A retrospective study of real-world effectiveness and safety of rivaroxaban in patients with non-valvular atrial fibrillation and venous thromboembolism in Saudi Arabia

Hind M. Alosaimi[1,2], Saeed Alqahtani[3], Bander Balkhi[3], Mishari Alqahtani[3], Faisal Alzamil[3], Abdulaziz Alhossan[3], Fatmah S. Alqahtany[4], Abdullah A. Alharbi[5], Nawaf Abdullah Alqahtani[5], Hanan Albackr[6], Ghada Elgohary[7,8] and Farjah H. Algahtani[9]

[1] Clinical Pharmacy Department, College of Pharmacy, Riyadh Elm University, Riyadh, Saudi Arabia
[2] Pharmacy Services, King Fahad Medical City, Riyadh Second Health Cluster, Riyadh, Saudi Arabia
[3] Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
[4] Hematopathology Unit, Department of Pathology, College of Medicine, King Saud University, King Saud University Medical City, Riyadh, Saudi Arabia
[5] College of Medicine, King Saud Bin Abdul Aziz University for Health Sciences, Riyadh, Saudi Arabia
[6] Department of Medicine, College of Medicine, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia
[7] Department of Adult Hematology/Oncology, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia
[8] Clinical Hematology and Bone Marrow Transplantation Unit, Division of Internal Medicine, Ain Shams University, Cairo, Egypt
[9] Division of Oncology/Hematology, Department of Medicine, College of Medicine, King Saud University, Kind Saud University Medical City, Riyadh, Saudi Arabia

ABSTRACT

Background: Real-world evidence on factor Xa inhibitor (rivaroxaban) prescribing patterns, safety, and efficacy in patients with non-valvular atrial fibrillation (NVAF) and venous thromboembolism (VTE) is rare. Herein, we sought to examine the above outcomes in the largest academic center in the Kingdom of Saudi Arabia (KSA).

Methods: This is a retrospective observational study designed to examine the prescribing pattern, safety and real-world effectiveness of the factor Xa inhibitor rivaroxaban in patients with NVAF and VTE. Data on rivaroxaban prescriptions were collected and analyzed. Bleeding outcomes were defined as per the International Society on Thrombosis and Hemostasis (ISTH) definition.

Results: A total of 2,316 patients taking rivaroxaban recruited through several departments of King Saud University Medical City (KSUMC). The mean age was 61 years (±17.8) with 55% above the age of 60 and 58% were females. Deep vein thrombosis and pulmonary embolism (VTE) was the most prevalent reason for prescribing rivaroxaban, followed by NVAF. A total daily dosage of 15 mg was given

to 23% of the patients. The incidence rate of recurrent thrombosis and recurrent stroke was 0.2%. Furthermore, rivaroxaban had a 0.04 percent incidence rate of myocardial infarction. Half of the patients with recurrent thrombosis and stroke were taking 15 mg per day. The incidence rate of major bleeding was 1.1%. More over half of the patients who experienced significant bleeding were taking rivaroxaban at a dosage of 20 mg per day. According to the HAS-BLED Score (>2 score), 48 percent of patients who experienced significant bleeding had a high risk of bleeding. Non-major bleeding occurred in 0.6% of cases. Similarly, 40% of patients with non-major bleeding were taking rivaroxaban at a dosage of 20 mg per day. According to the HAS-BLED Score, just 6.6% of these individuals had a high risk of bleeding. 93.4% of the patients, on the other hand, were at intermediate risk.

Conclusion: The prescription of rivaroxaban in this real-life cohort study differs from the prescribing label and the outcomes of a phase 3 randomised clinical trial. However, for individuals with VTE and NVAF, the 20 mg dose looked to be more efficacious than the pivotal trial outcomes. Furthermore, among patients with VTE and NVAF, rivaroxaban was linked to a decreased incidence of safety events such as recurrent thrombosis, recurrent stroke, MI, major bleeding, and non-major haemorrhage in a real-world environment.

INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two manifestations of venous thromboembolism (VTE), and they have similar predisposing factors (*Torbicki et al., 2008*). VTE is the third most frequent cardiovascular disease in the world, and it is one of the main causes of mortality (*Goldhaber, Visani & De Rosa, 1999*). Anticoagulant therapy is the cornerstone of VTE treatment (*Cabral & Ansell, 2015*). Warfarin was the only available option as an oral anticoagulant (OAC) for more than 50 years for the treatment of atrial fibrillation and other thrombotic conditions (*Julia & James, 2017*). Moreover, the use of warfarin has also been linked with a large number of safety reports and associated with several adverse events during routine clinical practice (*McMahan et al., 1998*; *Hylek et al., 2007*; *Lee & Crowther, 2011*).

