Cilostazol reduces Angiographic Restenosis after Endovascular Therapy for Femoropopliteal Lesions in the Sufficient Treatment of Peripheral Intervention by Cilostazol (STOP-IC) Study

Running title: Iida et al.; Cilostazol for angiographic restenosis

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Journal Subject Codes: Treatment:[123] Restenosis, Treatment:[23] Catheter-based coronary and valvular interventions:other
Abstract:

**Background**—It remains unclear whether cilostazol, which has been shown to improve the clinical outcomes of endovascular therapy (EVT) for femoropopliteal (FP) lesions, also reduces angiographic restenosis.

**Methods and Results**—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 FP lesions. Two hundred patients with FP lesions treated from March 2009 to April 2011 at 13 cardiovascular centers were randomized 1:1 to receive oral aspirin with or without cilostazol. The primary endpoint was 12-month angiographic restenosis rate. Secondary endpoints were restenosis rate on duplex ultrasound and of major adverse cardiac events (MACE), and target lesion event-free survival. Researchers evaluated all follow-up data and assessed the endpoints in a blinded fashion. The mean lesion length and reference vessel diameter at the treated segment was 128±86 mm and 5.4±1.4 mm, respectively. Frequency of stent used was similar between groups (88% versus 90% in the cilostazol and non-cilostazol group, respectively, \( p=0.82 \)). During the 12-month follow-up period, 11 patients died and 152 patients (80%) had evaluable angiographic data at 12 months. The angiographic restenosis rate at 12 months was 20% (15/75) in the cilostazol group versus 49% (38/77) in the non-cilostazol group (\( P=0.0001 \)) by intention-to-treat analysis. The cilostazol group also had a significantly higher event-free survival at 12 months (83% versus 71%, \( p=0.02 \)), although cardiovascular event rates were similar in both groups.

**Conclusions**—Cilostazol reduced angiographic restenosis after PTA with provisional nitinol stenting for FP lesions.

**Clinical Trial Registration Information**—URL: http://www.clinicaltrials.gov. Identifier: NCT00912756; https://www.umin.ac.jp Unique identifier: UMIN000002091

**Key words**: angioplasty, peripheral artery disease, restenosis, Nitinol stent, cilostazol
Introduction

Femoropopliteal (FP) lesions are found in 60 to 70% of patients with symptomatic peripheral artery disease (PAD).\(^1\)\(^-\)\(^3\) Restenosis occurs in 40-60% of patients with FP disease by 12 months after percutaneous balloon angioplasty, which has been the standard and traditional endovascular revascularization procedure.\(^4\)\(^-\)\(^6\) Recently, implantation of nitinol stents has improved the long-term outcome of endovascular therapy (EVT) for FP lesions compared with balloon angioplasty,\(^7\)\(^-\)\(^8\) and guidelines have been revised to extend the indications of EVT because of these improvements.\(^9\)\(^-\)\(^10\) However, despite the use of stents, there remains a 20-50% incidence of restenosis at 1 year as an important challenge for endovascular intervention.\(^4\)\(^-\)\(^6\)

Current guidelines do not recommend any specific medical intervention to reduce the incidence of restenosis after EVT for FP disease. Several studies have shown that medical intervention with statins and cilostazol decrease the risk of restenosis after EVT for FP disease.\(^11\)\(^-\)\(^13\) However, all had limitations such as a small sample size or use of inappropriate methods and criteria to determine the incidence of restenosis.

The present study therefore was designed to determine by angiographic follow-up whether treatment with cilostazol reduces restenosis at 12 months after PTA with provisional nitinol stenting for FP disease.

Methods

Study design

This was a prospective, randomized, open-label, multicenter study. During the period from March 2009 to March 2011, 200 patients with symptomatic PAD due to *de novo* FP lesions were enrolled and randomized. Analysis of angiographic data and diagnosis of restenosis at 12 months
after EVT was routinely done at a core laboratory in an endpoint-blinded manner.

