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Global Prospective Safety Analysis of Rivaroxaban

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ABSTRACT

BACKGROUND The efficacy of direct oral anticoagulants (DOACs) for stroke prevention in patients with atrial fibrillation (AF) has been established in clinical trials. However, well-conducted, prospective, real-world observational studies of the safety and effectiveness of DOACs are needed.

OBJECTIVES This study sought to assess the real-world safety profile of rivaroxaban through a pooled analysis of patients with AF enrolled in the XANTUS (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation) program worldwide.

METHODS A pre-planned pooled analysis of the XANTUS, XANAP (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Asia), and XANTUS-EL (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Latin America and EMEA Region) registries was performed. Patients with AF newly starting rivaroxaban for stroke prevention were followed for 1 year. Primary outcomes were treatment-emergent major bleeding, adverse events (AEs)/serious AEs, and all-cause death. Secondary outcomes included treatment-emergent thromboembolic events and nonmajor bleeding. Major outcomes were centrally adjudicated.

RESULTS Overall, 11,121 patients were included (mean age 70.5 ± 10.5 years; female 42.9%). Comorbidities included heart failure (21.2%), hypertension (76.2%), and diabetes (22.3%). Event rates were: events/100 patient-years: major bleeding 1.7 (95% confidence interval [CI]: 1.5 to 2.0; lowest: Latin America 0.7; highest: Western Europe, Canada, and Israel 2.3); all-cause death 1.9 (95% CI: 1.6 to 2.2; lowest: Eastern Europe 1.5; highest: Latin America, Middle East, and Africa 2.7); and stroke or systemic embolism 1.0 (95% CI: 0.8 to 1.2; lowest: Latin America 0; highest: East Asia 1.8). One-year treatment persistence was 77.4% (lowest: East Asia 66.4%; highest: Eastern Europe 84.4%).

CONCLUSIONS This large, prospective, real-world analysis in 11,121 patients from 47 countries showed low bleeding and stroke rates in rivaroxaban-treated patients with AF, with low treatment discontinuation in different regions of the world. Results were broadly consistent across regions. (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation [XANTUS]; NCT01606995; Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Latin America and EMEA Region [XANTUS-EL]; NCT01800006; and Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Asia [XANAP]; NCT01750788) (J Am Coll Cardiol 2018;72:141–53) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AE = adverse event
AF = atrial fibrillation
CNS = central nervous system
CrCl = creatinine clearance
DOAC = direct oral anticoagulant
ICH = intracranial hemorrhage
ISTH = International Society on Thrombosis and Haemostasis
MI = myocardial infarction
o.d. = once daily
SAE = serious adverse event
SE = systemic embolism
TIA = transient ischemic attack
VKA = vitamin K antagonist

Atrial fibrillation (AF) is estimated to affect 33.5 million patients worldwide (1). Although often asymptomatic, AF is associated with a major disease burden, including stroke, cardiovascular death, and heart failure, as well as unplanned hospitalizations, which often have cardiovascular causes (2,3). Use of appropriate anticoagulation can greatly reduce the risk of ischemic stroke in patients with AF (4,5), with options including vitamin K antagonists (VKAs) and the direct oral anticoagulants (DOACs) (apixaban, dabigatran, edoxaban, and rivaroxaban). On the basis of the results of large phase III trials that demonstrated the favorable benefit-risk profile of DOACs over VKAs (5–9), various guidelines recommend DOACs as an alternative, or in preference to, VKAs (10,11). DOACs are increasingly used for stroke prevention in patients with AF (12). Real-world evidence complements the results from phase III trials and is important for assessing the safety and effectiveness of approved medications and in obtaining information on patterns of use in routine clinical practice (13).

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The XANTUS program provides a unique source of real-world data on the use of rivaroxaban for stroke prevention in patients with AF. The XANTUS program included 3 prospective studies conducted in 47 countries from different regions of the world, providing a broad spectrum of global data. Patients were enrolled from Western and Eastern Europe, Canada, and Israel in the XANTUS (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation) study, the Asia-Pacific region in the XANAP (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Asia) study, and Eastern Europe, the Middle East, Africa, and Latin America in the XANTUS-EL (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Latin America and EMEA Region) study (14,15). The purpose of this pooled analysis of the XANTUS, XANAP, and XANTUS-EL studies was to assess the global safety profile of rivaroxaban in routine clinical practice.

METHODS

We performed a pre-planned pooled analysis of the studies in the XANTUS program (the XANTUS, XANAP, and XANTUS-EL studies). Detailed methods have been described previously (14,15). The XANTUS, XANAP, and XANTUS-EL studies were international, prospective, observational, noninterventional cohort studies in consenting adult patients (≥18 years of age) with AF initiating rivaroxaban for the prevention of stroke or non-central nervous system (non-CNS) systemic embolism (SE). Patients were prescribed rivaroxaban in accordance with country-specific drug approvals. The label-recommended dose is rivaroxaban 20 mg once daily (o.d.) in patients with creatinine clearance (CrCl) ≥50 ml/min and 15 mg o.d. in patients with CrCl <50 ml/min in all included countries except Taiwan, where either rivaroxaban 15 mg o.d. or 20 mg o.d. can be prescribed for patients with CrCl >50 ml/min and either 10 mg o.d. or 15 mg o.d. can be prescribed for patients with CrCl 15 to 50 ml/min (16,17). In order to limit selection bias, participating investigators were asked to enroll consecutive patients by screening and documenting patients with a diagnosis of AF in an anonymous patient log file. The screening documentation was completed before eligible, consenting patients signed an informed consent form, and it was not permitted for patient-related data to be collected from the remaining ineligible or nonconsenting patients.

Patients were enrolled from 47 countries across 5 regions of the world (Western Europe/Canada/Israel: Austria, Belgium, Canada, Denmark, France, Germany, Ireland, Israel, the Netherlands, Norway,

Markers for Atrial Fibrillation WO 2016012783). Dr. Radaideh has received consulting fees and honoraria from Bayer, Sanofi, Merck Sharp & Dohme, Takeda, and Servier. Dr. Lanas has been a consultant for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. Dr. Haas has been a consultant for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Pfizer, and Sanofi. Dr. Amarenco has been a consultant for Boehringer Ingelheim, Edwards, GlaxoSmithKline, Lundbeck, Medtronic, Merck, ShingPoon, and Kowa Pharmaceutical; has served as an executive committee member for AstraZeneca, Bayer, and Pfizer: has served on the Data Safety Monitoring Board for Fibrogen; has served on the advisory boards for Bristol-Myers Squibb and Daiichi-Sankyo; and has received grants from AstraZeneca, Bristol-Myers Squibb, Boston Scientific, Pfizer, and Sanofi. Dr. Turpie has been a consultant for Bayer, Janssen Pharmaceutical Research & Development, and Portola. Drs. Bach and Hess are employees of Bayer AG. Dr. Bach holds stock in Bayer AG. Mr. Lambelet is an employee of Chrestos Concept, which received funding for this analysis from Bayer AG. Dr. Camm has been a consultant for Aryx, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Johnson & Johnson, Pfizer, and Sanofi; and has received grants from Bayer, Boehringer Ingelheim, and Daiichi-Sankyo. Dr. Kim has reported that he has no relationships relevant to the contents of this paper to disclose.

