Pharmacologic Options for Treating Restenosis

The role of cilostazol in the treatment of patients with infrainguinal lesions.

BY OSAMU IIDA, MD, AND YOSHIMITSU SOGA, MD

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).[1,2] 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.[3-5] 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.[6-8] 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,[8,9] 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.[7] 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.[6-8]

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

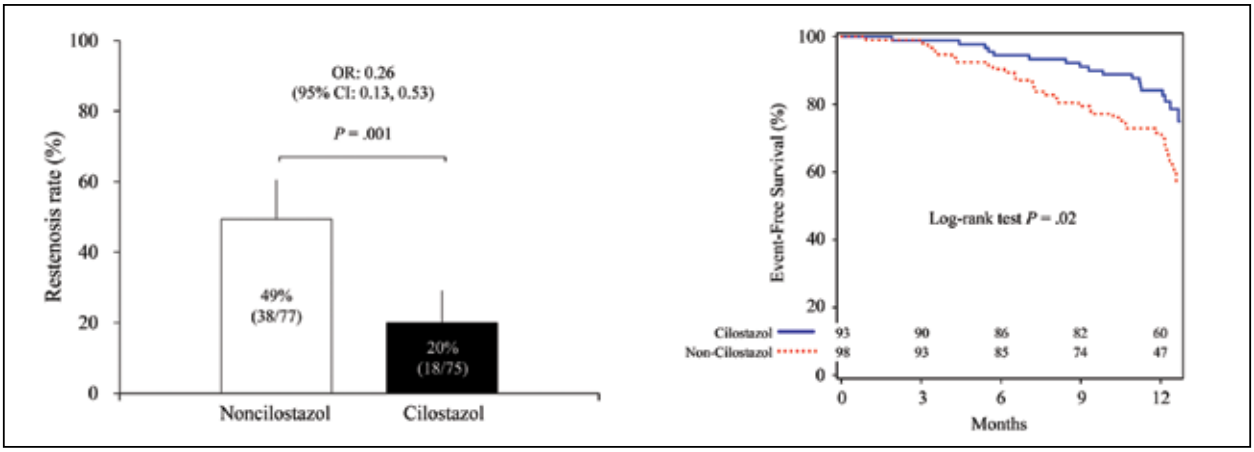

Figure 1. Twelve-month angiographic restenosis rates and event-free survival (intention-to-treat [ITT] analysis) after PTA with provisional nitinol stenting for symptomatic de novo femoropopliteal lesions in the cilostazol group and the noncilostazol group. Primary endpoint, ITT analysis. The angiographic restenosis rate was significantly lower in the cilostazol group than in the noncilostazol group. Restenosis (defined as ≥ 50% stenosis) was evaluated by angiography. The angiographic restenosis rate was 24% at 12 months in the cilostazol group and 49% in the noncilostazol group by ITT analysis (*P* = .0001). At 12 months, event-free survival was significantly higher in the cilostazol group than in the noncilostazol group (83% vs 71%; *P* = .02). Adapted with permission from Iida O, Yokoi H, Soga Y, et al. Cilostazol reduces angiographic restenosis after endovascular therapy for femoropopliteal lesions in the sufficient treatment of peripheral intervention by cilostazol study. *Circulation*. 2013;127:2307–2315.[10]

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.

(primary prevention), in particular, intensive management of hypertension (target in normal [and high] risk individuals for systolic blood pressure of < 140 mm Hg [130 mm Hg], and for diastolic blood pressure of < 90 mm Hg [80 mm Hg]), dyslipidemia (LDL < 100 mm Hg [70 mm Hg]), and diabetes (HbA1c < 7%); (2) systematic management of atherothrombosis (ATIS), for reduction of risk for myocardial infarction (MI), stroke, or vascular death; and (3) local management, namely symptomatic improvement, including relief of claudication and reduction of target lesion revascularization (TLR) and restenosis.

In the latest ACC/AHA 2013 guidelines,[11] antiplatelet therapy is recommended as first-line therapy for risk reduction of myocardial infarction, stroke, or vascular death in both symptomatic and asymptomatic patients with an ABI ≤ 0.9. Clopidogrel is considered an attractive alternative to aspirin; the level of evidence for aspirin use has changed from A to B.

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. In the setting of local management after revascularization, recommendation 41 from TASC II states that antiplatelet therapy should be started preoperatively and continued as adjuvant pharmacotherapy after an endovascular or surgical procedure. Antiplatelet therapy should be continued on an indefinite basis unless subsequently contraindicated. No specific medical intervention was recommended for local management (ie, reduction of TLR and restenosis after revascularization).

