Treatment of TASC C and D Femoropopliteal Lesions with Paclitaxel eluting Stents: 12 month Results of the STELLA-PTX Registry

J.-M. Davaine a,b,d, J. Querat a,d, A. Kaladjia a, B. Guyomarch a,c, P. Chaillou a, A. Costargenta, T. Quillard b, Y. Gouëffic a,b,*

a CHU Nantes, l'institut du thorax, service de chirurgie vasculaire, Nantes, France
b Laboratoire de physiopathologie de la résorption osseuse, UMR-957, Nantes, France
c CHU Nantes, l'institut du thorax, centre d'investigation clinique, Nantes, France

WHAT THIS PAPER ADDS
In the present study the safety and the efficacy of paclitaxel-eluting stents for Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC) C/D femoropopliteal lesions have been prospectively assessed. It was found that critical limb ischemia (CLI) and TASC D lesions had poorer outcomes than claudicants and TASC C lesions.

Objective: The aim was to evaluate the safety and the efficacy of primary stenting with paclitaxel eluting stents for TASC C and D femoropopliteal lesions.

Methods: Patients with TASC C/D de novo femoropopliteal lesions were treated by implanting paclitaxel eluting stents. Patients were included in a single center registry and prospectively followed by clinical and ultrasound evaluation. X-ray of the stented zone was systematically performed 12 months after implantation. The primary endpoint was primary sustained clinical improvement after 12 months.

Results: A total of 45 patients (48 limbs) suffering from claudication (25 limbs) or CLI (23 limbs) were enrolled. Lesions were either TASC C (28 limbs) or TASC D (20 limbs). The mean length of the treated segment was 252 ± 90 mm. The mean number of stents was 2.9 ± 1 (2—5). Mean follow up was 12.7 months. No patient was lost to follow up. At 1 year post procedure, primary and secondary sustained clinical improvements were 56.3 ± 7.4% and 80.1 ± 5.9% respectively. Freedom from target lesion and target extremity revascularization were 63.6% and 90.1%, respectively. Primary and secondary patency rates were 52.5% and 79.6%. One year primary sustained clinical improvement rates for TASC C/D were 63.3 ± 9.2% and 45.6 ± 11.7%, respectively (p = .34). One year primary sustained clinical improvement rates for claudication/CLI patients were 68 ± 9.3% and 41.6 ± 11.1%, respectively (p = .13). The incidence of in stent re-stenosis and in stent thrombosis were 25% and 14%, respectively. The incidence of stent fracture was 12.5% on a limb basis and 9% on a per stent basis.

Conclusions: The paclitaxel eluting stent did not achieve its goal in terms of prevention of in stent re-stenosis for TASC C/D femoropopliteal lesions. It requires frequent re-interventions during the first year to maintain satisfactory clinical results.

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INTRODUCTION
Indications for endovascular treatment of femoropopliteal lesions have been steadily increasing over the past decade. Recent studies have shown that even the most challenging lesions are successfully treated, with technical success rates up to 95%. An increasing number of tools are continuously enriching the armamentarium of endovascular specialists, and require regular updates to the available evidence. Previous studies have established the superiority of bare and paclitaxel eluting stents (PES) over plain balloon angioplasty (POBA) for the Trans-Atlantic Inter-Society Consensus Document II on Management of Peripheral Arterial Disease (TASC) A/B femoropopliteal lesions. However, treatment of more challenging femoropopliteal lesions such as TASC C/D is still unresolved. Implantation of the latest generation of nitinol stents for femoropopliteal long lesions has given promising results. However, in stent re-stenosis remains a major concern after femoropopliteal stent implantation, with in stent re-stenosis occurring in up to 37%. In this perspective, PES
represents an interesting technology for the treatment of long femoropopliteal lesions. Herein, the 1 year outcomes of a single center prospective registry assessing the safety and the efficacy of PES in the treatment of TASC C/D femoropopliteal lesions are reported.

**METHODS**

**Study design**

STEnting Long de L’Artère fémorale superficielle par Zilver-PTX (STELLA-PTX) is a single center, prospective registry in which patients presenting with femoropopliteal TASC C/D de novo lesions were included between March 2011 and April 2012. Endovascular treatment by primary stenting was considered as a first line treatment. This registry was established as a pilot study to determine the safety and the feasibility of drug eluting stents for TASC C/D femoropopliteal lesions. As a result, no size calculations were made prior to the start of the study, but all the patients treated over a 1 year period were included. Inclusion and exclusion criteria are summarized in the Supplementary data. Patients had either one or two limbs treated in this study. The protocol was approved by the local ethics committee and all patients gave their informed consent.

**Endpoints and definitions**

The primary endpoint was primary sustained clinical improvement at 12 months.

