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ORIGINAL ARTICLE

Impact of three major risk factors on clinical outcomes in patients with nonvalvular atrial fibrillation receiving rivaroxaban: Sub-analysis from the XAPASS study

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Abstract

Background: To evaluate the impact of three risk factors (age [≥75 years], renal impairment [creatinine clearance <50 ml/min], and low body weight [≤50 kg]) on the risk of any bleeding events, all-cause mortality, and stroke, non-central nervous system (non-CNS) systemic embolism (SE), and myocardial infarction (MI) in patients with nonvalvular atrial fibrillation (NVAF) treated with rivaroxaban in a real-world clinical setting.

Methods: The Xarelto Post-Authorization Safety and Effectiveness Study in Japanese Patients with Atrial Fibrillation (XAPASS) is a prospective, single-arm, observational study. Enrolled patients were divided into four subgroups by the number of risk factors.

Results: Overall, 9823 patients were included: 4299 with low risk, 2816 with moderate risk, 1574 with high risk, and 1134 with very high risk. The hazard ratios (95% confidence interval) (reference: low risk) for the moderate-, high-, and very-high-risk groups were 1.62 (1.19, 2.21) ($p = 0.002$), 2.15 (1.47, 3.15) ($p < 0.001$), and 2.49 (1.60, 3.87) ($p < 0.001$) for major bleeding, and 1.98 (1.47, 2.66), 2.29 (1.59, 3.29), and 2.74 (1.81, 4.16) ($p < 0.001$ for all) for stroke/non-CNS SE/MI, respectively.

Conclusions: Age ≥75 years and renal impairment, but not low body weight, were determinants for major bleeding. The accrual of three risk factors was associated with increased risk for major bleeding and stroke/non-CNS SE/MI in patients with NVAF receiving rivaroxaban; there was no increase in the cumulative risk for these with an increasing number of risk factors.

KEYWORDS
atrial fibrillation, anticoagulant, body weight, elderly, renal insufficiency

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in adults worldwide.[1,2] Patients with AF are at increased risk of experiencing stroke and heart failure, and as such the condition is associated with a substantial mortality rate.[3] The estimated prevalence of AF in Japan was 0.56% in 2009.[4] Prevalence is predicted to increase to 1.09% in 2050.[4]

Treatment with anticoagulants is the current standard-of-care for patients with AF who are considered to be at a high risk of stroke.[5–7] Rivaroxaban, a direct oral anticoagulant (DOAC), and other DOACs provide an alternative anticoagulant treatment to vitamin K antagonists for preventing stroke in patients with nonvalvular AF (NVAF).[8]

In some phase 3 clinical trials involving DOACs, advanced age,[9,10] renal impairment,[10,11] and low body weight[10] were indicated as independent risk factors for bleeding and stroke in patients with NVAF. Additionally, in real-world studies, age[12] and renal impairment[12,13] were identified as independent determinants of major bleeding in patients with NVAF receiving DOACs. In Japan, which has an aging population, the proportion of patients with AF who have these factors is high: 53.7% are reported to be 75 years of age or older, 26.4% have renal impairment (chronic kidney disease), and 25.7% have low body weight (<50 kg).[14] In addition, in post-marketing surveillance studies of DOACs in Japan, these three factors were the main reasons why DOACs were inappropriately underdosed in patients with NVAF.[15,16] Although many patients with AF in Japan have these risk factors and physicians are concerned about bleeding risk, measuring their impact on the incidence of bleeding and thromboembolic events has been difficult due to a general underrepresentation of patients of advanced age with renal impairment and low body weight in clinical trials. Therefore, the clinical characteristics and outcomes of patients treated with DOACs in real-world clinical practice who have more than one of these risk factors and NVAF remain unknown.

The Xarelto Post-Authorization Safety and Effectiveness Study in Japanese Patients with Atrial Fibrillation (XAPASS) is a post-marketing surveillance study designed to evaluate the safety and effectiveness of rivaroxaban treatment in real-world clinical practice.[17] The primary safety outcome of the study is a composite of the incidence of major and non-major bleeding episodes, and the primary effectiveness outcome is the incidence of ischemic or hemorrhagic stroke, non-central nervous system (non-CNS) systemic embolism (SE), and myocardial infarction (MI).

In the present sub-analysis, we examined the impact of advanced age (≥75 years), renal impairment (creatinine clearance [CrCl] <50 ml/min), and low body weight (≤50 kg) on the risk of bleeding and thromboembolic episodes in patients with NVAF from Japan treated with rivaroxaban, through analysis of follow-up data (5 years) from the XAPASS.

2 | METHODS

2.1 | Study design

The design of the XAPASS (ClinicalTrials.gov identifier: NCT01582737), a post-authorization, prospective, case-only, observational, cohort surveillance study that took place in Japan, has been described previously.[17] The study was approved by the Ministry of Health, Labour, and Welfare (MHLW) of Japan and was conducted in accordance with the standards for Good Post-Marketing Study Practice (GPSP) provided by the MHLW.

2.2 | Study population

In total, 11308 patients were recruited across 1416 Japanese sites between April 2012 and June 2014 in the XAPASS. All patients received rivaroxaban for treatment of NVAF and ultimately, prevention of stroke and SE. Patients with contraindications to rivaroxaban therapy, as described in the Japanese package insert, were excluded. In this current sub-analysis, patients were divided into four risk groups (low, moderate, high, and very high) according to the number of the following risk factors: elderly (≥75 years), renal impairment (CrCl <50 ml/min), and low body weight (≤50 kg). Low-risk (LoR) patients presented none of the aforementioned risk factors, moderate-risk (MoR) patients had one risk factor, high-risk (HiR) patients had two risk factors, and very-high-risk (vHiR) patients had all three risk factors (Figure 1).

