Clinical Risk Factors of Thromboembolic and Major Bleeding Events for Patients with Atrial Fibrillation Treated with Rivaroxaban in Japan

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Background: It is important to understand the risk of thromboembolism and bleeding in patients with nonvalvular atrial fibrillation (NVAF) receiving direct oral anticoagulants; however, data on risk factors in Japanese patients are limited. *Methods:* XAPASS (Xarelto Post-Authorization Safety and Effectiveness Study in Japanese Patients with Atrial Fibrillation) is a prospective observational study examining the safety and effectiveness of rivaroxaban in Japanese real-world clinical practice. We investigated risk factors for stroke/noncentral nervous system systemic embolism (non-CNS SE)/myocardial infarction (MI) and major bleeding using 1-year follow-up data. Associations between baseline characteristics and outcomes were examined by Cox regression analysis. *Results:* During April 2012-June 2014, 11,308 patients newly started with rivaroxaban treatment were enrolled. Of 9578 patients with 1-year data fixed as of September 2017, 6220 patients who received appropriate dosages of rivaroxaban for their creatinine clearance were included in the present safety outcomes subanalysis, and 6198 were included in the effectiveness outcomes analysis. Stroke/non-CNS SE/MI was observed in 97 of 6198 patients (1.6%, 1.8 events/100 patient-years), and major bleeding occurred in 102 of 6220 patients (1.6%, 1.9 events/100 patient-years). Age greater

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than or equal to 75 years (hazard ratio [HR]: 2.27; [95% confidence interval (CI): 1.49, 3.47]), prior ischemic stroke/transient ischemic attack (2.08; [1.38, 3.13]), and antiplatelet use (3.23; [1.83, 5.70]) were associated with stroke/non-CNS SE/MI. Creatinine clearance less than 50 mL/min (HR: 1.86; [95% CI: 1.26, 2.75]), diabetes (1.55; [1.02, 2.35]), and antiplatelet use (3.04; [1.70, 5.45]) were associated with major bleeding. *Conclusions:* These results would help physicians to assess risks in Japanese patients with NVAF receiving rivaroxaban.

Key Words: Atrial fibrillation—bleeding—predictive factor—risk factor—rivaroxaban—thromboembolic event—stroke

Introduction

Atrial fibrillation (AF) is a common arrhythmia globally,[1,2] and is associated with mortality and morbidity owing to stroke and thromboembolism.[3-5] In Japan, the estimated prevalence of AF is .56%, and this is projected to increase to 1.09% by the year 2050.[3]

Direct oral anticoagulants, such as rivaroxaban, are recommended for the prevention of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF) in many countries, including Japan.[6] The efficacy and safety of rivaroxaban in patients with NVAF compared with warfarin were established globally in the 'Rivaroxaban Once Daily Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trials in Atrial Fibrillation' study (ROCKET AF; ClinicalTrials.gov ID, NCT00403767),[7] and specifically in Japanese patients with NVAF in the Japanese-ROCKET AF study (J-ROCKET AF; NCT00494871).[8]

When determining whether or not to prescribe anticoagulant treatments, physicians assess the risk of thromboembolism and bleeding. Both $CHADS_2$ and CHA_2DS_2-VASc scores are used to assess the risk of stroke in patients with NVAF,[9,10] and the CHA_2DS_2-VASc score has shown improved predictive value for thromboembolism compared with the $CHADS_2$ score.[10] The tool names are acronyms of risk factors for stroke: $CHADS_2$ stands for Congestive heart failure, Hypertension, Age >75 years, Diabetes, prior Stroke/transient ischemic attack/thromboembolism; VASc stands for Vascular disease, Age 65-74 years, Sex category. The risk of bleeding in patients receiving anticoagulants is commonly assessed using HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly [>65 years], Drugs/alcohol concomitantly).[11] A potential drawback of using these tools, however, is that they were constructed using data from Western countries in the vitamin K antagonist era (ie warfarin), and risk factors under DOAC treatments may be different. Furthermore, although the predictive ability of the CHA_2DS_2-VASc and HAS-BLED scores has been validated in Japanese patients,[12] risk factors for thromboembolic and bleeding events differ between Japanese and Western populations. For example, it is reported that fewer Japanese patients with AF have hypertension or congestive heart failure, but more have diabetes than Western patients with AF.[13]

Mandated by the Japanese regulatory authority, the 'Xarelto Post-Authorization Safety and Effectiveness Study' in Japanese Patients with Atrial Fibrillation (XAPASS; ClinicalTrials.gov ID: NCT01582737) is a post-marketing surveillance study aimed at evaluating the effectiveness and safety of rivaroxaban in real-world clinical practice.[14] In the present subanalysis, we examined the baseline risk factors associated with thromboembolism and major bleeding in Japanese patients with NVAF using data from the 1-year follow-up of XAPASS.[15]

Materials and Methods

Study Design

XAPASS is a postauthorization, real-world, prospective, observational, open-label, single-arm, cohort study conducted in Japan, and has been described previously.[14] In brief, enrolled patients will be monitored for a standard period of 2 years, with data-collection periods at 6 months, 1 year, and 2 years after the initiation of rivaroxaban treatment.

