Impact of cilostazol after endovascular treatment for infrainguinal disease in patients with critical limb ischemia

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Background: Cilostazol reduces restenosis and repeat revascularization after endovascular therapy (EVT) in claudicant patients with femoropopliteal lesions. However, the efficacy of cilostazol in patients with critical limb ischemia (CLI) is unclear. Therefore, we investigated the effect of cilostazol on outcomes in patients with CLI.

Methods: From January 2004 to December 2009, 618 patients (30.8% women, 356 treated with cilostazol, 72.4 ± 7.3 years old) with CLI underwent EVT for de novo infrainguinal lesions. Their data were retrospectively analyzed. The primary outcome measure was amputation-free survival (AFS). The secondary outcome measures were overall survival, limb salvage, freedom from repeat revascularization, and freedom from surgical conversion. Mean follow-up was 21 ± 14 months.

Results: AFS and the limb salvage rate at 5 years were significantly higher in the cilostazol-treated group (47.7% vs 32.7%, P < .01; 86.6% vs 75.3%, P < .01; respectively). However, overall survival and freedom from repeat revascularization at 5 years did not differ significantly between the two groups (43.9% vs 46.0%, P = .24; 39.9% vs 31.8%, P = .21, respectively). Freedom from surgical conversion at 5 years was significantly higher in the cilostazol-treated group (91.0% vs 81.2%, P < .01). After correcting all end points with baseline variables, cilostazol was effective for prevention of AFS (hazard ratio [HR], 0.67; 95% confidential interval [CI], 0.49-0.91; adjusted P = .01) and improvement of limb salvage rate (HR, 0.42; 95% CI, 0.25-0.69; adjusted P < .01). There was no significant difference in overall survival, repeat revascularization, and surgical conversion between the groups.

Conclusions: Cilostazol may improve AFS and limb salvage rate after EVT for infrainguinal disease in patients with CLI.

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The primary goals of treatment of patients with critical limb ischemia (CLI) are pain control and ischemic release by revascularization.1,2 However, age, comorbidities, and general conditions often make it difficult to perform surgical revascularization. Many recent studies have shown the efficacy of endovascular therapy (EVT) in patients with CLI,3-7 and several studies have reported that EVT has outcomes similar to those of surgery.8-10 This suggests that more patients with CLI are likely to undergo EVT, but appropriate medical therapy after EVT has not been investigated.

Cilostazol has an inhibitory effect on restenosis after percutaneous coronary intervention,11 and several studies in patients with peripheral artery disease (PAD) have shown improvement of walking distance in intermittent claudication,12 restenosis after femoropopliteal stenting,13 and a reduced need for revascularization in claudicant patients.14 However, the efficacy of cilostazol has not been examined in patients with CLI.

The basic treatment methods for CLI patients are pain control and revascularization. At present, therapy that improves the outcome of CLI has not been established, and there has been limited discussion of the efficacy of adjunct therapy after revascularization in CLI patients. In addition, several drugs are being used empirically for treatment of this condition without clear evidence of the reasons for their use. Therefore, we evaluated the efficacy of cilostazol after EVT in patients with CLI due to infrainguinal lesions.

METHODS

The study protocol was approved by the Ethics Committees of the participating hospitals, and the study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

Study design. The study was performed as a multicenter, prospective maintained database, retrospective analysis. Between January 2004 and December 2009, consec-
Table I. Patients’ characteristics

