

## The EXPAND study: Efficacy and safety of rivaroxaban in Japanese patients with non-valvular atrial fibrillation



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### ABSTRACT

**Aims:** The EXPAND study examined the real-world efficacy and safety of rivaroxaban for the prevention of stroke and systemic embolism (SE) in Japanese patients with non-valvular atrial fibrillation (NVAF).

**Methods and results:** This multicenter, prospective, non-interventional, observational, cohort study was conducted at 684 medical centers in Japan. A total of 7141 NVAF patients  $\geq 20$  years of age (mean,  $71.6 \pm 9.4$  years) who were being or about to be treated with rivaroxaban (10 mg/day, 43.5%; 15 mg/day, 56.5%) were followed for an average of  $897.1 (\pm 206.8)$  days with a high follow-up rate (99.65%). The mean CHADS<sub>2</sub> score at baseline was 2.1 (1.3) (0–1, 37%; 2, 29%;  $\geq 3$ , 34%). The total incidence rate of symptomatic stroke and SE (primary efficacy endpoint) was 1.0%/year, and 0.5%, 0.9%, and 1.7%/year for those with CHADS<sub>2</sub> scores of 0–1, 2, and  $\geq 3$ , respectively. Cumulative incidence rates for major bleeding (primary safety endpoint) and non-major bleeding (secondary safety endpoint) were 1.2%/year and 4.9%/year, respectively. Differences were noted between new and current users only for major bleeding event rate (1.7% vs. 1.1%/year,  $P = 0.0024$ ). Comparisons with previous studies suggested that rivaroxaban is effective and safe for low-risk patients (0–1 CHADS<sub>2</sub>), as shown for warfarin in the XANTUS international prospective post-marketing study.

**Abbreviations:** AF, atrial fibrillation; CrCl, creatinine clearance; ISTH, International Society on Thrombosis and Haemostasis; NOAC, non-vitamin K antagonist OACs; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant; PT-INR, prothrombin time-international normalised ratio; SE, systemic embolism; MI, myocardial infarction; TIA, transient ischemic attack.

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**Conclusions:** The EXPAND study demonstrated that low dosages of rivaroxaban for Japanese NVAF patients in real-world clinical practice, including those with CHADS<sub>2</sub> scores 0–1, resulted in low rates of stroke and SE, and major and non-major bleeding.

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## 1. Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias in daily clinical practice [1]. The current prevalence of AF in Japan is <1% of the total population; however, the prevalence increases with age, reaching 2–3% among individuals ≥80 years old. Furthermore, the overall prevalence of AF in Japan is expected to increase to 1.09% by 2050 [2,3]. AF is an independent risk factor for stroke, as it is associated with an increased risk of systemic embolism (SE) and subsequent poor prognosis [4]. Oral anticoagulant (OAC) therapy with warfarin is beneficial in preventing embolism, but frequent monitoring of anticoagulation status and surveillance for potential side effects are required. Additionally, warfarin has numerous drug–drug and food–drug interactions, and a narrow therapeutic window for safety, requiring periodic prothrombin time-international normalised ratio (PT-INR) monitoring [5,6]. Thus, warfarin imposes a heavy burden on healthcare systems and patients [7,8].

In patients with non-valvular AF (NVAF) without renal dysfunction who are eligible for anticoagulation, treatment with non-vitamin K antagonist OACs (NOACs) rather than warfarin is recommended [9]. In addition to reducing the risk of stroke and SE, NOACs improve patient quality of life by reducing PT-INR monitoring and dietary restrictions [10]. Rivaroxaban, one of the NOACs approved in Japan since 2012 [11], is a factor Xa inhibitor indicated for reducing the risk of stroke and SE in patients with NVAF [12].

The efficacy and safety of once-daily rivaroxaban 20 mg was demonstrated in the international, randomised, double-blind, ROCKET AF (Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) trial [13]. In a separate but similar trial in Japan (J-ROCKET AF), the efficacy and safety of a lower dosage of rivaroxaban (15 mg once daily in patients with creatinine clearance [CrCl] ≥50 mL/min or 10 mg once daily in those with CrCl 30–49 mL/min) were compared with those of warfarin administered according to the Japanese guidelines in Japanese patients with NVAF at increased risk for stroke [14]. The J-ROCKET AF trial demonstrated the non-inferiority of rivaroxaban to warfarin for safety outcomes of major and non-major relevant bleeding [14]. At present, rivaroxaban is approved and prescribed at a lower dose due to the unique pharmacokinetics in Japanese patients when compared to Caucasian patients [14]. Pharmacokinetic studies on apixaban, edoxaban, and dabigatran showed that in Japanese patients the same dosages were judged as optimal for these 3 NOACs to conduct phase III global studies as in Caucasian patients. Based on the results of global studies, clinical use of these 3 NOACs was approved in Japan with the same dosages as in other countries.