This postmarketing surveillance study was approved by the Ministry of Health, Labour, and Welfare in Japan and is conducted in accordance with the Ministry of Health, Labour, and Welfare standards for Good Post-marketing Study Practice.

Study Population and Treatment

Patients with NVAF who initiated rivaroxaban for the purposes of reducing their risk of stroke/SE were eligible for enrollment, and ineligible patients were those in whom rivaroxaban treatment was contraindicated according to the Japanese package insert.[14]

The dosage and duration of treatment were determined by the prescribing physician. In Japan, rivaroxaban is approved for use at 2 doses: 10 mg or 15 mg once daily (o.d.) in patients with a creatinine clearance (CrCl) less than 50 mL/min or greater than or equal to 50 mL/min, respectively.

In this subanalysis, only patients who started an appropriate dosage of rivaroxaban in accordance with their CrCl were included to avoid the effect of dosage selection.

Outcomes

The primary effectiveness outcome was a composite of stroke (hemorrhagic or ischemic), noncentral nervous system (non-CNS) SE, and myocardial infarction (MI). Hemorrhagic stroke and ischemic stroke were recorded separately, and transient ischemic attack (TIA) was not included as an outcome event. The primary safety outcome was a composite of nonmajor and major bleeding events (defined according to the International Society on Thrombosis and Haemostasis criteria).[16] In the present subanalysis, only major bleeding was considered. Intracranial bleeding events were included as both effectiveness and safety outcomes. As described previously,[14,15] all outcomes in XAPASS were recorded as adverse events.

Statistical Analysis

Baseline characteristics were compared between patients with and without reported event(s) of stroke/non-CNS SE/MI during the 1-year follow-up period using Wilcoxon rank-sum tests for continuous variables and Pearson's chi-squared tests for categorical variables. Similar comparisons were also assessed between patients with and without a reported event of major bleeding.

For both effectiveness (stroke/non-CNS SE/MI) and safety (major bleeding) events, hazard ratios (HRs) (95% confidence interval [CI]) and *P* values were estimated using Cox proportional hazards models after adjusting for several baseline patient characteristics, including age, sex, body weight, CrCl, comorbidities (hypertension, diabetes, congestive heart failure, prior ischemic stroke/TIA, vascular disease [MI, peripheral artery disease or aortic plaque], liver dysfunction), and concomitant use of antiplatelet agents. Associations between baseline characteristics and clinical events were further examined using stepwise multivariable analysis with a significance level of 5%. The explanatory variables of medical interest were selected based on data availability and multicollinearity. The statistical analyses were performed using SAS software, version 9.2 or higher (SAS Institute, Inc., Cary, NC).

Results

Patients and Treatment

A patient-selection flow chart is shown in Figure 1. XAPASS included 11,308 patients, and 9578 patients completed 1-year follow-up as of September 2017. The present subanalysis included 6220 patients who received rivaroxaban at appropriate doses approved in Japan. Twenty-two patients were excluded from the effectiveness analysis because they received rivaroxaban before enrollment or did not have NVAF. The baseline characteristics of patients are shown in Table 1.

In total, 4185 patients (67.3%) had CrCl greater than or equal to 50 mL/min and received rivaroxaban 15 mg o.d., and 2035 patients (32.7%) had CrCl less than 50 mL/min and received rivaroxaban 10 mg o.d. Overall, 4086 patients (65.7%) continued rivaroxaban treatment through 1 year of follow-up, 1202 patients (19.3%) were lost to follow-up (including patient transfer), and 932 patients (15.0%) discontinued rivaroxaban treatment (mainly owing to adverse events) within 1 year. The mean ± standard deviation treatment duration was 300.1 ± 118.1 days.

