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Original article

Real-world outcomes of the Xarelto Post-Authorization Safety & Effectiveness Study in Japanese Patients with Atrial Fibrillation (XAPASS)

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ABSTRACT

Background: Although the efficacy and safety of the factor Xa inhibitor rivaroxaban for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) were shown in global and Japanese phase III clinical trials, safety and effectiveness data from unselected patients in everyday clinical practice are limited. The objective of the XAPASS (Xarelto Post-Authorization Safety & Effectiveness Study in Japanese Patients with Atrial Fibrillation) is to investigate the safety and effectiveness of rivaroxaban in Japanese real-world clinical practice.

Methods: The XAPASS is a prospective, single-arm, real-world observational study mandated by the Japanese authority as post-marketing surveillance. In total, 11,308 patients with NVAF who began treatment with rivaroxaban were enrolled from April 2012 to June 2014, and 9578 patients were analyzed to examine the one-year outcomes.

Results: The mean treatment duration was 300 ± 119 days. The patients' age was 73.2 ± 9.8 years, and their $CHADS_2$ score was 2.2 ± 1.3. Any bleeding and major bleeding occurred in 602 patients (7.6 events per 100 patient-years) and 143 patients (1.8 events per 100 patient-years), respectively. Stroke/non-central nervous system systemic embolism/myocardial infarction was observed in 144 patients (1.8 events per 100 patient-years).

Conclusions: Real-world outcomes of the XAPASS showed incidence rates of major bleeding and thromboembolic events, suggesting that rivaroxaban is safe and effective in Japanese daily clinical practice (Clinicaltrials.gov: NCT01582737).

Introduction

Atrial fibrillation (AF) is the most common arrhythmia [1], and its prevalence is higher in the elderly population [2,3]. Based on the finding that the risk of stroke is 4–5-fold higher in patients with

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than without AF [4], clinical guidelines recommend anticoagulation for patients with AF according to their $CHADS_2$ score [5–7]. Although dose-adjusted vitamin K antagonists have been used for stroke prevention in patients with AF, they have clinical limitations such as drug/food interactions and the need for frequent coagulation monitoring. Since 2011, four non-vitamin K antagonist oral anticoagulants (NOACs) have been approved for the prevention of stroke and systemic embolism (SE) in patients with non-valvular AF (NVAF) in Japan. These NOACs are now widely used in daily clinical practice because of their rapid onset of action, no requirement for dose adjustment, and few drug and food interactions.

The direct factor Xa inhibitor rivaroxaban is one of these NOACs, and its efficacy and safety compared with vitamin K antagonists were evaluated in global and Japanese phase III clinical trials (Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET AF] [8]; Japanese Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [J-ROCKET AF] [9]). Generally, phase III clinical trials are strictly designed for the purpose of approval by the regulatory authorities, and the patients enrolled in these trials tend to be restricted. Because a broad range of patients is possibly medicated after approval, the safety and effectiveness of these drugs in daily clinical practice should be examined by post-marketing studies.

The Xarelto Post-Authorization Safety & Effectiveness Study in Japanese Patients with Atrial Fibrillation (XAPASS) is a prospective, single-arm, real-world observational study mandated by the Japanese regulatory authority as post-marketing surveillance [10]. We herein report the one-year results of the XAPASS, which was performed to examine the safety and effectiveness of rivaroxaban in Japanese real-world clinical practice.

Methods

The XAPASS (NCT01582737) was an open-label, single-arm, observational, non-interventional cohort study. This post-marketing surveillance study was approved by the Ministry of Health, Labour and Welfare (MHLW) and was carried out in accordance with the standards for Good Post-marketing Study Practice provided by the MHLW in Japan. The detailed design has been published previously [10].

Patient population

Men and women with NVAF starting rivaroxaban therapy to reduce the risk of stroke/SE were enrolled. Contraindications to rivaroxaban therapy were considered according to the Japanese package insert.

Drug administration

In Japan, rivaroxaban is approved at a dosage of 15 mg once daily (od) for patients with a creatinine clearance (CrCl) of $\geq$50 ml/min and 10 mg od for patients with a CrCl of $<$50 ml/min. In the XAPASS, the dosage (15 or 10 mg od) and treatment duration were determined at the physician's discretion.