2.3 | Treatment

All patients received rivaroxaban, ingested orally, at a daily dose of 15 mg or 10 mg, as prescribed by the treating physician. Rivaroxaban

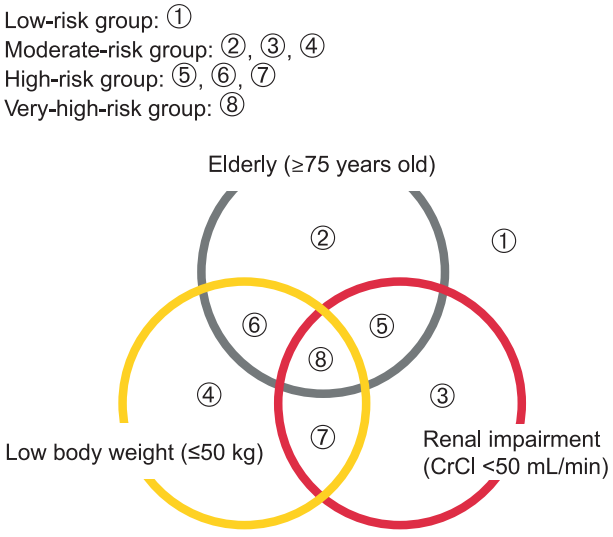

FIGURE 1 Low-, moderate-, high-, and very-high-risk groups. 1. Low-risk group = 0 risk factors; 2. Moderate-risk group = 1 risk factor (age ≥75 years); 3. Moderate-risk group = 1 risk factor (renal impairment [CrCl <50 ml/min]); 4. Moderate-risk group = 1 risk factor (low body weight [≤50 kg]); 5. High-risk group = 2 risk factors (age ≥75 years + CrCl <50 ml/min); 6. High-risk group = 2 risk factors (age ≥75 years + weight ≤50 kg); 7. High-risk group = 2 risk factors (CrCl <50 ml/min + weight ≤50 kg); 8. Very-high-risk group = 3 risk factors (age ≥75 years + CrCl <50 ml/min + weight ≤50 kg). CrCl, creatinine clearance

doses of 15 mg or 10 mg correspond to those approved in Japan for patients with CrCl ≥50 ml/min and <50 ml/min, respectively.

2.4 | Outcomes

All outcomes were reported as adverse events. The primary safety outcome was a composite of major bleeding and nonmajor bleeding. Major bleeding was defined in accordance with the International Society on Thrombosis and Haemostasis criteria.[18] Also reported as a safety event was all-cause mortality. The primary effectiveness outcome was a composite of ischemic stroke (excluding transient ischemic attack [TIA]), hemorrhagic stroke, and non-CNS SE/MI. All the outcomes were defined previously.[17,19]

All data collected from the XAPASS were incorporated into a single-centralized database, and the resultant data were analyzed independently. Data collected from May 30, 2012, to May 31, 2019, were used for this study.

2.5 | Statistical analysis

Patient baseline characteristics were presented as frequencies and percentages. For each safety and effectiveness outcome, the crude incidence (defined as the number and proportion of patients who experience the outcome), incidence (defined as the number of patients who experience the event per 100 patient-years), and associated 95% confidence intervals (CIs) were calculated. The onset of any bleeding, major bleeding, stroke/non-CNS SE/MI, and all-cause mortality for each risk group was analyzed using the Kaplan–Meier estimator. Hazard ratios (HRs) for key outcomes for each risk group, each risk factor and combination of risk factors (Figure 1) was calculated using univariable and multivariable Cox regression analyses. Parameters collected following enrollment to the XAPASS as confounding variables included: sex, initial dose and history of hypertension, diabetes, congestive heart failure, prior ischemic stroke/TIA, vascular disease, hepatic dysfunction, and oral antiplatelet use. Initial variable selection demonstrated that inappropriate dosage (off-label low or overdose) did not meet the predefined significance level (5%) and was, therefore, not included in the multivariable analysis. Data processing was conducted with SAS version 9.4 (SAS Institute Inc.).

3 | RESULTS

Of the 11308 patients enrolled in the XAPASS, 10664 comprised the safety analysis set (Figure 2). Following the exclusion of patients because they did not have data on body weight ($n = 3$), CrCl ($n = 99$), or body weight and CrCl ($n = 739$), 9823 patients were included in the analyses reported here. Of the 9823 patients analyzed, 4299 (43.8%), 2816 (28.7%), 1574 (16.0%), and 1134 (11.5%) had zero, one, two, and three risk factors, forming the LoR, MoR, HiR, and vHiR groups, respectively. In the MoR group, 78.9% ($n = 2222$) were elderly, 7.6% ($n = 215$) had renal impairment, and 13.5% ($n = 379$) had low body weight (Table 1). In the HiR group, almost two-thirds

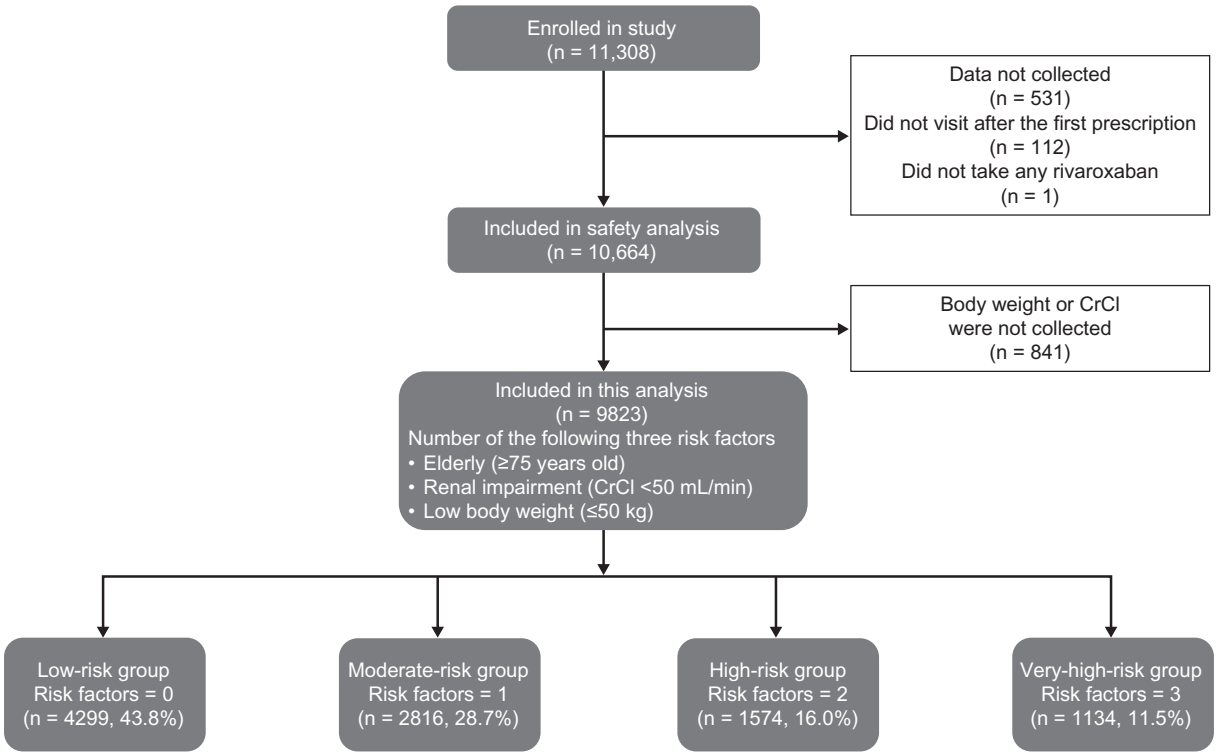

FIGURE 2 Patient selection flowchart. CrCl, creatinine clearance

TABLE 1 Baseline characteristics of patients by risk group (low, moderate, high, and very high)

