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Original article

Cost effectiveness of rivaroxaban versus warfarin among nonvalvular atrial fibrillation patients in Saudi Arabia: A Single–Center retrospective cohort study

Yazed AlRuthia [a,d,*], Bushra Q. AlOtaibi [a], Reem M. AlOtaibi [a], Najla Q. AlOtaibi [b], Miteb Alanazi [c], Ghadah Asaad Assiri [a]

[a] Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia
[b] Department of Medicine, King Saud Medical City, Riyadh 11451, Saudi Arabia
[c] Department of Pharmacy, King Khalid University Hospital, P.O. Box 3145, Riyadh 12372, Saudi Arabia
[d] Pharmacoeconomics Research Unit, Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia

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ABSTRACT

Background: Rivaroxaban is a novel oral anticoagulant (NOAC) that is commonly used for stroke prevention among patients with atrial fibrillation (AF). However, its cost effectiveness in reducing the risk of hospitalization and mortality in comparison to warfarin among nonvalvular AF patients in Saudi Arabia is largely unknown.

Methods: This was a single-center retrospective chart review of adult patients (≥18 years) with nonvalvular AF who were treated with warfarin or rivaroxaban for at least 12 months. Patients with mitral valve stenosis were excluded from the study. Multiple logistic regression was conducted to examine the risk of hospitalization and mortality as a composite outcome, and all annual healthcare costs were captured. Inverse probability treatment weighting with bootstrapping was conducted to determine the mean costs and effectiveness rates.

Results: Two-hundred and twenty-six patients (142 on rivaroxaban and 84 on warfarin) met the inclusion criteria and were included in the analysis. Most of the patients were females (65.91 %), had diabetes (50.57 %) and hypertension (73.76 %), and with a mean age of 68.95 ± 12.55 years. No significant difference in the odds of the composite outcome for rivaroxaban versus warfarin was found (OR = 0.785, 95 % CI = [0.427–1.446], p = 0.443). Rivaroxaban resulted in a mean annual cost saving of $13,260.79 with an 87.65 % confidence level that it would be more effective than warfarin with a mean difference in effectiveness rate of 0.168 % (95 % CI [-5.210–18.36]).

Conclusion: Rivaroxaban was associated with lower direct medical costs and non-inferior effectiveness among nonvalvular AF patients in comparison to warfarin.

1. Background

Atrial fibrillation (AF) is the most common cardiac arrhythmias and is a major risk factor for ischemic stroke which is associated with high rates of morbidity and mortality and immense economic costs. Globally, there are 37,574 million cases of AF, an increase of 33 % during the past two decades (Lippi et al., 2021). The increasing incidence and prevalence rates of AF put affected patients at higher risk of serious complications, such as cardiovascular disease and stroke (Zulkifly, Lip, & Lane, 2018). Fortunately, the use of oral anticoagulants, such as warfarin, has proven to be effective in minimizing the risk of major AF complications, such as stroke. Despite the high efficacy of warfarin in reducing the incidence rates of ischemic stroke and myocardial infarction (MI) among patients with non-valvular atrial fibrillation, its use is associated with higher risk of bleeding complications and hospitalization due to its side effects in comparison to the new oral anticoagulants (NOACs) (Molteni & Cimminiello, 2014). Moreover, the use of war-

* Corresponding author at: Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia.
E-mail addresses: yazeed@ksu.edu.sa (Y. AlRuthia), mitalanazi@KSU.EDU.SA (M. Alanazi), gassiri@ksu.edu.sa (G. Asaad Assiri).

