Treatment of Femoropopliteal In-Stent Restenosis With Paclitaxel-Eluting Stents

Thomas Zeller, MD,* Michael D. Dake, MD,† Gunnar Tepe, MD,‡ Klaus Brechel, MD,‡ Elias Noory, MD,* Ulrich Beschorner, MD,* Patricia L. Kultgen, PtD,§ Aljoscha Rastan, MD*
Bad Krozingen and Rosenheim, Germany; Stanford, California; and West Lafayette, Indiana

Objectives This study sought to evaluate the outcomes of drug-eluting stent treatment for femoropopliteal in-stent restenosis (ISR).

Background ISR after femoropopliteal interventions is an increasing problem. Although the role of drug-eluting stents in the treatment of coronary ISR is well defined, no published studies have examined drug-eluting stents in the treatment of femoropopliteal ISR.

Methods This study examines 108 patients with 119 ISR lesions who were enrolled in the Zilver-PTX single-arm study, a prospective, multicenter clinical trial of 787 patients. All patients were treated with paclitaxel-eluting nitinol stents.

Results Mean patient age was 68.3 ± 9.4 years; 61.1% of patients were men. Mean lesion length was 133.0 ± 91.7 mm; 33.6% of lesions were >150 mm long and 31.1% of lesions were totally occluded. Procedural success was achieved in 98.2% of lesions with 2.1 ± 1.2 stents placed per lesion. Primary patency was 95.7% at 6 months and 78.8% at 1 year. Freedom from target lesion revascularization was 96.2% at 6 months, 81.0% at 1 year, and 60.8% at 2 years. Forty patients experienced major adverse events, exclusively target lesion revascularization. Before treatment, 81.1% of patients had Rutherford scores ≥3; at 2 years, 60.9% of patients had Rutherford scores ≤1. Both ankle brachial index and walking impairment questionnaire scores significantly improved following treatment. The 1-year fracture rate of stents used in ISR lesions was 1.2%. No significant risk factors associated with loss of patency were identified.

Conclusions Treatment of femoropopliteal ISR with paclitaxel-eluting stents results in favorable acute, midterm, and long-term outcomes. (Zilver PTX Global Registry [ZILVER-PTX]; NCT01094678) (J Am Coll Cardiol Intv 2013;6:274 – 81) © 2013 by the American College of Cardiology Foundation
Stent placement has become a standard treatment modality in peripheral vascular interventions. Randomized controlled studies using second-generation stents have shown superior technical and clinical outcomes over percutaneous transluminal angioplasty (PTA) in lesions of the superficial femoral and proximal popliteal arteries (1–5). Therefore, the Trans-Atlantic Inter-Society Consensus (TASC) II guidelines (6) favor endovascular approaches over surgical revascularization in femoropopliteal lesions ≤15 cm in length. However, in-stent restenosis (ISR) has been reported in 19% to 37% of femoropopliteal lesions treated with bare-metal stents within 1 year of treatment (2,3,5,7–10). Moreover, the risk of ISR increases with increasing lesion length (10–12).

The treatment of ISR in the femoropopliteal artery is 1 of the major remaining challenges of endovascular therapy because treatment modalities such as PTA and cutting balloon angioplasty have failed to provide acceptable midterm results (13,14). To avoid bypass surgery, alternative endovascular approaches are needed to achieve durable long-term results in the treatment of ISR, particularly in long lesions.

Drug-eluting stents, which are available globally, and drug-eluting balloons, which are available in Europe and Latin America, are established therapies for the treatment of coronary ISR (15–17) and may also be useful in the treatment of peripheral ISR. The ZILVER-PTX single-arm study investigated the performance of a paclitaxel-eluting nitinol stent in the superficial femoral and the above-the-knee popliteal arteries (18). This study had very broad inclusion criteria, which allowed for the treatment of patients with femoropopliteal ISR. Here we report the outcomes of patients with ISR lesions who were treated within the ZILVER-PTX single-arm study and compare the results with the current literature.

