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Original article

# Effect of oral cilostazol on acute neurological deterioration and outcome of noncardioembolic minor stroke

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ABSTRACT

*Background/Purpose:* Stroke recurrence in the acute phase is not rare, even in minor stroke patients. We investigated whether combined antithrombotic therapy with early oral cilostazol prevents progressive stroke and improves outcomes in ischemic stroke patients.
*Methods:* For the present study, 311 first-time stroke patients who were admitted within 48 hours after the onset and were diagnosed as having a noncardioembolic stroke with National Institutes of Health Stroke Scale (NIHSS) scores of $\leq 7$ were prospectively included. All patients were classified into two groups according to oral cilostazol. In Group A, 154 patients were treated with conventional antithrombotic agents with or without oral aspirin (100–200 mg/d), during the first 7 hospital days. In Group C, 157 patients were treated with oral cilostazol 200 mg/d (100 mg twice daily) plus conventional antithrombotic agents during the first 7 hospital days. Neurological deterioration during the first 21 days, stroke recurrence, cardiovascular events, and any deaths during a 3-month follow-up period were compared between Groups A and C.
*Results:* The frequencies of neurological deterioration, stroke recurrence, acute myocardial infarction, or death from all causes did not differ between Groups A and C. A good outcome at 3 months after admission was observed more frequently in Group C than in Group A patients (68% vs. 56%, $p = 0.0253$). In the multivariate analysis, age [odds ratio (OR), 0.94; 95% confidence interval (CI), 0.91–0.97; $p < 0.0001$] and initial NIHSS score (OR, 0.65; 95% CI, 0.56–0.76; $p < 0.0001$) were negatively associated, and cilostazol (OR, 1.99; 95% CI, 1.05–3.77; $p = 0.0353$) was positively associated with a good outcome.
*Conclusion:* In noncardioembolic stroke, combined antithrombotic therapy with early oral cilostazol in the acute phase appears to be associated with a good outcome in patients with progressive stroke.


## 1. Introduction

An ischemic stroke with a low initial National Institutes of Health Stroke Scale (NIHSS) score, that is a minor stroke, is usually considered to have a good outcome. Nedeltchev et al[1] reported that 75% of patients with a minor stroke had a favorable outcome after 3 months. By contrast, several studies demonstrated that neurological deterioration or stroke recurrence in the acute phase (progressive stroke) is not rare, even in minor stroke patients.[2,3]

In accordance with the subtype of ischemic stroke, patients with large artery atherosclerosis or a deep perforating artery infarct often show acute neurological deterioration or a progressive motor deficit.[4–8] Furthermore, a deep perforating artery infarct caused by an atherothrombotic process at the origin or the proximal portion of a major cerebral artery, which is called branch atheromatous disease, is considered to be associated with a particularly high risk for progressive stroke.[9–11] In Japan, such stroke patients are usually treated with oral aspirin, intravenous ozagrel sodium (thromboxane A2 inhibitor), or argatroban hydrate (thrombin inhibitor) in

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the acute phase,[12–14] however, treatment with these antithrombotic agents is insufficient for preventing progressive stroke.

In the Japanese aging society, safety of antiplatelet therapy should be emphasized as well as effectiveness, because bleeding events with antiplatelet therapy are not rare. Toyoda et al[15] revealed that bleeding was more frequent in dual than single antithrombotic therapy. By contrast, a randomized trial demonstrated that dual antiplatelet therapy (DAPT) with aspirin and clopidogrel in the acute phase of minor stroke was beneficial and safe.[16] In a previous Japanese study, combined therapy including oral cilostazol improved the outcome of acute larger lacunar-type infarction patients.[17] Cilostazol is an antiplatelet agent that also causes vasodilation by increased production of nitric oxide,[18] and it inhibits smooth muscle proliferation and inflammation.[19,20] The second Cilostazol Stroke Prevention Study (CSPS2) proved that cilostazol was superior to aspirin for the secondary prevention of stroke in the subacute or chronic phase of noncardioembolic ischemic stroke.[21]

The purpose of the present preliminary study was to investigate whether combined antithrombotic therapy in the acute phase of minor stroke including oral cilostazol and conventional antithrombotic agents, such as aspirin, ozagrel sodium, or argatroban prevents progressive strokes and improves outcomes.

## 2. Methods

### 2.1. Patients

For the present study, from April 2009 to March 2013, among 1089 stroke patients, 311 noncardioembolic ischemic stroke (Trial of org 10172 in acute stroke treatment (TOAST) classification[22]) patients who were admitted to the Stroke Center, Steel Memorial Yawata Hospital, (Kitakyushu, Japan) within 48 hours from symptom onset with an initial NIHSS score of $\leq 7$ and a prestroke modified Rankin scale (mRS) score of 0 or 1 were prospectively included. Among the 1089 patients, 456 patients admitted after 48 hours from the onset, 143 patients with an initial NIHSS score of $> 7$ or mRS score of $\geq 2$, 115 patients with moderate or high risk sources for cardioembolism in the TOAST classification, 34 patients treated with antithrombotic agents other than cilostazol, aspirin, ozagrel sodium, and argatroban, and 30 patients with prior symptomatic coronary disease were excluded in order. All patients gave informed consent to be included into the present study which was approved by the local ethical committee.