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farin for prophylaxis against ischemic stroke and MI requires close monitoring of international normalized ratios (INRs) in anticoagulation clinics, and patient adherence to therapy and clinic visits to ensure optimal treatment outcomes (Björck et al., 2016; Molteni & Cimminiello, 2014). On the other hand, NOACs with an approved indication for prevention of stroke among AF patients, such as dabigatran, apixaban, edoxaban, rivaroxaban, do not require close and frequent laboratory monitoring, dosing adjustments, dietary restrictions, and have better drug-drug interaction profiles (Wanat, 2013). Although NOACs have proven to be efficacious in the prevention of stroke among AF patients (Dogliotti, Paolasso, & Giugliano, 2013; Hanley & Kowey, 2015), their higher acquisition costs may not make them cost effective in comparison to warfarin (You, 2014). The uncertainty of the cost effectiveness of different NOACs versus warfarin are attributable to different factors, such as patient characteristics, drug costs, and CHADS2 score (Coyle et al., 2013). Rivaroxaban, is one of the most commonly prescribed NOACs and has been found to be cost effective for prevention of ischemic stroke among AF patients using real-world data and hypothetical cohorts in Iran, France, and China (Bowrin et al., 2020; Jaberi et al., 2021; Lee et al., 2012; Wei, Cui, Cui, Liu, & Li, 2021).

In addition, rivaroxaban and dabigatran showed comparable effectiveness rates for the prevention of systemic thromboembolism and favorable safety profiles in comparison to warfarin among a large cohort of Medicare beneficiaries with AF and valvular heart disease in the United States (U.S.) (Briasoulis et al., 2018). Although rivaroxaban and dabigatran, were associated with higher risk of hospitalization and death from bleeding in comparison to warfarin among hemodialysis patients with AF,(Chan, Edelman, Wenger, Thadhani, & Maddux, 2015) patients on NOACs with glomerular filtration rate $\geq$ 15 mL/(min·1.73 m^2) had lower risk of stroke, major bleeding, and mortality in comparison to warfarin according to a large retrospective study that used U.S. administrative claims database with linked laboratory data (Rutherford, Jonasson, Ghanima, Söderdahl, & Halvorsen, 2020). Moreover, rivaroxaban was associated with higher quality adjusted life years (QALYs) gained in comparison to warfarin (5.69 versus 5.22 QALYs) with lower treatment cost among elderly male patients with nonvalvular AF exhibiting worsening renal function in the U.S. according to a cost effectiveness analysis that used a Markov model (Salcedo, Hay, & Lam, 2019). Additionally, rivaroxaban was associated with lower risk of stroke, systemic embolism, MI, major bleeding, and intracranial hemorrhage compared to warfarin among AF patients with diabetes according to a large systematic review and *meta*-analysis (Hua et al., 2021). However, rivaroxaban was associated with a lower risk of stroke/thromboembolism but a higher risk of gastrointestinal bleeding in comparison to warfarin, and a higher risk of all-cause mortality in comparison to dabigatran according to another systematic review and *meta*-analysis that compared the safety and efficacy of rivaroxaban to dabigatran and warfarin among AF patients (Bai, Deng, Shantsila, & Lip, 2017).

In Saudi Arabia, the use of NOACs, such as dabigatran and rivaroxaban, are common among non-valvular AF patients for prevention of ischemic stroke (Alajami et al., 2021). Although multiple studies have evaluated the safety, efficacy, and cost effectiveness of NOACs among non-valvular AF patients in different countries, no study has so far evaluated the cost effectiveness of NOACs in Saudi Arabia with the exception of a single study that evaluated the cost effectiveness of apixaban using an adapted lifetime Markov model from United Kingdom (Hersi, Osenenko, Kherraf, Aziz, & Sambrook, 2019). Therefore, we aimed to examine the cost effectiveness of rivaroxaban, which is one of the most commonly used NOACs in Saudi Arabia for the prevention of hospitalization and all-cause mortality versus warfarin using real-world data among non-valvular AF patients from the public payer's perspective.

