

XANAP: A real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation in Asia

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Abstract

Background: ROCKET AF and its East Asian subanalysis demonstrated that rivaroxaban was non-inferior to warfarin for stroke/systemic embolism (SE) prevention in patients with non-valvular atrial fibrillation (NVAF), with a favorable benefit–risk profile. XANAP investigated the safety and effectiveness of rivaroxaban in routine care in Asia-Pacific.

Methods: XANAP was a prospective, real-world, observational study in patients with NVAF newly starting rivaroxaban. Patients were followed at ~3-month intervals for 1 year, or for ≥ 30 days after permanent discontinuation. Primary outcomes were major bleeding events, adverse events (AEs), serious AEs and all-cause mortality; secondary outcomes included stroke/SE. Major outcomes were adjudicated centrally.

Results: XANAP enrolled 2273 patients from 10 countries: mean age was 70.5 years and 58.1% were male. 49.8% of patients received rivaroxaban 20 mg once daily (od), 43.8% 15 mg od and 5.9% 10 mg od. Mean treatment duration was 296 days, and 72.8% of patients had received prior anticoagulation therapy. Co-

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morbidities included heart failure (20.1%), hypertension (73.6%), diabetes mellitus (26.6%), prior stroke/non-central nervous system SE/transient ischemic attack (32.8%) and myocardial infarction (3.8%). Mean CHADS₂, CHA₂DS₂-VASc and HAS-BLED scores were 2.3, 3.7 and 2.1, respectively. The rates (events/100 patient-years [95% confidence interval]) of treatment-emergent major bleeding, stroke and all-cause mortality were 1.5 (1.0-2.1), 1.7 (1.2-2.5) and 2.0 (1.4-2.7), respectively. Persistence was 66.2% at the study end.

Conclusions: The real-world XANAP study demonstrated low rates of stroke and bleeding in rivaroxaban-treated patients with NVAF from Asia-Pacific. The results were consistent with the real-world XANTUS study and ROCKET AF.

KEYWORDS

Asia-Pacific, bleeding risk, real world, rivaroxaban, stroke prevention

1 | INTRODUCTION

The prevalence of non-valvular atrial fibrillation (NVAF) is growing rapidly in Asia, and it is estimated that the number of patients with NVAF in Asia will be greater than the number in Europe and the USA combined by 2050.¹ Data from large clinical trials have clearly indicated differences in the benefit–risk profiles of Asian and Caucasian patients, particularly a higher overall risk of stroke, and greater stroke-related morbidity and mortality in Asian patients.^{2–4} Although treatment with vitamin K antagonists (VKAs) has long been the mainstay of therapy in this setting, warfarin is under-prescribed in Asian countries; antiplatelet therapy is commonly prescribed instead.⁴ As an alternative to VKAs, non-VKA oral anticoagulants (NOACs) could be prescribed in Asian patients with NVAF. The phase III ROCKET AF study showed that rivaroxaban was non-inferior to warfarin for stroke prevention in patients with NVAF, with a reduced incidence of hemorrhagic stroke and ICH compared with warfarin.⁵ A subgroup analysis in East Asian patients showed similar efficacy and safety of rivaroxaban vs warfarin,⁶ as did J-ROCKET AF, which assessed reduced-dose rivaroxaban (15 mg once daily [od]) in Japanese patients with NVAF.⁷ In 2013, the Asia Pacific Heart Rhythm Society (APHRS) added recommendations for the use of NOACs in patients with NVAF.⁸

Real-world evidence is increasingly being recognized as an essential component of the clinical evidence base, to complement phase III data in unselected patient populations and provide additional safety information after approval of new drugs. The prospective, observational XANTUS study investigated the safety and effectiveness of rivaroxaban in patients with NVAF in routine clinical practice in Europe, Israel and Canada.⁹ The results demonstrated low rates of bleeding and stroke/non-central nervous system (CNS) systemic embolism (SE) in a broad, unselected patient population with NVAF.

Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Asia (XANAP) was a sister study to XANTUS and enrolled patients from the Asia-Pacific region. The main goal of this

observational study was to investigate the safety of rivaroxaban use in clinical practice, thereby providing data under real-life conditions.

2 | METHODS

XANAP was a prospective, observational cohort study in unselected patients with NVAF starting rivaroxaban treatment to prevent stroke or non-CNS SE. The study was part of the XANTUS program and, as such, the study protocol was aligned with that of XANTUS, which is published elsewhere.¹⁰

2.1 | Study population and data collection

All study sites were in 10 countries across the Asia-Pacific region: Hong Kong, Indonesia, Malaysia, Pakistan, Philippines, Singapore, South Korea, Taiwan, Thailand and Vietnam. Eligible patients were adults (aged ≥ 18 years) with a diagnosis of NVAF who provided written informed consent to participate in the study and who started rivaroxaban treatment for the prevention of stroke or non-CNS SE in accordance with the country-specific drug approval. Participating investigators were asked to screen all patients with NVAF receiving pharmacological treatment for stroke prevention regardless of the prescribed treatment. This screening documentation occurred before eligible and consenting patients signed the informed consent forms and it was not permissible to collect any patient-related data from the remaining patients. Each patient was consecutively screened and documented in an anonymous patient log file. To reduce selection bias, enrollment was consecutive and no eligible patients were to be omitted.

