INTERNATIONAL, LARGE-SCALE, REAL-WORLD CLINICAL DATA CONFIRM THE SAFETY PROFILE OF RIVAROXABAN

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ABSTRACT

Rivaroxaban is a direct factor Xa inhibitor and a non-vitamin K antagonist (VKA) novel oral anticoagulant (NOAC) approved for a number of indications. It has been approved since 2011 by both the United States Food and Drug Administration and the European Medicines Agency for use in patients with non-valvular atrial fibrillation (NVAF) to reduce the risk of stroke and systemic embolism. However, anticoagulant therapy (both VKAs and NOACs) has been associated with an increased risk of bleeding. Although the majority of bleeding events are minor from a clinical standpoint (e.g. ecchymoses), major bleeding events have also been reported. This warrants the need for robust and large-scale clinical and safety data to guide physicians in patient selection, risk stratification, and treatment choice. While NOACs have been subject to a number of randomised clinical trials, observational studies, and real-world registries, large-scale observational studies are still scarce. This article reviews the newly published data from the XANTUS and the United States Department of Defense post-marketing safety surveillance studies, two landmark real-world observational studies on rivaroxaban use and safety in NVAF patients, and puts them in perspective with regard to clinical trial data and other real-world data. Both sets of results were presented at the European Society of Cardiology Congress on 31st August, 2015. This data collection represents more than 45,000 patients from 22 countries.

Keywords: Non-valvular atrial fibrillation, bleeding, stroke, rivaroxaban, real-world data.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is estimated to affect about 10 million patients in Europe.[1] This number is expected to rise, with a lifetime risk of 22–26%. Patients with AF display a 5-fold risk of experiencing a stroke.[2-4]

Oral anticoagulation therapy to reduce the risk of stroke in patients with AF is partly represented by vitamin K antagonists (VKAs), such as warfarin, which have been available for decades and are a standard prophylactic therapy. However, warfarin use has been associated with a number of challenges in daily clinical practice, including many drug–drug and drug–food interactions, and can represent a burden for many patients due to the need for strict monitoring, dose titration, and patient education in order to remain in the therapeutic window with an international normalised ratio of 2.0–3.0.

A novel pharmacological class, novel oral anticoagulants (NOACs), has emerged in the past decade. This class includes, in historical order, dabigatran, rivaroxaban, apixaban, and edoxaban. All four of these compounds have been demonstrated to be as effective as VKAs for stroke prevention in patients with non-valvular AF (NVAF), and subsequently approved in that indication.[5-8] Rivaroxaban is a direct factor Xa inhibitor NOAC approved for a number of indications. It has been approved since 2011 by both the United States

Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the reduction of risk of stroke and systemic embolism (SE) in patients with NVAF. However, anticoagulant therapy (both VKAs and NOACs) has been associated with an increased risk of bleeding.[7,9] Although the majority of bleeding events are minor from a clinical standpoint (e.g. ecchymoses), major bleeding events have also been reported. This warrants the need for robust and large-scale efficacy and safety data to guide physicians in patient selection, risk stratification, and treatment choice. While NOACs have been subject to a number of randomised clinical trials, observational studies, and real-world registries, large-scale observational studies are still scarce.

This article reviews the newly published data from the XANTUS and the United States Department of Defense post-marketing safety surveillance (US DoD PMSS) studies, two landmark real-world observational studies on rivaroxaban use and safety in NVAF patients, and puts them in perspective with regard to both clinical trial data and other real-world data. Both sets of results were presented at the European Society of Cardiology (ESC) Congress on 31st August, 2015. This data collection represents more than 45,000 patients from 22 countries.

THE XANTUS STUDY

The XANTUS study (NCT01606995) was a large, international, real-world, prospective, single-arm, observational, post-authorisation, non-interventional study that aimed to collect clinical safety and efficacy data on rivaroxaban for stroke prevention in a cohort of patients with NVAF.[10] This study was the first large study to describe the use of rivaroxaban in routine clinical practice for NVAF in a broad patient population, and was designed in agreement with the EMA. Camm et al.[11] presented the preliminary results of this study at ESC Congress 2015. This presentation was accompanied by a peer-reviewed article published on the same date in the *European Heart Journal*.[12]

Methods

Consenting patients with NVAF and who were initiated on rivaroxaban were included in the study, irrespective of stroke risk, and followed for 1 year, with 3-monthly follow-up visits, or for at least 30 days after permanent discontinuation. Dosing regimens were determined by the treating physician. Safety findings were reported, with all adverse events (AEs) being labelled as 'AE' or as 'serious AE' (SAE); the latter were followed-up until final outcome. Some AEs, such as major bleeding (as defined by the International Society on Thrombosis and Haemostasis criteria), symptomatic thromboembolic events (TEEs; including stroke, SE, transient ischaemic attacks [TIAs], myocardial infarction [MI]), and all-cause death were centrally adjudicated.