2. Methods

2.1. Study design and population

This was a single center retrospective cohort study that compared the direct medical cost and effectiveness of rivaroxaban versus warfarin in reducing the rates of stroke, MI, emergency department (ED) visits, hospitalization, and death as a composite outcome among patients with nonvalvular AF. The study took place at King Khalid University Hospital (KKUH) in Riyadh, Saudi Arabia. KKUH is a tertiary care academic institution with more than 1200 staffed beds affiliated with King Saud University, which is the largest and oldest academic institution in Saudi Arabia. Adult patients aged 18 years and above with nonvalvular AF treated with either rivaroxaban or warfarin for at least 12 months were included in the study. Patients with valvular AF, cancer, heart failure (e.g., reduced ejection fraction of 40 % or less), aortic stenosis, mitral stenosis, and/or mechanical heart valves were excluded as rivaroxaban is not approved for patients with mechanical heart valves or mitral stenosis (Guimarães et al., 2020). Additionally, patients on other NOACs, such as dabigatran and apixaban, those treated for less than 12 months, and patients with missing observations were excluded. All data were retrospectively retrieved from the electronic medical records (EMRs) between June 2020 and September 2021.

2.2. Data collection

The medical record numbers of patients with nonvalvular AF treated with rivaroxaban or warfarin were retrieved from the pharmacy department at KKUH. A structured data collection sheet was created to facilitate the EMRs review and data retrieval. Two pharmacy interns were trained to collect the data and were granted access to patients' EMRs. The collected data were checked and verified by two clinical pharmacists and a senior cardiology resident. Any incidence of stroke, MI, ED visits, hospital admission (general ward or intensive care units), and death which represented the composite outcome were collected. Moreover, patients' weight, height, age, gender, and other comorbidities, such as diabetes, hypertension, and dyslipidemia were collected. Additionally, the frequency of lab tests (e.g., international normalized ratio (INR), glycated hemoglobin A1C, complete blood count (CBC), renal function tests, liver function tests, cardiac enzymes, etc.....), imaging studies (e.g., magnetic resonance imaging (MRI), X-ray), prescription drugs and their dosages and frequencies, and the length of stay (LOS) if hospitalization was observed were collected to estimate the direct medical cost for patients treated with rivaroxaban and warfarin. The cost of medical resources including the prescription drugs were retrieved from the Saudi Ministry of Health cost center.

2.3. Ethical consideration

The study was approved by the institutional review board of the College of Medicine at King Saud University, Riyadh, Saudi Arabia. No personal identifiers, such as patient's name or address, were collected, and the informed consent form was waived by the institutional review board since the data only involved retrospective EMRs review. The collected data was encrypted and stored in a safe place, and the study adhered to the ethical principles of the declaration of Helsinki (Association, 2001).

2.4. Statistical analysis

The minimum sample size needed for this study was estimated to be 196 patients based on an odds ratio of 1.35 for the composite

Table 1
Patients' baseline characteristics.

Characteristic	Oral Anticoagulant		*p*-value	Total
	Rivaroxaban	**Warfarin**		
Gender, N (%)				
Female	91(64.08)	56(66.67)	0.694	147(65.04)
Male	51(35.92)	28(33.33)		79(34.96)
Age, mean ± SD	72.14 ± 11.18	66.77 ± 13.47	0.0014	68.95 ± 12.55
Duration of illness, mean ± SD	5.61 ± 0.99	5.82 ± 1.57	0.2771	5.69 ± 1.244
Body Mass Index, mean ± SD	31.23 ± 6.67	29.36 ± 6.07	0.0745	30.51 ± 6.49
Number of prescription medications, mean ± SD	6.04 ± 3.24	4.74 ± 2.77	0.0024	5.55 ± 3.128
Beta-blockers (β-blockers) (e.g., metoprolol, bisoprolol), N (%)	115(80.99)	65(77.38)	0.5154	180(79.65)
Calcium Channel-blockers (CCBs) (e.g., verapamil, diltiazem), N (%)	49(34.51)	18(21.43)	0.0375	67(29.65)
Digoxin, N (%)	12(8.45)	10(11.90)	0.3973	22(9.73)
Comorbidities, N (%)				
Diabetes	84(59.15)	35(41.67)	0.0092	119(52.65)
Hypertension	121(85.21)	49(58.33)	less than0.0001	170(75.20)
Heart failure	26(18.30)	13(15.48)	0.570	39(17.25)
Cardiovascular disease (CVD)	39(27.46)	11(13.10)	0.0110	50(22.12)
Dyslipidemia	74(52.11)	22(26.19)	0.0001	96(42.47)
Respiratory diseases (e.g., asthma, COPD), N (%)	22(15.49)	8(9.52)	0.1945	30(13.27)
International normalized ratio (INR), mean ± SD	–	2.159	0.889	–
Number of annual hospitalizations, N (%)				
0	79(55.63)	47(55.95)	0.875	126(55.75)
1	44(30.99)	24(28.57)		68(30.09)
≥2	19(13.38)	13(15.48)		32(14.16)
Death				
No	136(95.77)	77(91.67)	0.2411	213(94.25)
Yes	6(4.23)	7(8.33)		13(5.75)
Composite outcome (e.g., death and/or hospitalization), N (%)				
No	78(54.93)	46(54.76)	0.981	124(54.87)
Yes	64(45.07)	38(45.24)		102(45.13)
Length of stay (LOS) in days, mean ± SD	2.91 ± 4.28	9.92 ± 32.72	0.053	5.52 ± 20.44