Outcomes

Overall, stroke/non-CNS SE/MI was observed in 97 of 6198 patients (1.6%, 1.8 events/100 patient-years), and

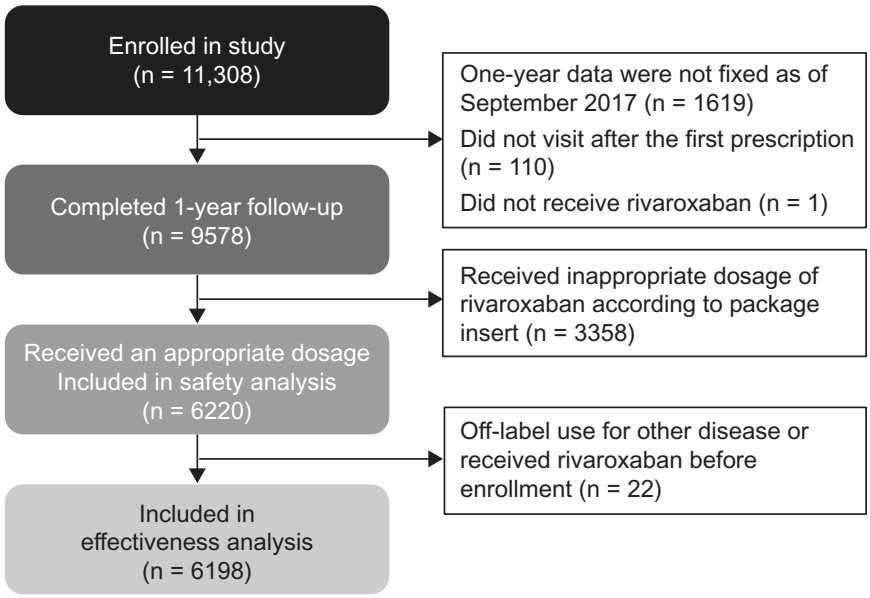

Figure 1. *Patient-selection flow chart.*

Table 1. *Baseline characteristics*

		Stroke/non-CNS SE/MI			Major bleeding		
	Total population	Not observed	Observed		Not observed	Observed	
Characteristic	(n = 6220)	(n = 6101)	(n = 97)	*P* value	(n = 6118)	(n = 102)	*P* value
Age, years, mean (SD)	72.4 (10.4)	72.3 (10.4)	76.7 (8.8)	<.0001	72.3 (10.4)	75.5 (9.6)	.0008
≥75 years, n (%)	2762 (44.4)	2685 (44.0)	64 (66.0)	<.0001	2702 (44.2)	60 (58.8)	.0031
Female sex, n (%)	2273 (36.5)	2229 (36.5)	38 (39.2)	.5922	2228 (36.4)	45 (44.1)	.1092
Body weight, kg, mean (SD)	61.38 (13.47)	61.44 (13.47)	58.07 (12.58)	.0296	61.42 (13.48)	58.79 (12.35)	.0411
≤50 kg	1337 (21.5)	1301 (21.3)	31 (32.0)	.0115	1307 (21.4)	30 (29.4)	.0499
BMI, kg/m^2, mean (SD)	23.76 (4.02)	23.78 (4.02)	23.09 (3.99)	.1196	23.76 (4.02)	23.75 (4.44)	.5399
SCr, mg/dL, mean (SD)	.872 (.258)	.871 (.257)	.942 (.322)	.0393	.872 (0.258)	.910 (.264)	.0926
CrCl, mL/min, mean (SD)	68.3 (32.6)	68.5 (32.6)	57.0 (29.6)	<.0001	68.5 (32.7)	59.0 (25.7)	.0005
<50 mL/min, n (%)	2035 (32.7)	1978 (32.4)	51 (52.6)	<.0001[#]	1988 (32.5)	47 (46.1)	.0037[#]
50 to <80 mL/min, n (%)	2239 (36.0)	2197 (36.0)	34 (35.1)		2205 (36.0)	34 (33.3)	
≥80 mL/min, n (%)	1946 (31.3)	1926 (31.6)	12 (12.4)		1925 (31.5)	21 (20.6)	
$CHADS_2$ score, mean (SD)	2.2 (1.3)	2.1 (1.3)	2.9 (1.3)	<.0001	2.1 (1.3)	2.7 (1.5)	<.0001
Score, n (%)							
0	571 (9.2)	563 (9.2)	4 (4.1)	-	565 (9.2)	6 (5.9)	-
1	1551 (24.9)	1544 (25.3)	5 (5.2)	-	1534 (25.1)	17 (16.7)	-
2	1858 (29.9)	1819 (29.8)	30 (30.9)	-	1834 (30.0)	24 (23.5)	-
3	1213 (19.5)	1183 (19.4)	27 (27.8)	-	1190 (19.5)	23 (22.5)	-
4	693 (11.1)	672 (11.0)	20 (20.6)	-	675 (11.0)	18 (17.6)	-
5	277 (4.5)	265 (4.3)	9 (9.3)	-	265 (4.3)	12 (11.8)	-
6	57 (.9)	55 (.9)	2 (2.1)	-	55 (.9)	2 (2.0)	-
CHA_2DS_2-VASc score, mean (SD)	3.3 (1.6)	3.3 (1.6)	4.3 (1.4)	<.0001	3.3 (1.6)	4.2 (1.7)	<.0001
Score, n (%)							
0	192 (3.1)	189 (3.1)	1 (1.0)	-	192 (3.1)	0	-
1	667 (10.7)	662 (10.9)	2 (2.1)	-	669 (10.9)	7 (6.9)	-
2	1133 (18.2)	1126 (18.5)	5 (5.2)	-	1122 (18.3)	11 (10.8)	-
3	1368 (22.0)	1342 (22.0)	21 (21.6)	-	1348 (22.0)	20 (19.6)	-
4	1362 (21.9)	1335 (21.9)	23 (23.7)	-	1342 (21.9)	20 (19.6)	-
5	879 (14.1)	851 (13.9)	26 (26.8)	-	860 (14.1)	19 (18.6)	-
6	424 (6.8)	407 (6.7)	13 (13.4)	-	408 (6.7)	16 (15.7)	-
