Risks of Bleeding and Stroke Based on CHA2DS2-VASc Scores in Japanese Patients With Atrial Fibrillation: A Large-Scale Observational Study Using Real-World Data

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Background—This large-scale observational study on negative events in a real-world setting investigated Japanese patients with atrial fibrillation who were not on anticoagulants. This study aims to evaluate the incidence of ischemic stroke and bleeding events (intracranial hemorrhage, gastrointestinal bleeding, others) based on CHA2DS2-VASc scores in Japanese patients with atrial fibrillation who were not anticoagulated.

Methods and Results—We used health checkups and insurance claim data from a Japanese insurance organization. Altogether, 9733 atrial fibrillation patients were not prescribed anticoagulation during their follow-up periods. Patients’ risk levels were defined by their CHA2DS2-VASc scores (range 0–≥3): Men with scores of 0, 1, or ≥2 and women with scores of 1, 2, or ≥3 were considered at low, intermediate, or high risk, respectively. Cox proportional hazards model was used to assess the association between the CHA2DS2-VASc-determined risk and the incidence of ischemic stroke and intracranial, gastrointestinal, and other bleeding. The mean 2.5-year follow-up revealed 143 ischemic strokes and 332 bleeding events. Annual event rates were 0.58% for ischemic stroke and 1.17% for total bleeding events. Annual incidence of ischemic stroke increased with elevated predicted risks based on CHA2DS2-VASc scores: 0.18% for low-risk, 0.44% intermediate-risk, and 1.29% high-risk groups (P<0.001 for trend). Annual incidences of total bleeding also increased with elevated predicted risks: 0.51% for low-risk, 1.28% intermediate-risk, and 2.02% high-risk groups (P<0.001 for trend).

Conclusions—Risks of ischemic stroke and bleeding events were high, particularly among those with high CHA2DS2-VASc scores. (J Am Heart Assoc. 2020;9:e014574. DOI: 10.1161/JAHA.119.014574.)

Key Words: atrial fibrillation • bleeding • CHA2DS2-VASc score • ischemic stroke

Atrial fibrillation is one of the most prevalent arrhythmias, with its prevalence increasing with the aging of the population.1–3 It has been estimated that the number of people with atrial fibrillation would be enormous by 2050 in Japan4 and the United States.3 Patients with atrial fibrillation have been shown to be at high risk of death and various diseases, including ischemic stroke.5,6 Although the CHA2DS2-VASc score has been widely used to evaluate the risk of ischemic stroke in patients with atrial fibrillation, there has been limited real-world evidence of the burden of atrial fibrillation according to CHA2DS2-VASc scores in Japan.

The aim of the present large-scale observational study was to use real-world data to evaluate not only the incidence of ischemic stroke but also that of total bleeding events (intracranial hemorrhage, gastrointestinal bleeding, others) according to CHA2DS2-VASc scores in Japanese patients with atrial fibrillation who were not on anticoagulation.

Methods

Study Participants

The data that support the findings of this study are available from the corresponding author upon reasonable request. This observational study used health check-ups and insurance
Clinical Perspective

What Is New?

- This large-scale observational study on negative events in a real-world setting investigated Japanese patients with atrial fibrillation who were not on anticoagulants.
- The study aimed to evaluate the incidence of ischemic stroke and bleeding events (intracranial hemorrhage, gastrointestinal bleeding, others) based on CHA2DS2-VASc scores in Japanese patients with atrial fibrillation who were not anticoagulated.

What Are the Clinical Implications?

- This study showed a relatively low incidence of ischemic stroke and a relatively high incidence of intracranial bleeding in Japanese patients with atrial fibrillation who were not on oral anticoagulants.
- Although present guidelines for managing atrial fibrillation in Japan recommend anticoagulant therapy for patients with a CHADS2 score of ≥2, physicians should be aware that bleeding risk also increases with the elevation of ischemic risk.

Follow-Up and Outcomes

Participants were followed from the first diagnosis of atrial fibrillation to the last visit during the study period (fiscal years 2005–2017). Individuals who died or moved out of the health insurance society because of retirement, job change, or age ≥75 years during the follow-up were censored. We defined outcomes as admission to a hospital because of ischemic stroke, intracranial hemorrhage, gastrointestinal bleeding, or other non-traumatic bleeding. Total bleeding was defined as any bleeding (intracranial hemorrhage, gastrointestinal bleeding, and/or other non-traumatic bleeding). Ischemic stroke was defined as ICD-10 code I63. Intracranial hemorrhage was defined as ICD-10 codes I60 (subarachnoid hemorrhage), I61 (intracerebral hemorrhage), and I62 (other and unspecified non-traumatic intracranial hemorrhage). Gastrointestinal and other non-traumatic bleeding was identified using claims database disease codes as listed in Tables S1 and S2.