<table>
<thead>
<tr>
<th>Variable^a</th>
<th>Yes (n = 356)</th>
<th>No (n = 262)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>72.0 ± 11.3</td>
<td>71.3 ± 9.5</td>
<td>.44</td>
</tr>
<tr>
<td>Male (%)</td>
<td>242 (68.0)</td>
<td>165 (63.0)</td>
<td>.20</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.4 ± 3.4</td>
<td>21.9 ± 2.9</td>
<td>.09</td>
</tr>
<tr>
<td>Hypertension</td>
<td>291 (81.7)</td>
<td>218 (81.3)</td>
<td>.89</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>252 (70.8)</td>
<td>189 (72.1)</td>
<td>.71</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>258 (72.5)</td>
<td>205 (78.2)</td>
<td>.10</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>170 (47.8)</td>
<td>151 (57.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Current smoker</td>
<td>107 (30.1)</td>
<td>61 (23.3)</td>
<td>.06</td>
</tr>
<tr>
<td>COPD</td>
<td>22 (6.2)</td>
<td>13 (5.0)</td>
<td>.52</td>
</tr>
<tr>
<td>CAD</td>
<td>179 (50.3)</td>
<td>150 (57.3)</td>
<td>.09</td>
</tr>
<tr>
<td>CVD</td>
<td>131 (36.8)</td>
<td>92 (35.1)</td>
<td>.67</td>
</tr>
<tr>
<td>CABG</td>
<td>179 (50.3)</td>
<td>150 (57.3)</td>
<td>.09</td>
</tr>
<tr>
<td>LV dysfunction^b</td>
<td>31 (8.7)</td>
<td>18 (6.9)</td>
<td>.40</td>
</tr>
<tr>
<td>Rutherford class</td>
<td>3.4 ± 2.9</td>
<td>3.4 ± 2.9</td>
<td>.75</td>
</tr>
</tbody>
</table>

^aContinuous data are presented as mean ± standard deviation; categoric data as number (%).

^bLV dysfunction was defined as a left ventricular ejection fraction <40%.

For femoropopliteal lesion, balloon angioplasty was performed with an optimal size after a 0.035- or 0.018-inch guidewire crossed the lesion. If a suboptimal result caused by flow-limiting dissection or residual stenosis of >30% was found for the femoropopliteal lesion, a stent was implanted. The entire lesion was covered by the stent. Two types of nitinol stents were implanted: Luminexx (Bard, Murray Hill, NJ) and SMART (Cordis, Johnson & Johnson, Miami, Fla). The stent type was determined by the operators, and the stent size chosen was 1 to 2 mm larger than the reference vessel diameter.

<table>
<thead>
<tr>
<th>Variable^a</th>
<th>Yes (n = 356)</th>
<th>No (n = 262)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length, mm</td>
<td>161 ± 83</td>
<td>155 ± 93</td>
<td>.61</td>
</tr>
<tr>
<td>Ref vessel diameter, mm</td>
<td>5.1 ± 0.7</td>
<td>5.1 ± 0.8</td>
<td>.75</td>
</tr>
<tr>
<td>Stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prediameter, %</td>
<td>89.8 ± 15.8</td>
<td>88.5 ± 16.1</td>
<td>.52</td>
</tr>
<tr>
<td>Postdiameter, %</td>
<td>32.7 ± 16.2</td>
<td>33.5 ± 14.4</td>
<td>.68</td>
</tr>
<tr>
<td>Chronic total occlusion</td>
<td>84 (63.2)</td>
<td>51 (52.6)</td>
<td>.11</td>
</tr>
</tbody>
</table>

^aContinuous data are presented as mean ± standard deviation; categoric data as number (%).

^bLV dysfunction was defined as a left ventricular ejection fraction <40%.

All patients were medicated with dual antiplatelet therapy consisting of aspirin (100 mg/day) and clopidogrel (75 mg/day) before the procedure. After insertion of a 4F or 6F sheath from a crossover approach or an antegrade ipsilateral approach, an intra-arterial bolus of 3000 to 5000 IU of heparin was injected, with additional heparin given intravenously during the procedure to maintain the activated clotting time at 200 seconds.
After the procedure, all patients were prescribed lifelong aspirin (100-200 mg/day), and prolonged (≥1 month) clopidogrel (75 mg/day) was recommended for patients who received femoropopliteal stenting. For patients who received balloon angioplasty, aspirin alone was recommended. At the discretion of the surgeon, thienopyridine or cilostazol (200 mg/day) was added. Aspirin and thienopyridine or cilostazol were started by the day before EVT or earlier. Additional dosage was determined by the doctor in charge of each patient.

Cilostazol administration was continued after hospital discharge for an average of 20±17 months, but was discontinued in some patients because of side effects. Patients who were receiving cilostazol at hospital discharge were included in the cilostazol group. Patients who had already taken cilostazol before the procedure continued to receive cilostazol after the procedure.

