flow velocity ratio (PVR) was between 2.4 and 5.0 (intermediate restenosis), and the patient had clinical symptoms or >5.0 PVR (severe restenosis) regardless of clinical symptoms and in case of stent occlusion (5).

Classification of ISR. The ISR lesions were classified by a visual estimate on angiography: class I, the focal (<50 mm in length) ISR group included lesions located at the stent body, the stent edge, or a combination of these sites; class II, the diffuse (>50 mm in length) ISR group, included not only stent body lesions, but also stent edge lesions; and class III is the totally occluded ISR group (5).

Definitions. Technical success was defined as the ability to successfully perform PTA and DEB post-dilation with a residual stenosis <30%. Procedural success was defined as technical success without the occurrence of any in-hospital major adverse cardiac and cerebrovascular events. The primary endpoint was primary patency defined as a PVR <2.4 documented by duplex ultrasound at 12 months without target lesion revascularization (TLR). Secondary endpoints included freedom from TLR at 2 years, and secondary patency at 2 years documented by duplex ultrasound (patency defined as a PVR <2.4). Stent fractures were classified as minor, moderate, or severe (6).

The below-the-knee artery was considered patent if free of obstructive lesions demonstrating angiographic stenosis >70%.

Statistics. Statistical analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, Illinois). Variables were expressed as absolute numbers and percentage or mean ± SD. Comparisons were made using the *t* test for unpaired samples, the chi-square test, or the Mann-Whitney *U* test, as appropriate. Additionally, the Kaplan-Meier estimate was used for presentation of primary patency and the freedom from TLR through 24 months.

An exploratory analysis was undertaken to identify predictors of restenosis. The methodology used was a 2-step approach. First, possible predictors (stent length, stent diameter, stent fracture, stent located in the distal SFA, ISR class, age, sex, smoking history, hypertension, diabetes mellitus, hypercholesterolemia, number of below-the-knee patent vessels, laser use, and bail-out stenting) were selected from the baseline variables and evaluated by analysis of variance for continuous variables and chi-square test versus restenosis for categorical variables. The second step was to enter the variables in a binary logistic linear model. Variables with $p < 0.05$ were considered significant predictors of restenosis.

Results

Patients' clinical characteristics and procedural features were previously reported (2). Technical and procedural

success was achieved in all 39 patients (100%). No procedure-related adverse events occurred. Summarized procedural characteristics were previously reported (2). All restenosis classes were represented: 20.5% (n = 8) were class I, 48.7% (n = 19) were class II, and 30.8 % (n = 12) were class III.

No major adverse cardiac and cerebrovascular events occurred in hospital. During the 2-years follow-up, 1 patient died due to heart failure after 3 months, and 1 patient died due to sudden death at 18 months, resulting in 2.56% 1-year and 5.12% 2-year rates of all-cause and cardiovascular mortality.

The primary endpoint, primary patency at 2 years, was obtained in 70.3% (26 of 37 patients) completing the 2-year follow-up (Fig. 1); consequently, a total of 11 patients experienced recurrent ISR during the follow-up. Freedom from TLR rate at 2 years was 78.4% (Fig. 2).

In 1 patient, the 3-month follow-up duplex scan showed a significant class I restenosis, which was treated by PTA and DEB.

At the 6-month follow-up, recurrent restenosis was treated with DEB in a patient (class I) and with an endovascular graft in another (class II). One patient underwent an in-stent recanalization with DEB for a class III ISR at 14 months. At 16 months, 1 patient underwent a femorotibial bypass graft after an unsuccessful PTA of a class III ISR. After 17 months, a duplex scan showed a significant class II ISR in 1 patient; despite the presence of symptoms; patient refused further treatment.

At 18 months, 1 patient with class II ISR was treated by implantation of an endovascular graft. A second patient, in whom class III ISR occurred after omolateral common femoral artery (CFA) clamping due to emergency surgery for a ruptured abdominal aortic aneurysm, was placed on medical therapy.

