



Cilostazol-Aspirin Therapy Against Recurrent Stroke With Intracranial Artery Stenosis (CATHARSIS)

Shinichiro Uchiyama, M.D. PhD.,¹⁾ Nobuyuki Sakai, M.D. PhD.,²⁾ Yumi Kimura, M.D.,¹⁾ Masayuki Ezura, M.D. PhD.,³⁾ Yasushi Okada, M.D. PhD.,⁴⁾ Makoto Takagi, M.D. PhD.,⁵⁾ Youji Nagai, M.D. PhD.,⁶⁾ Kazuo Minematsu, M.D. PhD.⁷⁾ for the CATHARSIS Study Group
ClinicalTrials.gov Identifier : NCT00333164

1) Department of Neurology, Tokyo Women's Medical University, 2) Department of Neurosurgery, Kobe City General Hospital, 3) Department of Neuroendovascular Therapy, Tohoku University, 4) Cerebrovascular center and Clinical Research Institute, National Hospital Organization Kyushu Medical Center, 5) Department of Neurology, Saiseikai Central Hospital, 6) Translational Research Informatics Center, Kobe, 7) Cerebrovascular Division, National Cardiovascular Center

Background

Intracranial arterial stenosis (IAS) is more common in Japanese than in Caucasian. Stroke recurrence rate is high in patients with IAS despite medical treatment. According to the results of The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID), warfarin is not recommended because of the concern of safety, whereas the efficacy of aspirin is not enough for stroke prevention.

Objective

To compare the effect of aspirin plus cilostazol and aspirin alone on the progression of IAS as well as ischemic and hemorrhagic events, and surrogate markers for inflammation and endothelial impairment in stroke patients with IAS in order to establish the best medical treatment, and to provide important information for the future randomized controlled studies to compare medical treatment alone and intravascular intervention (PTA and/or stenting) in symptomatic IAS patients.

Study Design

Subjects: Two hundred patients at age of 45-85 years with ischemic stroke after two weeks to six months from onset and IAS >50% in responsible supraclinoid internal carotid artery, M1 portion of middle cerebral artery, or basilar artery on MRA.
Intervention: All patients will receive aspirin 100 mg/day plus cilostazol 200 mg/day orally (n=100) or aspirin 100 mg/day alone orally (n=100)
Study Design: Prospective, randomized, open-labelled, blinded endpoint (PROBE) study
Study Period: Registration has been started on April 1, 2006 and will be ended on March 31, 2010.

Patient Selection Criteria

Inclusion Criteria

- Ischemic stroke after two weeks to six months from onset
- Responsible lesion identified on MRI
- IAS >50% on MRA in the territory of responsible lesion
- IAS in supraclinoid internal carotid artery, M1 portion of middle cerebral artery, or basilar artery
- Age of 45 to 85 years
- Able to visit out-patient clinic and to obtain written informed consent obtained from patient or family

Exclusion Criteria

- Patients with potential cardiac embolic sources
- Patients receiving cilostazol
- Patients on warfarin treatment
- Patients in whom MRI cannot be performed
- Patients in whom PTA or bypass surgery is planned
- Patients with history of symptomatic intracranial hemorrhage, other hemorrhagic diseases (active peptic ulcer etc.), hemophilia or coagulation abnormalities
- Patients with hypersensitivity to cilostazol or aspirin
- Patients with congestive heart failure or uncontrollable angina pectoris
- Patients with thrombocytopenia ($< 100,000/\text{mm}^3$)
- Patients with liver dysfunction (AST or ALT $> 100 \text{ IU/L}$)
- Patients with renal dysfunction (creatinine $> 2.0 \text{ mg/dL}$)
- Patients who cannot to be followed up during the study period
- Patients who are enrolled in other clinical trials or inadequate for this study by other reasons

Outcome Measure

1) Primary endpoint

- Progression of IAS on MRI during two-year observation period

2) Secondary endpoints

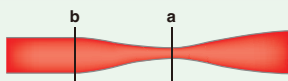
- Cardiovascular events (ischemic stroke, myocardial infarction, and other vascular events)
- Death
- Serious adverse events including hemorrhagic events
- New silent brain infarcts
- Activity of daily living (ADL) during two-year observation period

