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Study Design and Baseline Characteristics of the EXPAND Study: Evaluation of Effectiveness and Safety of Xa Inhibitor, Rivaroxaban for the Prevention of Stroke and Systemic Embolism in a Nationwide Cohort of Japanese Patients Diagnosed as Non-Valvular Atrial Fibrillation

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The use of rivaroxaban, a factor Xa inhibitor, has been increasing for prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF) in Japan. We conducted the nationwide multicenter study, termed as the EXPAND Study, to address its effectiveness and safety in the real-world practice of patients with non-valvular AF in Japan. The EXPAND Study is a prospective, non-interventional, observational cohort study to evaluate the effectiveness and safety of rivaroxaban in non-valvular AF patients in a real-world clinical practice. A total of 7,178 patients with non-valvular AF were enrolled in 684 medical institutes between November 20, 2012 and June 30, 2014. As for the baseline demographic and clinical characteristics of 7,164 patients, the proportion of female patients was 32.2%, and those of patients with creatinine clearance < 50 mL/min and non-paroxysmal (persistent or permanent) AF were 21.8% and 55.1%, respectively. The proportions of patients complicated with hypertension, congestive heart failure, diabetes mellitus, and a history of ischemic stroke were 70.9%, 25.9%, 24.3%, and

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20.2%, respectively. The proportions of patients with a $CHADS_2$ score ≤ 1 and a CHA_2DS_2-VASc score ≤ 1 were 37.3% and 13.6%, respectively. They were followed up until March 31, 2016 for a mean follow-up period of approximately 2.5 years. The findings of the EXPAND Study will help to establish an appropriate treatment with rivaroxaban for Japanese patients with non-valvular AF.

Keywords: anticoagulants; atrial fibrillation; Japanese; real world evidence; stroke
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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia (Wolf et al. 1996). Several non-vitamin K oral anticoagulants (NOACs) have recently been launched for the prevention of ischemic stroke and systemic embolism in patients with non-valvular AF (Savelieva and Camm 2014). The Japanese Circulation Society (JCS) Guidelines 2013 for pharmacotherapy of AF recommended to control the optimal prothrombin time international normalized ratio (PT-INR) range in case of warfarin use for non-valvular AF. Optimal PT-INR range for patients older than 70 years and those under 70 years is 1.6-2.6 and 2.0-3.0, respectively (Inoue et al. 2014). Among them, rivaroxaban was approved in January 2012, and was available since April 2012 in Japan. It is an orally direct inhibitor of factor Xa with considerably fewer interactions with other drugs or food (Carter and Plosker, 2013), requires no routine coagulation monitoring and thus overcomes drawbacks of warfarin (Savelieva and Camm, 2014). Based on rivaroxaban pharmacokinetics in Japanese subjects and lower anti-coagulation preference in Japan, particularly in elderly patients, the optimal dose regimen for Japanese AF patients was considered (Tanigawa et al. 2013). Approved dosage of rivaroxaban was 15 mg once daily for adult patients with non-valvular AF, 10 mg once daily in patients with moderate renal impairment defined as creatinine clearance (CCr) of 30(15)-49 mL/min.

The ROCKET AF Trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) is a global randomized, double-blind, controlled phase III trial, which evaluated the effectiveness and safety of rivaroxaban 20 mg once daily versus dose-adjusted warfarin in 14,264 patients with non-valvular AF (Patel et al. 2011). Patients with a CCr of 39 to 49 mL/min were assigned to receive fixed-dose rivaroxaban 15 mg daily at randomization in the ROCKET AF Trial (Patel et al. 2011). The ROCKET-AF Trial demonstrated that rivaroxaban has the non-inferiority to warfarin in the incidence rate of stroke and systemic embolism in patients with non-valvular AF and that the overall rate of major bleeding and non-major bleeding in the rivaroxaban group was similar to that in the warfarin group (Patel et al. 2011). The J-ROCKET AF Trial, a randomized, double-blind, controlled phase III trial, was conducted to evaluate the effectiveness and safety of rivaroxaban 15 mg once daily versus dose-adjusted warfarin in 1,280 Japanese patients with non-valvular AF (Hori et al. 2012). Patients with a CCr of 30 to 49 mL/min were assigned to receive fixed-dose rivaroxaban 10 mg daily at randomization in the J-ROCKET AF Trial (Hori et al. 2012). The J-ROCKET Trial demonstrated that rivaroxaban has the non-inferiority to warfarin in the rate of the primary safety outcomes of major and non-major clinically relevant bleeding and that rivaroxaban use was associated with a significantly greater reduction in ischemic stroke than warfarin (Hori et al. 2012).

