Research Article

The Efficacy and Safety of Rivaroxaban as an Alternative to Warfarin for the Prevention of Thromboembolism in Patients with Atrial Fibrillation

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ABSTRACT

The aim of this study was to compare the efficacy and safety of fixed dose rivaroxaban administered orally once daily with dose-adjusted warfarin in patients with nonvalvular atrial fibrillation. This study was a randomized, prospective, open-labeled, controlled study directed to evaluate the efficacy of rivaroxaban compared with warfarin in the prevention of stroke in patients with nonvalvular atrial fibrillation who were at risk of stroke or noncentral nervous system (NCNS) systemic embolism. Sixty patients with nonvalvular atrial fibrillation wererandomly assigned into two groups; each group consisted of 30 patients. Group one (control group) received warfarin (in a titrated dose of warfarin adjusted according to international normalized ratio (INR) of each patient); group two received rivaroxaban 20 mg once daily. The efficacy endpoint is a composite of all-cause stroke and NCNS systemic embolism. The safety endpoint is the composite of major and nonmajor clinically relevant bleeding events. Only 6.66%of the patients in the rivaroxaban treatment group haddeveloped stroke compared with 13.33% of the patients in the warfarin treatment group (*P*=0.386). There was a nonsignificant increase in the rate of the transient ischemic attack in warfarin treatment group compared with the rivaroxaban treatment group (6.66% and 3.33%, respectively, *P*=0.386). Rivaroxaban was associated with a nonsignificant difference in the risk of NCNS systemic embolism and myocardialinfarction (MI) compared with warfarin (6.66% and 3.33% of the patients in each group, respectively, *P*=0.999). Critical organ and intracranial bleeding orfatal bleeding were nonsignificantly lower in rivaroxaban-treated patients (6.66% of the patients in warfarin-treated group and no cases reported in the rivaroxaban-treated group, *P*=0.143). There was no statistically significant difference between the two studied groups in nonmajor clinically relevant bleeding (26.66% and 16.66% of the patients in warfarin and rivaroxaban-treated group, respectively, *P*=0.344). Bleeding that led to a drop in the hemoglobin level was observed in 20% of patients in the warfarin-treated group but no cases were reported in the rivaroxaban-treated group, *P*=0.006. Bleeding that required transfusions frequently reported more in the warfarin-treated group(6%) but no cases were reported in rivaroxaban-treated group, *P*=0.143. This study demonstrated that the rivaroxaban is more effective than dose-adjusted warfarin for the prevention of thromboembolic events in subjects with nonvalvular atrial fibrillation as measured by the composite of stroke and NCNS systemic embolism. Rivaroxaban may be superior attractive in reducing the overall risk of major and nonmajor clinically relevant bleeding and a lower risk of intracranial hemorrhage and fatal bleeding than warfarin.

Keywords: Nonvalvular atrial fibrillation; Rivaroxaban; Warfarin; International Normalized Ratio (INR); Thromboembolism.

INTRODUCTION

Atrial Fibrillation (AF) is the most prevalent cardiac arrhythmia of clinical significance. It predisposes patients to the development of atrial thrombi, which may subsequently travel to the brain, resulting in ischemic stroke.[1] Patients with atrial fibrillation have an approximately five-fold increased the risk of stroke compared with those who have normal sinus rhythm.[1,2] Up to 15% of all strokeoccurrences in all age groups and 36% of stroke in individuals aged >80 years are attributable to atrial fibrillation.[3,4]

Atrial fibrillation-related stroke and its disabling consequences impose a considerable economic burden on healthcare system, of which the main cost driver is inpatient care, where patients who have had prior stroke are at increased risk of a subsequent stroke.[4]

Warfarin is the most widely prescribed vitamin K antagonist worldwide and the most effective therapy currently available for stroke prevention in patients with atrial fibrillation.[5] However, the use of warfarin is associated with an increased risk of adverse bleeding events, particularly intracranial hemorrhage. It is also associated with various practical challenges that limit its successful implementation in practice, including a high degree of inter- and intra-patient variability in dose response, the need for frequent coagulation monitoring and dose adjustments to maintain the International Normalized Ratio (INR) within the target range of 2.0-3.0, and the need for dietary restrictions. Warfarin has the narrow therapeutic range and delayed the onset of action.[5,6] Euro Heart Survey demonstrates that these restrictions have led to the underuse of warfarin in routine practice.[7] The new oral anticoagulants in development may avoid many of the drawbacks associated with warfarin. There are two main classes: direct Factor-Xa inhibitors and direct thrombin inhibitors.[5, 7]