Definition of Explanatory Variables

The CHA2DS2-VASc score included the patient’s age and sex; presence of congestive heart failure, hypertension, diabetes mellitus; history of ischemic stroke/transient ischemic attack, and/or vascular disease. Participants were divided into 2 groups by age (<65 or 65–74 years). Elderly people aged ≥75 years were not included in this study because they move to the public late-elderly health insurance system in Japan. Congestive heart failure was defined according to the Charlson comorbidity index based on a prior diagnosis using the ICD-10 code in the claims data.7 Hypertension was defined by ICD-10 codes I11 to 115 based on the claims data, blood pressure levels of ≥140/90 mm Hg, or use of blood pressure-lowering medication at the most recent health checkup before the diagnosis of atrial fibrillation. Diabetes mellitus was defined based on the Charlson comorbidity index using the ICD-10 code in the claims data, a fasting serum glucose level of ≥6.99 mmol/L, a casual serum glucose level of ≥11.1 mmol/L, Hemoglobin A1c ≥6.5%, or use of glucose-lowering medication at the health checkup. Previous ischemic stroke/transient ischemic attack was defined by ICD-10 code G45 or I63 based on the claims data, or a disease history according to questionnaires administered at the health checkup. Vascular disease was defined based on the Charlson comorbidity index or questionnaires administered at the health checkup. We did not include suspicious diagnoses on the claims data. Finally, we calculated the CHA2DS2-VASc score.8 A CHA2DS2-VASc score of 0 in men or 1 in women classified them as at low risk; 1 in men or 2 in women as at intermediate risk; and ≥2 in men or ≥3 in women as at high risk.5,9 Using the claims data, we identified the use of antiplatelet medication, which included cyclooxygenase.
inhibitors, adenosine diphosphate receptor antagonists, or other antiplatelet medications according to the Japanese pharmaceutical classification. We also identified peptic ulcer disease medications, which included proton-pump inhibitors, histamine H2 receptor antagonists, and others. Antiarrhythmic agents were identified and classified as Ia, Ib, Ic, II, III, or IV, according to the Vaughan Williams classification, and digitalis.

**Statistical Analysis**

We used the 1-way ANOVA for continuous variables and the Chi-squared test for categorical variables. A person-year approach was used to calculate incidence. We used the Cox proportional hazards model to adjust for competing risks of death from other causes using the Fine and Gray method to investigate the association between CHA2DS2-VASc risk classification and the incidence of each outcome. The multivariable models included the use of antiplatelet agents, antiarrhythmic agents, and anti-ulcer agents (for the outcomes of gastrointestinal bleeding and total bleeding only). Stratified analysis was also conducted for men and women. STATA release 14 (STATA Corp, College Station, TX).

**Figure 1.** Flow diagram shows the process for selecting our study participants. AF indicates atrial fibrillation.

**Table 1. Distribution of CHA2DS2-VASc Scores**

| CHA2DS2-VASc Score | Total (N=9733) | Men (n=7079) | Women (n=2654) |
|--------------------|----------------|--------------|----------------|
|                    | n (%)          | n (%)        | n (%)          |
| 0                  | 2507 (25.8)    | 2507 (35.4)  | 0 (0.0)        |
| 1                  | 2972 (30.5)    | 2012 (28.4)  | 960 (36.2)     |
| 2                  | 2138 (22.0)    | 1464 (20.7)  | 674 (25.4)     |
| 3                  | 1279 (13.1)    | 741 (10.5)   | 538 (20.3)     |
| 4                  | 556 (5.7)      | 239 (3.4)    | 317 (11.9)     |
| 5                  | 204 (2.1)      | 99 (1.4)     | 105 (4.0)      |
| 6                  | 51 (0.5)       | 13 (0.2)     | 38 (1.4)       |
| 7                  | 24 (0.2)       | 4 (0.1)      | 20 (0.8)       |
| 8                  | 2 (0.0)        | 0 (0.0)      | 2 (0.1)        |
was used for statistical analyses. All reported $P$ values are 2-tailed, and the level of significance was set at $P<0.05$.

## Results

### Descriptive Analysis

In total, 7079 of the 9733 (72.7%) participants were men. Table 1 shows the distribution of the CHA2DS2-VASc scores for men and women. Most men had CHA2DS2-VASc scores of $\leq 3$, and most women had scores of $<4$. In all, 3467 (35.6%) participants were classified as being at low risk (CHA2DS2-VASc score of 0 in men or 1 in women), 2686 (27.6%) at intermediate risk (scores of 1 in men or 2 in women), and 3580 (36.8%) at high risk (scores of $\geq 2$ in men or $\geq 3$ in women). The results of descriptive analysis according to CHA2DS2-VASc risk groups are shown in Table 2. The mean (SD) ages of CHA2DS2-VASc low-, intermediate-, and high-risk groups were 48.2 (11.0), 54.4 (10.6), and 58.2 (10.5), respectively. There was a trend toward older age in accordance with higher estimated CHA2DS2-VASc risk. Participants aged $\geq 65$ years were most frequently (31.7%)

| Table 2. Analysis According to CHA2DS2-VASc-Determined Risk Groups |
|--------------------------|--------------------------|--------------------------|--------------------------|
|                          | Low                      | Intermediate              | High                     |
|                          | (n=3467)                 | (n=2686)                 | (n=3580)                 |
| Sex                      |                          |                          |                          |
| Men, %                   | 2507                     | 2012                     | 2560                     |
| Age (y) mean, SD         | 48.2                     | 54.4                     | 58.2                     |
| $\geq 65$ y, %           | 0                        | 0.0                      | 394                      |
| Comorbidities            |                          |                          |                          |
| Congestive heart failure, % | 0                        | 0.0                      | 610                      |
| Hypertension, %          | 0                        | 0.0                      | 1330                     |
| Diabetes mellitus, %     | 0                        | 0.0                      | 240                      |
| Past history of ischemic stroke /TIA, % | 0                        | 0.0                      | 0                        |
| Vascular disease, %      | 0                        | 0.0                      | 112                      |
| Medication               |                          |                          |                          |
| Antiplatelet drug, %     |                          |                          |                          |
| Cyclooxygenase inhibitor, % | 271                     | 7.8                      | 319                      |
| ADP receptor antagonist, % | 27                      | 0.8                      | 71                       |
| Other antiplatelet, %    | 0                        | 0.0                      | 1                        |
| Antiulcer drug, %        |                          |                          |                          |
| Proton pomp inhibitor, % | 189                      | 5.5                      | 294                      |
| H2 blocker, %            | 172                      | 5.0                      | 212                      |
| Other antiulcer drug, %  | 727                      | 21.0                     | 600                      |
| Antiarrhythmic drug      |                          |                          |                          |
| Ia, %                    | 307                      | 8.9                      | 184                      |
| Ib, %                    | 19                       | 0.5                      | 22                       |
| Ic, %                    | 535                      | 15.4                     | 421                      |
| II, %                    | 387                      | 11.2                     | 308                      |
| III, %                   | 5                        | 0.1                      | 10                       |
| IV, %                    | 41                       | 1.2                      | 33                       |
| Digitalis, %             | 134                      | 3.9                      | 139                      |
| HAS-BLED mean, SD        | 0.12                     | 0.33                     | 0.39                     |