The J-RHYTHM registry [15] was conducted to determine the current status of anticoagulant therapy in patients with AF; however, real-world data of patients using NOACs are needed because these patients were not included in the J-RHYTHM registry. In the real world, rivaroxaban is widely used for NVAF patients with diverse demographics, clinical characteristics, and stroke risks. Thus, we conducted the EXPAND (Evaluation of effectiveness and safety of Xa inhibitor for the Prevention of stroke And systemic embolism in a Nationwide cohort of Japanese patients Diagnosed as NVAF) study to examine the efficacy and safety of rivaroxaban when used for the prevention of stroke and SE in Japanese NVAF patients in daily clinical practice in Japan.

## 2. Methods

### 2.1. Study protocol

EXPAND (NCT02147444, UMIN000009376) was a multicenter, prospective, non-interventional, observational cohort study to obtain real-world evidence of rivaroxaban (Bayer Pharma AG/Janssen Pharmaceuticals, Inc.; Leverkusen, Germany) [16]. The registration period at 684 medical centers lasted from 20 November 2012 to 30 June 2014, and surveillance lasted from 20 November 2012 to 31 March 2016. Data (demographics, baseline clinical characteristics before the start of rivaroxaban treatment, and follow-up observational data [e.g. physical/medical conditions and disease outcomes]) were obtained at all participating medical centers at baseline and at regular intervals during the observation period (March and September in 2013, March and September in 2014, March 2015, and March 2016). If a patient was transferred to another hospital or discontinued or completed the rivaroxaban treatment during the survey period, data were collected for as long as possible until the end of the observation period [16].

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The study was conducted in accordance with the Ethical Guidelines for Clinical Studies from the Japanese Ministry of Health, Labour and Welfare, and all applicable laws and regulations in Japan. The protocol was reviewed and approved by the Institutional Review Boards and/or Ethics Committee at all participating study sites. All subjects provided written informed consent before enrolment [16].

### 2.2. Patients

Patients ≥20 years of age who were diagnosed with NVAF and using or about to use rivaroxaban were enrolled, except for the following: patients for whom rivaroxaban was contraindicated, patients with a history of hypersensitivity to rivaroxaban or its components, clinically significant bleeding, liver disease associated with coagulopathy or moderate or severe liver dysfunction (equivalent to Child-Pugh classification B or C), renal failure (CrCl <15 mL/min), pregnancy or possibility of pregnancy, or acute bacterial endocarditis; and patients using HIV protease inhibitors or formulations of azole antifungal agents, excluding fluconazole [16]. Patients who were newly treated with rivaroxaban were defined as new users, while those who had already received it as current users. The recommended dose of rivaroxaban is 15 mg once daily in patients with creatinine clearance CrCl ≥50 mL/min and 10 mg once daily in those with CrCl 30–49 mL/min.

### 2.3. Efficacy and safety endpoints

The primary efficacy endpoint was the composite cumulative incidence of symptomatic stroke (ischemic or hemorrhagic) and SE [16]. The secondary efficacy endpoints were the composite cumulative incidence of symptomatic stroke (ischaemic or haemorrhagic), SE, myocardial infarction (MI), and cardiovascular death, as well as individual events including symptomatic ischemic stroke, symptomatic hemorrhagic stroke, SE, acute MI/unstable angina pectoris, cardiovascular death, deep vein thrombosis/pulmonary thromboembolism, transient ischemic attacks (TIAs), percutaneous coronary interventions, surgical treatment (coronary artery bypass grafting), and all-cause death [16].

The primary safety endpoint was the cumulative incidence of major bleeding events. Major bleeding was reported in accordance with the International Society on Thrombosis and Haemostasis (ISTH) criteria by participating physicians [16,17]. The secondary safety endpoint was the cumulative incidence of non-major bleeding events [16,18].

All data of the events that occurred in this study, including imaging (e.g. computed tomography, magnetic resonance imaging, and magnetic resonance angiography) and clinical data, were evaluated by the Clinical Events Committee for Cardiac and Brain Regions. This committee was independent from the steering committee members of the present study.

### 2.4. Statistical analysis

Sample size calculation and statistical analysis plans were previously described [16]. Briefly, cumulative incidence rates (%/year) for primary and secondary endpoints were calculated; annual data summaries and Kaplan-Meier curves were produced for each endpoint from the time of first rivaroxaban prescription to the time of onset of the first event [16]. For the primary efficacy endpoint, CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASC scores were calculated, and for the primary safety endpoint, CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASC, and HAS-BLED scores were calculated [9,10,19]. Differences in incidence rates between patient populations were analyzed using the chi-square test or log-rank test, with a 2-sided significance level of 5%.

