Infrapopliteal Application of Paclitaxel-eluting Stents for Critical Limb Ischemia: Midterm Angiographic and Clinical Results

Dimitris Siablis, PhD, Dimitris Karnabatidis, PhD, Konstantinos Katsanos, MD, Athanassios Diamantopoulos, MD, Nikolaos Christeas, MD, and George C. Kagadis, PhD

PURPOSE: To report the midterm (≤1 year) angiographic and clinical outcomes of a prospective study investigating the infrapopliteal application of paclitaxel-eluting stents (PES) in patients with critical limb ischemia (CLI).

MATERIALS AND METHODS: Infrapopliteal angioplasty was chosen as first-line therapy in patients with unilateral or bilateral CLI and additional femoropopliteal angioplasty was performed in case of multilevel disease. Implantation of coronary PES was performed in case of a suboptimal angioplasty result (eg, elastic recoil, residual stenosis >30%, or flow-limiting dissection). Patients were followed up with regular clinical evaluation, and digital subtraction angiography was scheduled at 6 months and 1 year. Life-table analysis and Kaplan-Meier plotting of angiographic and clinical variables were performed. Cox proportional-hazards regression analysis was employed to adjust for various covariates and search for independent adverse predictors of angiographic and clinical outcome.

RESULTS: Infrapopliteal procedures were performed in 29 patients with 32 limbs with CLI; 79.3% of the patients had diabetes and 34.5% had renal disease. A total of 62 coronary PES were deployed in 50 below-knee lesions (mean stent-implanted length, 25.51 mm ± 12.16). Technical success rate was 100%. The 1-year mortality rate was 16.9%, and the limb salvage rate was 88.5%. The 1-year angiographic in-stent primary patency rate was 30.0%, whereas the incidence of in-stent binary (>50%) restenosis was 77.4%. The 1-year incidence of clinically driven repeat interventions was 30.5%. The Cox model calculated renal disease as the only independent predictor of decreased primary patency and increased repeat intervention events. Initial occlusions also adversely affected primary patency.

CONCLUSIONS: Infrapopliteal PES achieved acceptable clinical results in CLI, even though they failed to inhibit vascular restenosis and decrease the need for repeat interventions. Renal disease and initial occlusions are adverse prognostic factors for infrapopliteal endovascular procedures.

CRITICAL limb ischemia (CLI) is the end stage of peripheral arterial occlusive disease and occurs when blood flow to the distal leg is severely dimin-

ished because of diffuse multilevel atherosclerosis, which particularly affects the infrapopliteal arteries (1–3). It is associated with a mortality rate of almost 45% at 5 years as a result of cardiovascular causes and a major amputation rate as high as 25% at 1 year (4–6). Current treatment strategies encompass medical treatment, alteration of lifestyle habits, and open surgical or endovascular revascularization options. Invasive surgical or percutaneous endoluminal treatment is the mainstream approach for limb-threatening ischemia (ie, Rutherford categories 4, 5 and 6) (5,7,8).

Although surgical bypass is the traditional therapeutic modality for ischemic tissue reperfusion in CLI (9,10), endovascular recanalization procedures of the infrapopliteal arteries are rapidly emerging as a promising alternative tactic in the management of below-knee arterial occlusive disease (2,11–13). In the modern endovascular era, this paradigm shift is mainly driven by the facts that (i) patients with CLI are usually inappropriate surgical candidates because of associated comorbidities and lack of proper distal outflow vessels, (ii) technologies of low-profile interventional instruments are advancing along with increasing endovascular skills of inter-

[Note: The text continues with additional content, but it is not fully transcribed due to the constraints of the image and the nature of the task.]
ventional radiologists, and (iii) these techniques can be applied without ruling out future surgical intervention (2,3,14–16).

