The incidence of peripheral artery disease (PAD) has risen over recent years due to an aging society as well as an increase in the number of patients with risk factors for atherosclerosis, especially diabetes mellitus (DM). Accordingly, the management and prevention of PAD is of particular interest from both medical cost and public health perspectives. Approximately two-thirds of obstructive lesions responsible for symptomatic PAD are femoropopliteal lesions. Although percutaneous balloon angioplasty (PTA) has been the standard and traditional endovascular revascularization procedure, restenosis develops within 12 months in 40% to 60% of patients with femoropopliteal lesions. The introduction of nitinol stents for endovascular therapy has resulted in their widespread use in patients with femoropopliteal lesions, largely due to their satisfactory durability compared with balloon angioplasty, which also has been reflected in updated guidelines. The impact of nitinol stent use on long-term patency is significant for femoropopliteal lesions, except for those shorter than 5 cm. However, there remains a 20% to 50% incidence of restenosis at 1 year, and achieving better results in these lesions is an important challenge for endovascular therapy.

THE ROLE OF MEDICAL INTERVENTION FOR PATIENTS WITH PAD

The objectives of medical intervention in patients with PAD are: (1) systemic management of risk factors
Cilostazol is first-line therapy for patients with PAD presenting with intermittent claudication (class I and level A evidence), and this recommendation has persisted in recent guidelines.

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Cover Story

Impact of Cilostazol After Endovascular Therapy for Infrapopliteal Disease

Many patients who require revascularization for infrapopliteal lesions exhibit symptoms of critical limb ischemia (CLI). The basic therapy for CLI involves pain control and revascularization, typically through surgical means, but endovascular therapies have also been applied broadly in CLI patients, with many reports showing favorable outcomes. Lower extremity lesions in patients with CLI are often challenging, presenting in a variety of scenarios that can include combinations of focal, long, occlusive, and diffuse disease. If treated via endovascular means, most lesions are initially attempted with balloon angioplasty alone; however, the rate of restenosis can be extremely high after treatment. Although aspirin is often administered for restenosis management, the optimal medical therapy after endovascular treatment for CLI patients has not yet been determined.

Recently, cilostazol has been reported as a pharmacologic option after endovascular therapy. We present our findings for cilostazol as drug therapy after intervention for lower extremity lesions in patients with CLI.

Using Cilostazol to Avoid Major Amputations

In a multicenter retrospective study, we examined whether cilostazol could improve limb salvage rates in patients with CLI (Figure 1). The subgroup analysis in this study (nonelderly men younger than 75 years with infrapopliteal lesions, diabetes, tissue loss, who were not on dialysis) showed that cilostazol could be effective, especially for improving amputation-free survival rates in patients with isolated infrapopliteal lesions (hazard ratio [HR], 0.7; 95% confidence [CI], 0.51–0.96; P = .03), diabetes (HR, 0.56; 95% CI, 0.37–0.86; P < .01), and Rutherford class 5 (HR, 0.68; 95% CI, 0.49–0.95; P = .02).

We examined the efficacy of cilostazol alone on 386 extremities with isolated infrapopliteal lesions and showed that administration of cilostazol was effective for amputation-free survival (HR, 0.7; 95% CI, 0.51–0.96; P = .03) and limb salvage (HR, 0.51; 95% CI, 0.3–0.85; P = .01). However, efficacy was not confirmed regarding overall survival rates (HR, 0.85; 95% CI, 0.6–1.22; P = .38). Based on these data, it was suggested that cilostazol after endovascular therapy was effective for managing restenosis in infrapopliteal lesions and that further discussions are necessary to evaluate the drug.

Effects of Cilostazol on Preventing Infrapopliteal Restenosis

According to our subanalysis findings, administration of cilostazol improves limb salvage rates in CLI patients with infrainguinal disease and may decrease the need for repeat revascularization after balloon angioplasty for infrapopliteal lesions. But, the question arises: In what ways does cilostazol contribute to the avoidance of major amputation and improve repeat revascularization? In addition to the antiplatelet effects of cilostazol, various pharmacological effects have been observed. These include vasodilatory actions and effects to improve the vascular endothelium and microcirculation. However, the mechanism underlying the prevention of restenosis remains unclear.

In a multicenter prospective registry, we found that the rate of restenosis 3 months after balloon angioplasty for below-the-knee lesions was approximately 70%, as measured by angiography. This was similar to the findings of Schmidt et al. Based on results of the sub-analysis of J-BEAT Angio, we found that administration of cilostazol significantly reduced the number of cases with restenosis or reocclusion during the 3 months after angioplasty, decreasing the need for repeat revascularization. These results support the possibility that cilostazol may improve limb salvage after endovascular intervention, as noted previously (Figure 2).

We examined the usefulness of cilostazol based on the wound healing time in CLI patients. The median wound healing time in the OLIVE registry was 97 ± 10 days, compared with 117 ± 79 days in the J-BEAT Angio study. Based on these data, it was suggested that wound care would require 3 to 4 months, depending on the size of the wound and the development of infection. During the 3 months after balloon angioplasty, the rate of restenosis for infrapopliteal lesions was 70%, and administration of cilostazol was considered to be useful for its prevention. It was reported that stent placement for infrapopliteal lesions (especially drug-eluting stents) would be effective for the prevention of restenosis compared with balloon angioplasty. The primary patency rate up to 1 year after balloon angioplasty was as low as 58.1% ± 4.6%, with a limb salvage rate as high as 86% ± 2.7%.

These data do not necessarily confirm a positive correlation between the rate of restenosis and the requirement for major amputation, and to date, the efficacy of stent use has not been established in diffuse obstructing lesions or lesions in the ankle and lower parts of below-the-knee artery, which are observed in many patients with infrapopliteal lesions. Therefore, stent use is currently limited to being a bailout option for infrapopliteal proximal lesions.

The efficacy of drug-coated balloons has also been evaluated, and their use in infrapopliteal lesions may help prevent restenosis. However, from the perspective of medical economy, their cost effectiveness must still be evaluated.

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In 2005, a retrospective and nonrandomized study (therefore corresponding to evidence level C) showed that orally administered cilostazol reduced the frequency of TLR after successful endovascular therapy for de novo femoropopliteal lesions. TLR was significantly reduced in the cilostazol (+) group (12% [8/68] vs 32% [23/73], P < .01).

Two subsequent studies with prospective randomized design investigated whether cilostazol reduces restenosis (not TLR) after successful endovascular therapy for de novo femoropopliteal lesions. In one of these studies, the rate of restenosis for infrapopliteal lesions was 70%, and administration of cilostazol was considered to be useful for its prevention. It was reported that stent placement for infrapopliteal lesions (especially drug-eluting stents) would be effective for the prevention of restenosis compared with balloon angioplasty. The primary patency rate up to 1 year after balloon angioplasty was as low as 58.1% ± 4.6%, with a limb salvage rate as high as 86% ± 2.7%.

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yielded similar favorable clinical outcomes in association with the use of cilostazol in patients with PAD presenting with femoropopliteal lesions in an Asian population (Figure 2). The results of these studies suggest that cilostazol can be used as first-line medical therapy for reducing the incidence of restenosis in patients undergoing endovascular therapy with stenting for femoropopliteal disease, in addition to aspirin or clopidogrel. ■

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CONCLUSION
A recent retrospective study, a prospective single-center study, and prospective multicenter studies yielded similar favorable clinical outcomes in associa-