These two pivotal clinical trials of rivaroxaban clearly showed the effectiveness and safety of rivaroxaban in patients with non-valvular AF. However, there may be limitations due to the carefully-selected and well-managed study populations in those clinical trials. The number of patients without a history of ischemic stroke, TIA, or non-CNS systemic embolism, and with only 2 of the risk factors, was limited to less than 10% of the total patients (Hori et al. 2012), and the patients with a $CHADS_2$ score of 0 or 1 were not included in these two trials (Patel et al. 2011; Hori et al. 2012). Thus, the clinical evidence for this population remains unclear. In the real-world clinical practice, it is evident that rivaroxaban is widely administered to non-valvular AF patients with various demographic and clinical characteristics compared with those in the clinical trials.

Thus, in order to address the clinical utility of rivaroxaban in Japanese non-valvular AF patients, we aimed to conduct a multicenter, prospective, non-interventional, observational cohort study, named the EXPAND Study (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 non-valvular atrial fibrillation). Here, we report the study design and baseline demographic and clinical characteristics of the 7,164 patients enrolled in the EXPAND Study during the registration period between November 2012 and June 2014.

Methods

Study design

The EXPAND Study is a multicenter, prospective, non-interventional, observational cohort study to evaluate the effectiveness and safety of rivaroxaban for the prevention of stroke and systemic embolism in Japanese patients with non-valvular AF in the real-world clinical practice. In this study, eligible patients were consecutively enrolled in 684 medical institutions during the registration period between November 20, 2012 and June 30, 2014. The surveillance was planned to be performed from November 20, 2012 to March 31, 2016. The information on each patient during the follow-up observa-

tion was obtained by implementing the survey in all participating medical centers at regular intervals (March 2013, September 2013, March 2014, September 2014, March 2015, and March 2016). The collected information included the baseline demographic and clinical characteristics prior to the start of rivaroxaban treatment, and the follow-up observation data, such as physical/ medical conditions and disease outcomes of the patients. If a patient was transferred to another hospital or discontinued or completed the rivaroxaban treatment during the survey period, the information will be collected as long as possible until the end of the survey.

This study was conducted in accordance with the principles of the Declaration of Helsinki, 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 the participating study sites. All subjects provided written informed consent before enrollment.

The study is registered with Clinical trials.gov., number NCT02147444, and with the University Hospital Medical Information Network clinical trials registry, number UMIN000009376.

Patients

Patients who met the following inclusion criteria were eligible; male or female aged 20 years or older at enrollment, a diagnosis of non-valvular AF, and use or future use of rivaroxaban. Exclusion criteria included the followings; a history of hypersensitivity to rivaroxaban or its components, bleeding (clinically significant intracranial hemorrhage or gastrointestinal hemorrhage), liver diseases associated with coagulation disorder or moderate-to-severe liver disorder classified into Child-Pugh class B or C, renal failure (defined as CCr of < 15 mL/min), pregnancy or a possibility of pregnancy, use of human immunodeficiency virus protease inhibitors, use of azole antifungal agents excluding fluconazole, and acute bacterial endocarditis. We excluded the cases treated with fluconazole to avoid any interactions because rivaroxaban is a substrate of CYP3A4 and fluconazole is a CYP3A4 inhibitor.

Assessment and endpoints

The primary effectiveness endpoint was a composite of symptomatic stroke (ischemic or hemorrhagic) and systemic embolism. The secondary effectiveness endpoints included a composite of symptomatic stroke (ischemic or hemorrhagic), systemic embolism, myocardial infarction, and cardiovascular death, thus including symptomatic ischemic stroke, symptomatic hemorrhagic stroke, systemic embolism, acute myocardial infarction/unstable angina, cardiovascular death, deep vein thrombosis/pulmonary thromboembolism, transient ischemic attack (TIA), and interventions/surgical treatment, and all-cause mortality. The primary safety endpoint was major bleeding, as defined by the International Society on Thrombosis and Haemostasis (Schulman et al. 2005). The secondary safety endpoint was non-major bleeding.