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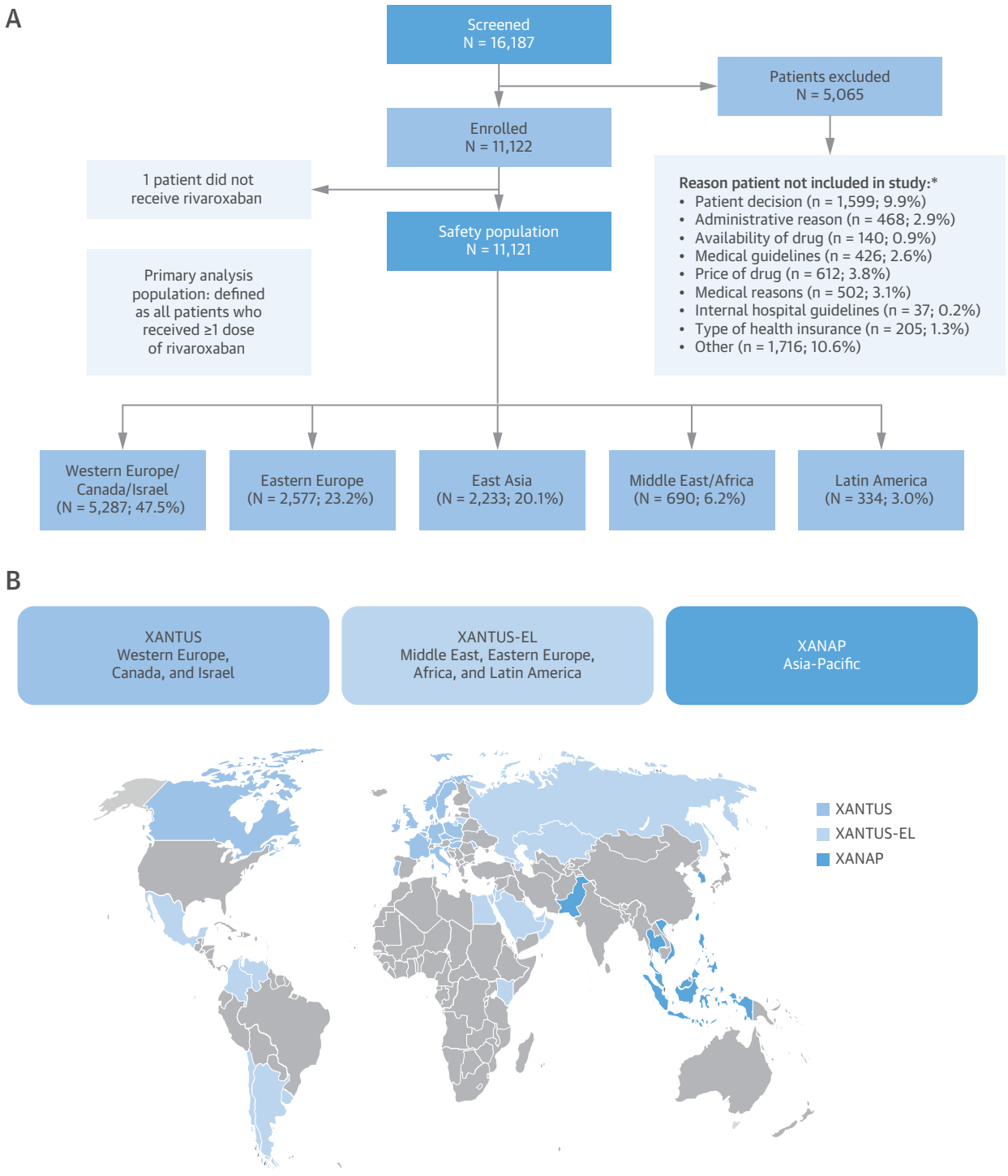
FIGURE 1 **Overview of the XANTUS Pooled Analysis**



(A) Patient disposition in the XANTUS pooled analysis. **(B)** Countries involved in the 3 studies that make up the XANTUS program. *Reasons for not continuing in the study included, but were not limited to, patient decision and administrative and medical reasons; some patients could have >1 reason for exclusion. XANAP = Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Asia; XANTUS = Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation; XANTUS-EL = Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Latin America and EMEA Region.

TABLE 1 Baseline Demographics and Patient Characteristics of Patients Enrolled in the Worldwide XANTUS Program (N = 11,121)

Age, yrs	70.5 ± 10.5
<65	2,884 (25.9)
65 to 75	4,372 (39.3)
>75	3,865 (34.8)
Male	6,354 (57.1)
First available weight, kg	80.0 ± 17.8
BMI, kg/m^2	28.0 ± 5.2
BMI >30 kg/m^2	2,523 (22.7)
First available creatinine clearance, ml/min	
<15	47 (0.4)
≥15 to <30	166 (1.5)
≥30 to <50	1,061 (9.5)
≥50 to ≤80	3,478 (31.3)
>80	2,320 (20.9)
Missing	4,049 (36.4)
Pre-existing comorbidities	
Hypertension	8,476 (76.2)
Diabetes mellitus	2,484 (22.3)
Prior stroke/TIA/non-CNS SE	2,372 (21.3)
Congestive HF	2,359 (21.2)
Prior MI	994 (8.9)
Hospitalization at baseline	2,072 (18.6)
Type of AF	
First diagnosed	2,049 (18.4)
Paroxysmal	4,147 (37.3)
Persistent	1,798 (16.2)
Permanent	3,084 (27.7)
Missing	43 (0.4)
$CHADS_2$ score	2.0 ± 1.3
$CHADS_2$ score	
0	1,016 (9.1)
1	3,199 (28.8)
2	3,351 (30.1)
3	1,956 (17.6)
4	1,140 (10.3)
5	401 (3.6)
6	58 (0.5)
Missing	0
CHA_2DS_2-VASc score	3.5 ± 1.7
CHA_2DS_2-VASc score	
0	301 (2.7)
1	1,045 (9.4)
2	2,026 (18.2)
3	2,527 (22.7)
4	2,305 (20.7)
5	1,446 (13.0)
6–9	1,468 (13.2)
Missing	3 (<0.05)
HAS-BLED score	2.0 ± 1.1
HAS-BLED score	
0	742 (6.7)
1	3,051 (27.4)
2	4,293 (38.6)
≥3	3,016 (27.1)
Missing	19 (0.2)
Prior antithrombotic therapy	
Yes	7,583 (68.2)
No	3,538 (31.8)
Type of prior antithrombotic therapy	
VKA	4,119 (37.0)
DTI	427 (3.8)
ASA (excluding DAPT)	2,004 (18.0)
DAPT	115 (1.0)
Factor Xa inhibitor (excluding rivaroxaban)	17 (0.2)
Heparin	264 (2.4)
Other antithrombotic agents	80 (0.7)
Multiple	557 (5.0)

Values are mean ± SD or n (%).