ADP indicates adenosine diphosphate; TIA, Transient Ischemic Attack. *CHA2DS2-VASc scores are interpreted as follows: low risk was 0 in men and 1 in women; intermediate risk was 1 in men and 2 in women; high risk was $\geq 2$ in men and $\geq 3$ in women.
found in the high-risk group. Participants with prevalent comorbidities were also most frequently observed in the high-risk group: hypertension 86.5%, congestive heart failure 60.6%, and diabetes mellitus 33.4%. Cyclooxygenase inhibitors, class II antiarrhythmic agents, and proton-pump inhibitors were the most frequently used antiplatelet, antiarrhythmic, and antiulcer agents, respectively. The frequencies of participants who were on antiplatelet and antiulcer agents increased with heightened CHA2DS2-VASc risk. HAS-BLED scores also significantly increased in accordance with increased CHA2DS2-VASc-defined risk.

Incidence and Crude and Hazard Ratios for Ischemic Stroke and Major Bleeding

During the mean 2.5-year follow-up, 143 ischemic strokes and 332 total bleeding events (59 intracerebral hemorrhage, 125 gastrointestinal bleeding, 148 others) were observed. Annual event rates were 0.58% (95% CI 0.49%–0.68%) for ischemic stroke and 1.17% (95% CI 1.03%–1.31%) for total bleeding events; 0.24% (95% CI 0.18%–0.31%) for intracerebral hemorrhage, 0.50% (95% CI 0.42%–0.60%) for gastrointestinal bleeding, and 0.60% (95% CI 0.50%–0.70%) for others.

Table 3 shows incidences and hazard ratios for ischemic stroke, total bleeding events, intracranial hemorrhage, gastrointestinal bleeding, and other hemorrhage according to the CHA2DS2-VASc risk groups. Annual incidences of ischemic stroke increased with an elevation of predicted risks based on CHA2DS2-VASc scores: 0.18% (95% CI 0.11%–0.27%) for low-risk, 0.44% (95% CI 0.39%–0.77%) for intermediate-risk, and 1.29% (95% CI 1.05%–1.58%) for high-risk groups (P<0.001 for trend). Annual incidences for total bleeding also increased with elevation of predicted risks: 0.51% (95% CI 0.39%–0.67%) for low-risk, 1.28% (95% CI 1.02%–1.58%) for intermediate-risk, and 2.02% (95% CI 1.71%–2.37%) for high-risk groups (P<0.001 for trend). Similar findings were observed for each type of bleeding event (intracerebral hemorrhage, gastrointestinal bleeding, others; all P<0.001 for trend). Linear association of the CHA2DS2-VASc risk group with ischemic stroke and bleeding events (intracranial hemorrhage, gastrointestinal bleeding, others) remained significant even after adjusting for medications, such as antiplatelet and antiarrhythmic agents (all P<0.001 for trend) (Table 3, Figure 2).

Table 3. Incidences and Crude and Adjusted Hazard Ratios for Ischemic Stroke and All Types of Bleeding/Hemorrhage