Secondary endpoints were secondary sustained clinical improvement, primary and secondary patency, technical success, minor and major complications, MACE, limb salvage, target lesion revascularization (TLR), target extremity revascularization (TER), in stent re-stenosis (ISR), in stent thrombosis, and stent fracture. Detailed definitions of outcomes are as follows.

Primary sustained clinical improvement was defined as a sustained upward shift of the \( \geq 1 \) category of the Rutherford classification for claudicants and by wound healing and resolution of rest pain for patients with critical limb ischemia (CLI), without the need for repeated TLR in surviving patients. Secondary sustained clinical improvement was defined as a sustained upward shift of \( \geq 1 \) category of the Rutherford classification for claudicants and by wound healing and resolution of rest pain for patients with CLI, including the need for repeated TLR in surviving patients. Primary patency was defined as patency without any percutaneous or surgical re-intervention in the treated segment or in the adjacent areas. Technical success was defined as achievement of a final residual diameter stenosis of \(<30\%\) on the procedural completion angiogram. Minor complications are those following the procedure (within the first month) and not requiring further treatment and not extending hospital stay. Major complications refer to complications occurring during the first month following the procedure and requiring re-intervention or delay (more than 24 hours) in patient discharge. Major cardiovascular events included all deaths, major amputation, procedure related serious adverse events, and device failure or malfunction.

Target lesion revascularization expresses the frequency of the need for repeated procedures to endovascular or surgical due to a problem arising from the lesion \((\pm 1 \text{ cm proximally and distally to include edge phenomena})\) in surviving patients with preserved limb. Target extremity revascularization expresses the frequency of the need for repeated procedures (endovascular or surgical) due to a problem arising remotely from the lesion initially treated in surviving patients with a preserved limb. In stent re-stenosis was assessed by duplex ultrasound and was defined by stenosis of more than 50% and by a peak systolic velocity index greater than 2.4 at the target lesion. The diagnosis of stent thrombosis was considered when a complete occlusion was seen on duplex scan without any previous sign of re-stenosis. The occurrence of stent fracture was determined by biplanar radiography at 12 months. Stent fractures were classified according to the Jaff et al. classification.

**Follow up**

Patients were prospectively followed up on an outpatient basis. Major adverse clinical events (MACE) and treatment observations were intentionally sought. Follow up included medical examination, ankle brachial index (ABI) measurements and duplex scan at 1, 3, 6, 9, 12, and 18 months, and annually thereafter. Stent fractures were assessed by biplanar X-rays at 12 months with two different projections separated by at least 45\(^\circ\) using the highest available magnification.

**Statistical analysis**

Statistical analysis results were reported prospectively on an intention to treat basis and analyzed. Continuous variables
were presented as mean ± SD, categorical variables as count and percentages. Demographic and comorbidity data were recorded per patient and patency data were calculated on a per limb basis. Survival rate curves for outcomes were plotted and calculated using the Kaplan—Meier method. The timing of events (primary sustained clinical improvement) was analyzed with a univariate Cox proportional hazards model to assess the specific effect of each predictor. For patients who died before the final follow up examination or for patients lost to follow up, the status of the last follow up examination was recorded. In stent restenosis at 12 months was analyzed with univariate logistic models. A p value < .05 was considered statistically significant. Data were analyzed using the SPSS software (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients’ characteristics and demographics

A total of 45 patients (48 limbs) were enrolled. The baseline characteristics of the study population are described in Table 1. During the 1 year inclusion period, 481 infrainguinal revascularizations (67 open surgery and 414 endovascular) were performed in the center.

Intra- and peri-operative data

Indications for intervention included 25 limbs for claudication and 23 limbs for CLI. Twenty-eight limbs were classified as TASC C and 20 limbs as TASC D. The mean length of the treated lesions was 252 ± 90 mm and the total stenting length was 291 ± 98 mm. A mean number of 2.9 ± 0.8 (2–5) stents per limb were implanted. Concomitant endovascular treatment was performed for 21 limbs. Details of these procedures are given in Table 2. No death occurred within the 30 days of the procedure. During the peri-operative period, five major complications were observed: one in stent thrombosis occurred in a patient presenting with CLI (Rutherford 6 at baseline) that required a major amputation after a failed attempt at fibrinolysis. Four puncture site hematomas were noted and required an extension of hospital stay without re-intervention. Two minor amputations were performed during the first month. The average length of hospital stay was 4.9 days (0–42). Nine limbs were treated as day case vascular procedures. In these cases, an arterial femoral closure device (Angioseal 6F, St Jude Medical) was used. Five patients stayed longer than 20 days due to extensive ulcers that required prolonged care.

Subgroup analysis showed that CLI patients were significantly older (p ≤ 0.001), more frequently women (p = .04) and smokers (p = .004) than intermittent claudication (IC) patients. Patients with CLI also more frequently presented with TASC D lesions than claudicants (p = .01). Treatment of TASC D lesions required the use of more stents than TASC C lesions (p = .01).