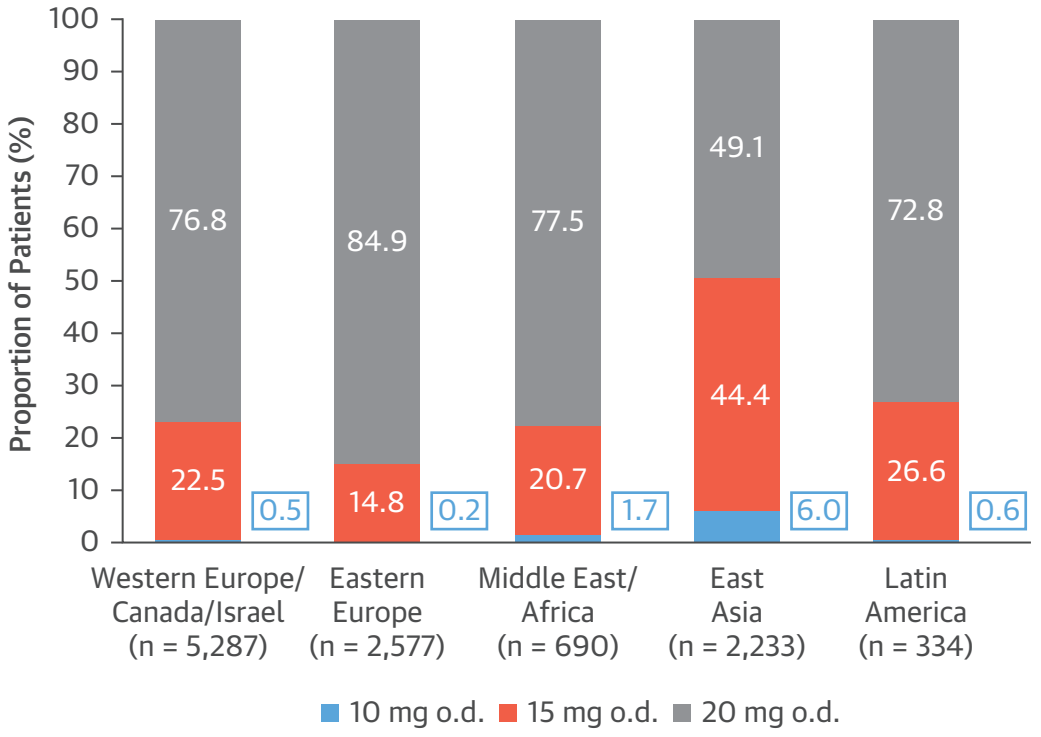
AF = atrial fibrillation; ASA = acetylsalicylic acid; BMI = body mass index; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack; CHA_2DS_2 -VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65-74 years, sex category (female); CNS = central nervous system; DAPT = dual antiplatelet therapy; DTI = direct thrombin inhibitor; HAS-BLED = hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; HF = heart failure; MI = myocardial infarction; SD = standard deviation; SE = systemic embolism; TIA = transient ischemic attack; VKA = vitamin K antagonist.

Continued in the next column

Portugal, Sweden, and the United Kingdom; Eastern Europe: Azerbaijan, the Czech Republic, Georgia, Hungary, Kazakhstan, Moldova, Poland, Russia, Slovakia, Slovenia, and Ukraine; the Middle East/Africa: Bahrain, Egypt, Jordan, Kenya, Lebanon, Pakistan, Saudi Arabia, and the United Arab Emirates; East Asia: Hong Kong, Indonesia, Malaysia, the Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam; and Latin America: Argentina, Chile, Colombia, Mexico, Uruguay, and Venezuela). All patients were followed up for 1 year, or for ≥30 days after permanent discontinuation of rivaroxaban (if <1 year); investigators were asked to collect data at approximately 3-month intervals. Differences in the timing of regulatory approval between countries meant that the studies were completed in subsets of global regions.

Primary outcomes were related to the safety of rivaroxaban and recorded as treatment-emergent adverse events (AEs) or serious adverse events (SAEs). They included major bleeding events (using the International Society on Thrombosis and Haemostasis [ISTH] definition), all-cause death, and any other AEs and SAEs. Events were considered treatment-emergent if they occurred from the day of the first dose of rivaroxaban, and up to 2 days after the last dose in the event of permanent discontinuation of rivaroxaban. Secondary outcomes included symptomatic thromboembolic events, nonmajor bleeding,

FIGURE 2 Initial Daily Dose of Rivaroxaban by Region



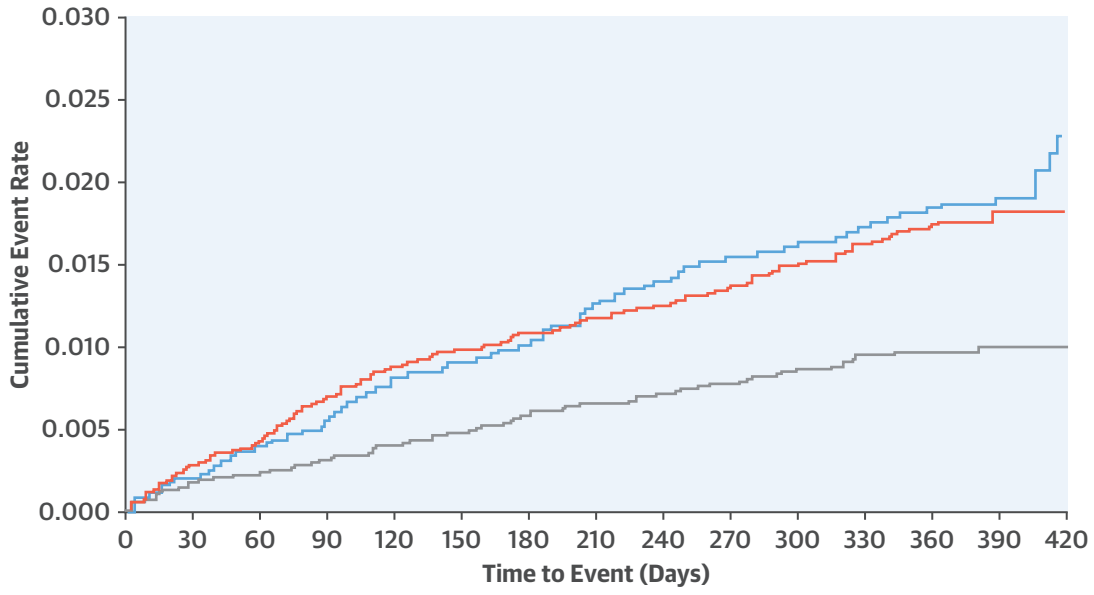
Other rivaroxaban doses included doses <10 mg o.d. and >20 mg o.d., and were received by 0.10% in Western Europe/Canada/Israel; 0.04% in Eastern Europe; 0% in the Middle East and Africa; 0.54% in East Asia; and 0% in Latin America. Only 3 patients, all from Western Europe/Canada/Israel (0.1%), had missing dosing information. o.d. = once daily.

treatment satisfaction, treatment persistence, and reasons for treatment interruption. Treatment satisfaction was assessed using standardized patient questionnaires (Anti-Clot Treatment Scale) in selected countries and additionally by the physician at the final visit. Hemorrhagic strokes were reported as both stroke and major bleeding events. All major outcomes (including major bleeding, stroke, SE, transient ischemic attack [TIA], myocardial infarction [MI], and all-cause death) were reviewed and adjudicated by a central adjudication committee, which had access to all patient data. Statistical analyses, performed on the full safety population, were exploratory and included a descriptive analysis of the primary and secondary outcome variables.