Study outcomes

The primary safety outcome was a composite of major bleeding, defined using the International Society on Thrombosis and Haemostasis (ISTH) criteria, and non-major bleeding. The primary effectiveness outcome was stroke (ischemic or hemorrhagic), non-central nervous system (non-CNS) SE, or myocardial infarction (MI). Outcomes were recorded as adverse events. Intracerebral bleeding was counted as both stroke and major bleeding events. Transient ischemic attack (TIA) was not included in stroke endpoint. The secondary outcomes were all-cause mortality and the rates of adverse events across patients with different baseline risk profiles ($CHADS_2$ score, CHA_2DS_2-VASc score, or modified HAS-BLED score) or with different rivaroxaban doses (15 or 10 mg). The modified HAS-BLED score was calculated by the following eight factors: hypertension, abnormal renal function, abnormal liver function, stroke, bleeding, age of $>$65 years, medication use, and alcohol use; the labile international normalized ratio (INR) was excluded from the HAS-BLED score in this study.

Statistical analysis

To examine the one-year outcomes, the maximum 365-day data from patients who completed follow-up for at least 11 months, who discontinued rivaroxaban treatment within one year, or who were lost to follow-up (including patient transfer) within one year as of September 2017 were analyzed. Patients who discontinued rivaroxaban treatment were followed up until 30 days after discontinuation. Continuous variables and frequency or percentage of categorical variables are presented as mean $\pm$ standard deviation. Events are presented as both raw incidence proportions (patients with events/patients in each analysis set) and incidence rates (patients with events per 100 patient-years) with the corresponding 95% confidence interval. Kaplan–Meier plots were created to show the time course up to the first event of interest.

Administrative organization

The XAPASS is a post-marketing surveillance study funded by Bayer Yakuhin, Ltd. (Osaka, Japan). The steering committee (Online Appendix A) and Bayer Yakuhin, Ltd. developed the protocol and case report form, provided oversight of the study execution, and were accountable for analysis of the results and publications. Operation of the study was performed by Bayer Yakuhin, Ltd.

Results

Patient characteristics

In total, 11,308 Japanese patients with NVAF who were newly prescribed rivaroxaban were enrolled from April 2012 to June 2014. Among them, 9578 and 9543 patients were included in the safety analysis and effectiveness analysis for the one-year results, respectively (Fig. 1). The mean treatment period was 300 $\pm$ 119 days (median, 365 days; maximum, 365 days), and

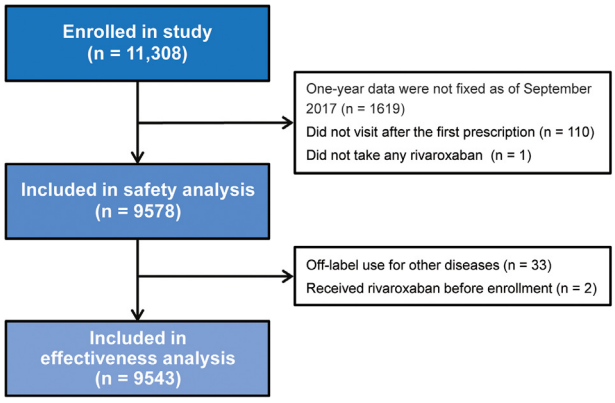


Fig. 1. Study flow chart.

Table 1
Patient characteristics.

Characteristic	All patients (*N* = 9,578)
Age, years	73.2 ± 9.8
Age, years	
<75	4,893 (51.1)
≥75	4,685 (48.9)
Female sex	3,657 (38.2)
Height, cm	160.1 ± 9.8
Body weight, kg	61.4 ± 13.1
Body weight, kg	
≤50	1,865 (19.5)
>50	7,028 (73.4)
Unknown	685 (7.2)
BMI, kg/m^2	23.9 ± 4.1
BMI, kg/m^2	
<18.5	542 (5.7)
18.5 to <25	4,410 (46.0)
25 to <30	2,167 (22.6)
≥30	499 (5.2)
Unknown	1,960 (20.5)
CrCl, ml/min	67.8 ± 29.4
CrCl, ml/min	
<15	3 (<0.1)
15 to <30	269 (2.8)
30 to <50	2,011 (21.0)
50 to <80	4,065 (42.4)
≥80	2,456 (25.6)
Unknown	774 (8.1)
Baseline comorbidities	
Hypertension	7,179 (75.0)
Diabetes mellitus	2,139 (22.3)
Prior stroke/TIA	2,245 (23.4)
Congestive heart failure	2,378 (24.8)
Type of AF	
Paroxysmal	3,221 (33.6)
Persistent	3,426 (35.8)
Permanent	2,343 (24.5)
Other	22 (0.2)
Unknown	566 (5.9)
Concomitant use of antiplatelet(s)	
No	8,043 (84.0)
Yes	1,455 (15.2)
Single antiplatelet	942 (9.8)
More than two antiplatelets	513 (5.4)
Prior use of antithrombotics	
No	3,507 (36.6)
Yes	6,068 (63.4)
Warfarin	3,366 (35.1)
Dabigatran	1,501 (15.7)
Apixaban	21 (0.2)
Edoxaban	3 (<0.1)
Aspirin	967 (10.1)
Clopidogrel	250 (2.6)
Cilostazol	98 (1.0)
Ticlopidine	42 (0.4)
Other	285 (3.0)
Unknown	3 (<0.1)
Reason for switching from (or adding rivaroxaban to) the prior antithrombotics	
Unstable INR	1,740 (18.2)
Patient's intention	1,217 (12.7)
Lack of effectiveness	1,098 (11.5)
Poor compliance	1,035 (10.8)
Adverse event	715 (7.5)
Other	961 (10.0)