Sample size

The target sample size in this study was set to be 7,000 patients based on the feasibility. In the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy Trial) (Connolly et al. 2009) or the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial) (Granger et al. 2011), the number of patients with $CHADS_2 \leq 1$ was approximately 3,000 to 4,000. Thus, the target number of patients with $CHADS_2 \leq 1$ in this study was set to be 3,500. Additional 3,500 patients with $CHAD_2 \geq 2$ were also included in this study, so that the patients with $CHADS_2 \leq 1$ and those with $CHADS_2 \geq 2$ accounted for approximately 50% of the overall population as in the J-RHYTHM Registry (Atarashi et al. 2011). As a result, we planned to include a total of 7,000 patients with non-valvular AF in this study.

Statistical analysis

The analyses for effectiveness of rivaroxaban were performed based on the followings; the incidence rate (% per year) of the primary effectiveness endpoint, the incidence rate of each secondary effectiveness endpoint, the incidence rates of the primary and secondary effectiveness endpoints by the $CHADS_2$ or a CHA_2DS_2-VASc score, the incidence rate of the primary effectiveness endpoint by the presence or absence of complication or medical history, and analysis of prognostic factors associated with the onset of the primary and secondary effectiveness endpoints. The $CHADS_2$ score (ranging from 0 to 6 points) and CHA_2DS_2-VASc score (0 to 9 points) were used to assess the risk of cerebral infarction (ischemic stroke) in patients with non-valvular AF, where higher scores indicate a greater risk of ischemic stroke (Gage et al. 2001; European Heart Rhythm Association et al. 2010).

The analyses for safety of rivaroxaban were performed based on the followings; the incidence rates (% per year) of major and non-major bleeding, the incidence rate of major and non-major bleedings by a HAS-BLED score (Pisters et al. 2010), and the analysis of baseline prognostic factors associated with the development of the primary and secondary safety endpoints. The HAS-BLED score (0 to 9 points) was used to assess the risk of bleeding, with higher scores representing a higher risk of bleeding (Lip et al. 2011). The labile prothrombin time-international normalized ratio was not counted in this study.

The difference in the incidence rate between the patient populations were analyzed by the chi-squares test or log-rank test, with a 2-sided significance level of 5%.

Results

A total of 7,178 patients were enrolled in this study from 684 institutions in Japan, and 7,164 of them were considered to be eligible for effectiveness and safety analyses. The baseline demographic and clinical characteristics of the patients are summarized in Table 1.

The proportion of female patients was 32.2%, and that of elderly patients aged ≥ 75 years 40.9%, that of patients weighed < 50 kg 13.9%, and that of patients with CCr < 50 mL/min 21.8%. As for complication and medical history, patients with hypertension accounted for 70.9%, those with congestive heart failure (CHF) 25.9%, those with diabetes mellitus 24.3%, and those with a history of stroke/TIA/systemic embolism 24.1% (ischemic stroke, 20.2%). Regarding the $CHADS_2$ score, patients with the score 2 accounted for 29.0% and those with score ≤ 1 37.3% (Table 2). As for the CHA_2DS_2-VASc score, patients with the score 3 accounted for 23.1%, those with the score 2 18.4%, and those with the score ≤ 1 13.6% (Table 2). With respect to the HAS-BLED score, patients with the score 1 accounted for 48.3%, those with the score 2 28.5%, and

Table 1. Baseline Demographic and Clinical Characteristics of Patients.