7	163 (2.6)	157 (2.6)	6 (6.2)	-	155 (2.5)	8 (7.8)	-
8	31 (.5)	31 (.5)	0	-	30 (.5)	1 (1.0)	-
9	1 (.02)	1 (<.01)	0	-	1 (<.01)	0	-
Modified HAS-BLED score*, mean (SD)	1.5 (1.0)	1.5 (1.0)	2.2 (1.0)	<.0001	1.5 (1.0)	2.0 (1.2)	<.0001
Score, n (%)							
0	936 (15.1)	929 (15.2)	2 (2.1)	-	928 (15.2)	8 (7.8)	-
1	2446 (39.3)	2417 (39.6)	21 (21.6)	-	2421 (39.6)	25 (24.5)	-
2	1887 (30.3)	1841 (30.2)	39 (40.2)	-	1851 (30.3)	36 (35.3)	-
3	776 (12.5)	747 (12.2)	27 (27.8)	-	753 (12.3)	23 (22.5)	-
4	154 (2.5)	147 (2.4)	7 (7.2)	-	147 (2.4)	7 (6.9)	-
5	20 (.3)	19 (.3)	1 (1.0)	-	17 (.3)	3 (2.9)	-
6	0	0	0	-	0	0	-
7	0	0	0	-	0	0	-
8	0	0	0	-	0	0	-
Baseline comorbidities, n (%)							
Congestive heart failure	1599 (25.7)	1560 (25.6)	31 (32.0)	.1529	1565 (25.6)	34 (33.3)	.0756
Hypertension	4678 (75.2)	4584 (75.1)	80 (82.5)	.0966	4595 (75.1)	83 (81.4)	.1461
Diabetes	1418 (22.8)	1393 (22.8)	22 (22.7)	.9718	1385 (22.6)	33 (32.4)	.0204
Prior ischemic stroke/TIA	1418 (22.8)	1373 (22.5)	40 (41.2)	<.0001	1387 (22.7)	31 (30.4)	.0653

Table 1 (*Continued*)

		Stroke/non-CNS SE/MI			Major bleeding		
	Total population	Not observed	Observed		Not observed	Observed	
Vascular disease[†]	215 (3.46)	207 (3.4)	6 (6.2)	.1341	208 (3.4)	7 (6.9)	.0576
Liver dysfunction	377 (6.1)	370 (6.1)	5 (5.2)	.7089	368 (6.0)	9 (8.8)	.2386
Type of AF, n (%)							
Paroxysmal	2057 (33.1)	2025 (33.2)	31 (32.0)	.9079[‡]	2022 (33.1)	35 (34.3)	.2825[‡]
Persistent	2242 (36.1)	2208 (36.2)	34 (35.1)		2212 (36.2)	30 (29.4)	
Permanent	1554 (25.0)	1528 (25.0)	26 (26.8)		1523 (24.9)	31 (30.4)	
Other	15 (.2)	15 (.2)	0		15 (.2)	0	
Unknown	352 (5.7)	325 (5.3)	6 (6.2)		346 (5.7)	6 (5.9)	
Concomitant use of antiplatelet(s), n (%)	283 (4.6)	265 (4.3)	14 (14.4)	<.0001	270 (4.4)	13 (12.7)	<.0001

Abbreviations: AF, atrial fibrillation; BMI, body mass index; $CHADS_2$, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Prior stroke or TIA or thromboembolism; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Prior stroke or TIA or thromboembolism, Vascular disease (eg peripheral artery disease, myocardial infarction or aortic plaque), Age 65-74 years, Sex category; CNS, central nervous system; CrCl, creatinine clearance; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol; INR, international normalized ratio; MI, myocardial infarction; SCr, serum creatinine; SD, standard deviation; SE, systemic embolism; TIA, transient ischemic attack.