Data are presented as n (%) or mean ± standard deviation.
BMI, body mass index; CrCl, creatinine clearance; TIA, transient ischemic attack; AF, atrial fibrillation; INR, international normalized ratio.

outpatients constituted 84.6% of all patients. In this analysis, 6276 patients continued rivaroxaban treatment, 1892 patients were lost to follow-up (including patient transfer), and 1410 patients discontinued rivaroxaban treatment (Online Table 1). Interruption of rivaroxaban was reported in 341 patients (3.6%) for reasons such as surgery (132 patients) and adverse events (121 patients).

Patient characteristics are summarized in Table 1. Their mean age was 73.2 ± 9.8 years, and female patients constituted 38.2%. Patients aged ≥75 years, patients with a body weight of ≤50 kg, and patients with a CrCl of <50 ml/min constituted 48.9%, 19.5%, and 23.8%, respectively. With respect to baseline comorbidities, 75.0% of patients had hypertension, 22.3% had diabetes mellitus, 23.4% had prior stroke/TIA, and 24.8% had congestive heart failure. The mean $CHADS_2$ score was 2.2 ± 1.3, the mean CHA_2DS_2-VASc score was 3.4 ± 1.6, and the mean modified HAS-BLED score was 1.5 ± 1.0 (Table 2). The maximum modified HAS-BLED score was 8 because of exclusion of the labile INR as a factor (this factor is used for warfarin users). Patients diagnosed with paroxysmal AF constituted 33.6%, patients with persistent AF constituted 35.8%, and patients with permanent AF constituted 24.5%. Concomitant use of antiplatelet(s) was recorded in 1455 (15.2%) patients, including 942 (9.8%) patients prescribed a single antiplatelet and 513 patients (5.4%) prescribed more than two antiplatelets. During the 30 days before starting rivaroxaban, 63.4% of patients had used antithrombotics such as warfarin (35.1%), dabigatran (15.7%), and aspirin (10.1%). The reasons for switching from or adding rivaroxaban to the prior antithrombotics included an unstable INR (18.2%), patient's intention (12.7%), lack of effectiveness (11.5%), poor compliance (10.8%), and occurrence of adverse events (7.5%).

Fig. 2 shows that 89.1% of patients with a CrCl of <50 ml/min received 10 mg od of rivaroxaban and that 64.2% of patients with a CrCl of ≥50 ml/min received 15 mg od of rivaroxaban as the recommended dose, whereas 10.9% of patients with a CrCl of <50 ml/min were prescribed 15 mg od of rivaroxaban (over-dose) and 35.8% of patients with a CrCl of ≥50 ml/min were prescribed 10 mg od of rivaroxaban (under-dose). The reasons for the under-

Table 2
Patient risk scores.

Risk score	All patients (*N* = 9578)
$CHADS_2$ score	2.2 ± 1.3
Score	
0	842 (8.8)
1	2333 (24.4)
2	2903 (30.3)
3	1876 (19.6)
4	1106 (11.5)
5	428 (4.5)
6	90 (0.9)
CHA_2DS_2-VASc score	3.4 ± 1.6
Score	
0	258 (2.7)
1	908 (9.5)
2	1633 (17.0)
3	2246 (23.4)
4	2158 (22.5)
5	1379 (14.4)
6	700 (7.3)
7	250 (2.6)
8	44 (0.5)
9	2 (<0.1)
Modified HAS-BLED score[a]	1.5 ± 1.0
Score	
0	1211 (12.6)
1	3941 (41.1)
2	3008 (31.4)
3	1151 (12.0)
4	238 (2.5)
5	26 (0.3)
6	1 (<0.1)
7	0 (0)
8	0 (0)

Data are presented as *n* (%) or mean ± standard deviation.
[a] Maximum score is 8 because of the exclusion of the factor "labile international normalized ratio" from the HAS-BLED score.

