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

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Objectives
The purpose of this prospective registry was to evaluate the safety and efficacy, at 1 year, of the use of drug-eluting balloons (DEB) for the treatment of superficial femoral artery (SFA) in-stent restenosis (ISR).

Background
The use of the self-expanding nitinol stent has improved the patency rate of SFA after percutaneous transluminal angioplasty (PTA). As the population with SFA stenting continues to increase, occurrence of ISR has become a serious problem. The use of DEB has showed promising results in reducing restenosis recurrence in coronary stents.

Methods
From December 2009 to December 2010, 39 consecutive patients underwent PTA of SFA-ISR in our institution. All patients underwent conventional SFA PTA and final post-dilation with paclitaxel-eluting balloons (IN.PACT, Medtronic, Minneapolis, Minnesota). Patients were evaluated up to 12 months.

Results
Technical and procedural success was achieved in every patient. No in-hospital major adverse cardiac and cerebrovascular events occurred. At 1 year, 1 patient died due to heart failure. Primary endpoint, primary patency rate at 12 months, was obtained in 92.1% (35 patients). At 1 year, patients were asymptomatic for claudication, and duplex assessment demonstrated lack of recurrent restenosis (100% rate of Secondary patency). The presence of an occlusive restenosis at the time of treatment was not associated with an increased restenosis rate, when compared with non-occlusive restenosis, at 1 year.

Conclusions
The data suggest that adjunctive use of DEB for the treatment of SFA-ISR represents a potentially safe and effective therapeutic strategy. These data should be considered hypothesis-generating to design a randomized trial. (J Am Coll Cardiol 2012;60:1739–42) © 2012 by the American College of Cardiology Foundation

Endovascular therapy for superficial femoral artery (SFA) disease has been recognized as a safe and efficient therapy (1). The patency rate of treated SFA has been improved through use of the self-expanding nitinol stents (2–4). As the population with SFA stenting continues to increase, occurrence of in-stent restenosis (ISR) has become a thoughtful problem. Treatment of SFA-ISR is associated with increased risks of recurrent ISR, recurrent occlusion, and surgical revascularization when compared with focal or diffuse restenosis (5). No standard treatment exists for the treatment of SFA-ISR.

The use of drug-eluting balloons (DEB) reduces restenosis rate after femoro-popliteal percutaneous transluminal angioplasty (PTA) (6,7). Drug-eluting balloon use has showed promising results in reducing restenosis recurrence in coronary stents (8). At this moment, no data are available on the use of DEB for the treatment of SFA-ISR.

The purpose of this prospective registry was to evaluate the safety and efficacy of the use of DEB for the treatment of ISR.

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

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

PTA technique. All procedures were performed percutaneously, with the patient under local anesthesia. Vascular access was achieved via contralateral common femoral artery. A 6-F long sheath was placed in cross-over technique to achieve adequate support. Once diagnostic angiography was completed, the wire was advanced in the distal popliteal artery. A filter for distal protection (Spider, EV3, Plymouth, Minnesota) was placed distal to the stenosis at operator discretion. All patients underwent balloon angioplasty (plain old 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 predilation, at operator discretion.

A final post-dilation, at least 180 s, was performed with DEB (IN.PACT, Medtronic, Minneapolis, Minnesota); sizing was 1:1 to the reference vessel diameter. The IN.PACT balloon has a surface-specific matrix coating consisting of Paclitaxel combined with a hydrophilic spacer (Freepac, Medtronic Invatec, Frauenfeld, Switzerland). Paclitaxel is an anti-proliferative drug, and the spacer (Freepac, Medtronic Invatec, Frauenfeld, Switzerland) consists of Paclitaxel combined with a hydrophilic spacer, necessary to separate paclitaxel molecules and extend toward 10 mm distal to the target SFA lesion. A 6-F balloon overlap was allowed to obtain a uniform drug elution into the arterial wall, is urea.

The DEB-treated segment should begin 10 mm proximal and extend toward 10 mm distal to the target SFA lesion. A 5-mm balloon overlap was allowed to obtain a uniform drug elution in the treated vessel. Nitinol stent implantation was allowed, for bail-out stenting (residual stenosis >30% or flow-limiting dissections).

Post-procedural patient management. Femoral sheaths were removed when activated clotting time was <150 s. Access site hemostasis was achieved by manual compression in all patients. A complete blood count was obtained before the procedure and before hospital discharge.

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

Classification of ISR. The ISR lesions were classified by visual estimate on angiography: class I, the focal (<50 mm in length) ISR group, included lesions positioned 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. “Primary endpoint” was primary patency defined as PVR of <2.4 documented by duplex ultrasound at 12 months without target lesion revascularization (TLR). “Secondary endpoints” included: 1) freedom from TLR at 1 year; 2) secondary patency at 1 year documented by duplex (patency defined as a PVR <2.4); 3) clinical success as defined by >1 category improvement in the Rutherford scale from baseline (or 2 categories if there was pre-existing tissue loss) at 1 year; and 4) hemodynamic success, defined by a 0.1 improvement in the ankle-brachial index during the period from baseline to 30 days post-procedure and no deterioration >0.15 from the maximum early post-procedure level at 1 year. Stent fractures were classified as minor, moderate, or severe (9). Below the knee artery was considered patent if free of obstructive lesions determining angiographic stenosis >70%.