RESULTS

PATIENT POPULATION. In total, 16,187 patients were screened between June 2012 and December 2014, and 11,122 of these patients were enrolled from 554 centers worldwide (311, 111, and 132 centers for the XANTUS, XANAP, and XANTUS-EL studies, respectively); 1 patient did not receive rivaroxaban and was excluded from this analysis (**Figure 1**). A total of 5,287 (47.5%) patients were included in the safety analysis from Western Europe/Canada/Israel, 2,577 (23.2%) from Eastern Europe, 2,233 (20.1%) from East Asia, 690 (6.2%) from the Middle East/Africa, and 334 (3.0%) from Latin America. Israel was grouped with Western Europe and Canada on the basis of a similar health care system. Baseline demographics and clinical characteristics are summarized in **Table 1**. Mean patient age was 70.5 years, and 57.1% of patients were male. Comorbidities associated with stroke and/or bleeding events were common and included congestive heart failure (21.2%), hypertension (76.2%), diabetes mellitus (22.3%), and prior stroke/non-CNS SE/TIA (21.3%). The mean $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack) and CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65-74 years, sex category [female]) scores were 2.0 and 3.5, respectively. In total, 31.8% of patients were

CENTRAL ILLUSTRATION **Safety of Rivaroxaban: Cumulative Rates**



Major bleeding	11,121	10,720	10,394	10,138	9,823	9,618	9,439	9,239	9,091	8,917	8,703	8,313	6,734	1,862	844
Stroke/non-CNS SE	11,121	10,729	10,404	10,155	9,842	9,637	9,456	9,257	9,108	8,939	8,724	8,332	6,748	1,864	843
Death	11,121	10,726	10,403	10,153	9,847	9,646	9,471	9,272	9,125	8,961	8,751	8,351	6,772	1,871	845

Kirchhof, P. et al. J Am Coll Cardiol. 2018;72(2):141–53.

Kaplan-Meier curves for treatment-emergent all-cause death, major bleeding events, and stroke/non-CNS SE.

anticoagulation- or antiplatelet therapy-naive at baseline; 37.0% of patients previously received a VKA; 4.0% received a direct thrombin inhibitor or Factor Xa inhibitor; and 18.0% received acetylsalicylic acid.

Of 11,121 patients who completed the study, 8,540 patients (76.8%) were observed for the full 12 months. Rivaroxaban treatment was prematurely discontinued in 2,566 patients (23.1%), and data for 15 patients were missing. Of those patients in whom rivaroxaban was prematurely ended, the documented reason for treatment discontinuation was given by the investigator as patient decision in 794 (7.1%) patients; an AE in 724 patients (6.5%); a reason other than an AE in 381 (3.4%) patients; and entering stable sinus rhythm in 176 (1.6%) patients. The majority of patients (n = 8,126 [73.1%]) initially received rivaroxaban 20 mg o.d., with 2,795 (25.1%), 179 (1.6%), and 18 (0.2%) patients initially receiving rivaroxaban 15 mg o.d., rivaroxaban 10 mg o.d., and other rivaroxaban doses (30 mg, 25 mg, 7.5 mg, or 2.5 mg o.d.), respectively. Dosing information was missing for 3 patients. The reasons for initial dose selection were not recorded during the study. Breakdown of dosing by region (**Figure 2**) revealed that rivaroxaban 15 mg o.d. was prescribed least often in Eastern Europe (14.8% of patients) and prescribed most often in East Asia (44.4% of patients), where local labeling recommendations differ; in Taiwan (n = 614), the approved rivaroxaban dose for patients with CrCl >50 ml/min is 15 or 20 mg o.d., and is 10 or 15 mg o.d. for patients with CrCl 15 to 50 ml/min (16). The approved doses of rivaroxaban in other countries included in the study are 20 mg o.d. for patients with CrCl ≥50 ml/min and 15 mg o.d. for patients with CrCl 15 to 49 ml/min (17). The median duration of treatment was 366 days (interquartile range: 330 to 379 days), and the mean treatment duration was 324.5 ± 117.80 days.

Differences in patient demographics, clinical characteristics, and stroke and bleeding risks were apparent between study regions (Online Table 1). Patients enrolled from Western Europe/Canada/Israel, East Asia, and Latin America were older, on average,

than patients enrolled in Eastern Europe and the Middle East/Africa, whereas obesity (body mass index >30 kg/m^2) was more prevalent in patients from Eastern Europe, the Middle East/Africa, and Latin America compared with other regions. The highest prevalence of hypertension, congestive heart failure, and prior MI was reported in patients from Eastern Europe, whereas patients from East Asia had the highest prevalence of prior stroke/TIA/non-CNS SE. Almost twice as many Middle Eastern/African patients had diabetes mellitus versus other regions of the world. The lowest stroke risk scores were found in patients from Western Europe/Canada/Israel and the Middle East/Africa; Middle Eastern/African and Latin American patients had the lowest bleeding risk scores.

OUTCOMES. Overall, the number of patients experiencing treatment-emergent major bleeding or thromboembolic events or death was low (**Central Illustration**). More than 96% of patients did not experience any of the outcomes of treatment-emergent stroke/non-CNS SE, major bleeding, or all-cause death.

There were 190 treatment-emergent major bleeding events in 172 patients (1.7 events/100 patient-years) (**Table 2**). The incidence of fatal bleeding was 0.2 events/100 patient-years; critical organ bleeding occurred at a rate of 0.6 events/100 patient-years and included intracranial hemorrhage (ICH) at a rate of 0.4 events/100 patient-years. The most common site for major bleeding was the gastrointestinal tract: 71 patients experienced major gastrointestinal bleeding (0.7 events/100 patient-years). Overall, 179 patients experienced 196 symptomatic thromboembolic events (1.8 events/100 patient-years) (**Table 2**). These included 87 patients with stroke (0.9 events/100 patient-years), 41 with TIA (0.4 events/100 patient-years), 11 with systemic embolic events (0.1 events/100 patient-years), and 42 with MI (0.4 events/100 patient-years). The incidence of ischemic and hemorrhagic stroke was 0.6 and 0.2 events/100 patient-years, respectively. Rates of major safety and effectiveness outcomes are summarized in **Figure 3**.