THE IMPACT OF CILOSTAZOL IN SFA DISEASE TREATMENT

Cilostazol is a phosphodiesterase type 3 (PDE3) inhibitor, which increases the concentration of cyclic adenosine monophosphate. It has multifaceted effects, such as inhibition of platelet activation, vasodilation, antiproliferation of vascular smooth muscle cells, and improvement of endothelial cell function. Although cilostazol has the best overall evidence for treatment benefit in patients with claudication, side effects such as headache, diarrhea, and palpitations were reported. Also, since the drug is in the phosphodiesterase 3 inhibitor class of drugs, it should not be given to patients with any evidence of congestive heart failure because of a theoretical concern for increased risk of mortality.[2]

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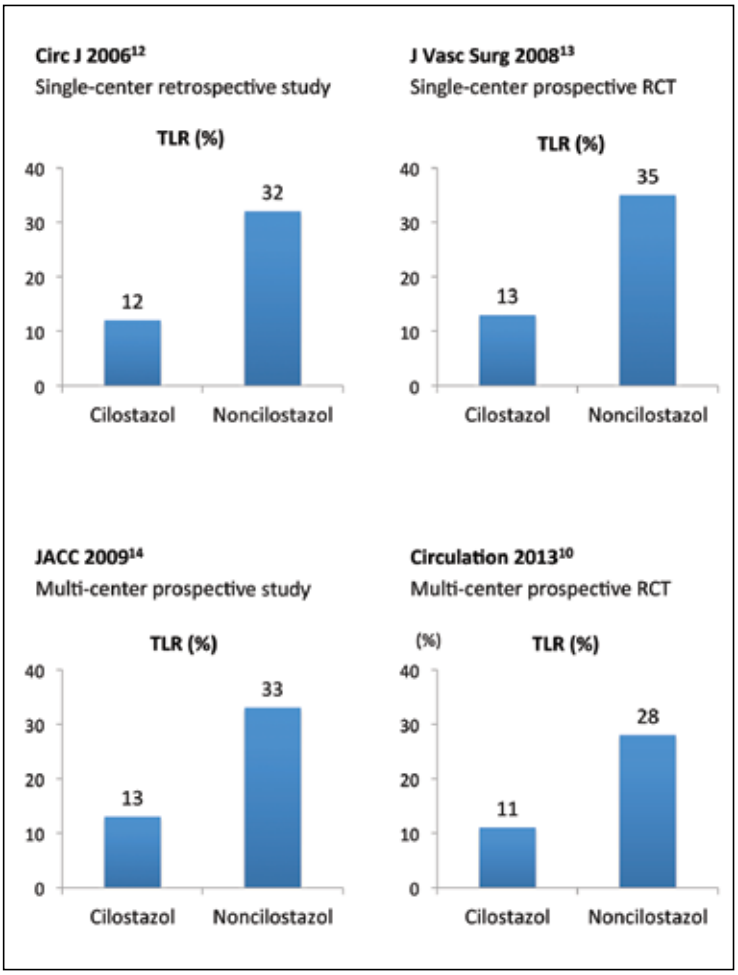
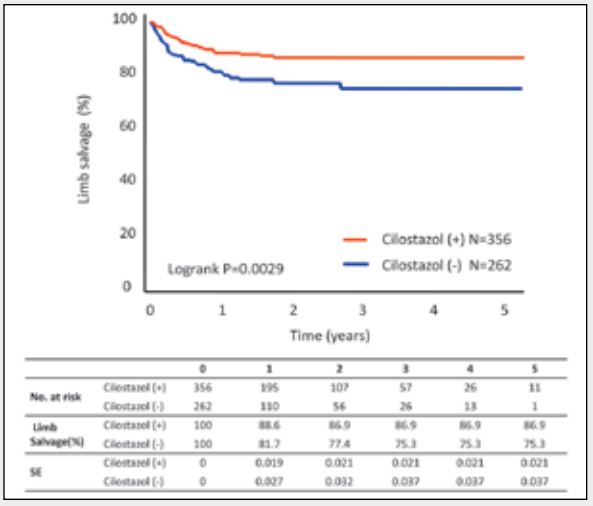


Figure 2. Cilostazol reduces TLR after femoropopliteal intervention. A recent retrospective study, a prospective single-center study, and prospective multicenter studies yielded almost similar results for use of cilostazol on patients with PAD presenting with femoropopliteal lesions.

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.