In the study period, from January 1, 2011 to September 30, 2012, 157 patients were treated with oral cilostazol 200 mg/d (100 mg twice daily) plus conventional antithrombotic agents: intravenous ozagrel sodium (160 mg/d), or argatroban (60 mg/d during the initial 48 hours and 20 mg/d during the following 5 days) with or without oral aspirin (100–200 mg/d), during the first 7 hospital days (Group C). After initial treatment, only oral cilostazol was continued. The other 154 patients, admitted from April 1, 2009 to December 31, 2010 and from October 1, 2012 to March 31, 2013 were treated only with conventional antithrombotic agents during the first 3–14 hospital days (Group A). After the initial treatment, any single antiplatelet agent was used. The choice between ozagrel sodium and argatroban and the decision to use aspirin were left to each attending doctor. All patients were treated at the stroke unit.

### 2.2. Clinical evaluations

For all patients, infarcts were identified using magnetic resonance imaging (MRI) studies including diffusion-weighed imaging (DWI), and vascular lesions were evaluated using both MR angiography and duplex carotid ultrasonography. MRI studies were performed for all patients on the 1st hospital day. The MRI apparatus was a 1.5-T MR (Philips, Andover, MA, USA) unit with echo planar capability. DWI was performed simultaneously using a multislice, single-shot, spin echo planar imaging sequence. Diffusion gradients were applied in each of the *x*-, *y*-, and *z*-axes with two *b* values (0 s/mm$^2$ and 1000 s/mm$^2$). A focal hyperintensity on DWI was defined as an acute infarct.

Stroke subtypes were evaluated by the TOAST classification. A diagnosis of diabetes mellitus was determined by the diagnostic criteria of the Japan Diabetes Society (JDS) in the chronic stage or based on a medical history of diabetes. Hypertension was defined as a systolic blood pressure $\geq$ 140 mmHg or a diastolic pressure $\geq$ 90 mmHg in the chronic stage, or current treatment with antihypertensive drugs. Dyslipidemia was defined as one of a low density lipoprotein (LDL) cholesterol level $\geq$ 140 mg/dL, high density lipoprotein (HDL) cholesterol level $<$ 40 mg/dL, triglycerides $\geq$ 150 mg/dL, or current treatment with a cholesterol-lowering drug. Atrial fibrillation was diagnosed based on electrocardiographic findings on admission or during hospitalization.

The NIHSS score was assessed on admission and at 48 hours, 7 days, and 21 days after admission. NIHSS score worsening by $\geq 1$ point was defined as neurological deterioration. Stroke recurrence was defined as neurological deterioration with a new ischemic lesion on DWI. An mRS score of 0 or 1 was defined as a good outcome.

Neurological deterioration during the first 21 days, stroke recurrence, cardiovascular events, and any deaths during a 3-month follow-up period were compared between Group A and Group C. Clinical factors associated with a good outcome were also investigated.

### 2.3. Data analysis

Statistical analyses were performed using the JMP version 9 software program (SAS Institute Inc., Cary, NC, USA). On univariate analysis, the Chi-square test and paired *t* test were used. In the multivariate analysis, multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for each study outcome were estimated by logistic regression analysis. A two-tailed probability $p < 0.05$ was considered to indicate a significant difference.

## 3. Results

### 3.1. Background characteristics and clinical course

There were no significant differences in background characteristics, stroke subtype (TOAST classification), and conventional antithrombotic agents between Group A and Group C (Table 1). Although there were no differences in the NIHSS scores between the two groups on admission, 48 hours, and 7 days after admission, the NIHSS score 21 days after admission was significantly lower in Group C (2.0 ± 2.3) than in Group A (2.8 ± 2.4, $p = 0.0016$; Table 2, Figure 1).

The frequencies of neurological deterioration, stroke recurrence, acute myocardial infarction, or death from all causes did not differ between Group A and Group C (Table 2). One patient in Group C had a fatal myocardial infarction 4 days after admission. One patient in Group A had fatal pneumonia 14 days after admission. A fatal stroke recurrence occurred in two patients in Group C and in one patient in Group A during the observation period. No patients in either group developed symptomatic intracranial hemorrhagic transformation or other major bleeding.

A good outcome was relatively more frequent at 21 days after admission (62% vs. 51%, $p = 0.0622$) and significantly more frequent at 3 months after admission (68% vs. 56%, $p = 0.0253$) in Group C than in Group A (Table 2). In patients with neurological