The proportion of patients alive and free from major bleeding or stroke/non-CNS SE was consistent between regions (95.7% to 97.4%) (Online Figure 1, Online Table 2). Although broadly similar, there were subtle differences in the incidences of major outcomes between regions. Major bleeding was higher in Western Europe/Canada/Israel compared with the range of rates observed in the other regions assessed (2.3 vs. 0.7 to 1.6 events/100 patient-years), stroke/non-CNS SE was highest in East Asia (1.8 vs. 0 to 1.0), and mortality was highest in the Middle East/Africa and Latin America (2.7 vs. 1.5 to 2.0). The rates of major bleeding, stroke/non-CNS SE, and all-cause death were generally consistent between patients with and without prior antithrombotic therapy across regions (Online Figure 2, Online Table 3).

In total, 3,796 patients (34.1%) had a treatment-emergent AE and 1,647 patients (14.6%) had a treatment-emergent SAE. As expected, the incidence of major bleeding and stroke/non-CNS SE increased with age; the incidence rates of major bleeding in patients <65, 65 to 75, and >75 years of age were 0.8, 1.4, and 2.9 events/100 patient-years, respectively.

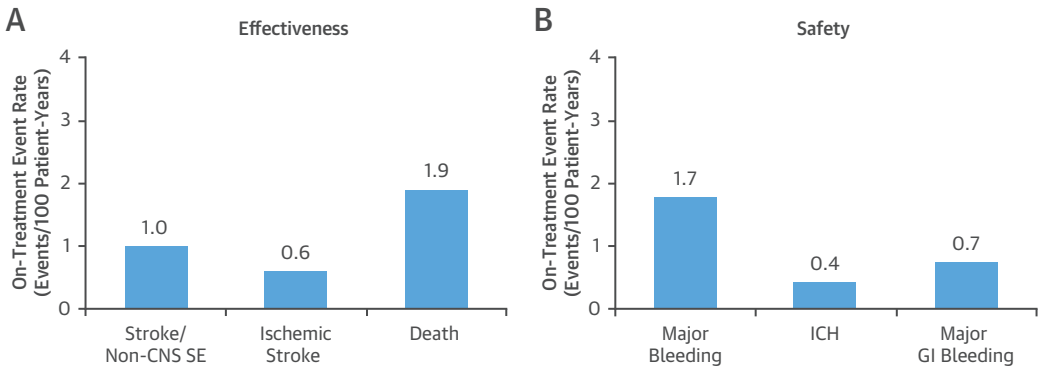
TABLE 2 Treatment-Emergent Thromboembolic and Bleeding Events, and All-Cause Death in the Study Population

	Incidence Proportion	Incidence Rate Events/100 Patient-Years (95% CI)
All-cause death	187 (1.7)	1.9 (1.6–2.2)
Major bleeding	172 (1.5)	1.7 (1.5–2.0)
Fatal bleeding*	17 (0.2)	0.2 (0.1–0.3)
Critical organ bleeding	62 (0.6)	0.6 (0.5–0.8)
Intracranial hemorrhage	42 (0.4)	0.4 (0.3–0.6)
Intraparenchymal	12 (0.1)	–
Subarachnoid	6 (0.1)	–
Intraventricular	9 (0.1)	–
Subdural hematoma	8 (0.1)	–
Epidural hematoma	1 (<0.05)	–
Hemorrhagic transformation of ischemic stroke	6 (0.1)	–
Missing	4 (<0.05)	–
Mucosal bleeding	80 (0.7)	0.8 (0.6–1.0)
Gastrointestinal bleeding	71 (0.6)	0.7 (0.6–0.9)
Hemoglobin decrease ≥2 g/dl	58 (0.5)	0.6 (0.4–0.8)
Transfusion of ≥2 U of packed RBCs or whole blood	73 (0.7)	0.7 (0.6–0.9)
Nonmajor bleeding events	1,195 (10.7)	12.8 (12.1–13.5)
Symptomatic thromboembolic events (stroke, non-CNS SE, TIA, or MI)	179 (1.6)	1.8 (1.6–2.1)
Stroke/non-CNS SE	98 (0.9)	1.0 (0.8–1.2)
Stroke†	87 (0.8)	0.9 (0.7–1.1)
Primary hemorrhagic	20 (0.2)	0.2 (0.1–0.3)
Primary ischemic	64 (0.6)	0.6 (0.5–0.8)
Hemorrhagic transformation	6 (0.1)	–
No hemorrhagic transformation	58 (0.5)	–
Uncertain	6 (0.1)	–
Non-CNS SE	11 (0.1)	0.1 (0.1–0.2)
TIA	41 (0.4)	0.4 (0.3–0.6)
MI	42 (0.4)	0.4 (0.3–0.6)
Any treatment-emergent AE	3,796 (34.1)	47.2 (45.7–48.8)
Any treatment-emergent serious AE	1,627 (14.6)	17.7 (16.8–18.5)

Values are n (%) unless otherwise indicated. *Fatal bleeding using narrow definitions (the patient experienced a treatment-emergent major bleeding event and died within 30 days of the major bleeding event and the adjudicated primary cause of death was either intracranial hemorrhage or extracranial bleeding. †hemorrhagic strokes and hemorrhagic transformations of ischemic stroke were adjudicated as both stroke and major bleeding. Multiple reasons for major bleedings were possible.

AE = adverse event; RBC = red blood cell; other abbreviations as in **Table 1**.

FIGURE 3 Summary of the Key Effectiveness and Safety Outcomes in the XANTUS Pooled Analysis



The **(A)** effectiveness and **(B)** safety outcomes are shown. CNS = central nervous system; GI = gastrointestinal; ICH = intracranial hemorrhage; SE = systemic embolism.

The corresponding rates of stroke/non-CNS SE were 0.5, 1.1, and 1.2 events/100 patient-years, respectively. Likewise, outcome analysis according to $CHADS_2$ and CHA_2DS_2-VASc scores showed that rates of major bleeding, stroke/non-CNS SE, and all-cause death tended to increase with increasing risk scores (**Figure 4**).