Methods

The ZILVER-PTX single-arm study is a prospective, multicenter clinical trial that enrolled 787 patients in Europe, Canada, and Korea between April 2006 and June 2008. A detailed description of the study and the 1-year outcomes for the entire cohort, as well as limited, preliminary results for the ISR subgroup, have been previously published (18,19). Approval was obtained from each site’s ethics committee, and patients provided written informed consent before enrollment. Patients were eligible for the study if they had ≥1 de novo or restenotic lesions of the above-the-knee segment of the femoropopliteal artery with >50% diameter stenosis and baseline clinical symptoms classified as Rutherford category ≥2. Patients could have multiple lesions requiring treatment, a history of prior stent placement within the lesion, bilateral lesions requiring treatment, and lesions of unlimited length. This report describes the 2-year results for patients who were treated for ISR. Patients treated for multiple lesion types (e.g., both de novo and ISR) were excluded from this analysis.

Study device. Patients were treated with the Zilver PTX drug-eluting stent (Cook Medical, Bloomington, Indiana), a nitinol stent with a polymer-free paclitaxel coating at 3 µg/mm² dose density. Pharmacokinetics of the device have been previously described (20). Available stents were 6 to 10 mm in diameter and 20 to 80 mm in length. Although lesions could be of unlimited length, the protocol specified planned treatment with a maximum of 4 Zilver PTX stents per patient. Placement of bare Zilver stents was allowed if additional stents were required. Pre- and post-dilation were performed at the interventionist’s discretion.

Medication. Clopidogrel was administered at least 24 h before the procedure or as a loading dose during the procedure. Following treatment, clopidogrel therapy was continued for ≥60 days and aspirin therapy was continued indefinitely. Heparin was administered periprocedurally if heparinization was part of an institution’s standard practice. Administered doses of all anticoagulants were based on the standard practice at each institution.

Pre- and post-procedural diagnostic workup. Prior to the procedure and at 1-, 6-, 12-, and 24-month follow-ups, patient-perceived walking speed and distance were assessed using the Walking Impairment Questionnaire (21), symptoms were categorized using the Rutherford-Becker classification, and lower limb hemodynamics were assessed with the ankle-brachial index. Stent integrity was assessed by radiography within 3 days after the procedure and at 6 and 12 months. Target lesion patency was assessed by angiography immediately after stent implantation. Duplex ultrasound was conducted within 3 business days of the procedure and at 6- and 12-month follow-up. Per protocol, duplex ultrasound assessment of lesion patency was not required after 12-month follow-up. Restenosis was confirmed by angiography before target lesion revascularization (TLR).

Definitions. Procedural success was defined as <30% residual diameter stenosis following stent placement. Patency was defined as <50% diameter stenosis, including the region within 5 mm proximal and/or distal to the target lesion as assessed by angiography or duplex ultrasound. For this analysis, a peak systolic velocity ratio <2.5 was used as the patency threshold. Clinically driven TLR was defined as a reintervention performed for >50% diameter stenosis within 5 mm of the target lesion after documentation of recurrent clinical symptoms of peripheral artery disease...
following the initial procedure. Event-free survival (EFS) was defined as freedom from major adverse events (e.g., procedure- or device-related death, clinically driven TLR, target limb ischemia requiring bypass surgery or amputation, and surgical repair of the target vessel) and freedom from worsening of Rutherford classification by ≥2 classes or to class 5 or 6.

**Statistics.** Continuous variables were summarized with means and standard deviations; categorical variables were summarized with counts and percentages. As appropriate, the number of observations is the number of patients, treated limbs, or implanted stents. Kaplan-Meier analyses were performed to estimate patency, freedom from TLR, and EFS over time. A paired t test was used to compare pre-procedure ankle brachial index and Walking Impairment Questionnaire values to the follow-up values. A generalized estimating equation model was used to evaluate the association between potential risk factors (e.g., diabetes, lesion length, smoking history, Rutherford classification, occlusion, calcification, lesion location, patent runoff vessels, fracture in prior stent, type of prior stent, days from previous intervention, number of previous interventions, proximal reference vessel diameter, and percentage of diameter stenosis) and 12-month patency; p values <0.05 were considered significant. Data were analyzed using SAS software (version 9.3, SAS Institute Inc., Cary, North Carolina).

**Results**

One hundred and eight patients with 119 ISR lesions of the femoropopliteal artery were treated with Zilver PTX drug-eluting stents. Most patients were male (61.1%), hypertensive (84.3%), hypercholesterolemic (74.1%), and had a history of smoking (81.5%) (Table 1). Mean lesion length was 133.0 ± 91.7 mm and 33.6% (40 of 119) of lesions were ≥150 mm long (Table 2). Most ISR lesions had little to no calcification (68.9%, 82 of 119); however, 31.1% (37 of 119) of the ISR lesions were totally occluded before treatment. Of the 119 ISR lesions, 8.4% (10 of 119) had severely fractured stents (i.e., type III or IV fracture, complete transection of stent) before Zilver PTX treatment, 22.7% (27 of 119) had been previously treated within the last 6 months since last intervention, and 51.3% (61 of 119) had undergone ≥2 previous interventions.

