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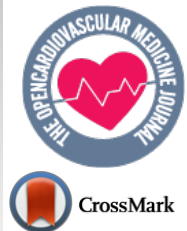
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## RESEARCH ARTICLE

### Comparative Effectiveness and Safety of Rivaroxaban and Warfarin for Stroke Prevention in Patients with Non-Valvular Atrial Fibrillation in an Omani Tertiary Care Hospital

Maya Said Al-Maawali<sup>1,\*</sup>, Hamed Hilal Al-Naamani<sup>2</sup>, Leila Neshat Mokadem<sup>3</sup>, Ghalib Al-Maawali<sup>2</sup>, Bushra Salman<sup>4</sup> and Ibrahim Al-Zakwani<sup>5,6</sup>

<sup>1</sup>Department of Pharmacy, National Heart Center, The Royal Hospital, Muscat, Oman

<sup>2</sup>Department of Pharmacy, The Royal Hospital, Muscat, Oman

<sup>3</sup>School of Pharmacy & Life Sciences, Robert Gordon University, Aberdeen, Scotland, UK.

<sup>4</sup>Sultan Qaboos Comprehensive Cancer Care and Research Center, Muscat, Oman

<sup>5</sup>Department of Pharmacy, Sultan Qaboos University Hospital, Muscat, Oman

<sup>6</sup>Department of Pharmacology & Clinical Pharmacy, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman

#### Abstract:

#### Objective:

The aim of the study was to compare the effectiveness and safety of rivaroxaban and warfarin as well as to determine the appropriateness of dosing and prescribing of rivaroxaban in Omani patients with non-valvular atrial fibrillation (NVAF).

#### Methods:

This retrospective cohort study was conducted using the Royal Hospital data registry. The study included all adults newly diagnosed with NVAF and treated with rivaroxaban or warfarin. The outcomes measured include ischaemic stroke, gastrointestinal bleeding (GIB), non-gastrointestinal bleeding (NGIB), as well as appropriateness of dosing and prescribing of rivaroxaban.

#### Results:

The analysis included 96 rivaroxaban users and 183 warfarin users; 51% of the cohort included males. There were no significant differences observed in the risk of ischaemic stroke between the two groups (hazard ratio (HR), 1.1; 95% confidence interval (CI): 0.4-3.4;  $p=0.8$ ). However, those on rivaroxaban exhibited a significantly higher rate of GIB compared to those on warfarin (HR, 5.9; 95% CI: 2.9-11.7;  $p=0.001$ ). There were no differences observed with regards to NGIB between the two groups (HR, 0.9; 95% CI: 0.4-1.9;  $p=0.8$ ). Dosing and prescribing of rivaroxaban were found to be appropriate in 89% of the patients, with only 6% being prescribed an inappropriately lower dose.

#### Conclusion:

The study demonstrated no significant differences in the risk of ischaemic stroke or NGIB between rivaroxaban and warfarin groups in newly diagnosed NVAF patients. However, rivaroxaban users were found to have a significantly higher risk of GIB. Rivaroxaban was appropriately prescribed to the majority of the patients, and only a small proportion of the group received an inappropriately lower dose of rivaroxaban.

**Keywords:** Non-valvular atrial fibrillation, Rivaroxaban, Warfarin, Ischaemic stroke, Gastrointestinal bleeding, Non-gastrointestinal bleeding.

#### Article History

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## 1. INTRODUCTION

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia causing higher rates of mortality and morbidity [1].

\* Address correspondence to this author at, Department of Pharmacy, National Heart Center, The Royal Hospital, Muscat, Oman;  
E-mail: m.sm22@hotmail.com

AF patients in the Middle East (ME) are around 10 years younger than Western patients, with high rates of diabetes mellitus (DM), hypertension and heart failure [2]. Zubaid *et al.* reported that around 84% of AF cases in ME countries have non-valvular atrial fibrillation (NVAF) [3]. Patients with NVAF have five times greater risk of thromboembolic ischaemic stroke compared to patients without NVAF [4]. For

several years, warfarin has been the main anticoagulant that could be administered orally [5]. It decreased the stroke risk in AF patients by approximately 60% [1]. However, safety concerns regarding fluctuating international normalised ratio (INR) as well as serious drug-drug and drug-food interactions have limited the use of warfarin [1].