### 3. Results

#### 3.1. Patient enrolment

Overall, 7141 patients, including two additional patients not part of the previous report [16], were enrolled in the study (Fig. S1). Twelve patients (five not administered rivaroxaban, six who withdrew consent, and one for other reasons) were excluded from the baseline analysis, and 25 were lost to follow-up. Thus, we included 7141 patients for both baseline and efficacy/safety analysis (Fig. S1). The mean (standard deviation [SD]; median) observation period was 897.1 (206.8; 918.0) days (2.46 years).

#### 3.2. Patient characteristics

Most (67.8%) patients were men, and the mean age of patients was 71.6 (9.4; 72.0) years; 40.9% of patients were  $\geq 75$  years-old (Table 1). The mean body weight was 62.8 (12.5; 62.2) kg, with 59.0% of patients weighing  $\geq 60$  kg. The mean CrCl was 69.7 (26.2; 65.7) mL/min, and 78.2% patients had CrCl  $\geq 50$  mL/min. Of 7141 patients, 3717 were prescribed 15 mg/day rivaroxaban in accordance with a package insert for normal renal function (CrCl  $\geq 50$  mL/min) and 1372 patients, 10 mg/day for moderate renal impairment (CrCl  $< 50$  mL/min). A total of 5401 (75.6%) patients were prescribed rivaroxaban prior to giving informed consent (current users), and 1740 (24.4%) patients were administered rivaroxaban after providing informed consent (new users). Demographics and baseline clinical characteristics of patients by CHA<sub>2</sub>DS<sub>2</sub>-VASc score are shown in Table S1. Table S3 compares adjusted demographic and baseline characteristics between the EXPAND and the Xarelto for Prevention of Stroke in Patients with Atrial Fibrillation (XANTUS) studies [20]. XANTUS was a prospective, observational, post-marketing international study conducted in Europe, Israel, and Canada in NVAF patients for patients treated with rivaroxaban for stroke prevention with a one-year follow-up [20]. In the EXPAND study, the mean CHADS<sub>2</sub> score was 2.1 (1.3; 2.0) points, with an even distribution across scores of  $< 2$  (37.4%), 2 (28.9%), and  $\geq 3$  (33.8%) points at baseline (Table S4). The mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score was 3.4 (1.7; 3.0) points, with more than half (57.2%) of patients having a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 3–5 points at baseline. CrCl decreased and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score

**Table 1**  
Demographics and baseline clinical characteristics of patients (efficacy and safety populations).

	Total (N = 7141)	New users (N = 1740)	Current users (N = 5401)
Sex (male), n (%)	4838 67.7	1192 68.5	3646 67.5
Age (years), mean (SD)	71.6 (9.4)	71.9 (9.3)	71.5 (9.4)
Body weight (kg), mean (SD)	62.8 (12.5)	63.0 (12.3)	62.7 (12.5)
Creatinine clearance (mL/min), mean (SD)	69.7 (26.2)	69.1 (26.8)	69.9 (26.0)
CHADS <sub>2</sub> score, mean (SD)	2.1 (1.3)	2.1 (1.3)	2.1 (1.3)
CHA <sub>2</sub> DS <sub>2</sub> -VASc score, mean (SD)	3.4 (1.7)	3.4 (1.7)	3.3 (1.7)
HAS-BLED score, mean (SD)	1.4 (0.9)	1.4 (0.9)	1.4 (0.9)
Comorbidity/medical history			
Any complication or medical history	6707 93.9	1643 94.4	5064 93.8
Hypertension	5065 70.9	1244 71.5	3821 70.7
Congestive heart failure	1864 26.1	428 24.6	1436 26.6
Diabetes mellitus	1737 24.3	445 25.6	1292 23.9
Angina pectoris	833 11.7	206 11.8	627 11.6
Dyslipidaemia	2995 41.9	782 44.9	2213 41.0
History of stroke	1529 21.4	381 21.9	1148 21.3
Type of AF (paroxysmal)	3200 44.8	783 45.0	2417 44.8
Dosage of rivaroxaban (15 mg/day)	4036 56.5	1070 61.5	2966 54.9
Anticoagulant naive	2920 40.9	659 37.9	2261 41.9
Prior history of anticoagulant	4221 59.1	1081 62.1	3140 58.1
Prior history of warfarin	2834 39.7	768 44.1	2066 38.3
Using concomitant antiplatelets	1029 14.4	278 16.0	751 13.9

SD, standard deviation; AF, atrial fibrillation.