Wilcoxon rank-sum tests were used to compare continuous variables, and Pearson's chi-squared tests were used to compare categorical variables.

*Maximum score was 8 because of the exclusion of the factor "labile INR" from the HAS-BLED score.

[†]Vascular disease was defined as MI and/or peripheral artery disease and/or aortic plaque.

[‡]Statistical analysis comparing the distributions of all types of AF between the two cohorts.

[#]Statistical analysis comparing the distributions of values of CrCl between the two cohorts.

major bleeding occurred in 102 of 6220 patients (1.6%, 1.9 events/100 patient-years). The incidence rates and adjusted HRs of stroke/non-CNS SE/MI and major bleeding stratified by key risk factors are shown in Figures 2 and 3, respectively. In a stepwise multivariable analysis, concomitant use of antiplatelet(s) (HR: 3.23; [95% CI: 1.85, 5.70]), age greater than or equal to 75 years (HR: 2.27; [95% CI: 1.49, 3.47]), and history of stroke/TIA (HR: 2.08; [95% CI: 1.38, 3.13]) were identified as predictors of stroke/non-CNS SE/MI, and concomitant use of antiplatelet(s) (HR: 3.04; [95% CI: 1.07, 5.45]), CrCl less than 50 mL/min (HR: 1.86; [95% CI: 1.26, 2.75]), and diabetes (HR: 1.55; [95% CI: 1.02, 2.35]) were identified as predictors of major bleeding (Table 2).

Discussion

This subanalysis of XAPASS was conducted to determine the risk factors for effectiveness (stroke/non-CNS SE/MI) and safety (major bleeding) outcomes in Japanese patients with NVAF receiving Japan-specific dosages of rivaroxaban for stroke prevention in routine clinical practice. Only patients who started an appropriate dosage of rivaroxaban in accordance with their CrCl were included in this subanalysis to avoid the effect of dosage selection. Of a total of 9578 patients, 3358 (35.1%) were excluded from this analysis. Almost all excluded patients received 10 mg rivaroxaban o.d. despite a CrCl greater than or equal to 50 mL/min. Outcomes associated with the underdosing of rivaroxaban have been reported elsewhere.[17] Baseline characteristics of patients included in this subanalysis were similar to those of patients who completed 1-year follow-up.[15] Concomitant use of antiplatelets was predictive of both stroke/non-CNS SE/MI and major bleeding, whereas a history of ischemic stroke/TIA and age greater than or equal to 75 years were predictors of stroke/non-CNS SE/MI only, and renal impairment (CrCl <50 mL/min) and diabetes were predictors of major bleeding only.

Of the risk factors identified for stroke/non-CNS SE/MI, age greater than or equal to75 years and prior ischemic stroke/TIA are components of the $CHADS_2$ and CHA_2DS_2-VASc scores,[9,10] and are therefore expected to be associated with stroke/non-CNS SE/MI. Although concomitant use of antiplatelets is not a component of the $CHADS_2$ or CHA_2DS_2-VASc scores, patients receiving concomitant antiplatelets are likely to have comorbid conditions, such as atherosclerosis, that increase their risk of thromboembolism. Other components of these risk scores, for example diabetes and hypertension, were not significantly associated with the primary effectiveness outcome, suggesting that these comorbidities among patients in the XAPASS cohort may have been well controlled with appropriate treatment.

