Two-Year Recurrence After First-Ever Stroke in a General Population of 1.4 Million Japanese Patients — The Shiga Stroke and Heart Attack Registry Study —

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Background: Despite many effective strategies for the prevention of recurrent stroke, individuals who survive an initial stroke have been shown to be at high risk of recurrent stroke. The aim of this study was to investigate the current status of stroke recurrence after first-ever stroke using a population-based stroke registry in Japan.

Methods and Results: As part of the Shiga Stroke and Heart Attack Registry, the Shiga Stroke Registry is an ongoing population-based stroke registry study that covers approximately 1.4 million residents of Shiga Prefecture, Japan. A total of 1,883 first-ever stroke survivors at 28 days was registered in 2011 and followed-up until the end of 2013. Recurrence was defined as any type of stroke after 28 days from the onset of an index event. Two-year cumulative recurrence rates were estimated using cumulative incidence function methods. Over a mean 2.1-year follow-up period, 120 patients experienced recurrent stroke and 389 patients died without recurrence. The 2-year cumulative recurrence rate was higher in patients with index ischemic stroke (6.8%) than in those with index hemorrhagic stroke (3.8%).

Conclusions: Two-year cumulative recurrence rate after first-ever stroke remained high, particularly among patients with ischemic stroke, in the present population-based registry study in a real-world setting in Japan. Further intensive secondary prevention strategies are required for these high-risk individuals.

Key Words: Asian; Population studies; Recurrence event; Stroke

Age-standardized stroke mortality in Japan has decreased rapidly over the past 5 decades.¹ However, stroke remains one of the leading causes of death² and disability.³ Furthermore, despite a number of effective strategies for the secondary prevention of stroke, individuals who survive an initial stroke have been shown to be at very high risk of recurrent stroke.⁴ Studies in several countries have indicated that the risk of stroke recurrence has decreased over past decades,^{5,6} with one recent study from Ireland reporting a 2-year recurrence rate of approximately 11%.⁷ However, only limited up-to-date information is available regarding stroke recurrence, particularly type-specific ischemic stroke, from population-based studies in East Asian countries, where there is a higher prevalence of hemorrhagic stroke and lacunar infarction.⁸

As part of the Shiga Stroke and Heart Attack Registry (SSHR), the Shiga Stroke Registry is an ongoing comprehensive, population-based, large-scale stroke registry study in Japan. We have previously reported the incidence rate⁹ and 2-year survival rate¹⁰ of stroke using data from the registry. The aim of the present study was to investigate current cumulative stroke recurrence after first-ever stroke using the population-based stroke registry in Shiga Prefecture, Japan.

Methods

Study Design

The methodology of the Shiga Stroke Registry Study has been described in detail elsewhere.^{9,10} Briefly, as part of the

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Table 1. Characteristics of Patients With First-Ever Stroke According to Type of Index Stroke: Shiga Stroke Registry, 2011, Shiga, Japan