**Table 2**  
Efficacy and safety endpoints (efficacy and safety populations).

	No. of events	%/year	95% CI
<b>Primary efficacy endpoint</b>			
Stroke (ischemic/hemorrhagic)/SE	176	1.0	0.86–1.15
<b>Secondary efficacy endpoints</b>			
Stroke (ischemic/hemorrhagic)/ SE/MI/cardiovascular death	291	1.7	1.47–1.85
Stroke (ischemic/hemorrhagic/ unclassifiable)	171	1.0	0.83–1.12
Ischemic stroke	130	0.7	0.61–0.87
Hemorrhagic stroke	40	0.2	0.16–0.30
SE	6	0.03	0.01–0.06
AMI/unstable angina pectoris	35	0.2	0.13–0.27
Cardiovascular death	127	0.7	0.60–0.85
Deep vein thrombosis/pulmonary thromboembolism	6	0.03	0.01–0.06
TIA	37	0.2	0.14–0.28
Percutaneous coronary intervention/ coronary artery bypass graft	44	0.3	0.18–0.32
All-cause death	281	1.6	1.41–1.79
<b>Primary safety endpoint</b>			
Major bleeding (ISTH criteria) [17] (ISTH criteria)	215	1.2	1.06–1.39
Fatal bleeding	4	0.02	0.00–0.05
Bleeding in a critical area or organ	58	0.3	0.25–0.42
Decrease in hemoglobin $\geq 20$ g/L	106	0.6	0.49–0.72
Transfusion of two or more units of whole blood or red cells	57	0.3	0.24–0.41
(Bleeding area or organ)			
Intracranial bleeding	84	0.5	0.38–0.58
Gastrointestinal bleeding	83	0.5	0.37–0.58
Upper tract	32	0.2	0.12–0.25
Lower tract	19	0.1	0.06–0.16
Rectum	3	0.02	0.00–0.04
Unclear tract	23	0.1	0.08–0.18
Suspected gastrointestinal bleeding	15	0.1	0.04–0.13
Other location	48	0.3	0.20–0.35
(Hospitalisation)	107	0.6	0.49–0.73
<b>Secondary safety endpoints</b>			
Non-major bleeding	856	4.9	4.55–5.21
(Bleeding area or organ)			
Upper gastrointestinal tract	27	0.2	0.10–0.21
Lower gastrointestinal tract	65	0.4	0.28–0.46
Rectum	29	0.2	0.11–0.23
Epistaxis	206	1.2	1.01–1.33
Subcutaneous bleeding	174	1.0	0.84–1.14
Gingival bleeding	86	0.5	0.39–0.59
Other location	467	2.7	2.42–2.90
(Hospitalisation)	94	0.5	0.43–0.64

AMI, acute myocardial infarction; CI, confidence interval; ISTH, International Society on Thrombosis and Haemostasis; SE, systemic embolism; TIA, transient ischemic attack.

increased with advancing age. The mean HAS-BLED score was 1.4 (0.9; 1.0) points; 88.8% of patients had a score of  $< 2$  at baseline.

Most (93.9%) patients had comorbidity with or without complications/medical history; comorbidities included stroke/SE/TIA (24.1%), stroke (21.4%), hypertension (70.9%), congestive heart failure (26.1%), diabetes mellitus (24.3%), MI (4.2%), and angina pectoris (11.7%). Overall, 14.4% of patients were using concomitant antiplatelet agents at baseline.

In the new users, 1081 patients had history of anticoagulant use, but 659 did not (Table 1).

#### 3.3. Efficacy

Symptomatic stroke (ischemic or hemorrhagic) and SE occurred in 176 patients, and the cumulative incidence rate was 1.0%/year (95% confidence interval [CI]: 0.86–1.15) from 2012 to 2016 (Table 2, Fig. 1). According to CHADS<sub>2</sub> score groups, stroke and SE in patients with scores 0 or 1, 2, and  $\geq 3$  occurred in 32 (0.5%/year), 44 (0.9%/year), and 100 (1.7%/year) patients, respectively (log-rank test,  $P < 0.0001$ ) (Table S5, Fig. 2A). Symptomatic stroke (ischemic and hemorrhagic), SE, MI, and cardiovascular death occurred in 291 patients, and the cumulative