The finding that concomitant use of antiplatelet agents was associated with an increased risk of major bleeding is expected. Indeed, several studies in Western populations and Japanese populations have established that concomitant use of an anticoagulant and an antiplatelet agent, or use of dual antiplatelet therapy, is associated with an increased risk of major bleeding without additional benefit in terms of efficacy outcomes.[18-21] It is therefore

Variables[a]		Number of patients	Incidence rate, 100 patient-years (95% CI)	Adjusted HR
Age	< 75 years old	3449	1.1 (.7–1.5)	1 (reference)
	≥ 75 years old	2749	2.9 (2.2–3.6)	1.69
Sex category	Male	3931	1.8 (1.3–2.2)	1 (reference)
	Female	2267	2.0 (1.4–2.6)	.87
Body weight	> 50 kg	4864	1.6 (1.2–2.0)	1 (reference)
	≤ 50 kg	1332	2.9 (1.9–4.0)	1.30
Creatinine clearance	≥ 50 mL/min	4169	1.3 (.9–1.6)	1 (reference)
	< 50 mL/min	2029	3.1 (2.3–4.0)	1.41
Hypertension	No	1534	1.4 (.7–2.0)	1 (reference)
	Yes	4664	2.0 (1.6–2.4)	1.32
Diabetes	No	4783	1.9 (1.4–2.3)	1 (reference)
	Yes	1415	1.8 (1.0–2.5)	.91
Congestive heart failure	No	4607	1.7 (1.3–2.1)	1 (reference)
	Yes	1591	2.4 (1.5–3.2)	1.20
Prior ischemic stroke/TIA	No	4785	1.4 (1.0–1.8)	1 (reference)
	Yes	1413	3.5 (2.4–4.6)	2.05
Vascular disease[b]	No	5985	1.8 (1.4–2.2)	1 (reference)
	Yes	213	3.4 (.7–6.2)	1.25
Liver dysfunction	No	5822	1.9 (1.5–2.2)	1 (reference)
	Yes	375	1.6 (.2–3.0)	.95
Concomitant use of antiplatelet(s)	No	5919	1.7 (1.3–2.0)	1 (reference)
	Yes	279	6.3 (3.0–9.6)	3.14

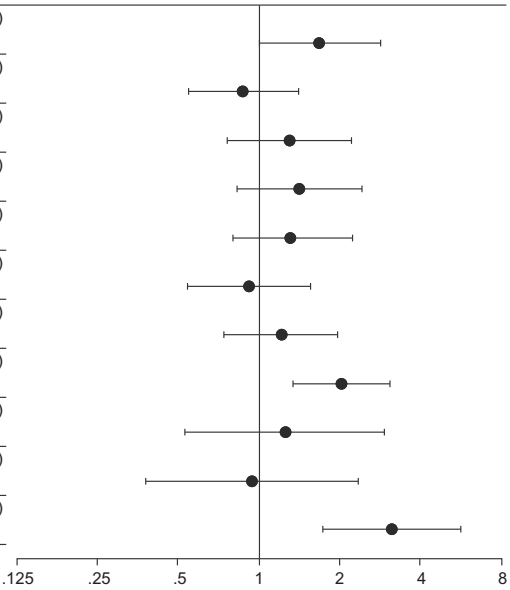

Figure 2. *Stroke/non-CNS SE/MI incidence rates and adjusted hazard ratios (n = 6198). Data availability was 99.9%. Adjusted HRs were calculated by multivariable regression analysis. The chart plots adjusted HRs for categorical groups compared with their reference group. [a]Variables were selected from baseline data. [b]Vascular disease was defined as MI and/or peripheral artery disease and/or aortic plaque. Abbreviations: CI, confidence interval; CNS, central nervous system; HR, hazard ratio; MI, myocardial infarction; SE, systemic embolism; TIA, transient ischemic attack.*

Variables[a]		Number of patients	Incidence rate, 100 patient-years (95% CI)	Adjusted HR
Age	< 75 years old	3458	1.4 (1.0–1.8)	1 (reference)
	≥ 75 years old	2762	2.7 (2.0–3.3)	1.45
Sex category	Male	3947	1.7 (1.3–2.1)	1 (reference)
	Female	2273	2.4 (1.7–3.1)	1.22
Body weight	> 50 kg	4881	1.7 (1.3–2.1)	1 (reference)
	≤ 50 kg	1337	2.8 (1.8–3.9)	1.23
Creatinine clearance	≥ 50 mL/min	4185	1.5 (1.1–1.9)	1 (reference)
	< 50 mL/min	2035	2.9 (2.1–3.7)	1.20
Hypertension	No	1542	1.5 (.8–2.2)	1 (reference)
	Yes	4678	2.1 (1.6–2.5)	1.15
Diabetes	No	4802	1.7 (1.3–2.1)	1 (reference)
	Yes	1418	2.7 (1.8–3.6)	1.54
Congestive heart failure	No	4621	1.7 (1.3–2.1)	1 (reference)
	Yes	1599	2.6 (1.7–3.5)	1.26
Prior ischemic stroke/TIA	No	4802	1.7 (1.3–2.1)	1 (reference)
	Yes	1418	2.7 (1.7–3.6)	1.36
Vascular disease[b]	No	6005	1.9 (1.5–2.2)	1 (reference)
	Yes	215	4.0 (1.0–6.9)	1.44
Liver dysfunction	No	5842	1.9 (1.5–2.3)	1 (reference)
	Yes	377	2.9 (1.0–4.8)	1.61
Concomitant use of antiplatelet(s)	No	5937	1.8 (1.4–2.1)	1 (reference)
	Yes	283	5.8 (2.6–8.9)	2.81