However, novel oral anticoagulants (NOACs) or direct oral anticoagulants (DOACs) such as rivaroxaban, edoxaban and apixaban are recently approved factor Xa inhibitors that provide anticoagulation *via* oral route (*Tellor et al., 2015*). These NOACs have expanded the options of OACs available to the healthcare professionals. Due to numerous challenges with warfarin therapy including frequent monitoring, drug interactions, delayed time to onset and a narrow therapeutic index, make the NOACs attractive treatment options (*Ageno et al., 2012*).

In 2011, rivaroxaban was initially approved by the US. Food and Drug Administration in knee and hip replacement surgery patients for preventing DVT (*Janssen*

Pharmaceuticals Inc, 2018). In the same year, it was approved for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF). Whereas in 2012, rivaroxaban was also approved for the treatment of DVT and PE and for the risk reduction of recurrent DVT and PE (*Burness & Perry, 2014*).

The oral factor Xa inhibitors such as rivaroxaban represent a major advance in the prevention and treatment of thromboembolic disease (*Rupprecht & Blank, 2010*). Rivaroxaban is potent, oral, highly selective direct inhibitor of factor Xa with high oral bioavailability (*Rupprecht & Blank, 2010*). It works effectively for DVT and PE therapy, as well as primary and secondary thromboprophylaxis (*Rupprecht & Blank, 2010*). Direct factor Xa inhibitors inhibit platelet activation and fibrin clot formation *via* direct, selective and reversible inhibition of factor Xa (*Rupprecht & Blank, 2010*). These agents have several advantages over the vitamin K antagonists such as rapid onset of action, no requirement for dose adjustment, and few drug and food interactions. Thus, these agents become widely used in the treatment and prevention of all VTE related diseases.

Although the efficacy and safety of the factor Xa inhibitor for the prevention of VTE and stroke in patients with NVAF were shown in global clinical trials, the safety and effectiveness data from unselected patients in everyday clinical practice are yet limited. Recently, the use of those medications was increased which raise a concern about it risk-benefit ratio specially in real practice in our region. Real-world data on Factor Xa inhibitor are essential in determining whether evidence from randomized controlled clinical trials translate into meaningful clinical benefits for patients in everyday practice. Overall, only limited number of studies have been published assessing the real-life use of direct oral Factor Xa inhibitors. The aim of this study is to investigate the prescribing pattern, efficacy and safety of Factor Xa inhibitor (rivaroxaban) in real-world clinical practice in the KSA.

MATERIALS AND METHODS

Design and setting

This was a retrospective observational study designed to examine the use of rivaroxaban in patients with documented symptomatic VTE or documented non-valvular atrial fibrillation. Data collected from January 2015 to December 2019 from a large academic center were analyzed.

The primary safety outcome in this study is major bleeding (MB) and clinically relevant nonmajor bleeding (CRNMB). Major bleeding is defined according to International Society on Thrombosis and Hemostasis (ISTH) major bleeding can be defined as any fatal bleeding or bleeding that causes a decrease of hemoglobin level in blood dropped to 20 g/dL or which required a transfusion of packed blood cells of atleast two units, or any hemorrhage into any major antomical sites whether intracranial, peritoneal, pericardial *etc*. Those which does not satisfy criterion for major bleeding constitutes non major bleeding types (*Schulman, Kearon & Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, 2005*). Patients weighing ≤50 kg and/or aged ≥75 years were analyzed separately.

The primary effectiveness endpoints were recurrent thrombosis which was defined as a new sudden thrombosis confirmed by Duplex ultrasound or CT scan, V/Q scan; recurrent stroke which was defined as a neurological deficit due to any vascular abnormalities persisting beyond a day; noncentral nervous system side effect which was defined as any sudden vascular insufficiency with instances of arterial occlusion other than due to trauma atherosclerosis *etc.*; and myocardial infarction defined as inclusion of myocardial symptoms together with increase in level of cardiac biomarkers (troponin I, troponin T, or creatinine kinase-MB) above normal upper limit.

The secondary outcomes includes all-cause mortality, and rate of treatment discontinuation. All outcomes were stratified by major comorbidities such as stroke or bleeding (*e.g.*, CHADS2 or HAS-BLED), other baseline subgroups (*e.g.*, age, body weight, CrCl, use of antiplatelet agents, or prior stroke/transient ischemic attack/noncentral nervous system SE), or with different rivaroxaban dosing (10, 15, 20 mg).