**Procedural outcomes.** Procedural success (i.e., <30% restenosis following stent placement) was achieved in 98.2% (112 of 114) of ISR lesions. Most patients were treated for a single lesion (91.7%, 99 of 108); 7 patients were treated for 2 lesions; and 2 patients were treated for 3 lesions. On average, 2.1 ± 1.2 stents were placed in each lesion.

### Table 2. Baseline Lesion Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ISR Lesions (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length, mm</td>
<td>133.0 ± 91.7</td>
</tr>
<tr>
<td>&gt;70</td>
<td>63.0 (75)</td>
</tr>
<tr>
<td>&gt;150</td>
<td>33.6 (40)</td>
</tr>
<tr>
<td>Proximal reference vessel diameter, mm</td>
<td>5.6 ± 0.7</td>
</tr>
<tr>
<td>Distal reference vessel diameter, mm</td>
<td>5.3 ± 0.8</td>
</tr>
<tr>
<td>Minimum lumen diameter, mm</td>
<td>0.7 ± 0.7*</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>87.0 ± 12.4*</td>
</tr>
<tr>
<td>TASC I class</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>22.7 (27)</td>
</tr>
<tr>
<td>B</td>
<td>28.6 (34)</td>
</tr>
<tr>
<td>C</td>
<td>26.9 (32)</td>
</tr>
<tr>
<td>D</td>
<td>16.0 (19)</td>
</tr>
<tr>
<td>Not assessed</td>
<td>5.9 (7)</td>
</tr>
<tr>
<td>Total occlusion</td>
<td>31.3 (37)</td>
</tr>
<tr>
<td>Calcification</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>12.6 (15)</td>
</tr>
<tr>
<td>Moderate</td>
<td>18.5 (22)</td>
</tr>
<tr>
<td>Little</td>
<td>33.6 (40)</td>
</tr>
<tr>
<td>None</td>
<td>35.3 (42)</td>
</tr>
<tr>
<td>Lesion location</td>
<td></td>
</tr>
<tr>
<td>Proximal SFA</td>
<td>23.5 (28)</td>
</tr>
<tr>
<td>Proximal SFA/distal SFA</td>
<td>29.4 (35)</td>
</tr>
<tr>
<td>Proximal SFA/distal SFA/popliteal</td>
<td>6.7 (8)</td>
</tr>
<tr>
<td>Distal SFA</td>
<td>32.8 (39)</td>
</tr>
<tr>
<td>Distal SFA/popliteal</td>
<td>5.9 (7)</td>
</tr>
<tr>
<td>Popliteal</td>
<td>1.7 (2)</td>
</tr>
<tr>
<td>Previous interventions, n</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>48.7 (58)</td>
</tr>
<tr>
<td>2</td>
<td>24.4 (29)</td>
</tr>
<tr>
<td>3</td>
<td>16.8 (20)</td>
</tr>
<tr>
<td>4–8</td>
<td>10.1 (12)</td>
</tr>
<tr>
<td>≤6 months since last intervention</td>
<td>22.7 (27)</td>
</tr>
<tr>
<td>Type III or IV fracture in previously placed stents</td>
<td>8.4 (10)</td>
</tr>
</tbody>
</table>

Values are mean ± SD or % (n). *Mean values for minimum lumen diameter and diameter stenosis are based on available data for 118 of 119 lesions.

ISR = in-stent restenosis; SFA = superficial femoral artery; TASC I = Trans-Atlantic Inter-Society Consensus 2000.
Lesion patency, TLR, and event-free survival. The Kaplan-Meier estimate of primary patency was 95.7% at 6 months and 78.8% at 12 months (Fig. 1). Per protocol, duplex ultrasound assessments of patency were not required after 12-month follow-up; however, clinical follow-up continued through 24 months. Kaplan-Meier estimates of freedom from clinically driven TLR at 6 and 12 months were similar to the patency estimates over the same period. Specifically, the Kaplan-Meier estimate of freedom from TLR was 96.2% at 6 months, 81.0% at 12 months, and 60.8% at 24 months (Fig. 2).