outcome (ED visit, hospitalization, stroke, myocardial infarction, and death) for warfarin versus rivaroxaban,(Bai et al., 2017) α = 0.05, β = 0.2, and power of 80 %. Descriptive statistics, such as frequencies, percentages, means, and standard deviations were used to present the patients' baseline characteristics and costs for eligible nonvalvular AF patients on warfarin and rivaroxaban. Multiple logistic regression to compare the odds of the composite outcome between rivaroxaban and warfarin controlling for the differences between patients in the two treatment groups at the baseline, such as age, gender, duration of illness, and comorbidities, was conducted. Furthermore, inverse probability treatment weighting was conducted to match comparable groups of patients on rivaroxaban with their counterparts on warfarin based on gender, age, number of comorbidities, duration of illness, and follow-up periods. Bootstrapping with 10,000 replications was conducted to generate the 95 % confidence limits for both the effectiveness rates (%) and costs in United States Dollar (USD). All statistical analyses were conducted using SAS® version 9.4 (SAS institute, Cary, NC, United States).

3. Results

3.1. Baseline characteristics

Out of 1,717 EMRs for patients treated with warfarin or rivaroxaban that were reviewed, 226 patients (142 on warfarin and 84 on rivaroxaban) met the inclusion criteria and were included in the analysis. About two-thirds of the patients were females (65.04 %) with a mean duration of illness (e.g., nonvalvular AF) of 5.69 years. Patients on rivaroxaban mean age was five years older than their counterparts on warfarin (72.14 years versus 66.77 years, p = 0.0014). Moreover, the mean number of prescription drugs for patients on rivaroxaban was higher than their counterparts on warfarin (6.04 versus 4.74, p = 0.0024). The majority of patients (79.65 %) were taking β-blockers (e.g., metoprolol, bisoprolol) with no significant difference between patients on rivaroxaban and warfarin. On the other hand, 34.51 % of the patients on rivaroxaban were taking calcium channel-blockers (CCBs) (e.g., verapamil, diltiazem) compared to 21.43 % of the patients on warfarin (p = 0.0375). The percentages of patients on rivaroxaban with diabetes, hypertension, cardiovascular disease (CVD), and dyslipidemia were significantly higher than their counterparts on warfarin. About 44 % of patients had at least one hospital admission within the last 12 months with patients on rivaroxaban having lower mean LOS in comparison to their counterparts on warfarin as shown in Table 1.

