# Subsequent Vascular Events after Ischemic Stroke: The Japan Statin Treatment Against Recurrent Stroke—Longitudinal

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*Background:* We undertook a multicenter cohort observational study to investigate the frequency and type of subsequent vascular events after an ischemic stroke and to compare the rates of vascular events between patients with and without hyperlipidemia. *Methods:* This nationwide study was conducted in 19 hospitals participating in the Japan Standard Stroke Registry Study. We enrolled ischemic stroke patients, including those with a transient ischemic attack, who had not experienced any vascular events before enrollment after their ischemic stroke events. Each subject was observed prospectively from September 1, 2003, to October 1, 2005, or until a primary end point or death. Primary end points included subsequent fatal or

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nonfatal vascular events: stroke, angina pectoris, acute myocardial infarction, aortic aneurysm, or arteriosclerosis obliterans. *Results:* A total of 449 patients (mean age, 67.6 years; 64.8% men) were enrolled in this study. Of the 41 vascular events observed during follow-up, 40 were stroke. The median observation period was 568 days. We found that patients with hyperlipidemia had a significantly higher rate of vascular events compared with those without hyperlipidemia according to the Kaplan–Meier method and the log-rank test ($P = .013$). Hyperlipidemia significantly increased the risk of vascular events (hazard ratio, 2.169 [1.125-4.312]; $P = .021$) according to the Cox proportional hazard model after adjusting for confounding factors (age, sex, days from ischemic stroke until enrollment, smoking habits, and daily drinking habits). *Conclusions:* This study demonstrated that stroke was the most common subsequent vascular event after ischemic stroke; the study also indicated that hyperlipidemia could be a risk factor for subsequent vascular events after ischemic stroke. **Key Words:** Ischemic stroke—hyperlipidemia—hypertension—diabetes mellitus—statin.


Stroke remains one of the leading causes of death in Japan. However, the stroke mortality rate (compared with the incidence rate) has been decreasing for several decades.[1] Epidemiologic studies have reported that the most frequent vascular event after ischemic stroke was stroke and that hypertension and diabetes mellitus could be the risk factors for recurrent stroke.[2-5] Unfortunately, few studies from eastern Asia have addressed these questions. Furthermore, the incidence of each type of vascular event (eg, stroke or myocardial infarction) is markedly different between Japan[1] and the Western countries.[6]

Hyperlipidemia is less well established as a risk factor for first or recurrent stroke compared with its role in cardiac disease.[7] However, when the stroke subtype is limited to ischemic, some reports have indicated that hyperlipidemia could be a risk factor.[8,9] At present, hyperlipidemia is considered to be a relatively weak risk factor for the first ischemic stroke; however, a positive association between hyperlipidemia and a subsequent vascular event after ischemic stroke has not been reported. Beyond these epidemiologic studies, a meta-analysis of large-scale clinical trials indicated that statins could decrease the incidence of stroke events in patients with hypercholesterolemia and atherosclerosis.[10] Most of these stroke events were primary in nature; however, 1 study reported that recurrent strokes were also reduced with statins.[11]

We are currently carrying out the follow-up for a randomized control study called Japan Statin Treatment Against Recurrent Stroke (J-STARS; ClinicalTrials.gov trial ID: NCT00221104) to investigate whether an ordinary dose of statins can reduce the recurrence of stroke in Japanese patients.[12] Before the J-STARS study, we investigated the clinical characteristics of ischemic stroke with hyperlipidemia and found that ischemic stroke patients with hyperlipidemia had an earlier age of onset and higher frequency of hypertension and diabetes mellitus than those without hyperlipidemia, although the frequency of a history of ischemic heart disease was unexpectedly low (10.5%) and did not differ between the groups.[13] This cross-sectional study was called J-STARS—Cross-sectional.

The present observational study, designated J-STARS—Longitudinal, investigated the rate of recurrence and type of vascular event after ischemic stroke in Japan and compared findings between patients with or without hyperlipidemia. The frequency of statin use and its effect on subsequent vascular events were also investigated.

## Subjects and Methods

This study was a multicenter cohort observational study conducted nationwide in 19 hospitals participating in the Japan Standard Stroke Registry Study (JSSRS), which is maintained by the Japan Stroke Association.[14,15] Patients with ischemic stroke, including those with a transient ischemic attack, were enrolled in this study who had been registered previously in the JSSRS or were newly registered between September 1, 2003, and August 31, 2005, and who had not experienced any vascular events before enrollment after their ischemic stroke events. The clinical characteristics of the patients were collected, including total cholesterol, triglyceride, and high-density lipoprotein cholesterol on admission; ischemic stroke subtype; lipid-lowering treatment while presenting hyperlipidemia; and height and body weight. Informed consent was obtained from all participants on enrollment.

The enrolled subjects were observed prospectively from September 1, 2003, to October 1, 2005, or until they reached a primary end point or death. Each hospital obtained information on the patient outcome and details of hyperlipidemia treatment using interviews, letters, or phone calls. The data were collected by the JSSRS office through the Internet. The Ethical Committee of the Hiroshima University approved this study.