	Ischemic stroke	Hemorrhagic stroke	Total stroke
Total no. patients	1,299	583	1,883
Male sex	743 (57.2)	260 (44.6)	1,003 (53.3)
Age (years)	74.2±13.2	68.2±15.1	72.3±14.1
Past history			
Transient ischemic attacks			
Yes	71 (5.5)	8 (1.4)	79 (4.2)
No	1,225 (94.3)	572 (98.1)	1,798 (95.5)
Unknown	3 (0.2)	3 (0.5)	6 (0.3)
Atrial fibrillation			
Yes	288 (22.2)	38 (6.5)	326 (17.3)
No	1,005 (77.4)	540 (92.6)	1,546 (82.1)
Unknown	6 (0.5)	5 (0.9)	11 (0.6)
Myocardial infarction			
Yes	79 (6.1)	27 (4.6)	107 (5.7)
No	1,218 (93.8)	554 (95.0)	1,772 (94.1)
Unknown	2 (0.2)	2 (0.3)	4 (0.2)
Hypertension			
Yes	915 (70.4)	419 (71.9)	1,335 (70.9)
No	379 (29.2)	160 (27.4)	539 (28.6)
Unknown	5 (0.4)	4 (0.7)	9 (0.5)
Diabetes			
Yes	360 (27.7)	114 (19.6)	474 (25.2)
No	933 (71.8)	466 (79.9)	1,400 (74.3)
Unknown	6 (0.5)	3 (0.5)	9 (0.5)
Dyslipidemia			
Yes	510 (39.3)	158 (27.1)	668 (35.5)
No	751 (57.8)	377 (64.7)	1,129 (60.0)
Unknown	38 (2.9)	48 (8.2)	86 (4.6)
Smoking status			
Non-smoker	737 (56.7)	352 (60.4)	1,090 (57.9)
Past smoker	152 (11.7)	57 (9.8)	209 (11.1)
Current smoker	309 (23.8)	129 (22.1)	438 (23.3)
Unknown	101 (7.8)	45 (7.7)	146 (7.8)
Drinking status			
Non-drinker	645 (49.7)	296 (50.8)	941 (50.0)
Past drinker	21 (1.6)	7 (1.2)	28 (1.5)
Current drinker	468 (36.0)	213 (36.5)	682 (36.2)
Unknown	165 (12.7)	67 (11.5)	232 (12.3)
Index stroke subtype			
Intracerebral hemorrhage		447 (76.5)	447 (23.7)
Subarachnoid hemorrhage		136 (23.3)	136 (7.2)
Lacunar infarction	347 (26.7)		347 (18.4)
Large artery infarction	413 (31.8)		413 (21.9)
Cardioembolic infarction	307 (23.6)		307 (16.3)
Other/undetermined	232 (17.9)		232 (12.3)

Unless indicated otherwise, data are given as n (%) or the mean±SD.

SSHR, the Shiga Stroke Registry is an ongoing multicenter, population-based registry study of stroke designed to build a complete information system on acute ischemic and non-traumatic hemorrhagic stroke management in Shiga Prefecture, Japan. Shiga Prefecture is located in the central part of Honshu Island. Based on the 2011 census, the population of Shiga Prefecture is 1,400,745 (689,859 men, 710,866 women).

Diagnosis of index stroke was defined as a sudden onset of focal neurological deficits persisting for more than 24 h, according to the World Health Organization (WHO) Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project.¹¹ All registered cases were adjudicated by more than 2 independent investigators. Index stroke was classified as ischemic stroke, hemorrhagic stroke (intracerebral hemorrhage and sub-

Table 2. Cumulative Recurrence Rate After First-Ever Stroke According to Sex, Age, and Type of Index Stroke in the Shiga Stroke Registry

	At 1 year			At 2 years		
	No. cases recurrence*	Cumulative recurrence rate (%)	95% CI	No. cases recurrence*	Cumulative recurrence rate (%)	95% CI
Total stroke	60 (45/15)	3.2	2.5–4.1	110 (81/29)	5.8	4.8–7.0
Men	32 (25/7)	3.2	2.2–4.4	62 (50/12)	6.2	4.8–7.8
Women	28 (20/8)	3.2	2.2–4.5	48 (31/17)	5.5	4.1–7.1
Age (years)						
<70	17 (14/3)	2.3	1.4–3.6	32 (25/7)	4.3	3.0–6.0
≥70	43 (31/12)	3.8	2.8–5.0	78 (56/22)	6.8	5.5–8.4
Ischemic stroke	45 (41/4)	3.5	2.6–4.6	88 (76/12)	6.8	5.5–8.2
Ischemic stroke subtype						
Lacunar infarction	11 (10/1)	3.2	1.7–5.4	21 (18/3)	6.1	3.9–8.9
Large artery infarction	18 (15/3)	4.4	2.7–6.6	39 (34/5)	9.4	6.9–12.5
Cardioembolic infarction	10 (10/0)	3.3	1.7–5.7	19 (15/4)	6.2	3.9–9.3
Other/undermined	6 (6/0)	2.6	1.1–5.3	9 (9/0)	3.9	1.9–7.0
Hemorrhagic stroke	15 (4/11)	2.6	1.5–4.1	22 (5/17)	3.8	2.4–5.6

*Data show the number of cases of recurrence of total stroke (ischemic stroke/hemorrhagic stroke). CI, confidence interval.

arachnoid hemorrhage), and undetermined type of stroke. Based on the criteria for subtypes of stroke in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study,¹² ischemic stroke was further divided into lacunar infarction, large artery infarction, cardioembolic infarction, and undetermined type of ischemic stroke.