Rivaroxaban is an oral, direct Factor-Xa inhibitor approved bytheEuropean Union for the prevention of

venous thromboembolism in adults after an elective hip or knee replacement surgery.[8]It consistently provides a significant relative risk reduction in the incidence of total venous thromboembolism compared with enoxaparin, with similar rates of major bleeding. It is also in advanced clinical development for the prevention or treatment of several thromboembolic disorders, including stroke prevention in atrial fibrillation.[9,10] Rivaroxaban significantly reduces the risk of stroke in patients with nonvalvular atrial fibrillation with comparable safety versus warfarin. Rivaroxaban demonstrates prevention of major and nonmajor clinically relevant bleeding, as well as significantly lower rates of intracranial hemorrhage versus warfarin which show the noninferiority of once-daily rivaroxaban over dose-adjusted warfarin. This may explain the expected beneficial role of rivaroxaban over warfarin in protecting AF patients from stroke and noncentral nervous system (NCNS) systemic embolism.[8, 11, 12]

METHODS

This study design was a randomized, prospective, open-labeled, controlled clinical study that was conducted in the Cardiac Department, Tanta University Hospital (Tanta, Egypt) between March 2013 and June 2015. The protocol for this study was approved by the National Research Ethics Committee of Tanta University; Tanta, Egypt with Institutional Review Board (IRB) protocol. Diagnosis of nonvalvular atrial fibrillation was based on clinical and physical examination, electrocardiogram and/or echocardiography. A total number of 60 adult Middle-Eastern Egyptian patients of both sexes were enrolled in this study. At admission, patients were randomly divided into two groups. Group one (control group) received warfarin (Marivan® tablet, Bristol Laboratories Ltd, the United Kingdom in a dose ranging from 3-10mg/day adjusted according to INR for each patient) (n=30) for 12 weeks according to guidelines of warfarin therapy and guideline for the management of patients with atrial fibrillation.[13,14] This group consistedof 21 female patients (70%) and 9 male patients (30%) whose ages ranged from 50 to 60 years old with a mean value of 55 ±5years. Group two received rivaroxaban 20 mg tablet (Elliproxaban®20 mg tablet, Ellitpharma, Egypt) daily (n=30) according to 2014 guideline for the management of patients with atrial fibrillation.[14,15] The treatment continued for 12 weeks for both groups.

Inclusion criteria includedparticipantsaged between 18 and 60 years old whogave their written informed consent. Patients with either a history of stroke, transientischemic attack (TIA) or NCNS systemic embolism which is confirmed by computed tomography (CT) scan of brain and at least other cardiac risk factors such as: hypertension, clinical diagnosis of heart failure and/or left ventricular ejection fraction<40% and diabetes mellitus, were included in our study. Exclusion criteria included patients ofagefewer than 18 to more than 60 years old, organic valvular heart disease and hepatic or renal failure.

The etiology of nonvalvular atrial fibrillation for all patients encountered in this study was hemodynamic stress, atrial ischemia, myocarditis and pericarditis, non-cardiovascular or respiratory causes, diabetes and/or subarachnoid stroke. Patients were classified according totocongestive heart failure or a left ventricular ejection fraction of 35% or less, hypertension, age of 75 years or more, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (CHADS2) score classification. At the time of enrollment, physical examination, liver and renal function tests, red blood cells count, platelets count, hemoglobin level, prothrombin time, and INR were measured at baseline and12 weeks after treatment. The use of concomitant aspirin up to 100 mg/day waspermitted in accordance with treatment guidelines for patients with AF and atherosclerotic disease.[16]Thienopyidineswerenot permitted for five days before randomization or during the study, whilefibrinolytic therapy wasnot permitted for 10 days before randomization. Chronic use of nonsteroidal anti-inflammatory drugs, defined as daily use for more than two weeks, wasprohibited. Specific strong cytochrome P450 3A4 inhibitors and inducers werealso prohibited. Patients were followed up for the intended treatment duration and checked fixed intervals (every week) that were identical for bothgroups, at which time a check list was used to elicit information on symptoms and signs of recurrent stroke, bleeding, and adverse events. Patients were instructed to report to the hospital immediately if any of these events occurred. The principal efficacy endpoint of this study was defined as the rate of development of stroke and NCNS systemic embolism. The principal safety endpoint of this study was defined as major bleeding or nonmajor clinically relevant bleeding. Major bleeding was defined as that which was clinically overt and associated with any of the following: fatal outcome; involvement of a critical anatomic site (intracranial, spinal, ocular, pericardial, articular, and retroperitoneal, intraparenchymal, intraventricular, and subdural subarachnoid); fall in hemoglobin concentration>2 g/dl; transfusion of>2 U of whole blood; or packed red blood cells. Nonmajor clinically relevant bleeding was defined as overt bleeding not meeting criteria for major bleeding but requiring medical intervention, unscheduled contact (visit or telephone) with a physician, temporary interruption of the study drug (i.e., delayed dosing), pain, or impairment of daily activities.

