Primary Everolimus-Eluting Stenting Versus Balloon Angioplasty With Bailout Bare Metal Stenting of Long Infrapopliteal Lesions for Treatment of Critical Limb Ischemia

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Purpose: To report the long-term outcomes of a single-center prospective study investigating primary placement of everolimus-eluting metal stents for recanalization of long infrapopliteal lesions compared to a matched historical control group treated with plain balloon angioplasty and provisional placement of bare metal stents in a bailout manner.

Methods: The study included 81 patients (63 men; mean age 71 years, range 45–85) suffering from critical limb ischemia (CLI) and angiographically proven long-segment (at least 1 lesion >4.5 cm) de novo infrapopliteal artery disease who underwent below-the-knee revascularization with either primary placement of everolimus-eluting stents (n=47, 51 limbs, 102 lesions) or angioplasty and bailout bare metal stenting (n=34, 36 limbs, 72 lesions). Clinical and angiographic follow-up was collected at regular time intervals. Primary clinical and angiographic endpoints included patient survival, major amputation-free survival, angiographic primary patency, angiographic binary restenosis (>50%), and overall event-free survival. Results were stratified according to endovascular treatment received. Multivariable Cox proportional hazards regression analysis was applied to adjust for confounding factors of heterogeneity.

Results: Baseline demographics were well matched. No significant differences were identified between the 2 groups with regard to overall 3-year patient survival (82.2% versus 65.7%; p=0.90) and amputation-free survival (77.1% versus 86.9%; p=0.20). Up to 3 years, lesions fully covered with everolimus-eluting stents were associated with significantly higher primary patency [hazard ratio (HR) 7.98, 95% CI 3.69 to 17.25, p<0.0001], reduced binary restenosis (HR 2.94, 95% CI 1.74 to 4.99, p<0.0001), and improved overall event-free survival (HR 2.19, 95% CI 1.16 to 4.13, p=0.015) versus the matched historical control group.

Conclusion: Primary infrapopliteal everolimus-eluting stenting for CLI treatment significantly inhibits restenosis and improves long-term angiographic patency and overall patient event-free survival compared to balloon angioplasty and bailout bare metal stenting.

J Endovasc Ther. 2011;18:1–12

The authors have no commercial, proprietary, or financial interest in any products or companies described in this article.

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Given the perioperative morbidity and mortality of femorodistal surgical bypass, lack of proper vein conduit, advent of low-profile interventional instruments, and increasing technical expertise of endovascular specialists, percutaneous angioplasty of the tibial arteries has evolved to the mainstream therapy for below-the-knee arterial occlusive disease. Infrapopliteal angioplasty is now an established cornerstone treatment for the extensive infrapopliteal arterial obstructions typically associated with critical limb ischemia (CLI), especially in patients with diabetes or on dialysis.

The enthusiastic results of drug-eluting stents (DES) in the coronary arteries was the impetus for the widespread application of these devices in other vascular territories, including but not limited to the intracranial, renal, and infrainguinal arteries. Amassed experience with infrapopliteal placement of DES has shown great promise for the treatment of below-the-knee arterial occlusive disease. Following encouraging short-term results, investigators have documented significant inhibition of restenosis, with sustained clinical improvement and significantly fewer repeat revascularizations up to 3 years postimplantation.

Primary stenting has been proposed by interventional cardiologists as an alternative approach of endovascular recanalization, with a view to eliminating abrupt vessel closure and thrombosis, limiting negative vessel wall remodeling, and preventing distal microembolization that may result in the no-reflow phenomenon. In parallel, full lesion coverage with drug-eluting stents is more effective in inhibiting neointimal hyperplasia and avoiding the “candy-wrapper” in-segment restenosis of bare metal spot stenting. In fact, the current practice of percutaneous coronary interventions involves primary drug-eluting stenting in the majority of cases, especially in the diabetic patient subset.

Published data of below-the-knee DES is limited to controlled or cohort studies involving relatively short lesions up to 4 cm. However, the diffuse, multilevel nature of below-the-knee occlusive disease usually mandates extensive revascularization procedures to achieve at least one straight line of blood flow to the foot. We herein report the long-term clinical and angiographic outcomes of a single-center prospective study comparing primary placement of everolimus-eluting metal stents for recanalization of long (≥4.5 cm) infrapopliteal lesions in CLI patients to a matched historical control group from the same center treated with plain balloon angioplasty and provisional placement of bare metal stents in a bailout manner.