In all, 2,176 patients with first-ever stroke with onset dates ranging from 1 January to 31 December 2011 were followed-up until December 2013. After excluding 293 patients who died within 28 days of the index stroke, 1,883 participants were included in the present analysis. The SSHR study was approved by the Institutional Review Board of Shiga University of Medical Science (Reference no. 23-186-1) and followed the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation.

Clinical Features and Medical Histories

Information on medical history, including transient ischemic attack (TIA), atrial fibrillation, myocardial infarction (MI), hypertension, diabetes, dyslipidemia, and smoking and drinking status, was extracted from the medical records. Atrial fibrillation was defined as a history of atrial fibrillation and/or clinical diagnosis based on electrocardiogram (ECG) and/or ECG monitoring during hospitalization. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, using antihypertensive medication, and/or a history of hypertension. Diabetes was defined as casual blood glucose ≥11.1 mmol/L, the use of antidiabetic medication, and/or a history of diabetes. Dyslipidemia was defined as total cholesterol ≥5.69 mmol/L, low-density lipoprotein cholesterol ≥4.14 mmol/L, medication for dyslipidemia, and/or a history of dyslipidemia. Smoking status was categorized as non-smoker, past smoker, and current smoker. Alcohol consumption was categorized into non-drinker, past drinker, and current drinker.

Follow-up Survey

All patients with first-ever stroke who were alive at 28 days

after the index stroke were followed-up until end of 2013 using the population-based Shiga Stroke Registry and death certificate information of all deceased residents in the region, with the permission of the Japanese Ministry of Health, Labour and Welfare. The definition of recurrent stroke was the same as for the index stroke. In the Registry, a stroke recurring within 28 days of the index stroke is considered part of the original episode, as per the WHO MONICA Project.¹¹ The main outcome of the present study was the recurrence of any stroke, which was defined as a sudden onset of focal neurological deficits persisting for more than 24 h,¹¹ from 28 days after the onset of an index event.

Statistical Analysis

Cumulative recurrence rates of first-ever stroke were estimated using cumulative incidence function methods, considering death as a competing risk, and compared using Gray's test.¹³ Two-sided $P < 0.05$ was considered significant. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

The baseline characteristics of first-ever stroke survivors at 28 days are given according to the type of index stroke in **Table 1**. The mean age of patients with an index ischemic stroke was 74.2 years, and 68.2 years for patients with index hemorrhagic stroke. The prevalence rates of a history of TIA, atrial fibrillation, and MI for all stroke patients were 4.2%, 17.3%, and 5.7%, respectively.

During the follow-up period (mean 2.1 years), 120 patients experienced recurrent stroke after 28 days from the onset of an index events and 389 patients died without recurrence. Cumulative recurrence rates of all patients with stroke and those in subgroups according to type of index stroke and sex are given in **Table 2**. Cumulative recurrence rates after first-ever stroke were 3.2% (3.2% in men, 3.2% in women) at 1 year and 5.8% (6.2% in men, 5.5% in women) at 2 years. The cumulative recurrence rates after first-ever stroke were 4.3% in the younger (age <70 years) group and 6.8% in the

Figure. Two-year recurrence rate curves after first-ever stroke by (A) index stroke subtype, (B) index ischemic stroke subtype, and (C) sex. Cumulative recurrence rates were estimated using cumulative incidence function methods, considering death as a competing risk, and compared using Gray's test.

older (age ≥ 70 years) group. The cumulative recurrence rates at 2 years for patients with index ischemic stroke and index hemorrhagic stroke were 6.8% and 3.8%, respectively. The cumulative recurrence rates at 2 years for patients with index lacunar infarction, large artery infarction, and cardioembolic infarction were 6.1%, 9.4%, and 6.2%, respectively. The cumulative incidence of recurrent stroke is shown according to type of index stroke and sex in **Figure**. Higher recurrence rates were observed in individuals with index ischemic stroke, especially those with large artery infarction, than in those with index hemorrhagic stroke. The incidence rates of recurrent stroke were similar between men and women.