Data collection and ethical approval

The following baseline data was collected: age, sex, body weight, height, smoking history, and any history of allergy, history of VTE, NVAF and other medical history, vital signs and laboratory tests, use of an anticoagulant or antiplatelet agent ≤30 days prior to rivaroxaban administration. Recurrent thrombosis/stroke and bleeding risk profiles based on risk scores such as: D-dimer, thrombophilia, CHADS2 (congestive heart failure, hypertension, age, diabetes mellitus, stroke) or HAS-BLED (hypertension, abnormal liver/renal function, stroke history, bleeding predisposition, labile international normalized ratio, elderly, drug/alcohol use). This study was initiated after the approval of research ethics committee of King Saud University Medical City (ethical approval reference number: E-19-4514) and written informed consent was obtained from the participants.

Statistical analysis

For baseline characteristics, descriptive analysis was performed and categorical variables are compared using the two-sided Chi-square and Fisher's Exact tests.

RESULTS

Baseline characteristics

A total of 2,316 patients with a mean age of 60.9 years (±17.8) were enrolled in this study. More than half (55.3%) of the patients were over 60 years of age. Fifty-eight percent of the study participants were female. Table 1 shows the baseline and clinical characteristics of the study patients. The average ± SD body weight was 80.3 ± 19.9, height was 1.61 ± 0.09 and the BMI was 30.9 ± 7.4. Two-third of the patients were obese. The prescriptions for VTE (DVT and PE) were relatively higher than NVAF. In a group of VTE, 76% of patients had DVT and 24% were diagnosed with PE.

Rivaroxaban dosing

We observed four different total daily dosing of rivaroxaban 10, 15, 20, and 30 mg. The most common dose on these patients was 20 mg/day with 50% of the patients using

Table 1 Demographics and clinical characteristics of study patients.

Variables	Overall (n = 2,316)
Age, years; mean ± SD	60.9 ± 17.8
≤60 years	1,035 (44.7)
>60 years	1,281 (55.3)
Gender; n (%)	
Male	963 (41.6)
Female	1,353 (58.4)
Weight, kg; mean ± SD	80.3 ± 19.9
Height, m; mean ± SD	1.61 ± 0.09
BMI, kg/m^2; mean ± SD	30.9 ± 7.4
Underweight (<18.5)	45 (1.9)
Normal-weight (18.5–22.9)	220 (9.5)
Overweight (23–27.5)	513 (22.2)
Obese (>27.5)	1,538 (66.4)
Smoking Status; n (%)	89 (3.8)
VTE Hx; n (%)	684 (29.5)
DVT	520 (76)
PE	164 (24)
NVAF Hx; n (%)	521 (22.5)
Atrial fibrillation	452 (86.8)
Atrial flutter	23 (4.4)
Unknown atrial rhythm	46 (8.8)
Daily dose of rivaroxaban, n (%)	
10 mg	579 (25)
15 mg	537 (23)
20 mg	1,168 (50)
30 mg	32 (2)
Antiplatelets, n (%)	
Aspirin; n (n%)	496 (21.4)
Clopidogrel; n (%)	76 (3.3)
Comorbidities; n (%)	
Hypertension	1,147 (49.5)
Dyslipidemia	439 (19)
Hypothyroidism	180 (7.8)
Renal dysfunction	132 (5.7)
Heart failure	270 (11.7)
Diabetes mellitus	952 (41.1)
ALT, unit/L; mean ± SD	35 (67.9)
ALT groups; n (n%)	
≤41 units/L	2,040 (88.1)
42–123 units/L	236 (10.2)
>123 units/L	40 (1.7)

(Continued)

Table 1 (continued)	
Variables	Overall (n = 2,316)
AST, unit/L; mean ± SD	30.6 (148)
AST groups; n (n%)	
≤31 units/L	2,015 (87)
32–93 units/L	248 (10.7)
>93 units/L	53 (2.3)
ALP, unit/L; mean ± SD	98.9 (72.3)
ALP groups; n (n%)	
≤150 units/L	2,126 (91.8)
151–450 units/L	179 (7.7)
>450 units/L	11 (0.5)
Albumin, gm/L; mean ± SD	34.6 (56.2)
Albumin groups; n (n%)	
≤50 g/L	2,308 (99.7)
>50 g/L	8 (0.3)
Bilirubin, mcmol/L; mean ± SD	12.4 (19.4)
Bilirubin groups; n (n%)	
≤17 mcmol/L	2,062 (89)
>17 mcmol/L	254 (11)
Serum creatinine; mcmol/L; mean ± SD	84.4 (51)
Serum creatinine groups; n (n%)	
≤106 mcmol/L	1,969 (85)
>106 mcmol/L	347 (15)
Creatinine clearance; ml/min; mean ± SD	111.4 (61.7)
Creatinine clearance groups; n (n%)	
≤M:137/F:128 ml/min	1,613 (69.6)
>M:137/F:128 ml/min	703 (30.4)