|                        | Case/PY | % IR (95% CI) | P for Trend | Crude HR (95% CI) | P Value | P for Trend | Adjusted HR (95% CI) | P Value | P for Trend |
|------------------------|---------|---------------|-------------|-------------------|---------|-------------|----------------------|---------|-------------|
| **Brain infarction**   |         |               |             |                   |         |             |                      |         |             |
| Low                    | 19/10   | 0.18 (0.11–0.27) | <0.001      | 1.00 (Reference) |         |             |                      |         |             |
| Intermediate           | 29/663  | 0.44 (0.39–0.77) | <0.001      | 2.25 (1.26–4.01) | 0.006   |             | 2.14 (1.20–3.84)    | 0.010   |             |
| High                   | 95/7359 | 1.29 (1.05–1.58) | <0.001      | 6.15 (3.75–10.09)| <0.001 |             | 4.88 (2.90–8.23)    | <0.001 |             |
| **Any bleeding**       |         |               |             |                   |         |             |                      |         |             |
| Low                    | 55/10   | 0.51 (0.39–0.67) | <0.001      | 1.00 (Reference) | <0.001 | 1.00 (Reference) | 1.00 (Reference) | <0.001 |
| Intermediate           | 84/6554 | 1.28 (1.02–1.58) | <0.001      | 2.30 (1.64–3.22) | <0.001 | 2.04 (1.45–2.86) | <0.001         |         |
| High                   | 147/7272| 2.02 (1.71–2.37) |             | 3.43 (2.53–4.65) | <0.001 |             | 2.56 (1.87–3.51)    | <0.001 |             |
| **Intracranial hemorrhage** |       |               |             |                   |         |             |                      |         |             |
| Low                    | 9/10    | 0.08 (0.04–0.16) | <0.001      | 1.00 (Reference) | <0.001 | 1.00 (Reference) | 1.00 (Reference) | <0.001 |
| Intermediate           | 20/6654 | 0.30 (0.18–0.46) |             | 3.38 (1.56–7.29) | 0.002  |             | 3.34 (1.53–7.29)    | 0.002  |             |
| High                   | 30/7471 | 0.40 (0.27–0.57) |             | 4.28 (2.07–8.85) | <0.001 |             | 4.23 (2.00–8.93)    | <0.001 |             |
| **Gastrointestinal bleeding** |      |               |             |                   |         |             |                      |         |             |
| Low                    | 21/10   | 0.19 (0.12–0.30) | <0.001      | 1.00 (Reference) | <0.001 | 1.00 (Reference) | 1.00 (Reference) | <0.001 |
| Intermediate           | 37/6636 | 0.56 (0.39–0.77) |             | 2.64 (1.55–4.48) | <0.001 |             | 2.36 (1.38–4.04)    | 0.002  |             |
| High                   | 67/7399 | 0.91 (0.70–1.15) |             | 4.06 (2.51–6.57) | <0.001 |             | 3.18 (1.95–5.19)    | <0.001 |             |
| **Other bleeding**     |         |               |             |                   |         |             |                      |         |             |
| Low                    | 32/10   | 0.30 (0.20–0.42) | <0.001      | 1.00 (Reference) | <0.001 | 1.00 (Reference) | 1.00 (Reference) | <0.001 |
| Intermediate           | 39/6644 | 0.59 (0.42–0.80) |             | 1.85 (1.15–2.95) | 0.010  |             | 1.81 (1.13–2.90)    | 0.013  |             |
| High                   | 77/7383 | 1.04 (0.82–1.30) |             | 3.13 (2.08–4.72) | <0.001 |             | 2.76 (1.83–4.17)    | <0.001 |             |

CHA2DS2-VASc scores are interpreted as follows: low risk was 0 in men and 1 in women; intermediate risk was 1 in men and 2 in women; high risk was ≥2 in men and ≥3 in women. Total bleeding includes those with any following types of bleeding: intracranial, gastrointestinal, and other. Variables used for multivariate analyses were the use of antiplatelet agents and antiarrhythmic agents for all outcomes and use of anti-ulcer and antiplatelet agents for total bleeding and gastrointestinal bleeding. HR indicates hazard ratio; IR, incident rate; PY, person-year.

Table 3 shows incidences and hazard ratios for ischemic stroke, total bleeding events, intracranial hemorrhage, gastrointestinal bleeding, and other hemorrhage according to the CHA2DS2-VASc risk groups. Annual incidences of ischemic stroke increased with an elevation of predicted risks based on CHA2DS2-VASc scores: 0.18% (95% CI 0.11%–0.27%) for low-risk, 0.44% (95% CI 0.39%–0.77%) for intermediate-risk, and 1.29% (95% CI 1.05%–1.58%) for high-risk groups (P<0.001 for trend). Annual incidences for total bleeding also increased with elevation of predicted risks: 0.51% (95% CI 0.39%–0.67%) for low-risk, 1.28% (95% CI 1.02%–1.58%) for intermediate-risk, and 2.02% (95% CI 1.71%–2.37%) for high-risk groups (P<0.001 for trend). Similar findings were observed for each type of bleeding event (intracerebral hemorrhage, gastrointestinal bleeding, others; all P<0.001 for trend). Linear association of the CHA2DS2-VASc risk group with ischemic stroke and bleeding events (intracranial hemorrhage, gastrointestinal bleeding, others) remained significant even after adjusting for medications, such as antiplatelet and antiarrhythmic agents (all P<0.001 for trend) (Table 3, Figure 2).
When participants were stratified by sex, linear associations were still observed for each outcome (all $P \leq 0.001$ for trend) except for intracerebral hemorrhage in women ($P = 0.060$ for trend) (Table 4, Figure 3).

Discussion

This large-scale observational study in the current real-world setting in Japan comprehensively evaluated the natural history of patients with atrial fibrillation who were not on anticoagulants. Among them, the annual incidence of ischemic stroke was as high as 0.58%. Patients with atrial fibrillation were also at high risk of bleeding events (annual event rate 1.17%) even though not on oral anticoagulants. The risks of ischemic stroke and bleeding events increased with elevation of the CHA2DS2-VASc score. The highest risks were observed for the high-risk group with CHA2DS2-VASc scores of $\geq 2$ (for men) or $\geq 3$ (for women) (annual incidence of ischemic stroke was 1.29% and that of total bleeding events was 2.02%). Similar findings were observed for different types of bleeding event (intracranial hemorrhage, gastrointestinal bleeding, others) or in stratified analysis according to sex.