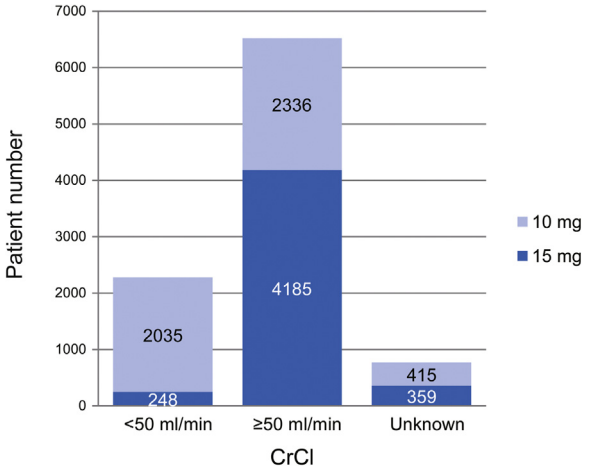


Fig. 2. Creatinine clearance and dosing. CrCl, creatinine clearance.

dosed prescription included a high bleeding risk (1067 patients), old age (633 patients), renal impairment (457 patients), low body weight (72 patients), concomitant drug use (41 patients), patient's intention (21 patients), female sex (17 patients), and low $CHADS_2$ score (10 patients). Some patients had multiple reasons for underdosing.

Real-world outcomes

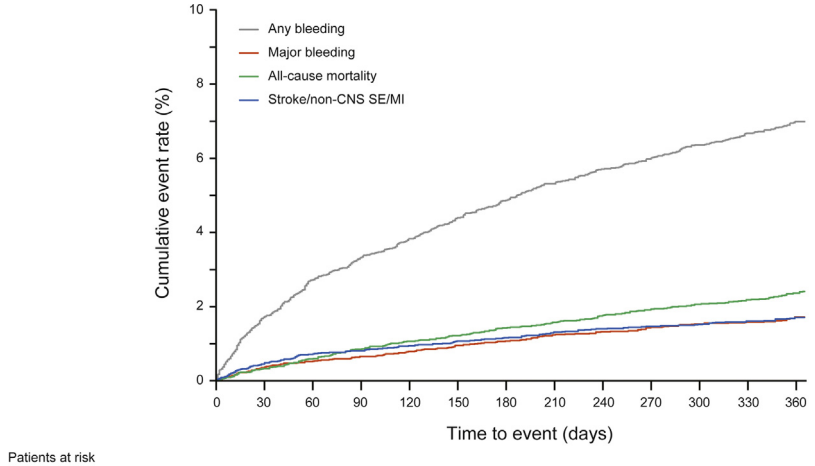
The cumulative event rate of any bleeding, major bleeding, all-cause mortality and the primary effectiveness outcome [stroke (ischemic or hemorrhagic), non-CNS SE, or MI] increased over time (Fig. 3). Table 3 shows that any bleeding, major bleeding, and non-major bleeding occurred in 602 patients (6.3%, 7.6 events per 100 patient-years), 143 patients (1.5%, 1.8 events per 100 patient-years), and 473 patients (4.9%, 6.0 events per 100 patient-years), respectively. The incidence of all-cause mortality was 2.5 events per 100 patient-years. Adverse events leading to death are listed in Online Table 2. Death caused by adverse drug reaction occurred in 27 patients (0.3%, 0.3 events per 100 patient-years). All adverse events are listed in Online Table 3. Among 9543 patients, the primary effectiveness outcome (stroke/non-CNS SE/MI) occurred in 144 patients (1.5%, 1.8 events per 100 patient-years), and stroke/non-CNS SE occurred in 132 patients (1.4%, 1.6 events per 100 patient-years). A total of 128 patients had stroke (1.3%, 1.6 events per 100 patient-years), 91 had ischemic stroke (1.0%, 1.1 events per 100 patient-years), 42 had hemorrhagic stroke (0.4%, 0.5 events per 100 patient-years), 5 had non-CNS SE (0.1%, 0.1 events per 100 patient-years), and 12 had MI (0.1%, 0.1 events per 100 patient-years). The rates of major bleeding and stroke/non-CNS SE/MI in patients with a CrCl of ≥50 ml/min who were prescribed 15 mg od were 1.5 and 1.3 events per 100 patient-years, respectively. These incidence rates in patients with a CrCl of ≥50 ml/min who were prescribed 10 mg od were 1.3 and 1.8 events per 100 patient-years, respectively. Any bleeding, major bleeding and stroke/non-CNS SE/MI increased with higher $CHADS_2$, CHA2DS2-VASc, and modified HAS-BLED risk scores (Fig. 4A–C).