Note:
BMI, body mass index; NVAF, nonvalvular atrial fibrillation; DVT, deep venous thrombosis; PE, pulmonary embolism; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase, ALT: 7–55 units per litre (U/L); AST: 8–48 units per litre (U/L); ALP: 44–147 units per litre (U/L); albumin: 3.5–5.5 grams per decilitre; bilirubin (total): 0.3–1.0 milligrams per decilitre; indirect bilirubin: 0.2–0.8 milligrams per decilitre. Normal serum creatinine levels: For adult men: 0.74–1.35 milligrams per decilitre (Mg/dL); for adult women: 0.59–1.04 milligrams per decilitre (Mg/dL).

this dose. While the 10 mg dose was prescribed in 25% of patients followed by 15 mg for 23% of the patients. A total of 30 mg dose were only used by 2% of the patients.

Antiplatelets therapy and comorbidities

Concomitant use of antiplatelets was noted in 572 patients (24%) The prevalence of comorbidities ranged from 5.7% to 49.5%, with hypertension being diagnosed in 49.5% of our cohort. Diabetes and dyslipidemia were reported in 41.1%, 19%, respectively (Table 1). Prevalence rates for renal dysfunction, hypothyroidism, and heart failure ranged from 5.7%, 7.8% and 11.7%.

Table 2 Risk of stroke and major bleeding in study patients on different dosing.

Variables	Total daily dose of rivaroxaban					
	Overall (n = 2,316)	10 mg (n = 579)	15 mg (n = 537)	20 mg (n = 1,168)	30 mg (n = 32)	*P*-value
Risk of stroke as per CHADS$_2$-score; n (%)						
Low risk	730 (31.5)	215 (37.1)	87 (16.2)	416 (35.6)	12 (37.5)	0.892
Intermediate risk	1,149 (49.6)	296 (51.1)	284 (52.9)	556 (47.6)	13 (40.6)	0.062
High risk	437 (18.9)	68 (11.7)	166 (30.9)	196 (16.8)	7 (21.9)	0.537
Risk of major bleeding as per HAS-BLED score; n (%)						
Low risk	622 (26.9)	187 (32.3)	64 (11.9)	362 (31)	9 (28.1)	0.834
Intermediate risk	1,418 (61.2)	349 (60.3)	370 (68.9)	677 (58)	22 (68.8)	0.172
High risk	276 (11.9)	43 (7.4)	103 (19.2)	129 (11)	1 (3.1)	0.505

Table 3 Effectiveness and safety outcomes of patients.

Variables	Dose of rivaroxaban					
	Overall (n = 2,316)	10 mg (n = 579)	15 mg (n = 537)	20 mg (n = 1,168)	30 mg (n = 32)	*P*-value
Effectiveness outcomes						
Recurrent thrombosis; n (%)	4 (0.2)	0	2 (0.4)	2 (0.2)	0	0.513
Recurrent stroke; n (%)	4 (0.2)	0	2 (0.4)	2 (0.2)	0	0.513
Myocardial infarction; n (%)	1 (0.04)	0	0	1 (0.1)	0	0.805
Safety outcomes						
Major bleeding; n (%)	25 (1.1)	4 (0.7)	6 (1.1)	15 (1.3)	0	0.652
Minor bleeding; n (%)	15 (0.6)	4 (0.7)	5 (0.9)	6 (0.5)	0	0.748

Note:
$P > 0.05$ Not significant.

CHADS2 score and HAS-BLED score

CHADS2 Score and HAS-BLED Score were calculated for the patients and presented in Table 2. Nearly half of the patients had an intermediate risk of stroke per CHADS2-Score. A total of 437 patients (18.9%) had a high risk of stroke and 31.5% of patients had a low risk of stroke. On the other hand, majority of the patients (61.2%) had an intermediate risk of bleeding as per HAS-BLED score. 26.9% of the patients had a low risk for bleeding and 11.9% had high risk for bleeding.

Effectiveness outcomes

Effectiveness outcome variables listed in Table 3 indicate the following parameters. The table evaluated recurrent thrombotic and stroke events. Those having 10 and 30 mg rivaroxaban dose showed nil for the study and cases having 15 and 30 mg dosages each attributed to 50% recurrent thrombotic and stroke incidences. While the total incidence rate measured 0.2% for each of the variables, it summed up to 0.04% for MI. There was no association between the recurrent rates and the dosage of rivaroxaban (Table 3). All of the patients who had recurrent thrombosis, stroke and MI had a high risk for VTE according

Table 4 Effectiveness and safety outcomes of patients.

