Atrial fibrillation as a predictive factor for severe stroke and early death in 15,831 patients with acute ischaemic stroke

K Kimura, K Minematsu, T Yamaguchi, for the Japan Multicenter Stroke Investigators’ Collaboration (J-MUSIC)

Background: Atrial fibrillation (AF) is a common arrhythmia and a major risk factor for stroke. The admission National Institutes of Health Stroke Scale (NIHSS) score of the AF group was higher than that of the non-AF group (median, 12 vs 5; p < 0.0001). Multivariate logistic regression analyses found that female sex, advanced age, AF, and a history of stroke were independent factors associated with severe stroke (NIHSS score, ≥ 11). The mortality rate within 28 days after admission was 11.3% in the AF group and 3.4% in the non-AF group (p < 0.0001). Multivariate logistic regression analyses identified older age, AF, and NIHSS score at admission as independent factors associated with early death.

Conclusion: AF was a predictive factor for severe stroke and early death in acute ischaemic stroke. Careful cardiac evaluation and appropriate treatment are needed to improve outcome in patients with acute stroke and AF.

Materials and Methods

We conducted a multicentre prospective hospital based registration study (J-MUSIC) from May 1999 to April 2000 in which 156 hospitals participated. In total, 16,922 consecutive patients with acute ischaemic stroke and transient ischaemic attack (TIA) within seven days of onset were registered in our study. We excluded 1091 TIA patients, and thus enrolled 15,831 patients with acute stroke into our present study. First, we divided patients into two groups based on the presence of AF: the AF group and the non-AF group. We compared the baseline and clinical characteristics and outcome between these two groups. Second, we used multivariate logistic regression analyses to investigate the association between AF and severe stroke and early death. Early death was defined as death within 28 days after admission. Informed consent was obtained from all patients participating in our study.

For all patients, the following data from the common stroke protocol were assessed: (1) age and sex; (2) past history of stroke; (3) National Institutes of Health Stroke Scale (NIHSS) score on admission; (4) time from stroke onset to arrival at hospital; (5) cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidaemia, AF, and current smoking); (6) treatment, including thrombolytic treatment, heparin, and aspirin; (7) death within 28 days after admission; (8) hospital discharge status; and (9) residence after hospital discharge.

AF included both paroxysmal AF and persistent AF identified by electrocardiography (ECG) and/or 24 hour ECG monitoring during admission. Patients with a history of paroxysmal AF and persistent AF identified by electrocardiography (ECG) and/or 24 hour ECG monitoring during admission. Patients with a history of paroxysmal AF and persistent AF identified by electrocardiography (ECG) and/or 24 hour ECG monitoring during admission. Patients with a history of paroxysmal AF and persistent AF identified by electrocardiography (ECG) and/or 24 hour ECG monitoring during admission. Patients with a history of paroxysmal AF and persistent AF identified by electrocardiography (ECG) and/or 24 hour ECG monitoring during admission. Patients with a history of paroxysmal AF and persistent AF identified by electrocardiography (ECG) and/or 24 hour ECG monitoring during admission. Patients with a history of paroxysmal AF and persistent AF identified by electrocardiography (ECG) and/or 24 hour ECG monitoring during admission. Patients with a history of paroxysmal AF and persistent AF identified by electrocardiography (ECG) and/or 24 hour ECG monitoring during admission. Patients with a history of paroxysmal A...
Statistical analysis

Statistical analyses were performed with a commercially available software package (Stat-view, version 4.5; SAS Institute, Cary, North Carolina, USA). The Mann-Whitney U test was used to detect differences in age and NIHSS scores among the groups. All other differences were assessed using the \( \chi^2 \) test. We divided the patients into five groups based on stroke severity (NIHSS score: \( \leq 6 \), 7–10, 11–15, 16–22, and \( \geq 23 \)) according to those in the TOAST study. Multivariate logistic regression models were used to identify factors associated with mild stroke (NIHSS scores, \( \leq 6 \)) and severe stroke (NIHSS scores, \( \geq 11 \)) at admission. Furthermore, multivariate logistic regression models were applied to identify factors associated with early death after admission. Next, we examined the early death rate in patients with and without AF by five groups based on stroke severity. According to the results, we divided patients into subgroups and applied multivariate logistic regression models to identify factors associated with early death for each group. Variables (\( p < 0.20 \)) associated with stroke severity and early death in the univariate analysis were selected to be evaluated in the multivariate logistic regression analyses. Differences were considered significant at the level of \( p < 0.05 \).

RESULTS

The mean age of all patients (6130 women and 9701 men) was 70.7 (SD, 11.5) years (median, 71; range, 18–107). The AF group comprised 3335 patients (21.1%) and the non-AF group comprised 12,496 patients (78.9%). Table 1 shows the baseline features of the patients with and without AF.