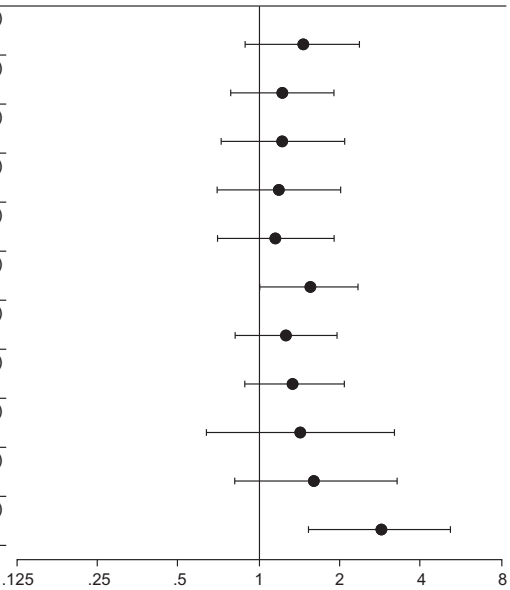

Figure 3. *Major bleeding incidence rates and adjusted hazard ratios (n = 6220). Data availability was 99.9%. Adjusted HRs were calculated by multivariable regression analysis. The chart plots adjusted HRs for categorical groups compared with their reference group. [a]Variables were selected from baseline data. [b]Vascular disease was defined as MI and/or peripheral artery disease and/or aortic plaque. Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; TIA, transient ischemic attack.*

recommended that rivaroxaban be used with caution in patients receiving concomitant treatment with antiplatelet agents such as aspirin, which is consistent with other direct oral anticoagulants.[22-24]

Various bleeding-risk prediction scores, including the HAS-BLED,[11] ATRIA,[25] ORBIT,[26] and HEMORR$_2$HAGES[27] scores, have been proposed for use in patients with AF. In the present study, renal impairment (defined as CrCl

Table 2. *Predictive factors of the effectiveness and safety outcomes*

Variable	Stepwise analysis HR (95% CI)	*P* value
Stroke/non-CNS SE/MI		
Age ≥75 years old	2.27 (1.49-3.47)	.0001
Prior ischemic stroke/TIA	2.08 (1.38-3.13)	.0005
Concomitant use of antiplatelet(s)	3.23 (1.83-5.70)	<.0001
Major bleeding		
Creatinine clearance of <50 mL/min	1.86 (1.26-2.75)	.002
Diabetes	1.55 (1.02-2.35)	.040
Concomitant use of antiplatelet(s)	3.04 (1.70-5.45)	.0002

Abbreviations: CI, confidence interval; CNS, central nervous system; HR, hazard ratio; MI, myocardial infarction; SE, systemic embolism; TIA, transient ischemic attack.

Data availability was 99.9%. Stepwise regression analysis was performed with a 5% significance level.

<50 mL/min) was also identified as a predictor of major bleeding, which is consistent with real-world data in Japan.[28] Renal impairment is a component of the HAS-BLED, ATRIA, ORBIT, and HEMORR$_2$HAGES bleeding-risk scores; however, there are differences between the scores in terms of how renal impairment is defined. For the HAS-BLED score, renal impairment includes patients who received chronic dialysis or renal transplantation therapy, or whose serum creatinine is greater than or equal to 2.26 mg/dL; for the ATRIA, ORBIT, and HEMORR$_2$HAGES bleeding scores, however, renal impairment is defined as severe renal disease (estimated glomerular filtration rate [eGFR] <30 mL/min or on dialysis), insufficient kidney function (eGFR <60 mL/min/1.73m^2), and renal disease according to the International Classification of Diseases, Ninth Revision, respectively.[11,25-27] Furthermore, there are differences between scores in terms of the weightings applied to the component risk factors. For example, in the ATRIA bleeding-risk score, severe renal disease is assigned 3 points, and anemia, age greater than or equal to75 years, prior bleeding, and hypertension are assigned 3, 2, 1, and 1 point(s), respectively. In contrast, in the ORBIT bleeding score, treatment with antiplatelets and insufficient kidney function are assigned 1 point each, and anemia, older age, and bleeding history are assigned 2, 1, and 2 points, respectively. Additionally, in the HEMORR$_2$HAGES bleeding scores, hepatic or renal disease, age greater than 75 years, reduced platelet count or function (including aspirin use), hypertension, anemia, and stroke history are assigned 1 point, and rebleeding risk is assigned 2 points. A study comparing the predictive ability of various bleeding scores in Asian patients with AF reported that the HAS-BLED score was most appropriate for use in this population.[29] However, the findings of the present study suggest that clinicians may need to consider an individualized approach to assessment of bleeding risk when using bleeding-risk scores in Japanese patients with AF.