Discussion

The XAPASS is a prospective real-world study designed to examine the safety and effectiveness of rivaroxaban for stroke/SE prevention in a large number and broad range of patients with NVAF, including patients with a $CHADS_2$ score of 0 or 1 who were not enrolled in phase III clinical trials. In total, 11,308 patients with NVAF who were newly prescribed rivaroxaban were enrolled, making the XAPASS one of the largest AF registries in Japan. This paper shows the one-year results of 9578 patients.

Patient population

The patient population in the XAPASS was clearly different from that in the Japanese phase III trial J-ROCKET AF [9]. Patients with a low risk of stroke ($CHADS_2$ score of 0 or 1) were not enrolled in the J-ROCKET AF; conversely, the XAPASS included patients with a $CHADS_2$ score of 0 (8.8%) and 1 (24.4%). The percentages of male patients (61.8% vs. 80.6%), patients with an age of <75 years (51.1% vs. 61.0%), and patients with baseline comorbidities such as diabetes mellitus (22.3% vs. 38.0%), and congestive heart failure (24.8% vs. 40.8%) were lower in the XAPASS than in the J-ROCKET AF. Patients with prior stroke/TIA constituted 23.4% in the XAPASS, while 63.6% of patients had prior stroke/TIA/SE in J-ROCKET AF. The patient characteristics including age, body weight, CrCl, baseline



Patients at risk													
Any bleeding	9578	9105	8751	8504	8286	8080	7847	7571	7386	7260	7132	7017	6764
Major bleeding	9578	9219	8922	8694	8492	8303	8079	7805	7630	7504	7383	7277	7023
All-cause mortality	9578	9248	8949	8726	8529	8351	8129	7857	7682	7558	7437	7331	7079
Stroke/non-CNS SE/MI	9543	9180	8881	8658	8458	8273	8052	7780	7606	7483	7364	7258	7004

Fig. 3. Cumulative rates of any bleeding, major bleeding, all-cause mortality, and stroke/non-CNS SE/MI. The incidence rates of any bleeding, major bleeding, all-cause mortality, and stroke/non-CNS SE/MI were 7.62, 1.76, 2.48, and 1.78 events per 100 patient-years, respectively. MI, myocardial infarction; non-CNS SE, non-central nervous system systemic embolism.

Table 3
Study outcomes.

Safety outcome	*N* = 9578	
	Incidence proportion, *n* (%)	Incidence rate, event per 100 patient-years (95% CI)
Any bleeding	602 (6.3)	7.6 (7.0–8.2)
Major bleeding	143 (1.5)	1.8 (1.5–2.1)
Fatal	15 (0.2)	0.2 (0.1–0.3)
Critical organ bleeding	65 (0.7)	0.8 (0.6–1.0)
Intracranial hemorrhage	58 (0.6)	0.7 (0.5–0.9)
Hemoglobin decrease ≥2 g/dl	50 (0.5)	0.6 (0.4–0.8)
Transfusion of ≥2 units of packed red blood cells or whole blood	19 (0.2)	0.2 (0.1–0.3)
Non-major bleeding	473 (4.9)	6.0 (5.4–6.5)
All-cause mortality	202 (2.1)	2.5 (2.1–2.8)
Effectiveness outcome	***N* = 9543**	
	Incidence proportion, *n* (%)	Incidence rate, event per 100 patient-years (95% CI)
Stroke/non-CNS SE/MI	144 (1.5)	1.8 (1.5–2.1)
Stroke	128 (1.3)	1.6 (1.3–1.9)
Ischemic stroke	91 (1.0)	1.1 (0.9–1.4)
Hemorrhagic stroke	42 (0.4)	0.5 (0.4–0.7)
Non-CNS SE	5 (0.1)	0.1 (0.0–0.1)
MI	12 (0.1)	0.1 (0.1–0.2)
Stroke/non-CNS SE	132 (1.4)	1.6 (1.4–1.9)

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

comorbidities, and risk scores in the XAPASS were similar to those observed in another Japanese real-world study of rivaroxaban, the EXPAND study [11,12]. These similarities suggest that the XAPASS and EXPAND study reflect the prescription pattern of rivaroxaban in Japanese real-world clinical practice. In contrast to the XAPASS, which included 11,308 patients newly prescribed rivaroxaban, 1740 patients of the EXPAND study were newly prescribed rivaroxaban, indicating that the XAPASS reinforces the real-world evidence in new users of rivaroxaban.