Severity of stroke (NIHSS on admission)

The mean (SD) and median NIHSS scores for all patients were 8.3 (7.9) and 5. The scores were significantly higher in the AF group (mean, 13.7; SD, 9.7; median, 12) than in the non-AF group (mean, 6.9; SD, 6.7; median, 5) (\( p < 0.0001 \); fig 1). AF was seen in 11.5% of patients with NIHSS scores of 0–6, 17.4% of patients with scores of 7–10, 32.5% of patients with scores of 11–15, 46.3% of patients with scores of 16–22, and 54.0% of patients with scores \( \geq 23 \) (\( p < 0.0001 \)). Thus, the frequency of AF rose steeply as NIHSS scores increased. The mean (SD) and median NIHSS scores were 7.4 (8.2) and 4 in patients aged less than 45 years, 5.8 (6.2) and 4 in patients aged 45–54 years, 6.6 (6.9) and 4 in patients aged 55–64 years, 7.8 (7.6) and 5 in patients aged 65–74 years, 9.6 (8.3) and 7 in patients aged 75–84 years, and 12.3 (9.0) and 10 in patients aged 85 years or older (\( p < 0.0001 \)). Multivariate logistic regression analysis identified female sex, increased age, AF, and history of stroke as independent factors associated with severe stroke (table 2).

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Table 1  Baseline characteristics of patients with and without AF

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total N = 15831</th>
<th>With AF N = 3335</th>
<th>Without AF N = 12496</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD; median) age (years)</td>
<td>70.7 (11.5; 71)</td>
<td>74.5 (9.8; 75)</td>
<td>69.6 (11.7; 70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;45 (%)</td>
<td>1.9</td>
<td>0.4</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>45–54 (%)</td>
<td>7.6</td>
<td>2.8</td>
<td>8.9</td>
<td></td>
</tr>
<tr>
<td>55–64 (%)</td>
<td>19.5</td>
<td>14.4</td>
<td>20.8</td>
<td></td>
</tr>
<tr>
<td>65–74 (%)</td>
<td>33.2</td>
<td>31.8</td>
<td>33.5</td>
<td></td>
</tr>
<tr>
<td>75–84 (%)</td>
<td>28.2</td>
<td>36.0</td>
<td>26.1</td>
<td></td>
</tr>
<tr>
<td>&gt;84 (%)</td>
<td>9.8</td>
<td>14.6</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>38.7</td>
<td>46.5</td>
<td>38.0</td>
<td>0.0003</td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>34.2</td>
<td>35.6</td>
<td>30.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>61.2</td>
<td>48.7</td>
<td>64.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>24.7</td>
<td>16.9</td>
<td>25.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperlipidaemia (%)</td>
<td>16.6</td>
<td>10.2</td>
<td>19.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>17.3</td>
<td>12.7</td>
<td>16.2</td>
<td></td>
</tr>
<tr>
<td>NIHSS score (mean, SD, median)</td>
<td>8.3, 7.9, 5</td>
<td>13.7, 9.7, 12</td>
<td>6.9, 6.7, 5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>0–6 (%)</td>
<td>57.4</td>
<td>31.3</td>
<td>64.4</td>
<td></td>
</tr>
<tr>
<td>7–10 (%)</td>
<td>15.5</td>
<td>12.7</td>
<td>16.2</td>
<td></td>
</tr>
<tr>
<td>11–15 (%)</td>
<td>9.9</td>
<td>15.3</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>16–22 (%)</td>
<td>9.6</td>
<td>21.0</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>&gt;23 (%)</td>
<td>7.7</td>
<td>19.7</td>
<td>4.5</td>
<td></td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; NIHSS, National Institutes of Health Stroke Scale.
Time between stroke onset and hospital arrival
Thirty-five per cent of patients were admitted within three hours of stroke onset. The cumulative frequency was 48.1% within six hours, 71.7% within 24 hours, 83.6% within 48 hours, and 91.0% within 72 hours. Both the frequency of AF and the NIHSS score at admission were higher in patients admitted within 24 hours of onset than in those admitted after 24 hours (frequency of AF: 85.6% vs. 68.1%; p < 0.0001; NIHSS score: mean, 9.5; SD, 8.5; median 6 vs. mean, 5.5; SD, 5.4; median, 4; p < 0.0001).

Treatment within 12 hours of stroke onset
When we define thrombolytic treatment as intravenous tissue plasminogen activator or intra-arterial urokinase or tissue plasminogen activator, 7.3% of the AF group and 1.3% of the non-AF group received thrombolytic treatment during the superacute phase of their stroke.