Clinical outcomes were also reported, in the form of management of bleeding events and stroke occurrence, as well as treatment persistence, self-reported patient satisfaction, and healthcare resource use.

Results

Patient demographics

A total of 6,784 patients (mean age: 71.5 years, range: 19–99; patients >75 years: 37%) from 311 centres in Europe, Israel, and Canada were enrolled in the study between June 2012 and December 2013 and received rivaroxaban. The most common rivaroxaban dosing regimen was 20 mg once daily (OD; 78.7%), with 20.8% of patients receiving 15 mg OD and 0.5% receiving a different dose. Overall, 59% of patients were male and 54.5% of patients were VKA-naïve. With regard to renal function, 9.4% of patients had moderate or severe renal impairment (as defined by creatinine clearance [CrCl] <50 mL/min), with 1.4% displaying CrCl ≤30 mL/min. Paroxysmal AF was present in 40.6% of patients, persistent or permanent AF present in 40.7%, and 18% of patients were first diagnosed with AF. Regarding patient history: 19.0% of patients had prior stroke, TIA, or SE; 18.6% had congestive heart failure; 74.7% had hypertension; and 19.6% had diabetes.

The mean CHADS2 (congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke) score[13] was 2.0 (median: 2.0), for a mean CHA2DS2-VASc score[14] (incorporating the CHADS2 score plus female gender, vascular disease, and age 65–74 years) of 3.4 (median: 3.0); 13% of patients had a CHA2DS2-VASc score of 0 or 1. Mean treatment duration in the overall cohort was 329 days (standard deviation [SD]: 115 days; median: 366 days).

Treatment persistence was high, with 79.9% of patients remaining on rivaroxaban therapy

throughout the 1-year study period, which is of clinical importance with respect to the protective effects of NOACs against the risk of stroke. A total of 598 patients (8.8%) had at least one therapy interruption (median duration: 4 days), mainly due to the need for surgery or the occurrence of bleeding or another AE.

Primary outcomes: safety

AEs were reported in 2,709 patients (39.9%), of whom 1,203 (18% of the overall cohort) experienced an SAE (Table 1). Overall, 1.9% of the patients experienced treatment-emergent major bleeding (n=128; 2.1 events per 100 patient-years). The on-treatment all-cause mortality rate was 1.7% (1.9 events per 100 patient-years), with fatal bleeding occurring in 0.2% of all cases (0.2 events per 100 patient-years). Unadjusted AE rates and comorbidities were higher in patients receiving rivaroxaban 15 mg OD. Overall, the rates of stroke and major bleeding were low and increased progressively over time in this real-world, clinical practice cohort.

Secondary outcomes

The overall rate of symptomatic TEEs (stroke, TIA, SE, MI) was 1.6% (108 patients), which comprised of 0.6% experiencing stroke, 0.1% experiencing SE, 0.5% experiencing TIA, and 0.4% experiencing MI (Table 2).

Table 1: Treatment-emergent adverse events in the XANTUS study.

Adjudicated endpoint	Rivaroxaban (n=6,784), incidence (%)
All-cause mortality	118 (1.7%)
Thromboembolic event (stroke, SE, TIA, MI)	108 (1.6%)
Major bleeding	128 (1.9%)
Mucosal bleeding	60 (0.9%)
Haemoglobin decrease ≥2 g/dL	52 (0.8%)
Transfusion of ≥2 units of packed red blood cells or whole blood	53 (0.8%)
Critical organ bleeding	43 (0.6%)
Intracranial haemorrhage	26 (0.4%)
Fatal bleeding	12 (0.2%)
Non-major bleeding events	878 (12.9%)
Major bleeding is collected as serious or non-serious adverse event and defined as overt bleeding associated with a fall in haemoglobin of ≥2g/dL or a transfusion of ≥2 units of packed red blood cells or whole blood or a critical site bleeding or a fatal outcome. Treatment emergent: period at start of study medication to 2 days after last dose. Note: only specific adverse events are shown, not all, namely thromboembolic, bleeding, and all-cause mortality.	

MI: myocardial infarction; SE: systemic embolism; TIA: transient ischaemic attack.

Table 2: Treatment-emergent secondary outcomes (symptomatic thromboembolic events) in the XANTUS study.