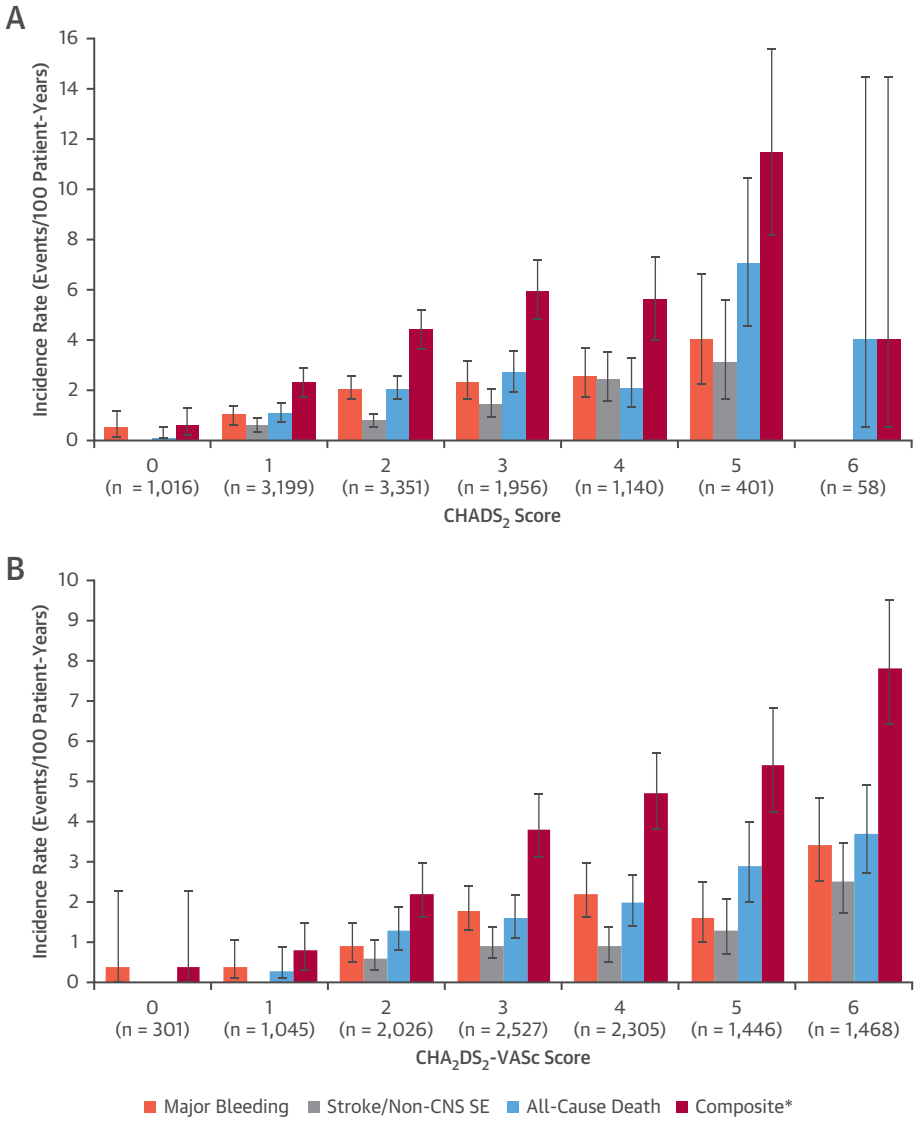
CrCl values were reported in 7,072 patients (63.6%) during the study; of these, 18.0% had CrCl <50 ml/min and 82% had CrCl ≥50 ml/min. CrCl measurements were available for more patients in Western Europe/Canada/Israel and Eastern Europe than in the other regions of the world (66.4% to 71.7% vs. 51.8% to 55.1%) (Online Table 1). Incidence rates for major bleeding, all-cause death, and stroke/non-CNS SE tended to increase with decreasing renal function; rates tended to be lowest in patients with no available CrCl data (**Figure 5A**). Rates (events/100 patient-years) in patients with CrCl ≥15 to <30 ml/min versus patients with CrCl >80 ml/min were major bleeding 6.1 versus 1.6; all-cause death 6.7 versus 1.3; and stroke/non-CNS SE 1.5 versus 0.8.

According to the rivaroxaban label, dosing is determined solely by renal function; in all countries included in the XANTUS program, with the exception of Taiwan, the label-recommended dose is rivaroxaban 20 mg o.d. in patients with CrCl ≥50 ml/min and 15 mg o.d. in patients with CrCl 15 to 49 ml/min. Analysis of rivaroxaban dosing by renal function showed that, of 5,798 patients with a documented CrCl ≥50 ml/min, 4,677 (80.7%) received the label-recommended dose of rivaroxaban 20 mg o.d., 1,061 (18.3%) received rivaroxaban 15 mg o.d., and 58 (1.0%) received other nonrecommended doses. In Taiwan, both rivaroxaban 15 mg o.d. and 20 mg o.d. are approved in patients with a CrCl >50 ml/min. Thus, the 117 of the 1,061 patients with CrCl ≥50 ml/min receiving rivaroxaban 15 mg o.d. from Taiwan likely received a label-recommended dose.

Of the 1,227 patients with CrCl 15 to 49 ml/min, 467 (38.1%) received a nonrecommended dose of rivaroxaban 20 mg o.d., 705 (57.5%) received the recommended dose of rivaroxaban 15 mg o.d., and 55 (4.5%) received doses <15 mg o.d. In Taiwan, both rivaroxaban 10 mg o.d. and 15 mg o.d. are approved for use in patients with CrCl 15 to 50 ml/min, and 61 of the 190 patients who received rivaroxaban doses <15 mg o.d. were Taiwanese; therefore, some of the patients with CrCl 15 to 49 ml/min who received rivaroxaban doses <15 mg o.d. were likely to have been Taiwanese and dosed in accordance with their local label. In total, 47 patients with CrCl <15 ml/min received a nonrecommended dose of rivaroxaban. Incidence rates for major bleeding, stroke/non-CNS SE, and all-cause death tended to increase with decreasing rivaroxaban dose (**Figure 5B**). Rates (events/100 patient-years) in patients receiving rivaroxaban 20 mg, 15 mg, or <15 mg o.d. were: major bleeding 1.5, 2.3, and 4.6; all-cause death 1.4, 3.2, and 5.8; and stroke/non-CNS SE 0.8, 1.3, and 4.6, respectively.

ADDITIONAL OUTCOMES. Overall, treatment persistence at 1 year (defined as patients who continued treatment after their 1-year visit; patients who died before 1 year were classified as nonpersistent) was 77.4%; between regions, persistence rates varied from 66.4% in East Asia to 76.2%-78.8% in the Middle East/Africa, Latin America, and Western Europe/Canada/Israel, and 84.4% in Eastern Europe. At the final visit, the majority of patients (72.9%) were either