New oral anticoagulants called direct oral anticoagulants (DOACs), like rivaroxaban, have been approved. Patients on DOACs generally do not involve any regular follow-ups for reviews and blood tests, unlike those on warfarin [6]. DOACs provide efficient management of anticoagulation compared to warfarin; however, several patients are not managed with DOACs due to concerns regarding inadequate experience with these drugs [7, 8]. Rivaroxaban is recommended for the prevention of stroke and systemic embolism in NVAF patients with  $\geq 1$  of the following risk factors: hypertension, transient ischaemic attack, age  $\geq 75$  years, previous stroke, heart failure or diabetes mellitus, unless it is contraindicated [9, 10]. *The Scottish Medicines Consortium* has restricted the use of rivaroxaban for stroke prophylaxis in NVAF patients with unstable INR, poor compliance, or who have intolerance or allergy to warfarin [10]. The standard dose of rivaroxaban to prevent strokes in NVAF patients is 20 mg daily. The dose is decreased to 15 mg daily in patients with renal impairment (creatinine clearance (CrCl) 15-49 mL/min) [6, 11].

Although there is no locally published data on how hospital doctors use rivaroxaban, the American Heart Association, American College of Cardiology and Heart and Rhythm, and European Society of Cardiology guidelines consider using oral anticoagulation (OAC) in NVAF patients with CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> (congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, stroke or transient ischaemic attack (TIA), vascular disease, age 65 to 74 years, sex category) score  $\geq 2$  in women or  $\geq 1$  in men [6, 11]. Selection of OAC should be based on clinical benefits and consideration of patient preference [6, 11]. As rivaroxaban had recently been started to be used (2016) in the hospital, warfarin is used as first-line anticoagulant for NVAF patients, unless it is contraindicated or patients have unstable INR or poor compliance.

Most studies comparing the effectiveness and safety of rivaroxaban and warfarin in NVAF patients have been conducted in Western countries. There is currently only scant literature on the subject, not only in Oman but also in the Arabian Gulf region [3]. Furthermore, despite regional and global variations in clinical characteristics related to AF patients, concerns have been raised regarding proper patient selection for rivaroxaban [12, 13]. Thus, the objectives of this study were to compare the effectiveness and safety of rivaroxaban and warfarin as well as to determine the appropriateness of dosing and prescribing of rivaroxaban in

Omani patients with NVAF.

## 2. MATERIALS AND METHODS

### 2.1. Data Source

Data were collected from the Royal Hospital (Muscat, Oman) data registry, using *Al Shifa 3Plus* software (healthcare data system established by the Ministry of Health, Muscat, Oman). The indication for the use of these medications was retrieved by the codes based on the International Classification of Diseases (ICD) for AF and atrial flutter Clinical Modification (ICD-10-CM) codes I48.91 [14].

### 2.2. Study Design and Population

This retrospective cohort study was carried out using medical records. The study included all adult patients  $\geq 18$  years old, newly diagnosed with NVAF between June 1<sup>st</sup>, 2016, and June 1<sup>st</sup>, 2018 (identification period), who had been on warfarin or rivaroxaban. Although rivaroxaban use started in January 2016, June 1<sup>st</sup>, 2016, was selected as the starting date of the study to allow for an adjustment period and reduce possible bias [15]. The first prescription date of rivaroxaban or warfarin was selected as the index date. Patients were followed from the index date to the ischaemic stroke, gastrointestinal bleeding (GIB) and non-gastrointestinal bleeding (NGIB) events (leading to hospitalisation), or to the end of the follow-up period (September 30<sup>th</sup>, 2019), whichever event occurred first. The selected patients were ideally followed up at the hospital for  $\geq 12$  months after the index date to reduce bias from differing follow-up times due to differences in the uptake times of rivaroxaban or warfarin [16].

The initial sample involved 1433 patients *via* ICD-10-CM codes for AF identification. The patient selection criteria are presented in Fig. (1). Eventually, after excluding some patients due to specific criteria, the final sample only included 279 patients. Patients who switched from warfarin to rivaroxaban were excluded to control confounding, as switching may influence the outcomes of the study [15]. Expatriate patients were also excluded because some of them paid for their medications, and this access issue might have affected the outcomes of the study.