Randomization

Patients with symptomatic PAD who were classified as greater than Rutherford 1 were screened by noninvasive tests to detect limb ischemia and presence of de novo FP lesions. Exclusion criteria were 1) patients treated with drug-eluting coronary stents; 2) patients with heart failure (HF) defined as history of hospital admission due to heart failure or presence of heart failure symptoms with systolic or diastolic dysfunction evaluated by cardiac echocardiography; 3) FP lesion with inflow aorto-iliac lesions; 4) FP lesions with severe calcification which preclude adequate balloon dilatation; and 5) poor below-the-knee (BTK) run-off defined as number of BTK run-off<1. After informed consent was obtained, eligible patients were randomized to groups with or without cilostazol treatment. Randomization was done centrally using a computer algorithm. Within 1 week after randomization, each patient was admitted and underwent PTA with provisional nitinol stenting. Patients in the non-cilostazol group received aspirin at 100 mg/day for 12 months, while those in the cilostazol group received the same dose of aspirin plus cilostazol (200 mg/day) for 12 months. Patients who received stents in both groups were also treated with a thienopyridine for 1 month after procedure to prevent acute stent occlusion.

EVT

The lesion was dilated by using a balloon with a diameter equal to the reference vessel diameter, as determined by quantitative angiography. After balloon inflation for at least 1 minute, stenting was done if there was flow-limiting dissection, a pressure gradient>10 mmHg, or >30% residual stenosis. Patients received S.M.A.R.T stents (Cordis Corp., Miami Lakes, FL) with a diameter 1 mm larger than the reference vessel diameter.

Follow-up protocol
At 1, 3, 6 and 12 months after EVT, each patient was assessed for symptoms, the ankle-brachial index (ABI) was measured, and duplex ultrasound was performed to assess the presence of restenosis. At 12 months after EVT, patients who had not died without any reintervention were routinely scheduled for readmission at the study institution and underwent follow-up angiography to determine whether there was restenosis at the treated lesion. Quantitative angiographic data obtained before EVT, immediately after EVT, and 12 months after EVT were analyzed at a core laboratory using CAASV software ver. 5.7 (Pie Medical Imaging).

Endpoints

The primary endpoint of this study was the angiographic restenosis rate at 12 months after EVT. Secondary endpoints were: 1) The restenosis rate assessed by duplex ultrasound at 1, 3, 6 and 12 months after EVT; 2) Angiographic findings including minimum lumen diameter (MLD), late lumen loss (%), %diameter stenosis and frequency of stent fracture at 12 months; 3) Event-free survival; 4) Temporal changes in ABI and Rutherford category after EVT; and 5) Major adverse cardiovascular events (MACE), which were defined as all-cause death, myocardial infarction, and stroke.

Definitions

Event-free survival was defined as freedom from death, major amputation, clinically driven target lesion revascularization (TLR) and target limb ischemia requiring surgical intervention. Clinically driven TLR was defined as re-intervention performed for greater than 50% diameter stenosis identified by angiography within 5 mm of the target lesion after documentation of recurrent clinical symptoms of PAD. Angiographic restenosis was defined as recurrence of ≥50% diameter stenosis as determined by quantitative vascular angiography (QVA). A peak systolic velocity ratio (PSVR)≥2.0 on Duplex ultrasound was interpreted as indicating restenosis.
according to the objective performance goals of the Vascular InterVentional Advances (VIVA) group. Initial success was defined as ≤30% residual stenosis and a pressure gradient ≤10 mmHg.

**Statistical analysis**

The sample size was estimated based on the binary restenosis rates from two previous trials. An overall sample size of 200 subjects was expected to have 82% power to detect a difference in 12-month angiographic restenosis rate for cilostazol compared to non-cilostazol at a two-sided alpha of 0.05, assuming binary restenosis rate of 30% in the cilostazol group and 50% in the non-cilostazol group. All analyses were based on intention-to-treat (ITT) analyses. We compared the primary outcome of 12-month angiographic restenosis rate and other dichotomous outcomes between the groups using chi-square test with odds ratio (OR) and its 95% confidence interval.