	Patients (n = 7,164)	
	n	%
Gender		
Male	4,856	67.8
Female	2,308	32.2
Age (year-old), mean (SD)	71.6 (9.4)	
< 65	1,441	20.1
65 - 74	2,793	39.0
≥ 75	2,930	40.9
Body weight (kg), mean (SD)	62.8 (12.5)	
< 50	957	13.9
50 - 59	1,866	27.1
≥ 60	4,058	59.0
$CHADS_2$ score, mean (SD)	2.1(1.3)	
Creatinine clearance (mL/min), mean (SD)	69.7 (26.2)	
< 30	134	2.0
30 - 49	1,352	19.8
≥ 50	5,341	78.2
Type of AF		
Paroxysmal	3,210	44.8
Non-paroxysmal (persistent/permanent)	3,953	55.1
History of warfarin use	2,843	39.7
Comorbidity/medical history		
Any complication or medical history	6,728	93.9
Hypertension	5,078	70.9
Congestive heart failure	1,859	25.9
Diabetes mellitus	1,740	24.3
Peripheral arterial disease	187	2.6
History of myocardial infarction	298	4.2
Angina pectoris	831	11.6
Deep venous thrombosis	37	0.5
Pulmonary embolism	18	0.3
Aortic aneurysm	95	1.3
Dyslipidemia	2,998	41.8
Liver dysfunction	413	5.8
History of stroke/TIA/systemic embolism	1,725	24.1
History of stroke	1,579	22.1
History of ischemic stroke	1,444	20.2
History of hemorrhagic stroke	135	1.9
History of TIA	219	3.1
History of systemic embolism	59	0.8
Therapy of AF		
Pharmacotherapy	4,297	60.0
Non-pharmacotherapy	437	6.1

AF, atrial fibrillation; TIA, transient ischemic attack.

Table 2. Prevalence of Patients by Baseline $CHADS_2$, CHA_2DS_2-VASc or HAS-BLED Scores.

	Patients %
$CHADS_2$ score (n = 7,164)	
0	10.1
1	27.2
2	29.0
3	18.7
4	10.2
5	3.9
6	0.9
CHA_2DS_2-VASc score (n = 7,164)	
0	3.1
1	10.5
2	18.4
3	23.1
4	20.7
5	13.6
6	7.0
7	2.6
8	0.8
9	0.1
HAS-BLED score (n = 6,698)	
0	12.0
1	48.3
2	28.5
3	9.4
4	1.7
5	0.1
6 to 9	0.0

those with the score ≥ 3 11.2% (Table 2).

Discussion

The EXPAND Study will help to establish an appropriate treatment with rivaroxaban for Japanese patients with non-valvular AF. In Japan, the EXPAND Study could help to answer medical questions at least in part that came up and were not possible to answer until now with clinical trials. In the EXPAND Study, we will investigate effectiveness and safety of rivaroxaban such as in patients with early phase of cerebral infarction, those received antiplatelet drugs concomitantly or complicated with vascular diseases, in terms of stroke prevention (primary/secondary), risk factor, and type of AF.

Comparison with the two previous clinical trials of rivaroxaban

As compared with the ROCKET AF (Patel et al. 2011), and the J-ROCKET AF (Hori et al. 2012) Trials, the EXPAND Study is characterized by the following patient characteristics; the proportion of paroxysmal and non-paroxysmal (persistent and permanent) AF was similar in the EXPAND Study, while that of paroxysmal AF was lower compared with ROCKET AF. Creatinine clearance was comparable between the EXPAND Study and the ROCKET AF Trial. Regarding comorbidities, the patients enrolled in the previous 2 trials had higher percentages compared with the EXPAND Study. Comorbidities of the East Asian cohort of the ROCKET AF Trial had similar distribution as in the J-ROCKET AF Trial compared with the previous 2 trials. Incidentally, the East Asian cohort of the ROCKET AF Trial did not include Japanese patients and a secondary analysis included the randomized patients from 73 sites in 4 geographic areas in the East Asia (China, Korea, Taiwan, and Hong Kong) who participated in the full ROCKET AF study (Wong et al. 2014) (Table 3).

Patients with the $CHADS_2$ score ≤ 1 were not enrolled in the ROCKET AF (Patel et al. 2011) or J-ROCKET AF (Hori et al. 2012), while 37.3% of patients who were enrolled in EXPAND had the $CHADS_2$ score ≤ 1. This indicates that a higher proportion of high-risk patients were enrolled in the ROCKET AF and J-ROCKET AF Trials compared with the EXPAND Study, resulting in the higher proportion of patients with comorbidities.