**METHODS**

**Study Design**

In December 2006, a prospective study was begun to evaluate the primary infrapopliteal application of balloon-expandable cobalt-chromium everolimus-eluting stents (XIENCE V Everolimus Eluting Coronary Stent System [Abbott Vascular, Santa Rosa, CA, USA] and PROMUS Everolimus-Eluting Coronary Stent System [Boston Scientific Corporation, Natick, MA, USA]) as a limb salvage therapy in patients with CLI. The study was approved by the institutional review board of the hospital’s Ethical and Scientific Committee. The nature and purpose of the study protocol were explained to all patients, who signed a written informed consent form.

The primary inclusion criteria for the Xience-Promus group (XP group) were (1) atherosclerotic disease manifesting symptoms of CLI (Rutherford stage 4–6) and (2) identification of at least 1 hemodynamically significant (≥70% by visual estimation) infrapopliteal stenosis or occlusion ≥4.5 cm long documented by either digital subtraction angiography (DSA) or computed tomographic angiography. Exclusion criteria were lifestyle-limiting intermittent claudication, acute limb ischemia, Buerger disease, deep vein throm-
basis, infected tissue loss, a history of severe contrast allergy or hypersensitivity, intolerance to aspirin and/or clopidogrel, systemic coagulopathy, or hypercoagulation disorders.

To obtain a control group for comparison with the treatment group on defined covariates, a retrospective search of the hospital’s database was performed to obtain a matched group of patients undergoing plain balloon angioplasty with provisional placement of bare metal stents in a bailout manner. Matches were extracted from a pool of patients constituting historical groups of previously published data. The applied selection criteria were designed to identify patients suffering from CLI attributed to infrapopliteal atherosclerotic disease with baseline variables and lesions comparable to the study group. The basic criterion for matching was the lesion length: at least 1 infrapopliteal lesion ≥4.5 cm long treated with percutaneous angioplasty and bailout stenting. All the previously mentioned inclusion and exclusion criteria valid for the XP group were applied to achieve a homogeneous, appropriately matched control cohort (group C).

Medical history and clinical assessment were the sources of baseline demographics, initial patient clinical status, and Rutherford classification. Procedural variables and morphological details of the treated lesions were registered at baseline for the treatment group and extracted from the medical records of the control group.

**Procedural Technique**

All patients were premedicated with aspirin (100 mg/d) and clopidogrel (75 mg/d) for 3 days before the procedure. A femoral artery access (preferably antegrade, but also retrograde) was obtained, and a bolus dose (3000–5000 units) of unfractionated heparin was administered immediately after sheath placement; heparin infusion (~1000 U/h) was continued during the procedure. Typical endovascular techniques with a variety of guidewires and catheters were used to cross the lesion as necessary. In all cases, stent size was chosen according to reference vessel diameter on visual estimate, and stents were placed primarily with or without undersized balloon predilation. All lesions over 33 mm were treated with tandem stents in an overlapping manner (overlap ≤5 mm). Primary full lesion coverage with an everolimus-eluting metal jacket was the goal of treatment. In the historical control group, stenting was performed after suboptimal angioplasty for bailout in case of elastic recoil, postdilation residual stenosis >30%, or severe flow-limiting dissection (type C). Inflow femoropopliteal lesions were treated as necessary in both groups. A detailed description of the rest of the procedure in the control group may be found elsewhere. Patients were discharged with a routine 6-month prescription for dual antiplatelet therapy (75 mg/d clopidogrel and 100 mg/d aspirin), followed by lifelong sole clopidogrel or aspirin therapy.

**Follow-up Protocol**

Prospective follow-up included regular patient visits at 3, 6, and 12 months and yearly after the index intervention for clinical assessment, whereas imaging with selective DSA was performed at 6 and 12 months and yearly thereafter unless clinical recurrence of peripheral artery disease dictated otherwise. Patient mobility status was examined, and all angiographic endpoints were evaluated with intra-arterial DSA.

**Endpoints and Definitions**

Primary clinical endpoints included overall patient survival, minor amputations, target lesion revascularizations (TLR), and limb salvage reported as amputation-free survival. Below-the-knee TLR events were clinically driven by recurrent leg ischemia and are reported as TLR-free survival. Event-free survival was defined as a composite endpoint including freedom from death, major or minor amputation, and any repeat endovascular or surgical revascularization above or below the knee in the index limb involving either the target lesions or any other new lesion.