Variables	Risk of stroke according to CHADS2-score				
	Overall (n = 2,316)	Low risk (n = 730)	Intermediate risk (n = 1,149)	High risk (n = 437)	P-value
Effectiveness outcomes					
Recurrent thrombosis; n (%)	4 (0.2)	0	0	4 (0.9)	0.732
Recurrent stroke; n (%)	4 (0.2)	0	0	4 (0.9)	0.861
Myocardial infarction; n (%)	1 (0.04)	0	0	1 (0.2)	0.236
	Risk of bleeding according HAS-BLED score				
		Low risk (n = 622)	Intermediate risk (n = 1,418)	High risk (n = 276)	
Safety outcomes					
Major bleeding; n (%)	25 (1.1)	0	13 (0.92)	12 (4.3)	0.141
Minor bleeding; n (%)	15 (0.6)	0	14 (0.98)	1 (0.35)	0.516

to CHADS2 Score (Table 4). Moreover, there were no association between the rates of recurrent and other variables.

Safety outcomes

Major bleeding episodes were documented in 25 patients (1.1%) (Table 3). Approximately half of those patients who had major bleeding were on 20 mg daily dose of rivaroxaban. A total of 48% of the patients who had major bleeding had a high risk for bleeding according to HAS-BLED Score (>2 score) (Table 4). No patients with low risk HAS-BLED score had an event of major bleeding.

Fifteen patients had clinically relevant non-major bleeding (0.6%). 40% of the patients who had non-major bleeding were on 20 mg daily dose of rivaroxaban. Only 6.6% of these patients had a high risk for bleeding according to HAS-BLED Score (Table 4). 93.4% of the patients had moderate risk (Table 4). Moreover, there were no association between the rates of bleeding and other variables.

DISCUSSION

Although, the randomized control trials (RCTs) remain the gold standard in assessing drugs safety and efficacy, these studies do not, necessarily, reflect the real clinical practice. To our knowledge, this is the first study in the Kingdom of Saudi Arabia to assess the prescribing pattern, effectiveness and safety of rivaroxaban in patients with VTE and or NVAF in a large cohort. The findings of this study are based on a real-world clinical practice's data collected from a tertiary care healthcare setting during a period of 5 years.

This study revealed several important findings about the effectiveness and the incidence of safety events. Interestingly, the prescriptions of rivaroxaban for females particularly with VTE were relatively higher than their male counterparts. However, the role of gender in the causation of VTE is uncertain (*Tormene et al., 2011*). A large number of study

participants were aged 60 years and over which is consistent with previous VTE and NVAF literature study as the incidence of VTE and NVAF increases with age (*ESHRE Capri Workshop Group et al., 2013*). Patients in our study mostly administered rivaroxaban for the treatment of VTE.

In this study we noted that half of the patients received appropriately a 20 mg total daily dose of rivaroxaban for VTE. On the other hand, 23% of patients were taking 15 mg total daily dose. For the subgroups of VTE such as DVT and PE, the recommended dose of rivaroxaban is 15 mg orally twice a day followed by 20 mg once daily and the treatment continues for as long as the risk of VTE recurrence persists, balancing benefits and harms and patient preference (*Streiff et al., 2016*). This unusual dosing was also noted in the RIvaroxaban for Valvular heart diseasE and atRial fibrillation (RIVER) study were 76.5% of the patient received rivaroxaban 20 mg and 20% received 15 mg while 10 mg dose was prescribed in only 2.1% (*Beyer-Westendorf et al., 2019*).

Regarding the effectiveness outcomes, there was no correlation between the dose and response. In general, the rate of recurrent thrombosis, stroke, and MI was very low in our reported findings. Furthermore, the recurrent rates were lower than what have been reported in the clinical trials (*Hori et al., 2014*) and other real-world outcomes studies (*Patel et al., 2011*; *Hori et al., 2012*, *2014*; *Laliberté et al., 2014*; *Tellor et al., 2015*; *Ntaios et al., 2017*; *Huang et al., 2018*). Moreover, all those patients who had recurrent events had high risk for stroke according to CHADS2 scores. This may suggest using higher doses of rivaroxaban in this group of patients. In general, patients in the present study had less baseline risk for thromboembolism as indicated by lower average CHADS2 scores compared to the previous studies which may explain the more prominent effectiveness of rivaroxaban in our data. The majority of cohort in the current study had an intermediate risk of stroke (49.6) compared to average CHADS2 scores of 3.27 and 3.2 in J-ROCKET AF, ROCKET AF (rivaroxaban once daily oral direct Factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation), respectively (*Patel et al., 2011*; *Hori et al., 2012*).

