ORIGINAL RESEARCH

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 Japan[4] 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 CHA_2DS_2-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 CHA_2DS_2-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

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Accompanying Tables S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014574

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Received September 24, 2019; accepted January 31, 2020.

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.

claims data obtained from JMDC Inc, which handles claims data of 90 of the 1400 Japanese health insurance society members (mainly for company employees and their family members aged <75 years). Elderly people aged ≥75 years were not included in this study because at that age they move to the public late-elderly health insurance system in Japan. Also, our claims data do not include those from small- and medium-scaled enterprises. As for the data validation system in Japan, the Health Insurance Claims Review & Reimbursement services validate the coding. As the coding in Japan is directly linked to payments, the audit is supposed to be rigorous. Informed consent was waived following national guidelines in Japan.

The total number of people contained in the data numbered 4 203 282 from fiscal years 2005 to 2017. Altogether, 22 940 individuals who belonged to the organization during the study period and who had definitive diagnoses of atrial fibrillation or atrial flatter (*International Classification of Diseases, Tenth Revision* [*ICD-10*]: I48) were extracted. After excluding individuals with a mechanical heart valve (n=28) or hematologic disorder (n=1124), those aged ≤20 years (n=207), and patients who had had anticoagulant therapy any time during the study period (n=11 848), we enrolled 9733 participants with atrial fibrillation who had never been prescribed anticoagulation during their follow-up in our analysis (Figure 1). The study was approved by the Fukuoka University Clinical Research and Ethics Center (2017M008).

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 CHA_2DS_2-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 I10 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 CHA_2DS_2-VASc score.[8] A CHA_2DS_2-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