Study outcomes

The incidence of major bleeding in patients in the XAPASS was numerically lower than that in patients treated with rivaroxaban in the phase III J-ROCKET AF (1.8 vs. 3.0 events per 100 patient-years, respectively). Although the mean $CHADS_2$ score was lower in the XAPASS than in the J-ROCKET AF, the incidence rates of stroke/non-CNS SE were similar (1.6 vs. 1.3 events per 100 patient-years). These results might be explained by the under-dosed prescription in the XAPASS, in which the rivaroxaban dose was determined at the physician's discretion. The incidence rates of major bleeding and stroke/SE were similar to those seen in the EXPAND study (1.2 and 1.0 events per 100 patient-years, respectively). J-RHYTHM Registry 2 [13] and Fushimi AF Registry [14] reported the real-world outcomes in Japanese patients with AF. These studies suggested that NOACs were not associated with major bleeding or thromboembolic events compared with warfarin. Considering the differences in patient characteristics, anticoagulant therapy, and follow-up period, the overall incidence rates in J-RHYTHM registry 2 (1.0 major bleeding event per 100 patient-years and 0.9 symptomatic ischemic stroke/TIA/SE events per 100 patient-years) and Fushimi AF Registry (1.8 major bleeding events per 100 patient-years and 2.3 stroke/SE events per 100 patient-years) were similar with those in the XAPASS. The number of patients prescribed NOACs was limited in these previous studies (923 patients and 545 patients, respectively). The XAPASS added evidence for the NOAC use in a larger number of real-world patients.

The incidence proportion of all-cause mortality was higher in the XAPASS (202 patients, 2.1%) than J-ROCKET AF (7 patients, 1.1%). Possible reasons are higher mean age in the XAPASS and stricter exclusion criteria of J-ROCKET AF. For example, J-ROCKET AF excluded patients with a serious concomitant illness associated with a life expectancy <2 years, but the XAPASS did not. The deaths caused by adverse drug reaction in the XAPASS occurred in 27 patients, including 15 patients who died from bleeding events. These results suggest that most of the deaths observed in the XAPASS were not associated with anticoagulation.

This paper also shows the outcomes among patients with a low risk of stroke who were not included in the phase III trials (Fig. 4). The incidence rates of major bleeding and thromboembolic events were low in patients with a $CHADS_2$ score of 0 or 1, and they gradually increased in patients with higher $CHADS_2$ scores. Patients with higher CHA_2DS_2-VASc scores or modified HAS-BLED scores also showed increased rates of both major bleeding and thromboembolic events. Therefore, careful assessment of the risk of stroke and bleeding is required in such high-risk patients. Outcomes in patients with bleeding risks such as patients with old age, low body weight, renal impairment, or prior stroke/TIA will be investigated in future subanalyses.

Dose of rivaroxaban

Rivaroxaban at 15 mg od for patients with a CrCl of ≥50 ml/min and 10 mg od for patients with a CrCl <50 ml/min are the recommended dose in Japan, and they are lower than those recommended in other countries (20 mg od for patients with a CrCl of ≥50 ml/min and 15 mg od for patients with a CrCl <50 ml/min). The Japanese dose was determined according to the difference in drug exposure between Japanese and Caucasians [15,16] and lower INR targets recommended by Japanese guidelines [7] and was evaluated in the phase III J-ROCKET AF conducted in Japan [9]. In the XAPASS, 27.0% of patients were prescribed a non-recommended dose of rivaroxaban because the dose and treatment duration were determined at the physician's discretion. In particular, 35.8% of patients with a CrCl of ≥50 ml/min were prescribed 10 mg of rivaroxaban (under-dose), suggesting that Japanese physicians were concerned about bleeding and chose a lower dose in consideration of not only the CrCl but also other risk factors. This paper describes the event rates in patients with a CrCl of ≥50 ml/min who were prescribed the recommended dose (15 mg od) and an under-dose (10 mg od) of rivaroxaban; however,

