Statins and the risks of stroke recurrence and death after ischemic stroke : The Fukuoka Stroke Registry

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Abstract

***Background and Purpose*—**The findings of recent clinical trials suggest that treatment with high-dose statins reduces the risk of stroke recurrence. However, the doses approved in Japan are much lower than those in the previous studies. This study aimed to elucidate whether prescribed doses of statins reduce the risks of cerebrovascular events (CVEs: stroke recurrence or transient ischemic attack) and all-cause mortality in a cohort of Japanese patients with first-ever ischemic stroke.

***Methods*—**The 2822 eligible patients registered in the Fukuoka Stroke Registry with first-ever acute ischemic stroke from June 2007 to February 2011 were classified into statin users (n=993) and non-users (n=1829) at discharge, and followed up until March 2012. We assessed the cumulative risks of CVE and all-cause mortality by the Kaplan-Meier method, and calculated hazard ratios (HRs) and 95% confidential intervals (CIs) using the Cox proportional hazards model.

***Results*—**During the follow-up time (median, 2.0 years), 305 patients had CVEs and 345 died. The cumulative risks of CVE and death after 4 years were significantly lower in statin users than in non-users (13.8% versus 19.5%, P=0.005 for CVE; 11.8% versus 21.7%, P<0.001 for death). After adjusting for multiple confounding factors, statin treatment significantly reduced the risks of CVE (HR, 0.70; 95% CI, 0.53 to 0.92;

P=0.011) and all-cause mortality (HR, 0.67; 95% CI, 0.50 to 0.89; *P*=0.006).

***Conclusions*—**Our findings suggest that low-dose statin may reduce the risks of CVE and death in Japanese patients with acute ischemic stroke.

Statins and the Risks of Stroke Recurrence and Death after Ischemic Stroke: The Fukuoka Stroke Registry

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Introduction

Many randomized controlled trials found that treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) was beneficial for the prevention of stroke.[1,2] Treatment with high-dose statins may also reduce the risk of stroke recurrence. A recent randomized controlled trial, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, showed that high-dose atorvastatin (80mg) decreased the risk of stroke recurrence in patients with recent stroke or transient ischemic attack (TIA).[3] In a meta-analysis of randomized controlled trials including the SPARCL trial, statin treatment was found to be associated with a significant reduction in the relative risk of stroke recurrence.[4] However, the maximal dose of atorvastatin approved by Japanese Ministry of Health, Labour and Welfare is 20mg for hypercholesterolemia. The doses of other statins used in Japan are similarly much lower than those in the previous studies.

It is unclear whether statins even in lower dosage than previously reported are effective for reducing the risk of stroke recurrence after ischemic stroke. Additionally, various types of statins are prescribed in a wide range of doses and treatment adherence declines with time in normal medical practice.[5,6] Therefore, the expected effects may not be obtained by the practical use. The aim of the present study was to elucidate

whether prescribing statin at discharge is associated with a reduced risk of stroke recurrence and death after first-ever ischemic stroke by analyzing a large cohort of patients with acute ischemic stroke in Japan.

Methods

Subjects

The Fukuoka Stroke Registry (FSR) is a multicenter, hospital-based registry of acute stroke patients. The study design has previously been reported.[7] Kyushu University Hospital and six stroke centers in Fukuoka, Japan participated in this registry (see Appendix). Patients were fully informed of the study objectives, design, and the risks and benefits of participation, and written informed consent was obtained from all participants. Data were collected prospectively, including demographic characteristics, medical history, prehospital treatment, emergency treatment, in-hospital treatment, and ability to manage activities of daily living, neurological symptoms, and laboratory data during hospitalization.