During the course of the study, major adverse events were experienced by 40 patients treated for ISR lesions. Thirty-eight patients each underwent a single TLR, and 2 patients each underwent 2 TLR; 50% of the revascularizations occurred within 12 months of treatment. No amputations or deaths occurred. Because all patients who failed EFS experienced a TLR, Kaplan-Meier estimates of freedom from EFS are identical to estimates of freedom from TLR (Fig. 2).

Multivariate analysis of risk factors for recurrent ISR. A generalized estimating equation model was used to evaluate the association between potential risk factors and loss of patency; however, no significant predictors of recurrent ISR were identified (Table 3).

Clinical outcomes. In addition to establishing vessel patency, treatment of ISR lesions with the Zilver PTX stent also provided clinical benefit to patients. Before treatment, 81.1% (86 of 106) of patients had Rutherford scores ≥3. After treatment, 63.2% (62 of 98) of patients at 12 months and 60.9% (53 of 87) of patients at 24 months had Rutherford scores ≤1. Significant improvements in limb hemodynamic status, as assessed by ankle brachial index, and in patient-perceived walking speed, walking distance, and climbing were also observed (Table 4).

Stent fracture rates. Based on x-ray data collected at the 12-month follow-up, the fracture rate of Zilver PTX stents used in ISR lesions was 1.2% (3 of 257).

Discussion

To date, the ZILVER-PTX single-arm study is the largest trial to prospectively investigate endovascular treatment of femoropopliteal ISR lesions. Of the 787 treated patients, 108 patients were treated for 119 ISR lesions. Treatment of ISR lesions with a paclitaxel-eluting stent had a primary patency estimate of 95.7% at 6 months and 78.8% at 12 months. Freedom from clinically driven TLR at 6 and 12 months was similar to the patency estimates over the same period. Compared with most other published reports of femoropopliteal ISR lesion treatment (13,14,22–27), treat-
ment of ISR lesions with paclitaxel-eluting stents resulted in higher midterm rates of primary patency (Table 5).

Notably, this is the first prospective study to report 2-year results for endovascular treatment of femoropopliteal ISR lesions. Although patency data were only systematically collected through 12-month follow-up, data on TLR, EFS, and other clinical outcomes were collected through 2 years. In this difficult-to-treat patient population, freedom from clinically driven TLR was 60.8% at 2 years. Although revascularization was required for some patients, the TLR procedures were predominantly percutaneous interventions (88%, 37 of 42) and no patients underwent amputation. These promising results are likely due to several advantageous features of the Zilver PTX stent, a self-expanding nitinol stent with a polymer-free paclitaxel coating. Local delivery of paclitaxel, a drug that disrupts normal microtubule function, may prevent neointimal hyperplasia by inhibiting smooth muscle cell migration, proliferation, and extracellular matrix secretion (28). Because low doses of paclitaxel can inhibit smooth muscle proliferation without inhibiting endothelial cell proliferation (29), local paclitaxel delivery may inhibit restenosis after endovascular interventions without preventing re-endothelialization. This mode of action may reduce the rate of subacute stent thrombosis. Additionally, unlike other drug-eluting stents, the Zilver PTX stent has no polymers, binders, or carriers within the drug coating that might elicit potential inflammatory or thrombotic reactions. Moreover, 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.

Few controlled prospective data are published about endovascular treatment of femoropopliteal ISR lesions. Dick et al. (13) performed a pilot trial randomly comparing PTA with cutting balloon angioplasty in femoropopliteal ISR lesions with a mean length of 8 cm. At 6 months, only 27% of PTA-treated lesions and 35% of cutting balloon-treated lesions were patent. In this small study, neither angioplasty method provided acceptable short-term outcomes. In a larger retrospective study by Tosaka et al. (14) that included 133 patients, PTA treatment of femoropopliteal ISR lesions resulted in 69% patency for stenosed lesions at 12 months; however, only 23% of treated occluded lesions were patent at 12 months.

The use of debulking strategies, such as laser atherectomy, directional atherectomy, and mechanical thrombectomy, for treatment of femoropopliteal ISR has been investigated in several case series (Table 5)(22–27,30,31). Supplemental PTA, stent, and/or stent-graft placement were often used adjunctively in these reported experiences. Most of the studies were small (treating 20 to 40 patients) and have reported 1-year primary patency rates ranging from 19% to 58%. Compared with available data on PTA alone or debulking strategies, the results of the Zilver-PTX single-arm study suggest that treatment of femoropopliteal ISR lesions with paclitaxel-eluting stents is quite promising.