The literature amassed to date emphasizes the clinical benefits of infrapopliteal angioplasty in terms of reduced peri-procedural morbidity and mortality and increased limb salvage (2,3,15,17). However, below-knee angioplasty procedures are usually limited by relatively high rates of vascular restenosis after angioplasty and increased need for repeat interventions as a result of CLI relapse (5,15,16,18).

Motivated by the groundbreaking results achieved with the use of drug-eluting stents in the coronary bed, researchers have pioneered their infrapopliteal application to forestall neointimal hyperplasia and recurrent obstruction and improve clinical results after percutaneous recanalization of the tibial arteries (17–19). However, published data regarding the infrapopliteal performance of drug-eluting stents are still scarce and limited to positive preliminary results with the coronary sirolimus-eluting stent (SES) platform (5,18,20–22).

Paclitaxel-eluting stents (PES) have also exhibited long-term superiority compared with bare metal stents in the field of coronary interventions by averting neointimal hyperplasia and reducing vascular restenosis and the need for repeat endovascular procedures (23–25). Prompted by this knowledge and based on our promising initial experience with below-knee deployment of SES (5,18), we conducted an open-label, single-arm prospective study investigating the safety and efficacy of the use of PES as an adjunct after suboptimal angioplasty of the infrapopliteal arteries in patients with CLI.

**MATERIALS AND METHODS**

The study was performed according to the latest Declaration of Helsinki and the protocol was approved by our hospital’s ethical and scientific committee. All patients were informed about the nature and the purpose of the study and gave written informed consent before the intervention. The study enrollment period ranged from May 2004 to October 2005. Eligibility criteria included clinical symptoms of unilateral or bilateral CLI (Rutherford categories 4–6), documentation of infrapopliteal arterial occlusive disease with digital subtraction angiography, and elective revascularization therapy with percutaneous transluminal angioplasty. Patients with a known history of severe allergic reaction to contrast medium, infected tissue loss, hypercoagulation disorders, contraindications to administration of anticoagulants or antiplatelet medications, and acute limb ischemia were excluded.

**Interventional Procedure**

Of the 29 total patients, 26 were receiving aspirin (100 mg/d) and clopidogrel (75 mg/d) for at least 4 days before the procedure. The other three were administered a loading dose of 300 mg clopidogrel the day of the intervention. During the procedure, patients received a nonweighted intraarterial heparin bolus of 5,000 IU immediately after femoral artery puncture and heath placement and approximately 1,000 U/h heparin for the rest of the procedure. After the procedure, all patients were instructed to continue aspirin and clopidogrel for 6 months and single antiplatelet therapy indefinitely thereafter unless they were already receiving warfarin treatment ($n = 4$).

After ipsilateral antegrade puncture of the common femoral artery, a 6-F sheath (Terumo, Tokyo, Japan) was placed to the superficial femoral artery. With use of appropriate endovascular instruments and maneuvers (ie, 0.035-inch guide wire and 4-F straight or angled hydrophilic catheter [Terumo] with over-the-wire technique), the popliteal artery was catheterized and a 0.014-inch guide wire was negotiated through the lesion. Infrapopliteal angioplasty was performed with conventional low-profile over-the-wire or monorail coronary balloon catheters of appropriate dimensions. Nominal balloon diameters were chosen according to visual estimate of the reference vessel diameter (range of diameters, 2.5–3.5 mm) and maximum stent–to–vessel lumen oversize was 0.5 mm. Tibial arteries were protected from vasospasm with regular intraarterial infusions of 100–300 μg of nitroglycerin according to systemic pressure monitoring.

The aim of the procedure was recanalization of one or more tibial arteries to establish at least one straight line of arterial blood flow to the distal foot. Stents were reserved for “bail-out” use in case of a suboptimal angioplasty outcome. Stent indications were elastic recoil after angioplasty and/or residual stenosis more than 30% and/or severe flow-limiting dissection of the treated lesion. Coronary PES (Taxus; Boston Scientific, Natick, Mass) were implanted as necessary. Coexisting femoropopliteal lesions were treated with standard balloon angioplasty and nitinol stent placement accordingly. After completion of the intervention, the sheath was removed and a vascular access closure device (StarClose; Abbott Vascular, North Chicago, Ill) was applied to achieve immediate hemostasis and avoid protracted femoral compression. Patients were then transferred to the interventional clinic.