2.2 | Medication and follow-up

The decision to treat with rivaroxaban was solely at the discretion of the treating physician. Label-recommended doses were prescribed in accordance with the country-specific drug approval. In Taiwan, the approved rivaroxaban dose is 15 or 20 mg od for patients with

creatinine clearance (CrCl) >50 mL/min, and 10 or 15 mg od for patients with CrCl 15–50 mL/min.¹¹ The approved doses of rivaroxaban in the other countries are similar to European label recommendations, ie, 20 mg od for patients with CrCl ≥50 mL/min and 15 mg od for patients with CrCl 15–49 mL/min.¹² Patients were followed up for 1 year or until 30 days after permanent discontinuation of rivaroxaban (if <1 year) and investigators were asked to collect data at approximately 3-month intervals.

2.3 | Study outcomes

The primary outcomes were related to the safety of rivaroxaban and recorded as treatment-emergent adverse events (AEs), serious AEs (SAEs), all-cause mortality and major bleeding events (defined using International Society on Thrombosis and Haemostasis criteria). Secondary outcomes were symptomatic thromboembolic events, non-major bleeding, treatment satisfaction, healthcare resource (number of healthcare professional visits and hospitalizations), treatment persistence and AE/SAE rates in different NVAF risk factor categories. A Central Adjudication Committee adjudicated the endpoints of major bleeding events, stroke, transient ischemic attack (TIA), non-CNS SE, myocardial infarction (MI), pulmonary embolism, deep vein thrombosis, atrial thrombus, and all-cause death.

2.4 | Study governance

The study complied with the Declaration of Helsinki and was approved by the appropriate Health Authorities, the independent

Ethics Committees and independent Review Boards as required. The study was conducted in accordance with Good Pharmacoepidemiological Practice. An independent academic steering committee oversaw the design, execution and conduct of the study; was responsible for manuscript development; had full access to all of the data; and approved all versions of the manuscript.

Data management and statistical analyses were overseen by the sponsor to keep within Good Clinical Practice standards. The lead statistician oversaw programming and validation of the statistical analyses.

2.5 | Statistical analysis

Descriptive statistical analyses were performed on the safety population, which included all patients who took at least 1 dose of rivaroxaban. Events were considered treatment-emergent if they occurred on or after the first dose of rivaroxaban and up to 2 days after the last dose. Statistical analyses were explorative and descriptive in nature. Incidence proportions (number of patients with events/number of treated patients) and incidence rates (events per 100 patient-years) are presented with corresponding Pearson–Clopper and Poisson rate 95% confidence intervals (CIs), respectively.

3 | RESULTS

3.1 | Patient population

A total of 2910 patients were screened between January 2013 and October 2015; 2273 were enrolled in the study. The main reasons for

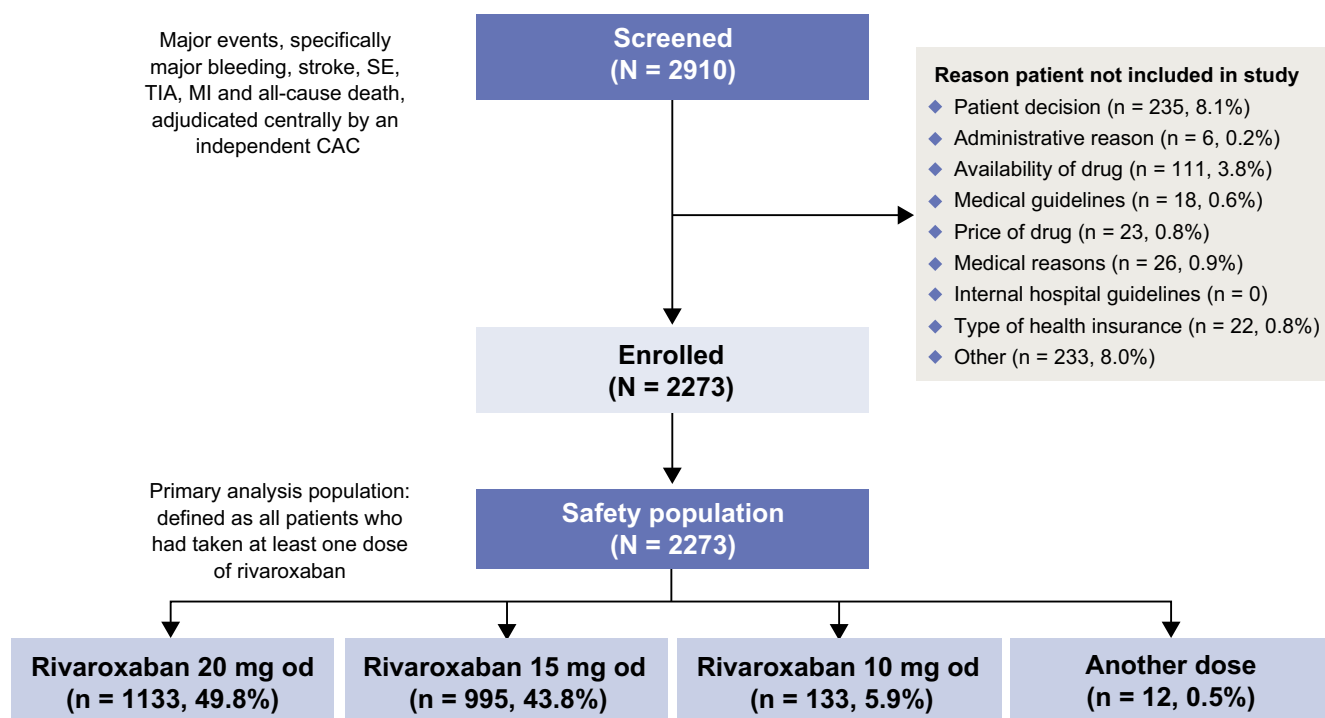


FIGURE 1 Patient disposition. CAC, Central Adjudication Committee; MI, myocardial infarction; od, once daily; SE, systemic embolism; TIA, transient ischemic attack