The incidence of ischemic stroke among atrial fibrillation patients without anticoagulation for the entire cohort and by the CHA2DS2-VASc score have been reported at 0.44% to 4.0% for overall,11–14 0% to 0.95% for low-risk patients,5,9,13–17 0.10% to 6.6% for intermediate-risk patients,5,9,12,13,15,16,18–29 and 2.4% to 6.2% for high-risk patients.14,16,17,24–28 Evidence from prior studies, however, was mainly derived from Western populations, with only limited evidence from a Japanese population. One Japanese study, which pooled 3 large-scale atrial fibrillation registries in Japan,12 showed a somewhat lower incidence of ischemic stroke for the entire cohort (0.95 in the Shinken database, 1.39 in the J-RHYTHM registry, 1.64 in the Fushimi atrial fibrillation registry) than those reported from other countries. Our study confirmed the findings of prior Japanese studies and revealed lower annual incidences of ischemic stroke (0.58% for the entire cohort; 0.18% for low-, 0.44% for intermediate-, and 1.29% for high-risk groups) in Japanese cohorts than in Western populations.

Many prior studies also reported the incidence of total bleeding events in patients with atrial fibrillation. Guo et al23 reported that the annual rate of major bleeding among atrial fibrillation patients without anticoagulation was 2.0%. Olesen et al18 reported annual incidences of total bleeding events at 3.34% overall, with 1.15% for CHA2DS2-VASc scores.
Table 4. Incidences and Crude and Adjusted Hazard Ratios for Ischemic Stroke and All Types of Bleeding/Hemorrhage, by Sex

|                  | Case/PY | % IR (95% CI) | P for Trend | Crude HR (95% CI) | P Value | P for Trend | Adjusted HR (95% CI) | P Value | P for Trend |
|------------------|---------|---------------|------------|-------------------|---------|------------|----------------------|---------|------------|
| **Men**          |         |               |            |                   |         |            |                      |         |            |
| **Ischemic stroke** |        |               |            |                   |         |            |                      |         |            |
| Low              | 15/8187 | 0.18 (0.10–0.30) | <0.001     | 1.00 (Reference)  | <0.001  | 1.00 (Reference)  | <0.001  |          |
| Intermediate     | 18/5143 | 0.35 (0.21–0.55) |           | 1.74 (0.88–3.46)  | 0.114   | 1.64 (0.82–3.28)  | 0.160   |          |
| High             | 66/5315 | 1.24 (0.96–1.58) |           | 5.68 (3.24–9.96)  | <0.001  | 4.33 (2.37–7.90)  | <0.001  |          |
| **Major bleeding** |        |               |            |                   |         |            |                      |         |            |
| Low              | 43/8134 | 0.53 (0.38–0.71) | <0.001     | 1.00 (Reference)  | <0.001  | 1.00 (Reference)  | <0.001  |          |
| Intermediate     | 57/5092 | 1.12 (0.85–1.45) |           | 1.93 (1.30–2.86)  | 0.001   | 1.73 (1.16–2.57)  | 0.007   |          |
| High             | 102/5233 | 1.95 (1.59–2.36) |           | 3.14 (2.21–4.45)  | <0.001  | 2.44 (1.70–3.50)  | <0.001  |          |
| **Intracranial hemorrhage** |   |               |            |                   |         |            |                      |         |            |
| Low              | 7/8205  | 0.09 (0.03–0.18) | 0.001      | 1.00 (Reference)  | 0.001   | 1.00 (Reference)  | <0.001  |          |
| Intermediate     | 9/5168  | 0.17 (0.08–0.33) |           | 1.95 (0.74–5.12)  | 0.175   | 2.01 (0.76–5.28)  | 0.158   |          |
| High             | 21/5384 | 0.39 (0.24–0.60) |           | 4.13 (1.81–9.40)  | 0.001   | 4.22 (1.81–9.82)  | 0.001   |          |
| **Gastrointestinal bleeding** | |               |            |                   |         |            |                      |         |            |
| Low              | 17/8177 | 0.21 (0.12–0.33) | <0.001     | 1.00 (Reference)  | <0.001  | 1.00 (Reference)  | <0.001  |          |
| Intermediate     | 25/5143 | 0.49 (0.31–0.72) |           | 2.15 (1.16–3.96)  | 0.014   | 1.92 (1.04–3.56)  | 0.038   |          |
| High             | 49/5324 | 0.92 (0.68–1.21) |           | 3.81 (2.23–6.53)  | <0.001  | 2.95 (1.70–5.14)  | <0.001  |          |
| **Other bleeding** |        |               |            |                   |         |            |                      |         |            |
| Low              | 25/8166 | 0.31 (0.20–0.45) | <0.001     | 1.00 (Reference)  | <0.001  | 1.00 (Reference)  | <0.001  |          |
| Intermediate     | 30/5143 | 0.58 (0.39–0.83) |           | 1.76 (1.03–3.00)  | 0.039   | 1.71 (0.997–2.92) | 0.051   |          |
| High             | 49/5321 | 0.92 (0.68–1.22) |           | 2.61 (1.62–4.23)  | <0.001  | 2.33 (1.44–3.77)  | 0.001   |          |
| **Women**        |         |               |            |                   |         |            |                      |         |            |
| **Ischemic stroke** |        |               |            |                   |         |            |                      |         |            |
| Low              | 4/2612  | 0.15 (0.04–0.39) | <0.001     | 1.00 (Reference)  | <0.001  | 1.00 (Reference)  | <0.001  |          |
| Intermediate     | 11/1492 | 0.74 (0.37–1.32) |           | 4.25 (1.35–13.38) | 0.013   | 4.07 (1.28–12.88) | 0.017   |          |
| High             | 29/2044 | 1.42 (0.95–2.03) |           | 7.87 (2.74–22.56) | <0.001  | 6.78 (2.32–19.78) | <0.001  |          |
| **Any bleeding** |         |               |            |                   |         |            |                      |         |            |
| Low              | 12/2591 | 0.46 (0.24–0.81) | <0.001     | 1.00 (Reference)  | <0.001  | 1.00 (Reference)  | <0.001  |          |
| Intermediate     | 27/1462 | 1.85 (1.22–2.68) |           | 3.72 (1.90–7.29)  | <0.001  | 3.16 (1.62–6.18)  | 0.001   |          |
| High             | 45/2039 | 2.21 (1.61–2.94) |           | 4.41 (2.35–8.27)  | <0.001  | 2.89 (1.50–5.58)  | 0.002   |          |
| **Intracranial hemorrhage** |   |               |            |                   |         |            |                      |         |            |
| Low              | 2/2613  | 0.08 (0.01–0.28) | 0.029      | 1.00 (Reference)  | 0.041   | 1.00 (Reference)  | 0.060   |          |
| Intermediate     | 11/1485 | 0.74 (0.37–1.32) |           | 8.64 (1.93–38.81) | 0.005   | 8.13 (1.78–37.17) | 0.007   |          |
| High             | 9/2086  | 0.43 (0.20–0.82) |           | 4.97 (1.07–23.06) | 0.041   | 4.61 (0.94–22.67) | 0.060   |          |
| **Gastrointestinal bleeding** | |               |            |                   |         |            |                      |         |            |
| Low              | 4/2614  | 0.15 (0.04–0.39) | 0.001      | 1.00 (Reference)  | 0.003   | 1.00 (Reference)  | 0.013   |          |
| Intermediate     | 12/1492 | 0.80 (0.42–1.40) |           | 4.85 (1.57–15.00) | 0.006   | 4.20 (1.34–13.13) | 0.014   |          |
| High             | 18/2075 | 0.87 (0.51–1.37) |           | 5.16 (1.75–15.21) | 0.003   | 4.04 (1.35–12.13) | 0.013   |          |
| **Other bleeding** |        |               |            |                   |         |            |                      |         |            |
| Low              | 7/2599  | 0.27 (0.11–0.55) | <0.001     | 1.00 (Reference)  | <0.001  | 1.00 (Reference)  | <0.001  |          |