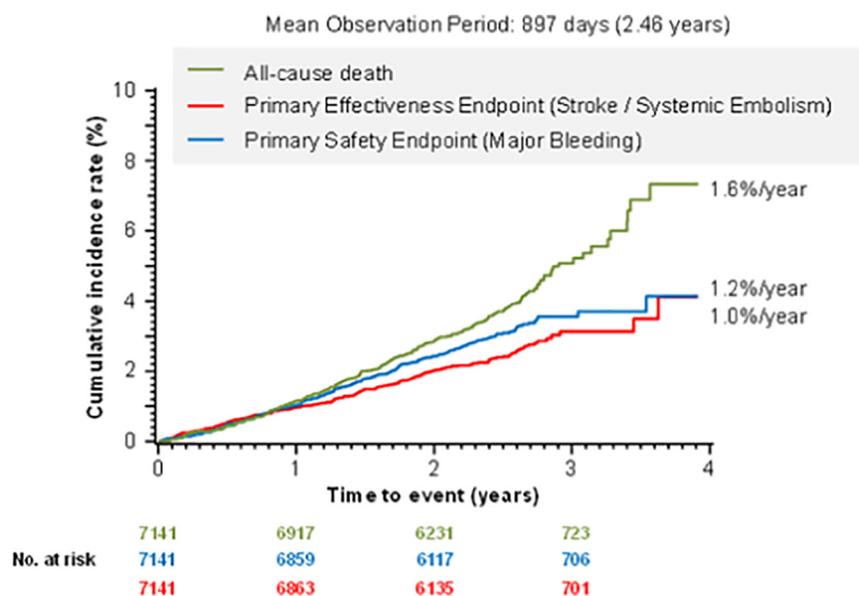


Fig. 1. Kaplan–Meier analysis for primary endpoints and all-cause deaths (efficacy and safety populations).

incidence rate was 1.7%/year (95% CI: 1.47–1.85) (Table 2). Ischemic or hemorrhagic stroke occurred in 130 (0.7% per year; 95% CI: 0.61–0.87) and 40 patients (0.2%/year; 95% CI: 0.16–0.30), respectively. SE occurred in six patients (0.03%/year; 95% CI: 0.01–0.06), TIA in 37 (0.2%/year; 95% CI: 0.14–0.28), and all-cause deaths and cardiovascular deaths in 281 (1.6%/year, 95% CI: 1.41–1.79) and 127 (0.7%/year, 95% CI: 0.60–0.85), respectively. The primary efficacy endpoint for new and current users occurred in 42 (1.1%/year) and 134 patients (1.0%/year), respectively ( $P = 0.4258$ ) (Table S2). The rate of stroke/SE in patients treated with rivaroxaban 10 mg/day and 15 mg/day was 1.1%/year and 0.9%/year, respectively ( $P = 0.0658$ ). The primary efficacy endpoint in patients treated with rivaroxaban 10 mg/day and 15 mg/day in normal renal function groups ( $\text{CrCl} \geq 50 \text{ mL/min}$ ) occurred in 36 (0.9%/year) and 76 patients (0.8%/year), respectively ( $P = 0.7950$ ).

#### 3.4. Safety

ISTH major bleeding events occurred in 215 patients (1.2%/year, 95% CI: 1.06–1.39), including intracranial hemorrhage in 84 (0.5%/year, 95% CI: 0.38–0.58) and gastrointestinal bleeding in 83 (0.5%/year, 95% CI: 0.37–0.58) (Table 2). Of the major bleeding events, bleeding with a decrease in hemoglobin levels  $\geq 20 \text{ g/L}$  occurred in 106 (0.6%/year, 95% CI: 0.49–0.72), and bleeding that required blood transfusion  $\geq 2$  units in 57 (0.3%/year, 95% CI: 0.24–0.41). Bleeding that required hospitalisation occurred in 195 (1.1%/year, 95% CI: 0.96–1.27). The rate of ISTH major bleeding was significantly lower for HAS-BLED scores  $\leq 2$  (1.2% per year; 95% CI: 0.99–1.34; 170 patients) compared with scores  $\geq 3$  (1.8%/year; 95% CI: 1.21–2.46; 33 patients) ( $P = 0.0131$ ) (Table S5). The rate significantly increased with increases in CHADS<sub>2</sub> scores from  $<2$  (0.8%/year; 95% CI: 0.56–0.99) to  $\geq 3$  (1.6%/year; 95% CI: 1.29–1.94) ( $P < 0.0001$ ) (Table S5, Fig. 2B). In new users, ISTH major bleeding events occurred in 39 (1.6%/year) and 26 (1.9%/year) patients with and without history of anticoagulant use, respectively ( $P = 0.5585$ ) (Table S6). The primary safety endpoint for new and current users occurred in 65 (1.7%/year) and 150 (1.1%/year), respectively ( $P = 0.0024$ ) (Table S2). The rate of major bleeding in patients treated with rivaroxaban 10 mg and 15 mg/day was 1.4%/year and 1.1%/year, respectively ( $P = 0.0635$ ). The primary safety endpoint in patients treated with rivaroxaban 10 mg/day and 15 mg/day in normal renal ( $\text{CrCl} \geq 50 \text{ mL/min}$ ) occurred in 46 (1.1%/year) and 92 patients (1.0%/year), respectively ( $P = 0.5064$ ).

The cumulative incidence rate for non-major bleeding events was 4.9%/year (95% CI: 4.55–5.21; 856 patients) (Table 2). Non-major

bleeding, included clinically relevant non-major bleeding, that required hospitalisation occurred in 94 (0.5%/year; 95% CI: 0.43–0.64) patients. Regarding the location of non-major bleeding, epistaxis occurred at the highest frequency, followed by subcutaneous bleeding.