Primary angiographic endpoints were primary patency and binary restenosis. Primary patency was maintained as long as angio-
graphic visualization detected flow within the previously treated lesion without any additional repeat interventional procedure; visualization of high-grade pre-occlusive restenosis with diminished thread-like blood flow was classified as vascular occlusion. Binary restenosis was defined as >50% reduction of the treated lesion lumen based on the reference vessel diameter. In the XP group, restenosis referred to >50% narrowing of the lumen within the implanted stent. Baseline and follow-up DSA images were analyzed by 2 expert vascular radiologists and a consensus was reached in cases of borderline differences. The rest of the clinical endpoints and complications were defined according to international published guidelines and reporting standards.22

Statistical Analysis

Discrete variables were expressed as counts and percentages and continuous variables were given as medians and interquartile ranges (IQR, between the 25th and 75th percentiles) for nonparametric distributions or as means ± standard deviation for normally distributed data as assessed by the Kolmogorov-Smirnov goodness-of-fit test. The unpaired Student t test was used to test the significance of differences in variables that passed the normality test. The Mann-Whitney test was used for discrete variables and for testing of nonparametric continuous variables. Proportions were compared by testing the null hypothesis that the proportions were equal, with an appropriate quantity as a standardized normal deviate test. Life-table analysis with the Kaplan-Meier method was employed to estimate proportional outcomes up to 36 months of follow-up. Subjects were censored in case of death, major amputation, repeat surgical or endovascular procedure, angiographically proven occlusion or binary restenosis, or at the time of the patient’s last follow-up visit. The Kaplan-Meier curves were compared with the log-rank test.

Results were stratified according to the type of treatment received (primary everolimus-eluting stenting versus bailout bare metal stenting). In order to identify independent risk factors affecting the endpoints, stepwise regression analysis was performed using the Cox proportional hazards regression model. Dependent variables were insulin-dependent diabetes mellitus, increased serum creatinine (>1.5 mg/dL), nicotine use (within the past 12 months), hyperlipidemia (more than mild increase controlled with diet or drugs), initial lesion grade (stenosis or occlusion), lesion length, and treatment type (primary everolimus-eluting stenting versus bailout bare metal stenting). The covariates included patient survival, major amputation-free survival, primary patency, binary restenosis, TLR-free survival, and overall event-free survival. The results were expressed as hazard ratios (HR) with 95% confidence intervals (CI) and the associated level of statistical significance. In cases of significant results, the adjusted curves of the identified covariate were plotted and presented. Statistical analysis was performed with use of the SPSS/PASW statistical software package (version 17.0; SPSS, Chicago, IL, USA). The threshold of statistical significance was set at 5% (p<0.05).

RESULTS

Between December 2006 and September 2009, 47 patients (35 men; mean age 71.0±10.6 years), with 51 CLI limbs and 102 lesions in total, were enrolled in the XP group. The control group consisted of 34 patients (28 men; mean age 71.0±8.9 years), with 36 CLI limbs and 72 treated lesions. Baseline demographics were well-matched between the groups (Table 1). Approximately three quarters of both patient groups suffered from diabetes mellitus (p=0.233). Median Rutherford stage classification was 4 (IQR 4–6) in the XP group versus 5 (IQR 4–6) in group C (p=0.258). In the vast majority of the cases, angioplasty of the inflow femoropopliteal segment was performed during the same session because of concomitant multilevel disease (92.2% in group XP versus 83.3% in group C, p=0.101).

Average infrapopliteal lesion length was similar between both groups (7.7±7.0 cm for the XP group versus 7.7±6.7 cm for controls, p=0.57). Most of the infrapopliteal lesions in
both groups were classified as stenoses (Table 2), but significantly more initial chronic occlusions were detected in the control group C (34.7%) versus the XP group (16.7%, \( p = 0.003 \)). In total, 332 stents were deployed in the XP group, while in the control group 86 stents were used due to elastic recoil and/or flow-limiting dissection. An average number of 3.2 stents per lesion were primarily implanted in the group XP compared to 1.2 bailout stents per lesion in group C. Mean length of the stented vessel segments was almost double in the XP group (7.7 ± 6.7 versus 4.2 ± 2.5 cm in group C, \( p = 0.017 \)). Mean clinical follow-up was 16.3 ± 9.9 months (range 1–36) for the XP group versus 22.8 ± 10.1 months (range 1–36) for the controls (\( p = 0.003 \)). The mean angiographic follow-up was 13.1 ± 8.6 months (range 3.4–36) for the XP group versus 14.4 ± 11.9 months (range 0.6–36) for the controls (\( p = 0.96 \)).