Stroke was defined as a sudden onset of focal neurological deficit due to brain ischemia or hemorrhage. All patients in this study underwent brain imaging examinations (computed tomography or magnetic resonance imaging). Stroke was

classified into ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, or other type of stroke. Ischemic stroke was further categorized into subtypes according to the criteria of the Trial of Org 10172 in Acute Stroke Therapy,[8] and non-cardioembolic stroke was defined as small-vessel occlusion, large-artery disease, or other (ischemic stroke of other determined or undetermined etiology). Of the 4535 cases of stroke presenting within 7 days after onset that were registered from June 2007 to February 2011, 3886 cases were classified as ischemic stroke. After excluding 908 cases with a previous stroke and 156 cases with stroke recurrence or death during hospitalization, 2822 patients with first-ever ischemic stroke were included in this study (Figure 1).

Clinical Assessments

Baseline characteristics such as demographic factors, risk factors, cardiovascular comorbidities, lipid profiles (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglyceride levels) and National Institutes of Health Stroke Scale score were assessed on admission. Smoking was defined as current or former habit of cigarette smoking. Hypertension was defined a history of systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or a history of treatment with antihypertensive medication. Diabetes mellitus was

defined as a fasting blood glucose level ≥126 mg/dL, a previous positive 75-g oral glucose tolerance test result, or a history of treatment with antidiabetic medication. Coronary heart disease was defined as a history of angina pectoris, myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery. Chronic kidney disease was defined as a glomerular filtration rate of (GFR) <60 mL/min/1.73 m^2 or proteinuria. GFR was calculated using the equation proposed by the Japanese Society of Nephrology:[9] GFR (mL/min/1.73 m^2) = $194 \times Cr^{-1.094} \times Age^{-0.287}$ (× 0.739 if female).

Medications at discharge were recorded, including statins, antithrombotics, and antihypertensives. Statins were administered at the discretion of each stroke neurologist based on the Japanese Atherosclerosis Society Guidelines, i.e. when the value of LDL-cholesterol was 120 mg/dl (100 mg /dl in case of patients who also had coronary heart diseases) or higher.[10] Statin-users were defined as patients treated with statins at discharge.

Clinical Outcomes

The primary outcome was cerebrovascular events (CVEs) including stroke recurrence and TIA. The secondary outcome was death from any cause. All patients were followed

up at 3, 6, and 12 months after onset, and yearly thereafter until March 2012, via direct or indirect interviews by trained nurses who were blinded to the clinical data. Details regarding stroke recurrence were further sought from general practitioners or hospital records if necessary. All information was reviewed by a member of the steering committee masked to the patients' clinical backgrounds.

Statistical Analysis

All statistical analyses were performed using JMP software, version 9 (SAS Institute Inc. Cary, NC). Baseline characteristics were compared between statin users and non-users at discharge using the χ^2 test, the unpaired t-test, or the Wilcoxon rank sum test, as appropriate. The cumulative risks of CVE or death during the follow-up period were estimated by the Kaplan-Meier method. The differences in cumulative risks between statin users and non-users were compared using the log-rank test. The Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for study outcomes with age- and sex-adjustment, and multivariate-adjustment. Sensitivity analysis was performed among 2208 patients with non-cardioembolic stroke at baseline. Subgroup analyses were performed according to age (<70 years or ≥70 years) and sex, and heterogeneity in the HRs between the subgroups was tested by

adding a multiplicative interaction term to the relevant Cox model. Probability values <0.05 were considered statistically significant.

Results

Patient Characteristics

The characteristics of patients are shown in Table 1. Of the 2822 patients included in this study, 993 (35.2%) were treated with statins at discharge. The types and doses of statins prescribed to the patients in this study were shown in supplementary table. Among patients treated with statins at discharge, 377 patients had already undergone statin treatment before stroke onset but other 616 patients started receiving statins during hospitalization. Statin users had a lower mean age than non-users. Statin users were also more likely to be female and to have a history of hypertension, diabetes mellitus, and coronary heart disease than non-users. Antithrombotic and antihypertensive medications were administered more frequently to statin users than to non-users. Atrial fibrillation and cardioembolic stroke were less prevalent in statin users than in non-users. Total cholesterol, LDL cholesterol, and triglyceride levels on admission were significantly higher in statin users than in non-users. Neurological symptoms were less severe in statin users than in non-users.