### 2.3. Patient Characteristics and Outcomes

Patients were divided into rivaroxaban and warfarin groups. The age and gender of each patient were recorded from the data registry (at index date). Furthermore, specific comorbidities (related to AF outcomes) and medications were also identified. To evaluate the presence of these comorbidities, two scoring systems were used to calculate stroke and bleeding risks for each patient at the index date:

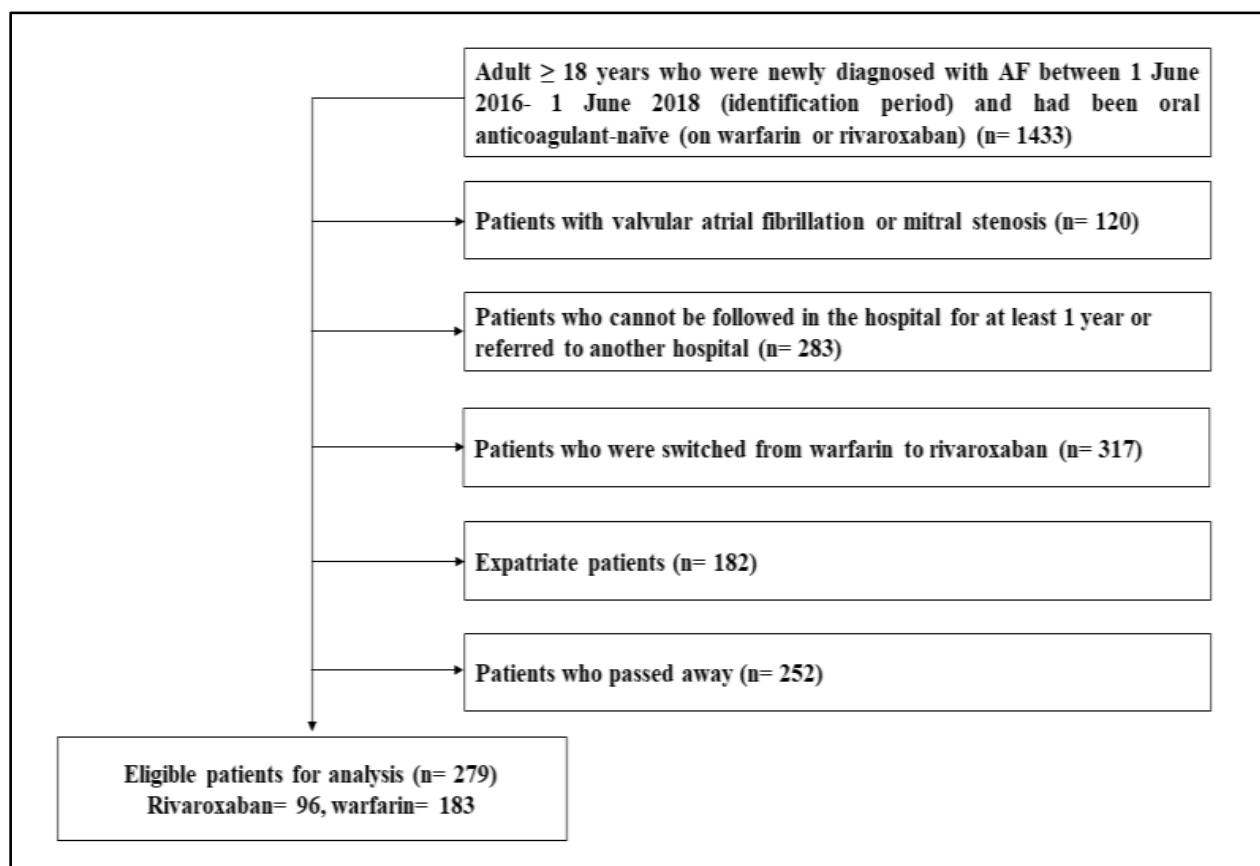


Fig. (1). Patient selection criteria. AF, Atrial Fibrillation.

