Temporal Trends in Stroke Severity and Prior Antithrombotic Use Among Acute Ischemic Stroke Patients in Japan

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Background: Few existing stroke registries allow for evaluation of stroke severity, stroke subtype and antithrombotic usage prior to stroke onset over a given time period. The present study aimed to elucidate temporal trends in initial presenting stroke severity, stroke subtype and prior antithrombotic use over a 12-year period in a Japanese multicenter stroke registry.

Methods and Results: We included 71,017 acute ischemic stroke patients (72±12 years old; 27,445 women) from the Japan Standard Stroke Registry Study (JSSRS) who were admitted to 94 hospitals between 2001 and 2012. The mean age of stroke onset increased gradually over time (P<0.001). Cardioembolic stroke patients (n=19,247) exhibited more severe NIHSS scores when compared with those with non-cardioembolic stroke (n=50,427). The proportion of cardioembolic stroke patients tended to increase over time, rising from 25.9% in 2001–2002 to 30.2% in 2011–2012 (P<0.001). Among the cardioembolic stroke patients, the frequency of prior anticoagulant use significantly increased from 15.6% in 2001–2002 to 24.8% in 2011–2012 (P<0.001). The frequency of prior antiplatelet use increased from 2001–2002 to 2007–2008 but decreased after 2007–2008. Among both cardioembolic and non-cardioembolic stroke patients, initial stroke severity at admission decreased over time, particularly after 2008.

Conclusions: In this Japanese study, the mean age of ischemic stroke onset increased, while the initial neurological severity at presentation decreased, over a 12-year period. (Circ J 2016; 80: 2033–2036)

Key Words: Anticoagulation; Atrial fibrillation; Cardioembolism; Stroke severity

Although stroke is a global problem, the disease burden is particularly serious in Asia.1 Many countries in Asia have higher mortality rates from stroke than from heart disease, whereas the opposite pattern is generally observed in Western countries.2 In Japan, although stroke-associated deaths have recently decreased, stroke remains the most frequent cause of disability. Also, Japan is aging faster than other Asian countries and thus, temporal trends in the epidemiological characteristics of stroke patients in Japan might provide illustrative examples for other Asian countries. The approval of intravenous recombinant tissue-type plasminogen activator (rt-PA) therapy in 2005 has also dramatically changed acute stroke management in Japan.3 However, recent trends in stroke severity at initial presentation remain unclear.

With respect to stroke severity, stroke subtype should be considered because cardioembolic stroke patients exhibit more severe neurological defects at presentation than patients with non-cardioembolic stroke. In addition, certain observational studies have revealed an association between prior antithrombotic use and initial stroke severity.4,5 However, few existing stroke registries allow for evaluation of stroke severity, stroke subtype and antithrombotic usage prior to stroke onset over a prolonged time period.