3.2. The rate of composite outcome

Controlling for age, gender, duration of illness, heart failure, CVD, diabetes, hypertension, and dyslipidemia, patients on rivaroxaban did not have a significantly lower odds of the composite outcome (hospitalization, stroke, myocardial infarction, and death) compared to their counterparts on warfarin (OR = 0.785, 95 % CI = [0.427–1.446], p = 0.443). On the other hand, patients with longer durations of illness had significantly lower odds of the composite outcome (OR = 0.428, 95 % CI = [0.210–0.869], p = 0.0189); while patients with heart failure had significantly higher odds of the composite outcome controlling for other covariates (e.g., age, gender, heart failure, CVD, diabetes, hypertension, type of anticoagulant (rivaroxaban or warfarin), and dyslipidemia) (OR = 2.279, 95 % CI = [1.006–4.783], p = 0.0189) as shown in Table 2.

3.3. The cost effectiveness of rivaroxaban versus warfarin

The mean cost per patient per year for rivaroxaban and warfarin were $3,269.34 versus $12,641.35, respectively, as shown in Fig. 1.

Table 2
Multiple logistic regression for the association between rivaroxaban and the composite outcome (e.g., death or hospitalization).

Variable	Odds ratio (OR)	*P*-value	95 % confidence interval
Rivaroxaban vs Warfarin	0.785	0.4430	0.427–1.446
Age	1.005	0.7087	0.981–1.029
Female vs male	1.539	0.1559	0.848–2.791
Duration of illness	0.428	0.0189	0.210–0.869
Heart failure	2.279	0.0336	1.066–4.873
Cardiovascular disease	1.200	0.6091	0.596–2.415
Diabetes mellitus	1.322	0.3703	0.718–2.437
Hypertension	1.543	0.2573	0.729–3.268
Dyslipidemia	1.006	0.9844	0544–1.862

The mean effectiveness rates for prevention of the composite outcome (ED visit, hospitalization, stroke, myocardial infarction, and death) for rivaroxaban and warfarin were 54.93 % and 54.76 %, respectively. On the other hand, the mean cost per patient for rivaroxaban and warfarin treatment groups during the variable follow-up periods which were at least 12 months were $3,329 and $16,589, respectively, as shown in Table 3. The mean difference in cost between rivaroxaban and warfarin was $-13,260.79 (95 % CI: $–32,964.83 – $-4,017.68); while the mean difference in the effectiveness rates in preventing the composite outcome between the rivaroxaban and warfarin was %0.168 (95 % CI: −5.21 – 18.36). The bootstrap cost effectiveness distributions show that rivaroxaban is dominant with 87.65 % confidence level, and cost saving but less effective than warfarin with 12.35 % confidence level as shown in Fig. 2.

4. Discussion

The use of oral anticoagulants in the prevention of stroke and all-cause mortality among nonvalvular AF patients has proven to be largely safe and effective (Wanat, 2013). In this study rivaroxaban has shown to be equally effective in reducing the rates of hospitalization and mortality in comparison to warfarin when used for thrombosis prophylaxis among nonvalvular AF patients. These findings are unsurprising and consistent with other previously published studies that have proven rivaroxaban to be at least as effective as warfarin among nonvalvular AF patients with respect to preventing stroke, MI, hospitalization, and all-cause mortality (Bowrin et al., 2020; Hua et al., 2021; Jaberi et al., 2021; Lee et al., 2012; Wei et al., 2021). Moreover, rivaroxaban was found to be cost saving in all of the bootstrap simulations, and dominant in more than 87 % of the simulations mainly because it does not require frequent lab monitoring. Thus, rivaroxaban seems to be an attractive NOAC from the perspective of the healthcare payer for the management of nonvalvular AF since it has shown better treatment outcomes and lower direct medical costs despite its higher acquisition cost. These findings are in line with two studies in both Iran and France which used real world data to examine the cost effectiveness of rivaroxaban versus warfarin among AF patients (Bowrin et al., 2020; Jaberi et al., 2021). However, rivaroxaban did not significantly reduce the rates hospitalization, MI, stroke, and