Comparison with the two observational studies on non-valvular AF in Japan

Although the J-ROCKET AF or ROCKET AF Trial did not include low-risk patients (the $CHADS_2$ score of 0 or 1), the EXPAND Study included those patients in 37.3% of the cohort (Fig. 1A). In the Japanese J-RHYTHM Registry, patients with $CHADS_2 \leq 1$ and those with $CHADS_2 \geq 2$ accounted for approximately 50% of the overall population (Atarashi et al. 2011). This is because the J-RHYTHM Registry was performed mainly by cardiologists with AF patients for primary prevention (Atarashi et al. 2011). In contrast, the clinical characteristics of the EXPAND patients are comparable with those of the Fushimi AF registry, another large-scale observational study on non-valvular AF in Japan (Akao et al. 2013), which examined ~3,100 AF patients from the community-based survey (Fig. 1A). In the Fushimi AF registry, it is not clear whether the registry reflects the risk distribution of thromboembolism in the entire Japanese patient population. However, since major participating sites of the registry are private clinics by general practitioners, it may reflect the real-world situation in daily practice of AF. In the rivaroxaban post marketing surveillance (n = 10,038), the proportion of low-risk AF patients was 36.2%, which is comparable with the present study (Ogawa et al. 2014). Thus, the EXPAND Study can be considered to reflect the real-world AF practice with rivaroxaban.

In addition, the J-RHYTHM Registry (Atarashi et al. 2011) and Fushimi AF Registry (Akao et al. 2013) showed similar patient characteristics to our EXPAND patients in terms of the type of AF, creatinine clearance, and comorbidities (Tables 4 and 5). Furthermore, the distribution of

Table 3. Comparison with the Two Previous Clinical Trials of Rivaroxaban.

	ROCKET AF Trial		J-ROCKET AF Trial	EXPAND Study
		East Asia cohort		
	(n = 7,131)	(n = 468)	(n = 639)	(n = 7,164)
Type of AF (%)				
Paroxysmal (%)	17.5	NA	NA	44.8
Non-paroxysmal (persistent/permanent) (%)	81.1	NA	NA	55.1 (20.3/34.8)
Newly diagnosed or new onset	1.4	NA	NA	NA
Creatinine clearance				
Mean (range) (mL/min)	67 (52-88) (median) (IR)	64.0	NA	69.7±26.2 (mean ± SD)
Range 30-49mL/min (%)	NA	NA	22.1	19.8
Comorbidity				
Previous stroke/TIA/ systemic embolism (%)	54.9	65.0	63.8	24.1
Congestive heart failure (%)	62.6	38.9	41.3	25.9
Hypertension (%)	90.3	79.3	79.5	70.9
Diabetes mellitus (%)	40.4	38.3	39.0	24.3
Previous myocardial infarction (%)	16.6	3.6	7.0	4.2

AF, atrial fibrillation; TIA, transient ischemic attack; NA, not available.

the HAS-BLED score in the EXPAND Study is similar to that in the J-RHYTHM Registry (Fig. 2) (Okumura et al. 2014). Thus, the patient demographic and clinical characteristics in the EXPAND Study are similar to those in the previous 2 observational studies with Japanese AF patients, and it is expected that the results of the EXPAND Study will reflect the real-world clinical practice with rivaroxaban.

Validation of the CHA_2DS_2-VASc score

The European Society of Cardiology (ESC) Guidelines 2012 for the management of AF recommend the use of the CHA_2DS_2-VASc score as a new assessment method to specify low-risk patients accurately (Camm et al. 2012). The CHA_2DS_2-VASc score adds vascular diseases, 65 years or older of age, and sex category (female sex), as additional risk factors to the $CHADS_2$ score, which leads to a greater reduction in the number of patients with C CHA_2DS_2-VASc score ≤ 1 than that with the $CHADS_2$ score ≤ 1, and enables us to stratify AF patients at low-risk more precisely. The results of the J-RHYTHM Registry showed that the proportion of patients with the CHA_2DS_2-VASc score ≤ 1 (22%) was lower compared with those with $CHADS_2$ score ≤ 1 (50%) (Fig. 1A, B) (Atarashi et al. 2011; Okumura et al. 2014). The results of the Fushimi AF Registry also showed that the proportion of patients with CHA_2DS_2-VASc score ≤ 1 (13.9%) was lower compared with those with $CHADS_2$ score ≤ 1 (36.9%) (Akao et al. 2013). Similarly, the present study showed that the proportion of patients with CHA_2DS_2-VASc score ≤ 1 (13.6%) was lower than that of patients with the $CHADS_2$ score ≤ 1 (37.3%). These results suggest that it is possible to apply CHA_2DS_2-VASc score to Japanese AF patients in order to stratify the patients at low-risk of ischemic stroke.