All patients were assessed at 1, 3, and 6 months after the procedure, and then every 6 months thereafter. Wound care was conducted together with revascularization in all cases by consulting a vascular surgeon or a plastic surgeon in each center. Repeat revascularization was performed on the basis of ischemic-driven symptoms or clinical findings.

**Outcome measures.** The primary outcome measure was amputation-free survival (AFS). Secondary outcome measures were overall survival, limb salvage rate, freedom from repeat revascularization, and freedom from surgical conversion.

**Definitions.** CLI was defined as Rutherford category 4, 5, or 6. Procedure success was defined as straight-line flow to the pedal arch with <30% of residual stenosis after EVT. Limb salvage was defined as freedom from the amputation above the ankle. Coronary artery disease (CAD) was defined as stable angina with documented CAD, history of percutaneous coronary intervention or coronary artery bypass grafting, or previous myocardial infarction. Cerebrovascular disease was defined as a hospital or neurologist report with the diagnosis of transient ischemic attack or ischemic stroke. A heart failure case was determined to be a patient with a previous diagnosis of heart failure, a history of hospitalization for heart failure, or current treatment for heart failure.

Diabetes was defined as glycosylated hemoglobin A1C (HbA1C) of >6.5%, casual plasma glucose of >200 mg/dL, or patients who were treated with oral hypoglycemic agents or insulin injection. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or both, or ongoing therapy for hypertension.

Below-the-knee (BTK) runoff was assessed by angiography before or after procedure. Poor runoff was defined as one or no BTK vessel runoff. Left ventricular ejection fraction was measured by contrast left ventriculography or echocardiography. Patients with left ventricular ejection fraction <40% were regarded as having left ventricular dysfunction.
dysfunction. Elderly patients were defined as patients aged >75 years.

Statistical analysis. Continuous variables are expressed as mean ± standard deviation, unless otherwise indicated, and were compared using the t test or Wilcoxon rank sum test based on the distribution. Categoric variables were compared by χ² test. Survival curves were estimated by the Kaplan-Meier method and compared with the log-rank test.

The consistency of the treatment effect was assessed among seven prespecified subgroups comprising gender, elderly, ambulatory, infrapopliteal lesion, diabetes, hemodialysis, or tissue loss. The effect in each subgroup was analyzed with the use of a Cox proportional hazard model, without adjustment for covariates. Hazard ratio (HR), 95% confidence intervals (CI), and P value were calculated with the use of models adjusted for the baseline characteristics with P < .10 on univariate analysis. A value of P < .05 was considered statistically significant.

RESULTS

Baseline characteristics. The baseline characteristics of the patients are listed in Table I. The average age was 72.4 ± 7.3 years, and 30.8% were women. Ischemic rest pain was present in 25.6% and tissue loss in 74.4%. The mean follow-up period was 21.0 ± 13.8 months. Use of thienopyridine was less frequent and body mass index and the incidence of coronary disease were lower in the cilostazol-treated group. All other baseline characteristics were similar in the two groups.

Femoropopliteal lesions alone were treated in 192 patients (31.1%), infrapopliteal lesions alone in 386 (62.5%), and both lesions in 20 (3.2%). Bilateral CLI was observed in 101 patients (16.3%). Postprocedure skin perfusion pressure (SPP) was significantly higher in the cilostazol-treated group (49.8 ± 19.9 vs 44.2 ± 22.0 mm Hg, P = .002). Lesion characteristics were similar in both groups (Table II).

Procedure success. EVT was performed in 618 legs and was successful in 568 (91.9%). Of the 50 legs with poor outcomes, 18 were treated with lower extremity bypass and 32 with drug therapy. Subsequently, major amputation was required in 3 patients who underwent lower extremity bypass and in 22 of those who received drug therapy.