TABLE 1 Baseline demographics and clinical characteristics of patients in XANAP

	Rivaroxaban (N = 2273)
Age, y, mean ± SD	70.5 ± 10.6
<75 y, n (%)	1364 (60.0)
≥75 y, n (%)	909 (40.0)
Gender, male, n (%)	1320 (58.1)
Weight, kg, mean ± SD	66.1 ± 12.8
BMI, kg/m ² , mean ± SD	25.0 ± 4.0
First available CrCl (mL/min), n (%)	
<15	15 (0.7)
≥15-<30	55 (2.4)
≥30-<50	301 (13.2)
≥50-<80	543 (23.9)
>80	257 (11.3)
Missing	1102 (48.5)
Existing co-morbidities, n (%)	
Congestive heart failure	456 (20.1)
Hypertension	1673 (73.6)
Diabetes mellitus	605 (26.6)
Prior stroke/non-CNS SE/TIA, n (%)	746 (32.8)
Prior MI	86 (3.8)
AF type, n (%)	
First diagnosed	504 (22.2)
Paroxysmal	693 (30.5)
Persistent	576 (25.3)
Permanent	477 (21.0)
Missing	23 (1.0)
CHADS ₂ score, mean ± SD	2.3 ± 1.3
CHA ₂ DS ₂ -VAsC score, mean ± SD	3.7 ± 1.8
HAS-BLED score, mean ± SD	2.1 ± 1.2
Prior antithrombotic therapy, n (%)	
Yes	1449 (63.7)
VKA	813 (35.8)
Direct thrombin inhibitor	149 (6.6)
Acetylsalicylic acid	364 (16.0)
Dual antiplatelet therapy	24 (1.1)
Factor Xa inhibitor (excluding rivaroxaban)	1 (<0.05)
Other	19 (0.8)
Multiple	69 (3.0)

AF, atrial fibrillation; BMI, body mass index; CNS, central nervous system; CrCl, creatinine clearance; MI, myocardial infarction; SD, standard deviation; SE, systemic embolism; TIA, transient ischemic attack; VKA, vitamin K antagonist.

exclusion were because of patient decision (n = 235) and availability of drug (n = 111). All enrolled patients were included in the XANAP safety population (Figure 1). The largest patient populations were from South Korea (844 [37.1%]) and Taiwan (614 [27.0%]). The 8 remaining countries each contributed <10% to the study population. The mean treatment

duration (±standard deviation) was 296 days (±129), with most patients (71%) treated with rivaroxaban for >270 days. Persistence with treatment was 66.2% at the end of the study.

The baseline demographics and clinical characteristics of these patients are shown in Table 1. Of note, the proportion of patients who had received prior anticoagulation therapy was high (72.8%), with 35.9% having received prior VKA monotherapy. Mean patient age was 70.5 years; 40.0% of all patients were aged ≥75 years and 58.1% were male. Overall, 49.8% of patients received an initial rivaroxaban dose of 20 mg od; 43.8% and 5.9% received an initial 15 mg od and 10 mg od dose, respectively (Figure 1). Approximately half (48.5%) of patients had missing CrCl data. Of those patients with reported data, 55.0% of patients with a CrCl ≤49 mL/min received rivaroxaban 15 mg od. In patients with a CrCl ≥50 mL/min, rivaroxaban 20 mg od was the most commonly used dose (in 57.4% of patients; Figure S1). Patients had a mean CHADS₂ score of 2.3, a mean CHA₂DS₂-VAsC score of 3.7 and a mean HAS-BLED score of 2.1. In total, 10.9% of patients had a CHA₂DS₂-VAsC score of 0 or 1. Co-morbidities were as follows: 456/2273 (20.1%) patients had congestive heart failure, 1673 (73.6%) had hypertension, 605 (26.6%) diabetes mellitus, 746 (32.8%) prior stroke/non-CNS SE/TIA and 86 (3.8%) prior MI. There were 504/2273 (22.2%) patients with a first diagnosis of non-valvular AF, 693 (30.5%) with paroxysmal AF, 576 (25.3%) with persistent AF and 477 (21.0%) with permanent AF.

3.2 | Outcomes

Overall, 1.2% (95% CI 0.8-1.7) of the cohort of 2273 patients had adjudicated treatment-emergent major bleeding events (primary

TABLE 2 Summary of causes of adjudicated treatment-emergent deaths

Adjudicated causes of death, ^a n (%)	Deaths (N = 36)
Bleeding	4 (11.1)
Extracranial hemorrhage	1 (2.8)
Intracranial bleeding	3 (8.3)
Cancer	0
Cardiovascular	21 (58.3)
Cardiac decompensation, heart failure	7 (19.4)
Arrhythmia	0
MI	0
Non-hemorrhagic stroke	3 (8.3)
Sudden or unwitnessed death	8 (22.2)
Venous thromboembolism	1 (2.8)
Other vascular events	2 (5.6)
SE	0
Infectious disease	7 (19.4)
Other	3 (8.3)
Unexplained	6 (16.7)

MI, myocardial infarction; SE, systemic embolism.