Safety assessment

Regarding the safety of rivaroxaban, bleeding events in the EXPAND protocol is classified into the following 2 categories; major and non-major bleeding. In contrast, in the ROCKET AF Trial, bleeding events were classified into the following 3 categories; (1) major bleeding (including subcategories such as a decrease in hemoglobin ≥ 2 g/dl, transfusion, critical bleeding, and fatal bleeding), (2) non-major clinically relevant bleeding, and (3) minor episodes (Patel et al. 2011). The J-ROCKET AF Trial also had the following 3 categories; (1) major bleeding, (2) non-major

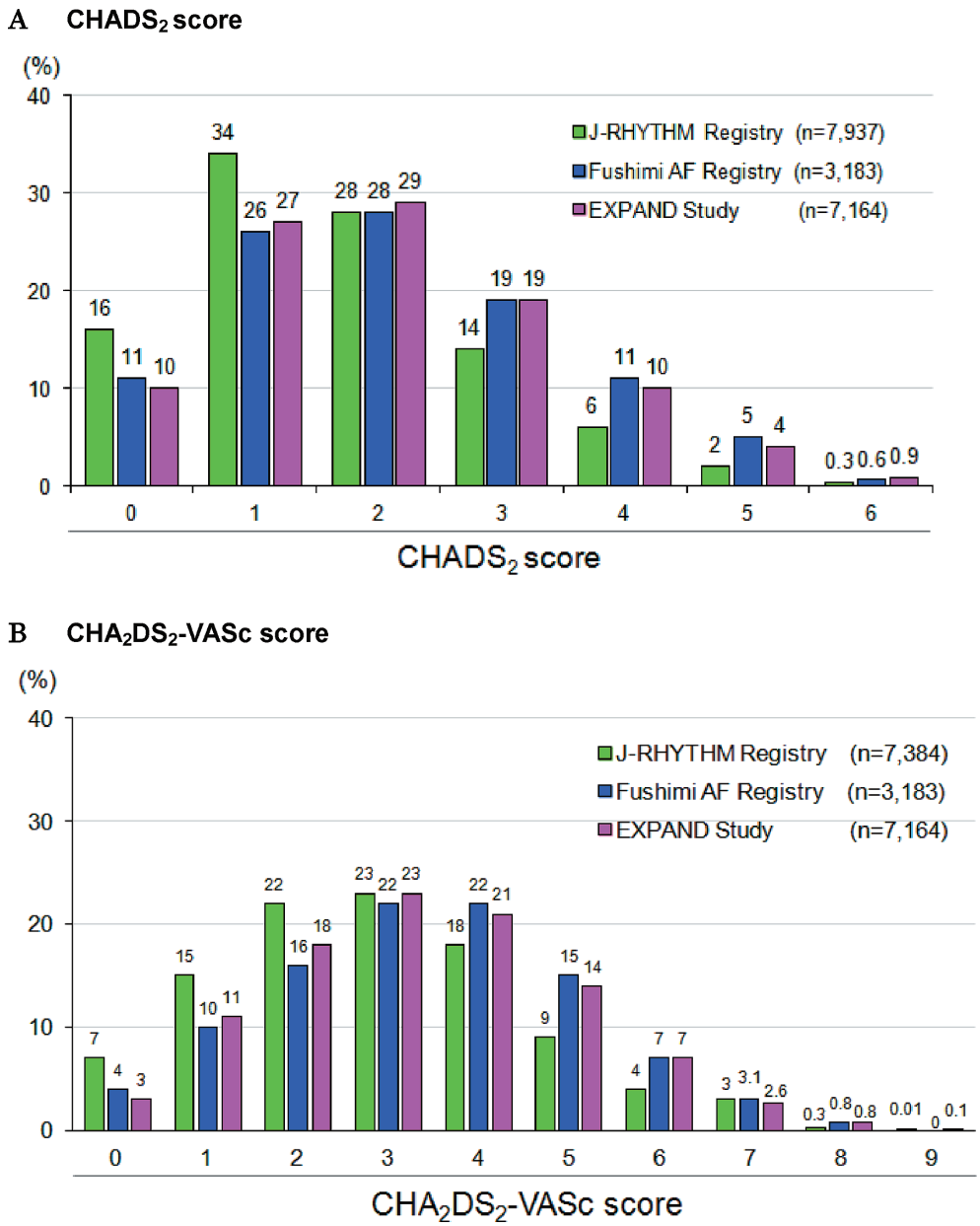

Fig. 1. Patient distribution by $CHADS_2$ score and CHA_2DS_2-VASc score.
The prevalence (%) is shown on the top of each bar. A. Patient distribution by $CHADS_2$ score. Adapted from Fushimi AF Registry (Akao et al. 2013), J-RHYTHM Registry (Atarashi et al. 2011). B. Patient distribution by CHA_2DS_2-VASc score. Adapted from Fushimi AF Registry (Akao et al. 2013) and J-RHYTHM Registry (Okumura et al. 2014) with permission.

clinically relevant breeding, and (3) minor bleeding events (Hori et al. 2012). Since bleeding is one of the important outcomes in anti-coagulation therapy, we plan to use these 3 categories when analyzing bleeding events.

Conclusions

The findings of the EXPAND Study will help to establish an appropriate rivaroxaban treatment for Japanese patients with non-valvular AF in the real-world clinical practice. The first results from this study will be available in 2017.

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Table 4. Comparison with the Previous Observational Studies on Non-valvular AF in Japan (Clinical Characteristics).

	J-RHYTHM Registry (n = 7,937)	Fushimi AF Registry (n = 3,183)	EXPAND Study (n = 7,164)
Gender			
Male	68.9	59.3	67.8
Female	31.1	40.7	32.2
Age (years), mean (SD)	69.7 (9.9)	74.2 (11.0)	71.6 (9.4)
< 75	65.8	46.3	59.1
≥ 75	34.2	53.7	40.9
Body weight (kg), mean (SD)	NA	58.5(13.2)	62.8 (12.5)
< 50	NA	25.7	13.9
≥ 50	NA	74.3	86.1
$CHADS_2$ score, mean (SD)	1.7 (1.2)	2.1 (1.4)	2.1 (1.3)
Creatinine clearance (mL/min), mean (SD)	NA	63.4 (31.6)	69.7 (26.2)
< 50	NA	35.6	21.8
≥ 50	NA	64.4	78.2
Type of AF			