3) Substudy on inflammation and endothelial function

Measurement of the following markers at randomization and after one year of follow-up in each group of patients

- Inflammation markers
hs-CRP, ICAM-1, MCP-1, and CD40L
- endothelial impairment markers
von Willebrand factor antigen, thrombomodulin, PAI-1, and E-selectin

Fig.1 Calculation method of stenosis rate on MRA

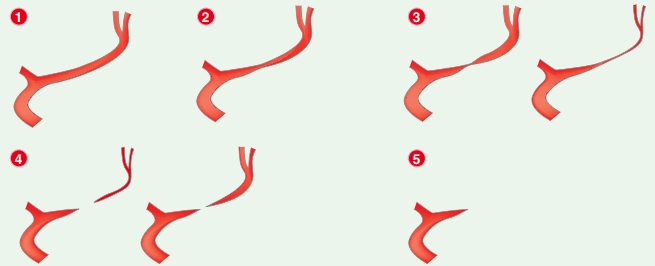


Stenosis rate (%) = $(b-a) / b \times 100$

a : Vessel diameter of most stenotic portion
b : Normal vessel diameter

Fig.2 Grading of IAS

- Normal : no evidence of stenosis
- Mild stenosis : less than 50% stenosis
- Moderate stenosis : more than 50% stenosis
- Severe stenosis : partial signal loss with the distal flow signal
- Occlusion : no distal flow signal



Criteria for diagnosis of progression and improvement of IAS :
One or more grades of change in IAS

Plan for Timing to Check Observation Items

Observation items	Pre-registration	Baseline data	Treatment period				
			3M	6M	12M	24M	When stroke occurred
Informed consent	●						
MRA scan	●						
MRI scan	●						
Medical history		●					
ADL		●	●				
History of medication		●					
CBC		●					
Serum biochemistry		●					
Follow-up visit			●	●			
Death/cardiovascular events (Stroke, MI, PAD, other vascular events)			●	●			
Serious adverse events			●	●			
Compliance check			●	●			

Statistical Analyses

- As for the primary endpoint, difference in the rate of IAS progression for two years between both groups is analyzed by the Fisher's exact test.
- Among the secondary endpoints, differences in ischemic stroke, MI, all vascular events, all strokes, and all causes of death between both treatment groups are analyzed by the Log-Rank test.
- Differences in the incidence of new silent brain infarcts and serious adverse events between both groups are analyzed by the Fisher's exact test.
- Difference in ADL between both groups is analyzed by the Wilcoxon's rank-sum test.
- Logistic regression and the Cox proportional hazard models are used for the analyses of prognostic factors.

Present Status

Ninety six centers have participated in the study, having enrolled 146 patients as of April 2009, and 134 patients out of whom are confirmed eligible.

Correspondence

CATHARSIS Central Secretariat: Department of Neurology, Tokyo Women's Medical University,
E-mail CATHARSISMED@tri-kobe.org
CATHARSIS Project Secretariat: Translational Research Informatics Center, Kobe
E-mail CATHARSIS@tri-kobe.org

Reference

- Sacco RL, Kargman DE, Gu Q, Zamanillo MC: Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction: the Northern Manhattan Stroke Study. *Stroke* 1995;26:14-20.
- Chimowitz MI, Lynn MJ, Howlett-Smith H et al for the Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators: Comparison of warfarin and aspirin for symptomatic intracranial stenosis. *N Engl J Med* 2005;352:1305-1316.
- Kwon SU, Cho Y-J, Koo J-S et al: Cilostazol prevents the progression of the symptomatic intracranial arterial stenosis. The multicenter double-blind placebo-controlled trial of cilostazol in symptomatic intracranial arterial stenosis. *Stroke* 2005;36:782-786.
- Uchiyama S, Yamazaki M, Nakamura T et al: New modalities and aspects of antiplatelet therapy for stroke prevention. *Cerebrovasc Dis* 2006;21 (suppl 1):7-16.
- Sacco RL, Adams R, Albers G et al: Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack. A statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke. *Stroke* 2006;37:577-617.