Treatment within seven days of stroke onset
Heparin was administered to 38.1% of the AF group and to 10.6% of the non-AF group (p < 0.0001), whereas aspirin was given to 7.0% of the AF group and to 10.5% of the non-AF group (p < 0.0001).

Length of hospital stay
The mean (SD) length of hospital stay for all patients was 35.3 (34.1) days (median, 25; range, 1–429). The mean (SD) length of hospital stay for the AF group was 40.5 (37.8) days (median, 29; range, 0–374) and for the non-AF group 34.0 (32.9) days (median, 24; range, 0–429) (p < 0.0001).

Death within 28 days of admission
A total of 804 patients (5.1%) died within 28 days of admission. Early death was more frequent in patients admitted within 24 hours of onset than in those admitted after 24 hours (frequency of AF: 85.6% vs. 68.1%; p < 0.0001; NIHSS score: mean, 9.5; SD, 8.5; median 6 vs. mean, 5.5; SD, 5.4; median, 4; p < 0.0001).

Table 2 Multivariate logistic regression analysis models for probability of mild and severe neurological deficits

<table>
<thead>
<tr>
<th>Variable</th>
<th>NIHSS score ≤ 6</th>
<th></th>
<th></th>
<th>p Value</th>
<th>NIHSS score &gt; 11</th>
<th></th>
<th></th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>0.85</td>
<td>0.789 to 0.914</td>
<td>&lt;0.0001</td>
<td>1.25</td>
<td>1.150 to 1.356</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age difference of 1 year</td>
<td>0.97</td>
<td>0.970 to 0.976</td>
<td>&lt;0.0001</td>
<td>1.03</td>
<td>1.025 to 1.033</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.15</td>
<td>1.068 to 1.230</td>
<td>0.0002</td>
<td>0.79</td>
<td>0.728 to 0.853</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.92</td>
<td>0.846 to 0.992</td>
<td>0.031</td>
<td>0.92</td>
<td>0.836 to 1.008</td>
<td>0.0728</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>1.22</td>
<td>1.109 to 1.338</td>
<td>&lt;0.0001</td>
<td>0.77</td>
<td>0.687 to 0.862</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.29</td>
<td>0.268 to 0.318</td>
<td>&lt;0.0001</td>
<td>4.43</td>
<td>4.067 to 4.828</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.09</td>
<td>0.985 to 1.195</td>
<td>0.097</td>
<td>0.83</td>
<td>0.735 to 0.929</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of stroke</td>
<td>0.72</td>
<td>0.667 to 0.772</td>
<td>&lt;0.0001</td>
<td>1.32</td>
<td>1.216 to 1.433</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

Figure 2 Death within 28 days of admission and age for patients with atrial fibrillation (AF) and non-AF patients.

Figure 3 Death in acute stroke in patients with and without atrial fibrillation (AF), according to the severity of stroke at admission. The death rate of patients with AF is higher than that of the non-AF patients in the subgroup of patients with mild stroke.
performed multivariate logistic regression analysis for probability of early death in patients with NIHSS scores < 11 and ≥ 11. AF was an independent factor associated with early death in patients with NIHSS scores < 11, but not in those with NIHSS scores ≥ 11 (Table 4).

**Hospital discharge status**

The proportions of patients with each mRS score at discharge in the AF and non-AF groups were as follows: 9.4% and 15.7% for score 0, 18.4% and 33.2% for score 1, 11.6% and 14.8% for score 2, 7.7% and 9.1% for score 3, 16.9% and 14.7% for score 4, 19.6% and 7.6% for score 5, and 16.4% and 5.0% for death, respectively. Good outcome was observed in 39.4% of patients with AF and in 63.7% of patients without AF, respectively (p < 0.0001).

Multivariate logistic regression analysis showed that older age (odds ratio (OR), 1.03; 95% confidence interval (CI), 1.02 to 1.04), the presence of AF (OR, 1.3; 95% CI, 1.14 to 1.55), diabetes mellitus (OR, 1.2; 95% CI, 1.02 to 1.44), and NIHSS score at admission (OR, 1.1; 95% CI, 1.14 to 1.15) were independent factors associated with death.

**Residence after hospital discharge**

Sixty two per cent of all patients were discharged home and 38% were sent to an institution. Of the patients without AF, 66.4% returned to their own homes, whereas only 45.1% of patients with AF returned home (p < 0.0001).