1) CHA<sub>2</sub>DS<sub>2</sub>-VASc score [6]: This score ranges from 0 to 9 with 1 point allocated for the existence of hypertension, patients aged 65-74 years, congestive heart failure, vascular disease (including prior myocardial infarction (MI) or peripheral artery disease), diabetes mellitus (DM) or female sex. Two points are assigned for a history of stroke or age  $\geq 75$  years. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score is divided into 3 groups: low (0 in men and 1 in women), moderate (1 in men and 2 in women), and high ( $\geq 2$  in men and  $\geq 3$  in women) stroke risk.

2) HAS-BLED (hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile INR, elderly, drug/alcohol usage) score [6]: This score ranges from 0 to 9. One point is allocated for the existence of hypertension, patients aged  $\geq 65$  years, prior stroke, previous bleeding, using drugs that increase bleeding risk, excessive alcohol intake, renal disease or liver disease. The score also includes an indicator for patients with a history of unstable high INR. The score is classified into 3 groups: low (1), moderate (2), or high ( $\geq 3$ ) bleeding risk.

The outcomes were defined as ischaemic stroke, GIB and NGIB (leading to hospitalisation), and the number of each outcome event was recorded. Furthermore, the appropriate rivaroxaban dosing and prescribing were also assessed by reviewing the adherence of clinicians to the recommended dose of rivaroxaban (based on the CrCl) [6, 11].

## 2.4. Statistical Analysis

Descriptive statistics were used. For categorical variables, frequencies and percentages were reported. Differences between groups were analysed using Pearson's  $\chi^2$  tests (or Fisher's exact tests for expected cells  $< 5$ ). For continuous variables, mean and standard deviation were used to summarize the data, and differences between groups (warfarin vs. rivaroxaban) were analysed using the Student's t-test.

The incidence rate of each outcome was calculated by dividing the number of patients who developed the outcome by the total time at risk during the study's follow-up period [16, 17]. A univariate Cox proportional hazards model was used to predict the relative risks (hazard ratios, HR) of developing the outcomes, with 95% confidence intervals (CI). Kaplan-Meier survival curves for the 3 outcomes were drawn to show the percentage of patients in both groups who did not experience outcomes during the study period (secondary analysis). Statistical significance was defined as a two-sided  $p < 0.05$ . All statistical tests were performed using SPSS version 25, IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.

## 2.5. Ethical Approval

Ethical approval was obtained from the Ethics Committee at the School of Pharmacy and Life Sciences, Robert Gordon University, Aberdeen, Scotland, United Kingdom (August 29<sup>th</sup>,

2019). Furthermore, since the data of the patients were collected from the data registry of the Royal Hospital, Muscat, Oman, the country's Research and Ethical Review and Approval Committee also granted approval on September 26<sup>th</sup>, 2019 (MOH/CSR/19/10898).

### 3. RESULTS

After exclusion criteria were applied, the study cohort included 96 new rivaroxaban users and 183 new warfarin users. Table 1 describes the patients' characteristics at the index date.

A total of 52% (145/279) of the cohort included males. The 3 most prevalent comorbidities were hypertension (72%; 201/279), diabetes mellitus (55%; 154/279), and congestive heart failure (36%; 101/279). The three most prescribed medication groups were statins (71%; 199/279), proton pump inhibitors (41%; 114/279), and non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin (27%; 76/279). The proportion of patients with high CHA<sub>2</sub>DS<sub>2</sub>VASc ( $\geq 2$ ) and HAS BLED ( $\geq 3$ ) risk scores was 37% (104/279) and 35% (98/279), respectively.