#### 4. Discussion

This EXPAND study identified the primary and secondary endpoints for the efficacy and safety of rivaroxaban at a lower dosage for the prevention of stroke and SE in Japanese patients with NVAF in real-world settings. To the best of our knowledge, this is the first study to prospectively address the efficacy and safety of rivaroxaban in a real-world setting, where 43.5% of NVAF patients were treated with 10 mg/day rivaroxaban.

The demographic and baseline clinical characteristics of patients in EXPAND were similar to those of patients in the two real-world Japanese AF registries, J-RHYTHM registry [15] and Fushimi AF registry [21]. Regional bias in Japan may be low because hospitals throughout the country participated in the EXPAND study [16]. Indeed, average age and sex distributions of patients in EXPAND (72 years and 68% men) were similar to those in the J-RHYTHM registry (71 years; 69% men; NVAF patients) [15] and the Fushimi AF registry (74 years; 59% men; AF patients) [21]. Additionally, all three populations had similar proportions of patients with paroxysmal AF (EXPAND, 45%; J-RHYTHM AF, 38%, and Fushimi AF, 46%). Furthermore, mean baseline CHADS<sub>2</sub> scores were also similar (2.1, 1.7, and 2.1, respectively) [15,21]. However, patient follow-up differed among the three studies. Patients in the J-RHYTHM registry were followed up for 2 years after registration (January 2003–March 2006) or until an endpoint occurred [15], those in the Fushimi AF registry for one year (March 2011–June 2012) [21], and those in the EXPAND study for 2.5 years (November 2012–March 2016).

A total of 75.6% patients registered to this study as current users were administered rivaroxaban prior to IC. Incidence rates of major and non-major bleeding were slightly but significantly lower in the current users than in the new users, a possible finding of selection of patients who had been given rivaroxaban safely. In the new users, the incidence rate of ISTH major bleeding was also numerically lower in anticoagulant-experienced patients than in anticoagulant-naïve patients, but the difference did not reach the significance level.

In a pooled analysis of the three studies in Japan (J-RHYTHM registry [15], Fushimi AF registry [21], and the Shinken database [22]) that