Paroxysmal	37.1	46.0	44.8
Non-paroxysmal (persistent/permanent)	62.9	54.0	55.1
Anticoagulant therapy			
Warfarin use	87.3	48.5	NA
History of warfarin use	NA	NA	39.7

AF, atrial fibrillation; NA, not available.

Conflict of Interest

T.I. has received research fund and/or lecture fees from Nippon Boehringer Ingelheim, Bayer Yakuhin Ltd., Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo Co., Ltd. H.A. has received research fund and/or lecture fees from Daiichi Sankyo Co., Ltd. H.I. received lecture fees from Daiichi Sankyo Co., Ltd., Bayer Yakuhin Ltd., and Bristol-Meyers Squibb. S.U. has received research fund and lecture fees from Bayer Yakuhin, Ltd., Nippon Boehringer Ingelheim and Daiichi Sankyo Co., Ltd. T.K. has received research fund from Mitsubishi Tanabe Pharma Corporation, Daiichi Sankyo Co., Ltd., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Eisai Co., Ltd., Chugai Pharmaceutical Co., Ltd., Merck Sharp and Dohme, Sanofi K.K., and Bayer Yakuhin, Ltd. and lecture fees from Daiichi Sankyo Co., Ltd. and Bayer Yakuhin, Ltd. T.Y. has received research fund and/or lecture fees from Bayer Yakuhin, Ltd., Daiichi Sankyo Co., Ltd., Bristol-Myers Squibb, Pfizer, Nippon Boehringer Ingelheim, Eisai Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Ono Pharmaceutical and Toa Eiyo. W.S. has received research fund and/or lecture fees from Bayer, Daiichi Sankyo Co., Ltd., Bristol-Myers Squibb, Pfizer, Nippon Boehringer Ingelheim and Eisai Co., Ltd. M.K. has received lecture fees from Bayer. K.K. has received research fund and/or lecture fees from Bayer, Daiichi Sankyo Co., Ltd., Novartis Pharma, and SBI Pharma. K.F. has received no research fund or lecture fees from any companies. H.O. has received no research fund or lecture fees from any companies. I.S. has received lecture fees from Takeda Pharmaceutical Co., Ltd. K.S. has an Endowed Department of Molecular Cardiovascular Therapeutics, Fukuoka University, supported by MSD Co., Ltd., and an Endowed Department of Advanced Therapeutics for Cardiovascular Disease Fukuoka University, which is supported by Boston Scientific Japan Co., Ltd., Japan Medtronic Co., Ltd., Japan Lifeline Co., Ltd., Biotronik Japan, Co., Ltd., and St Jude