Overall CVE and Mortality Rates

The median duration of follow-up was 2.0 years after the onset of stroke (interquartile range 1.0 to 3.0 years). CVE occurred in 305 patients during the follow-up period, including 221 cases of ischemic stroke, 33 of intracerebral hemorrhage, 3 of subarachnoid hemorrhage, 29 of unknown type, and 19 of TIA. The cumulative risk of CVE at 4 years was significantly lower in statin users than in non-users (13.8% versus 19.5%, P=0.005; Figure 2). After age- and sex-adjustment and multivariate-adjustment, statin treatment was independently associated with a reduced risk of CVE (HR, 0.70; 95% CI, 0.53 to 0.92; P=0.011 in the multivariate-adjustment model; Table 2).

There were 345 deaths during the follow-up period. The cumulative risk of death at 4 years was 11.8% in statin users and 21.7% in non-users (P<0.001; Figure 2). After age- and sex-adjustment and multivariate-adjustment, statin treatment was independently associated with a reduced risk of mortality after ischemic stroke (HR, 0.67; 95% CI, 0.50 to 0.89; P=0.006 in the multivariate adjustment model; Table 2).

Sensitivity analysis among patients with non-cardioembolic stroke

Of the 2208 patients with non-cardioembolic stroke, CVE occurred in 235 patients and

204 died during the follow-up period. The cumulative risks of CVE and death were significantly lower in statin users than in non-users (CVE 13.5% versus 19.4%, *P*=0.006; death 11.2% versus 17.1%, *P*<0.001). After multivariate-adjustment, statin use was independently associated with a reduced risk of CVE (HR, 0.66; 95% CI, 0.49 to 0.89; *P*=0.007) and tended to be associated with a reduced mortality rate (HR, 0.75; 95% CI, 0.53 to 1.04; *P*=0.084; Table 2).

Subgroup analyses

Subgroup analyses were performed according to age and sex. Multivariate-adjusted HRs (95% CIs) for CVE were 0.58 (0.36 to 0.92) in the middle-aged group (<70 years) and 0.78 (0.55 to 1.10) in the elderly group (≥70 years) (*P* for heterogeneity = 0.657), and those for death were 0.70 (0.35 to 1.35) and 0.59 (0.43 to 0.81), respectively (*P* for heterogeneity = 0.450). Multivariate-adjusted HRs (95% CI) for CVE were 0.68 (0.47 to 0.97) in men and 0.70 (0.44 to 1.09) in women (*P* for heterogeneity = 0.938), and those for death were 0.81 (0.56 to 1.15) and 0.50 (0.30 to 0.81), respectively (*P* for heterogeneity = 0.181). No evidence of heterogeneity was observed between the age groups or between men and women.

Discussion

This multicenter, hospital-based, prospective observational study demonstrated that treatment with statins at discharge was significantly associated with the reduced risks of both CVE recurrence and death after first-ever ischemic stroke. Therefore, normal practical use of statins may be effective to prevent stroke recurrence and improve survival after ischemic stroke in Japanese populations.

Several meta-analyses of randomized controlled trials found that treatment with statins reduced the risks of not only first-ever stroke but also stroke recurrence.[1,2,4] Moreover, a few observational studies also suggested that statins reduced the risks of stroke recurrence and death after stroke.[11-13] However, the doses of statins used in the previous studies were higher than those in the current study (see Supplementary Table). No study provided evidence that such low-dose range of statins used in this study was effective to reduce the risk of stroke recurrence. In Asian populations, lower doses of statins were shown to achieve sufficient lipid control.[14–20] Therefore, optimal doses of statins may vary among ethnic groups. If lower doses are similarly effective, it is advantageous because of reduced risk of the adverse events or hemorrhagic stroke. Validation studies are needed regarding the effects of lower doses of statins on stroke recurrence.