Per protocol set (PPS) analyses were also done to evaluate the robustness of conclusion from the intention-to-treat analyses for the primary outcome. To account for correlation among repeated measures from the same patient, the secondary endpoints of restenosis rates, ABI, and Rutherford classification were analyzed with the use of generalized estimating equations (GEE) and a Bonferroni adjusted p-value was calculated for the group comparisons at multiple time points, where baseline was included as a covariate for ABI, and Rutherford classification. Event-free survival was estimated with the use of Kaplan-Meier method and was compared between the groups by log-rank test. In addition, we performed subgroup analyses to investigate the effects of gender, diabetes mellitus, end stage renal disease on dialysis, Rutherford classification, TASC II classification, length of target lesion, reference vessel diameter, chronic total occlusion, poor BKT run off, number of stents, and stent implantation on the effect of cilostazol. The treatment-by-subgroup interaction was assessed for all subgroups; we either calculated the ORs between
subgroups, or used interaction terms in logistic regression models. All p values are two sided. Statistical analyses were done with SAS version 9.3 for Windows. This study was registered at ClinicalTrials.gov (NCT00912756).

Results

Study participants

Figure 1 shows the disposition of the 200 patients who were enrolled and randomized to receive cilostazol (n=100; cilostazol group) or not to receive cilostazol (n=100; non-cilostazol group). After randomization, 9 patients (7 in the cilostazol group and 2 in the non-cilostazol group; p=0.17) were withdrawn from the study without undergoing EVT. Of the 7 patients withdrawn from the cilostazol group, 1 took the drug and achieved symptomatic improvement, 2 had no FP disease on baseline angiography, and 4 withdrew their consent to the study after randomization. Of the 2 patients withdrawn from the non-cilostazol group, 1 had no FP disease on baseline angiography and the other withdrew consent after randomization. During the 12-month follow-up period after EVT, 11 patients died (7 versus. 4 patients in cilostazol versus. non-cilostazol group) and 28 patients (11 versus. 7 patients in the cilostazol versus. non-cilostazol group) were lost to follow up angiography. Thus, 80% of the enrolled patients (152/191) were evaluable at 12 months angiography after EVT.

Baseline characteristics and angiographic data

The baseline clinical characteristics of the ITT population, which are summarized in Table 1, were similar for the two groups, except for pre-procedural ABI. Baseline angiographic data for the target lesions are shown in Table 2. The mean length of the treated segment was 132±90 mm in the cilostazol group versus. 125±82 mm in the non-cilostazol group, while the proximal
reference vessel diameter was 5.4±1.4 mm and 5.3±1.4 mm, respectively. There was no significant difference between the two groups with regard to the TransAtlantic Inter-Society Consensus (TASC) classification of the lesions or the frequency of complete occlusion. The frequency of stent used also was similar between groups (88% [82/93] versus. 90% [88/98], for the cilostazol and non-cilostazol group, respectively, \( p=0.82 \)).

**Primary endpoint**

The angiographic restenosis rate (primary endpoint) is compared between the two groups in Figure 2. Of the 191 patients undergoing PTA with provisional stenting, 152 patients (80%) had evaluable angiographic data at 12 months. By ITT analysis, the angiographic restenosis rate at 12 months was 20% (15/75) in the cilostazol group compared with 49% (38/77) in the non-cilostazol group (\( p=0.001 \), Odds ratio: 0.26, 95% confidence interval: 0.13-0.53). Four patients in the cilostazol group and one patient in the non-cilostazol group were excluded from the per-protocol set. In the cilostazol group, one patient developed headache and another had a skin rash. For the former event, the dose of cilostazol was reduced from 200 mg/day to 100 mg/day, while the doses of both cilostazol and ticlopidine were reduced for the latter event. The remaining 2 patients underwent implantation of drug-eluting stents (DES) for new coronary lesions, which led to a change of antiplatelet therapy from cilostazol to clopidogrel. In the non-cilostazol group, a patient was excluded because of acute renal failure. Thus, analysis of the PPS revealed that the angiographic restenosis rate at 12 months was 21% (15/71) in the cilostazol group versus. 50% (38/76) in the non-cilostazol group (\( p=0.003 \), Odds ratio: 0.27, 95% confidence interval: 0.13-0.55, supplemental figure 1).