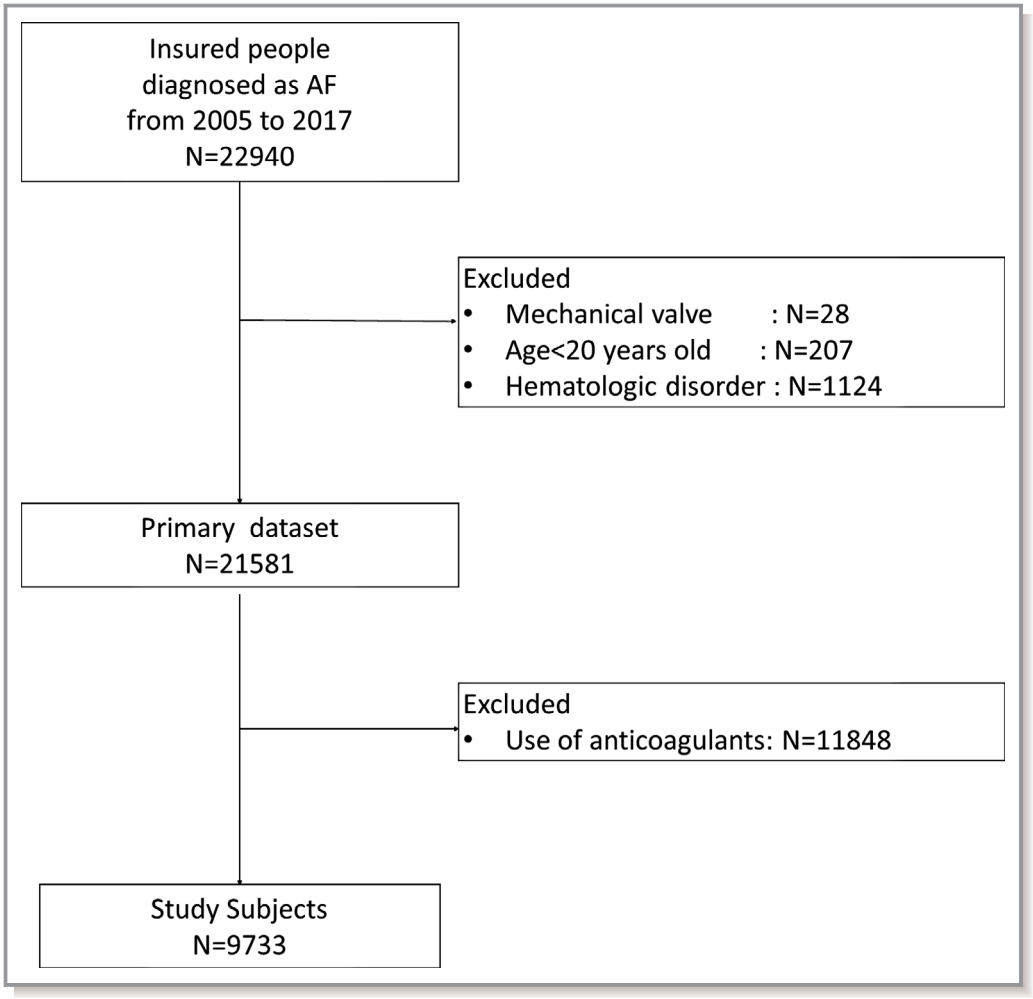

Figure 1. Flow diagram shows the process for selecting our study participants. AF indicates atrial fibrillation.

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 H_2 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[10] to investigate the association between CHA_2DS_2-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)

Table 1. Distribution of CHA_2DS_2-VASc Scores

CHA_2DS_2-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 CHA_2DS_2-VASc scores for men and women. Most men had CHA_2DS_2-VASc scores of ≤3, and most women had scores of <4. In all, 3467 (35.6%) participants were classified as being at low risk (CHA_2DS_2-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 ≥2 in men or ≥3 in women). The results of descriptive analysis according to CHA_2DS_2-VASc risk groups are shown in Table 2. The mean (SD) ages of CHA_2DS_2-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 ≥65 years were most frequently (31.7%)

Table 2. Analysis According to CHA_2DS_2-VASc-Determined Risk Groups

	CHA2DS2-VASc*						
	Low		Intermediate		High		
	(n=3467)		(n=2686)		(n=3580)		*P* Value
Sex							
Men, %	2507	72.3	2012	74.9	2560	71.5	0.009
Age (y) mean, SD	48.2	11.0	54.4	10.6	58.2	10.5	0.010
≥65 y, %	0	0.0	394	14.7	1134	31.7	
Comorbidities							
Congestive heart failure, %	0	0.0	610	22.7	2171	60.6	<0.001
Hypertension, %	0	0.0	1330	49.5	3095	86.5	<0.001
Diabetes mellitus, %	0	0.0	240	8.9	1195	33.4	<0.001
Past history of ischemic stroke /TIA, %	0	0.0	0	0.0	604	16.9	<0.001
Vascular disease, %	0	0.0	112	4.2	676	18.9	<0.001
Medication							
Antiplatelet drug, %							
Cyclooxygenase inhibitor, %	271	7.8	319	11.9	777	21.7	<0.001
ADP receptor antagonist, %	27	0.8	71	2.6	270	7.5	<0.001
Other antiplatelet, %	0	0.0	1	0.0	9	0.3	0.002
Antiulcer drug, %							
Proton pomp inhibitor, %	189	5.5	294	10.9	741	20.7	<0.001
H2 blocker, %	172	5.0	212	7.9	371	10.4	<0.001
Other antiulcer drug, %	727	21.0	600	22.3	834	23.3	0.062
Antiarrhythmic drug							
Ia, %	307	8.9	184	6.9	223	6.2	<0.001
Ib, %	19	0.5	22	0.8	43	1.2	0.012
Ic, %	535	15.4	421	15.7	410	11.5	<0.001
II, %	387	11.2	308	11.5	601	16.8	<0.001
III, %	5	0.1	10	0.4	111	3.1	<0.001
IV, %	41	1.2	33	1.2	36	1.0	0.665
Digitalis, %	134	3.9	139	5.2	218	6.1	<0.001
HAS-BLED mean, SD	0.12	0.33	0.39	0.58	0.80	0.82	<0.001

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 ≥2 in men and ≥3 in women.