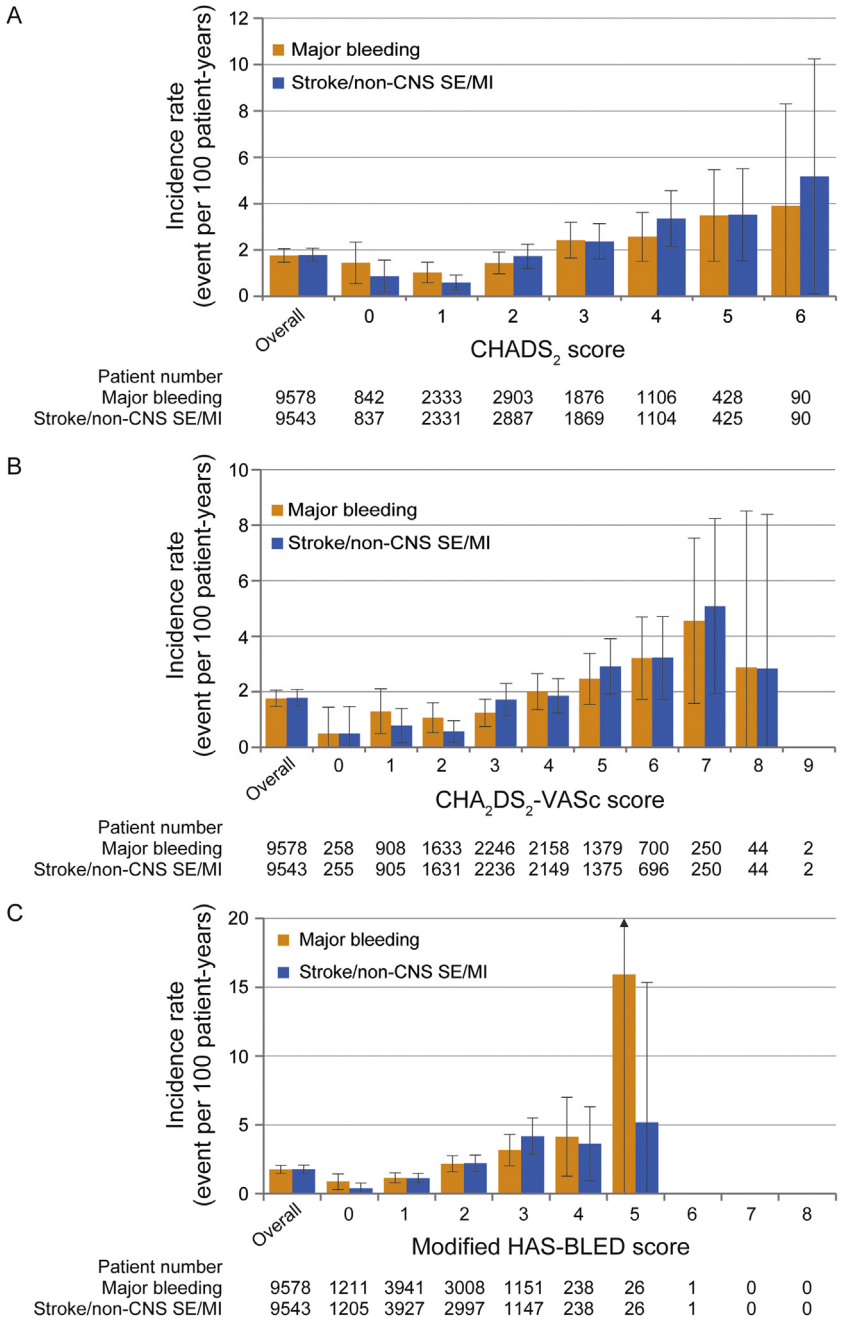


Fig. 4. Outcomes in patient groups with different (A) $CHADS_2$ scores, (B) CHA_2DS_2-VASc scores, and (C) modified HAS-BLED scores. MI, myocardial infarction; non-CNS SE, non-central nervous system systemic embolism.

the patient characteristics may have differed between the patient groups. The effects of the rivaroxaban dose on outcomes will be further investigated in future subanalyses.