Characteristics	Risk groups				
	Low ① (*n* = 4299)	Moderate ②③④ (*n* = 2816)	High ⑤⑥⑦ (*n* = 1574)	Very high ⑧ (*n* = 1134)	Overall ①~⑧ (*n* = 9823)
Age					
Years, mean (SD)	65.3 (7.5)	76.9 (6.1)	80.6 (5.4)	83.5 (4.9)	73.2 (9.8)
≥75 years	0 (0.0)	2222 (78.9)	1438 (91.4)	1134 (100.0)	4794 (48.8)
Female sex	986 (22.9)	1088 (38.6)	777 (49.4)	872 (76.9)	3723 (37.9)
Body weight					
kg, mean (SD)	68.4 (11.3)	61.8 (10.8)	54.2 (8.7)	43.7 (4.6)	61.4 (13.1)
≤50 kg	0 (0.0)	379 (13.5)	529 (33.6)	1134 (100.0)	2042 (20.8)
BMI, kg/m^2, mean (SD)	25.1 (3.8)	24.4 (4.0)	22.4 (3.4)	19.7 (2.4)	23.9 (4.1)
SCr, mg/dl, mean (SD)	0.84 (0.19)	0.82 (0.25)	0.97 (0.36)	0.86 (0.22)	0.86 (0.25)
CrCl, ml/min, mean (SD)	85.3 (24.2)	65.2 (16.6)	45.6 (12.9)	36.9 (7.6)	67.6 (26.3)
<15	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)	3 (0.0)
15 to <30	0 (0.0)	11 (0.4)	73 (4.6)	210 (18.5)	294 (3.0)
30 to <50	0 (0.0)	204 (7.2)	1106 (70.3)	923 (81.4)	2233 (22.7)
50 to <80	2026 (47.1)	2165 (76.9)	376 (23.9)	0 (0.0)	4567 (46.5)
≥80	2273 (52.9)	436 (15.5)	17 (1.1)	0 (0.0)	2726 (27.8)
$CHADS_2$ score, mean (SD)	1.6 (1.1)	2.6 (1.3)	2.9 (1.3)	2.9 (1.2)	2.2 (1.3)
0	654 (15.2)	110 (3.9)	22 (1.4)	0 (0.0)	786 (8.0)
1	1703 (39.6)	409 (14.5)	162 (10.3)	98 (8.6)	2372 (24.1)
2	1097 (25.5)	1011 (35.9)	498 (31.6)	378 (33.3)	2984 (30.4)
3	600 (14.0)	630 (22.4)	393 (25.0)	321 (28.3)	1944 (19.8)
4	210 (4.8)	461 (16.4)	305 (19.4)	203 (17.9)	1179 (12.0)
5	35 (0.8)	152 (5.4)	152 (9.7)	119 (10.5)	458 (4.7)
6	0 (0.0)	43 (1.5)	42 (2.7)	15 (1.3)	100 (1.0)
CHA_2DS_2-VASc score, mean (SD)	2.5 (1.3)	3.9 (1.4)	4.5 (1.3)	4.7 (1.3)	3.5 (1.6)
0	223 (5.2)	8 (0.3)	0 (0.0)	0 (0.0)	231 (2.4)
1	836 (19.4)	63 (2.2)	10 (0.6)	0 (0.0)	909 (9.3)
2	1284 (29.9)	276 (9.8)	64 (4.1)	24 (2.1)	1648 (16.8)
3	1059 (24.6)	771 (27.4)	329 (20.9)	142 (12.5)	2301 (23.4)
4	586 (13.6)	793 (28.2)	456 (29.0)	370 (32.6)	2205 (22.4)
5	241 (5.6)	541 (19.2)	366 (23.3)	313 (27.6)	1461 (14.9)
6	65 (1.5)	269 (9.6)	231 (14.7)	168 (14.8)	733 (7.5)
7	5 (0.1)	77 (2.7)	100 (6.4)	98 (8.6)	280 (2.9)
8	0 (0.0)	16 (0.6)	17 (1.1)	19 (1.7)	52 (0.5)
9	0 (0.0)	2 (0.1)	1 (0.1)	0 (0.0)	3 (0.0)
Modified HAS-BLED score,[a] mean (SD)	1.1 (0.9)	1.6 (0.8)	2.0 (0.9)	1.9 (0.9)	1.5 (1.0)
0	1151 (26.8)	75 (2.7)	6 (0.4)	0 (0.0)	1232 (12.5)
1	1890 (44.0)	1349 (47.9)	495 (31.4)	384 (33.9)	4118 (41.9)
2	953 (22.2)	982 (34.9)	629 (40.0)	479 (42.2)	3043 (31.0)
3	258 (6.0)	331 (11.8)	349 (22.2)	222 (19.6)	1160 (11.8)
4	40 (0.9)	73 (2.6)	84 (5.3)	43 (3.8)	240 (2.4)
5	6 (0.1)	5 (0.2)	11 (0.7)	6 (0.5)	28 (0.3)
6	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

TABLE 1 (Continued)