^aMultiple reasons were recorded for the cause of adjudicated treatment-emergent death of some patients.

outcome), and the incidence rate was 1.5 events/100 patient-years (95% CI 1.0-2.1). There were 4 fatalities (incidence rate: 0.2 events/100 patient-years; 95% CI 0.1-0.6) from adjudicated treatment-emergent major bleeding events. Incidence rates were 0.7 events/100 patient-years (95% CI 0.4-1.2) for ICH and 0.5 events/100 patient-years (95% CI 0.2-0.9) for gastrointestinal (GI) bleeding. Any treatment-emergent AEs and SAEs (primary outcome) occurred in 763/2273 (33.6%) and 272/2273 (12.0%) patients, respectively, with corresponding incidence rates of 50.3 events/100 patient-years (95% CI 46.8-54.0) and 15.6 events/100 patient-years (95% CI 13.8-17.5), respectively. Causes of adjudicated treatment-emergent deaths (primary outcome) are presented in Table 2. All-cause death occurred in 36 patients (1.6%), with cardiovascular death being the most common adjudicated cause of death (21 patients [58.3%], including 3 patients [8.3%] who died from non-hemorrhagic stroke).

Forty-seven patients had adjudicated treatment-emergent symptomatic thromboembolic events (secondary outcome) and the

incidence rate was 2.6 events/100 patient-years (95% CI 1.9-3.4). The incidence rates (number of events/100 patient-years [95% CI]) for stroke (any), TIA, non-CNS SE, stroke/non-CNS SE and MI were 1.7 (1.2-2.5), 0.2 (0.1-0.6), 0.1 (0.0-0.4), 1.9 (1.3-2.6) and 0.5 (0.2-0.9), respectively (Table 3).

Rates of major bleeding events and stroke/non-CNS SE generally rose with increasing CHADS₂ and CHA₂DS₂-VASc scores (Figure 2A, B). No major bleeding events were recorded for patients with a CHA₂DS₂-VASc score of 0 or 1, compared with an incidence rate of 1.6 events/100 patient-years (95% CI 1.1-2.4) in patients with a score of ≥ 2 . Similarly, there were no recorded incidents of stroke/non-CNS SE in patients with a CHA₂DS₂-VASc score of 0 or 1, rising to an incidence rate of 0.7 events/100 patient-years (95% CI 0.1-2.6) in patients with a score of 2, and 3.3 events/100 patient-years (95% CI 1.6-6.1) in patients with scores of 6-9. The incidence of major bleeding increased with age, occurring at a rate of 1.1 events/100 patient-years (95% CI 0.6-1.9) in patients aged <75 years and

TABLE 3 Adjudicated treatment-emergent thromboembolic and bleeding events and all-cause death

	Incidence proportion, % of patients (95% CI)	Incidence rate, number of patients/100 patient-years (95% CI)
Major bleeding	1.2 (0.8-1.7)	1.5 (1.0-2.1)
Fatal	0.2 (0.0-0.4)	0.2 (0.1-0.6)
Bleeding at a critical site	0.6 (0.3-1.0)	0.8 (0.4-1.3)
Intracranial hemorrhage	0.6	0.7 (0.4-1.2)
GI	0.4 (0.2-0.8)	0.5 (0.2-0.9)
Non-major bleeding events	8.8 (7.6-10.0)	11.2 (9.7-12.9)
Thromboembolic events (stroke, TIA, non-CNS SE and MI)	2.1 (1.5-2.7)	2.6 (1.9-3.4)
Stroke/non-CNS SE	1.5 (1.0-2.1)	1.9 (1.3-2.6)
Stroke	1.4 (1.0-2.0)	1.7 (1.2-2.5)
Primary hemorrhagic	0.4	NA
Primary ischemic	0.9	NA
Hemorrhagic transformation	0.1	NA
No hemorrhagic transformation	0.8	NA
Missing	0	NA
Non-CNS SE	0.1 (0.0-0.3)	0.1 (0.0-0.4)
TIA	0.2 (0.0-0.4)	0.2 (0.1-0.6)
MI	0.4 (0.2-0.8)	0.5 (0.2-0.9)
Composite endpoint (stroke/non-CNS SE, major bleeding and all-cause death)	3.4 (2.7-4.2)	4.2 (3.3-5.2)
All-cause death	1.6 (1.1-2.2)	2.0 (1.4-2.7)

CI, confidence interval; CNS, central nervous system; GI, gastrointestinal; MI, myocardial infarction; NA, not available; SE, systemic embolism; TIA, transient ischemic attack.