Although diabetes is not a component of the commonly used bleeding-risk scores, it was identified as an independent predictor of major bleeding in the present study. A similar finding has been reported in other studies, for example in patients with vascular disease receiving aspirin in clinical trials[30] and in a real-world study of patients with AF receiving vitamin K antagonists.[31] The influence of diabetes on the risk of major bleeding in patients with AF remains unclear, but diabetes-related vascular endothelial damage or additional confounding factors may underlie the findings of the present study. Further investigation into the effect of diabetes on bleeding risk in Japanese patients may be warranted.

The independent predictors for effectiveness and safety outcomes identified in the present study differ slightly from those identified previously in Japanese patients with NVAF receiving rivaroxaban for stroke prevention. For example, in the EXPAND study, history of stroke was the only factor associated with stroke/SE, whereas several components of the HAS-BLED score, including age greater than or equal to 65 years, CrCl 30-49 mL/min, liver dysfunction, history/disposition of bleeding, and concomitant use of antiplatelet agents, were associated with major bleeding.[32,33] In a subanalysis of the J-ROCKET AF study, the predictive factors for the efficacy outcome were not examined, and the only factor identified as a predictor of major bleeding related to rivaroxaban treatment was antiplatelet use at baseline.[34] The differences between these findings and those of the present study may be explained by differences in the patient populations and the methods of analysis used. The EXPAND study included patients who had been treated with off-label dosages of rivaroxaban; approximately 2% and 24% of patients received rivaroxaban overdose or underdose, respectively,[32,33] whereas the present study included only those patients who received rivaroxaban at appropriate dosages approved in Japan. The J-ROCKET study was a phase III clinical trial and therefore had strict inclusion and exclusion criteria that were not applied to the present real-world study.

There are some limitations to the present study. First, the loss of patients to follow-up and selection bias by physicians in prescribing rivaroxaban might lead to

underestimation of the event rates. Second, the study was limited to 1 year of follow-up, limiting the ability to assess late clinical events and evaluate whether predictive factors might change during treatment durations longer than 1 year. Third, this study was based on patient characteristics at baseline and did not account for changes during the study or for invasive treatment such as catheter ablation or surgery. Fourth, variables were selected based on clinical interest and data availability. Fifth, the current study used doses approved in Japan (15 mg or 10 mg o.d.), which differ from doses used globally (20 mg or 15 mg o.d.). However, pharmacokinetic modeling has shown that the level of rivaroxaban in blood samples obtained from Japanese patients receiving rivaroxaban at the 15 mg dose was similar to that in blood samples from Caucasian patients who were receiving the 20 mg dose.[35] Despite these limitations, our findings may help physicians to make decisions when prescribing rivaroxaban for Japanese patients with NVAF.

In conclusion, this subanalysis of the XAPASS showed that age greater than or equal to 75 years, prior ischemic stroke/TIA, and antiplatelet use were associated with stroke/non-CNS SE/MI and that CrCl less than 50 mL/min, diabetes, and concomitant use of oral antiplatelet agents were associated with major bleeding events. These results help physicians to assess the risks for Japanese patients with NVAF receiving rivaroxaban.

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Conflict of Interest

Dr. Miyamoto reports personal fees from Bayer Yakuhin Ltd., grants from Astellas, grants from Brainlab, grants from Bristol-Myers Squibb, grants from Carl Zeiss Meditec, grants from Chugai, grants from CSL Behring, grants from Daiichi Sankyo, grants from Eisai, grants from Medtronic, grants from Meiji, grants from Mitsubishi-Tanabe, grants from Mizuho, grants from MSD, grants from Pfizer, grants from Philips Electronics Japan, grants from Nihon Medi-Physics, grants from Otsuka, grants from Sanofi, grants from Siemens Healthcare, grants from Takeda, outside the submitted work.

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