**Secondary endpoints**

At 12 months post index procedure, assessment of restenosis by duplex ultrasound was done in
87% (167/191) of patients.

**Restenosis rate at 1, 3, 6, and 12 months after EVT**

*Figures 3* show the restenosis rates assessed by duplex ultrasound at different times up to 12 months. Both ITT and PPS analyses showed no significant differences between the two groups at 3 or 6 months. However, both analyses revealed that the restenosis rate at 12 months was significantly lower in the cilostazol group than in the non-cilostazol group [ITT: 22% versus. 45%; *p*=0.006 (*Figure 3*), PPS: 22% versus. 46%; *p*=0.005 (*supplemental figure 2*)].

**Angiographic findings**

*Table 3* shows angiographic outcomes at 12 months. The cilostazol group had a larger minimum lumen diameter (3.1±1.5mm versus. 2.2±1.1mm, *p*<0.001), a smaller late lumen loss (1.1±0.6.mm versus. 1.4±0.7mm, *p*=0.03) and percent diameter stenosis (39±23% versus. 52±22%, *p*<0.001), leading to a lower rate of TLR (17% versus. 40%) by ITT analysis.

Frequency of stent fracture in the overall cohort was 18%, without significant difference between the groups (*p*=0.64).

**Event-free survival**

*Figure 4* shows event-free survival. At 12 months, event-free survival was significantly higher in the cilostazol group than in the non-cilostazol group (83% versus. 71%; *p*=0.02). During the study period, there were no major amputations in either group.

**Changes in ABI and Rutherford classification**

*Figure 5* shows the changes in ABI over time. Although preprocedural ABI was significantly higher in the cilostazol group than in the non-cilostazol group, there were no other significant differences between the groups. At 12 months, ABI was not statistically different between groups (*p*=0.20). *Figure 6* shows changes in Rutherford classification. There were no other
significant differences between the groups preprocedure, and at 1, 3, and 6 months; at 12 months, it was significantly lower in the cilostazol group than in the non-cilostazol group (p=0.03).

**MACE**

The frequency of MACE was similar during follow-up between the two groups (12% [11/93] in the cilostazol group versus. 9% [9/98] in the non-cilostazol group; p=0.64).

Finally, subgroup analysis of the influence of cilostazol on 12-month angiographic restenosis is shown in **figure 7**. There was no significant treatment-by-subgroup interaction for all subgroups and the greater benefit of cilostazol versus. non-cilostazol was consistent across all subgroups.

**Discussion**

**Main findings of this study**

This prospective, randomized, multicenter study was conducted to determine whether cilostazol treatment reduces the incidence of angiographic restenosis rate after PTA with provisional nitinol stenting for FP disease. The angiographic patency rate at 1 year after PTA with provisional nitinol stenting was 76% in patients receiving cilostazol treatment compared with 51% in patients not receiving it, and cilostazol significantly reduced angiographic restenosis after EVT for FP disease. The cilostazol group also had a significantly higher event-free survival rate at 12 months, although the rate of cardiovascular events was similar between groups.

**Comparisons with previous studies - What are the differences?**

1) Comparison with conventional EVT and stent placement

EVT with nitinol stenting is associated with a lower incidence of restenosis after treatment of PAD, and this has led to a dramatic revision of the TASC guidelines for the
management of PAD. In the ABSOLUTE trial, patients who underwent stenting for target lesions with a mean length of 101 ± 75 mm had a stent fracture rate of 2% (1/49) and a 12-month restenosis rate of 37%.7 As is the case for coronary intervention, DES for the SFA has recently been introduced and this has further improved the outcome. The Zilver-PTX stent is a DES that has been reported to achieve 1-year patency of 83% for lesions with a mean length of 6.6 cm.15 Nevertheless, the risk of restenosis when peripheral lesions are treated with DES remains higher than after coronary intervention and should be reduced further.

2) Optimal antiplatelet therapy after EVT for PAD.