**PES**

The study investigated the Taxus balloon-expandable PES platform (Boston Scientific) in an off-label application in the infrapopliteal arteries. The Taxus stent is a stainless-steel stent coated with a drug formulation consisting of paclitaxel, which is the active antiproliferative element, and Translute, an inactive polymer carrier that helps in the controlled release of the drug. The stent is coated with 1 μg/mm² paclitaxel per unit of stent surface area (23,26). Paclitaxel is an antineoplastic alkaloid picked from a spectrum of Taxus species and hybrids. It is an antiproliferative agent that leads predominantly to M-phase arrest of the cell cycle of rapidly proliferating cells. Its main mechanism of action involves formation of stable nonfunctioning microtubules, which impairs vital interphase and mitotic cellular functions. At low cytotoxic doses, paclitaxel is mainly characterized by anti-inflammatory properties by selectively blocking proliferation and migration of smooth muscle cells while allowing stent endothelialization to protect against thrombosis (23). The Taxus stent is available in a wide range of lengths (8–32 mm) and diameters (2.50–3.50 mm). Hence, application of a PES was restricted to tibial vessels with a maximum reference diameter of 3.50 mm.

**Data Collection and Follow-up**

Patients’ demographics and initial clinical status were recorded before
the intervention. Morphologic characteristics of treated lesions, ie, anatomic location, initial lesion grade (stenosis >50%, stenosis >75%, or occlusion), initial lesion length, and accompanying femoropopliteal disease were determined by baseline preprocedural digital subtraction angiography and were analyzed by two independent radiologists. Procedural details were thoroughly recorded during the intervention. The follow-up of the study included clinical evaluation at 24 hours and then scheduled physical examination at 1, 3, 6, and 12 months, and yearly thereafter. Ankle-brachial index was not measured routinely as a result of the high prevalence of diabetes and Moeneckberg sclerosis producing falsely high measurements (1). Digital subtraction angiography was performed at 6 and 12 months unless clinical deterioration dictated otherwise. Results of the angiographic follow-up were also analyzed by the same radiologists. A consensus was reached in cases of borderline differences.

Endpoints and Definitions

The primary clinical endpoints were technical success and safety of the procedure, freedom from repeat interventions, overall survival, limb salvage, and minor amputations. Primary angiographic endpoints included primary patency and binary (>50%) vascular restenosis, both of which were investigated and reported on the bases of the stent, angioplasty alone, lesion, and artery.

Technical success was defined as successful recanalization of at least one infrapopliteal artery to the distal foot with residual stenosis of the treated lesion of less than 30%, and successful stent placement if that was deemed necessary. Primary patency was defined as absence of occlusion without any additional intervention. Binary restenosis was defined as more than 50% narrowing of the vessel lumen compared with the reference vessel diameter and the term “in-stent” was applied when referring to restenosis within the stents. Lesion and artery restenosis used the 50% criterion to describe the status of the whole lesion and respective tibial artery treated with angioplasty with or without stent placement. Target lesion repeat intervention, target stent repeat intervention, target angioplasty-alone repeat intervention, and target vessel repeat intervention were defined as any additional interventions within the treated lesions, stents, angioplasty alone, or overall vessels because of CLI relapse. The rest of the clinical endpoints were determined according to standard definitions (7,27).