7	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
8	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Baseline comorbidities					
Congestive heart failure	864 (20.1)	674 (23.9)	534 (33.9)	438 (38.6)	2510 (25.6)
Hypertension	3165 (73.6)	2177 (77.3)	1244 (79.0)	845 (74.5)	7431 (75.6)
Diabetes mellitus	1111 (25.8)	664 (23.6)	325 (20.6)	181 (16.0)	2281 (23.2)
Prior ischemic stroke/TIA	748 (17.4)	697 (24.8)	496 (31.5)	351 (31.0)	2292 (23.3)
Vascular disease[b]	143 (3.3)	136 (4.8)	92 (5.8)	45 (4.0)	416 (4.2)
Hepatic dysfunction	358 (8.3)	168 (6.0)	90 (5.7)	53 (4.7)	669 (6.8)
Type of AF					
Paroxysmal	1491 (34.7)	1003 (35.6)	442 (28.1)	373 (32.9)	3309 (33.7)
Persistent	1546 (36.0)	973 (34.6)	590 (37.5)	440 (38.8)	3549 (36.1)
Permanent	1045 (24.3)	674 (23.9)	425 (27.0)	254 (22.4)	2398 (24.4)
Other	12 (0.3)	7 (0.3)	4 (0.3)	4 (0.4)	27 (0.3)
Unknown	205 (4.8)	159 (5.7)	113 (7.2)	63 (5.6)	540 (5.5)
History of anticoagulants[c]					
Warfarin	1431 (33.3)	1035 (36.8)	621 (39.5)	424 (37.4)	3511 (35.7)
Dabigatran	681 (15.8)	442 (15.7)	256 (16.3)	163 (14.4)	1542 (15.7)
Apixaban	4 (0.1)	9 (0.3)	4 (0.3)	7 (0.6)	24 (0.2)
Edoxaban	2 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	3 (0.0)
Other	47 (1.1)	34 (1.2)	40 (2.5)	28 (2.5)	149 (1.5)
Treatment at baseline					
Dose of rivaroxaban					
10 mg/day	928 (21.6)	1584 (56.3)	1320 (83.9)	1014 (89.4)	4846 (49.3)
15 mg/day	3371 (78.4)	1231 (43.7)	254 (16.1)	120 (10.6)	4976 (50.7)
Other	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Oral antiplatelet use	192 (4.5)	140 (5.0)	82 (5.2)	39 (3.4)	453 (4.6)
Aspirin	147 (3.4)	94 (3.3)	61 (3.9)	35 (3.1)	337 (3.4)
Clopidogrel	48 (1.1)	36 (1.3)	15 (1.0)	6 (0.5)	105 (1.1)
Cilostazol	13 (0.3)	17 (0.6)	8 (0.5)	3 (0.3)	41 (0.4)
Ticlopidine	4 (0.1)	5 (0.2)	3 (0.2)	0 (0.0)	12 (0.1)

Note: Data are *n* (%) unless specified otherwise.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; $CHADS_2$, congestive heart failure, hypertension, age, diabetes, previous stroke/transient ischemic attack; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 years, sex category; CrCl, creatinine clearance; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs, or alcohol; INR, international normalized ratio; SCr, serum creatinine; SD, standard deviation; TIA, transient ischemic attack.

[a] Highest modified HAS-BLED score is 8, as the parameter "labile INR" is excluded from the analysis.

[b] Vascular disease is defined as myocardial infarction and/or peripheral artery disease and/or aortic plaque.

[c] Dosing history in the 30 days prior to administration of rivaroxaban.

(66.4%; *n* = 1045) were elderly with renal impairment, one-quarter (25.0%; *n* = 393) were elderly with low body weight, and 8.6% (*n* = 136) had a renal impairment and low body weight.

Table 1 displays the baseline characteristics of the safety analysis set. Table S1 presents the baseline characteristics of patients with each risk factor and combination of risk factors. Compared with the LoR group, the MoR, HiR, and vHiR groups had higher proportions of elderly and female patients. Mean body weight and mean CrCl were the lowest for patients in the vHiR group. The proportion of patients with comorbid hypertension and prior ischemic attack or TIA was highest in the HiR group and lowest in the LoR group. Mean $CHADS_2$, CHA_2DS_2-VASc, and modified HAS-BLED scores were numerically higher in patients in the MoR, HiR, and vHiR groups than in the LoR group (Table 1).

Mean (SD) duration of treatment was longer for patients in the LoR (961 [709] days) and MoR (938 [706] days) groups than for those in the HiR (787 [661] days) and vHiR (708 [662] days) groups. Proportionally, more patients in the vHiR (31.5%; *n* = 357) and HiR

(30.3%; $n = 477$) groups discontinued treatment than in the LoR (21.0%; $n = 901$) and MoR (23.1%; $n = 649$) groups. Overall, 9.4% of patients discontinued owing to adverse events, 3.0% discontinued owing to patient request, 2.6% died, and 7.3% discontinued owing to 'other' reasons. Of patients in the LoR, MoR, HiR, and vHiR groups, 18.4% ($n = 789$), 23.1% ($n = 651$), 27.5% ($n = 432$), and 31.0% ($n = 352$), respectively, were lost to follow-up.

Among patients with CrCl ≥50 ml/min, 928 (21.6%), 1402 (49.8%), and 264 (16.8%) of those in the LoR, MoR, and HiR groups, respectively, received rivaroxaban 10 mg once daily (underdosing). On the other hand, among patients with CrCl <50 ml/min, 33 (1.2%), 125 (7.9%), and 120 (10.6%) of those in the MoR, HiR, and vHiR groups, respectively, received rivaroxaban 15 mg once daily (overdosing).

3.1 | Safety and effectiveness outcomes

Table 2 displays the safety and effectiveness outcomes for patients in each risk group. Table S2 details these outcomes by risk factor and combination of risk factors. The incidence of any bleeding events (event/100 patient-years) was 3.05 (95% CI 2.72, 3.37) in the LoR group, 3.82 (95% CI 3.37, 4.28) in the MoR group, 5.02 (95% CI 4.26, 5.78) in the HiR group, and 5.46 (95% CI 4.49, 6.43) in the vHiR group (Table 2). Major bleeding events were reported in proportionally more patients in the HiR and vHiR groups (3.8% for both) than in the MoR (3.3%) and LoR (2.1%) groups (Table 2). In the univariable analysis, a significantly higher cumulative risk of major bleeding events was observed in the HiR and vHiR groups compared with the LoR group ($p < 0.001$ for both) (Figures 3 and 4). In the multivariable analysis, the HR for major bleeding relative to the LoR group was 1.62 (95% CI 1.19, 2.21; $p = 0.002$) for the MoR group, 2.15 (95% CI 1.47, 3.15; $p < 0.001$) for the HiR group, and 2.49 (95% CI 1.60, 3.87; $p < 0.001$) for the vHiR group.

The incidence of all-cause mortality per 100 patient-years (5.08 [95% CI 4.16, 6.00]) was highest in the vHiR group (Table 2).

Patients in the LoR group exhibited the lowest proportion of stroke/non-CNS SE/MI, (86 of 4286 patients; 2.0%; 0.75 [95% CI 0.59, 0.91] events/100 patient-years) (Table 2). The proportions of patients with stroke/non-CNS SE/MI in the MoR, HiR, and vHiR groups were 4.2%, 4.5%, and 4.6%, respectively, corresponding to incidences of 1.61 (95% CI 1.32, 1.90), 2.05 (95% CI 1.57, 2.53), and 2.29 (95% CI 1.67, 2.91) events/100 patient-years, respectively. Univariable and multivariable analyses of the risk groups revealed that cumulative incidence of stroke/non-CNS SE/MI in the vHiR group was almost three times higher than that in the LoR group (univariable analysis: HR 2.92 [95% CI 2.07, 4.13]; $p < 0.001$; multivariable analysis: HR 2.74 [95% CI 1.81, 4.16]; $p < 0.001$) (Figures 3 and 4).