**Clinical and Angiographic Outcomes**

There was no major procedure-related adverse event in either of the study groups.

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**TABLE 1**

**Patient Demographics and Clinical Status**

<table>
<thead>
<tr>
<th></th>
<th>Group XP (n=47)</th>
<th>Group C (n=34)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>35 (74.5%)</td>
<td>28 (82.4%)</td>
<td>0.199</td>
</tr>
<tr>
<td>Age, y</td>
<td>71.0 ± 10.6 (45–85)</td>
<td>71.0 ± 8.9 (50–83)</td>
<td>—</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>34 (72.3%)</td>
<td>27 (79.4%)</td>
<td>0.233</td>
</tr>
<tr>
<td>Smoking (during the past 12 mo)</td>
<td>19 (40.4%)</td>
<td>13 (38.2%)</td>
<td>0.421</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>41 (87.2%)</td>
<td>28 (82.4%)</td>
<td>0.270</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>31 (66.0%)</td>
<td>21 (61.8%)</td>
<td>0.348</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>28 (59.6%)</td>
<td>16 (47.1%)</td>
<td>0.132</td>
</tr>
<tr>
<td>Renal disease</td>
<td>9 (19.1%)</td>
<td>5 (14.7%)</td>
<td>0.301</td>
</tr>
<tr>
<td>General health status*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA 1</td>
<td>14 (29.8%)</td>
<td>8 (23.5%)</td>
<td>0.266</td>
</tr>
<tr>
<td>ASA 2</td>
<td>18 (38.3%)</td>
<td>21 (61.8%)</td>
<td>0.018</td>
</tr>
<tr>
<td>ASA 3</td>
<td>15 (31.9%)</td>
<td>5 (14.7%)</td>
<td>0.038</td>
</tr>
<tr>
<td>Baseline CLI stage/category</td>
<td>4 (4–6)</td>
<td>5 (4–6)</td>
<td>0.258</td>
</tr>
<tr>
<td>Fontaine III / Rutherford 4</td>
<td>27 (57.4%)</td>
<td>13 (38.2%)</td>
<td>0.044</td>
</tr>
<tr>
<td>Fontaine III / Rutherford 5</td>
<td>9 (19.1%)</td>
<td>13 (38.2%)</td>
<td>0.028</td>
</tr>
<tr>
<td>Fontaine IV / Rutherford 6</td>
<td>11 (23.4%)</td>
<td>8 (23.5%)</td>
<td>0.495</td>
</tr>
</tbody>
</table>

* ASA 1 denotes a healthy individual, ASA 2 denotes a mild systemic disease, and ASA 3 denotes a severe but not incapacitating disease.

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**TABLE 2**

**Procedural Variables per Limb**

<table>
<thead>
<tr>
<th></th>
<th>Group XP (n=51)</th>
<th>Group C (n=36)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioplasty of the inflow axis</td>
<td>47 (92.2%)</td>
<td>30 (83.3%)</td>
<td>0.101</td>
</tr>
<tr>
<td>Total number of arteries</td>
<td>75</td>
<td>57</td>
<td>—</td>
</tr>
<tr>
<td>Total number of lesions</td>
<td>102</td>
<td>72</td>
<td>—</td>
</tr>
<tr>
<td>Initial occlusions</td>
<td>17 (16.7%)</td>
<td>25 (34.7%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Number of stents per lesion</td>
<td>3.2</td>
<td>1.2</td>
<td>—</td>
</tr>
<tr>
<td>Total lesion length, cm</td>
<td>7.6 ± 7.0 (1.5–28.0)</td>
<td>7.7 ± 6.7 (1.5–28.0)</td>
<td>0.578</td>
</tr>
<tr>
<td>Stented segment length, cm</td>
<td>7.6 ± 7.0 (1.5–28.0)</td>
<td>4.2 ± 2.5 (1.5–12.0)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Continuous data are presented as mean ± standard deviation (range); categorical data are given as the count (percentage).
during the immediate or 30-day postprocedure period. According to the bivariable Kaplan-Meier survival analysis, overall patient and amputation-free survival rates did not differ significantly between the XP and control groups up to 3 years (82.2% versus 65.7% (p = 0.90 by log-rank test) and 77.1% versus 86.9% (p = NS by log-rank test), respectively). The Cox proportional regression model did not identify any independent predictive factor for overall patient or major amputation-free survival.

