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

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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.

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Abbreviations: CLI = critical limb ischemia, PES = paclitaxel-eluting stents, SES = sirolimus-eluting stents

CRITICAL limb ischemia (CLI) is the end stage of peripheral arterial occlusive disease and occurs when blood flow to the distal leg is severely diminished because of diffuse multilevel atherosclerosis, which particularly afflicts 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-

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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 periprocedural 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 sheath 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 inactivate polymer carrier that helps in the controlled release of the drug. The stent is coated with 1 $\mu g/mm^2$ 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 cytostatic doses, paclitaxel is mainly characterized by antiinflammatory 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