In a stepwise multivariable analysis, patients presenting with renal impairment and advanced age, but not low body weight, were independently significantly associated with a greater risk of major bleeding events compared with patients that did not present these risk factors ($p = 0.007$ and $p = 0.028$, respectively), while advanced age alone was significantly associated with a greater risk of stroke/non-CNS SE/MI ($p < 0.001$) (Figure 5). Together, patients presenting with advanced age and renal impairment were significantly associated with a greater risk for major bleeding (HR 2.42 [95% CI 1.60, 3.65]; $p < 0.001$) and stroke/non-CNS SE/MI (HR 2.25 [95% CI 1.51, 3.34]; $p < 0.001$) compared with patients that did not present with these risk factors (Figure 5). Increased risk for stroke/non-CNS SE/MI was also associated with renal impairment and low body weight (HR 3.57 [95% CI 1.74, 7.32]; $p = 0.001$). The combination of all three risk factors was associated with a greater risk of major bleeding and stroke/non-CNS SE/MI compared with the presence of no risk factors (Figure 5).

Among patients with NVAF treated with rivaroxaban who presented one or more risk factors, an increasing number of risk factors was not significantly associated with a greater incidence of major bleeding or stroke/non-CNS SE/MI (Figure S1).

4 | DISCUSSION

The aim of the present XAPASS sub-analysis was to investigate the effect that three risk factors (advanced age, renal impairment, and low body weight) had on safety and effectiveness outcomes in patients with NVAF who were treated with rivaroxaban in a real-world Japanese setting. Overall, it was determined that patients with at least one of the aforementioned risk factors had an increased cumulative risk for major and nonmajor bleeding, all-cause mortality, and stroke/non-CNS SE/MI than patients with no risk factors. However, an increasing number of risk factors did not result in an increased cumulative risk for major bleeding and stroke/non-CNS SE/MI in patients with NVAF.

Previous studies have demonstrated independent effects of each of these risk factors on safety and efficacy outcomes in patients with NVAF treated with DOACs, but these studies have not methodically evaluated the combined effects of these risk factors on effectiveness and safety outcomes.[9,11–13] Presently, we compared the independent and combined effects of these risk factors on effectiveness and safety outcomes compared with no risk factors. A majority of patients in the HiR group in the present study were elderly with renal impairment, while approximately one-quarter were elderly with low body weight. With these patients alone forming 15% of the total study cohort, it is evident that combinations of risk factors are not uncommon among patients with NVAF, and that their impact on treatment outcomes warrants investigation.

Of these risk factors, we found that advanced age and renal impairment, but not low body weight, were associated with increased risk for major bleeding. Similar findings from both the univariable and multivariable analyses underline the independent effects of advanced age and renal impairment on this outcome. Furthermore, in a multivariable analysis, we showed that patients with advanced age combined with renal impairment (HiR group) had an association with a significantly elevated risk of major bleeding versus patients in the LoR group. The finding that advanced age and renal

TABLE 2 Crude incidence (*n*, %) and incidence (events/100 patient-years) for safety and effectiveness outcomes by risk group (low, moderate, high, and very high)

	Low ①		Moderate ②③④		High ⑤⑥⑦		Very high ⑧	
	Incidence proportion, *n* (%)	Incidence, events/100 patient-years (95% CI)	Incidence proportion, *n* (%)	Incidence, events/100 patient-years (95% CI)	Incidence proportion, *n* (%)	Incidence, events/100 patient-years (95% CI)	Incidence proportion, *n* (%)	Incidence, events/100 patient-years (95% CI)
Safety outcomes	(*N* = 4299)		(*N* = 2816)		(*N* = 1574)		(*N* = 1134)	
Any bleeding	337 (7.8)	3.05 (2.72, 3.37)	270 (9.6)	3.82 (3.37, 4.28)	168 (10.7)	5.02 (4.26, 5.78)	121 (10.7)	5.46 (4.49, 6.43)
Major bleeding	91 (2.1)	0.79 (0.63, 0.95)	92 (3.3)	1.25 (1.00, 1.51)	60 (3.8)	1.72 (1.29, 2.16)	43 (3.8)	1.89 (1.32, 2.45)
Critical organ bleeding	38 (0.9)	0.33 (0.22, 0.43)	48 (1.7)	0.65 (0.47, 0.83)	26 (1.7)	0.74 (0.46, 1.03)	16 (1.4)	0.70 (0.36, 1.04)
Intracranial hemorrhage	35 (0.8)	0.30 (0.20, 0.40)	40 (1.4)	0.54 (0.37, 0.71)	24 (1.5)	0.68 (0.41, 0.96)	16 (1.4)	0.70 (0.36, 1.04)
Nonmajor bleeding	258 (6.0)	2.31 (2.03, 2.60)	189 (6.7)	2.65 (2.27, 3.03)	116 (7.4)	3.43 (2.81, 4.05)	80 (7.1)	3.58 (2.79, 4.36)
All-cause mortality	57 (1.3)	0.49 (0.36, 0.62)	140 (5.0)	1.88 (1.57, 2.19)	116 (7.4)	3.29 (2.69, 3.88)	117 (10.3)	5.08 (4.16, 6.00)
Effectiveness outcomes	(*N* = 4286)		(*N* = 2802)		(*N* = 1571)		(*N* = 1130)	
Stroke/non-CNS SE/MI	86 (2.0)	0.75 (0.59, 0.91)	118 (4.2)	1.61 (1.32, 1.90)	71 (4.5)	2.05 (1.57, 2.53)	52 (4.6)	2.29 (1.67, 2.91)
Stroke	79 (1.8)	0.69 (0.53, 0.84)	105 (3.7)	1.43 (1.16, 1.71)	57 (3.6)	1.64 (1.22, 2.07)	44 (3.9)	1.94 (1.36, 2.51)
Ischemic stroke	55 (1.3)	0.48 (0.35, 0.60)	82 (2.9)	1.12 (0.88, 1.36)	41 (2.6)	1.18 (0.82, 1.54)	34 (3.0)	1.49 (0.99, 2.00)
Hemorrhagic stroke	29 (0.7)	0.25 (0.16, 0.34)	27 (1.0)	0.37 (0.23, 0.50)	16 (1.0)	0.45 (0.23, 0.68)	10 (0.9)	0.44 (0.17, 0.71)
Non-CNS SE	2 (0.1)	0.02 (0.00, 0.04)	3 (0.1)	0.04 (0.00, 0.09)	3 (0.2)	0.09 (0.00, 0.18)	2 (0.2)	0.09 (0.00, 0.21)
MI	5 (0.1)	0.04 (0.01, 0.08)	12 (0.4)	0.16 (0.07, 0.25)	11 (0.7)	0.31 (0.13, 0.50)	6 (0.5)	0.26 (0.05, 0.47)
Stroke/non-CNS SE	81 (1.9)	0.70 (0.55, 0.86)	107 (3.8)	1.46 (1.19, 1.74)	60 (3.8)	1.73 (1.29, 2.17)	46 (4.1)	2.02 (1.44, 2.61)

Abbreviations: CI, confidence interval; CNS, central nervous system; MI, myocardial infarction; SE, systemic embolism.