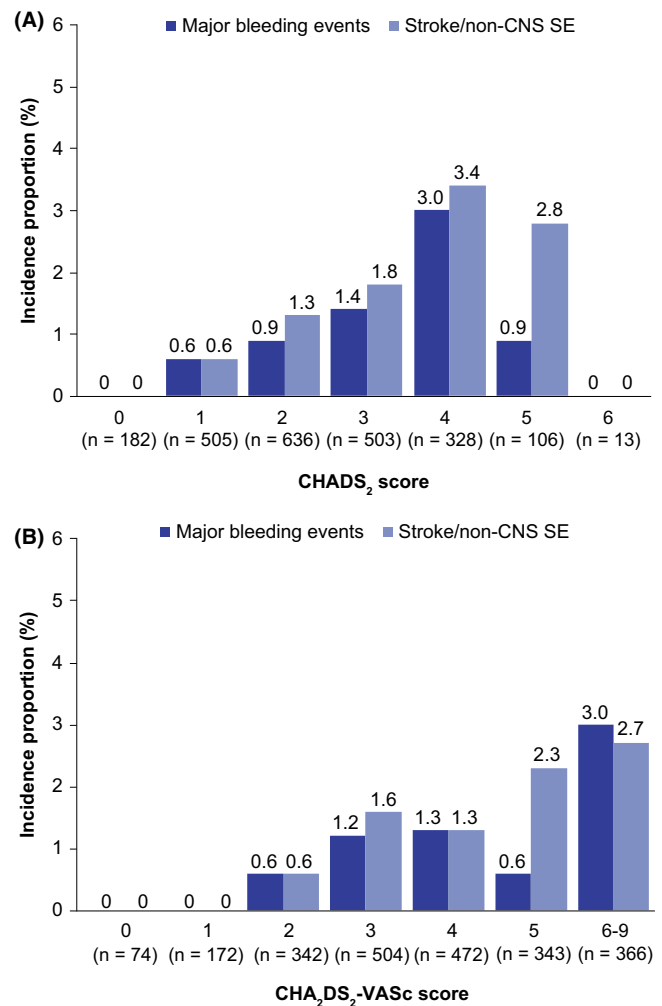
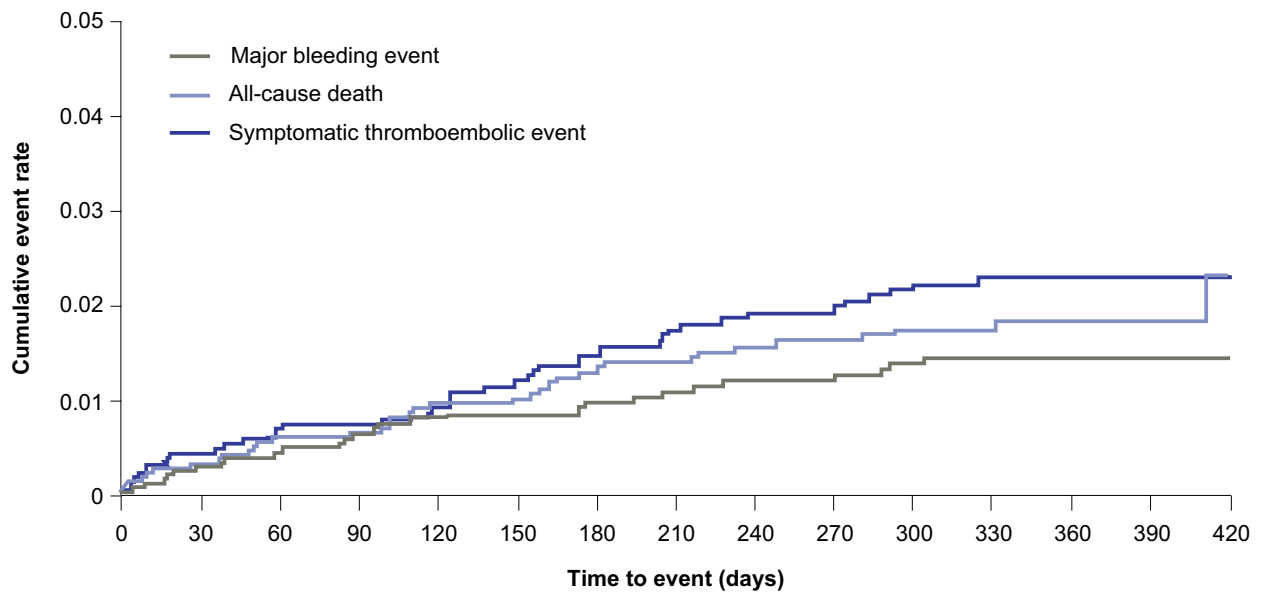


FIGURE 2 A, Incidence proportion of adjudicated treatment-emergent stroke/non-CNS SE and major bleeding by CHADS₂ score; B, Incidence proportion of adjudicated treatment-emergent stroke/non-CNS SE and major bleeding by CHA₂DS₂-VASc score. CNS, central nervous system; SE, systemic embolism



Patients at risk:	2273	2168	2072	1999	1902	1839	1767	1706	1663	1605	1521	1369	958	359	165
	2273	2170	2076	2002	1906	1844	1773	1715	1674	1617	1535	1385	970	361	166
	2273	2170	2076	2001	1904	1845	1773	1713	1672	1614	1530	1379	969	361	166

FIGURE 3 Cumulative rates (Kaplan–Meier) for adjudicated treatment-emergent all-cause death, major bleeding events and symptomatic thromboembolic events

2.1 events/100 patient-years (95% CI 1.2–3.4) in patients aged ≥ 75 years. The corresponding rates for stroke/non-CNS SE were 1.6 events/100 patient-years (95% CI 1.0–2.6) and 2.2 events/100 patient-years (95% CI 1.3–3.6).

The cumulative number of adjudicated treatment-emergent major bleeding events, deaths and symptomatic thromboembolic events increased gradually with time on treatment (Figure 3). Overall, very few patients experienced adjudicated treatment-emergent major bleeding, death, stroke or non-CNS SE (4.2 events/100 patient-years [95% CI 3.3–5.2]). The incidence rates (number of events/100 patient-years [95% CI]) of adjudicated treatment-emergent major bleeding and death were small but numerically higher for patients receiving rivaroxaban 15 mg od compared with those receiving rivaroxaban 20 mg od (1.5 [0.8–2.6] vs 1.1 [0.5–2.0] and 2.2 [1.3–3.5] vs 1.5 [0.8–2.6], respectively [Figure S2]). Rates of treatment-emergent outcomes by renal function, and by renal function and dose in patients receiving rivaroxaban 15 mg od or 20 mg od, are shown in Figures S3 and S4, respectively. The endpoints of adjudicated treatment-emergent thromboembolic, and bleeding events and all-cause death are detailed in Table 3.