Significant differences in favor of the XP group with regard to angiographic primary patency were noted in both the above- and below-the-knee arteries. Estimated proportional outcomes at 3 years showed that primary patency of the inflow femoropopliteal segment was 31.4% in XP group versus 0.0% in group C (p = 0.004 by log rank test; HR 2.9, 95% CI 1.4 to 6.3, p = 0.006). Focusing on angiographic outcomes of the infrapopliteal lesions, primary placement of everolimus-eluting stents was associated with improved primary patency (29.7% in XP group versus 20.6% in group C, p < 0.0001 by log rank test; HR 7.9, 95% CI 3.7 to 17.3, p < 0.0001 by the Cox model) and significantly less in-lesion restenosis (90.8% in group XP versus 87.8% in group C, p < 0.005 by log rank test; HR 2.9, 95% CI 1.7 to 4.9, p < 0.0001 by the Cox model) in both the bivariable and multivariable statistical analyses (Table 3).

As a result of the improved femoropopliteal and infrapopliteal primary patency achieved in the XP group, TLR events were significantly fewer and overall patient event-free survival was improved compared to group C. At 3 years, infrapopliteal TLR-free survival was significantly higher in the group of everolimus-treated lesions versus group C (81.1% versus 67.5%, p = 0.04 by log-rank test; HR 2.8, 95% CI 1.2 to 6.4, p = 0.014 by the Cox model). The composite endpoint of event-free survival was significantly better in the XP group on bivariable (34.9% versus 12.1%, p = 0.013 by log-rank test) and multivariable Cox analysis (HR 2.2, 95% CI 1.2 to 4.1, p = 0.015). Baseline Kaplan-Meier survival curves of the endpoints and respective multivariable regression plots adjusted for confounding factors of heterogeneity are graphically illustrated in Figures 1 and 2. In addition, the Cox model identified smoking and diabetes as independent adverse predictors associated with increased restenosis and reduced vessel patency (Table 4).

**DISCUSSION**

Use of coronary stents during percutaneous transluminal angioplasty was initially applied as a bailout procedure in case of poor angioplasty results. Ever since, primary stenting, i.e., stent implantation as the first choice of revascularization, has developed as
Figure 1 ◆ Kaplan-Meier plots demonstrating (A) patient survival and (B) limb salvage (on a per limb basis) for the treatment group XP and the control group C. Freedom from reintervention on a lesion basis is estimated for the 2 groups by a (C) Kaplan-Meier analysis and (D) a Cox model stratified for the type of treatment (primary everolimus-eluting stenting in group XP versus balloon angioplasty and provisional bailout stenting in group C). Finally, overall event-free survival on a patient basis is estimated by (E) Kaplan-Meier curves for the 2 groups and (F) a Cox model stratified for the type of treatment as noted above.
the treatment of choice for percutaneous coronary interventions to eliminate early abrupt vessel closure, avoid elastic recoil and negative vessel remodeling after plain balloon angioplasty, and maximize acute lumen gain. In addition, primary stenting may reduce vessel wall traumatic injury following balloon dilation, which has been implicated in both increased local inflammation and late restenosis.\textsuperscript{18,25} A number of clinical trials have shown that primary coronary stenting has a superior initial success rate and a lower incidence of restenosis compared to conventional balloon angioplasty.\textsuperscript{23,26}

Soon after DES achieved a fundamental shift in percutaneous treatment of coronary artery disease, use of drug-coated stents was introduced in the peripheral arteries with similar expectations.\textsuperscript{21} With the exception of mediocre results in the superficial femoral artery, DES have shown great promise in the infrapopliteal arteries. To date, both sirolimus- and paclitaxel-eluting balloon-expandable stents have been tested below the knee for CLI treatment. A systematic review of the literature analyzed outcomes of stenting below the knee in 18 non-randomized studies comprising 640 patients.\textsuperscript{27} After a median follow-up of 12 months, primary patency was 79\% (95\% CI 72\% to 86\%), improvement in Rutherford class was noted in 91\% (95\% CI 86\% to 97\%), target vessel revascularization was necessary in only 10\% (95\% CI 6\% to 14\%), and limb salvage was achieved in 96\% (95\% CI 95\% to 98\%) of the cases. Head-to-head comparisons showed that sirolimus-eluting stents appear to be superior to bare metal and paclitaxel-eluting stents with regard to both angiographic and clinical outcomes. Compared to balloon-expandable bare metal stents, sirolimus-eluting stents were better in preventing restenosis and increasing primary patency (both p<0.001).\textsuperscript{27}