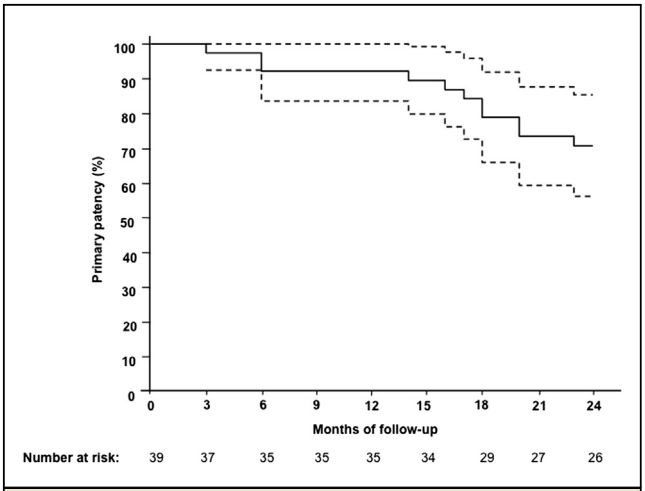

Figure 1. Kaplan-Meier Curve Representing Primary Patency

Curve shows primary patency up to 2 years after drug-eluting balloon–mediated percutaneous transluminal angioplasty of superficial femoral artery in-stent restenosis. **Dotted lines** indicate 95% confidence interval.

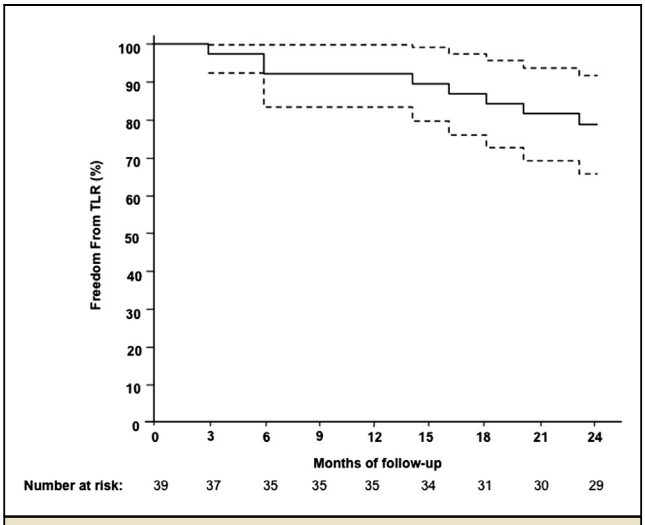

Figure 2. Kaplan-Meier Curve Representing Freedom From TLR

Curve shows freedom from target lesion revascularization (TLR) up to 2 years after drug-eluting balloon–mediated percutaneous transluminal angioplasty of superficial femoral artery in-stent restenosis. **Dotted lines** indicate 95% confidence interval.

At 20 months, significant target lesion restenosis occurred in 2 patients, 1 of whom underwent PTA with laser-mediated debulking and endovascular graft implantation for a class III ISR. The second patient, with class III ISR, was treated by medical therapy because of her advanced age and comorbidity. One patient had class II ISR at 23 months and was treated by a new stent implantation with successive DEBs.

At 2 years, duplex assessment demonstrated an 87% rate of secondary patency; Rutherford class was 0.6 ± 0.7 (baseline, 2.9 ± 0.7; $p < 0.05$), and the ankle-brachial index was 0.94 ± 0.09 (baseline, 0.77 ± 0.09; $p < 0.05$).

Of the 37 patients who completed the 2-year follow-up, a second PTA was performed in only 5 patients. Two patients underwent surgical revascularization, and 2 patients were treated medically.

The treatment of more complex ISR lesions (classes II and III) with DEBs was associated with an increased rate of recurrent restenosis compared with class I (33.3% and 36.3% vs. 12.5%; $p = 0.05$) (Fig. 3).

Discussion

This study demonstrates that the use of DEBs is associated with low rates of recurrences at 2 years. The treatment of ISR in the femoropopliteal artery is 1 of the remaining challenges of endovascular therapy because different treatment modalities, such as PTA and cutting balloon angioplasty, have failed to provide durable results (7). To avoid

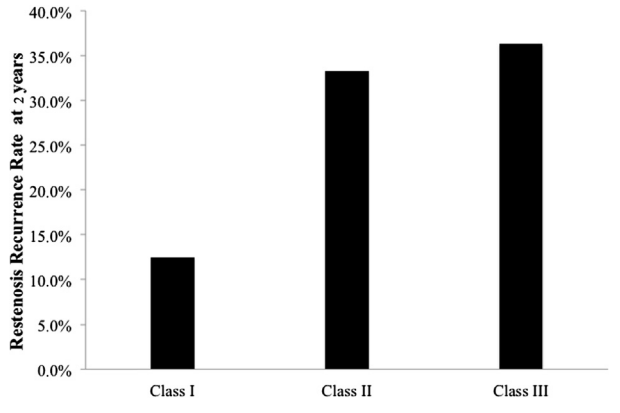

Figure 3. Restenosis Recurrence According to Baseline ISR Class

Bar graph representing superficial femoral artery in-stent restenosis (SFA ISR) recurrence at 2 years in patients treated with drug-eluting balloons for SFA ISR according to ISR class at baseline ($p = 0.05$).

bypass surgery, alternative endovascular approaches are needed to achieve better and more durable results.