3.3 | Additional outcomes

In total, 116 patients (5.1%) had at least 1 interruption to rivaroxaban treatment, which was most commonly due to bleeding (31 patients) or surgery (26 patients). The median treatment interruption was 7 days (interquartile range: 3–23 days). The majority of patients (83.2%) had no unscheduled hospital or general practitioner visits

because of the use of rivaroxaban. The majority of patients (60.6%) reported to their physicians that they were either “very satisfied” or “satisfied” with rivaroxaban treatment; a further 26.1% of patients were “neutral”, 6.9% were “unsatisfied”, 0.8% were “very unsatisfied” and data were missing for 5.5%.

4 | DISCUSSION

The XANAP study provides insights into the routine clinical use of rivaroxaban in Asian patients with NVAf. XANAP is the first prospective, observational study to describe rivaroxaban use in a broad, real-world patient population with NVAf in 10 countries of the Asia-Pacific region. Findings are broadly consistent when cautiously compared with those of the observational sister study (XANTUS) in Europe, Canada and Israel,⁹ and with the subanalysis of East Asian patients in the phase III ROCKET AF study,⁶ taking into consideration differences in baseline characteristics. In XANAP, rivaroxaban demonstrated relatively low rates of stroke/non-CNS SE and low rates of major bleeding, including intracranial and GI bleeding. Over 96% of patients with a mean CHADS₂ score of 2.3 receiving rivaroxaban did not experience any of the outcomes of stroke/non-CNS SE, treatment-emergent major bleeding or all-cause death.

The profile of the patient population in XANAP was substantially different from that in XANTUS (Table 4).⁹ Differences included a higher proportion of patients with prior stroke/non-CNS SE/TIA, lower mean weight (although weight data were unavailable for 28% of XANAP patients), a higher proportion of patients with moderate

or severe renal impairment (with the caveat that CrCl data were not reported for approximately half [48.5%] of patients in XANAP and approximately one-third [34.4%] of patients in XANTUS) and slightly higher mean CHADS₂, CHA₂DS₂-VASc and HAS-BLED scores. These scores were originally derived from Caucasian populations to calculate stroke and bleeding risk in patients with NVAF; however, they have also been shown to be predictive of future stroke and bleeding risk in some Asian populations.⁴ Based on these scores, NVAF can be calculated to raise the relative risk of stroke fivefold in Caucasian populations, compared with a more modest increase in risk of 2.8–3.7-fold, depending on the Asian population studied.⁴ Finally, persistence at 1 year was lower in XANAP compared with XANTUS (66%

vs 80%; Table 4). It is of note that this result is consistent with the treatment persistence reported in a recent large retrospective database analysis of US patients treated with rivaroxaban for stroke prevention (N = 10 878; 60.1% persistence to rivaroxaban therapy at 1 year).¹³ However, it should be pointed out that the US patient population in this analysis was enrolled in a different healthcare system to those countries in the XANAP studies.¹³ The lower persistence in XANAP vs XANTUS may reflect lower medication adherence in developing countries, which were highly represented in XANAP.¹⁴ Other reasons for the lower persistence rate in XANAP may include issues related to reimbursement, or a lack of follow-up provision of prescriptions from general practitioners after an initial

TABLE 4 XANAP results in the context of similar clinical trials in different patient populations with atrial fibrillation

	ROCKET AF global ^{a,b} 5,24 (N = 7131) ^c	J-ROCKET AF ^{b,d} 7 (N = 639) ^e	ROCKET AF East Asia ^{a,b} 6 (N = 468) ^f	XANTUS ^{a,g} 9 (N = 6784)	XANAP ^{a,g} (N = 2273)
Baseline characteristics					
Age, y, mean	73 ^h	71	70	71.5	70.5
Weight, kg, mean	–	–	67.3	83	66
CrCl <50 mL/min, %	20.7 ⁱ	22	–	9.4	16.3
Congestive heart failure, %	63	41	39	19	20
Hypertension, %	90	80	79	75	74
Diabetes, %	40	39	38	20	27
Prior stroke/SE/TIA, %	55	64	65	19	33
Mean CHADS ₂ score	3.5	3.3	3.2	2.0	2.3
Mean CHA ₂ DS ₂ -VASc score	–	–	4.4	3.4	3.7
Mean HAS-BLED score	2.8 ^j	–	2.9	2.0	2.1
Use of rivaroxaban 15 mg od dose, %	20.7 ⁱ	–	–	21	44 (+6% 10 mg)
Major outcomes (events/100 patient-years)					
Major bleeding	3.6	3.0	3.4	2.1	1.5
Fatal	0.2	0.1	0.2	0.2	0.2
In critical organ	0.8	1.5	0.7	0.7	0.8
ICH	0.5	0.8% ^k	0.6	0.4	0.7
GI	2.0 ^l	1.3% ^k	–	0.9	0.5
Stroke/SE	1.7	1.3	2.6	0.8	1.9
Stroke	1.7	1.6% ^k	2.6	0.7	1.7
Ischemic	1.3	1.1% ^k	2.1	0.5 ^k	0.9% ^k
Hemorrhagic	0.3	0.5% ^k	0.5	0.2 ^k	0.4% ^k
SE	<0.1	0.2% ^k	0	0.1	0.1
MI	0.9	0.5% ^k	1.0	0.4	0.5
Thromboembolism (stroke, SE, TIA, MI)	–	–	–	1.8	2.6
All-cause death	1.9	1.1% ^k	2.6	1.9	2.0
Hemoglobin drop	2.8	1.5	3	0.9	0.1
Transfusions	1.6	0.5	1.2	0.9	0.6
All bleeding	–	–	–	~17.5	~12.7
Major bleeding + clinically relevant non-major bleeding	15	18	21	–	–