It is recommended that patients who undergo EVT for PAD should receive antiplatelet therapy. However, there are no specific recommendations regarding the optimum drugs or duration of treatment. Administration of statins and cilostazol has been reported to reduce the risk of restenosis however previous studies had various limitations with regard to the method of detecting restenosis and/or sample size.

3) Detection of restenosis

Duplex ultrasound is the standard method for detection of restenosis after EVT for FP disease. However, the diagnostic threshold of peak systolic velocity ratio (PSVR) for restenosis has not been standardized, being variously reported as 2.0 to 2.8.14,16-18

The present study provides evidence that cilostazol reduces the incidence of angiographic restenosis at 12 months after PTA with provisional nitinol stenting. In patients treated with cilostazol, the restenosis rate was 20% for FP disease with a mean lesion length of 124 ± 88 mm despite a stent fracture rate of 16%. This long-term outcome was better than that previously reported after EVT with nitinol stenting. The lower incidence of restenosis in patients receiving cilostazol probably resulted from improvement of outflow due to its vasodilatory effect and
suppression of neointimal hyperplasia due to its anti-inflammatory effect together with improvement of vascular endothelial function and inhibition of vascular smooth muscle cell proliferation.

The restenosis rate evaluated by duplex ultrasound was similar for the two groups at 3 and 6 months after EVT, but was significantly different at 12 months. A similar trend was observed in recent randomized controlled trials of EVT with stenting for PAD. In a study that evaluated the efficacy of EVT with everolimus-eluting stents (STRIDE trial), the 12-month restenosis rate was a high 68%, which was in sharp contrast to a patency rate of 94% at 6 months. In patients treated with Zilver-PTX stents, however, the lesion patency rate was 95% at 6 months and 83% at 12 months compared with respective rates of 88% and 73% in patients receiving bare metal stents (BMS). The smaller reduction of the patency rate with this stent over time indicates that its effect persists for up to 12 months. Similar to the effect of DES, treatment with cilostazol for 12 months after EVT for PAD prevented restenosis from 6 to 12 months, a period with a high incidence of restenosis, thereby producing a significant reduction of restenosis at 12 months.

Clinical implications - What does this study teach us?

The results of this study suggest that cilostazol can be used as first-line antiplatelet therapy for reducing the incidence of restenosis in patients undergoing EVT with stenting for FP disease. In our ITT population, the 12-month restenosis rate was 20% in the cilostazol group compared with 49% in the non-cilostazol group.

Limitations

1) This study was not double-blinded and was not placebo-controlled. However, the angiographic data were analyzed in an endpoint-blinded manner.
2) EVT was performed using first-generation BMS. At the start of this study, the S.M.A.R.T stent was the only one available for peripheral lesions in Japan. However, newer generation stents such as nitinol stents or DES have not sufficiently reduced the incidence of restenosis compared with the effect of such stents on percutaneous coronary intervention. Cilostazol may be the most effective option to reduce the incidence of restenosis in patients treated for PAD with BMS, with maximum risk of occurrence at 6-12 months after intervention.

3) Rutherford classification at 12 months was significantly lower in the cilostazol group than in the non-cilostazol group, whereas ABI at 12 months was not significantly different between groups. Discrepancy between changes in symptom and objective testing results also has been documented elsewhere. To this end, cilostazol has been reported to have additional beneficial effects on arterial compliance, symptomatology and quality of life without associated significant improvement in objective testing parameters including ABI. Although ABI is an effective and practical method for diagnosis of PAD with 95% sensitivity, there remain 5% of false negatives. In this study, discrepancy potentially might be secondary to a high incidence of non-compliant vessel calcification leading to overestimation. ABI is helpful in the clinical setting however its use for assessment of treatment response is limited because patients can frequently improve walking distances without any significant change in ABI. Duplex or angiogram, instead of ABI, therefore is mandatory for assessing outcomes after endovascular reconstruction.

4) Finally, this study population is Asian and results should be confirmed in other ethnic groups.

Conclusion
Cilostazol reduces the risk of restenosis in patients undergoing PTA with provisional stenting for FP disease.
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Conflict of Interest Disclosures: Dr. Nanto has received grant support from Boston Scientific Japan K.K. Dr. Inoue has a consultancy relationship with Kaneka Medix Corp. and St. Jude Medical Japan Co., Ltd.