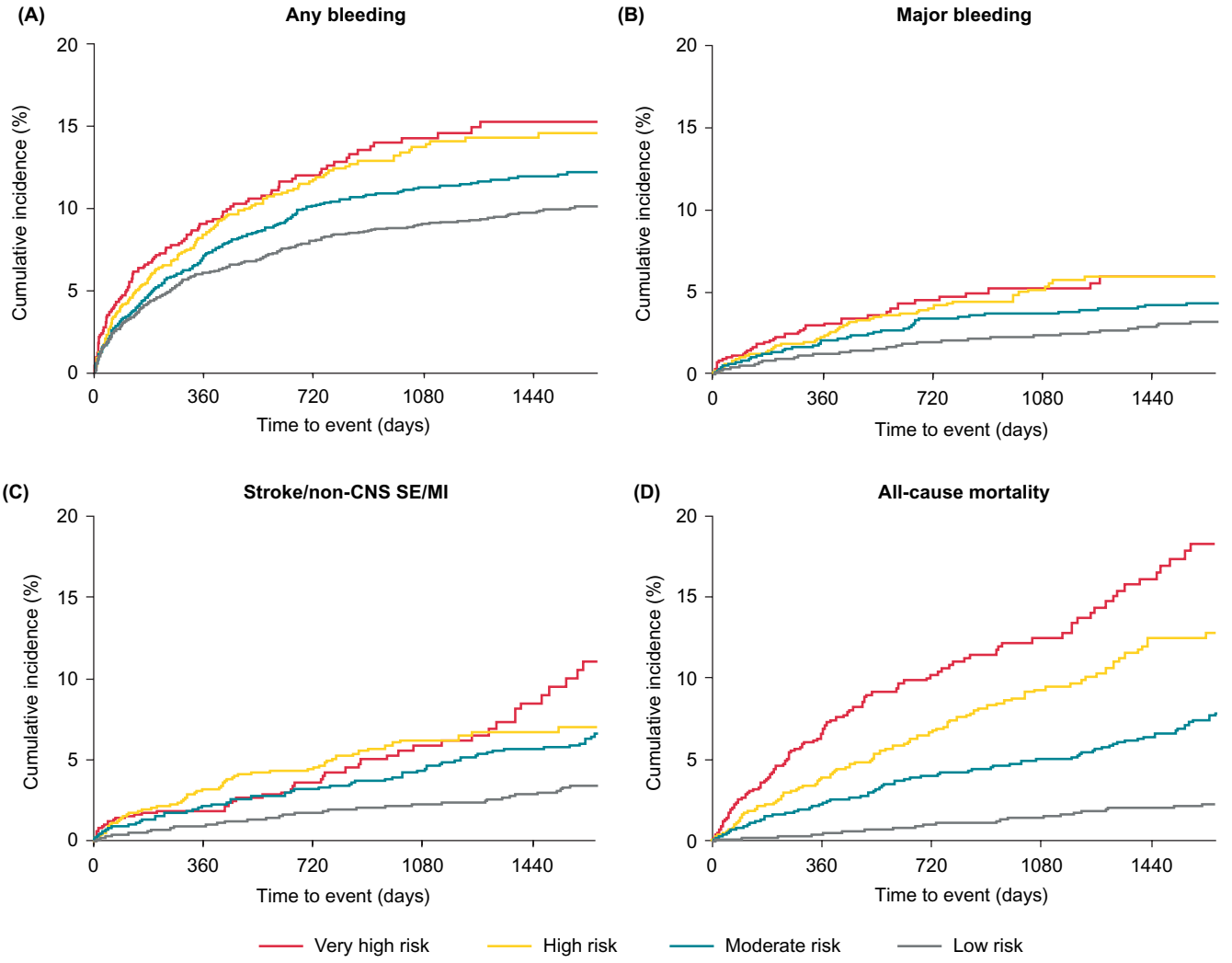

FIGURE 3 Cumulative incidence of (A) any bleeding, (B) major bleeding, (C) stroke/non-CNS SE/MI, and (D) all-cause mortality by risk group. CNS, central nervous system; MI, myocardial infarction; SE, systemic embolism

Major bleeding		Univariable analysis		Multivariable analysis	
Variables	n	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Low	4299	Reference		Reference	
Moderate	2816	1.58 (1.18, 2.11)	.002	1.62 (1.19, 2.21)	.002
High	1574	2.05 (1.48, 2.84)	<.001	2.15 (1.47, 3.15)	<.001
Very high	1134	2.21 (1.54, 3.18)	<.001	2.49 (1.60, 3.87)	<.001
Stroke/non-CNS SE/MI		Univariable analysis		Multivariable analysis	
Variables	n	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Low	4286	Reference		Reference	
Moderate	2802	2.15 (1.63, 2.84)	<.001	1.98 (1.47, 2.66)	<.001
High	1571	2.65 (1.94, 3.63)	<.001	2.29 (1.59, 3.29)	<.001
Very high	1130	2.92 (2.07, 4.13)	<.001	2.74 (1.81, 4.16)	<.001

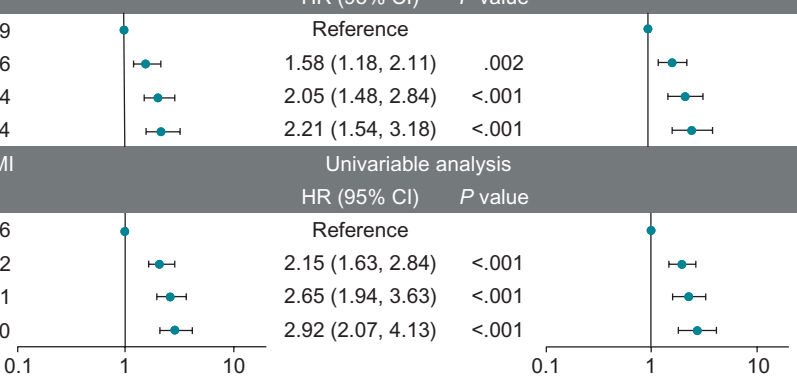

FIGURE 4 Univariable and multivariable analysis for risk of major bleeding and stroke/non-CNS SE/MI by risk group (low, moderate, high, and very high). Multivariable analysis adjusted by sex, initial dose, hypertension, diabetes mellitus, congestive heart failure, prior ischemic stroke/TIA, vascular disease, hepatic dysfunction, and oral antiplatelet use at study enrollment. CI, confidence interval; CNS, central nervous system; HR, hazard ratio; MI, myocardial infarction; SE, systemic embolism; TIA, transient ischemic attack