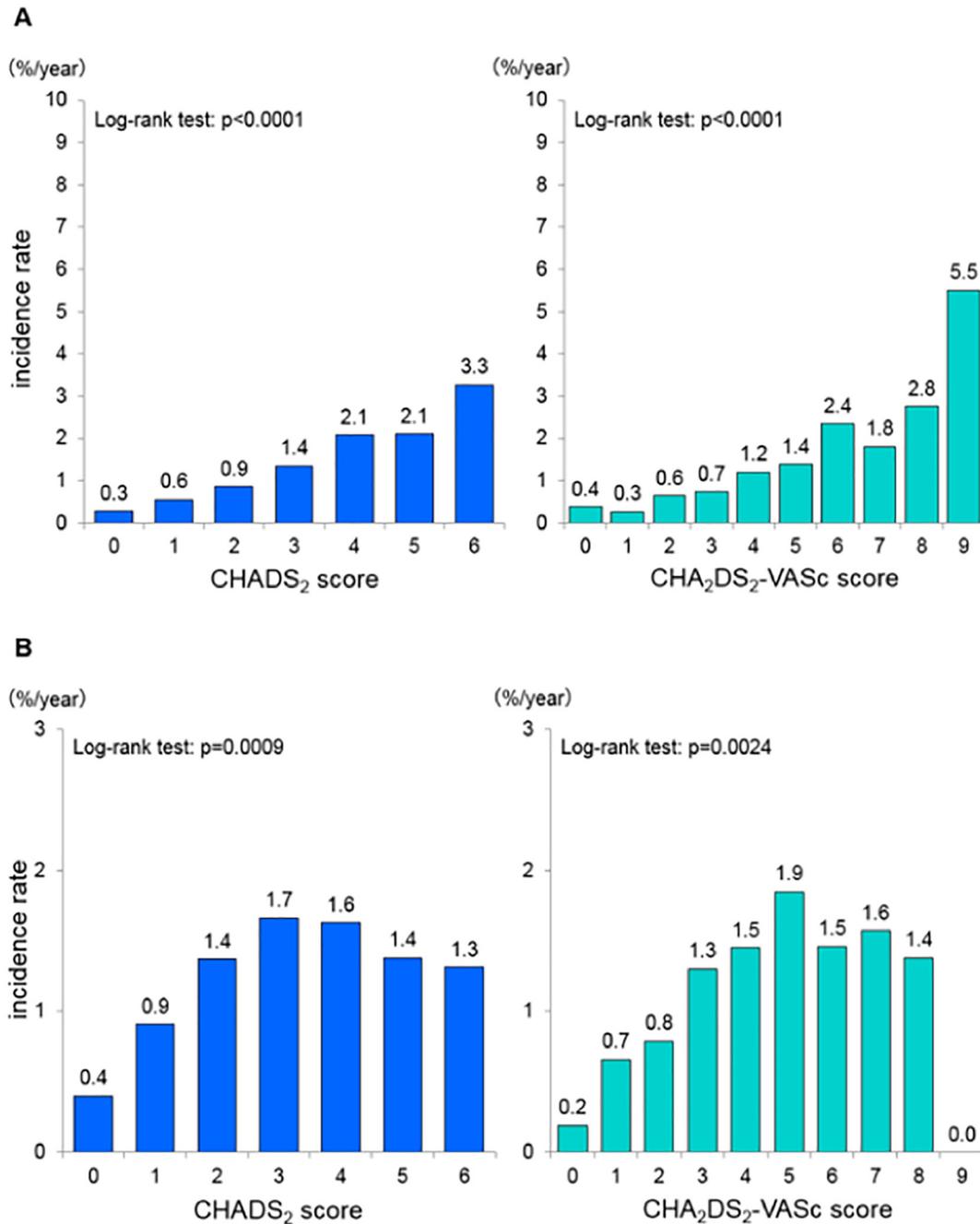


Fig. 2. The primary efficacy endpoint (A) (stroke or systemic embolism) and primary safety endpoint (B) (major bleeding) according to CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores.

evaluated 3588 Japanese NVAf patients not taking anticoagulation therapy, the incidence rate of ischemic stroke among those with CHADS<sub>2</sub> scores of 0 or 1 was 5.4 per 1000 patient years (95% CI: 2.8–10.2) and 9.3 per 1000 patient years (95% CI: 5.7–15.0), respectively [23], whereas the incidence rate of ischemic stroke in the EXPAND study was 0.2%/year and 0.4%/year for patients with CHADS<sub>2</sub> scores of 0 or 1, respectively. Although we are unable to directly compare the pooled analysis of the J-RHYTHM and Fushimi-AF registries by Suzuki et al. [23] and our EXPAND study, it is conceivable that low-risk groups (those with CHADS<sub>2</sub> scores of 0–1) could further benefit from anticoagulation therapy with rivaroxaban. For patients with CHADS<sub>2</sub> scores  $\geq 2$ , the incidence rate of stroke/SE was 1.26%/year in the J-ROCKET AF study and 1.31%/year in the EXPAND study, suggesting comparable efficacy in these two studies. However, when the major bleeding incidence rates of patients (CHADS<sub>2</sub> scores of 2–5) are compared to those in the J-ROCKET AF study, the data suggest a lower tendency of rivaroxaban to cause major

bleeding events in the present study. This could be possibly due to lower bleeding event rates in patients treated with rivaroxaban 10 mg/day in normal renal function groups (CrCl  $\geq 50$  mL/min).

When the results of EXPAND are compared with those of XANTUS [20], mean (SD) CHADS<sub>2</sub> (2.0 [1.3] and 2.1 [1.3], respectively) and CHA<sub>2</sub>DS<sub>2</sub>-VASc (3.4 [1.7] and 3.4 [1.7], respectively) scores were similar (Table S3). In contrast, the proportion of patients with renal dysfunction (CrCl  $< 50$  mL/min) was higher in EXPAND (20.8%) than XANTUS (9.4%), possibly because of the high rate (34.4%) of unmeasured/missing CrCl values in XANTUS [20]. Moreover, the mean body weight was higher in XANTUS (83.0 kg) than EXPAND (62.8 kg), and patients in XANTUS received higher rivaroxaban dosages (20 mg/day [78.7% patients], 15 mg/day [20.8% patients]) than those in EXPAND (15 mg/day [56.6% patients], 10 mg/day [43.4% patients]). Regarding efficacy, the cumulative incidence rate for ischemic stroke and SE was similar between the two studies (XANTUS, 0.8 per 100 patient years; EXPAND, 1.0 per 100

patient years). However, the incidence rate of major bleeding events was higher in XANTUS (2.1 per 100 patient years) than EXPAND (1.2 per 100 patient years), suggesting the importance of safety considerations related to patient characteristics including ethnicities and rivaroxaban dosage. Further sub-analysis of the data based on patient characteristics, risk factors, and outcome should be performed in future studies.

#### 4.1. Study limitations

The present study has several limitations. First, there may have been selection bias as patients who had adverse events, such as major bleeding after beginning rivaroxaban treatment may not have been registered as current users in this study. Second, event rates may have been underestimated or not reported as adverse events because of reporting bias. Third, rivaroxaban dosages may not have been selected according to the package insert because Japanese investigators were likely to choose a lower dose. For instance, 1609 of 5326 patients with CrCl  $\geq$ 50 mL/min used rivaroxaban 10 mg/day, which may have affected the efficacy and safety endpoints. In general, Japanese physicians carefully chose and prescribe the necessary dosage for NVAF patients to avoid a bleeding event, particularly in elderly patients and those who were on concomitant anti-platelet drugs. It is possible that bleeding events might have been reduced in these patients. Fourth, this was a single-arm observation trial; therefore, the results cannot be directly compared with another group. Additionally, 25 patients were lost to follow-up. However, this low rate of missing cases (0.35%) may not have affected the results. Fifth, adherence to drug therapy was not evaluated in the present study. Finally, the influence of risk factors other than CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc, and HAS-BLED scores was not evaluated, so the analysis of stroke and bleeding risks was limited.