Global real-world data

The Xarelto for Prevention of Stroke in Patients with Atrial Fibrillation (XANTUS), an international, prospective, real-world observational study conducted in Europe, Israel, and Canada, showed low rates of stroke/SE (0.8 events per 100 patient-years) and major bleeding (2.1 events per 100 patient-years) in a broad range of patients with NVAF receiving rivaroxaban [17] (vs. 1.7 stroke/SE events per 100 patient-years and 3.6 major bleeding events per 100 patient-years in the phase III ROCKET AF [8]). Pooled analysis of XANTUS program, which included 3 prospective real-world studies (the XANTUS, XANAP, and XANTUS-EL studies) conducted in 47 countries from Western Europe, Canada, Israel, Eastern Europe, East Asia, the Middle East, Africa, and Latin America, also showed low rates of stroke/SE (1.0 event per 100 patient-years) and major bleeding (1.7 events per 100 patient-years) [18]. Despite the difference in the recommended dose of rivaroxaban, such global studies also complement findings from phase III trials and support the usefulness of rivaroxaban in everyday clinical practice.

Study limitations

There are some limitations to the XAPASS because of its single-arm, open-label, observational design. First, selection bias was possibly introduced by the knowledge of the

treatment. Whether anticoagulation was initiated with rivaroxaban was determined by the physicians. Second, the XAPASS had no comparative arm. It is impossible to directly compare the outcomes of rivaroxaban treatment with those of other treatments such as warfarin and other NOACs. Third, this study did not enforce interventions including laboratory tests, and allowed decisions to be made at the physician's discretion. For example, the CrCl was not recorded in 8.1% of patients in the XAPASS. Finally, the loss of patients to follow-up might have led to underestimation of the event rates. Despite such limitations, the XAPASS was designed as a prospective study and involved a large number and broad range of patients (vs. 639 patients treated with rivaroxaban in the J-ROCKET AF [9]), which contributes to higher quality and clinical value of the data.

The XAPASS provides useful information for physicians to predict event rates and evaluate the benefits and risks of their patients under rivaroxaban treatment in real-world practice, which contributes to better patient outcomes.

Conclusions

The XAPASS provided information regarding practical use of rivaroxaban for stroke/SE prevention in a large number and broad range of patients with NVAF, including patients who were not enrolled in phase III clinical trials. Real-world outcomes showed incidence rates of major bleeding and thromboembolic events, suggesting that rivaroxaban is safe and effective in Japanese daily clinical practice.

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Conflict of interests

TI received research grants from Daiichi Sankyo, Bristol-Myers Squibb, Medtronic Japan, St. Jude Medical, and Bayer Yakuhin Ltd. and honoraria from Daiichi Sankyo, Ono Pharma, Bayer Yakuhin Ltd., Bristol-Myers Squibb, and Pfizer and was a member of advisory board for Bayer Yakuhin Ltd. and Bristol-Myers Squibb. SO was a member of advisory board for Bayer Yakuhin Ltd. TK received research grant from Bayer Yakuhin Ltd. and was a member of advisory board for Bayer Yakuhin Ltd. JN received research grant from Nihon Medi-Physics and was a member of advisory board for Bayer Yakuhin Ltd. KM received honoraria form Bayer Yakuhin Ltd., Otsuka Pharmaceutical, Boehringer-Ingelheim, AstraZeneca, Pfizer, Mitsubishi Tanabe Pharma Cooperation, Japan Stryker, Kowa, Nihon Medi-Physics Co, BMS, Sawai Pharmaceutical Co., Sumitomo Dainippon Pharma Co Ltd, Dai-ichi Sankyo, Asteras Pharma, and Nippon Chemiphar and was a member of advisory board for CSL Behring, Medico's Hirata, and Bayer Yakuhin, Ltd. SM received research grant from Takeda Pharma, CSL Behring, Meiji Seika Pharma, MSD, Astellas Pharma, Eisai, Otsuka Pharma, Carl Zeiss Meditec, Philips Electronics Japan, Sanofi, Siemens Healthcare, Daiichi Sankyo, Mitsubishi-Tanabe Pharma, Chugai Pharma, Nihon Medi-Physics, Pfizer, Bristol-Myers Squibb, Brainlab, Mizuho, and Medtronic and was a member of advisory board for Bayer Yakuhin Ltd. YM received research grant from Bayer Yakuhin Ltd., Daiichi Sankyo, and Boehringer-Ingelheim and honoraria from Bayer Yakuhin Ltd., Daiichi Sankyo, Boehringer-Ingelheim, and Bristol-Myers Szuibb and was a member of advisory board for Bayer Yakuhin Ltd. Y. Ohashi was an employee of Bayer Yakuhin, Ltd. and is an employeee of Novartis Pharma K.K. MT, Y. Okayama, TS, and SY are employees of Bayer Yakuhin, Ltd.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.01.001.

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