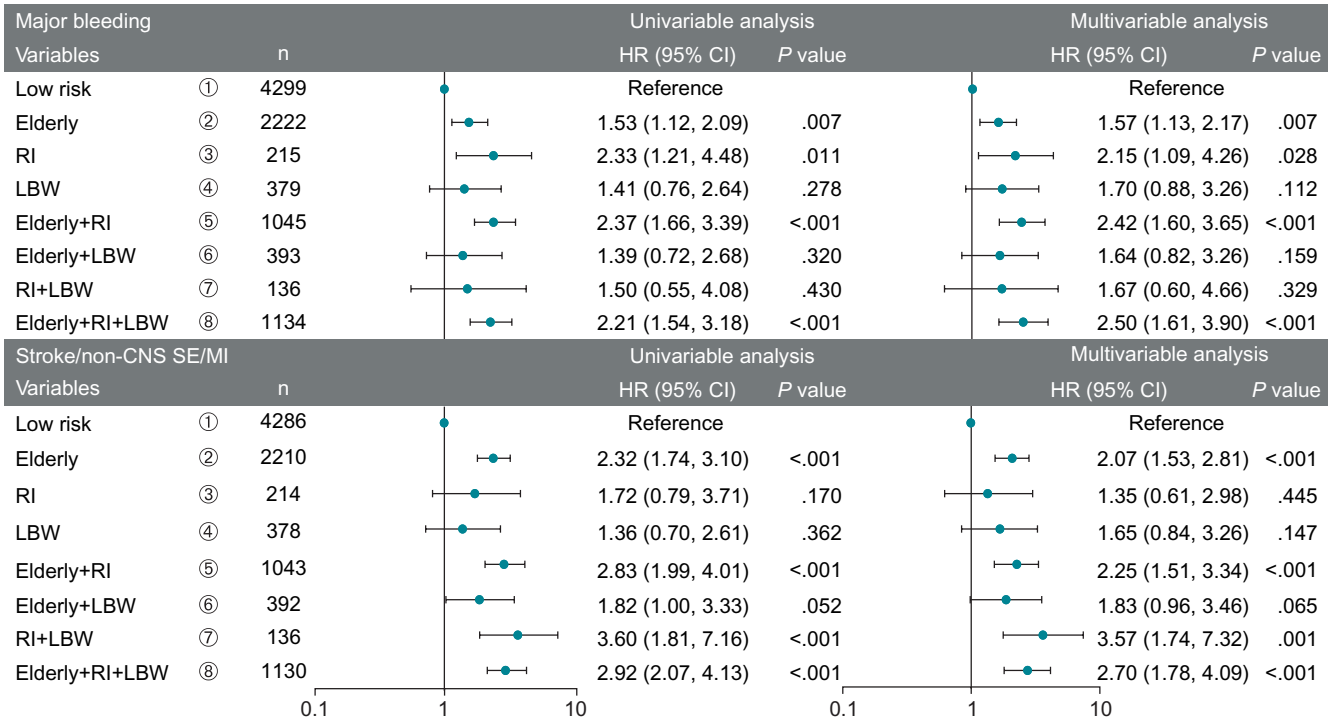

FIGURE 5 Univariable and multivariable analysis for risk of major bleeding and stroke/non-CNS SE/MI by risk factor (age ≥75 years [elderly], renal impairment [CrCl <50 ml/min], and low body weight [≤50 kg]). Multivariable analysis adjusted by sex, initial dose, hypertension, diabetes mellitus, congestive heart failure, prior ischemic stroke/TIA, vascular disease, hepatic dysfunction, and oral antiplatelet use at study enrollment. 1. Low-risk group = 0 risk factors; 2. Moderate-risk group = 1 risk factor (age ≥75 years); 3. Moderate-risk group = 1 risk factor (CrCl <50 ml/min); 4. Moderate-risk group = 1 risk factor (weight ≤50 kg); 5. High-risk group = 2 risk factors (age ≥75 years + CrCl <50 ml/min); 6. High-risk group = 2 risk factors (age ≥75 years + weight ≤50 kg); 7. High-risk group = 2 risk factors (CrCl <50 ml/min + weight ≤50 kg); 8. Very-high-risk group = 3 risk factors (age ≥75 years + CrCl <50 ml/min + weight ≤ 50 kg). CI, confidence interval; CNS, central nervous system; CrCl, creatinine clearance; HR, hazard ratio; LBW, low body weight; MI, myocardial infarction; RI, renal impairment; SE, systemic embolism; TIA, transient ischemic attack

impairment are determinants for major bleeding events in patients with AF receiving DOACs is in line with results from subgroup analyses of the J-ROCKET AF study, a randomized controlled clinical trial that compared the efficacy and safety of rivaroxaban versus warfarin.[20] Analysis of the J-ROCKET AF study revealed that elderly (≥75 years of age) rivaroxaban-treated patients exhibited a higher event rate (%/year) for all clinically relevant bleeding events (25.05) compared with younger patients (14.18).[9] Comparatively, the risk of the primary efficacy outcome of stroke with non-CNS SE did not change between age subgroups.[9] In a separate sub-analysis of the J-ROCKET AF study by renal impairment, patients with moderate renal impairment (CrCl 30–49 ml/min), all of whom were prescribed rivaroxaban 10 mg, had increased incidence of major bleeding events (events [%]/year) (5.09) than patients with preserved renal function (2.47).[11] Together, these data suggest that advanced age and renal impairment may confer an additional risk for major bleeding events among patients with NVAF receiving rivaroxaban.[20]

Certain limitations apply to the interpretation of findings from randomized controlled trials such as J-ROCKET AF, because of the limited number of participants and the exclusion of patients considered at HiR (e.g., with comorbid conditions). Furthermore, the trials were not devised to specifically evaluate the safety and efficacy of the DOACs when used to treat NVAF in special populations. Therefore, the exploratory results from these sub-analyses should only be regarded as hypothesis-generating.