FIGURE 4 Outcomes as a Function of $CHADS_2$ and CHA_2DS_2-VASc Scores

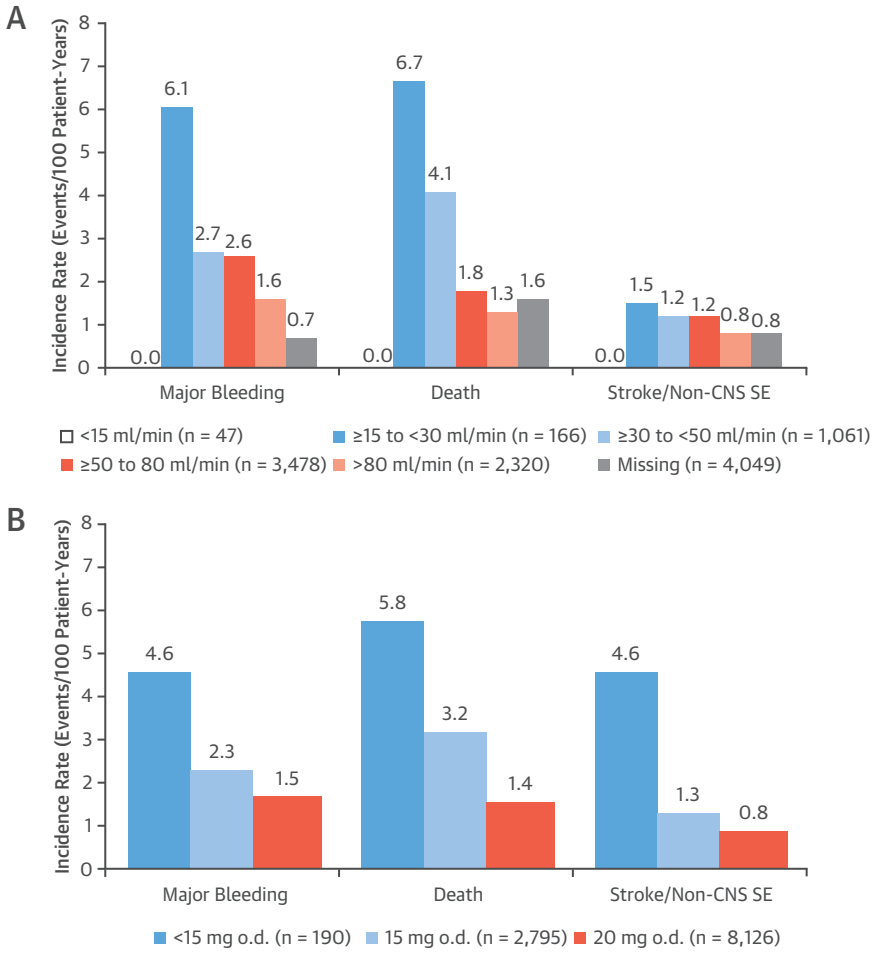


(A) $CHADS_2$ and **(B)** CHA_2DS_2-VASc scores. There were 3 patients with missing CHA_2DS_2-VASc scores who did not experience any of the outcomes of major bleeding, all-cause death, or stroke/non-CNS SE. *Composite of major bleeding, stroke/non-CNS SE, and all-cause death. $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category (female); other abbreviations as in Figure 3.

"satisfied" or "very satisfied" with their treatment. A further 16% of patients were "neutral," 4.9% were "unsatisfied," and 1.3% were "very unsatisfied." No treatment satisfaction data were available for 4.9% of patients.

In total, 914 treatment interruptions were reported in 771 patients (6.9%); the median duration of treatment interruption was 5 days (interquartile range: 2 to 13 days); heparin bridging therapy was used in 137 (15%) interruptions. The most common reasons for treatment interruption were bleeding in 236 patients (25.8%), surgery in 250 patients (27.4%), and nonbleeding AEs in 161 patients (17.6%). Among patients with treatment interruption, major bleeding and symptomatic thromboembolic events were reported in 37 patients (4.8%) and 15 patients (1.9%), respectively, during the interruption or until 2 days after the interruption. If the event occurred on the

FIGURE 5 Outcomes as a Function of CrCl and Initial Rivaroxaban Dose



(A) Creatinine clearance and **(B)** initial rivaroxaban dose. Data from 10 patients who received rivaroxaban doses >20 mg o.d. or had no dosing information available are not shown: 1 of these patients experienced a major bleeding event; none of these 10 patients died or had a stroke/non-CNS SE. CrCl = creatinine clearance; o.d. = once daily; other abbreviations as in Figures 2 and 3.

same date as the treatment interruption, however, the possibility that the outcome event occurred before the interruption cannot be excluded.

Rivaroxaban dose was changed at least once in 639 patients (5.7%); dose was changed only once in the majority of these patients (n = 567), with AEs being the most common reason for a dose change. Dose changes were more common in patients with CrCl <50 ml/min (10.6%) than in those with a CrCl ≥50 ml/min or unknown CrCl (5.1%). Major bleeding events were mostly treated medically, and nonspecific reversal agents were rarely used; of the 172 patients who experienced a major bleeding event, use of tranexamic acid was documented in 5 patients, blood coagulation factors in 3 patients, and the hemostatic agent etamsylate in 2 patients.

DISCUSSION

The entire XANTUS program, which analyzed data from 11,121 patients worldwide, is the largest prospective, observational, noninterventional study to date of a single DOAC for stroke prevention in patients with AF. The results from this pooled analysis showed that patients with AF throughout the world had low rates of stroke and major bleeding in the first year after initiating rivaroxaban, and that fatal and critical organ bleeding events, including ICH, were rare, occurring in ≤0.6% of patients.

In the XANTUS global pooled analysis, incidence rates of major outcomes, which were centrally adjudicated, were numerically lower than those reported in rivaroxaban-treated patients from other real-world

studies. In 1,204 patients with AF treated with rivaroxaban in the prospective Dresden NOAC Registry, the rates of major bleeding were 3.0 events/100 patient-years compared with 1.7 events/100 patient-years in the XANTUS program, whereas rates of thromboembolic events were broadly similar (1.7 events/100 patient-years for stroke/TIA/SE in the XANTUS program vs. 1.0 and 0.4 events/100 patient-years for stroke/non-CNS SE and TIA in the Dresden NOAC Registry, respectively) (18). In retrospective database studies, similar differences in major bleeding rates have been observed, with 2.84 events/100 patient-years being reported in 44,793 U.S. (Department of Defense) patients (vs. 1.7 events/100 patient-years in the XANTUS program) (19). By contrast, ICH rates reported from a large American retrospective database analysis were similar to those in the XANTUS pooled analysis, with 0.49%/year reported in 11,411 U.S. patients versus 0.4 events/100 patient-years in the XANTUS pooled analysis (20,21). The numerically lower rates of major bleeding reported in the XANTUS program compared with these other studies are likely to reflect differences in study design. A major strength of the XANTUS pooled analysis is the adjudication of outcome events by a central committee; this contrasts with large claims database analyses, which have relied on retrospective information coded in claims databases to define events in the absence of adjudication. Other factors that may account for the lower rates of bleeding in the XANTUS program include possible self-selection bias by patients for stroke and bleeding risk; investigator bias during patient selection; major bleeding definitions (ISTH major bleeding vs. major bleeding identified from coding in patient databases); differences in patient baseline characteristics and risk profiles (e.g., differences in prior use of antithrombotics); as well as differences in the rivaroxaban doses received (Online Table 4). The rates of major bleeding, stroke/non-CNS SE and all-cause death were generally similar between patients with and without prior antithrombotic therapy (Online Figure 2, Online Table 3). This suggested that the differences in event rates observed between regions were unlikely to be due to differences in prior antithrombotic therapy.