Adjudicated endpoint	Rivaroxaban (n=6,784), incidence (%)
Symptomatic thromboembolic events (stroke, TIA, SE, MI)	108 (1.6%)
Stroke and SE	51 (0.8%)
Stroke	43 (0.6%)
SE	8 (0.1%)
TIA	32 (0.5%)
MI	27 (0.4%)

MI: myocardial infarction; SE: systemic embolism; TIA: transient ischaemic attack.

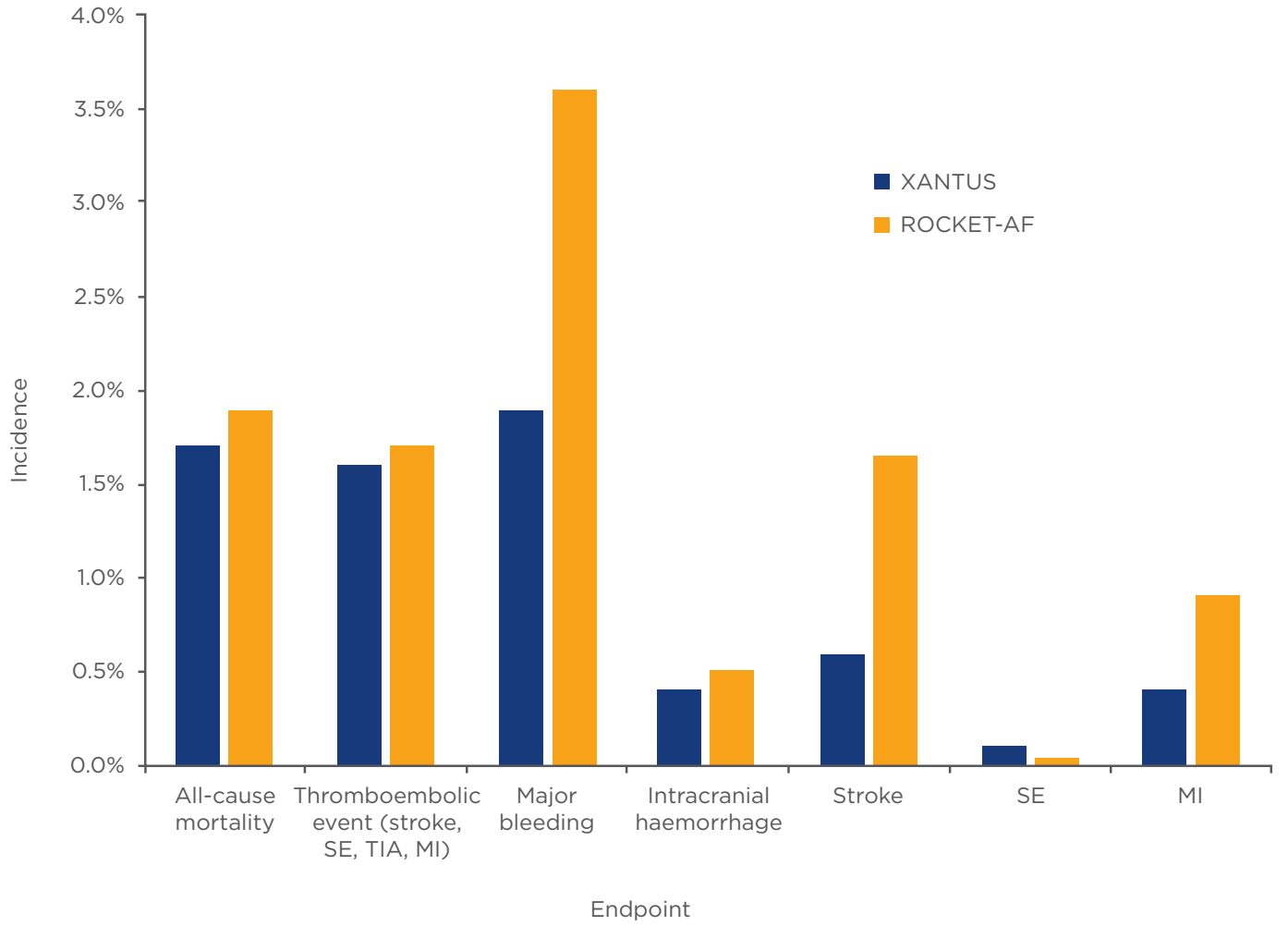

Figure 1: Safety endpoints and clinical outcomes in the XANTUS and ROCKET-AF studies.
MI: myocardial infarction; SE: systemic embolism; TIA: transient ischaemic attack.
Note: results are not intended for direct comparison.