ISR is determined by neointimal hyperplasia of smooth muscle cells; to reduce neointima formation, it is necessary to arrest smooth muscle cell proliferation and migration (8). Local arterial wall delivery of paclitaxel, a drug that impairs normal microtubule and cytoskeleton arrangement, may prevent neointimal hyperplasia by inhibiting smooth muscle cell migration and proliferation (9). This approach, thanks to the use of drug-eluting technologies, is being investigated as a potential treatment of SFA ISR.

Regarding the potential role of DEBs in the treatment of femoropopliteal ISR, we previously reported a 1-year primary patency rate of 92.1% (1). Similar data have been reported in diabetic patients. In the DEBATE trial, (Drug-Eluting Balloon in peripherAl inTErvention) treatment of ISR with DEBs demonstrated a significant reduction in restenosis recurrence compared with standard balloon angioplasty (10).

More recent data have been published on the role of drug-eluting stents for the treatment of SFA ISRS. In Zilver PTX (Cook Medical, Bloomington, Indiana), treatment of 119 ISR lesions with a paclitaxel-eluting stent had an estimated primary patency rate of 95.7% at 6 months and 78.8% at 12 months. The placement of a second stent layer does not appear to adversely affect the integrity of the Zilver PTX stent as only 1.2% (3 of 257) of stents used in this study had detectable fractures at 12 months (11).

It has to be considered that the initial experiences with the use of drug-eluting technologies have failed due to the occurrence of a "catch-up" phenomenon resulting in comparable clinical and angiographic event rates between groups in the long term (12,13).

When DEBs were used to treat SFA lesions, the occurrence of restenosis increased by 50% between the first and second years of follow-up. In the present study, the phenomenon was even more evident.

The value of longer follow-up when evaluating drug-eluting technologies for the treatment of SFA ISRS relies on the need to understand whether this is a catch-up phenomenon or is the natural history of ISR.

Notably, the Zilver-PTX single-arm trial is the first prospective study to report 2-year results for endovascular treatment of femoropopliteal ISR lesions. Freedom from clinically-driven TLR was 60.8% at 2 years. No predictors of recurrent ISR were identified.

We report the longest follow-up after DEB-based PTA for SFA ISR. At 2 years, a 70.3% primary patency rate was observed. Similar to Zilver PTX data, no predictors of restenosis were identified. A higher restenosis recurrence rate was observed with more complex restenosis patterns (type II and II). No difference in the class of ISR was observed between baseline and recurrence (Table 1).

Due to the limited number of patients enrolled in this study, the information obtained should be considered more to support the safety and feasibility of the proposed technique than to assess efficacy. Nevertheless, comparing the results of our study with those available in the literature (5), it is evident that the use of DEBs for the treatment of SFA ISR reduces restenosis recurrence. As of today, the only reported recurrence rates of SFA-ISR (5) are 49.9% when a class I lesion is treated, 53.3% for class II, and 84.8% for class III. Our study reports a robust reduction in recurrence rates (12.5% for class I, 38.9% for class II, and 27.3% for class III) because of the use of DEBs. The treatment of more complex ISR lesions (classes II and III) with DEBs was associated with an increased rate of recurrent restenosis compared with class I. Unfortunately, due to the limited number of patients enrolled in the study, this did not reach a full statistical significance.

These observations should be considered hypothesis generating and be confirmed by larger trials or registries.

Study limitations. The major limitation of our study lies in the absence of a control group. The relevance of these data in contemporary practice is somewhat increased by the fact that they could be used to design a randomized trial comparing the use of drug-eluting technologies for the treatment of SFA-ISR.

Table 1. Patterns of In-Stent Restenosis at Baseline and at Recurrence

Class	Baseline	Recurrence	p Value
I	20.5 (8)	18.2 (2)	NS
II	48.7 (19)	36.4 (4)	NS
III	30.8 (12)	45.4 (5)	NS

Values are % (n).

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Key Words: drug-eluting balloon ■ in-stent restenosis ■ superficial femoral artery.