Primary and secondary outcome measures. The AFS rate was significantly higher in the cilostazol (+) group at 5 years than in the cilostazol (−) group (47.7% vs 32.7%; log-rank P < .001; Fig 1). The limb salvage rate was also significantly higher in the cilostazol group at 5 years (86.6% vs 75.3%; log-rank P = .004; Fig 2). However, there was no significant difference in overall survival rate between the two groups at 5 years (43.9% vs 46.0%; log-rank P = .24;
Fig 3). Freedom from cardiovascular death at 5 years tended to be higher in the cilostazol (+) group (70.4% vs 65.7%; log-rank P = .08; Fig 4). No significant difference of freedom from repeat revascularization was found in either group at 5 years (39.9% vs 31.8%; log-rank P = .21; Fig 5). However, freedom from surgical conversion was significantly higher in the cilostazol group at 5 years (91.0% vs 81.2%; log-rank P = .001).

After correcting all end points with the prespecified baseline variables of sex, age, body mass index, diabetes, smoker, CAD, hemodialysis, and use of thienopyridine, cilostazol was effective for prevention of AFS (HR, 0.67; 95% CI, 0.49-0.91; adjusted P = .011) and limb salvage rate (HR, 0.42; 95% CI, 0.25-0.69; adjusted P < .001). There was no significant difference in overall survival (HR, 1.04; 95% CI, 0.73-1.47; adjusted P = .84) and cardiovascular death (HR, 1.04; 95% CI, 0.63-1.71; adjusted P = .89) between the groups. The observed reduction in conversion of bypass surgery after EVT observed in the cilostazol group did not attain statistical significance (HR, 0.46; 95% CI, 0.21-1.01; adjusted P = .052; Table III).

Univariate prespecified subgroup analysis for the AFS was performed (Fig 6). Cilostazol was effective for men, nonelderly patients (aged <75 years), patients with an infrapopliteal lesion, diabetic patients, nondialysis patients, and patients with tissue loss, especially, Rutherford class 5. Cilostazol also tended to be effective for women and ambulatory patients (Fig 6).

DISCUSSION

The results of this study showed that cilostazol improved AFS in patients with CLI due to lesions in the leg below the groin. The limb salvage rate was significantly higher in the cilostazol group, but the all-cause mortality was similar; therefore, the improved limb salvage rate appeared to contribute greatly to the improved AFS. However, although cilostazol did not affect repeat revascularization, limb salvage was improved. A postoperative increase in peripheral perfusion pressure may have contributed to the improved limb salvage rate, because the postoperative SPP measured at 1 week to 1 month after the procedure was significantly higher in the cilostazol group (49.8 vs 44.2 mm Hg; P = .002; Table I). Miyashita et al15 found that cilostazol increased SPP in PAD patients and suggested that cilostazol administration may increase microcirculation in a severely ischemic limb. Verification of this finding requires a prospective study of restenosis rate and changes in SPP based on periodic follow-up angiograms.

The results of subgroup analysis indicated that cilostazol was effective in patients with a severe background, including infrapopliteal lesions, diabetes and tissue loss, but was less effective in cases with a poor prognosis, including
elderly patients and dialysis patients (group with a short observation period).

In the subanalysis of 386 legs with one infrapopliteal lesion, cilostazol significantly improved AFS (HR, 0.70; 95% CI, 0.51-0.96; unadjusted \( P = .03 \)) and limb salvage (HR, 0.51; 95% CI, 0.30-0.85; unadjusted \( P = .01 \)) but did not influence overall survival (HR, 0.85; 95% CI, 0.60-1.22; unadjusted \( P = .38 \)). All patients in this study with infrapopliteal lesions were treated with balloon angioplasty. Cilostazol is more effective for prevention of restenosis after revascularization in CAD patients treated with balloon angioplasty than in those treated with stenting.\(^1\) This is because intimal proliferation is more active after balloon angioplasty than after stenting, especially drug-eluting stent implantation.

The effect on lower extremity vessels is unknown, but we also found that cilostazol-treated patients with an infrapopliteal lesion that was treated with balloon angioplasty had a decreased tendency for repeat revascularization (HR, 0.73; 95% CI, 0.50-1.05; unadjusted \( P = .08 \)), suggesting an effect of cilostazol. Stenting (especially drug-eluting stent implantation) for infrapopliteal lesions is more effective than balloon angioplasty than after stenting, especially drug-eluting stent implantation.