Types and doses of statins are varied depending on the individual patient and a general practitioner in normal practice. Additionally, adherence with statin therapy declines with time.[5,6] However, evidence is lacking with respect to whether the effects of statins are also observed in the normal medical practical. The present study demonstrated in a large cohort of Japanese patients with acute ischemic stroke that prescribing statins at discharge was independently associated with reduced risks of CVE recurrence and death after adjustment for multiple confounding factors. The effects of statin on CVE and death were similar between the middle-aged and the elderly, and between men and women. In this cohort, statins were associated with a reduced risk of CVE recurrence in patients with non-cardioembolic stroke. Treatment with statins may therefore be efficient for the prevention of stroke recurrence in Japanese patients with ischemic stroke due to thrombotic mechanisms in the normal practice.

A meta-analysis as well as the SPARCL trial suggested that the reduced risk for stroke in patients treated with statins was related to lowered LDL cholesterol levels.[1,4,21] A post-hoc analysis of the SPARCL trial showed that the relative risk of stroke was reduced by 28% in patients with an LDL cholesterol level <70 mg/dL compared with those with an LDL cholesterol level >100 mg/dL.[21] In the present study, the mean LDL cholesterol level at discharge was lower in statin users (91.0±28.5

mg/dL) than in non-users (108.3±28.3 mg/dL; $P<0.001$). Although long-term lipid levels after discharge were not available in this study, the lower LDL cholesterol levels in statin users may be related to the reduced risk of stroke recurrence and death after ischemic stroke.

The strengths of the present study include its multicenter prospective observational design, the high rate of patients who gave informed consent for inclusion (89% of the eligible patients), and the high rate of follow-up (95%). This study also enrolled only patients with first-ever stroke to exclude patients who might have received intensive preventive therapy after a previous stroke. This study also had some limitations. We did not have information regarding compliance with statin use during the follow-up period, but non-compliance would have decreased the estimated effects of statin use. Since the diagnosis of subtype of recurrent stroke was principally based on telephone interview and not all adjudicated by medical records including brain imagings, it was difficult to investigate the effects of statins on stroke recurrence in each subtype. As this was an observational study, prescription of statins was determined by attending doctors, leading to confounding by indication. We used multivariate models including factors which were identified in a risk score for predicting recurrence in Japanese patients with ischemic stroke (Fukuoka stroke risk score for Japanese: FSR-J),[22] and/or

clinically relevant factors. In addition to these factors, the unidentified factors may be also involved in their association as confounders. To the contrary, there may be the possibility of over adjustment in the model, whereas the results were unchanged in the multivariate analysis using simple model with only significant factors in univariate analysis.

Appendix

FSR Investigators

The following hospitals participated in the FSR: Kyushu University Hospital, National Hospital Organization Kyushu Medical Center, National Hospital Organization Fukuoka Higashi Medical Center, Fukuoka Red Cross Hospital, St. Mary's Hospital, Steel Yawata Memorial Hospital, and Japan Labor Health and Welfare Organization Kyushu Rosai Hospital.

The Steering Committee included: Takao Ishitsuka, MD (Steel Memorial Yawata Hospital); Shigeru Fujimoto, MD (Steel Memorial Yawata Hospital); Setsuro Ibayashi, MD (Seiai Rehabilitation Hospital); Kenji Kusuda, MD (Seiai Rehabilitation Hospital); Shuji Arakawa, MD (Japan Labour Health and Welfare Organization Kyushu Rosai Hospital); Katsumi Irie, MD (Hakujyuji Hospital); Kenichiro Fujii, MD (Fukuoka Red