References:


**Table 1. Baseline Clinical Characteristics of the Patients.**

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<th>Non-Cilostazol group, n=98</th>
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<td><strong>Age-yrs</strong></td>
<td>72±9</td>
<td>73±8</td>
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<td>22±3</td>
<td>22±3</td>
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<td>38 (39)</td>
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<td><strong>Glycosylated hemoglobin at baseline-%</strong></td>
<td>6.4±1.7</td>
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<td><strong>History of Smoking-no. (%)</strong></td>
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<td>15 (16)</td>
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<td>35 (38)</td>
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<td><strong>Cerebrovascular disease-no. (%)</strong></td>
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<td><strong>Rutherford classification-no. (%)</strong></td>
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<td>2</td>
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<td>3</td>
<td>61 (65)</td>
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<tr>
<td><strong>Baseline ankle brachial index ABPI</strong></td>
<td>0.71±0.15</td>
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Table 2. Baseline angiographic characteristics of lesions and intervention procedure

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<td>TASC II classification-no. (%)</td>
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<tr>
<td>A</td>
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<td>B</td>
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<td>26 (27)</td>
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<tr>
<td>D</td>
<td>17 (18)</td>
<td>16 (16)</td>
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<tr>
<td>Occlusion-no of patents (%)</td>
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<tr>
<td>Length of target lesion-mm</td>
<td>132±90</td>
<td>125±82</td>
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<td>Lesion calcification-%</td>
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<td>3 22 (24)</td>
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<td>Reference vessel diameter of target lesion -mm</td>
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<tr>
<td></td>
<td>2 20 (24)</td>
<td>34 (39)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 26 (32)</td>
<td>18 (20)</td>
<td></td>
</tr>
<tr>
<td>Diameter of stent-mm, no. (%)</td>
<td></td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>6 38 (46)</td>
<td>42 (48)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 16 (20)</td>
<td>19 (20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 28 (34)</td>
<td>27 (31)</td>
<td></td>
</tr>
<tr>
<td>Diameter of post dilation balloon-mm, no. (%)</td>
<td>0.8±0.9 3.8±0.9</td>
<td>0.9±1.0 3.9±1.0</td>
<td>0.66/0.47</td>
</tr>
<tr>
<td></td>
<td>4 15 (16)</td>
<td>10 (10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 46 (50)</td>
<td>60 (61)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 32 (34)</td>
<td>28 (29)</td>
<td></td>
</tr>
<tr>
<td>Degree of stenosis before and after intervention-%</td>
<td>81±21/22±15</td>
<td>82±20/21±14</td>
<td>1.0/0.76</td>
</tr>
<tr>
<td>Minimum lumen diameter (MLD) before and after intervention-mm</td>
<td>0.8±0.9/3.8±0.9</td>
<td>0.9±1.0/3.9±1.0</td>
<td>0.66/0.47</td>
</tr>
<tr>
<td>Procedure related complication -no. (%)</td>
<td>2 (2)</td>
<td>3 (3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Distal embolization -no. (%)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Puncture site complication -no. (%)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Table 3. Outcomes at 12 months.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cilostazol group</th>
<th>Non-Cilostazol</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of stenosis at 12 month- %</td>
<td>39±23</td>
<td>52±22</td>
<td>0.0006</td>
</tr>
<tr>
<td>Occlusion within 12 months-n. %</td>
<td>4 (5)</td>
<td>7 (9)</td>
<td>0.53</td>
</tr>
<tr>
<td>Minimum lumen diameter (MLD) at 12 months-mm</td>
<td>3.1±1.5</td>
<td>2.2±1.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Late lumen loss (LLL)-mm</td>
<td>1.1±0.6</td>
<td>1.4±0.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Stent fracture at 12 months-%</td>
<td>12 (17)</td>
<td>10 (20)</td>
<td>0.64</td>
</tr>
<tr>
<td>Target lesion revascularization within 12 months-no. (%)</td>
<td>14/82 (17)</td>
<td>34/85 (40)</td>
<td>0.001</td>
</tr>
<tr>
<td>Amputation within 12 months-no. (%)</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>0.50</td>
</tr>
<tr>
<td>Death within 12 months-no. (%)</td>
<td>7 (8)</td>
<td>4 (4)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Figure Legends:

Figure 1. Study flow chart. A total of 200 patients were enrolled in this study. Nine were excluded before receiving PTA with provisional nitinol stenting (cilostazol n=7, non-cilostazol n=2 P=0.17), leaving 191 evaluable patients (cilostazol n=93, non-cilostazol n=98). 28 more patients were lost to 12 months follow-up angiography and the remaining 152 patients (80%) completed 12-month angiographic follow-up.

Figure 2. Twelve-month angiographic restenosis rates following PTA with provisional nitinol stenting for symptomatic de novo femoropopliteal lesions in the cilostazol group and the non-cilostazol group. (Primary endpoint, ITT analysis). The angiographic restenosis rate was significantly lower in the cilostazol group than in the non-cilostazol group. Restenosis was evaluated by angiography (≥50% stenosis). The angiographic restenosis rate was 24% at 12 months in the cilostazol group and 49% in the non-cilostazol group by ITT analysis (p=0.0001).
Figure 3. The 12-month restenosis rate evaluated by duplex ultrasound following PTA with provisional nitinol stenting for symptomatic de novo femoropopliteal lesions in the cilostazol group and the non-cilostazol group. (Secondary endpoint, ITT analysis). Restenosis was defined as a peak systolic velocity ratio>2.0. According to ITT analysis, restenosis rates were similar between the cilostazol and non-cilostazol groups at 3 and 6 months, whereas the restenosis rate was significantly lower in the cilostazol group at 12 months.

Figure 4. Event-free survival (ITT analysis). At 12 months, event-free survival was significantly higher in the cilostazol group than in the non-cilostazol group (83% versus 71%; \( p=0.02 \)).

Figure 5. Changes in ABI (ITT analysis). ABI was assessed at six times: pre and postprocedure, and at 1, 3, 6, and 12 months. Although preprocedural ABI was significantly higher in the cilostazol group than in the non-cilostazol group, there were no other significant differences between the groups. At 12 months, ABI was not statistically different between groups (\( p=0.20 \)).

Figure 6. Changes in Rutherford classification (ITT analysis). Rutherford classification was assessed at five times: preprocedure, and at 1, 3, 6, and 12 months. There were no other significant differences between groups preprocedure, and at 1, 3, and 6 months. At 12 months, it was significantly lower in the cilostazol group than in the non-cilostazol group (\( p=0.03 \)).

Figure 7. Subgroup analysis of the influence of cilostazol on 12-month angiographic restenosis. (ITT analysis). Odds ratios for 12-month restenosis in selected patient subgroups are shown. The p-values for interaction indicate that none of the variables had a significant interaction with treatment.
12 months Angiography follow-up chart

Randomization according to inclusion/exclusion criteria
n = 200

Cilostazol group
Baseline  n = 100

7 patients  →  No indication for endovascular therapy after angiography assessment (n=9)

7 patients  →  Death before 12 months follow-up (n=11)
- Pneumonia  2
- Sepsis  1
- Lung cancer  1
- Myocardial infarction  2
- Unknown  1

11 patients  →  Lost to 12 months follow-up angiography (n=28)

12-month follow up Angiography or duplex  n=75

Non-Cilostazol group
Baseline  n = 100

2 patients  ←

4 patients  ←
- Pneumonia  2
- Myocardial infarction  1
- Multiple organ failure  1

17 patients  ←

12-month follow up Angiography or duplex  n=77

Figure 1
Figure 2

Restenosis rate (%)

Non-Cilostazol

Cilostazol

OR: 0.26
(95% CI: 0.13, 0.53)
P = 0.0001

49% (38/77)
20% (18/75)
Figure 3

- **3Mo**: Non-Cilostazol: 7% (6/85), Cilostazol: 11% (9/82), P = 0.73
- **6Mo**: Non-Cilostazol: 18% (15/85), Cilostazol: 18% (15/82), P = 1.00
- **12Mo**: Non-Cilostazol: 45% (38/85), Cilostazol: 22% (18/82), P = 0.006