In the current study, the efficacy of cilostazol was unclear in 158 patients without tissue loss, but with rest pain. At 2 years after treatment, the AFS in patients with rest pain was significantly higher than that in patients with tissue loss (80.3% vs 51.1%; \( P < .0001 \), log-rank test) and the rate of major amputation was significantly lower (5.0% vs 21.7%; \( P < .0001 \), log-rank test). Only six patients, two cilostazol (+) and four cilostazol (−), required major amputation during the observation period (\( P = .16 \)). The event incidence was not high in patients with rest pain; therefore, further larger-scale studies of the efficacy of cilostazol are required in these patients.

Diabetic patients with CLI have extremely high morbidity of 71% to 90%.\(^5\) Of the 618 patients in the current study, 463 (74.9%) were diabetic. The overall survival at 2 years was 68.6% in the diabetes group vs 64.5% in the nondiabetes group (\( P = .37 \), log-rank test); however, the limb salvage rate at 2 years was significantly lower in the diabetes group (80.7% vs 89.5%; \( P = .02 \), log-rank test).
Overall survival in the 173 diabetes patients with good glucose control (HbA1c >7%) was similar to that in the 290 patients with poor glucose control (HbA1c <7%), at 63.1% vs 72.5% at 2 years (P = .38, log-rank test). The limb salvage rate at 2 years was significantly lower in patients with poor glucose control (71.9% vs 85.9%; P = .0004, log-rank test).

Previous findings showed that the presence of diabetes and the HbA1c level have no relationship with death in patients with CLI who underwent EVT, but are prognostic factors for major amputation,21 and the results of this study supported these findings. In diabetic patients, cilostazol improved AFS (HR, 0.68; 95% CI, 0.50-0.90; unadjusted P = .008) and the limb salvage rate (HR, 0.49; 95% CI, 0.30-0.78; unadjusted P = .003), but was ineffective for all-cause mortality (HR, 0.84; 95% CI, 0.60-1.16; P = .28). A greater inhibitory effect of cilostazol on restenosis was shown in diabetes patients with coronary disease who underwent percutaneous coronary intervention,22 and the results of the current study also suggested that cilostazol may be more effective in patients with diabetes. Further studies are required to confirm the efficacy, but patients

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**Fig 5.** Kaplan-Meier curves show freedom from repeat revascularization in patients who did (+) and did not (−) receive cilostazol therapy.

**Table III.** Primary and secondary outcome measures

<table>
<thead>
<tr>
<th></th>
<th>Cilostazol therapy no. (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 356)</td>
<td>No (n = 262)</td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusteda</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amputation-free survival</td>
<td>126 (35.4)</td>
<td>110 (42.0)</td>
<td>0.70 (0.54-0.90)</td>
<td>.006</td>
<td>0.67 (0.49-0.91)</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limb salvage</td>
<td>38 (10.7)</td>
<td>46 (17.6)</td>
<td>0.54 (0.35-0.83)</td>
<td>.005</td>
<td>0.42 (0.25-0.69)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>114 (32.0)</td>
<td>85 (32.4)</td>
<td>0.85 (0.64-1.12)</td>
<td>.25</td>
<td>1.04 (0.73-1.47)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>47 (13.2)</td>
<td>43 (16.4)</td>
<td>0.69 (0.45-1.04)</td>
<td>.08</td>
<td>1.04 (0.63-1.71)</td>
</tr>
<tr>
<td>Repeat revascularization</td>
<td>112 (31.5)</td>
<td>83 (31.7)</td>
<td>0.83 (0.63-1.11)</td>
<td>.21</td>
<td>0.85 (0.61-1.18)</td>
</tr>
<tr>
<td>Surgical conversion</td>
<td>16 (4.5)</td>
<td>24 (9.2)</td>
<td>0.45 (0.24-0.84)</td>
<td>.013</td>
<td>0.46 (0.21-1.01)</td>
</tr>
</tbody>
</table>

CI, Confidence interval; HR, hazard ratio.

