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Efficacy of Cilostazol After Endovascular Therapy for Femoropopliteal Artery Disease in Patients With Intermittent Claudication

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Objectives The purpose of this study was to investigate whether cilostazol reduces restenosis and revascularization after endovascular therapy (EVT) for femoropopliteal lesions.

Background Cilostazol improves walking distance in patients with intermittent claudication and reduces restenosis after coronary intervention, but its efficacy remains unclear after EVT for femoropopliteal disease.

Methods This study was performed as a multicenter, randomized, open-label clinical trial. Eighty patients (mean age 70.7 ± 6.2 years, 84% men) with intermittent claudication due to a femoropopliteal lesion were randomly assigned to receive or not receive cilostazol in addition to aspirin. The primary end point was freedom from target vessel revascularization, and the secondary end points were the rate of restenosis and freedom from target lesion revascularization and major adverse cardiovascular events, defined as all-cause death, myocardial infarction, stroke, repeat revascularization, and leg amputation.

Results Clinical follow-up information was obtained in all patients. Patient, lesion, and procedural characteristics did not differ significantly between the 2 groups. Stenting was performed in 36 patients (cilostazol, 16; control, 20; $p = 0.36$). Freedom from target vessel revascularization at 2 years after EVT was significantly higher compared with the control group (84.6% vs. 62.2%, $p = 0.04$). The rate of restenosis was lower in the cilostazol group (43.6% vs. 70.3%, $p = 0.02$), and freedom from target lesion revascularization and major adverse cardiovascular events was higher in the cilostazol group (87.2% vs. 67.6%, $p = 0.046$, 76.8% vs. 45.6%, $p = 0.006$, respectively). There was no major bleeding in either group during follow-up period.

Conclusions Cilostazol reduced restenosis and repeat revascularization after EVT in patients with intermittent claudication due to femoropopliteal disease. (J Am Coll Cardiol 2009;53:48–53) © 2009 by the American College of Cardiology Foundation

Peripheral arterial disease (PAD) has a high prevalence worldwide. Furthermore, PAD damages the lower extremities and is complicated by ischemic disease in important organs, leading to a 5- or 6-fold increase in mortality due to coronary artery diseases and stroke in PAD patients (1).

Many PAD patients cannot undergo surgical revascularization and are often treated with endovascular therapy (EVT). The recently introduced nitinol stent has improved the patency rate for stenting of the femoropopliteal artery compared with conventional stents (2). However, the long-term patency rate of the nitinol stent is insufficient compared with bypass surgery, and many patients are still at high risk for restenosis and require adjuvant systemic therapy. The 2007 Trans-Atlantic Inter-Society Consensus II (TASC II) (3) recommended antiplatelet therapy as pharmacotherapy after percutaneous transluminal angioplasty and stent implantation. However, most evidence supporting perioperative antiplatelet therapy has emerged from studies on coronary artery disease, and little from EVT in PAD patients.

Cilostazol is an oral antiplatelet agent that is indicated for treatment of intermittent claudication (IC) (4), and in patients with coronary artery disease, cilostazol may lower restenosis and repeat revascularization after coronary intervention (5). Therefore, we conducted a multicenter trial to determine the efficacy of cilostazol in patients treated with EVT for femoropopliteal disease.

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Methods

Study design. The study was performed as a multicenter, randomized, open-label clinical trial. The effect of cilostazol in preventing restenosis and repeat revascularization after treatment of the femoropopliteal disease was evaluated for 24 months by comparison of cilostazol-treated patients and untreated patients. Patients with IC who had a de novo femoropopliteal disease without an inflow lesion, with an outflow artery, and with symptoms that were not improved by pharmacotherapy or exercise therapy were enrolled in the study before EVT. Other inclusion criteria were age ≥18 years and <80 years old, an ankle-brachial index of ≤0.9, and a percent diameter stenosis (%DS) of ≥50% by visual estimate on angiography. Patients with previous lower extremity bypass surgery, previous EVT in the femoropopliteal artery, acute onset limb ischemia, or severe lower extremity ischemic symptoms classified into Rutherford category 4, 5, or 6 were excluded.