Long-term results after drug-eluting stenting of the infrapopliteal arteries have been recently released. Siablis et al.\textsuperscript{12} reported positive angiographic and clinical outcomes

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**Figure 2** Primary patency (A, B) and binary restenosis (C, D) on a lesion basis were estimated by bivariant Kaplan-Meier survival analysis for groups XP and C (A and C, respectively) and after multivariate adjustment with the Cox model (B and D, respectively).
with infrapopliteal sirolimus-eluting stents. At 3 years, infrapopliteal lesions treated with bailout sirolimus-eluting stents were associated with significantly better primary patency (HR 4.81, 95% CI 2.91 to 7.94, \( p < 0.001 \)), reduced binary restenosis (HR 0.38, 95% CI 0.25 to 0.58, \( p < 0.001 \)), and better TLR-free survival (HR 2.56, 95% CI 1.30 to 5.00, \( p = 0.006 \)) versus lesions treated with bare metal stents. The authors concluded that infrapopliteal application of sirolimus-eluting stents for CLI significantly improves angiographic long-term patency and reduces infrapopliteal restenosis versus bare metal stents, thereby lessening the rate of ischemia-driven repeat interventions.

In line with these results, recently available outcomes from the nonrandomized single-center PARADISE (PReventing Amputations using Drug eluting StEnts) study investigating leg amputations in CLI patients treated with below-the-knee angioplasty and drug-eluting stents featured a 3-year cumulative amputation rate of 6%±2%; survival was 71%±5%, and amputation-free survival was 68%±5%.28

Rastan et al.29 have recently reported their experience with primary sirolimus-eluting stenting for infrapopliteal angioplasty. The authors applied polymeric sirolimus-eluting stents for treatment of either CLI or intermittent claudication. Analysis of midterm outcomes in 104 patients documented primary patency rates of 88.5% and 83.7% at 6 months and 1 year, respectively. Correspondingly, a considerable rate of sustained clinical improvement of the entire patient cohort was noted, as reflected by a mean change in the Rutherford classification that exceeded 2 stages (3.3 at baseline versus 0.9 after 1 year, \( p < 0.0001 \)).

However, increased rates of in-segment restenosis have been noted in previous studies investigating angioplasty with provisional/bailout sirolimus-eluting stenting of the infrapopliteal arteries. Early angiographic data of provisional sirolimus-eluting versus bare metal stents for bailout after suboptimal infrapopliteal angioplasty for CLI reported an association between provisional sirolimus-eluting stents and increased in-segment restenosis, i.e., within the 0.5 to 1 cm peri-stent margins.21

Everolimus is a derivative of sirolimus that is widely used as an immunosuppressant drug in organ transplantation and acts as an inhibitor of the mammalian target of rapamycin in a similar way with sirolimus. Everolimus-eluting stents are currently available in most major European and Asia-Pacific markets. The set of SPIRIT trials (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions I–III) has demonstrated durable suppression of neointimal growth and significantly improved event-free survival of everolimus-eluting stents in comparison with bare metal and paclitaxel-eluting stents in patients with de novo coronary artery disease.30–33

Full lesion coverage of long obstructive lesions during below-the-knee angioplasty with primary everolimus-eluting stenting aims to deliver the anti-restenotic agent along the entire length of the balloon-dilated lumen to prevent progressive neointimal growth. To date, published data of infrapopliteal drug-eluting stenting is limited to relatively short

### TABLE 4

<table>
<thead>
<tr>
<th>Variables Other Than Treatment Modality Identified by the Cox Model* as Significant Outcome Predictors</th>
</tr>
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<tbody>
<tr>
<td>Independent Variables</td>
</tr>
<tr>
<td>Primary patency</td>
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<tr>
<td></td>
</tr>
<tr>
<td>In-lesion binary restenosis</td>
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</table>

\( \beta \): regression coefficient, SE: standard error, CI: confidence interval.