*aAdjusted results were adjusted for prespecified risk factors: age, sex, body mass index, diabetes, current smoker, coronary artery disease, hemodialysis, and use of thienopyridine.

Overall survival in the 173 diabetes patients with good glucose control (HbA1c >7%) was similar to that in the 290 patients with poor glucose control (HbA1c <7%), at 63.1% vs 72.5% at 2 years (P = .38, log-rank test). The limb salvage rate at 2 years was significantly lower in patients with poor glucose control (71.9% vs 85.9%; P = .0004, log-rank test).

Previous findings showed that the presence of diabetes and the HbA1c level have no relationship with death in patients with CLI who underwent EVT, but are prognostic factors for major amputation,21 and the results of this study supported these findings. In diabetic patients, cilostazol improved AFS (HR, 0.68; 95% CI, 0.50-0.90; unadjusted P = .008) and the limb salvage rate (HR, 0.49; 95% CI, 0.30-0.78; unadjusted P = .003), but was ineffective for all-cause mortality (HR, 0.84; 95% CI, 0.60-1.16; P = .28). A greater inhibitory effect of cilostazol on restenosis was shown in diabetes patients with coronary disease who underwent percutaneous coronary intervention,22 and the results of the current study also suggested that cilostazol may be more effective in patients with diabetes. Further studies are required to confirm the efficacy, but patients
with CLI are very likely to have diabetes, and improvement of these cases by pharmacotherapy is important.

Cilostazol had no effect on end points in dialysis patients. At 2 years, the mortality rate was 40.2% in dialysis patients vs 23.9% in nondialysis patients (P < .0001, log-rank test), and the rate of major amputation was also significantly higher (21.8% vs 12.1% P < .002; log-rank test). The outcomes of dialysis patients complicated with CLI are extremely poor, and intervention with pharmacotherapy has limited ability to improve these outcomes. Therefore, an individual treatment strategy should be established for high-risk patients, including diabetic and dialysis patients, in addition to further accumulation of these cases.

Pharmacotherapy is often ineffective in patients with CLI. In TransAtlantic Inter-Society Consensus II, the basic treatment proposed for patients with CLI was revascularization and pain control. However, it remains unclear whether pharmacotherapy is a potential option for patients who are ineligible for revascularization or in whom revascularization has failed. Antiplatelet therapy is also preferable for patients with PAD after revascularization because it reduces the risks of systemic vascular events in all types of PAD; however, it is unclear whether antiplatelet therapy has a similar efficacy for patients with CLI, who have poor outcomes of the lower extremities and poor survival. This situation emphasizes the importance of the results of this study confirming the efficacy of cilostazol for AFS and limb salvage in patients with CLI after EVT.

This study has several limitations: First, this was a retrospective, nonrandomized analysis, despite being a large-scale, multicenter study; therefore, a prospective randomized investigation is needed to verify these findings.

Second, patients with infrapopliteal lesions were treated with balloon angioplasty and accounted for approximately two-thirds of the patients in the study. Further studies should be conducted to analyze whether bailout and primary stenting have similar effects.

Finally, because of potential adverse reactions to cilostazol, patients complicated with heart failure were excluded from the study. However, heart failure has been found to be a prognostic factor for patients with CLI, and further studies should also be conducted in patients with CLI complicated with heart failure.

**CONCLUSIONS**

In this retrospective study, CLI patients in whom cilostazol could be or was given before EVT for infragenital lesions and could be continued after the procedure experienced a better amputation-free survival and limb salvage rate than those in whom cilostazol could not or was not given.

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Hospital, and Toshio Makita at Sendai Kosei Hospital in performing catheterization.

AUTHOR CONTRIBUTIONS

Conception and design: YS, OI, KH, KS, DK, YM, TT
Analysis and interpretation: YS, OI, KH
Data collection: YS, OI, KH, KS, DK, YM, TT
Writing the article: YS
Critical revision of the article: YS
Final approval of the article: YS, OI, KH, KS, DK, YM, TT, MN
Statistical analysis: YS
Obtained funding: MN
Overall responsibility: YS

REFERENCES