Follow up

The mean follow up time was 12.7 months (range 12–26 months). No patient was lost to follow up. Four patients died during the follow up period. The 1 year primary and secondary sustained clinical improvement rates were 56.3 ± 7.4% and 80.1 ± 5.9%, respectively (Fig. 1A). The mean Rutherford indices at baseline and at 12 months were

Table 1. Demographic data.

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<tr>
<th></th>
<th>All patients (n = 45)</th>
<th>IC (n = 25)</th>
<th>CLI (n = 23)</th>
<th>P</th>
<th>TASC C (n = 28)</th>
<th>TASC D (n = 20)</th>
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<td>60 ± 7</td>
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<td>68 ± 13</td>
<td>67 ± 13</td>
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<td>4</td>
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<td>.63</td>
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<td>ABI (mean ± SD)</td>
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<td>0.64 ± 0.13</td>
<td>0.54 ± 0.15</td>
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<td>0.65 ± 0.12</td>
<td>0.52 ± 0.12</td>
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</table>

Note. All patients: n = 45, All limbs: n = 48. ABI = ankle brachial index; CAD = coronary arterial disease; CLI = critical limb ischemia; CVD = cerebrovascular disease; IC = intermittent claudication; TASC = Trans-Atlantic Inter-Society Consensus Document II on Management of Peripheral Arterial Disease.
4.1 ± 1.0 and 0.8 ± 1.3, respectively (p < .001) (Fig. 1B). Failure to improve clinical status was observed in six limbs. Subgroup analysis yielded a 1 year primary clinical improvement of 63.3 ± 9.2% for TASC C lesions and of 45.6 ± 11.7% for TASC D lesions (p = .34) (Fig. 2A). Secondary sustained clinical improvement rates were 85.1 ± 6.9% and 72.5 ± 10.6% for TASC C and D lesions, respectively (p = .03) (Fig. 2B). Focusing on clinical presentation, patients presenting with IC at baseline had a 1 year primary sustained clinical improvement rate of 68 ± 9.3% compared with 41.6 ± 11.1% for CLI patients (p = .13) (Fig. 2B). Finally, the corresponding secondary clinical improvement rates were 91.8 ± 5.5% and 65.9 ± 10.7%, respectively (p = .03) (Fig. 2B).

The 1 year limb salvage rate of CLI patients was 97.3%. The mean ABI of the whole cohort increased from baseline levels from 0.69 ± 0.1 to 0.92 ± 0.2 at 1 month and 0.90 ± 0.2 at 1 year (p < .001). The number of implanted stents, smoking status and antiplatelet regimen were not found to influence clinical outcome at 12 month follow up. In contrast, there was a trend towards a worse outcome when large diameter stents (7 mm diameter vs. 5 and 6 mm diameter) were used (p = .05, HR, 7.3; CI 95% 0.97–54.35).

At 1 year, primary and secondary patency rates were 52.5% and 79.6%, respectively. During follow up, in stent thrombosis was noted in seven limbs and ISR in 12 limbs. Amputation was necessary in one patient. Medical treatment with a daily walking program and strict clinical surveillance was chosen for two patients. The last four patients were symptomatic. Two patients underwent a venous femoropopliteal bypass and two patients an additional endovascular procedure.

Of the 12 cases of ISR, eight patients presented with symptom recurrence and four patients were asymptomatic. In asymptomatic patients, ISR were considered as threatening vessel patency in three cases. A total of 11 redo procedures, all endovascular, were performed. Only two patients were considered not improved at the 12 month follow up. Accordingly, TLR and TER free cumulative survival rates were 64% and 90%, respectively. All patients received at least one antiplatelet agent for the first 12 months and 50% of them were on both aspirin and clopidogrel for the first 6 months.

Complete X-ray follow up was obtained for 29 treated limbs. Eighty-nine stents were analyzed and eight fractures (4 type II and 4 type IV) were noted.
DISCUSSION

In this prospective registry, it has been shown that PES did not achieve their objective in terms of prevention of in stent re-stenosis for long femoropopliteal TASC C/D lesions. Although not recorded in this study, technical success was close to 90% as reported previously. Numerous re-interventions were required, however, to treat ISR and to maintain clinical improvement despite paclitaxel release. Moreover, there was a trend toward worse clinical improvement and patency in CLI patients and TASC D femoropopliteal lesions.