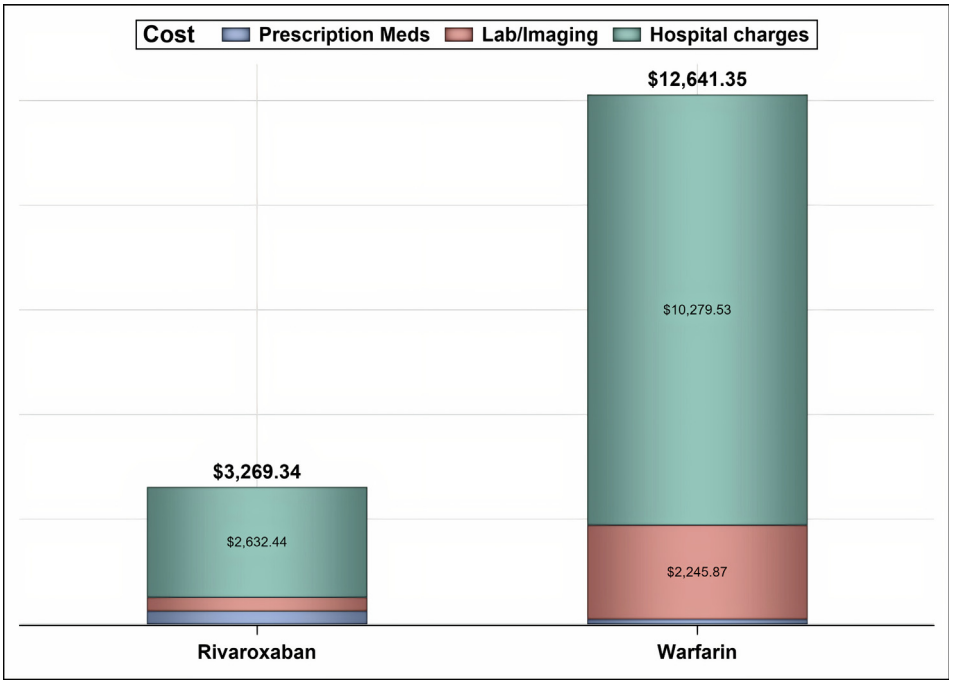

Fig. 1. The mean cost per patient per year in USD ($).

Table 3
The cost consequence analysis of rivaroxaban versus warfarin for the management of atrial fibrillation (AF).

	Rivaroxaban	Warfarin	Mean difference (95 % confidence interval)
Cost of treatment (USD), mean ± SD	3,329.10 ± 9,161.21	16,589.88 ± 81,127.43	−13,260.79 (–32,964.83– −4,017.68)
Effectiveness rate (%), mean ± SD	54.93 ± 49.93	54.76 ± 50.71	0.168 (-5.21–18.36)