Continued
indicating low risk, 1.95% for intermediate risk, and 4.14% for high risk in atrial fibrillation patients without anticoagulation.

Friberg et al.\textsuperscript{15} reported that annual rates of total major bleeding and intracranial hemorrhage were 2.3% and 0.6%, respectively, although the study included patients on anticoagulation. Banerjee et al.\textsuperscript{19} reported that annual rates of intracranial hemorrhage in patients without anticoagulation were 0.30% overall, 0.05% for low-risk, 0.10% for intermediate-risk, and 0.30% for high-risk scores. Our results showed that the annual incidences of total bleeding and intracranial hemorrhage, respectively, were 1.17% and 0.24% overall, 0.51% and 0.08% for low-risk, 1.28% and 0.30% for intermediate-risk, and 2.02% and 0.40% for high-risk scores. Although the overall risk of bleeding was comparable with those from prior studies, the risk of intracranial bleeding was equivalent or higher than those of prior studies, which were mainly from Western populations. The risks of intracranial hemorrhage among Japanese patients with atrial fibrillation who are not on anticoagulants appears to be higher than that among Western patients, which seems compatible with prior studies that showed higher rates of intracerebral hemorrhage in Japan and East Asian countries than in Western countries.\textsuperscript{30}

Oral anticoagulation is an established strategy to prevent ischemic stroke and other thromboembolic events among patients with atrial fibrillation, although they also increase the risk of bleeding.\textsuperscript{5,31} The risks and benefits of oral anticoagulants depend on an absolute reduction in the risk of ischemic stroke and an absolute increase in bleeding events associated with the treatment. This study showed a relatively low incidence of ischemic stroke and a relatively high incidence of intracranial bleeding in Japanese patients with atrial fibrillation who were not on oral anticoagulants. The present guidelines for managing atrial fibrillation in Japan recommend anticoagulant therapy for patients with a CHADS\textsubscript{2} score of ≥2. However, physicians should be aware that bleeding risk also increases with the elevation of ischemic risk. Further investigation based on the effects of oral anticoagulants and the absolute risks of both ischemic and bleeding events are

|           | Case/PY | % IR (95% CI) | P for Trend | Crude HR (95% CI) | P Value | P for Trend | Adjusted HR (95% CI) | P Value | P for Trend |
|-----------|---------|---------------|-------------|-------------------|---------|-------------|----------------------|---------|-------------|
| Intermediate | 9/1500 | 0.60 (0.27–1.14) | 0.129 | 2.13 (0.80–5.68) | 0.129 | 2.14 (0.81–5.64) | 0.126 |
| High       | 28/2062 | 1.36 (0.90–1.96) | <0.001 | 4.81 (2.13–10.86) | <0.001 | 4.04 (1.76–9.27) | 0.001 |

CHADS\textsubscript{2}-VASc scores are interpreted as follows: low risk was 0 in men and 1 in women; intermediate risk was 1 in men and 2 in women; high risk was ≥2 in men and ≥3 in women. Total bleeding includes those with any following types of bleeding: intracranial, gastrointestinal, and other. Variables used for multivariate analyses were the use of antiplatelet agents and antiarrhythmic agents for all outcomes and use of anti-ulcer and antiplatelet agents for total bleeding and gastrointestinal bleeding. HR indicates hazard ratio; IR, incident rate; PY, person-years.