Biochemical analytical methods

All kits used for testing liver and renal function tests were supplied by Siemens Healthcare Diagnostics Products Gmbh, Germany, Cat. No. OUHP 29. The optical density for all these parameters was measured using Shimadzu UV-PC 1601, spectrophotometer, Japan. Serum alanine amino transferase (ALT) and serum aspartate amino transferase (AST) were measured spectrophotometrically using kinetic method,[17,18] serum bilirubin level (total and direct) was measured spectrophotometrically using

colorimetric (Diazo) method,[19]and measurement of serum albumin concentration was determined spectrophotometrically using modified Bromo cresol green colorimetric method.[20]Blood urea nitrogen was determined spectrophotometrically using enzymatic (fixed rate) UV method with urease and glutamate dehydrogenase,[21] serum creatinine concentration was determined spectrophotometrically using buffered kinetic Jaffé reaction without deproteinization method,[22]and Creatinine clearance was estimated using Cockcroft-Gault method.[23]Complete blood count (CBC) and haemoglobin (Hb) were measured by Sysmex Automated Hematology Analyzer KX-21N, Japan, while red blood cells (RBCs) and platelets (PLTs) were measured by Sysmex Corporation, Kobe 651-0073, Japan.[24]About 3 mL of venous blood was drawn in Thromborel® S Reagent which was reconstituted in 4 ml of deionized water and mixing well by inverting the vial several times. The coagulation time of standard normal human plasma was determined as a sample using Thromborel® S Reagent vial (Siemens Healthcare Diagnostics Products Gmbh, Germany, Cat. No. OUHP 29).[25]

Statistical Analysis

The collected data were tabulated using Microsoft® Office Excel 2010, Microsoft Corporation. Statistical Package for the Social Science (SPSS®),version 20, 2010, USA was used for data analysis using an alpha error of 0.05 with a 95% confidence interval. Data are presented as mean ±SD for continuous data and frequency percentage for categorical variables. Independent samples t-test was used for testing the difference in mean of each quantitative variable in the two groups. Paired samples t-test was used for testing the difference in mean change of quantitative variables in each group before and after follow-up. Chi-square was used for qualitative variables. ANOVA test was used to test the mean change in INR from baseline in response to drugs after each time interval.

RESULTS

Demographic and clinical data of the participants in the two groups defined as age, gender, weight, VKA use prior to screening, other systemic disorders such as history of stroke, transient ischemic attack (TIA) or NCNS systemic embolism, hypertension, congestive heart failure (CHF) and/or left ventricular ejection fraction (LVEF)<40% and diabetes aredemonstrated in **Table 1.**

Measuring parameters include Liver and renal function tests, complete blood picture, random blood glucose and INR at the baseline data for patients in the two studied groups presented as mean ±SD areshowed in Table 2 that showed nonsignificant difference between them (student-test, *P*>0.05); there foreany changes happened after treatment was attributed to the used medications and not due to the individual variations. Laboratory features for patients in the two groups after 12 weeks treatments were demonstrated in Table 2 and Table 3, respectively.

In this study, the rates for the efficacy endpoint of stroke or systemic embolism were nonsignificantly higher in warfarin treatment group compared with rivaroxaban treatment group as shown in **Table 6**. The observed rate of all-cause stroke hemorrhagic stroke, ischemic stroke, disabling and disabling stroke was also found lower in the rivaroxaban treatment group. Overall, two patients (6.66%) in the rivaroxaban treatment group had a stroke compared with four patients (13.33%) in the warfarin treatment group (*P*=0.386). The rates of myocardial infarction were the same in both treatment groups (3.33%). These differences may be more remarkable if adjusted for the lower baseline CHADS2 score in patients. There was also a nonsignificant difference identified for the other efficacy endpoints as NCNS systemic embolism between the two treatment groups. There was a nonsignificant double increase in the rate of transient ischemic attack in warfarin treatment group compared with rivaroxaban treatment group (6.66% and 3.33 %, respectively).