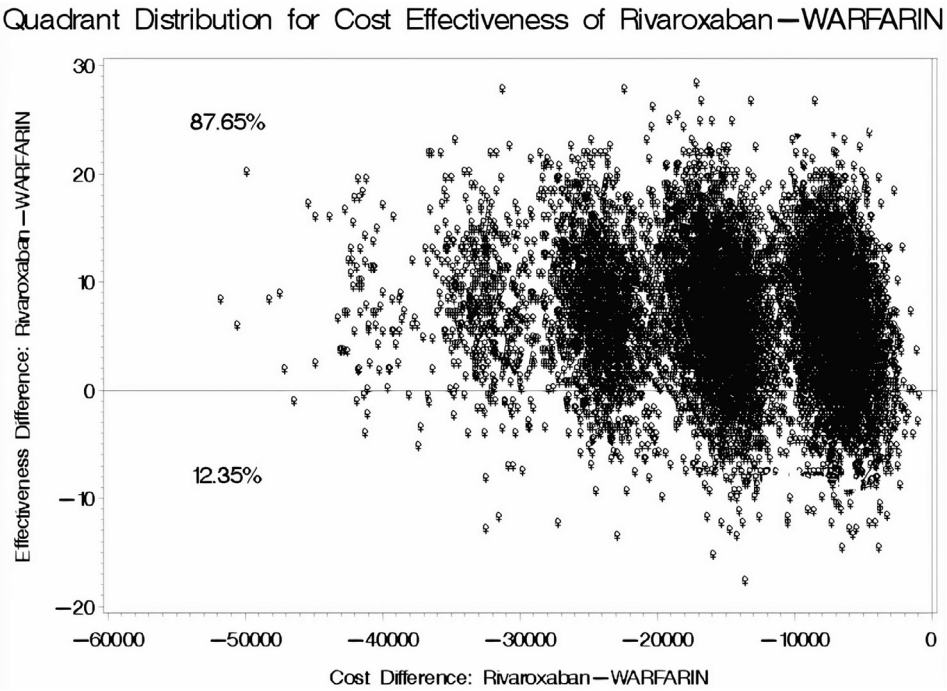

Fig. 2. Bootstrap distribution of cost-effectiveness for the rivaroxaban versus warfarin for patients for stroke prophylaxis among atrial fibrillation patients.

all-cause mortality in comparison to warfarin in the multiple logistic regression that controlled for age, gender, duration of illness, and different comorbidities, such as heart failure, despite a lower odds of the composite outcome. This might be attributable to the small sample size and the residual confounding effect of the patient medical characteristics, such as hypertension, diabetes, and cardiovascular disease (CVD) which are more prevalent among patients treated with rivaroxaban. On the other hand, patients with longer durations of illness (e.g., nonvalvular AF) had lower odds of hospitalization, MI, stroke, and all-cause mortality controlling for the used anticoagulant. This finding although interesting adds to the contrasting results that were reported in other studies (Sankaranarayanan, Kirkwood, Visweswariah, & Fox, 2015), and could be related to the higher medication adherence, better patient-physician relationship, and higher acceptance of illness as some studies have indicated that improved medication adherence and patient satisfaction with physicians among those with longer durations of illness (Al-Hajje et al., 2015; Donahue, Ashkin, & Pathman, 2005; Turen, Yilmaz, & Gundogdu, 2021). Age was not associated with higher risk of the composite outcome (e.g., hospitalization, MI, stroke, and all-cause mortality) despite a positive relationship between older age and higher risk of mortality among AF patients in multiple studies (Sankaranarayanan et al., 2015). However, this relationship could be related to AF as an independent risk factor associated with higher rates of mortality as older adults are more likely to develop other comorbidities that eventually increase their risk of early mortality (Sankaranarayanan et al., 2015); something that was controlled for in the analysis. Heart failure was associated with significantly higher risk of hospitalization, MI, stroke, and all-cause mortality, but diabetes, hypertension, and cardiovascular disease (CVD) were not despite the preponderance of evidence that suggest a positive relationship between these health conditions and stroke and/or mortality among AF patients (Sankaranarayanan et al., 2015; Yaghi & Kamel, 2017). On the other hand, patient gender was not associated with higher or lower risk of hospitalization, MI, stroke, and all-cause mortality despite some evidence that suggest higher risk of mortality among female patients with AF (Yaghi & Kamel, 2017).

Although this is the first study to the best of our knowledge that examined the cost effectiveness of rivaroxaban versus warfarin for the management nonvalvular AF in Saudi Arabia using real-world data, it has numerous limitations that must be acknowledged. First, this is a single center study with a relatively small sample size which limits the generalizability of its findings. Secondly, information bias cannot be excluded since the data were retrospectively retrieved from the EMRs. Furthermore, some confounding factors, such as medication adherence, were not adjusted for which may significantly impact the results. Additionally, only real acquisition costs of medications and other healthcare resources were used in the analysis and no deterministic or probabilistic sensitivity analyses were conducted since the aim of the study was to present the real-world cost effectiveness to the public healthcare payer.

5. Conclusions

The findings of this study support the use of rivaroxaban over warfarin as a cost-effective treatment option for the management of nonvalvular AF in Saudi Arabia in absence of any contraindication, such as mitral valve stenosis. Future studies with larger sample sizes and more diverse patient populations should be conducted to confirm these findings. Also, the cost effectiveness of rivaroxaban versus other NOACs for the management of valvular and nonvalvular AF should be examined.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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