Discussion

The present comprehensive population-based stroke registry study in Japan demonstrated the current status of

2-year recurrence after 28 days from the onset of first-ever stroke in a real-world setting in Japan. Cumulative recurrence rates for total stroke after first-ever stroke were 3.2% at 1 year and 5.8% at 2 year (6.2% for patients with ischemic stroke, 3.8% for those with hemorrhagic stroke). Higher risks of recurrence were observed among patients with ischemic stroke and those with a history of TIA.

To the best of our knowledge, this is the first study to report the 2-year cumulative recurrence rates of total stroke, ischemic stroke and its subtypes, and hemorrhagic stroke based on a recent comprehensive, population-based, large-scale registry in Asian countries. The definition of stroke recurrence was heterogeneous across different studies. According to a recent meta-analysis, the annual recurrence rate of stroke is 4.3%, but rates are higher in randomized control trials (4.6%) or hospital-based studies (4.5%) than in community-based studies (2.6%).¹⁴ That meta-analysis did not find a decreasing trend in stroke recurrence,¹⁴

although several longitudinal studies have reported decreasing trends in the recurrence of total or ischemic stroke.^{5,6,15–17} Previous studies showed that the rate of stroke recurrence after first-ever stroke was 8.0% and 13.2% in the UK^{18,19} and 16.0% in Australia.²⁰ In Japan, the recurrence rate after first-ever stroke at 1 year was reported to range from 6.5% to 12.8%;^{21,22} however, these studies were conducted 10–30 years ago. Recent studies have demonstrated lower recurrence rates at 1 year (excluding recurrence within 1 month after the onset of index stroke) than those reported in older studies (4.6% in Iran,²³ 6% in Sweden⁵). Recent hospital-based studies²⁴ or clinical trials^{25,26} conducted in Japan also reported an annual recurrence rate of stroke in the range 2.3–3.7%. The present study, which found a recurrence rate of 3.2% at 1 year, confirms the findings of other recent studies and indicates that the stroke recurrence rate may have decreased over recent decades in Japan, as in some other countries.

In the present study, higher recurrence rates were observed in patients with ischemic stroke (especially large artery infarction) than in those with hemorrhagic stroke. Previous studies have also reported a higher risk of recurrence among patients with ischemic stroke.^{7,22,23} Among the subtypes of ischemic stroke, large artery infarction has been shown to be associated with a higher risk of recurrence than other subtypes.²⁷

In Asian countries, the proportion of large artery infarction among patients with ischemic stroke has increased over recent decades, and it is now the most common subtype of ischemic stroke.²⁸ Moreover, patients with stroke events are at a high risk of recurrence of not only of the same type of event, but also other types of vascular events.²⁹ These findings emphasize the importance of secondary prevention for patients with ischemic stroke, especially for those with prior large artery infarction. Moreover, this type of infarction may be caused by atherosclerosis, and assessment and control of multiple risk factors may be needed.³⁰

This study has several limitations. First, patients who moved out of Shiga Prefecture after the onset of index stroke were lost to follow-up because information on death and recurrence was collected only for residents of Shiga Prefecture. Therefore, the recurrence rates after stroke may have been underestimated. However, reports on internal migration derived from Basic Resident Registers showed that only 3.6% of residents moved out of Shiga Prefecture during the 2-year study period. Another limitation of the study is a lack of information on medications after discharge, which make it difficult to assess long-term adherence to secondary prevention strategies.

Conclusions

In this population-based stroke registry study in a real-world setting in Japan, the 2-year cumulative recurrence rate after first-ever stroke remained high, particularly among patients with ischemic stroke. More intensive secondary prevention strategies are required for these high-risk individuals.

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Disclosures

The authors declare that there are no conflicts of interest.

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