In the present study, our aims were to elucidate the temporal trends in initial presenting stroke severity, stroke subtype and prior antithrombotic use among ischemic stroke patients over a 12-year period. We used a computerized database derived from stroke patients from 94 stroke management hospitals.
Between 1998 and 2012, 72,585 acute ischemic stroke patients were hospitalized in a total of 94 hospitals within 7 days of the onset of stroke. Relatively small numbers of patients (n=1,568) were recruited for the first 3 years (1998–2000), because JSSRS only started enrolling in 54 hospitals. After excluding 1,568 patients from those years, the remaining 71,017 patients (72.2±11.7 years old; 27,955 women) recruited from 94 stroke hospitals remained fairly constant over the study period. The baseline characteristics of the included and excluded patients in this study are provided in Table S1. Stroke subtypes were defined according to the National Institute of Neurological Disorders and Stroke criteria. Ischemic stroke severity at admission was evaluated using the National Institutes of Health Stroke Scale (NIHSS). Of all ischemic stroke patients, 19,632 patients (27.6%) had cardioembolic disease. Cardioembolic stroke patients were older (75.7±11.3 vs. 70.4±12.1 years; P<0.001); more frequently female (44.8% vs. 37.3%; P<0.001); exhibited more severe NIHSS scores (median [IQR], 9 [3–19] vs. 3 [2–6]; P<0.001); and had lower rates of hypertension (64.8% vs. 71.7%; P<0.001), diabetes mellitus (20.1% vs. 31.0%; P<0.001) and dyslipidemia (23.1% vs. 37.9%; P<0.001) when compared with non-cardioembolic stroke patients (Table S2). Among the cardioembolic stroke patients, 4,190 (22.5%) had prior anticoagulant use, with no significant difference for the initial NIHSS score between cardioembolic stroke patients with prior anticoagulant use and those without (9 [3–19] vs. 9 [3–19]; P=0.652). Of the cardioembolic stroke patients, 13,456 (73.0%) had AF. For the subgroup of cardioembolic stroke patients with AF, there was a trend of borderline statistical significance towards lower NIHSS scores among the anticoagulated patients at admission, when compared with the non-anticoagulated patients (10 [3–20] vs. 11 [4–20]; P=0.053). Table 1 summarizes the patients’ characteristics. The mean age of stroke onset increased gradually over time (Jonckheere-Terpstra test for trend, P<0.001). The frequencies of comorbidities (hypertension, diabetes mellitus, dyslipidemia and atrial fibrillation [AF]) also increased over time. During the period of study, the proportion of cardioembolic stroke patients generally increased, rising from 25.9% in 2001–2002 to 30.2% in 2011–2012. Of all ischemic stroke patients, 19,632 patients (27.6%) had cardioembolic disease. Cardioembolic stroke patients were older (75.7±11.3 vs. 70.4±12.1 years; P<0.001); more frequently female (44.8% vs. 37.3%; P<0.001); exhibited more severe NIHSS scores (median [IQR], 9 [3–19] vs. 3 [2–6]; P<0.001); and had lower rates of hypertension (64.8% vs. 71.7%; P<0.001), diabetes mellitus (20.1% vs. 31.0%; P<0.001) and dyslipidemia (23.1% vs. 37.9%; P<0.001) when compared with non-cardioembolic stroke patients (Table S2).

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Table 1 shows the temporal trends in initial NIHSS score and prior antithrombotic use among cardioembolic and non-cardioembolic stroke patients. Among the cardioembolic stroke patients, the frequency of prior anticoagulant use increased significantly over time, rising from 15.6% in 2001–2002 to 24.8% in 2011–2012 (Cochran-Armitage test for trend, P<0.001), and the frequency of prior antiplatelet use increased from 15.9% in 2001–2002 to 28.3% in 2007–2008, but subsequently decreased. Among the non-cardioembolic stroke patients, the frequency of prior antiplatelet use increased from

**Discussion**

In this Japanese multicenter stroke registry, the mean age of ischemic stroke onset increased, while the initial neurological severity at presentation decreased, over a 12-year period from 2001 to 2012. Second, a trend towards a higher proportion of cardioembolic stroke patients was observed.

Several population-based cohorts have indicated that lacunar infarction was the most frequent etiology for acute ischemic stroke in Japan prior to 2000. However, the Hisayama study demonstrated that the proportion of patients with lacunar infarction declined, particularly among men, over the 40 years from 1961 to 2002. The Japan Multicenter Stroke Investigator’s Collaboration (J-MUSIC), which included 16,922 acute ischemic stroke patients (including patients who experienced a transient ischemic attack) and was conducted in 156 hospitals from 1999 to 2000, revealed that lacunar infarction was the most common stroke subtype (38.8%), followed by atherothrombotic stroke (33.3%) and cardioembolic stroke (21.8%). This distribution of stroke subtypes might be equivalent to that observed during a previous stage of the present study (2001–2002) because of the tendency towards decreased lacunar infarction frequency. More recently, the Korean Stroke Registry Study indicated secular trends in ischemic stroke characteristics (n=46,098) from 2002 to 2010. During that time period, the proportion of strokes caused by small vessel occlusion (such as lacunar infarction) decreased, whereas the proportion of cardioembolic strokes increased. Indeed, that trend identified in the Korean Stroke Registry Study is similar to the time trends observed in the present registry study. The population of cardioembolic stroke patients was lower in the Korean registry (17.1%) than in the Japanese registry (27.6%), a difference that may have arisen because the Korean stroke patients (66.1±12.3 years) were younger than the Japanese stroke patients (72.2±12.1 years) during the 2 studies’ nearly identical time periods.