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	19/10 799	0.18 (0.11–0.27)	<0.001	1.00 (Reference)		<0.001	1.00 (Reference)		<0.001
Intermediate	29/6636	0.44 (0.39–0.77)		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)		6.15 (3.75–10.09)	<0.001		4.88 (2.90–8.23)	<0.001	
Any bleeding									
Low	55/10 723	0.51 (0.39–0.67)	<0.001	1.00 (Reference)		<0.001	1.00 (Reference)		<0.001
Intermediate	84/6554	1.28 (1.02–1.58)		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	9/10 818	0.08 (0.04–0.16)	<0.001	1.00 (Reference)		<0.001	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	21/10 791	0.19 (0.12–0.30)	<0.001	1.00 (Reference)		<0.001	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	32/10 765	0.30 (0.20–0.42)	<0.001	1.00 (Reference)		<0.001	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.

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 CHA_2DS_2-VASc risk. HAS-BLED scores also significantly increased in accordance with increased CHA_2DS_2-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 CHA_2DS_2-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 CHA_2DS_2-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).

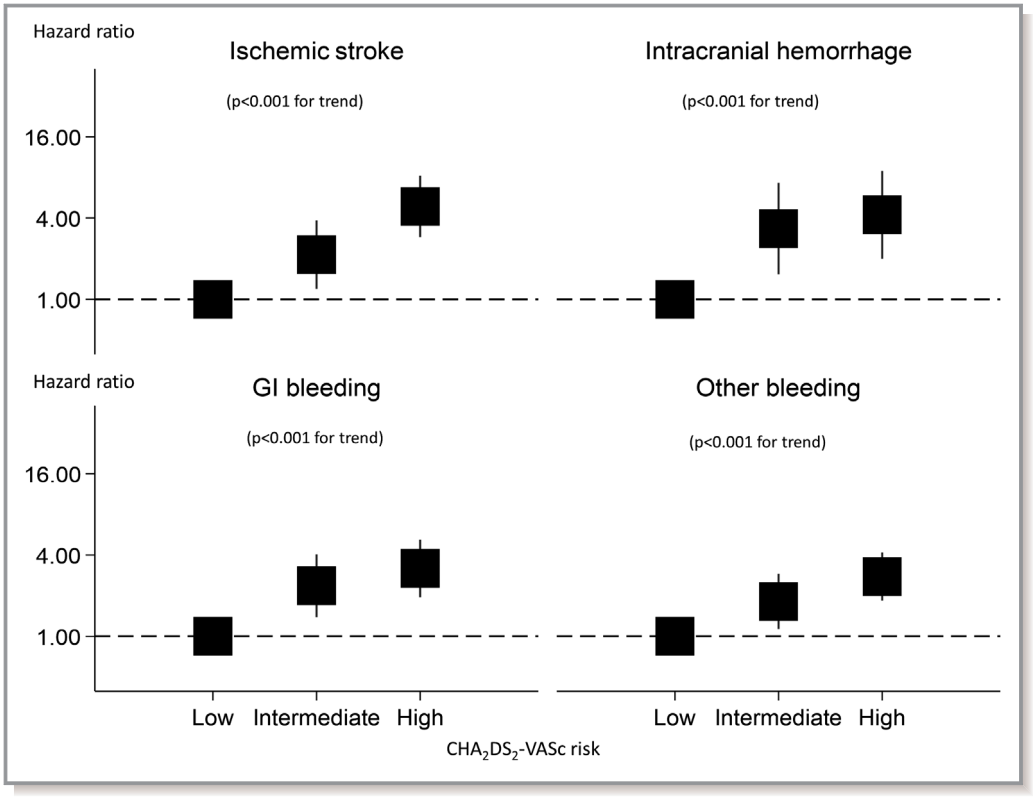

Figure 2. Hazard ratios for the CHA2DS2-VASc risk score for ischemic stroke and various types of bleeding/hemorrhage. CHA2DS2-VASc scores are interpreted as follows: low risk was 0 in men and 1 in women; intermediate risk was 1 in men and 2 in women; high risk was ≥2 in men and ≥3 in women. GI indicates gastrointestinal.