Recurrent thrombosis and recurrent stroke were almost nil for those taking rivaroxaban doses of 10 and 30 mg. Myocardial infarction recurrency lined up the same results. On accountable of BMI status, about 66% of cases counted obese, the overweight group calculated to 22%, the underweight percentage being meagre. About 21% were taking aspirin supplements as well. The coupling effect might reduce the risk of secondary athero thrombotic events during immediate post-acute coronary syndrome period. Almost 3% of cases were taking antiplatelet drug clopidogrel for caution of bleeding events.

NVAF was the second most common diagnosis in this study for which patients received the treatment of rivaroxaban with different doses. ROCKET-AF was the first trial assessing the effectiveness of rivaroxaban with a dose of 20 mg in NVAF patients (*Patel et al., 2011*). ROCKET-AF concluded that rivaroxaban caused less fatal bleeding and was noninferior to warfarin in patients with atrial fibrillation for preventing stroke or systemic embolism. Rivaroxaban has been shown to be well tolerated with superior safety with regards to bleeding events compared with warfarin (*Vimalesvaran, Dockrill & Gorog, 2018*).

Our findings in this study also showed the effectiveness of rivaroxaban in the preventing of stroke or systemic embolism and in agreement with the previous reports.

Rivaroxaban, a NOAC (noval oral anticoagulant) dosage tablets comes under 10, 15 and 20 and 30 mg strengths (*Konicki et al., 2020*). Dosages were regulated in some cases having other antiplatelet prophylaxis and in those taking vitamin k antagonistics. Dosages were minimised at times in mild contra-indicative cases and even discontinued as precaution for any preoperative surgical criterion. However, the study including the secondary outcomes, the efficacy of 20 mg dose proved better (*Blin et al., 2019*).

Regarding the safety outcomes, we observed a significantly lower risk of major and non-major bleeding compared to previous studies (*Patel et al., 2011*; *Hori et al., 2012*, *2014*; *Laliberté et al., 2014*; *Ntaios et al., 2017*; *Huang et al., 2018*). Our study also reported a lower incidence of bleeding events as major bleeding occurred in only 15 patients who received 20 mg dose of rivaroxaban. We noticed that the rate of bleeding increases with the dose as there were few cases in 10 mg dose compared to 15 and 20 mg doses. In addition, we found an association between increase risk of bleeding and occurrence of major bleeding. According to HAS-BLED score, most of the patients who had major bleeding has high and intermediate risk for bleeding. Whereas, no major bleeding events were found in patients with low risk for bleeding. The estimation of bleeding risk through HAS-BLED score is crucial as it helps clinicians to flag-up patients at potential risk for serious bleeding in an informed manner. HAS-BLED score also helps healthcare professionals to explore the potentially reversible risk factors of bleeding. Moreover, the use of CHADS2-score and HAS-BLED scores can help to inform the choice of antithrombotic agent and the management strategy, thus reducing the likelihood of adverse events (*Lane & Lip, 2012*).

There were some limitations to this study. First, the retrospective design of the study did not allow to control some confounders that may affect the final outcomes of this study. Second, some data were missing as the care of many women was partitioned between different disciplines and, frequently among several hospitals. Third, as it was conducted at a single tertiary care institution in the KSA, the results cannot be generalized to the entire population of the KSA. Fourth, this study had no comparative arm so it is impossible to directly compare the outcomes of rivaroxaban in this study with other NOACs. Therefore, these findings should be validated by a multicenter longitudinal study across tertiary care settings in the KSA.

CONCLUSIONS

In this real-life cohort study, rivaroxaban prescribing is not consistent with the prescribing label or phase 3 randomized clinical trial data. However, it appears that the efficacy of the 20 mg dose is better than pivotal trial data for patients with VTE and NVAF. Moreover, in real world setting, rivaroxaban was associated with a lower risk of safety events such as recurrent thrombosis, recurrent stroke, MI, major bleeding, and non-major bleeding in patients with VTE and NVAF.

In this real-life cohort study, rivaroxaban prescribing for VTE and NVAF is not consistent with evidence of randomized clinical trials. However, the efficiency and safety of

this drug is not too different from pivotal phase 3 trials. Subsequent larger scale studies are required to validate these findings.