The treatment of femoropopliteal ISR with endovascular brachytherapy has also been examined. In a retrospective case series, 90 consecutive patients underwent angioplasty and subsequent brachytherapy with liquid beta-emitting

<table>
<thead>
<tr>
<th>Potential Risk Factor</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>0.34</td>
</tr>
<tr>
<td>Lesion length</td>
<td>0.12</td>
</tr>
<tr>
<td>Smoking history</td>
<td>0.75</td>
</tr>
<tr>
<td>Rutherford classification</td>
<td>0.27</td>
</tr>
<tr>
<td>Total occlusion</td>
<td>0.80</td>
</tr>
<tr>
<td>Extent of calcification</td>
<td>0.18</td>
</tr>
<tr>
<td>Lesion location</td>
<td>0.67</td>
</tr>
<tr>
<td>Number of patent runoff vessels</td>
<td>0.77</td>
</tr>
<tr>
<td>Fracture in prior stent</td>
<td>0.55</td>
</tr>
<tr>
<td>Type of prior stent</td>
<td>0.53</td>
</tr>
<tr>
<td>Days from previous intervention to Zilver PTX treatment</td>
<td>0.70</td>
</tr>
<tr>
<td>Number of previous interventions</td>
<td>0.24</td>
</tr>
<tr>
<td>Proximal reference vessel diameter</td>
<td>0.52</td>
</tr>
<tr>
<td>Percentage of diameter stenosis</td>
<td>0.34</td>
</tr>
</tbody>
</table>
rhenium Re 188 (32). Similar to the results of the ZILVER-PTX single-arm study, primary patency was 95.2% at 6 months and 79.8% at 12 months. However, the utility of brachytherapy may be limited due to the time-consuming nature of the procedure, complex radiation safety measurements, and staffing requirements. Additionally, patients with stent fracture were excluded from brachytherapy treatment due to the potential risk of balloon rupture. In contrast, patients with stent fracture may be treated with the Zilver PTX stent.

### Table 4. Clinical Outcomes

<table>
<thead>
<tr>
<th>Clinical Measure</th>
<th>Pre-Procedures</th>
<th>6 Months</th>
<th>12 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI per limb</td>
<td>0.60 ± 0.28 (100)</td>
<td>0.87 ± 0.25* (102)</td>
<td>0.87 ± 0.28* (99)</td>
<td>0.84 ± 0.22* (87)</td>
</tr>
<tr>
<td>Median Rutherford score</td>
<td>3 (106)</td>
<td>0 (97)</td>
<td>0 (98)</td>
<td>1 (87)</td>
</tr>
<tr>
<td>Walking speed score</td>
<td>33 ± 28 (91)</td>
<td>62 ± 30* (94)</td>
<td>58 ± 32* (92)</td>
<td>63 ± 32* (87)</td>
</tr>
<tr>
<td>Walking distance score</td>
<td>27 ± 26 (93)</td>
<td>66 ± 34* (99)</td>
<td>68 ± 33* (95)</td>
<td>63 ± 37* (88)</td>
</tr>
<tr>
<td>Climbing score</td>
<td>37 ± 29 (86)</td>
<td>66 ± 33* (94)</td>
<td>65 ± 31* (92)</td>
<td>67 ± 34* (83)</td>
</tr>
</tbody>
</table>

Values are mean ± SD (n), unless otherwise noted. Walking and climbing scores were obtained from the Walking Impairment Questionnaire, a validated measure of patient-perceived walking performance. Patient responses are weighted and the weighted average is reported with a maximum possible score of 100% in each category. *Value differed significantly from pre-procedure (p < 0.001), as calculated by paired t test.