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 CHA_2DS_2-VASc score. The highest risks were observed for the high-risk group with CHA_2DS_2-VASc scores of ≥2 (for men) or ≥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 CHA_2DS_2-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.[14,16,17,26–28] 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 al[23] reported that the annual rate of major bleeding among atrial fibrillation patients without anticoagulation was 2.0%. Olesen et al[18] reported annual incidences of total bleeding events at 3.34% overall, with 1.15% for CHA_2DS_2-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)		0.002
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

Table 4. Continued

	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)		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)		4.81 (2.13–10.86)	<0.001		4.04 (1.76–9.27)	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-years.

indicating low risk, 1.95% for intermediate risk, and 4.14% for high risk in atrial fibrillation patients without anticoagulation. Friberg et al[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[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.[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.[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 CHADS2 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

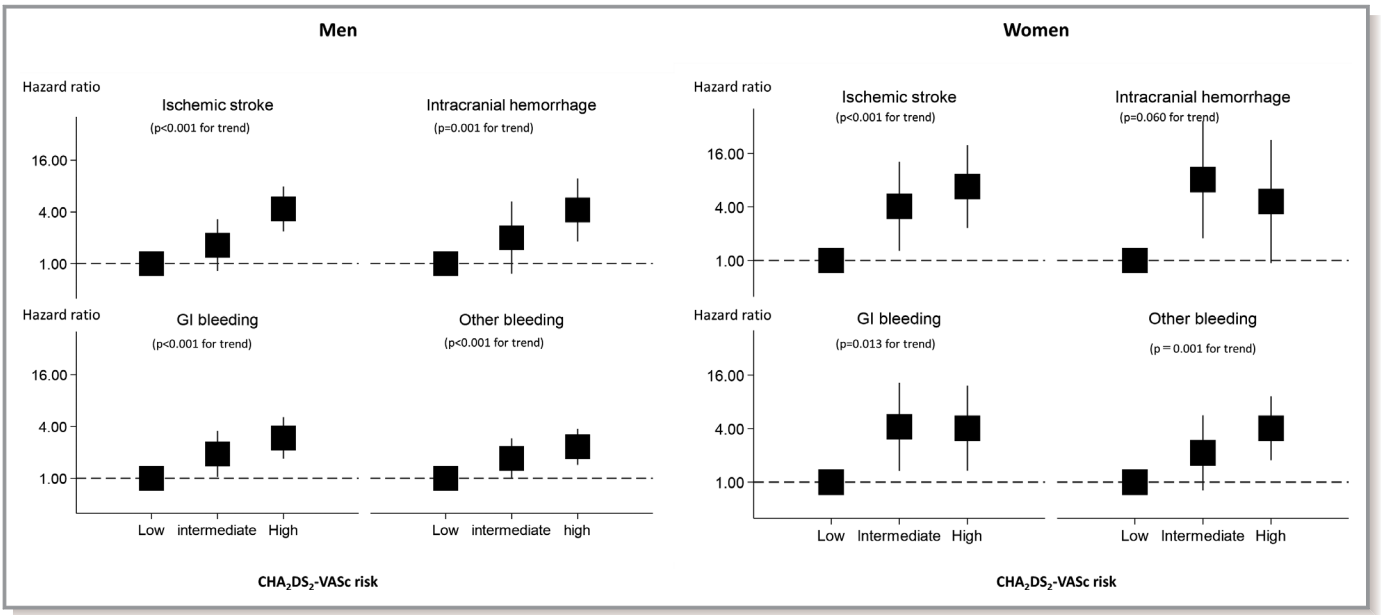

Figure 3. Hazard ratios for the CHA2DS2-VASc risk score for ischemic stroke and various types of bleeding/hemorrhage, by sex. CHA2DS2-VASc scores are interpreted as follows: low risk was 0 in men and 1 in women; intermediate risk was 1 in men and 2 in women; high risk was ≥2 in men and ≥3 in women. GI 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[32,33] 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.

Acknowledgments

We thank JMDC Inc. for providing data. We thank Nancy Schatken, BS, MT(ASCP), from Edanz Group (https://jp-author-services.edanzgroup.com/) for editing a draft of this manuscript.

Sources of Funding

This work was supported by Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 18K17404 and 19H03879.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

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

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

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

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