(Continues)

TABLE 4 (Continued)

	ROCKET AF global ^{a,b} 5,24 (N = 7131) ^c	J-ROCKET AF ^{b,d} 7 (N = 639) ^e	ROCKET AF East Asia ^{a,b} 6 (N = 468) ^f	XANTUS ^{a,g} 9 (N = 6784)	XANAP ^{a,g} (N = 2273)
Unknown type of stroke	0.1	0	0.1 ^m	0	0.2% ^k
AE	81% ^k	–	–	40	50.3
SAE	–	24% ^k	23.2% ^k	18	15.6
1-y persistence, %	–	–	–	80	66

AE, adverse event; CrCl, creatinine clearance; GI, gastrointestinal; ICH, intracranial hemorrhage; MI, myocardial infarction; od, once daily; SAE, serious adverse event; SE, systemic embolism; TIA, transient ischemic attack.

^aThe rivaroxaban dose was 20 mg od, with the ROCKET AF, ROCKET AF East Asian subanalysis, XANTUS and XANAP studies also having a rivaroxaban 15 mg od dose in patients with renal impairment (30–49 mL/min in ROCKET AF and East Asian subanalysis; 15–49 mL/min in XANTUS and XANAP).

^bThe primary outcome for ROCKET AF, ROCKET AF East Asian subanalysis and J-ROCKET AF was the composite of stroke (ischemic and hemorrhagic) and SE.

^cBleeding outcomes in the safety population (n = 7111), efficacy outcomes in the safety, on-treatment population, which excluded 1 site for violation of Good Clinical Practice (n = 7061).

^dThe rivaroxaban dose was 15 mg od in J-ROCKET AF, with a rivaroxaban 10 mg od dose in patients with renal impairment (CrCl 30–49 mL/min).

^eBleeding outcomes in the safety, on-treatment population (n = 639), efficacy outcomes in the per protocol, on treatment population (n = 637).

^fBleeding outcomes in the safety, on-treatment population (n = 466), efficacy outcomes in the intention-to-treat population (n = 468).

^gThe primary outcomes for XANTUS and XANAP were related to the safety of rivaroxaban and recorded as treatment-emergent AEs and SAEs, all-cause mortality and major bleeding events (defined using International Society on Thrombosis and Haemostasis criteria).

^hMedian age.

ⁱReported in Fox et al.²⁵

^jReported in Breithardt et al.²⁶

^kIncidence proportion.

^lReported in Sherwood et al.²⁴

^mIn intention-to-treat population.

hospital prescription. Taken together, these differences indicate that the Asian population in XANAP was at higher risk of stroke and bleeding than the European and Canadian population in XANTUS, which is consistent with the observed higher incidence of hemorrhagic stroke and ICH in Asian patients.⁴ Further comparisons show that XANAP patients were at lower risk of these outcomes than patients in the ROCKET AF East Asian subanalysis⁶ and J-ROCKET,⁷ with CHADS₂ scores of 2.3 vs 3.2 and 3.3, respectively (CHA₂DS₂-VASc score of 3.7 in XANAP, vs 4.4 in the ROCKET AF East Asian subanalysis; Table 4).

Overall rates of major bleeding, including major GI bleeding, were lower in patients in XANAP than observed in XANTUS, the ROCKET AF East Asian subanalysis and J-ROCKET (Table 4).^{6,9} The reason for the lower rates of bleeding in XANAP is not completely understood. It is unlikely to simply be a result of the higher proportion of patients in XANAP receiving rivaroxaban 15 mg od, as the findings are consistent with the lower overall bleeding rates observed in rivaroxaban-treated patients in ROCKET AF from East Asia⁶ and China,¹⁵ compared with patients outside these regions. However, rates of ICH were higher in XANAP compared with XANTUS, but similar to those in the ROCKET AF East Asian subanalysis. This concurs with previously observed higher rates of ICH in Asian populations,^{16,17} which are thought to be because of increased cerebral microbleeds in Asian patients⁴ and can be affected by extremes in body mass index and specific apolipoprotein alleles.¹⁶ By contrast, fatal bleeding rates in XANAP were similar to those in XANTUS, the ROCKET AF East Asian subanalysis and J-ROCKET (Table 4).^{6,9}