### Table 5. Comparison of Published Primary Patency and TLR Rates Following Treatment of Femoropopliteal ISR

<table>
<thead>
<tr>
<th>Study/First Author (Ref. #)</th>
<th>Treatment</th>
<th>Patients, n</th>
<th>Lesions, n</th>
<th>Lesion Length, mm</th>
<th>Primary Patency 6 Months</th>
<th>12 Months</th>
<th>24 Months</th>
<th>Freedom From TLR 6 Months</th>
<th>12 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZILVER-PTX single-arm study</td>
<td>Zilver PTX stent</td>
<td>108</td>
<td>119</td>
<td>133 ± 92</td>
<td>96%</td>
<td>79%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>96%</td>
</tr>
<tr>
<td>Tosaka et al. (14)</td>
<td>PTA</td>
<td>133</td>
<td>133</td>
<td>91 ± 67 for stenoses 198 ± 62 for occlusions</td>
<td>—</td>
<td>69%</td>
<td>48%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dick et al. (13)</td>
<td>PTA</td>
<td>22</td>
<td>22</td>
<td>74 ± 65</td>
<td>27%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>64%</td>
</tr>
<tr>
<td>Shammas et al. (30)</td>
<td>Directional atherectomy; adjunctive PTA and stenting in some cases</td>
<td>41</td>
<td>41</td>
<td>126 ± 79</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>66%</td>
</tr>
<tr>
<td>Trentmann et al. (24)</td>
<td>Directional atherectomy; adjunctive PTA and stenting for some cases</td>
<td>33</td>
<td>35</td>
<td>141 ± 81</td>
<td>68%*</td>
<td>25%*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Zeller et al. (26)</td>
<td>Directional atherectomy</td>
<td>—</td>
<td>43</td>
<td>131 ± 111</td>
<td>—</td>
<td>54%</td>
<td>49% at 18 months</td>
<td>—</td>
<td>53%</td>
<td>51% at 18 months</td>
</tr>
<tr>
<td>Shammas et al. (31)</td>
<td>Laser atherectomy + PTA; adjunctive stent</td>
<td>40</td>
<td>—</td>
<td>210 ± 104</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>49%</td>
<td>—</td>
</tr>
<tr>
<td>Laird et al. (22)</td>
<td>Laser atherectomy, PTA, and heparin-coated stent graft</td>
<td>27</td>
<td>—</td>
<td>207 ± 103</td>
<td>—</td>
<td>48%</td>
<td>—</td>
<td>—</td>
<td>83%</td>
<td>—</td>
</tr>
<tr>
<td>Yeo et al. (25)</td>
<td>Laser atherectomy, angioplasty, excisional atherectomy, and/or cryoablation</td>
<td>20</td>
<td>22 limbs</td>
<td>132 ± 113</td>
<td>55%</td>
<td>48%</td>
<td>—</td>
<td>—</td>
<td>77%</td>
<td>—</td>
</tr>
<tr>
<td>Silingardi et al. (23)</td>
<td>Rotational thrombectomy and PTA</td>
<td>32</td>
<td>32 limbs†</td>
<td>160</td>
<td>75%</td>
<td>58%</td>
<td>—</td>
<td>—</td>
<td>47%‡</td>
<td>—</td>
</tr>
<tr>
<td>Zeller et al. (27)</td>
<td>Rotational thrombectomy and PTA</td>
<td>40</td>
<td>40</td>
<td>—</td>
<td>46%</td>
<td>19%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Werner et al. (32)</td>
<td>PTA and brachytherapy</td>
<td>90</td>
<td>—</td>
<td>246 ± 122</td>
<td>95%</td>
<td>80%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stabile et al. (33)</td>
<td>Paclitaxel-eluting balloon; adjunctive stent and laser atherectomy</td>
<td>39</td>
<td>—</td>
<td>83 ± 79</td>
<td>—</td>
<td>92%</td>
<td>—</td>
<td>—</td>
<td>92%</td>
<td>—</td>
</tr>
</tbody>
</table>

For this analysis of the ZILVER-PTX single-arm study, PSVR < 2.5 was used as the patency threshold. Patency was defined as duplex ultrasound PSVR < 2.5 by Trentmann et al. (24); < 2.4 by Dick et al. (13), Zeller et al. (26), Werner et al. (32), and Stabile et al. (33); and < 2.0 by Yeo et al. (25) and Laird et al. (22). Tosaka et al. (14) defined patency as < 2.4 PSVR by duplex ultrasound or < 50% stenosis by angiography. Silingardi et al. (23) and Zeller et al. (27) did not provide a PSVR patency threshold in their reports. Dashes indicate data were unavailable. *Data only available for 25 lesions at 6 months and 17 lesions at 12 months. †Six iliac and 26 femoropopliteal arteries. ‡Mean follow-up of 13.1 months (range 3 to 45 months). ISR = in-stent restenosis; PSVR = peak systolic velocity ratio; PTA = percutaneous transluminal angioplasty; TLR = target lesion revascularization.
There is also much interest in the potential role of drug-eluting balloons in the treatment of femoropopliteal ISR. One small study of 39 patients reported an impressive 1-year primary patency rate of 92.1% (33). However, 10% of patients also underwent laser-mediated debulking, and 10% of patients required bailout stent placement to treat flow-limiting dissection. Therefore, the patency rate cannot be attributed to the effects of the drug-eluting balloon alone. Additional investigation is necessary, and several ongoing randomized controlled trials are comparing drug-eluting balloons to uncoated balloons for the treatment of femoropopliteal ISR.