**Table 1. Baseline demographics, comorbidities and medication for study participants at the index date.**

Characteristic	Rivaroxaban (n=96)		Warfarin (n=183)		P-value
<b>Demographics</b>					
<b>Age</b>					
Mean±SD, years	61.3	10.9	71.5	11.9	0.026
18-54	27	28.1%	29	15.8%	
55-64	30	31.2%	54	29.5%	
≥65	39	40.6%	100	54.6%	
<b>Gender, n (%)</b>					
Female	45	46.9%	89	48.6%	0.779
Male	51	53.1%	94	51.4%	
<b>Comorbidities, n (%)</b>					
<0.001					
Congestive heart failure	45	46.9%	56	30.6%	
Diabetes mellitus	52	54.2%	102	55.7%	
Hypertension	64	66.7%	137	74.9%	
Liver disease	0	0.0%	3	1.6%	
Peripheral artery disease	4	4.2%	13	7.1%	
Prior bleeding history	27	28.1%	32	17.5%	
Prior MI	8	8.3%	25	13.7%	
Renal disease	19	19.8%	32	17.5%	
Stroke/ TIA	9	9.4%	11	6.0%	
<b>Medications, n (%)</b>					
0.185					
Antidepressants	7	7.3%	13	7.1%	
Antiplatelet	6	6.2%	12	6.6%	
NSAIDs	16	16.7%	60	32.8%	
PPIs	41	42.7%	73	39.9%	
Statins	67	69.8%	132	72.1%	
<b>Risk Scores</b>					
<b>CHA<sub>2</sub>DS<sub>2</sub>VASc score<sup>a</sup></b>					
0.318					
Mean±SD	2.1	(1.1)	2.2	(1.2)	
Low Risk, (%)	16	16.7%	23	12.6%	
Moderate risk, (%)	41	42.7%	95	51.9%	
High risk, (%)	39	40.6%	65	35.5%	
<b>HAS BLED score<sup>b</sup></b>					
0.609					
Mean±SD	2.2	(1)	2.2	(0.9)	
Low risk, (%)	25	26.0%	43	23.5%	
Moderate risk, (%)	35	36.5%	78	42.6%	
High risk, (%)	36	37.5%	62	33.9%	

SD, standard deviation; MI, myocardial infarction; TIA, transient ischaemic attack; PPIs, proton pump inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs.

<sup>a</sup>CHA<sub>2</sub>DS<sub>2</sub>-VASc score ranges from 0 to 9; higher scores indicate a higher risk of stroke, transient ischaemic attack, or embolism.

<sup>b</sup>HAS-BLED score ranges from 0 to 9; higher scores indicate a higher bleeding risk.

Patients on rivaroxaban were significantly younger compared to those on warfarin (61 vs. 72 years;  $p=0.026$ ). However, those on rivaroxaban were more likely to have a diagnosis of congestive heart failure (CHF) (47 vs. 31%) and prior bleeding history (28 vs. 17%), compared to those on warfarin. Those on rivaroxaban were also less likely to be on NSAIDs than those on warfarin (17 vs. 33%). There were no significant differences in CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS BLED risk scores between the rivaroxaban and warfarin groups ( $p=0.318$  and  $p=0.609$ , respectively).

Regarding the appropriateness of rivaroxaban (Table 2), the results showed 89% (85/96) appropriateness of dosing and prescribing rivaroxaban to NVAf patients. Approximately 6% (6/96) of patients received an inappropriately lower dose (15 mg) of rivaroxaban with normal renal function ( $CrCl \geq 50$  ml/min). Additionally, 5% of the patients were inappropriately prescribed rivaroxaban (*i.e.*, rivaroxaban prescribed as first-line therapy for NVAf patients without risk factors [comorbidities] and no reasons recorded in the medical records). However, no

patients had inappropriately higher doses or a dose of 10 mg, which is not an approved rivaroxaban dose for NVAf patients.

The Cox proportional hazard regression analysis (Table 3) showed that there were no significant differences in the risk of ischaemic stroke (HR, 1.1; 95% CI: 0.4-3.4;  $p=0.8$ ) between the 2 groups. With regards to side effects, rivaroxaban use was associated with a significantly higher rate of GIB compared to warfarin (HR, 5.9; 95% CI: 2.9-11.7;  $p=0.001$ ). However, no differences were noted with regards to NGIB (HR, 0.9; 95% CI: 0.4-1.9;  $p=0.8$ ) between the rivaroxaban and warfarin groups.

### 3.1. Secondary Analysis

Kaplan-Meier survival curves for ischaemic stroke (2a), NGIB (2b) and GIB (2c) were used to show the survival probabilities of rivaroxaban and warfarin patients who did not experience outcomes at any time during the follow-up period of the study (Fig. 2).