#### 4.2. Conclusion

Despite the limitations mentioned above, the EXPAND study identified the rates of stroke and SE, and major and non-major bleeding following rivaroxaban treatment at a Japan-specific dosage in real-world clinical practice in Japanese NVAF patients.

#### Author contributions

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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The EXPAND study is an investigator-initiated clinical study based on a collaborative contract with Tohoku University Hospital and Bayer Yakuhin, Ltd. The company had no role in the study design, conduct of the study, data collection, data analysis, or preparation or submission of the manuscript design. The details of the EXPAND study group are shown in Supplementary material.

#### Conflict of interest

H.S. has received lecture fees from Bayer Yakuhin, Ltd., and Daiichi Sankyo Co., Ltd. T.Y. has received grants and personal fees from Bayer, Daiichi Sankyo, BMS, and Mitsubishi Tanabe; and personal fees from Pfizer, Eisai, Ono Pharmaceutical, Toa Eiyo, and Nippon Boehringer, outside the submitted work. S.U. has received personal fees from Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Sanofi, Daiinippon Sumitomo, Otsuka, Takeda Astellas, AstraZeneca, Sanwa Kagaku, Shionogi, Mitsubishi Tanabe, and Pfizer, outside the submitted work. T.K. has received grants and personal fees from Daiichi Sankyo Co., Ltd., Bayer Yakuhin, Ltd., Pfizer, Chugai Pharmaceutical Co., Ltd.,

Boehringer Ingelheim, Mitsubishi Tanabe Pharma Corporation, Shionogi & Co., Ltd., Astellas Pharma Inc., and MSD; personal fees from Bristol-Myers Squibb, Sanofi K.K., and AstraZeneca K.K.; and grants from Takeda Pharmaceutical Co., Kissei Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., EA Pharma Co., Ltd., Asahi Kasei Medical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Torii Pharmaceutical Co., Ltd., Eisai Co., Ltd., Ono Pharmaceutical Co., Ltd., ZERIA Pharmaceutical Co., Ltd., and Sumitomo Dainippon Pharma Co., Ltd., outside the submitted work. W.S. has received personal fees from Bayer Yakuhin, Ltd., outside the submitted work. T.I. has received grants and personal fees from Daiichi-Sankyo, and Bristol-Myers Squibb; personal fees from Bayer Healthcare, and Pfizer; and grants from Boehringer Ingelheim, outside the submitted work. M.K. has received personal fees from Tohoku University, during the conduct of the study; and personal fees from Bayer Yakuhin, Ltd., outside the submitted work. K.F. has received personal fees from Bayer Yakuhin Ltd., outside the submitted work. H.O. has received personal fees from Daiichi-Sankyo, and Bayer Japan, outside the submitted work. I.S. has received personal fees from Bayer Yakuhin Ltd., and Takeda Pharmaceutical Co., Ltd., outside the submitted work. K.S. has an Endowed Department of Molecular Cardiovascular Therapeutics, Fukuoka University, which is supported by MSD, an Endowed Department of Advanced Therapeutics for Cardiovascular Disease, Fukuoka University, which is supported by Boston Scientific Japan Co., Japan, Medtronic Co., Japan Lifeline Co., Biotronik Japan, and St Jude Medical Japan Co., and an Endowed Department of Future Medicine for Cardiovascular Disease, Fukuoka University, supported by Nihon Kohden Corp. Ltd., Japan. H.M. has received personal fees from Daiichi Sankyo Co., Ltd., Bayer Yakuhin, Ltd., Bristol-Myers Squibb, Boehringer Ingelheim, Otsuka Pharmaceutical Co., Ltd., Eisai Co., Ltd., Novo Nordisk Pharma Ltd., and Kowa Pharmaceutical Co., Ltd., outside the submitted work. N.M. has received personal fees from Bayer, Daiichi-Sankyo, and Boehringer Ingelheim; and grants and personal fees from Bristol-Myers, and Pfizer, outside the submitted work. J.A. has received grants and personal fees from Bayer Yakuhin, outside the submitted work. H.A. has received personal fees from Daiichi Sankyo, outside the submitted work. H.I. has received personal fees from Bayer Healthcare, Boehringer Ingelheim, Daiichi-Sankyo, and Bristol-Myers Squibb, outside the submitted work. K.K., Y.O., Y.N., N.S., S.S., and A.T. have nothing to disclose.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2018.01.141>.

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