Paclitaxel eluting stents and TASC C/D femoropopliteal lesions

Few studies evaluating PES for TASC C/D femoropopliteal lesions are available. The largest registry using the Zilver-PTX PES included 135 limbs and was published in 2013. One hundred and thirty five limbs were included. Of note, no clinical data (Rutherford stage and TASC C/D status) were provided. More recently, Zeller et al. have published a comparison between PES (Zilver-PTX) and paclitaxel eluting balloons (IN.PACT balloons, Medtronic Vascular, Roncadelle, Italy) based on the treatment of 239 patients. The 97 PES patients had lesions averaging 195.0 ± 64.5 mm (range 100–350 mm) in length with only 7.2% of the patients presenting with CLI. The main limitation of this study was the heterogeneity of the lesions, which were very heterogeneous since de novo (55.7%), re-stenotic (44.3%) and short lesions <10 cm were included. In 2014, Leopardi et al. published an evaluation of the effectiveness of Zilver-PTX for long femoropopliteal lesions. Again, the main drawback of this cohort was the heterogeneity of the treated lesions, with only 47.8% de novo lesions, and a short follow up of 5.3 months.

Patency and re-intervention

In STELLA PTX, primary and secondary patency rates at 1 year were 52.5% ± 7.6 and 79.6% ± 6.1%. The differences observed here contrast with the results of the Zilver PTX randomized controlled trial (1 year primary patency rate of 83.1% for PES) and highlights the specific feature of TASC C/D lesions. These patency results are also much lower than those of the Zilver PTX single arm registry (77.6% of primary patency). In contrast, the 79.6% secondary patency is within the 77.6–83.1% range observed in the two other studies. When comparing a drug eluting balloon and PES, Zeller et al. reported a binary re-stenosis rate of 30.4% in the PES cohort and the clinically driven TLR rate was 19.0%.

Figure 1. Clinical outcomes. (A) Primary and secondary sustained clinical improvement. (B) Rutherford stages at baseline and 1 year.
The authors observed a lack of prevention of in stent re-stenosis in the PES group, which is similar to the findings here (25% of in stent re-stenosis at 1 year). The TLR rate was lower in the Zeller study (19%) than here (36%). It may result from the fact that in STELLA-PTX, re-interventions were not just required for the recurrence of symptoms, but also in asymptomatic cases threatening re-stenosis. The occurrence of in stent re-stenosis or in stent thrombosis was not found to be related to the prescription of one or two antiplatelet agents (data not shown).

Clinical improvement

Despite a high rate of re-interventions, clinical improvement was achieved. Indeed, at baseline, 23 limbs presented with CLI versus one 1 year later, and the 1 year limb salvage rate of CLI patients was 97.3%. Some authors have evoked the negative impact of failed endovascular treatment on subsequent bypasses, which has not been confirmed by recent reports. On the other hand, failure of bypass as a first line treatment has a poor prognosis too. Indeed, the 2 year limb salvage rate for occluded grafts performed for rest pain and tissue loss are 55% and 34%, respectively.

Stent fractures

Eight stent fractures at 1 year (12.5% on a limb basis and 9% on a stent basis) were reported, compared with 2.1% in the single arm Zilver PTX study (subgroup TASC C/D). Previous reports have suggested a positive association between the number of stents implanted and stent fractures due to stent overlap. The results here challenge this suggestion. Indeed, the maximum stent length available here was 120 mm compared with 80 mm in the Zilver PTX TASC C/D subgroup, and the mean number of corresponding stents was 2.9 and 3.4, respectively. A more likely explanation for the higher stent fracture rate observed here could be related to the high proportion of TASC D with popliteal artery involvement. Indeed, seven out of the eight stent fractures occurred in the femoropopliteal transition zone, suspected to be critical in terms of material fatigue and stress.

Study limitations

The main limitations of this study were the absence of a control group and the relatively small patient sample size. The inclusion of patients in this study was influenced by certain criteria such as the ability to cross the target lesion.
with a guidewire and the presence of inflow and outflow lesions. Consequently, the conclusions of this study do not apply to these lesion subgroups and, in particular, to highly calcified lesions, which are predictive of technical failure. In 43% of the cases, concomitant endovascular procedures were performed to improve inflow or inflow. These procedures had an impact on the outcome of the femoral stenting, and this constitutes a potential bias in the assessment of clinical improvement. A subjective clinical scale to evaluate clinical status was used, and a quality of life questionnaire was not used. Moreover, no objective measure of a patient mobility, such as the treadmill test, was included.

To conclude, this registry confirms that endovascular repair may be considered as a first line of treatment for TASC C/D femoropopliteal lesions. The PES did not achieve its goal in terms of prevention of in stent re-stenosis for TASC C/D femoropopliteal lesions. It requires frequent re-interventions during the first year to maintain satisfactory clinical results. Besides, it appears that CLI and TASC D lesions had poorer outcomes than claudicians and TASC C lesions, respectively. Endovascular treatment modalities for long femoropopliteal lesions should be evaluated further.

CONFLICT OF INTEREST
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APPENDIX A. SUPPLEMENTARY DATA
Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejvs.2015.07.018

REFERENCES