**Figure 3.** Hazard ratios for the CHA2DS2-VASc risk score for ischemic stroke and various types of bleeding/hemorrhage, by sex. CHA2DS2-VASc scores are interpreted as follows: low risk was 0 in men and 1 in women; intermediate risk was 1 in men and 2 in women; high risk was ≥2 in men and ≥3 in women. GI indicates gastrointestinal.
needed in Japan to establish the effective antithrombotic therapy for patients with atrial fibrillation.

Limitations
The strengths of this study include the real-world setting, large sample size, and comprehensive assessment of outcomes, including gastrointestinal bleeding and other bleeding events as well as ischemic stroke and intracranial hemorrhage. There are some weaknesses as well. One weakness was selection bias because of exclusion of old people aged ≥75 years who move to the public insurance system. Another limitation is that outcome events and other comorbidities were identified using disease codes of the claims data. Although some studies reported the validity of Charlson comorbidity index or comorbidities based on claims data, there may be some uncertainty about their accuracy.

Conclusions
We evaluated the natural history of Japanese patients with atrial fibrillation in a large-scale observational study using real-world data. The risks of ischemic stroke and each type of bleeding event were high among Japanese patients with atrial fibrillation who were not on oral anticoagulants, particularly among those with high CHA2DS2-VASc scores. Optimal management strategies, blood pressure-lowering treatment, and glucose-lowering therapy are required for these high-risk patients with atrial fibrillation. Further studies are needed to establish the effective management considering racial differences.

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Disclosures
None.

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Table S1. Definition of GI bleeding.

| Japanese disease code | Disease                                           |
|-----------------------|--------------------------------------------------|
| 5789001               | Gastric bleeding                                 |
| 5781002               | Lower gastrointestinal bleeding                  |
| 8832368               | Acute hemorrhagic necrotizing pancreatitis       |
| 5319011               | Acute hemorrhagic gastric ulcer                  |
| 8831551               | Hepatic bleeding                                 |
| 5289010               | Oral bleeding                                    |
| 5308005               | Esophageal bleeding                              |
| 8834466               | Gingival bleeding                                |
| 5220084               | Pulp bleeding                                    |
| 8834631               | Hemorrhagic gastritis                            |
| 8834632               | Hemorrhagic gastric ulcer                        |
| 8834637               | Hemorrhagic jawbone cyst                         |
| 5280051               | Hemorrhagic stomatitis                           |
| 8834641               | Hemorrhagic duodenal ulcer                       |
| 5789007               | Digestive tract bleeding                         |
| 8833703               | Anal bleeding                                    |
| 5789008               | Upper gastrointestinal bleeding                  |
| 8836434               | Tongue base submucosal hemorrhage                |
| 8837732               | Intestinal bleeding                              |
| 5693001               | Rectal bleeding                                  |
| 8839763               | Peritoneal bleeding                              |
| 8837584               | Central hemorrhagic liver necrosis               |
| 8839651               | Intra-abdominal hemorrhage                       |
| 5789011               | Bleeding after defecation                        |
| 8845131               | Hemorrhagic duodenal ulcer perforation           |
| 8845130               | Hemorrhagic gastric ulcer perforation            |
| 8845122               | Acute hemorrhagic gastric ulcer perforation      |
| 8845123               | Acute hemorrhagic duodenal ulcer                |
| 8845814               | Diverticulum hemorrhage                          |
| 8845742               | Sigmoid diverticulum hemorrhage                  |
| 8845806               | Ascending colon diverticulum hemorrhage          |
| 8845749               | Transverse colon diverticulum hemorrhage         |
| 8845124               | Acute hemorrhagic duodenal ulcer perforation     |
| 8845800               | Duodenal diverticulum hemorrhage                 |
| 8845763               | Descending colonic diverticulum hemorrhage       |
| 8847762               | Hemorrhagic anastomotic ulcer                    |
| Code     | Description                      |
|----------|----------------------------------|
| 8847788  | Multiple hemorrhagic gastric ulcer|
| 8848141  | Small intestine bleeding         |
Table S2. Definition of other bleeding.