		0	1	2	3	4	5
No. at risk	Cilostazol (+)	356	195	107	57	26	11
	Cilostazol (-)	262	110	56	26	13	1
Limb Salvage(%)	Cilostazol (+)	100	88.6	86.9	86.9	86.9	86.9
	Cilostazol (-)	100	81.7	77.4	75.3	75.3	75.3
SE	Cilostazol (+)	0	0.019	0.021	0.021	0.021	0.021
	Cilostazol (-)	0	0.027	0.032	0.037	0.037	0.037

Figure 1. Cilostazol improved limb salvage rates after endovascular treatment for infrainguinal disease. Reprinted from *J Vasc Surg*, Vol. 54, Soga Y, Iida O, Hirano K, et al, Impact of cilostazol after endovascular treatment for infrainguinal disease in patients with critical limb ischemia, 1659–1667, Copyright (2011), with permission from Elsevier Limited.[1]

USING CILOSTAZOL TO AVOID MAJOR AMPUTATIONS

In a multicenter retrospective study,[1] 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* = 0.03) 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,[2] 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.[3] Based on results of the subanalysis of J-BEAT Angio,[2] 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.[4] 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,[5] compared with 117 ± 79 days in the J-BEAT Angio study.[2] 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%.[6]

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,[7] and their use in infrapopliteal lesions may help prevent restenosis. However, from the perspective of medical economy, their cost effectiveness must still be evaluated.

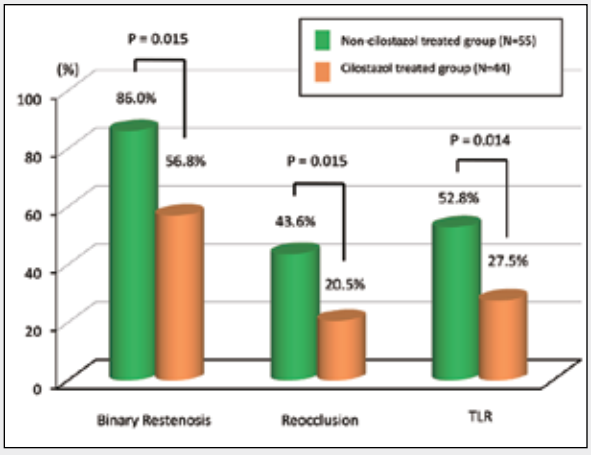


Figure 2. Cilostazol reduced 3-month angiographic restenosis, reocclusion, and reintervention rates in patients with CLI. Reprinted from *Eur J Vasc Endovasc Surg*, Vol. 44, Soga Y, Iida O, Kawasaki D, et al, Impact of cilostazol on angiographic restenosis after balloon angioplasty for infrapopliteal artery disease in patients with critical limb ischemia, 577–581, Copyright (2012), with permission from Elsevier Limited.[4]

Early data evaluating administration of cilostazol to CLI patients are encouraging, although further study is needed to determine its ideal applications in reducing restenosis rates after endovascular therapies. ■

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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], $P < .01$).[12]

Two subsequent studies[13,14] 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,[13] the primary patency rates were 87%, 82%, and 73% at 12, 24, and 36 months, respectively, in the cilostazol group, and 65%, 60%, and 51% at 12, 24, and 36 months, respectively, in the ticlopidine group, based on an intention-to-treat analysis (P = .013). In an as-treated analysis, patency rates were 87%, 82%, 73% at 12, 24, 36 months, respectively, in the cilostazol group, and 64%, 57%, 48% at 12, 24, 36 months, respectively, in the ticlopidine group (P = .0088). Similar trends were seen in both studies.

These results may reflect inhibition by cilostazol of neointimal hyperplasia after stent placement in femoropopliteal lesions and suggest the potential feasibility of cilostazol as a first-line oral drug after endovascular intervention for femoropopliteal lesions.

WHAT DOES THE STOP-IC STUDY TEACH US?

The Sufficient Treatment of Peripheral Intervention by Cilostazol (STOP-IC) study investigated whether cilostazol reduces the 12-month angiographic restenosis rate after PTA with provisional nitinol stenting for femoropopliteal lesions.[10] This study was prospective, randomized, open-label, and multicenter.

Analysis of angiographic data and diagnosis of restenosis at 12 months after intervention was routinely done at a core laboratory in an endpoint-blinded manner. The primary endpoint of this study was the angiographic restenosis rate at 12 months after endovascular therapy, while the main secondary endpoint was event-free survival defined as freedom from death, major amputation, clinically driven TLR, and target limb ischemia requiring surgical intervention.

The angiographic patency rate at 1 year after intervention was 80% in patients receiving cilostazol treatment compared with 51% in patients not receiving it, and cilostazol significantly reduced angiographic restenosis after intervention for femoropopliteal lesions. Also, the cilostazol group had a larger minimum lumen diameter (3.1 ± 1.5 mm vs 2.2 ± 1.1 mm; P < .001), less late lumen loss (1.1 ± 0.6 mm vs 1.4 ± 0.7 mm; P = .03) and less percent diameter stenosis (39% ± 23% vs 52% ± 22%; P < .001), leading to a lower rate of TLR (17% vs 40%; P < .01) by ITT analysis. Finally, the cilostazol group also had a significantly higher event-free survival rate at 12 months (83% vs 71%; P = .02), although the rate of cardiovascular events was similar in the two groups (Figure 1).

CONCLUSION

A recent retrospective study, a prospective single-center study, and prospective multicenter studies 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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