The label-recommended dose is similar in all countries (rivaroxaban 20 mg o.d. in patients with CrCl ≥50 ml/min; rivaroxaban 15 mg o.d. in patients with CrCl <50 ml/min) except Taiwan, where patients with CrCl >50 ml/min can be prescribed either rivaroxaban 15 mg o.d. or 20 mg o.d., and 10 mg o.d. or 15 mg o.d. can be prescribed in patients with CrCl 15 to 50 ml/min. The majority of patients received rivaroxaban doses in accordance with the label; over three-quarters of patients with available CrCl measurements received the recommended rivaroxaban dose in accordance with their renal function. The finding that overall rates of major outcomes increased with decreasing rivaroxaban dose received suggests that patients with an on-label recommendation to receive a reduced rivaroxaban dose may be of poorer health and more prone to AEs than patients who are label-recommended to receive the standard rivaroxaban dose. Accordingly, rates of major bleeding, all-cause death, and stroke/non-CNS SE stratified by CrCl increased with decreasing CrCl. The fact that just over one-fifth of patients received rivaroxaban doses not aligned with their renal function and that CrCl data were unavailable for more than one-third of patients indicates a need for continued education of physicians, with the aim of ensuring that rivaroxaban is prescribed in accordance with the label. Nonetheless, the fact that event rates for the major outcomes were low in patients with unreported CrCl data suggests that physicians are adept at identifying lower-risk patients without assessment of CrCl. Another factor that could have affected the results is the fact that the European Society of Cardiology (ESC) guidelines on the management of AF at the time of the XANTUS study recommended a dose reduction in patients with a HAS-BLED score ≥3 (22). Although this was not recommended by the label, and has been changed in the current ESC guidelines (22), it could account for the prescription of rivaroxaban 15 mg o.d. in some patients without renal impairment. This could be due to planned interventions (e.g., cardioversion or ablation), other stroke risk factors that are not captured in the CHA_2DS_2-VASc score, or other reasons. The proportion of patients in the XANTUS program receiving rivaroxaban with CHA_2DS_2-VASc scores of 0 or 1 was comparable to that of other reports, for example, the ORBIT AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), PREFER in AF (PREvention oF thromboembolic events—European Registry in Atrial Fibrillation), EORP (EURObservational Research Programme), or GARFIELD-AF (Global Anticoagulant Registry in the FIELD-Atrial Fibrillation) studies (23–25).

Subtle differences in patient baseline characteristics and event rates were noted between regions in the XANTUS program. The higher mortality in Middle Eastern/African and Latin American patients, the lower incidence of major bleeding in Eastern European and Latin American patients, and the higher incidence of stroke/non-CNS SE in East Asian patients (each vs. other regions) were broadly consistent with the results of the RE-LY (Randomized Evaluation of Long-Term Anticoagulation therapY) atrial fibrillation Registry and Cohort Study. This suggests regional differences in baseline characteristics of patients may account for differences in outcomes (26). In support

of this, the latter finding of a higher incidence of stroke/non-CNS SE in patients of Asian origin corroborates other findings identifying this patient population as being at particularly high risk of stroke (27,28). Patients from East Asia also had lower rates of major bleeding than patients from Western Europe, despite having a similar mean HAS-BLED (hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol) score; the reasons for these differences are not fully understood. A major cause is simply the higher proportion of patients from East Asia receiving the 15-mg dose, but the findings are also in keeping with the overall lower rates of major bleeding observed in rivaroxaban-treated patients from East Asia (29) and China (30) enrolled in the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), relative to the ROCKET AF population excluding these regions. By contrast, the lower rates of major bleeding and ICH observed in the XANTUS-EL study are consistent with a lower mean HAS-BLED score in these patients than the respective scores in both the XANTUS and XANAP studies. Regional variations in treatment persistence were also noted and broadly correlated with the differences in stroke/non-CNS SE event rates; the lowest persistence (66.4%) was observed in patients from East Asia, where the highest rate of stroke/non-CNS SE was observed (1.8 events/100 patient-years), whereas the highest persistence (84.4%) and lowest rate of stroke/non-CNS SE (0.5 events/100 patient-years) was observed in patients from Eastern Europe. Up to 33.6% of patients discontinued treatment, illustrating the need to develop care models that ensure consistent delivery of evidence-based therapy in different regions of the world.

Strengths of this analysis include the large sample size: with 11,121 patients analyzed, this is the largest, pre-planned, prospective pooling of studies of a DOAC for stroke prevention in patients with AF to date, identifying only minor regional variations in outcomes in patients with AF treated with rivaroxaban. Moreover, the prospective nature of the studies, with adjudicated endpoints, allows for greater completeness of data and the potential for higher quality data than retrospective designs. The independent endpoint adjudication by the same committee for the entire XANTUS program may have reduced reporting bias.

STUDY LIMITATIONS. Key limitations of the studies included in the XANTUS program were the single-arm, open-label design. As with any open-label study, the study design can introduce bias related to knowledge about treatment. This was a global analysis, but patients from the United States or regions of China besides Hong Kong were not included. Furthermore, interference with patient management was not allowed because of the noninterventional nature of the program; this resulted in a relatively low number of patients with available renal function data, which limits any implications these data may have. In addition, because patients agreed to participate in the study, this may have to some extent led to self-selection for risk of stroke and bleeding. A selection bias around, for example, intact cognitive function, could, therefore, have arisen with the investigator and might have had an impact on the low rates of stroke and bleeding.

CONCLUSIONS

The XANTUS program pooled is the largest prospective, observational analysis of a single DOAC used for stroke prevention in patients with AF. This unique pooled analysis, with central adjudication of outcomes, combined data from 3 prospective, noninterventional, multicenter analyses and enrolled >11,000 patients from Western Europe, Israel, Canada, Asia-Pacific, Eastern Europe, the Middle East, Africa, and Latin America. The results were consistent across different regions and patient populations worldwide, based on each of the individual rivaroxaban studies, and further expand the body of evidence on the safety of patients with AF receiving rivaroxaban for stroke prevention. Overall, rivaroxaban showed a favorable safety profile, with >96% of the pooled rivaroxaban population not experiencing any of the events of treatment-emergent major bleeding, stroke/non-CNS SE or all-cause death over a follow-up period of approximately 1 year. Low rates of major bleeding (including major gastrointestinal bleeding) and stroke/non-CNS SE were observed in these rivaroxaban-treated patients in routine clinical practice.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: In a pooled analysis of several practice-based registries, patients with AF had generally low rates of stroke, bleeding, and treatment discontinuation and results were broadly consistent across different regions of the world.

TRANSLATIONAL OUTLOOK: Additional research is needed to understand the reasons that rivaroxaban and other anticoagulant drugs are occasionally prescribed in doses and clinical situations other than as recommended.

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KEY WORDS atrial fibrillation, real-world, rivaroxaban, safety, stroke prevention, XANTUS

APPENDIX For supplemental figures and tables, please see the online version of this paper.