Statistical analysis. Nominal and categorical variables were presented as contingency tables with frequencies and percentages. Continuous variables were reported as the mean with SD or median and interquartile ranges. Variables were compared by t test for normally distributed values (p<0.05 was considered statistically significant).

Results

Patient clinical characteristics are summarized in Table 1.

Technical and procedural success was achieved in all 39 patients (100%). No procedure-related adverse events occurred. In 4 patients the operator decided to perform excimer laser mediated plaque debulking. Distal protection was adopted in 6 cases.

Table 1 Patient Clinical Characteristics

| Male | 32 (82.1) |
| Age (yrs) | 65.9 ± 9.6 |
| Diabetes (%) | 19 (48.7) |
| Hypertension (%) | 36 (93.4) |
| Hypercholesterolemia | 34 (87.2) |
| Smoking history | 34 (87.2) |
| eGFR <30 (ml/min) | 8 (20.5) |
| Rutherford class | 2.9 ± 0.7 |
| BTK patent vessels | 31 (79.5) |
| ≤2 | 8 (20.5) |

N = 39. Values are n (%) or mean ± SD.

BTK = below-the-knee; eGFR = estimated glomerular filtration rate.
Procedural characteristics are summarized in Table 2. Mean lesion length was 82.9 ± 78.9 mm. This required the use of almost 2 DEB/patients. Bail-out stenting was necessary in 4 patients due to flow limiting dissections at the treated stent edges.

Of the 39 lesions treated, 30.8% were class I, 48.7% were class II, and 20.5% were class III. Stent fractures were all minor and not geographically related to the restenosis site.

No major adverse cardiac and cerebrovascular events occurred in-hospital. Only 1 patient died, due to heart failure, determining a 2.56% rate of all-cause and cardiovascular mortality at 1 year.

The primary endpoint, primary patency, was obtained in 92.1% (Fig. 1); in 3 patients, duplex scan—performed at the 3-month follow-up in 1 patient and at 6-month follow-up in 2—showed a significant target lesion restenosis. These patients underwent re-PTA of the target lesion due to the presence of 2 focal (<50 mm) and 1 diffuse (>50 mm) recurrent restenosis. At index procedure, 1 of these was focal, and 2 were diffuse. Recurrent restenosis was treated with DEB in 2 cases and with an endovascular graft in the other case.

A further patient, 6 months post-procedure, underwent an ipsilateral external iliac artery PTA. Thus, the result was a 10.5% rate of target limb revascularization.

At 1 year, duplex assessment demonstrated no recurrent restenosis (100% rate of secondary patency), Rutherford class was 0.8 ± 0.5 (baseline 2.9 ± 0.7; p < 0.05), no amputation was necessary, and ankle-brachial index was 0.98 ± 0.02 (baseline 0.77 ± 0.09; p < 0.05); thus clinical and hemodynamic success was achieved in all patients.

In this small study, treatment of Type III ISR with DEB was not associated with an increased rate of recurrent restenosis, when compared with type I and II ISR. Unfortunately the available data are not sufficient to perform any proper statistical correlation between treated lesion length and restenosis rate or bail-out stenting at index procedure and restenosis rate.

Discussion

This study demonstrates that: 1) SFA-ISR can be safely treated with PTA with DEB; and 2) the use of DEB is associated with low rates of recurrences and good clinical outcomes.

The incidence of SFA-ISR has been reported to occur in up to 40% of patients within the first year (3,4). Experience to date suggests that SFA-ISR can be treated with high immediate procedural success, but durable long-term patency remains elusive. Balloon angioplasty for ISR lesions does not provide acceptable patency rates at 2 years, which are even worse when an occlusive class III ISR lesion is treated (5). Cutting balloon angioplasty and debulking strategies have been employed, but data are limited and not encouraging (10–12).

Although randomized trials of DEB for femoropopliteal disease included only a small number of patients with ISR (6), dedicated trials of DEB for femoropopliteal ISR are still ongoing. So far this is the largest report on the use of DEB for the treatment of ISR.

A larger experience to date with drug-eluting technology for femoropopliteal ISR comes from the Zilver PTX registry, where a freedom from TLR at 12 months of 78% was observed (13,14).

In our study a Class III ISR (occlusive) was not associated with an increased recurrence risk. These data are particularly important, because so far balloon angioplasty for occluded ISR had been unfavorable.
Study limitations. The lack of a control group limits any definitive conclusions that can be made with regard to the optimal approach to SFA-ISR, and the results of this study should be considered hypothesis-generating. A further limitation of this study is that procedural technique was not consistent throughout. The use of laser in a few cases complicates analysis of the results at this moment; nevertheless, this could be a potential advantage in the future, because this registry is still ongoing and could lead to a potential investigation of the role of laser before DEB treatment for SFA-ISR.

Conclusions

On the other end, the relevance of these data in the contemporary practice is somewhat increased because the availability of DEB can change the paradigm for the treatment of SFA-ISR.

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Key Words: drug-eluting balloon(s) • in-stent restenosis • superficial femoral artery.