XANTUS Results and Findings from the ROCKET-AF Registration Clinical Trial

The registration trial for rivaroxaban in NVAF was the Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study.[7,9] Patients in this trial had a mean $CHADS_2$ score of 3.5 (versus 2.0 in XANTUS) and incidence of major bleeding was 3.6 events per 100 person-years (versus 2.1 per 100 person-years in XANTUS). Therefore, the patients in XANTUS were at lower risk than those in the ROCKET-AF study.

The incidences of all-cause mortality, major bleeding, stroke, and MI were lower in the XANTUS study than in the ROCKET-AF study (Figure 1). Rates of fatal bleeding, critical organ bleeding, and intracranial haemorrhage per 100 person-years were similar between the two studies. It is to be noted that while methodological discrepancies limit the comparison of studies, this confirmation nevertheless provides some insight into the safety profile of rivaroxaban.

UNITED STATES DEPARTMENT OF DEFENSE POST-MARKETING SAFETY SURVEILLANCE STUDY

Methods

This PMSS study is a 5-year, retrospective, observational study with no comparator arm that aims to evaluate major bleeding in patients taking rivaroxaban who have NVAF or are undergoing total hip and/or knee replacement procedures. It was designed in collaboration with the US DoD, which possesses an integrated electronic health record database of almost 10 million patients. For the current analysis, the database

was used to identify major bleeding-related hospitalisations among patients with NVAF and treated with rivaroxaban. Additional data on fatal events and major bleeding management (surgical interventions, intensive care unit hospitalisations, and transfusions) were collected. Data on patient demographics, comorbidities, and risk factors were also collected to allow for in-depth analysis of major bleeding patterns and clinical settings. Of note, the major bleeding events in the US DoD PMSS did not go through any adjudication process, which may be a study limitation.

This study was developed in agreement with the FDA as part of a post-marketing requirement and is still ongoing. Preliminary results at 15 months have already been published, encompassing data in NVAF patients from 1st January 2013 to 31st March 2014. These results were published in *Clinical Cardiology* in February 2015.[15] Similarly, an 18-month update was presented at the 2015 American College of Cardiology Scientific Session on 15th March 2015.[16] Peacock et al.[17] presented the 2-year preliminary data at the ESC Congress on 31st August 2015.

Results

A total of 39,052 patients receiving OD rivaroxaban therapy were identified between January 2013 and December 2014. Descriptive data were reported including patient demographics, comorbidities, concomitant medications, bleeding hospitalisations and management, bleeding characteristics, and outcomes.[16,17]

Safety: major bleeding

The incidence of at least one major bleeding event, identified with the validated Cunningham database algorithm,[18] was 2.89 events per 100 person-years (95% confidence interval: 2.71–3.08; n=970). The majority (87.2%) of major bleeding events were gastrointestinal haemorrhages (n=846). Incidences of intracranial and genitourinary haemorrhages were 8.1% (n=79) and 0.6% (n=6), respectively. Other or unspecified bleeding represented 4.0% of cases of major bleeding (n=39). Most major bleeding patients were discharged to home, and the mean length of hospitalisation was 4.0 days (SD: 3.4). Overall, 42.3% of patients with major bleeding were transferred to an intensive care unit, and 51.5% received a blood transfusion.[16,17]