**Table 2. Rivaroxaban dosing and prescribing appropriateness criteria.**

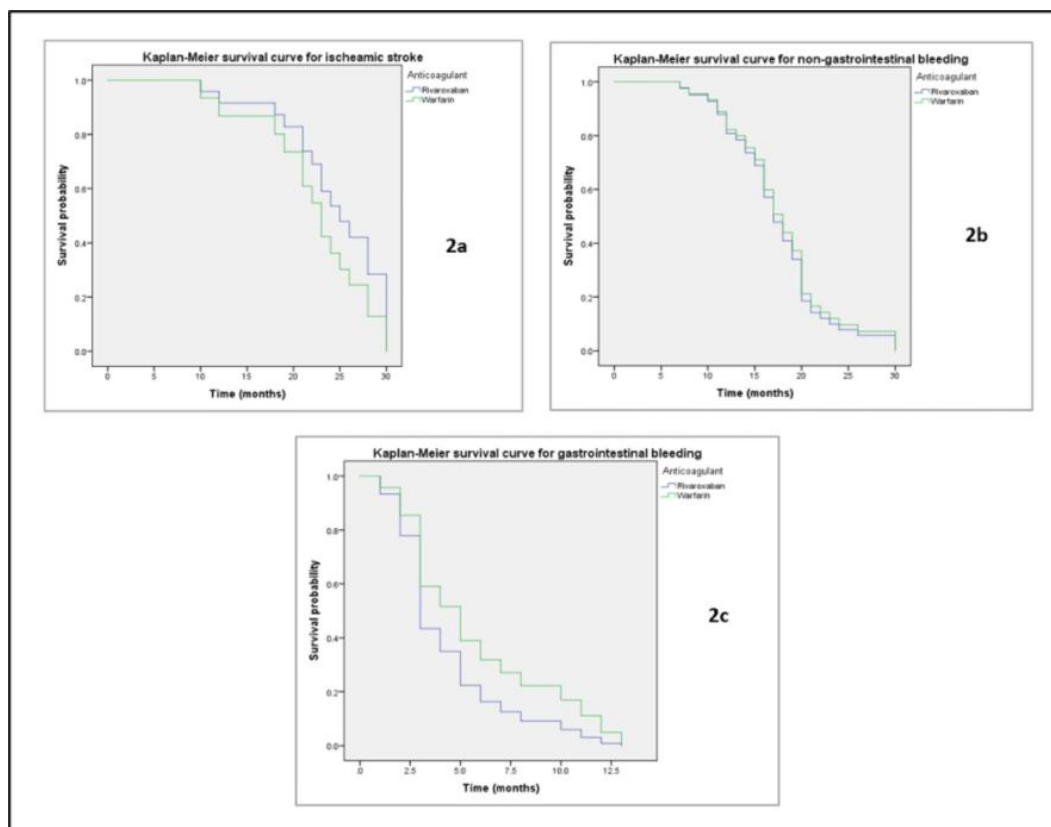
Appropriateness of rivaroxaban dosing and prescribing	N	%
<b>Dose of rivaroxaban</b>		
10 mg	0	0
15 mg	32	33.3
20 mg	64	66.7
<b>Overall appropriateness</b>		
Appropriate <sup>1</sup>	85	88.5
Inappropriate <sup>2</sup>	11	11.5
<b>Appropriateness according to dose per CrCl</b>		
Inappropriate lower dose	6	6.2
Inappropriate higher dose	0	0
<b>Appropriateness based on international guidelines</b>		
Appropriate prescribing	91	94.8
Inappropriate prescribing	5	5.2

<sup>1</sup>Based on creatinine clearance (CrCl) and recommendations of guidelines. <sup>2</sup>Rivaroxaban prescribed as first-line therapy for NVAf patients without risk factors (comorbidities) and no reasons recorded in the medical records or inappropriate dose.

