Baseline Carotid Intima-Media Thickness and Stroke Recurrence During Secondary Prevention With Pravastatin

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Background and Purpose—As a prespecified post hoc analysis of the J-STARS (Japan Statin Treatment Against Recurrent Stroke) Echo Study, the 5-year stroke recurrence rate according to the baseline mean carotid intima-media thickness (IMT) with and without pravastatin treatment was investigated.

Methods—Patients were randomly assigned to receive pravastatin 10 mg/day (pravastatin group) or control group (nonstatin treatment; 1:1) for 5 years. Baseline mean IMT of the common carotid artery was measured by ultrasonography. Cox proportional hazards models were used to investigate whether the stroke (any ischemic stroke, atherothrombotic brain infarction, or lacunar infarction) recurrence rate was different according to tertiles of baseline mean IMT.

Results—A total of 793 patients, including 388 in the pravastatin group and 405 in the control group, were investigated. In the control group, Cox proportional hazards models showed that participants in the highest tertile IMT group (≥0.931 mm) had a higher rate of atherothrombotic brain infarction than those in the lowest tertile IMT group (<0.812 mm; (hazard ratio, 9.08; 95% CI, 1.15–71.43)). Patients in the pravastatin group had a lower risk of atherothrombotic brain infarction than those in the control group only in the highest tertile IMT group by the log-rank test (P value=0.045).

Conclusions—Long-term pravastatin administration may prevent the occurrence of atherothrombotic brain infarction in noncardioembolic infarction patients with the highest tertile IMT.

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The relationship of carotid intima-media thickness (IMT) and stroke recurrence with pravastatin as secondary prevention has not been elucidated. The purpose of this study was to investigate the 5-year stroke recurrence rate according to the baseline mean carotid IMT in noncardioembolic stroke patients with and without pravastatin treatment as a post hoc analysis of the J-STARS (Japan Statin Treatment Against Recurrent Stroke) Echo Study.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

The study design and methods of the J-STARS Echo Study have been described elsewhere.1–3 The protocol and informed consent form were approved by the institutional review board of each center, and written, informed consent was obtained from each patient.

Patients were randomly assigned to the pravastatin group receiving pravastatin 10 mg/day or to the control group with nonstatin treatment (1:1). Carotid ultrasonography was performed at the study enrollment (baseline) and followed up annually for 5 years. IMT was measured automatically on the distal wall in a continuous 2-cm section on the central side of the common carotid artery bifurcation with IntimaScope software (Mediacross, Tokyo, Japan). Based on the tertiles of baseline mean IMT values, the patients were divided into 3 groups: the lowest tertile IMT group, the middle tertile IMT group, and the highest tertile IMT group. IMT change was calculated by...
mean IMT at 5 years (or just before when ischemic stroke occurred) minus that at baseline. Patients were followed up at least annually until study completion. The end point of this study was the onset of any ischemic stroke including each ischemic stroke subtype (atherothrombotic brain infarction [ATBI], lacunar infarction [LAC], cardioembolic infarction, and others).

Statistical Analysis
The survival curve for end point occurrence was estimated using the Kaplan-Meier method. The hazard ratios for the tertiles of mean IMT based on the low-tertile IMT were estimated using a Cox proportional hazards model stratified by stroke subtypes, high blood pressure, and diabetes mellitus. Allocated treatment groups in each baseline mean IMT group were compared using the log-rank test. Since this post hoc analysis is exploratory research aimed at generating a hypothesis, the adjustment for multiple comparisons was not done. The level of significance was set at \( P < 0.05 \) (2-tailed).

Results
Of 793 patients included in this study (age, 66.4±8.3 years old; 263 women), 388 (48.9%) were assigned to the pravastatin group, and 405 (51.1%) were to the control group. Because of protocol violations, 74 patients in the pravastatin group took no or <25% of total dose of pravastatin and 54 in the control group received statin treatment. The mean follow-up period was 4.9 year, and 20.7% were lost to follow-up at 5 years.

The patients’ baseline characteristics by the tertile groups of baseline mean IMT and those by the allocated groups are shown in Tables I and II in the online-only Data Supplement, respectively. The lower and upper tertiles of baseline mean IMT were 0.812 mm and 0.931 mm (the lowest tertile IMT group <0.812 mm; the middle tertile IMT group ≥0.812 mm and <0.931 mm; and the highest tertile IMT group ≥0.931 mm). During the follow-up period, 81 patients (10.2%) developed any ischemic stroke recurrence, with 19 (2.4%) having ATBI and 44 (5.5%) having LAC.

In the pravastatin group, there was no relationship between baseline mean IMT and recurrence of ischemic stroke, occurrence of ATBI, and occurrence of LAC (Figure 1; Table III in the online-only Data Supplement). In the control group, there was no relationship between baseline mean IMT and recurrence of ischemic stroke and occurrence of LAC. However, Cox proportional hazards models showed that patients in the highest tertile IMT group (≥0.931 mm) had a higher risk of ATBI than those in the lowest tertile IMT group (<0.812 mm; hazard ratio, 9.08; 95% CI, 1.15–71.43; Figure 1; Table III in the online-only Data Supplement).

Patients in the pravastatin group had a lower risk of ATBI than those in the control group only in the highest tertile IMT group by the log-rank test (hazard ratio, 0.29; 95% CI, 0.08–1.05; \( P = 0.045 \)), though there were no significant reduction of ischemic stroke, LAC, and ATBI in the lowest and middle tertile IMT groups (Figure 2; Table IV in the online-only Data Supplement). In the highest tertile IMT group, mean IMT change was 0.024 mm in patients who developed ATBI and −0.015 mm in those without ATBI in the pravastatin group (\( P = 0.57 \)) and that was 0.042 mm and 0.010 mm, respectively, in the control group (\( P = 0.39 \); Table V in the online-only Data Supplement).

Discussion
In this study, the relationship between baseline mean IMT and stroke recurrence was examined. Patients with the highest tertile of baseline mean IMT in the control group more frequently developed ATBI than those in the pravastatin group. Moreover, the higher was the baseline mean IMT, the lower was the hazard ratio of ATBI with long-term pravastatin. Previous large randomized trials showed that statin treatment reduced stroke recurrence including ATBI and neurological severity at recurrence. However, no study has randomly tested the effect of statins based on the stratified baseline mean IMT.\(^6\)–\(^11\) Administering pravastatin to noncardioembolic stroke patients with the highest tertile IMT may reduce ATBI through the statin effects, for example, lowering low-density lipoprotein cholesterol, anti-inflammatory action, improving endothelial function, reducing oxidative stress, and inhibiting smooth muscle growth.\(^6\)–\(^11\)

This study is unique in that it shows the risk of ATBI and the preventive effect of statins in patients with noncardioembolic stroke with a high baseline mean IMT, though this relationship with multiple testing was borderline significant. Moreover, in the J-STARS Echo study, we proved usual Japanese dose of pravastatin significantly reduced the progression of carotid IMT at 5 years.\(^7\) It was suggested that patients who developed ATBI had higher IMT change during the follow-up periods than those who did not develop ATBI in the highest tertile IMT group despite administering pravastatin. However, as these relationships were not observed clearly because of the small sample size in our study, further investigation is needed.
with a large sample size to examine the relationship between IMT and ATBI occurrence with statin administration together with plaque instability assessment.

Conclusions
Our post hoc explanatory analysis showed that noncardioembolic stroke patients who had high baseline mean IMT more frequently developed ATBI than those with low baseline mean IMT.

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References