Rivaroxaban was associated with reductions in critical organ bleeding and intracranial hemorrhage relative to warfarin. Overall, no patients demonstrated any critical organ bleeding the rivaroxaban-treated group, whilst about two (6.66%) ofpatients developed critical organ bleeding events in the warfarin-treated group. Among the patients receiving rivaroxaban, there was anonsignificant lower rate of intracranial hemorrhage compared with patients receiving warfarin. However, the rate of intracranial hemorrhage with rivaroxaban was zero, while warfarin two events were reported. There were no events with hemoglobin drop≥2g/dL was found in the rivaroxaban-treated group versus six events (20%) were reported in the warfarin-treated group. Rivaroxaban was associated with no transfusion events compared with two events (6.66%) in the warfarin-treated group. The risk of major or nonmajor clinically relevant bleeding was significantly higher in warfarin treatment group compared with rivaroxaban treatment group as demonstrated in **Table 7**. Overall, there were five (16.66%) and eight (26.66%) nonmajor clinically relevant bleeding serious adverse events in the rivaroxaban and warfarin treatment groups, respectively. Observed rates of all-cause mortality due to bleeding as demonstrated in **Table 7**showed that there was a nonsignificant differencebetween rivaroxaban and warfarin-treated groups (no death cases were reported).

Table 1: Demographic and clinical characteristics of the population.

Patients characteristics		Group				*P-value*
		Group I (Warfarin) N=30		Group II(Rivaroxaban) N=30		
		Range	Mean ±SD	Range	Mean ±SD	
Age (years)		45-60	55±5	38-60	54±6	0.293
Weight (Kg)		65-102	77.43±9.48	72-98	91.6±12.80	<0.001*
		No.	**%**	**No.**	**%**	
Gender	**(Female)**	21	70	12	40	0.014*
	(Male)	9	30	18	60	
CHADS2 score						
0-1		20	66.66	18	60	0.592
2		5	16.66	8	26.66	0.347
≥3		5	16.66	4	13.33	0.718
VKA use prior to screening		14	46.66	9	26.6	0.184
Risk factors						
a) CHF or LVEF ≤40%						
b) Hypertension		9	30	12	36.6	0.417
c) Age ≥75		12	40	17	53.3	0.196
d) Diabetes mellitus		0	0	0	0	.....
e) Pervious stroke, TIA		8	26.6	4	13.3	0.197
or NCNS systemic		3	10	5	26.6	0.448
embolism						

CHADS2 score= Congestive heart failure or a left ventricular ejection fraction of 35% or less, Hypertension, Age of 75 years or more, diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism; VKA=Vitamin K Antagonist; CHF= Congestive heart failure; LVEF=left ventricular ejection fraction; TIA= transient ischemic attack; NCNS=noncentral nervous system. *Significant difference.

Table 2: Selected laboratory data of patients at baseline.

Parameters	Group I (Warfarin) N=30	Group II (Rivaroxaban) N=30	*P-value*
	Mean ±SD	*Mean* ±SD	
AST(IU/L)	28.60±8.02	27.30±9.92	0.579
ALT(IU/L)	28.13±8.50	25.50±7.88	0.218
Total bilirubin (mg/dL)	0.84±0.14	0.88±0.3	0235
Direct bilirubin (mg/dL)	0.20±0.02	0.24±0.16	0.277
Albumin (g/dL)	3.61±0.47	3.8±0.45	0.115
BUN (mg/dL)	28.00±16.67	21.73±8.75	0.073
S.Cr (mg/dL)	1.25±0.35	1.08±0.34	0.070
CrCl (ml/min)	57.43±13.97	74.54±20.91	<0.001*
Hb (g/dL)	11.37±1.83	12.0±2.33	0.249
RBCs (10^6 / uL)	4.23±0.53	4.36±0.64	0.410
Platelets (10^3 /uL)	214.50±54.59	223.63±73	0.587
Random blood glucose (mg/dL)	139.57±58.38	143.70±57.64	0.783
PT (Sec.)	15.52±3.41	16.67±5.85	0.360
INR	1.35±0.47	1.53±0.80	0.285

AST=Aspartate transaminase; ALT=Alanine aminotransferase; BUN=Blood urea nitrogen; S.Cr=Serum creatinine; CrCl=Creatinine clearance; Hb=Hemoglobin; RBCs=Red blood cells; PT=Prothrombin time; INR=International normalized ratio. *Significant difference.