**Table 3. Outcome event rates and hazard ratios for the rivaroxaban and warfarin groups.**

Characteristics	Rivaroxaban (n=96)			Warfarin (n=183)					
	n	%	IR*	n	%	IR*	HR*	95%CI*	p
Ischaemic stroke	5	5.2%	0.5	12	6.6%	0.5	1.1	(0.4-3.4)	0.8
Gastrointestinal bleeding	35	36.5%	2.9	16	8.7%	1.9	5.9	(2.9-11.7)	0.001
Non-gastrointestinal bleeding	11	11.5%	0.7	33	18.0%	0.7	0.9	(0.4-1.9)	0.8

\*IR, incidence rate; HR, hazard ratio; CI, confidence intervals.



**Fig. (2).** Kaplan-Meier survival curves for ischaemic stroke (2a), non-gastrointestinal bleeding (2b), and gastrointestinal bleeding (2c).

#### 4. DISCUSSION

This study demonstrated no significant differences in the risk of ischaemic stroke between the rivaroxaban and warfarin groups among Omani NVAF patients. With regards to safety, rivaroxaban was associated with significantly higher rate of GIB compared to those on warfarin but no differences were noted with regards to NGIB rates. Of note, rivaroxaban was appropriately indicated in the majority of the patients and only a small proportion of the cohort received an inappropriately lower dose of rivaroxaban.

The findings of the current study are consistent with the ROCKET-AF (Rivaroxaban Once daily oral direct factor Xa inhibition Compared to vitamin K antagonism for prevention of stroke and Embolism Trial in AF) trials, which reported the risk of ischaemic stroke to be comparable in the rivaroxaban and warfarin groups [18 - 20]. With regards to the safety profile, rivaroxaban generally exhibited less intracranial, critical and fatal bleeding than warfarin, but it was associated with a significantly higher rate of GIB [20 - 22]. Interestingly, most patients had a moderate-high risk of stroke (mean CHADS<sub>2</sub> score: 3.5) [21]. The results of the XANTUS-EL (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Eastern Europe, the Middle East and Africa [EEMEA] and Latin America) study (first real-world, prospective, observational cohort study to describe rivaroxaban use in a broad patient population with NVAF in Eastern Europe, the Middle East and Africa and Latin America) were generally comparable with the ROCKET-AF trial, considering differences in baseline characteristics of the patients [2].

A systemic review that included 22 network meta-analyses reported rivaroxaban to have the highest rates of GIB compared to other DOACs [23]. It is possible that GIB events occurred due to factors associated with an increased risk of bleeding events [24]. In the present study, old age and prior history of bleeding were associated risk factors as well as concomitant use of acetylsalicylic acid and other antiplatelet medications, which are known risk factors for GIB [25].

As most of the patients were elderly, it is important to address the risk factors and comorbidities that are more common among the elderly and could increase the probability of bleeding episodes [24, 26]. These factors include decreased body mass index, renal dysfunction, uncontrolled blood pressure, and frequent falls [24, 26]. In the present study, these factors were not significantly different between the groups.

A recent meta-analysis of 20 observational studies compared the effectiveness and safety of DOACs against VKAs in NVAF patients over 75 years old [27]. They found that the incidence rate of GIB increased by 46% among DOAC users compared to VKA users. Furthermore, rivaroxaban had a higher rate of major bleeding compared to other DOACs [27]. This supports the finding of the present study, which showed a significant increase in GIB risk in rivaroxaban users.

In the present study, there was a statistically significant difference observed in the presence of comorbidities in the rivaroxaban and warfarin groups. Hypertension and DM had the highest comorbidities percentages in both the groups. The present finding is consistent with a study conducted in the United Arab Emirates that showed the common comorbidities

as hypertension, DM and coronary arterial disease in NVAf patients [12]. A long duration of DM in NVAf patients can be associated with increased risk of ischaemic stroke [28]. Another study conducted found that rivaroxaban users had more GIB events than warfarin users, mainly in NVAf patients with  $\geq 3$  comorbidities [22]. The rivaroxaban group had higher rates of CHF than the warfarin group. A study conducted to describe bleeding events in CHF patients showed GIB risk to be higher in CHF patients who are on OAC [29].