Patient randomization and allocation to groups was performed using the envelope method by a researcher who was not involved in any other aspect of the study and who was blinded to the study procedure. The study was approved by the Institutional Review Board of each institution, and written informed consent was obtained from each subject. This study is registered with the University Hospital Medical Information Network–Clinical Trials Registry (UMIN-CTR), as accepted by the International Committee of Medical Journal Editors (no. UMIN000001434).

Study procedures. All patients were taking aspirin (81 to 100 mg/day) and ticlopidine (200 mg/day) and had been assigned to the cilostazol or noncilostazol (control) group by the day before EVT or earlier. Patients assigned to the cilostazol group received cilostazol (200 mg/day) for 2 consecutive years, with the initial administration of cilostazol on the morning of the day EVT was performed. Hemodialysis patients in the cilostazol group received the drug at a dose of 100 mg. For patients who were already taking cilostazol before EVT, oral treatment was suspended when informed consent was obtained, and they were assigned to a group. At the discretion of the surgeon, patients were treated with a commercially available balloon or a cutting balloon for stent implantation, and ticlopidine was stopped in these patients on or after the day of the procedure. Other patients who underwent stent implantation received oral ticlopidine for 4 weeks after the procedure.

Interventions. All procedures were performed using a 6- or 7-F sheath. Unfractionated heparin was injected intra-arterially before the intervention at a dose of 3,000 to 5,000 IU and added as required to maintain the active clotting time at ≥200 s. The target lesion was passed with a 0.018- or 0.014-inch guidewire, the diameter and length of the balloon or cutting balloon were determined by the surgeon on the basis of angiography, and the vessel was expanded. After balloon angioplasty for at least 60 s, angiography was conducted and stent implantation was then performed in patients who had a residual stenosis of >30% or a flow-limiting dissection. A commercially available self-expandable stent was used. The stent type was determined by the operators, and the stent size was chosen to be 1 to 2 mm larger than the vessel diameter determined.

Abbreviations and Acronyms

EVT = endovascular therapy
IC = intermittent claudication
MACE = major adverse cardiovascular events
MI = myocardial infarction
PAD = peripheral arterial disease
%DS = percent diameter stenosis
TLR = target lesion revascularization
TVR = target vessel revascularization

Follow-up. Patients were contacted 1 month after the procedure and asked to return for a clinic visit at 6, 12, and 24 months. At these times, evaluation of restenosis was performed using Duplex ultrasonography. Occurrences of bleeding, myocardial infarction (MI), stroke, repeat revascularization, and leg amputation were recorded.

Study end points. The primary end point was defined as the freedom from target vessel revascularization (TVR) at 2 years after treatment, and the secondary end points were binary restenosis rate and freedom from target lesion revascularization (TLR) and major adverse cardiovascular events (MACE) after 2 years. MACE included death, nonfatal MI, stroke, percutaneous or surgical repeat revascularization, and leg amputation. Independent observers blinded to the medication evaluated the clinical follow-up data. Binary restenosis was defined as a peak systolic velocity ratio of ≥2.4 (6). No detectable signal was graded as complete occlusion.

Procedural success was defined as a residual stenosis of <30% and the absence of a flow-limiting dissection in angiography. Myocardial infarction was defined by a significant elevation of serum biomarkers (troponin above the MI level or creatinine kinase levels twice normal) or new Q waves on the electrocardiogram. Stroke was defined as cerebral stroke that persisted for at least 24 h and indicated the occurrence of a neurological deficit. Major bleeding was defined as a need for transfusion, surgical intervention, or hypotension requiring inotropic support. The target lesion was defined as the treated segment from 10 mm proximal to 10 mm distal. The target vessel was defined as the entire vessel of the treated limb. TLR was defined as any repeat EVT for restenosis or other complication of the target lesion with a %DS of ≥50% in angiography (core laboratory assessment). TVR was defined as any repeat revascularization by EVT or bypass surgery of any segment of the target vessel with a %DS of ≥50% in angiography.

Statistical analysis. Values are reported as mean ± SD. All analyses were based on an intention-to-treat principle. Continuous variables were examined by use of the unpaired *t* test or nonparametric analysis by the Mann-Whitney *U*