Table 5. Comparison with the Previous Observational Studies on Non-valvular AF in Japan (Comorbidity and Medical History).

	J-RHYTHM Registry (n = 7,937)	Fushimi AF Registry (n = 3,183)	EXPAND Study (n = 7,164)
Comorbidity/medical history			
Any complication or medical history	NA	NA	93.9
Hypertension	59.1	60.6	70.9
Congestive heart failure	NA	27.9	25.9
Diabetes mellitus	18.2	23.2	24.3
Peripheral arterial disease	NA	4.3	2.6
History of myocardial infarction	NA	6.4	4.2
Angina pectoris	NA	NA	11.6
Deep venous thrombosis	NA	NA	0.5
Pulmonary embolism	NA	NA	0.3
Aortic aneurysm	NA	NA	1.3
Dyslipidemia	NA	42.4	41.8
Liver dysfunction	NA	NA	5.8
History of stroke/TIA/systemic embolism	NA	21.9	24.2
History of stroke	NA	19.4	22.1
History of ischemic stroke	NA	17.8	20.2
History of hemorrhagic stroke	NA	1.8	1.9
History of TIA	NA	2.4	3.1
History of systemic embolism	NA	1.3	0.8
Therapy of AF			
Pharmacotherapy	NA	NA	60.0
Non-pharmacotherapy	NA	NA	6.1

AF, atrial fibrillation; TIA, transient ischemic attack; NA, not available.

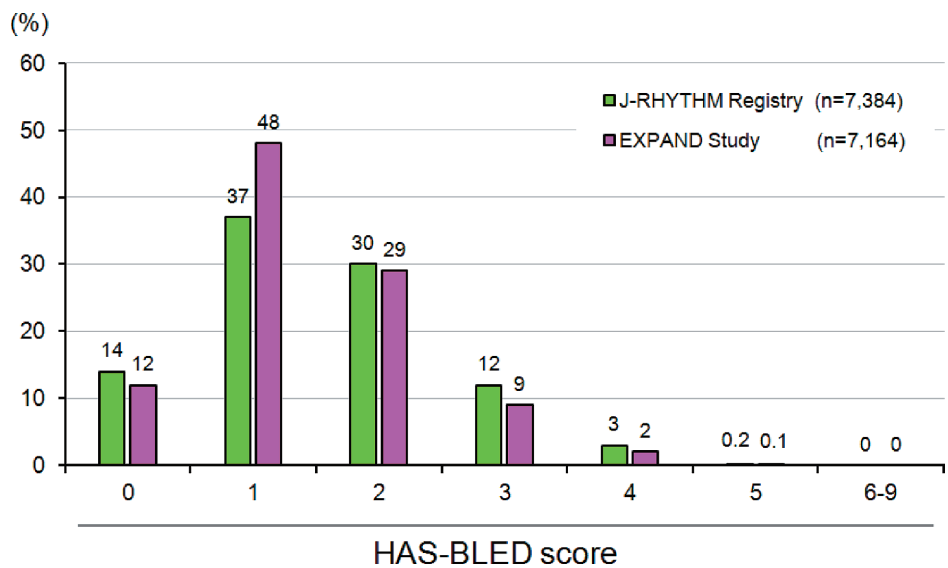

Fig. 2. Patient distribution by HAS-BLED score.
Adapted from J-RHYTHM Registry (Okumura et al. 2014) with permission. HAS-BLED data were not available for the Fushimi registry.

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