The XAPASS aimed to assess the safety and effectiveness of rivaroxaban in Japanese patients with NVAF in a real-world setting.[17] Low reported incidences of treatment-emergent adverse events after 12 months of follow-up in a cohort of 9578 patients to support the assertion that rivaroxaban is well tolerated and is suitable for preventative treatment against stroke onset in patients with NVAF.[19] Compared with the randomized controlled J-ROCKET AF study, the study population included in this XAPASS *post-hoc* analysis was more diverse with respect to demographic characteristics, with a higher proportion of patients who were elderly, had renal impairment, and had low body weight. The demographic diversity inherent to the XAPASS study, therefore, imparts the dataset with a greater suitability for evaluating the potential associations between various risk factors and safety outcomes in patients treated with rivaroxaban than data from the J-ROCKET AF study. The finding in our analysis that patients with NVAF receiving rivaroxaban in a clinical setting who were elderly, had renal impairment, or had low body weight were at higher risk of bleeding events, all-cause mortality, and stroke/non-CNS SE/MI than patients with none of these risk factors

is not unexpected. Indeed, similar findings had been reported from the EXPAND study, a study in patients with NVAF who received treatment with rivaroxaban at dosages set according to Japanese approval. In a multivariable analysis of the EXPAND study involving 7141 participants, elderly (≥65 years of age) patients presented with an increased risk of major bleeding compared with younger patients, supporting a body of evidence that suggests that advanced age is an independent determinant for major bleeding in this context.[12] In addition, renal impairment (CrCl 30–49 ml/min and <30 ml/min) was also an independent determinant for major bleeding.[12] However, unlike the present study, no significant impact of advanced age or renal impairment on the incidence of stroke/SE was found. The proportion of patients who had a $CHADS_2$ score ≤1 (37.3%) in EXPAND was similar to that in the XAPASS (36.2%)[17] and may be considered representative of real-world patients with AF receiving rivaroxaban.

Nevertheless, we found that among patients with NVAF recruited to the XAPASS who received rivaroxaban, there was no significant association between an increasing number of risk factors and a higher incidence of major bleeding and stroke. This finding is reassuring, as it supports the safety profile of rivaroxaban when administered to patients included in the HiR and vHiR groups in our study.

We did not find an independent effect of low body weight on risk for major bleeding events or stroke/non-CNS SE/MI in patients enrolled in the XAPASS. A higher incidence of major bleeding events and ischemic stroke was reported in an observational cohort study involving Korean patients with AF receiving DOACs who were elderly (≥75 years of age) and had low body weight (≤50 kg).[21] A relatively common characteristic of Asian patient populations is low body weight, typically found with comorbidities, such as advanced age, renal impairment, and frailty; together, these may increase the risk of bleeding and thromboembolic events.

To summarize, the observations presented here underline the impact that the clinical risk factors of advanced age, renal impairment, and low body weight have on clinical safety and effectiveness outcomes in patients with NVAF receiving rivaroxaban in a real-world setting. These observations are generally in line with findings from the subgroup analyses of the EXPAND and J-ROCKET AF studies. Furthermore, safety and effectiveness outcomes of patients in the HiR and vHiR groups in the present study were comparable to those of equivalent populations in prior analyses. Differences in outcomes between study findings may be due to variations in patient populations and the methodologies used. For example, approximately 24% of patients were underdosed with rivaroxaban in the EXPAND study,[12] whereas, in the LoR, MoR, and HiR groups in the present study, 21.6%, 49.8%, and 16.8% of patients with CrCl >50 ml/min, respectively, experienced underdosing with rivaroxaban. Due to its design, the ROCKET-AF phase 3 clinical study had conservative eligibility criteria which did not apply to the XAPASS sub-analysis.

This XAPASS sub-analysis has some limitations. In common with most observational studies, the XAPASS did not have a control arm. The safety and effectiveness outcomes of rivaroxaban treatment in this study cannot be directly compared with those of other DOACs, such as warfarin.[19] There was also a relatively high proportion of patients who were taking a lower dose of rivaroxaban than recommended for Japanese patients in this study, especially in the MoR group. We acknowledge that this may have overestimated the event rate for stroke/non-CNS SE/MI, but may have underestimated the rate for major bleeding. Approximately 23% of patients were lost to follow-up over the 5-year timeframe of the present study; reasons for loss to follow-up were not collected as part of the study and we are, therefore, unable to provide further insight into these patients. We acknowledge that the exclusion of data from patients lost to follow-up may have affected the final interpretation of event incidence; however, with the limited duration of treatment, different incidences and predictive factors may have become evident with a longer treatment duration. Furthermore, in the multivariable analyses, there were very few patients and events in certain groups (e.g., renal impairment plus low body weight, and advanced age plus low body weight), which could have possibly affected the findings. Notwithstanding such limitations, it is evident that the conclusions made following completion of this sub-analysis could aid physicians when deciding to prescribe rivaroxaban, particularly for patients with the associated risk factors of advanced age, renal impairment, and low body weight.

5 | CONCLUSIONS

This real-world study of rivaroxaban-treated Japanese patients with NVAF showed that Age ≥75 years and renal impairment, but not low body weight, were determinants for major bleeding. The accumulation of three risk factors was associated with risk for major bleeding and stroke/non-CNS SE/MI. Particular management of NVAF treatment in patient populations that exhibit one or more of these risk factors is, therefore, recommended.

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CONFLICT OF INTEREST

T. Ikeda, S. Ogawa, T. Kitazono, J. Nakagawara, K. Minematsu, S. Miyamoto, and Y. Murakawa were advisory board members for Bayer Yakuhin. T. Ikeda received research grants from Daiichi Sankyo, Medtronic, and Japan Lifeline, and lecture fees from Bayer Yakuhin, Bristol Myers Squibb, Ono, and Toa Eiyo. T. Kitazono received a research grant from Bayer Yakuhin. J. Nakagawara received a research grant from Nihon Medi-Physics. K. Minematsu received lecture fees from Astellas, AstraZeneca, Bayer Yakuhin, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Japan Stryker, Kowa, Mitsubishi Tanabe, Nihon Medi-Physics, Nippon Chemiphar, Otsuka, Pfizer, Sawai, and Sumitomo Dainippon, and

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DISCLOSURE

The XAPASS study is registered in the ClinicalTrials.gov database (ClinicalTrials.gov identifier: NCT01582737). To avoid compromising patient confidentiality, we are unfortunately unable to publicly release the dataset analyzed for this manuscript. This decision is compliant with the Ethical Guidelines for Medical and Health Research Involving Human Subjects, and with the GPSP, two guidelines set by the Japanese MHLW. This study conformed to the provisions of the Declaration of Helsinki. Ethical approval or written informed consent from patients for the XAPASS was not necessary under current GPSP standards.

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SUPPORTING INFORMATION

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