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Disclosures

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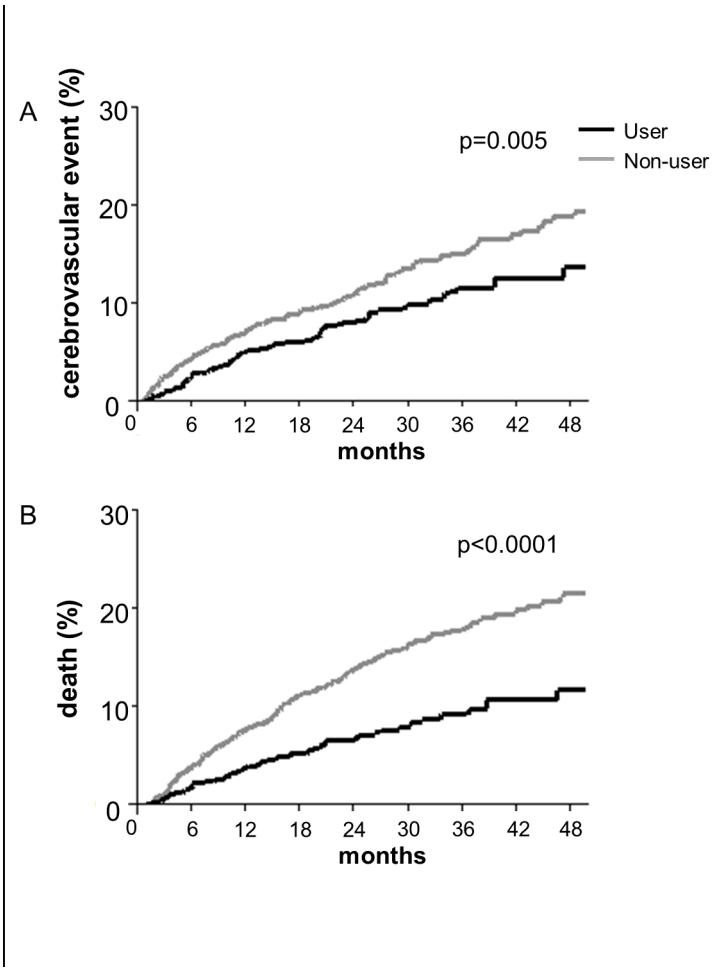
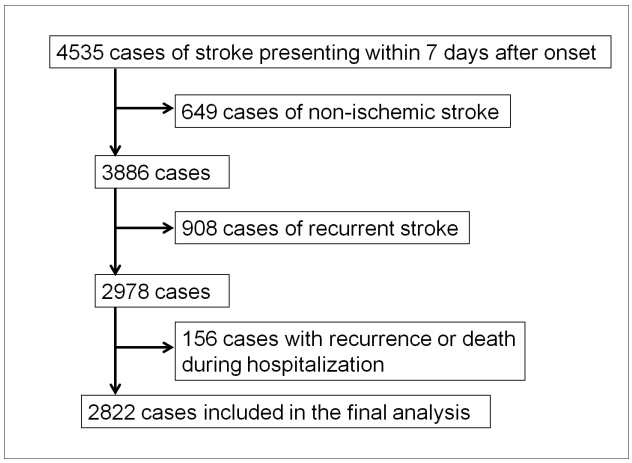
Figure legends

Figure 1. Flow chart of patient selection

Figure 2. Kaplan-Meier curves for cerebrovascular event (A) and death (B)


A
cerebrovascular event (%)
30
20
10
0
0
6
12
18
24
30
36
42
48
months
p=0.005
User
Non-user
B
death (%)
30
20
10
0
0
6
12
18
24
30
36
42
48
months
p<0.0001


4535 cases of stroke presenting within 7 days after onset
649 cases of non-ischemic stroke
3886 cases
908 cases of recurrent stroke
2978 cases
156 cases with recurrence or death during hospitalization
2822 cases included in the final analysis

Supplementary Table. Comparison of the dose of statins between the Fukuoka Stroke Registry (FSR) and other studies