Statistical Analysis

Discrete variables were expressed as counts and percentages and continuous variables were given as medians and interquartile ranges (ie, between the 25th and 75th percentiles) in parentheses or as means ± SD if they passed the normality test as described later. The Kolmogorov-Smirnov goodness-of-fit test was used to determine whether continuous data should be treated as originating from normal distributions. The unpaired Student t test was used to test the significance of difference of variables that passed the normality test. The Mann-Whitney test was used for qualitative variables and for continuous variables that did not pass the normality test. Comparison of two proportions was done by testing the null hypothesis that the proportions were equal, with an appropriate quantity as a standardized normal deviate test. Life-table survival analysis with Kaplan-Meier plots were employed for mortality, limb salvage, target lesion repeat intervention, target repeat intervention with a stent or angioplasty, and target vessel repeat intervention, as well as for in-stent, lesion, angioplasty-alone, and whole-artery primary patency and restenosis. Calculated curves were compared with the log-rank test.

To define independent prognostic factors associated with the aforementioned covariates, stepwise regression analysis was performed with use of the Cox proportional-hazards regression model during the total follow-up period. Dependent variables were diabetes mellitus (insulin-dependent and non–insulin dependent), increased serum creatinine level (>1.5 mg/dL), initial lesion grade (stenosis or occlusion), initial lesion length, application of PES stents, and stent-implanted length. Results were expressed as hazard ratios with the associated 95% CIs and level of statistical significance. In cases of statistical significance, the Kaplan-Meier survival curves regarding the identified covariate are presented. All statistical tests performed were two-sided and the threshold of significance was set at 5% (ie, α = 0.05). All statistical calculations and analysis were performed with the SPSS statistical software package (version 14.0; SPSS, Chicago, Ill).

RESULTS

A total of 29 patients (21 men and eight women; mean age, 72.9 y ± 9.6) with de novo atherosclerotic infrapopliteal disease and CLI (Rutherford categories 4–6) underwent endovascular treatment with standard balloon angioplasty and selective use of a PES. A total of 79.3% of the patients (n = 23) had diabetes and 34.5% (n = 10) had moderate to end-stage renal disease with increased serum creatinine levels (>1.5 mg/dL). Three patients had bilateral CLI. Detailed demographics of the whole cohort of patients are outlined in Table 1. In total, 79 lesions in 61 arteries of 32 limbs were recanalized (mean lesion length, 4.6 cm ± 5.0); 63.3% of the lesions (n = 50) required additional stent placement, and a total of 62 PES were implanted (overlapping PES were placed in 11 lesions; mean stent-implanted length, 2.6 cm ± 1.2). Initial occluded lesions were more prone to require bail-out stent implantation compared with initially stenosed ones (73.7% vs 53.3%; P = .0585). Simultaneous femoropopliteal interventions as a result of coexisting multilevel atherosclerosis were performed in 90.6% of the limbs (n = 29; Table 2). The immediate technical success rate was 100% (n = 32), with no major complications other than a sole case of distal thromboembolism after angioplasty and stent implantation in the posterior tibial artery, which was successfully treated with immediate catheter-directed thrombolysis. There was also one case of local hematoma and another case of self-limited retroperitoneal bleeding caused by a high femoral puncture; the patient was discharged after a 3-day period without any blood transfusions. All patients followed the recommended antiplatelet regimen except those who were already receiving warfarin treatment (n = 4).
Clinical Outcomes

There were no major adverse events or deaths recorded in association with the intervention and/or stent placement in the immediate and 30-day postprocedural period. Clinical results were available in 96.5% of the patients (n = 28), with a mean clinical follow-up period of 10.3 months ± 4.2. Kaplan-Meier survival curves regarding overall patient survival and limb salvage are displayed in Figures 1a and 1b, respectively. Six-month and 1-year survival rates were 100% and 83.1%, respectively. One death was a result of drowning and the other was attributed to myocardial infarction. Six-month and 1-year limb salvage rates were 93.4% and 88.5%, respectively. The first major amputation occurred at 3 months as a result of early recurrence of occlusion of the stent-implanted infrapopliteal vessels and the second occurred at almost 9 months as a result of advanced atherosclerosis and clinical deterioration. There was also one patient with three-vessel occlusion below the knee who experienced reperfusion syndrome of the treated limb after a long recanalization of the anterior tibial artery requiring two bail-out stent placement procedures. Despite hospitalization and appropriate treatment, amputation of the limb was deemed necessary as a result of extensive tissue damage.