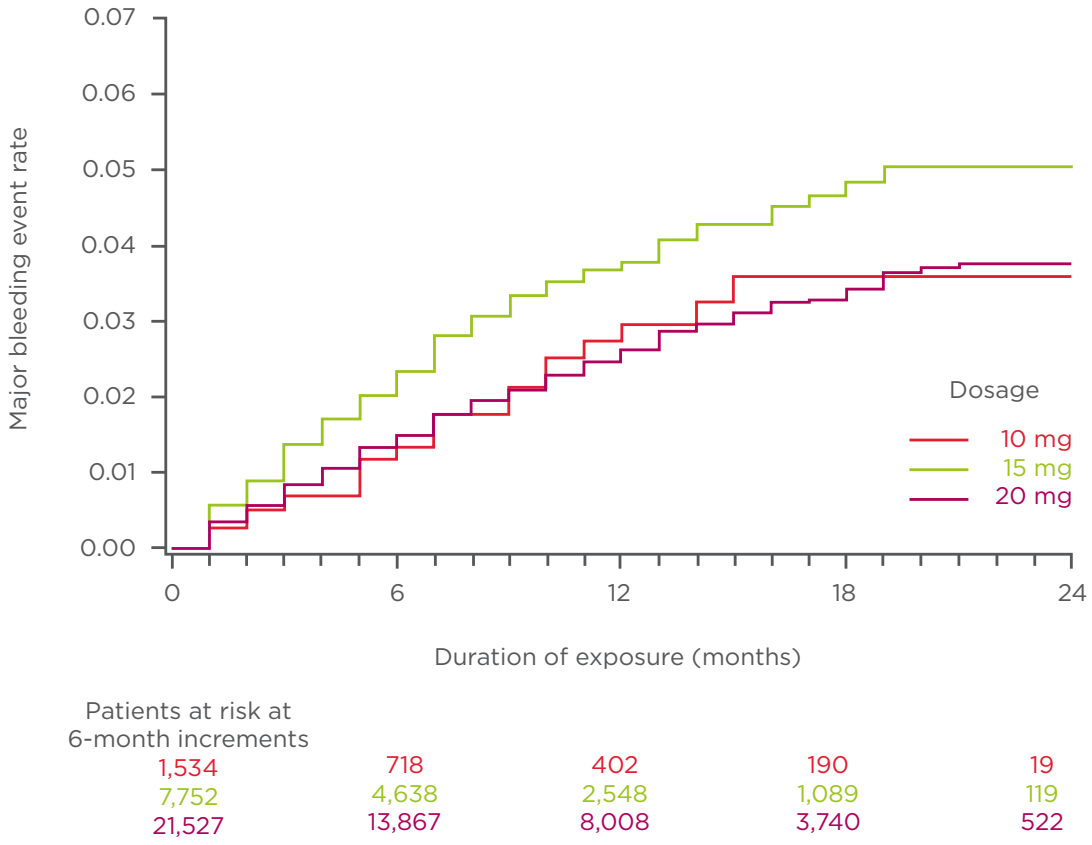

Figure 2: Cumulative incidence of major bleeding by rivaroxaban dose in the United States Department of Defense post-marketing safety surveillance study: preliminary analysis of the first 30,813 patients.

Safety: mortality rates

The researchers observed a very low incidence of fatal bleeding (0.1%, 95% CI: 0.07–0.15; n=35); the mean age at time of death was 80.3 years. Of the fatal bleedings, 74.3% were intracranial haemorrhages and 25.7% were gastrointestinal bleedings.[16,17] Tamayo et al.[16,17] also presented the results of the cumulative incidences of major bleeding according to rivaroxaban dose, which were produced through an earlier interim analysis on the first 30,813 patients (Figure 2).

United States Department of Defense Post-Marketing Safety Surveillance Study Results and Findings from the ROCKET-AF Registration Clinical Trial

Overall, patterns and rates of major bleeding in real-world clinical practice were consistent with those reported in the ROCKET-AF study, as was previously observed in the earlier reporting from the 15-month results.[7,9,15] The incidence of major bleeding seems to be low in this post-marketing setting; the upcoming 5-year results should continue to provide insights into the use of rivaroxaban in routine clinical practice.

DISCUSSION

Randomised clinical trials are the most rigorous way to evaluate a drug, and are designed to produce a new hypothesis. This hypothesis can be placed into perspective with observational prospective studies or registries, which conversely aim to produce a picture of routine clinical care, clinical settings, and patient characteristics at a given time and place.

While the initiation of randomised clinical trials is pivotal to determine the efficacy and safety of a potential new drug versus standard therapy, their impact can be challenged by a variety of factors. Patients in such trials are selected with narrow inclusion criteria, alongside multiple exclusion criteria, and are treated in selected expert centres which are likely to monitor them more closely. Quality of care, study requirements, and strict protocols can impact the benefit–risk balance, thus creating differences compared with what may be obtained in a real-world, routine clinical practice cohort.

Registries and large-scale observational studies providing a broad range of clinical settings and patient baseline characteristics are essential to complement the results from randomised clinical trials, and these designs are complementary. However, the limitations of prospective, observational data collection are mainly based on the generation of residual confounding and false/under-reported data. In addition, data comparison between centres can sometimes be challenging due to differences in baseline characteristics and socioeconomic factors across diverse regions. Nevertheless, these initiatives can provide a picture of what to expect in daily clinical practice. This further insight, when taken into account alongside clinical trial evidence, can help to refine guidelines, patient stratification rationales, and standardised treatment protocols.

CONCLUSION

In conclusion, the findings of the XANTUS and the US DoD PMSS studies reaffirm the benefit-to-risk profile of rivaroxaban, as determined in pivotal clinical trials such as the Phase III ROCKET-AF study, and may help physicians make informed decisions on treatment selection. While any direct comparison cannot be performed between clinical trials and observational studies due to strong differences in design, data collection, exposure, patient population, and inclusion/exclusion criteria, the real-world data may help physicians put the results of the ROCKET-AF study into context.

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