Restenosis rate (%)
Figure 4

Event-Free Survival (%)

Cilostazol 93 90 86 82 60
Non-Cilostazol 98 93 85 74 47

Log-rank test p=0.02

Months

0 3 6 9 12
Figure 5
Figure 6
Subgroup analysis for efficacy of cilostazol on 12 months angiographic restenosis

Figure 7
Cilostazol Reduces Angiographic Restenosis after Endovascular Therapy for Femoropopliteal Lesions in the Sufficient Treatment of Peripheral Intervention by Cilostazol (STOP-IC) Study
Osamu Iida, Hiroyoshi Yokoi, Yoshimitsu Soga, Naoto Inoue, Kenji Suzuki, Yoshiaki Yokoi, Daizo Kawasaki, Kan Zen, Kazushi Urasawa, Yoshiaki Shintani, Akira Miyamoto, Keisuke Hirano, Yusuke Miyashita, Taketsugu Tsuchiya, Norihiko Shinozaki, Masato Nakamura, Takaaki Isshiki, Toshimitsu Hamasaki and Shinsuke Nanto
on behalf of the STOP-IC investigators

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Supplemental Material
Supplemental Figure 1

OR: 0.27
(95%CI: 0.13, 0.55)
P=0.0003

Restenosis rate (%)

Non-Cilostazol  Cilostazol

50% (38/76)  21% (15/71)
Supplemental Figure 2

![Supplemental Figure 2](image-url)
Supplemental Figure Legends

Supplemental figure 1.

Twelve-month angiographic restenosis rates following PTA with provisional nitinol stenting for symptomatic de novo femoropopliteal lesions in the cilostazol group and the non-cilostazol group. (Primary endpoint, PPS analysis)

The angiographic restenosis rate was significantly lower in the cilostazol group than in the non-cilostazol group. By PPS analysis, the patency rate was 21% and 50%, respectively (p=0.0003).

Supplemental figure 2.

The 12-month restenosis rate evaluated by duplex ultrasound following PTA with provisional nitinol stenting for symptomatic de novo femoropopliteal lesions in the cilostazol group and the non-cilostazol group. (Secondary endpoint, PPS analysis)

Restenosis was defined as a peak systolic velocity ratio>2.0. According to PPS analysis, restenosis rates were similar between the cilostazol and non-cilostazol groups at 3 and 6 months, whereas the restenosis rate was
significantly lower in the cilostazol group at 12 months.
STOP-IC participants: interventional cardiologist, participating JPN centers (overall number of endovascular intervention for femoropopliteal lesions and patients enrolled into this trial); asterisk denotes centers taking part in the STOP-IC)

Osamu Iida, *Kansai Rosai Hospital, Amagasaki (344, 69); Hiroyoshi Yokoi, Yoshimitsu Soga, *Kokura Memorial Hospital, Kitakyushu (378, 56); Naoto Inoue, Kenji Suzuki, *Sendai Kosei Hospital, Sendai (131, 21); Yoshiaki Yokoi, *Kishiwada Tokushukai Hospital, Kishiwada (277, 19); Daizo Kawasaki, Hyogo College of Medicine, Nishinomiya (115, 8); Kan Zen, *Omihachiman Community Medical Center, Omihachiman (218, 6); Kazushi Urasawa, *Tokeidai Memorial Hospital, Sapporo (320, 5); Yoshiaki Shintani, *Shin-Koga Hospital, Kurume (72, 5); Akira Miyamoto, *Kikuna Memorial Hospital, Yokohama (465, 4); Keisuke Hirano, *Saiseikai Yokohama-City Eastern Hospital, Yokohama (116, 3); Yusuke Miyashita,

* Shinshu University Graduate School of Medicine, Matsumoto (53, 2); Taketsugu Tsuchiya, *Kanazawa Medical University Hospital, Kanazawa (63, 1); Norihiko Shinozaki, *Tokai University Hospital,
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