Six-month repeat intervention rates were 4.9% on a PES basis, 0% on an angioplasty-alone basis, 2.9% on an overall lesion basis, and 4.2% on an artery basis. The corresponding 12-month results were 30.5%, 16.4%, 22.5%, and 26.4%, respectively (Fig 2c). No significant differences among the distinct survival curves were noted. Repeat intervention rates in the inflow femoropopliteal axis were 7.3% at 6 months and 24.4% at 12 months (Fig 3c).

After adjustment for specific covariates (ie, diabetes, uremia, initial lesion grade, lesion length, and stent use) with a Cox proportional-hazards regression model, increased creatinine level (>1.5 mg/dL) was found to be the only independent adverse predictive factor for increased incidence of lesion repeat intervention (Table 3). Individual Kaplan-Meier curves for patients with and without increased serum creatinine levels and separately for initially occluded and stenosed lesions are displayed in Figures 4 and 5, respectively.

Angiographic Outcomes

The mean angiographic follow-up period was 9.0 months ± 4.1. In total, follow-up digital subtraction angiography was performed in 79.3% of the patients (n = 23). According to the life-table analysis, estimated 6-month primary patency rates were 90% on a stent basis, 100% on an angioplasty-
alcohol lesion, 94.1% on an overall lesion basis, and 92.7% on an artery basis. The respective 12-month results were 30%, 82%, 50.4%, and 47.8% (Fig 2b). The binary in-stent, lesion, angioplasty-alone, and whole-artery restenosis rates at 6 months were 18.3%, 14.4%, 4.3%, and 17.5%, respectively. The corresponding 12-month rates were 77.4%, 70.0%, 70.0%, and 73.8% (Fig 2a). Again, no significant differences were detected among the distinct survival curves. Primary patency rate of the femoropopliteal arteries were 82.7% at 6 months and 43.8% at 1 year, whereas the respective restenosis rates were 24.2% and 75.3% (Fig 3).

Cox proportional-hazards regression adjustment for hyperglycemia, increased creatinine level, initial lesion grade, lesion length, and stent use identified renal disease and initial occlusions as the only independent predictive factors for decreased in-stent and in-lesion primary patency. Moreover, renal disease was calculated as a predictive factor for increased lesion restenosis (Table 3). Individual Kaplan-Meier curves with respect to patients’ initial renal disease status (ie, patients with and without increased serum creatinine levels) and separately for initial lesion grade are displayed in Figures 4 and 5, respectively. No case of stent deformation and/or fracture was observed during the follow-up period.

**DISCUSSION**

CLI represents one of the most challenging and cost-consuming cardiovascular health care problems in the world. It refers to limb-threatening peripheral atherosclerotic ischemia and is typically characterized by multilevel, multivessel infrapopliteal and tibial arterial occlusive disease, primarily afflicting patients with diabetes and end-stage renal disease (1,2,18,28). It is estimated that almost 1% of all people older than 50 years of age manifest symptoms of CLI, which corresponds to 1.5 million patients in Europe and approximately 2 million patients in the United States (1,28). In the interest of prevention of limb loss, patients with CLI are candidates for revascularization attempts by surgical or percutaneous methods. Restoration of at least one unobstructed straight line of blood flow to the distal foot with adequate pedal runoff is claimed to relieve ischemia symptoms and promote tissue healing (2,3,17,18). Unfortunately, most patients with CLI are not eligible for a surgical bypass procedure because of associated comorbidities and/or lack of appropriate distal vessels. Moreover, surgery is related to an additional 1.8%–6% periprocedural mortality rate, is technically demanding, and may require prolonged periods of hospitalization (8–10). To the contrary, percutaneous techniques of infrapopliteal revascularization are associated with reduced morbidity and mortality rates and shorter hospitalization periods and do not preclude future surgical options (2,9). Most importantly, technologic advancements and additions to the “endovascular toolbox” have increased their versatility and applicability in the highly morbid and fragile population of patients with CLI, with consistently favorable clinical results (2,15,16,18,19).

