The Effect of Cilostazol on Carotid Intima–Media Thickness Progression in Patients with Symptomatic Intracranial Atherosclerotic Stenosis

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Background: The progression of carotid intima–media thickness (CIMT) is closely associated with ischemic stroke recurrence. However, the efficacy of cilostazol on preventing CIMT progression in stroke patients has never been investigated properly by a prospective trial. *Methods:* This study is a part of "Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis-2." Six centers that are available to measure CIMT according to the protocol participated in this substudy. After 7 months of randomization, the changes of CIMT were compared between cilostazol group and clopidogrel group. CIMT was measured by a semiautomated software (Intimascope) and was presented as the mean of maximum (CIMT-max) and average (CIMT-ave) of both common carotid arteries. Linear logistic regression analysis and analysis of covariance were performed to verify the independent factors associated with CIMT progression. *Results:* Among the 85 patients, 39 subjects were assigned to cilostazol group and 46 subjects to clopidogrel group. Follow-up CIMT significantly decreased in cilostazol group (CIMT-max: $-.03 \pm .11$ and CIMT-ave: $-.02 \pm .08$) compared with the increase in clopidogrel group (CIMT-max: $.04 \pm .20$ and CIMT-ave: $.04 \pm .11$; $P = .05$ and $P = .04$, respectively). Female, diabetes, and smoking were independently associated with the progression of CIMT, whereas the use of cilostazol was against CIMT progression from the results of linear regression analysis ($P = .03$ for both CIMT-max and CIMT-ave). The use of cilostazol also well predicted less progression of CIMT at follow-up after adjusting for baseline CIMT values and conventional risk factors (CIMT-max: $P = .04$ and CIMT-ave: $P = .03$). *Conclusion:* Cilostazol has a beneficial effect in preventing the progression of CIMT in ischemic stroke patients. **Key Words:** Intracranial arterial stenosis—intima–media thickness—atherosclerosis—antiplatelets.

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Introduction

Increased carotid intima–media thickness (CIMT) is associated with the risk of ischemic stroke or coronary artery disease.[1] Though CIMT progression in general population demonstrated a limited clinical implication on predicting cardiovascular events,[2] ischemic stroke patients with CIMT progression are still prone to long-term stroke recurrence.[3] CIMT has been widely used as a surrogate marker of generalized atherosclerosis and an alternative outcome measure for vascular events in studies that had investigated the efficacy of lipid-modifying agents or antiplatelet agents.[4]

Cilostazol is a selective phosphodiesterase-3 inhibitor that demonstrated antiproliferative and anti-atherogenic effects from various clinical trials. Cilostazol prevented the progression of atherosclerosis in multiple vascular beds. The restenosis after coronary stenting was less frequent with the use of cilostazol,[5] and it was also effective for preventing the progression of CIMT in diabetic patients.[6] Recently, we demonstrated that cilostazol is protective against the progression of symptomatic intracranial atherosclerotic stenosis (ICAS).[7] However, the effect of cilostazol on CIMT progression among ischemic stroke patients has never been investigated by a well-organized randomized trial.

Therefore, we have performed this study to investigate the effect of cilostazol on CIMT progression in symptomatic ICAS patients, as a substudy of "Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis" (TOSS)-2.[7]

Methods

Study Design

TOSS-2 was a double-blinded randomized controlled trial that compared the safety and efficacy against the progression of ICAS between cilostazol plus aspirin and clopidogrel plus aspirin (unique identifier: NCT00130039). The progression rate of symptomatic ICAS was compared. Acute ischemic stroke patients aged 35 years or older with symptomatic ICAS within 2 weeks of symptom onset were recruited. However, to avoid other etiologies of intracranial stenosis, subjects suspicious of (1) nonatherosclerotic vasculopathy such as arterial dissection or moyamoya disease, (2) cardioembolism, or (3) significant proximal artery stenosis were excluded. A detailed description including the inclusion and exclusion criteria of the subjects were previously published.[7] Among the 20 centers that participated in TOSS-2, 6 centers that are available to perform carotid ultrasonography were included. However, the proposal review and accreditation of the study center delayed the initiation of CIMT substudy after the first enrollment of the patient to TOSS-2.

The subjects were randomly assigned either to cilostazol group (aspirin 100 mg plus cilostazol 200 mg, daily) or clopidogrel group (aspirin 100 mg plus clopidogrel 75 mg, daily) for 7 months after an informed consent by themselves or their next-on-kin. All the participants received the best medical treatment, which is currently available, and were strongly recommended for angiotensin receptor blocker and statin treatment, according to the protocol. Demographic characteristics, risk factors of atherosclerosis, and laboratory data including fasting glucose, C-reactive protein (CRP), and lipid profiles (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], apolipoprotein A1 [Apo A1], and apolipoprotein B [Apo B]) were obtained. Carotid ultrasonography was performed for the purpose of measuring CIMT according to a standardized protocol. Seven months after the randomization, laboratory data (fasting glucose, lipid profiles, and CRP) and carotid ultrasonography were followed up, and concomitant medication used during the study period was also obtained. The protocol was approved by the ethics committee of each participating center.

Measurement of CIMT

Carotid ultrasonography was performed at each center by skilled sonographers. A high-resolution linear array vascular probe (10 MHz) was used to obtain the images from right and left carotid arteries. CIMT was measured from the standardized longitudinal B-mode images, which were obtained from the far wall of each common carotid artery, extending from 10 to 20 mm proximal to the tip of bifurcation site according to the Mannheim carotid intima-media thickness consensus.[8] All the DICOM (digital imaging and communications in medicine) images, which contain the proper CIMT of both sides, were electronically archived from each center to the central laboratory for CIMT measurement. To avoid a possible inter-rater disagreement,[9] CIMT was measured using dedicated semiautomated software (Intimascope; Media Cross Co., Tokyo, Japan) by a reader blinded to all clinical information (S.R.K.). The results of automated evaluation were presented as the maximum (CIMT-max) and average (CIMT-ave). CIMT-max was calculated as the mean of maximal points in both common carotid arteries, and CIMT-ave represented the mean of average value obtained from 250 computer-based points from each common carotid artery (Fig 1).

Statistical Analysis

Demographic characteristics and clinical data were compared between the 2 groups using Student *t* test, Pearson chi-square test, and Fisher exact test appropriately. The changes of laboratory data and CIMT progression after 7 months were compared between the 2 groups using Student *t* test. For the purpose to identify the factors independently associated with CIMT progression, multivariate linear regression analysis was performed. Factors with potential association ($P < .20$) from univariate