ABBREVIATION

NVAF	Non-valvular atrial fibrillation
VTE	Venous thromboembolism
ISTH	International Society on Thrombosis and Haemostasis
DVT	Deep vein thrombosis
PE	Pulmonary embolism
MB	Major bleeding
CRNMB	Nonmajor bleeding
RCT	Randomized control trials
MI	Myocardial infarction

ADDITIONAL INFORMATION AND DECLARATIONS

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Hind M. Alosaimi conceived and designed the experiments, prepared figures and/or tables, and approved the final draft.
- Saeed Alqahtani conceived and designed the experiments, prepared figures and/or tables, and approved the final draft.
- Bander Balkhi conceived and designed the experiments, performed the experiments, prepared figures and/or tables, and approved the final draft.
- Mishari Alqahtani conceived and designed the experiments, performed the experiments, prepared figures and/or tables, and approved the final draft.
- Faisal Alzamil conceived and designed the experiments, performed the experiments, prepared figures and/or tables, and approved the final draft.
- Abdulaziz Alhossan performed the experiments, prepared figures and/or tables, and approved the final draft.

- Fatmah S. Alqahtany conceived and designed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Abdullah A. Alharbi conceived and designed the experiments, prepared figures and/or tables, and approved the final draft.
- Nawaf Abdullah Alqahtani conceived and designed the experiments, prepared figures and/or tables, and approved the final draft.
- Hanan Albackr analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Ghada Elgohary analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Farjah H. Algahtani conceived and designed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.

Human Ethics

The following information was supplied relating to ethical approvals (*i.e.*, approving body and any reference numbers):

The Institutional Review Board, College of Medicine, King Saud University granted approval to carry out the study (Approval Ref: E-19-4514).

Data Availability

The following information was supplied regarding data availability:

The raw data is available in the Supplemental File.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.13974#supplemental-information.

REFERENCES

Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. 2012. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 141(2):e44S–e88S DOI 10.1378/chest.11-2292.

Beyer-Westendorf J, Camm AJ, Fox KAA, Le Heuzey J-Y, Haas S, Turpie AGG, Virdone S, Kakkar AK, RIVER Registry Investigators. 2019. International longitudinal registry of patients with atrial fibrillation and treated with rivaroxaban: RIVaroxaban evaluation in real life setting (RIVER). *Thrombosis Journal* 17(1):7 DOI 10.1186/s12959-019-0195-7.

Blin P, Fauchier L, Dureau-Pournin C, Sacher F, Dallongeville J, Bernard M-A, Lassalle R, Droz-Perroteau C, Moore N. 2019. Effectiveness and safety of rivaroxaban 15 or 20 mg versus vitamin K antagonists in nonvalvular atrial fibrillation. *Stroke* 50(9):2469–2476 DOI 10.1161/STROKEAHA.119.025824.

Burness CB, Perry CM. 2014. Rivaroxaban: a review of its use in the treatment of deep vein thrombosis or pulmonary embolism and the prevention of recurrent venous thromboembolism. *Drugs* 74(2):243–262 DOI 10.1007/s40265-013-0174-4.

Cabral KP, Ansell JE. 2015. The role of factor Xa inhibitors in venous thromboembolism treatment. *Vascular Health and Risk Management* **11**:117–123 DOI 10.2147/VHRM.S39726.

ESHRE Capri Workshop Group, Eichinger S, Evers JLH, Glasier A, La Vecchia C, Martinelli I, Skouby S, Somigliana E, Baird DT, Benagiano G, Crosignani PG, Gianaroli L, Negri E, Volpe A, Glasier A, Crosignani PG. 2013. Venous thromboembolism in women: a specific reproductive health risk. *Human Reproduction Update* **19(5)**:471–482 DOI 10.1093/humupd/dmt028.

Goldhaber SZ, Visani L, De Rosa M. 1999. Acute pulmonary embolism: clinical outcomes in the international cooperative pulmonary embolism registry (ICOPER). *Lancet (London, England)* **353(9162)**:1386–1389 DOI 10.1016/S0140-6736(98)07534-5.

Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, Izumi T, Koretsune Y, Kajikawa M, Kato M, Ueda H, Iekushi K, Yamanaka S, Tajiri M, Investigators on behalf of the J-RAS. 2014. Rivaroxaban vs. warfarin in Japanese patients with non-valvular atrial fibrillation in relation to age. *Circulation Journal* **78(6)**:1349–1356 DOI 10.1253/circj.cj-13-1324.

Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, Izumi T, Koretsune Y, Kajikawa M, Kato M, Ueda H, Iwamoto K, Tajiri M, J-ROCKET AF Study Investigators. 2012. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation – the J-ROCKET AF study. *Circulation Journal: Official Journal of the Japanese Circulation Society* **76(9)**:2104–2111 DOI 10.1253/circj.CJ-12-0454.

Huang H-Y, Lin S-Y, Cheng S-H, Wang C-C. 2018. Effectiveness and safety of different rivaroxaban dosage regimens in patients with non-valvular atrial fibrillation: a nationwide, population-based cohort study. *Scientific Reports* **8(1)**:3451 DOI 10.1038/s41598-018-21884-y.

Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. 2007. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation* **115(21)**:2689–2696 DOI 10.1161/CIRCULATIONAHA.106.653048.

Janssen Pharmaceuticals Inc. 2018. FDA approves XARELTO® (rivaroxaban tablets) to help prevent deep vein thrombosis in patients undergoing knee or hip replacement surgery. *Available at* https://www.prnewswire.com/news-releases/fda-approves-xarelto-rivaroxaban-tablets-to-help-prevent-deep-vein-thrombosis-in-patients-undergoing-knee-or-hip-replacement-surgery-124872829.html (accessed 31 January 2022).

Julia S, James U. 2017. Direct oral anticoagulants: a quick guide. *European Cardiology* **12(1)**:40–45 DOI 10.15420/ecr.2017:11:2.

Konicki R, Weiner D, Herbert Patterson J, Gonzalez D, Kashuba A, Cao YC, Gehi AK, Watkins P, Powell JR. 2020. Rivaroxaban precision dosing strategy for real-world atrial fibrillation patients. *Clinical and Translational Science* **13(4)**:777–784 DOI 10.1111/cts.12766.

Laliberté F, Cloutier M, Nelson WW, Coleman CI, Pilon D, Olson WH, Damaraju CV, Schein JR, Lefebvre P. 2014. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. *Current Medical Research and Opinion* **30(7)**:1317–1325 DOI 10.1185/03007995.2014.907140.

Lane DA, Lip GYH. 2012. Use of the CHA(2)DS(2)-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. *Circulation* **126(7)**:860–865 DOI 10.1161/CIRCULATIONAHA.111.060061.

Lee A, Crowther M. 2011. Practical issues with vitamin K antagonists: elevated INRs, low time-in-therapeutic range, and warfarin failure. *Journal of Thrombosis and Thrombolysis* **31(3)**:249–258 DOI 10.1007/s11239-011-0555-z.

McMahan DA, Smith DM, Carey MA, Zhou XH. 1998. Risk of major hemorrhage for outpatients treated with warfarin. *Journal of General Internal Medicine* **13(5)**:311–316 DOI 10.1046/j.1525-1497.1998.00096.x.

Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GYH. 2017. Real-world setting comparison of nonvitamin-K antagonist oral anticoagulants versus vitamin-K antagonists for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. *Stroke* **48(9)**:2494–2503 DOI 10.1161/STROKEAHA.117.017549.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KAA, Califf RM, ROCKET AF Investigators. 2011. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *The New England Journal of Medicine* **365(10)**:883–891 DOI 10.1056/NEJMoa1009638.

Rupprecht H-J, Blank R. 2010. Clinical pharmacology of direct and indirect factor Xa inhibitors. *Drugs* **70(15)**:2153–2170 DOI 10.2165/11538030-000000000-00000.

Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. 2005. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *Journal of Thrombosis and Haemostasis: JTH* **3(4)**:692–694 DOI 10.1111/j.1538-7836.2005.01204.x.

Streiff MB, Agnelli G, Connors JM, Crowther M, Eichinger S, Lopes R, McBane RD, Moll S, Ansell J. 2016. Guidance for the treatment of deep vein thrombosis and pulmonary embolism. *Journal of Thrombosis and Thrombolysis* **41(1)**:32–67 DOI 10.1007/s11239-015-1317-0.

Tellor KB, Patel S, Armbruster AL, Daly MW. 2015. Evaluation of the appropriateness of dosing, indication and safety of rivaroxaban in a community hospital. *Journal of Clinical Pharmacy and Therapeutics* **40(4)**:447–451 DOI 10.1111/jcpt.12288.

Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, Bengel F, Brady AJB, Ferreira D, Janssens U, Klepetko W, Mayer E, Remy-Jardin M, Bassand J-P, ESC Committee for Practice Guidelines (CPG). 2008. Guidelines on the diagnosis and management of acute pulmonary embolism: the task force for the diagnosis and management of acute pulmonary embolism of the european society of cardiology (ESC). *European Heart Journal* **29(18)**:2276–2315 DOI 10.1093/eurheartj/ehn310.

Tormene D, Ferri V, Carraro S, Simioni P. 2011. Gender and the risk of venous thromboembolism. *Seminars in Thrombosis and Hemostasis* **37(3)**:193–198 DOI 10.1055/s-0031-1273083.

Vimalesvaran K, Dockrill SJ, Gorog DA. 2018. Role of rivaroxaban in the management of atrial fibrillation: insights from clinical practice. *Vascular Health and Risk Management* **14**:13–21 DOI 10.2147/VHRM.