Moderate to high HAS-BLED scores were observed in most patients in both groups in the present study. However, the percentage of prior bleeding history was higher in rivaroxaban users than warfarin users. Lip *et al.* showed that patients (newly initiating rivaroxaban) were numerically more likely to encounter major bleeding episodes, compared to warfarin [16]. Warfarin needs a longer time than other DOACs to reach the maximum anticoagulation effect, therefore, warfarin has a lower rate of clinical events during the initial months, resulting in a lower level of effectiveness and lower chance of bleeding episodes [16].

Another key objective of the current study was to ensure that rivaroxaban had been prescribed appropriately for all eligible patients with NVAf. The results of the current study indicate a low proportion (6%) of inappropriately low doses of rivaroxaban (15 mg) in patients with normal renal function ( $\text{CrCL} \geq 50$  mL/min). A study reported that 16% of rivaroxaban patients had inappropriately low doses, and 20% of patients had inappropriately high doses based on their renal function at the start of treatment with rivaroxaban [30]. Another study conducted in a Saudi tertiary hospital [13] reported that 42% of rivaroxaban patients had inappropriate doses and that most of these patients had low doses of rivaroxaban (83%). Although the percentage of inappropriate dosing in the present study is low compared to the results of other studies, ineffective doses of anticoagulant may lead to significant clinical effects, such as stroke, particularly with NVAf which carries a greater risk of thromboembolic ischaemic stroke than other types of AF [13]. Inappropriate dosing based on renal function status of the patient can be explained by the information required to calculate the CrCl, such as laboratory test results, age and weight; however, the latter is not always requested on admission [13, 31]. Another possible explanation for this is that some physicians fear the risk of bleeding [13]. This finding, therefore, needs to be interpreted with caution, particularly in patients with NVAf to prevent thrombosis due to ineffective dosage or major bleeding possibly from overdose [13, 31]. Furthermore, the results showed a small percentage (5%) of prescribing inappropriateness of rivaroxaban. A systemic review reported that patients' views and preferences should be highlighted when choosing an oral anticoagulant for NVAf patients [32].

This study has several limitations. The number of patients on rivaroxaban was small and not sufficient to ensure enough statistical power for some of the outcomes including ischaemic stroke which may take longer time to occur [15]. However, the findings are in agreement with the results of many previous observational studies and ROCKET-AF trials. As this was a retrospective observational study, there is a possibility of

selection bias. The data of the current study was derived from a registry database, the findings of which may be confounded by missing data and important uncollected variables [33, 34]. Further, INR monitoring data were not available in the hospital registry database since INR monitoring is performed in secondary healthcare units.

Despite these limitations, the present study provided information about the safety profile of rivaroxaban, particularly regarding the risk of GIB. These results indicate the importance of developing evidence-based protocols to guide clinicians in their selection of a proper anticoagulant and the effective dose for stroke prevention in NVAf patients; treatment recommendations should also consider the patient's underlying bleeding risk profile, renal function, age, medical and medication histories [13, 33]. One of the issues that emerges from these findings is the importance of the bleeding scoring systems, such as the HAS-BLED score in the *Al Shifa 3Plus* (as an electronic calculator). This may facilitate identification of the bleeding risk severity in each patient and reduce adverse events by selecting a suitable oral anticoagulant. Moreover, the results demonstrate the need to reduce modifiable risk factors for GIB (*e.g.*, antiplatelet medications and non-steroidal anti-inflammatory drugs) in patients on anticoagulants [12].

## CONCLUSION

This study has shown no significant differences in the risk of ischaemic stroke or NGIB between the rivaroxaban and warfarin groups in a population of Omani patients with NVAf. However, those on rivaroxaban had a significantly higher risk of GIB compared to those on warfarin. Rivaroxaban was appropriately indicated in the majority of the patients and only a small proportion of the cohort received an inappropriately lower dose of rivaroxaban. The findings should be interpreted with caution due to low study power.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Research and Ethical Review and Approval Committee on September 26, 2019 (MOH/CSR/19/10898).

## HUMAN AND ANIMAL RIGHTS

All human procedures were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

## CONSENT FOR PUBLICATION

Informed consent has been obtained from the subjects for the publication of the data.

## STANDARDS OF REPORTING

STROBE guidelines and methodologies were followed in this study.

## AVAILABILITY OF DATA AND MATERIALS

Not applicable.



## FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest or personal relationships that could have influenced this study.

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