A metaanalysis of published literature regarding traditional balloon angioplasty of the infrapopliteal arteries (14) reported overall limb salvage rates of 79% at 1 year and 74% after 2 years. Unfortunately, the rate of short-term angiographic vascular restenosis is high, and occlusion reportedly recurs in as many as 50% of cases by 6 months (18,22). Although scarce and variant, research of infrapopliteal balloon angioplasty shows clinical primary patency rates of 48%–81% at 1 year and 40%–78% at 2 years (15,16,18,29,30). A suboptimal balloon angioplasty result; increased serum C-reactive protein, and poor pedal runoff have been implicated as the main parameters that adversely influence vascular restenosis of the tibial arteries (18).

In the modern endovascular era, application of bare metal stents has eliminated acute elastic recoil and/or dissection after angioplasty and abrogated late negative remodeling of the injured arterial wall, along with the considerable downside of increased neointimal formation. One-year patency rates after infrapopliteal bare
Figure 1. Kaplan-Meier plots of (a) overall patient survival and (b) limb salvage.

Figure 2. Kaplan-Meier plots of (a) binary (>50%) vascular restenosis on a stent, angioplasty-alone (PTA), lesion, and artery basis; (b) primary patency on a stent, angioplasty-alone (PTA), lesion, and artery basis; and (c) freedom from repeat intervention on a stent, angioplasty-alone (PTA), lesion, and artery basis.
metal stent implantation range between 41% and 66% according to angiographic follow-up studies (17–19, 31). Stent scaffold elution of antirestenotic drugs, with sirolimus and paclitaxel being the most prominent, has revolutionized interventional therapy of coronary artery disease by significantly reducing in-stent neointimal hyperplasia and the need for repeat procedures (24,25). Stimulated by the promising results in the coronary arena, application of drug-eluting stents is one of the latest innovations in CLI management in the effort to enhance the durability and long-term clinical benefit after percutaneous revascularization of the infrapopliteal arteries. To our knowledge, published reports of below-knee application of drug-eluting stents are limited to SES (5,18,20–22). With the present study, we have reported a study of a PES in the infrapopliteal arteries in a CLI population.

Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Independent Variable</th>
<th>Regression Coefficient β</th>
<th>SE</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion</td>
<td>Primary patency</td>
<td>Lesion grade</td>
<td>-2.043</td>
<td>0.716</td>
<td>0.130</td>
<td>0.032–0.527</td>
</tr>
<tr>
<td></td>
<td>Renal status</td>
<td>Renal status</td>
<td>-2.533</td>
<td>0.882</td>
<td>0.079</td>
<td>0.014–0.447</td>
</tr>
<tr>
<td></td>
<td>Binary Restenosis</td>
<td>Renal status</td>
<td>1.095</td>
<td>0.576</td>
<td>2.994</td>
<td>0.996–9.259</td>
</tr>
<tr>
<td></td>
<td>Repeat intervention</td>
<td>Renal status</td>
<td>1.768</td>
<td>0.722</td>
<td>5.848</td>
<td>1.422–24.390</td>
</tr>
<tr>
<td>Stent</td>
<td>Primary patency</td>
<td>Renal status</td>
<td>-2.088</td>
<td>1.163</td>
<td>0.124</td>
<td>0.13–1.211</td>
</tr>
<tr>
<td></td>
<td>Renal status</td>
<td>Renal status</td>
<td>-3.029</td>
<td>1.185</td>
<td>0.048</td>
<td>0.005–0.493</td>
</tr>
<tr>
<td></td>
<td>Lesion grade</td>
<td>Lesion grade</td>
<td>-3.029</td>
<td>1.185</td>
<td>0.048</td>
<td>0.005–0.493</td>
</tr>
</tbody>
</table>

Note.—HR = hazard ratio.