Statin	n (%)	Range (median), mg/day		Mean ± SD, mg/day	
		Prescribed doses in FSR	Milionis et al.[11]	Prescribed doses in FSR	Sicras-Mainar et al.[12]
Atorvastatin	466 (46.9)	2.5-20 (10)	10-40	10 ± 2	20 ± 12
Pravastatin	280 (28.2)	5-10 (10)	20-40	9 ± 2	21 ± 19
Fluvastatin	44 (4.4)	10-40 (30)	40-80	29 ± 5	21 ± 5
Rosuvastatin	107 (10.8)	2.5-15 (2.5)	-	3 ± 2	-
Simvastatin	26 (2.6)	2.5-10 (5)	10-40	5 ± 1	26 ± 19
Pitavastatin	69 (7.0)	1-2 (1)	-	2 ± 1	-
Unknown	1 (0.1)				

Table 1. Baseline characteristics

	Statin user n=993	Statin non-user n=1829	p value
Age (years)	70.0 ± 10.9	71.2 ± 13.5	0.001
Female	453 (45.6)	692 (37.8)	<0.001
Risk factors			
Smoking	476 (47.9)	935 (51.1)	0.106
Hypertension	836 (84.2)	1327 (72.6)	<0.001
Diabetes mellitus	388 (39.1)	429 (23.5)	<0.001
Atrial fibrillation	147 (14.8)	506 (27.7)	<0.001
Coronary heart disease	185 (18.6)	207 (11.3)	<0.001
Chronic kidney disease	332 (33.6)	641 (35.1)	0.436
Stroke subtype			<0.001
Small-vessel occlusion	260 (26.2)	452 (24.7)	
Large-artery disease	239 (24.1)	316 (17.3)	
Cardioembolic	139 (14.0)	475 (26.0)	
Others	355 (35.7)	586 (32.0)	
Pre-stroke statin therapy	377 (38.0)	70 (3.8)	<0.001
Lipid profiles on admission (mg/dL)			
Total cholesterol	215.4 ± 44.7	186.8 ± 35.8	<0.001
LDL cholesterol	132.3 ± 39.6	110.2 ± 30.5	<0.001
HDL cholesterol	52.6 ± 13.9	52.8 ± 14.8	0.644
Triglyceride	144.5 ± 91.7	113.5 ± 77.5	<0.001
Baseline NIH Stroke Scale score	3 (1-5)	3 (2-7)	<0.001
Medications at discharge			
Antithrombotics	980 (98.7)	1757 (96.1)	<0.001
Antiplatelets	834 (84.0)	1216 (66.5)	<0.001
Anticoagulants	227 (22.9)	670 (36.6)	<0.001
Antihypertensives	520 (52.4)	806 (44.1)	<0.001

Data are number of patients (%), median (interquartile range) for discontinuous variables, and mean ± SD for continuous variables. Statin-users were defined as patients treated with statins at discharge.

Table 2. Hazard ratio of statin use for overall and stroke subtype subpopulations

	Cerebrovascular event					Death				
	Statin user Event/No.	Statin non-user Event/No.	HR	95% CI	p value	Statin user Event/No.	Statin non-user Event/No.	HR	95% CI	p value
Overall	85/993	220/1829				73/993	272/1829			
Age- and sex-adjusted			0.75	0.58-0.96	0.023			0.64	0.49-0.83	<0.001
Multivariate-adjusted*			0.70	0.53-0.92	0.011			0.67	0.50-0.89	0.006
Non-cardioembolic subpopulation	70/854	165/1354				54/854	150/1354			
Age- and sex-adjusted			0.71	0.53-0.93	0.014			0.73	0.53-0.99	0.043
Multivariate-adjusted**			0.66	0.49-0.89	0.007			0.75	0.53-1.04	0.084

* Multivariate model included age, sex, smoking, hypertension, diabetes mellitus, atrial fibrillation, coronary heart disease, chronic kidney disease, stroke subtype, baseline NIH Stroke Scale score, antithrombotics or/and antihypertensives at discharge and LDL-cholesterol on admission.

** Multivariate model included age, sex, smoking, hypertension, diabetes mellitus, atrial fibrillation, coronary heart disease, chronic kidney disease, baseline NIH Stroke Scale score, antithrombotics or/and antihypertensives at discharge and LDL-cholesterol on admission.

Statin-users were defined as patients treated with statins at discharge.