In the present study, among the cardioembolic stroke patients, the frequency of prior antiplatelet use decreased after 2007–2008. In Japan, prior to 2008, aspirin treatment was considered for patients with AF who were at low risk for stroke. However, the Japan Atrial Fibrillation Stroke Trial published in 2006 indicated that low-dose aspirin was neither effective nor safe for the prevention of stroke among patients with AF, even if low risk. Therefore, in 2008, the use of aspirin for preventing stroke in patients with AF was not recommended by the Japanese Circulation Society’s (JCS) national guidelines for pharmacotherapy for AF. This revision of the guidelines might have contributed to the observed decrease in prior antiplatelet use after 2007–2008.

From an analysis of the same registry examined in this study, we previously demonstrated that female sex was independently associated with initial neurological severity among AF-related cardioembolic stroke patients. The results of the present study indicated that stroke severity at admission decreased over time, although the proportion of women among cardioembolic stroke patients increased. Therefore, the secular trends for initial stroke severity may not be associated with trends in the proportion of female patients, but may instead be associated with other factors. For example, prior anticoagulant use before stroke onset, particularly with good-quality anticoagulation control, is associated with reduced stroke severity.

In the present study, there was a trend of borderline statistical significance towards lower NIHSS scores among anticoagulated patients at admission, when compared with those who were non-anticoagulated in the subgroup of cardioembolic stroke patients with AF. Of note, the present study was largely performed before the approval of non-vitamin K antagonist oral anticoagulants (NOACs) in Japan. Therefore, in the

### Table 2. Secular Trends for Prior Antithrombotic Agents and Initial Stroke Severity Among Cardioembolic and Non-Cardioembolic Stroke Patients in Japan, 2001–2012

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>19,632</td>
<td>1,678</td>
<td>2,637</td>
<td>4,258</td>
<td>3,650</td>
<td>3,952</td>
<td>3,457</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td>75.7±11.3</td>
<td>73.4±11.3</td>
<td>74.3±11.4</td>
<td>75.4±11.2</td>
<td>75.9±11.3</td>
<td>76.4±11.3</td>
<td>77.4±11.1</td>
<td>0.273</td>
</tr>
<tr>
<td>Female</td>
<td>8,793 (44.8)</td>
<td>715 (42.6)</td>
<td>1,160 (44.0)</td>
<td>1,901 (44.7)</td>
<td>1,642 (45.0)</td>
<td>1,817 (46.0)</td>
<td>1,558 (45.1)</td>
<td>0.073</td>
</tr>
<tr>
<td>Prior antiplatelet use (n=18,616)</td>
<td>4,706 (25.3)</td>
<td>187 (15.9)</td>
<td>577 (22.3)</td>
<td>1,179 (28.1)</td>
<td>1,018 (28.3)</td>
<td>932 (25.1)</td>
<td>813 (23.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior anticoagulant use (n=18,616)</td>
<td>4,190 (22.5)</td>
<td>188 (15.6)</td>
<td>507 (20.2)</td>
<td>948 (22.6)</td>
<td>796 (22.1)</td>
<td>905 (24.3)</td>
<td>846 (24.8)</td>
<td>&lt;0.001</td>
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<tr>
<td>NIHSS score at admission (n=19,259)</td>
<td>9 (3–19)</td>
<td>10 (3–19)</td>
<td>9 (3–19)</td>
<td>11 (4–21)</td>
<td>10 (3–19)</td>
<td>9 (3–19)</td>
<td>8 (3–19)</td>
<td>&lt;0.001</td>
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</table>