* Model adjusted for hyperglycemia, increased creatinine, initial lesion grade (stenosis vs occlusion), initial lesion length, application of Taxus stents, and stent-implanted length.

Figure 3. Kaplan-Meier plots of the inflow femoropopliteal results regarding (a) binary (>50%) restenosis, (b) primary patency, and (c) freedom from repeat vessel intervention.
Infrapopliteal angioplasty with provisional application of PES proved to be safe and efficacious in the treatment of CLI with favorable limb salvage in the midterm period. However, as portrayed in the Kaplan-Meier plots, treated lesions were characterized by deteriorating arterial occlusive disease necessitating secondary revascularization procedures. Interestingly, no noteworthy difference was observed between lesions treated with balloon angioplasty only and lesions treated with additional PES implantation. In the medium term, PES exhibited unexpectedly poor performance with high rates of vascular restenosis producing diminishing patency and increasing need for repeat intervention. According to survival analysis–derived calculations, PES primary patency decreased from 90.0% at 6 months to 30.0% after 1-year angiographic follow-up, whereas the incidence of PES repeat interventions increased from 4.9% to 30.5%, respectively (Fig 2).

To the contrary, data from previously published studies by our group, which investigated bare metal and sirolimus-eluting infrapopliteal stents in an analogous patient cohort, with 29 subjects assigned to each study arm (5,18), showed a great discrepancy between the results of PES and SES in the tibial arteries. The use of SES achieved a 86.4% primary patency and 9.1% repeat intervention rate at 1 year, whereas bare metal stents were characterized by a 40.5% primary patency rate and a 26.2% repeat intervention rate (both \( P < .001 \)) (5). These observations seem to be in agreement with emerging data from major coronary trials suggesting greater efficacy of SES (Cypher; Cordis, Miami Lakes, Fla) compared to PES (Taxus; Boston Scientific) for the inhibition of in-stent restenosis (26,32,33). A recent meta-analysis in the coronary field concluded that SES exhibit a significantly better antirestenotic profile than PES, which was primarily characterized by reduced angiographic restenosis (9.3% vs 13.1%; \( P = .001 \)) and clinically
driven target lesion repeat interventions (5.1% vs 7.8%; \( P = .001 \)) (32).

Various disparities between the two types of drug-eluting stents in terms of their pharmacologic properties, release kinetics, and distinct impact on vascular healing have been proposed to account for this differential outcome (26). First, sirolimus inhibits the mammalian target of rapamycin and ultimately arrests degradation of a cyclin-dependent kinase inhibitor, which is a vital regulator of vascular smooth muscle cell cycle and migration, whereas paclitaxel exerts a wide range of cytostatic and cytotoxic properties by impairing spindle formation and microtubule dynamics (26). In addition, paclitaxel accumulates mainly in the outer adventitial vessel layer, which is not the primary origin of neo-intimal hyperplasia, whereas sirolimus diffuses equally among all three arterial wall layers (26). Moreover, the release kinetics of the two stent platforms deviate significantly. Taxus stents have a biphasic release polymer system with an initial burst of approximatively one third of the total 10-day dose during the first 48 hours after implantation and a second slow release period by day 10 (23,25). Conversely, Cypher stents employ a dual polymer system, which gradually releases 80% of the drug dose during the first month after implantation and the rest as long as 3 months after implantation, thereby providing a larger period of local treatment (25). Finally, various dissimilarities have been observed in the pattern of in-stent neointima formation and the incidence of stent thrombosis. In most of the cases, the restenosis within the Cypher stents is focal, whereas more diffuse stenosis, if not complete occlusion, is seen within the Taxus stents (26). Late stent thrombosis, although rare, is also believed to occur more frequently in Taxus stent–treated lesions, although this may reflect only a numeric trend (26,34).