Previously, Tosaka et al. (14) identified total occlusion and reference vessel diameter as independent, predictive factors for recurrent ISR following PTA treatment of femoropopliteal ISR. Additionally, in a study that treated femoropopliteal restenosis with angioplasty and stenting, treatment within 180 days of the initial endovascular intervention was identified as a significant predictor for recurrent restenosis (34). In contrast, of the 14 risk factors considered (Table 3), none was predictive for recurrent ISR following treatment with a paclitaxel-eluting stent in this study.

Study limitations. This study lacked a control group. However, the 12-month patency rate for the ISR lesions was only slightly lower than the patency rate for the entire ZILVER-PTX single-arm trial (78.8% vs. 86.2%), which included 76.7% de novo lesions (18). Furthermore, all angiography and duplex ultrasound data are self-reported by sites, and no core laboratory was used to standardize data. Although these results are promising, head-to-head comparative studies are necessary to determine whether the Zilver PTX stent is more effective than other endovascular modalities for treatment of femoropopliteal ISR.

Future perspectives. Several ongoing randomized controlled trials are comparing drug-eluting balloons to uncoated balloons for treatment of femoropopliteal ISR (ISAR-PEBIS [Paclitaxel Eluting Balloon and Conventional Balloon for In-Stent Restenosis of the Superficial Femoral Artery], FAIR [Femoral Artery In-Stent Restenosis Trial], PACUBA I [Paclitaxel Balloon Versus Standard Balloon in In-Stent Restenoses of the Superficial Femoral Artery], COPA CABANA [Cotavance Paclitaxel-Coated Balloon Versus Uncoated Balloon Angioplasty for Treatment of In-stent Restenosis in SFA and Popliteal Arteries], PLAISIR [Paclitaxel Eluting Balloon Application in SFA In-Stent Restenosis], and DEBATE-ISR [Drug Eluting Balloon in Peripheral Intervention for In-Stent Restenosis]). Additionally, other trials are investigating the performance of the Viabahn endoprosthesis (RELINE [Gore Viabahn Versus Plain Old Balloon Angioplasty for Superficial Femoral Artery Restenosis]), drug-coated balloons with and without prior photoablation (PHOTOPAC [Photoablative Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis in In-Stent Femoro-Popliteal Obstructions]), laser atherectomy with PTA (EXCITE ISR [Randomized Study of Laser and Balloon Angioplasty Versus Balloon Angioplasty to Treat Peripheral In-Stent Restenosis]), and photoablation alone (PATENT [Photo-Ablation using the TURBO-Booster and Excimer Laser for In-stent Restenosis Treatment]) for treatment of femoropopliteal ISR.

Conclusions

The subcohort of the ZILVER-PTX single-arm trial is to date the largest prospective investigation of the midterm and long-term outcomes of femoropopliteal ISR lesions following endovascular treatment. Stent-in-stent placement of a paclitaxel-eluting stent results in promising 1- and 2-year clinical outcomes with a low stent fracture rate.

Acknowledgments

The authors thank Shraddha Mehta, PhD, and Alan Saunders, MS, of MED Institute Inc. (a Cook Group Company) for serving as study statisticians and Tony Ragheb, PhD, and Aaron Lottes, PhD, of MED Institute Inc. for providing critical review of the manuscript.

Reprint requests and correspondence: Prof. Dr. Thomas Zeller, Universitäts-Herzzentrum Freiburg–Bad Krozingen, Südring 15, D-79189 Bad Krozingen, Germany. E-mail: thomas.zeller@universitaets-herzzentrum.de.

REFERENCES


Key Words: drug-eluting stent(s) ■ femoral artery ■ in-stent restenosis ■ paclitaxel ■ peripheral occlusive artery disease ■ revascularization.