| Japanese disease code | Disease                                      |
|-----------------------|----------------------------------------------|
| 7827001               | Petechia in lower extremity                  |
| 8830641               | Throat bleeding                              |
| 8830697               | Intravaginal hemorrhage                      |
| 7848002               | Pharyngeal bleeding                          |
| 6078036               | Penile bleeding                              |
| 3628002               | Macular bleeding                             |
| 8830975               | Submacular hemorrhage                        |
| 6245002               | Vulvar bleeding                              |
| 7863001               | Bronchial bleeding                           |
| 8832116               | Multiple facial subcutaneous bleeding        |
| 6266004               | Organic genital bleeding                     |
| 3628025               | Fundus hemorrhage                            |
| 8832068               | Subcutaneous bleeding in eye                 |
| 8832181               | Bleeding in tracheostomy site                |
| 5191010               | Endotracheal bleeding                        |
| 5950002               | Acute hemorrhagic cystitis                   |
| 8831810               | Outer ear subcutaneous bleeding              |
| 8832240               | Airway bleeding                              |
| 6268001               | Functional uterine bleeding                  |
| 6260001               | Functional genital hemorrhage                |
| 8832247               | Hypofunction uterine bleeding                |
| 8831990               | Eyelids bleeding                             |
| 8833488               | Lip labial bleeding                          |
| 8832022               | Subcutaneous bleeding around the eye         |
| 3727006               | Subconjunctival hemorrhage                   |
| 3604008               | Intraocular bleeding                         |
| 9211007               | Glasses-like subcutaneous bleeding           |
| 8831968               | Conjunctival hemorrhage                      |
| 3644003               | Iris bleeding                                |
| 7848003               | Laryngeal bleeding                           |
| 8833510               | Thyroid bleeding                             |
| 8832405               | Acute massive bleeding                       |
| 8832664               | Local bleeding                               |
| 2879002               | Petechia on the extremities                 |
| 6268005               | Uterine bleeding                             |
| 3848003               | Tympanic bleeding                            |
4560002  Esophageal varices hemorrhage
7827013  Diffuse subcutaneous hemorrhage
8833946  Umbilical cord subcutaneous bleeding
8834774  Small artery hemorrhage
8834262  Uterine irregular bleeding
8834344  Optic nerve pericapsular bleeding
4590002  bleeding
2869010  Bleeding tendency
8834634  Hemorrhagic keratitis
8834635  Hemorrhagic otitis externa
8834636  Hemorrhagic external hemorrhoid
8834638  Hemorrhagic tracheitis
8834639  Hemorrhagic iritis
9584004  Hemorrhagic shock
8834640  Hemorrhagic hemorrhoid
7573086  Hemorrhagic urticarial
5789018  Hemorrhagic colitis
8834642  Hemorrhagic otitis media
7847002  Habitual nasal bleeding
8833916  Post bleeding
8834333  Optic nerve sheath hemorrhage
5789014  Hemorrhagic enteritis
8834643  Hemorrhagic internal hemorrhoid
4709003  Bleeding nasal polyp
2809005  Hemorrhagic anemia
8842024  Hemorrhagic cystitis
8834644  Hemorrhagic retinitis
8834645  Hemorrhagic follicle follicles
3659001  Hemorrhagic glaucoma
8835174  Pinnacle subcutaneous bleeding
3809001  Ear bleeding
6269004  Genital bleeding
4590003  Venous bleeding
6263005  Juvenile uterine bleeding
7848005  Vocal cord hemorrhage
8834734  Subvitreal hemorrhage
3792006  Vitreous hemorrhage
3361019  Intrathecal hemorrhage
3621012  Juvenile recurrent retinal vitreous hemorrhage
8835604  Perirenal hemorrhage
5938028  Renal hemorrhage
| Code     | Description                                               |
|----------|-----------------------------------------------------------|
| 4789006  | Upper airway bleeding                                     |
| 3361005  | Spinal cord hemorrhage                                   |
| 3361013  | Spinal subdural hemorrhage                               |
| 4320004  | Spinal epidural hemorrhage                               |
| 8835227  | Parenchymatous organ bleeding                             |
| 8837065  | Multiple subcutaneous bleeding                            |
| 7827005  | Subcutaneous thigh bleeding                              |
| 8837085  | Massive bleeding                                         |
| 8844477  | Postoperative hemorrhagic shock                           |
| 9980002  | Postoperative digestive tract hemorrhagic shock          |
| 8836485  | Forehead subcutaneous bleeding                           |
| 8842779  | Bleeding after biopsy                                    |
| 6117032  | Papillary bleeding                                       |
| 4590006  | Internal bleeding                                        |
| 9209062  | Subcutaneous head bleeding                               |
| 8837515  | Vaginal stump bleeding                                   |
| 8837244  | Third stage bleeding                                     |
| 8836580  | Anterior chamber bleeding                                |
| 6117024  | Breast bleeding                                          |
| 6021002  | Prostate bleeding                                        |
| 7847006  | Septal hemorrhage                                        |
| 8839531  | Nasal subcutaneous bleeding                              |
| 3888004  | Middle ear bleeding                                      |
| 7827007  | Patchy hemorrhage                                        |
| 5938021  | Idiopathic renal hemorrhage                              |
| 5997011  | Urethral bleeding                                        |
| 8838196  | Idiopathic plaque hemorrhage                             |
| 7847003  | Idiopathic nasal bleeding                                |
| 6269007  | Illegal genital bleeding                                 |
| 7848006  | Sudden onset pharyngeal bleeding                         |
| 8839467  | Nasal bleeding                                           |
| 7827006  | Petechiae bleeding                                       |
| 5258013  | Bleeding after tooth extraction                          |
| 4590005  | Arterial bleeding                                        |
| 8839683  | Adrenal hemorrhage                                       |
| 3628019  | Superficial retinal hemorrhage                           |
| 9983022  | Bleeding due to suture failure                           |
| 4462004  | Alveolar hemorrhage                                      |
| 8840624  | Subretinal pigmentary subcutaneous hemorrhage            |
| 8840631  | Retinal hemorrhage                                       |
| 3628018  | Preretinal hemorrhage                                    |
| Code       | Description                                      |
|------------|--------------------------------------------------|
| 7827008    | Subcutaneous bleeding                            |
| 8840635    | Deep retinal hemorrhage                          |
| 2872016    | Geriatric bleeding                               |
| 7827002    | Lumbar subcutaneous bleeding                     |
| 3628013    | Subretinal hemorrhage                            |
| 4489012    | Capillary hemorrhage                             |
| 6201004    | Ovarian bleeding                                 |
| 5967004    | Bladder bleeding                                 |
| 3628022    | Reticular choroidal hemorrhage                   |
| 8845850    | Gastric varices hemorrhage                       |
| 8838831    | Pulmonary hemorrhage                             |
| 8847483    | Hemorrhagic retinal pigment epithelial detachment|