In the context of CLI, in which atherosclerosis is abundant in the tibial vessels and almost two thirds of the patients have diabetes (18), it is reasonable to consider the diversity of in-stent neointimal hyperplasia and continue sirolimus diffusion equally among all tissue processes. Diabetes mellitus is well known to escalate the risk of CLI by a factor of four, and diabetic patients with CLI are as much as 10 times more vulnerable to amputation than normoglycemic patients. Notably, almost half of all amputees have diabetes (1,2,28). Should one focus on the demographics of major company-sponsored coronary trials, diabetes has a 13.5%–32.3% incidence, whereas infrapopliteal studies have a corresponding incidence of 68.6%–75.9% (18,19). Interestingly, the worst in-stent late lumen loss (LLL) was observed in the Intracoronary Stenting and Angiographic Results (ISAR)-Diabetes study (35), in which diabetes was an a priori enrollment criterion and SES and PES showed the highest-ever record of LLL (0.19 mm and 0.46 mm, respectively; \( P < .001 \)) (25,35). Apart from that, we should underline that the lesions treated with stents are significantly longer in the tibial vessels than in the coronary arteries (2.5–3.0 mm vs 9.6–17.1 mm, respectively) (19,22,26). Therefore, it is a logical assumption that longer lesions are associated with a higher burden of neointimal hyperplastic response, and the more complex the lesions are, the higher the risk of recurrent obstruction in general. Of course, because premature discontinuation of antiplatelet therapy has been put forward as the greatest independent predictor of late stent thrombosis and infrapopliteal arteries have low flow volume hemodynamics (2,34), the importance of strict patient compliance and discipline cannot be stressed enough, especially in the severely morbid group of patients with CLI.

Apart from diabetes, renal disease is believed to adversely affect vascular structure and limb salvage of patients with CLI and is incriminated for its synergistic effect in their deteriorating clinical status (36). Indeed, in the present study, increased creatinine level was identified by the Cox proportional-hazards model as the sole comorbidity causing a decrease of stent and lesion primary patency rates and an increase in target lesion repeat

---

**Figure 5.** Individual survival plots of lesion that were initially stenoses or occlusions after identification of initial lesion grade as an adverse predictor by the Cox model after adjustment for hyperglycemia, increased creatinine level, initial lesion grade (stenosis vs occlusion), initial lesion length, application of Taxus stents, and stent-implanted length: (a) lesion primary patency (hazard ratio [HR], 0.130 [CI, 0.032–0.527]; \( P = .004 \)) and (b) stent primary patency (HR, 0.048 [CI, 0.005–0.493]; \( P = .011 \)).
intervention. Likewise, it proved that initially occluded lesions were more prone to recurrent obstruction than stenosed ones, which is also in agreement with data published elsewhere (36).

This was a single-center, single-arm prospective study involving a relatively small cohort of patients, which may limit the statistical value of the results. In addition, stent implantation was carried out on a bail-out basis and coronary PES were applied in an off-label use below the knee. Finally, angiographic results were not evaluated by an independent laboratory analysis.

In conclusion, the infrapopliteal application of PES proved safe and achieved acceptable clinical results, despite the notable rates of vascular restenosis and repeat intervention events. Renal disease and initial occluded lesions are adverse prognostic factors for infrapopliteal endovascular procedures. Evidently, large-scale multicenter randomized controlled trials are necessary to determine whether PES actually have a role in the revascularization of the infrapopliteal arteries in this patient population.

References

31. Frankenberg H, Sorge I, Zeller T, Tubler T. Percutaneous transluminal