**DISCUSSION**

Our study showed that AF was clearly associated with an increased risk of severe neurological deficits. The fact that patients with AF have more severe stroke than those without AF supports the hypothesis that the pathogenetic mechanism of stroke may be different. First, strokes in patients with AF may chiefly be cardioembolic, which causes a sudden occlusion of large cerebral arteries without sufficient collateral blood flow, resulting in more severe strokes.1–11 Several studies have reported that stroke patients with AF more often have large cortical infarcts on computed tomography, and less frequently have lacunar infarction compared with patients without AF.12–14 Second, a previous study found a significant reduction in hemispheric cerebral blood flow in patients with AF compared with those with sinus rhythm.15 The effect of the decreased hemispheric cerebral blood flow may contribute to the development of large infarcts and neurological severity in patients with AF.

Our present study showed that older age and higher NIHSS score at admission were independent factors associated with early death, results that agreed with previous reports.16–20 Furthermore, we identified AF as an independent factor for early death, in particular, for patients with NIHSS scores 0–10. Previous studies have reported that AF was associated with an increased risk of early death.17–19 This was explained by its association with severe neurological deficits and the older age of patients with AF. However, not all investigators agreed that AF itself increased the risk of death.20–22 In our present study, after adjustment for age and NIHSS score using multivariate logistic analysis, AF was identified as an independent risk factor for early death, which was compatible with the results of the Oxfordshire community stroke project.23

Heart diseases are more frequent in patients with AF than in those without.24–26 Some studies have suggested that

<table>
<thead>
<tr>
<th>Variable</th>
<th>NIHSS score &lt;11</th>
<th>NIHSS score ≥11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.02*</td>
<td>1.004 to 1.041</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.96</td>
<td>0.985 to 1.145</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.85</td>
<td>0.953 to 1.153</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.02</td>
<td>0.813 to 1.250</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.95</td>
<td>0.880 to 1.119</td>
</tr>
<tr>
<td>Thrombolytic treatment</td>
<td>0.96</td>
<td>0.805 to 1.119</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.92</td>
<td>0.813 to 1.119</td>
</tr>
<tr>
<td>Heparin</td>
<td>0.92</td>
<td>0.813 to 1.119</td>
</tr>
</tbody>
</table>

*Analysis by difference of 1 year; †analysis by difference of 1 point.
CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.
cardiac causes of death in the acute phase of stroke predominate in patients with AF compared with those without AF. Tomita et al reported that 77% of 2677 patients with AF had heart diseases such as hypertensive heart disease, ischemic heart disease, valvular heart disease, sick sinus syndrome, and cardiomyopathy. In our study, the mortality rate in patients with NIHSS scores of < 11 was higher in patients with AF than in non-AF patients. Death in such patients may be caused by stroke complications, such as heart diseases and pneumonia, rather than stroke itself. Careful cardiac evaluation and treatment are needed in acute stroke patients with AF even if patients' neurological deficits are mild. Furthermore, Lin et al reported that the one year survival rate was lower in patients with AF compared with those without AF. Secondary prevention of embolic events is one of the most important issues for patients with AF.

Our present study has some limitations. First, the definition of AF in our study included both chronic AF and paroxysmal AF. The frequency of paroxysmal AF is reported to be about half of that of chronic AF in Japan. Thus, the presence of paroxysmal AF may not have been fully recognised in our present study. Second, we did not assess stroke recurrence and the cause of death, such as severe stroke, stroke recurrence, heart failure, renal failure, pneumonia, and pulmonary embolism. Some studies reported no difference in the frequency of stroke recurrence between acute stroke patients with and without AF, whereas other studies disagreed with these findings. Further studies are needed to investigate stroke recurrence and the cause of death related to AF. Third, Saxena et al reported that AF was a high risk carried early death, which could be explained by older age and large infarcts. Unfortunately, we did not examine the neuroimaging findings, such as computed tomography and magnetic resonance imaging. Fourth, the NIHSS score at admission may be affected by some previous neurological deficits, particularly in patients with a history of stroke. The severity of stroke at admission in patients with AF might be estimated to be severe compared with those without AF because patients with AF more often had a history of stroke than those without AF. Finally, early aspirin use is of benefit in acute ischaemic stroke. However, few patients in our study were treated with aspirin during the acute phase of stroke. The death rate in our present study might have been lower if aspirin had been used more frequently in patients at the acute phase of stroke.

In conclusion, our study showed that AF was a predictive factor for both severe stroke and early death in acute ischaemic stroke. Therefore, careful cardiac evaluation and appropriate treatment are needed to improve the outcome in patients with acute stroke and AF.

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Authors’ affiliations
K Kimura, K Minematsu, T Yamaguchi, Cerebrovascular Division, Department of Medicine, National Cardiovascular Centre, Kawasaki Medical School, 557 Matsushima, Kurashiki City, Okayama 701–0192, Japan

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References
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