* Adjusted for hyperlipidemia, diabetes, renal status, smoking, initial lesion grade (stenosis or occlusion), and median lesion length.
lesions, mostly up to 4 cm.\textsuperscript{12–17,20,21} Long lesion length, i.e., at least $4.5 \text{ cm}$, was an a priori inclusion criterion for the present study. In comparison to a historical matched-control group of angioplasty and bailout bare metal stenting, we have shown that primary stenting of long infrapopliteal lesions with multiple everolimus-eluting stents (Fig. 3) is associated with a notable significant benefit in terms of reduced restenosis (adjusted HR 2.9), improved primary patency (adjusted HR 7.9), and fewer TLRs (adjusted HR 2.8). Most importantly, the composite endpoint of overall event-free survival, which could be interpreted as an equivalent endpoint of sustained clinical improvement without recurrent ischemia of the index limb, was significantly improved during the 3-year period of analysis, with an adjusted HR of 2.2.

Although improved limb salvage remains the cornerstone endpoint for evaluation of all new infrapopliteal instruments and technologies, inhibition of neointimal hyperplasia by drug-eluting stents plausibly leads to improved vessel patency and sustained clinical improvement as reflected by the significantly improved Rutherford classification and reduced TLR due to recurrent CLI. The patients’ quality of life may also be dramatically improved if we prevent or even lessen the extent of amputation.

Interestingly, in the present study we have also found that primary everolimus-eluting stenting was also related to significantly improved primary patency of the femoropopliteal segment (adjusted HR 2.9), with fewer repeat TLRs. There is increasing evidence supporting the contention that patency outcomes after superficial femoral artery procedures are negatively affected by poor tibial runoff.\textsuperscript{34,35} Another group reported that compromised postprocedural infrapopliteal runoff predisposes to early restenosis and/or reocclusion after femoropopliteal angioplasty. In addition, deterioration of infrapopliteal runoff in the first year after femoropopliteal angioplasty resulted also in worse long-term femoropopliteal patency.\textsuperscript{36} Contrary to single femorodistal surgical bypass, the inherent advantage of infrapopliteal angioplasty and stenting in recanalizing $>1$ vessel to the foot cannot be overstressed. In a recent elegant retrospective analysis of $>1000$ limbs suffering from CLI and treated primarily with infrapopliteal angioplasty, Peregrin et al.\textsuperscript{37} have documented the added benefits of revascularization of $>1$ artery below the knee. The number of patent tibial arteries after angioplasty was the most significant factor affecting limb salvage, i.e., patients with 0, 1, 2, and 3 patent arteries after the index procedure had 1-year limb salvage rates of 56%, 73%, 80%, and 83%, respectively.

**Limitations**

The present study mainly suffers from the inherent bias of its single-center design and the limitations in assembling an appropriately matched historical control group. Moreover, the control group included $\sim30\%$ fewer patients and lesions, and both groups had a quite heterogeneous follow-up period with a
limited number of subjects reaching the final 3-year time point. Therefore, a multivariable Cox proportional hazards regression analysis was applied to adjust for confounding factors of heterogeneity and eliminate bias. Absence of quantitative vessel angiography is another shortcoming.

In addition, the diffuse, multilevel nature of tibial occlusive disease, coupled with the higher-cost DES, prohibits recommending drug-eluting stenting as the primary treatment of long infrapopliteal lesions at the moment. Therefore, the design of DES with appropriate lengths for primary treatment of routinely encountered infrapopliteal lesions, i.e., 5 to 10 cm long, is necessary for widespread adoption of this new technology in the below-the-knee arteries.

Arguably, primary infrapopliteal stenting may also have considerable advantages over angioplasty and bailout stenting with respect to cost savings in angioplasty balloons, contrast load, fluoroscopy time, and overall procedural time. However, long, heavily calcified lesions in small and distal infrapopliteal vessels or lesions in excessively tortuous arteries may not be amenable to primary stenting.

Conclusion

Primary stenting of long infrapopliteal lesions with everolimus-eluting stents significantly inhibits restenosis and improves primary patency with sustained clinical improvement. Patients treated with primary everolimus-eluting stenting had less clinically-driven revascularization and significantly better event-free survival. Multicenter randomized trials are warranted to further investigate the primary application of drug-eluting stents in below-the-knee arteries.

REFERENCES