<table>
<thead>
<tr>
<th>Non-cardioembolic stroke</th>
<th>n=49,218</th>
<th>4,790</th>
<th>7,563</th>
<th>11,379</th>
<th>10,115</th>
<th>9,545</th>
<th>7,993</th>
</tr>
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<tbody>
<tr>
<td>Age, years</td>
<td>70.9±12.1</td>
<td>69.8±11.8</td>
<td>70.1±11.8</td>
<td>70.6±12.0</td>
<td>70.9±12.1</td>
<td>71.4±12.2</td>
<td>72.1±12.3</td>
</tr>
<tr>
<td>Female</td>
<td>19,162 (37.3)</td>
<td>1,789 (37.4)</td>
<td>2,825 (37.4)</td>
<td>4,267 (37.5)</td>
<td>3,763 (37.2)</td>
<td>3,513 (36.8)</td>
<td>3,005 (37.6)</td>
</tr>
<tr>
<td>Prior antiplatelet use (n=49,218)</td>
<td>12,181 (24.8)</td>
<td>701 (18.8)</td>
<td>1,599 (21.9)</td>
<td>2,902 (25.9)</td>
<td>2,609 (26.0)</td>
<td>2,277 (25.3)</td>
<td>2,093 (26.5)</td>
</tr>
<tr>
<td>Prior anticoagulant use (n=49,218)</td>
<td>2,432 (4.9)</td>
<td>163 (4.4)</td>
<td>421 (5.8)</td>
<td>594 (5.3)</td>
<td>511 (5.1)</td>
<td>381 (4.2)</td>
<td>362 (4.6)</td>
</tr>
<tr>
<td>NIHSS score at admission (n=51,125)</td>
<td>3 (2–6)</td>
<td>4 (2–7)</td>
<td>4 (2–7)</td>
<td>4 (2–7)</td>
<td>3 (2–6)</td>
<td>3 (1–6)</td>
<td>3 (1–6)</td>
</tr>
</tbody>
</table>

The data are presented as the mean±SD for age; as median (interquartile range) for National Institutes of Health Stroke Scale (NIHSS) score at admission; and as n (%) of patients for the remaining characteristics. The Jonckheere-Terpstra test for trend was used for age and NIHSS, and the Cochran-Armitage test for trend was used for other factors (sex, prior antiplatelet use and anticoagulant use).
examined database, “anticoagulation” essentially refers to warfarin therapy. A limitation of our study was our inability to collect prothrombin time-international normalized ratio (PT-INR) data at admission for cardioembolic stroke patients. However, the increasing use of prior anticoagulation before stroke onset seen in the present study might have contributed to the decreased stroke severity at admission. Widespread NOAC use for preventing stroke in AF patients is expected to influence stroke severity in the future.

In this study, initial neurological severity decreased over time among both non-cardioembolic and cardioembolic stroke patients. Among the non-cardioembolic stroke patients, the frequency of prior antiplatelet use increased from 2001–2002 to 2005–2006. Although antiplatelet use prior to stroke onset might be associated with decreased NIHSS score at admission among the non-cardioembolic stroke patients, the relationship between stroke severity and prior antiplatelet use remains controversial. At the minimum, aspirin use for the primary prevention of stroke is not recommended in Japan.

Study Limitations
First, hospital-based stroke studies cannot estimate stroke incidence in the general population. However, a strength of the database used in the present study is the inclusion of stroke severity and stroke subtype evaluations by stroke specialists. Second, we were unable to collect PT-INR data, as noted earlier. Third, our study was observational rather than a randomized trial involving prescribed antithrombotic agents. Therefore, the association between initial stroke severity and prior antithrombotic agents observed in the present study reflects association rather than causality. The effect of antithrombotic therapy for the prevention of ischemic stroke and reducing its severity requires testing in a prospective randomized trial. Finally, we did not evaluate the temporal trends for stroke severity, and prior antithrombotic use in patients with intracranial hemorrhage, which may also be important for any discussions about stroke epidemiology.

In conclusion, the mean age of ischemic stroke onset has increased, while the initial neurological severity at presentation has decreased, over a 12-year period in this Japanese stroke registry study.

Acknowledgments
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Conflicts of Interest / Disclosures
M.M. reports grants from Mochida Pharmaceutical Co. Ltd, Otsuka Pharmaceutical, and Daiichi Sankyo Co. Ltd and honoraria from Sanofi K.K., Bayer Health Care, Otsuka Pharmaceutical, Daiichi Sankyo Co. Ltd, Boehringer Ingelheim, and Sumitomo Dainippon Pharma Co, Ltd, which are outside the submitted work.

N.H. reports an honorarium from Mochida Pharmaceutical Co, Ltd, which is outside the submitted work.

G.Y.H.L. has acted as a consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife Medtronic, and Daiichi Sankyo. He has also been on the speakers’ bureau for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichii Sankyo.

References

Supplementary Files
Supplementary File 1
Appendix S1
Table S1. Comparison of clinical characteristics of included and excluded patients in this study of stroke in Japan
Table S2. Comparison of clinical characteristics of patients with cardioembolic or non-cardioembolic stroke in a Japanese registry study
Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-16-0374