The rates of stroke/non-CNS SE in XANAP were higher than those in XANTUS, but lower than those observed in the ROCKET AF East Asian subanalysis; this was consistent with the higher stroke risk and proportion of patients with prior stroke/SE/TIA involved in the ROCKET AF East Asian subanalysis (65%, vs 19% in XANAP; Table 4). Stroke is noted in the literature as being a particular risk for Asian patients with NVAf compared with their Caucasian counterparts.^{4,18–20} This is consistent with the higher proportion of patients with prior stroke/non-CNS SE/TIA at baseline in XANAP (33%, vs 19% in XANTUS). It is possible that this apparently inherent higher risk of stroke in Asian populations contributed to the higher rate of stroke/non-CNS SE in XANAP. In addition, a potential effect of the ~twofold higher proportion of patients receiving the rivaroxaban 15 mg od dose on increased stroke/SE rates in XANAP cannot be completely excluded. However, it is unclear to what extent the higher proportion of patients receiving the reduced dose would represent inappropriate dosing, as there was a large proportion (48.5%) of patients with unreported CrCl data in XANAP. Additionally, regional differences in the Taiwan label (27% of the XANAP population: recommended dose of rivaroxaban 15 or 20 mg od in patients with CrCl >50 mL/min and rivaroxaban 10 or 15 mg od in patients with CrCl 15–50 mL/min¹¹) mean that the majority of the Taiwanese patients with CrCl ≥50 mL/min receiving the 15 mg dose were on label. It is also possible that physicians prescribed reduced rivaroxaban 15 mg od to patients with a higher co-morbidity burden who were more at risk of AEs; in XANTUS, rates of major outcomes were worse in patients receiving the reduced rivaroxaban dose.⁹ However, it is also of note that the rivaroxaban 15 mg od dose was not

associated with higher stroke/SE rates than warfarin in Japanese patients enrolled in the J-ROCKET AF trial or in patients included in a large retrospective Danish registry analysis.^{21,22} Another possible contributor to the higher stroke/SE rate in XANAP was the lower rate of persistence observed in XANAP compared with XANTUS (66% vs 80%), because breaks in anticoagulation could leave patients with NVAF at higher risk of stroke. Of note, the incidence rate of stroke/non-CNS SE in XANAP of 1.9 events/100 patient-years is lower than that reported in a recent retrospective cohort study of Taiwanese patients with NVAF; the annual rate in patients taking rivaroxaban (N = 3916) was 3.07 events/100 patient-years (95% CI 2.12-4.02) vs 5.62 events/100 patient-years (95% CI 4.48-6.76) in those receiving warfarin (N = 5251).²³ However, caution must be exercised in comparing data from a retrospective database with the observational study presented here.

Unlike XANTUS, where cancer was one of the main adjudicated causes of death in 19.5% of the patients who died,⁹ the number of patients with active cancer at baseline, and consequently of patients who died of cancer, was much lower in XANAP than in XANTUS. This may explain why the proportion of cardiovascular deaths was higher in XANAP compared with XANTUS (58.3% vs 41.5%). These results cannot be compared with those of the phase III ROCKET AF study because XANAP, like other observational studies, did not select patients based on strict inclusion criteria. In contrast, phase III studies typically exclude patients with competing co-morbidities, such as active cancer or short life expectancy. The baseline characteristics of patients enrolled in these trials and the follow-up periods were different; therefore, it is difficult to make meaningful comparisons of mortality rates between such different types of studies.

4.1 | Limitations

XANAP was a real-world, single-arm study and, as with any open-label study, the study design can introduce bias related to knowledge about treatment. Moreover, interference with patient management was not allowed because of the non-interventional nature of the study. In particular, this resulted in a relatively high proportion of patients (48.5%) with missing renal function data, similar to observations in the XANTUS study (in which CrCl measurements were unavailable for 34.4% of patients).⁹ Because of the observational nature of the study, it is possible that CrCl was measured but not documented by the prescribing physician for some patients, which would have contributed to the missing data. Additionally, because rivaroxaban prescription was at the discretion of the treating physician, and a relatively important proportion of CrCl data were missing, some patients may not have received the label-recommended dose of rivaroxaban.

5 | CONCLUSIONS

XANAP is the first real-world, prospective, observational study to describe rivaroxaban use in a broad patient population with NVAF in

10 countries of the Asia-Pacific region. XANAP had low rates of stroke/non-CNS SE and major bleeding, including GI and fatal bleeding. When taking differences in baseline risk factors into consideration, findings were consistent with XANTUS and the phase III ROCKET AF study and the subsequent subanalysis in East Asian patients. This is particularly relevant in terms of CHADS₂ and CHA₂DS₂-VASc scores, which were similar to those in XANTUS, but lower than those in the ROCKET AF East Asian subanalysis.

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CONFLICT OF INTEREST

YHK, JS and SM have nothing to disclose. CTT has been a speaker/moderator/story investigator for Bayer, Boehringer Ingelheim, Daiichi Sankyo and MSD. CCW has received consulting fees and honoraria from Bayer, Boehringer Ingelheim, Daiichi Sankyo and Pfizer/Bristol-Myers Squibb. GV has received consulting fees and honoraria from Bayer, Sanofi and Novartis. MK has advised and spoken for Bayer, Boehringer Ingelheim and Pfizer. OM has been involved in research for Bayer, Boehringer Ingelheim and Pfizer/Bristol-Myers Squibb, and received consulting fees and honoraria from Bayer, Boehringer Ingelheim and Pfizer/Bristol-Myers Squibb. LFH has been involved in research for Bayer and Boehringer Ingelheim. THN has been a speaker/moderator/story investigator for AstraZeneca, Bayer, Boehringer Ingelheim, Medtronic and Sanofi. AJC has conducted research, advised and spoken for Bayer, Boehringer Ingelheim, Pfizer/Bristol-Myers Squibb and Daiichi Sankyo. KS is an employee of Bayer AG; TT was an employee of Bayer AG during the study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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