Table 3: Selected laboratory data of patients after 12 weeks of treatment (at end of treatment).

Parameters	Group I (Warfarin) N=30	Group II (Rivaroxaban) N=30	*P-value*
	Mean ±SD	Mean ±SD	
AST (IU/L)	29.17±7.36	22.50±7.01	0.002*
ALT (IU/L)	28.43±5.37	21.43±5.81	<0.001*
Total bilirubin (mg/dL)	0.83±0.11	0.78±0.25	0.277
Direct bilirubin (mg/dL)	0.22±0.09	0.25±0.16	0.441
Albumin (g/dL)	3.94±0.50	4.12±0.60	0.208
BUN (mg/dL)	26.93±15.99	23.73±9.42	0.349
S.Cr (mg/dL)	1.26±0.38	1.18±0.30	0.328
CrCl (ml/min)	57.93±14.21	64.40±13.05	0.071
Hb (g/dL)	12.37±1.50	12.34±1.47	0.938
RBCs (10^6 /uL)	4.62±0.65	4.60±0.51	0.853
Platelets (10^3 /uL)	262.67±70.69	236.03±55	0.109
Random blood glucose (mg/dL)	146.67±37.17	138.07±26.86	0.309
PT (Sec.)	17.38±4.52	22.58±2.29	<0.001*
INR	1.42±0.50	2.42±0.28	<0.001*

AST=Aspartate transaminase; ALT=Alanine aminotransferase; BUN=Blood urea nitrogen; S.Cr=Serum creatinine; CrCl=Creatinine clearance; Hb=Hemoglobin; RBCs=Red blood cells; PT=Prothrombin time; INR=International normalized ratio. *Significant difference.

Table 4: Change in INR level by treatment groups at baseline and after one week, two weeks, three weeks, four weeks, eight weeks, and 12 weeks of treatment.

INR	Groups				t-test	
	Group I (Warfarin) N=30		Group II (Rivaroxaban) N=30			
	Range	Mean ±SD	Range	Mean ±SD	*t*	*P-value*
At baseline	1.0-3.34	1.35±0.47	1.0-4.8	1.53±0.80	1.079	0.11
After 1 week of treatment	1.0-2.27	1.49±0.40	1.9-4.8	2.42±0.59	7.093	<0.001*
After 2 weeks of treatment	1.02-3.95	1.77±0.79	1.53-4.15	2.43±0.50	3.885	<0.001*
After 3 weeks of treatment	1.0-3.95	1.85±0.76	1.76-3.15	2.39±0.36	3.512	<0.001*
After 4 weeks of treatment	1.0-2.50	1.62±0.48	1.83-3.09	2.35±0.37	6.625	<0.001*
After 8 weeks of treatment	1.05-3.9	1.77±0.68	1.76-3.17	2.40±0.34	4.487	<0.001*
After 12 weeks of treatment	1.0-3.34	1.42±0.50	1.96-2.9	2.42±0.28	9.590	<0.001*
Paired t-test						
	P-value					
At baseline and after 1 week of treatment	0.219		<0.001*			
At baseline and after 2 weeks of treatment	0.025*		<0.001*			
At baseline and after 3 weeks of treatment	0.005*		<0.001*			
At baseline and after 4 weeks of treatment	0.026*		<0.001*			
At baseline and after 8 weeks of treatment	0.012*		<0.001*			
At baseline and after 12 weeks of treatment	0.137		<0.001*			

INR= International Normalized Ratio. * Significant difference.

Table 5: Comparison in INR level by treatment groups at baseline and after one week, two weeks, three weeks, four weeks, eight weeks, and 12 weeks of treatment.

INR		Groups	
		Group I (Warfarin) N=30	Group II (Rivaroxaban) N=30
		Mean ±SD	Mean ±SD
At baseline		1.35±0.47	1.53±0.80
After 1 week of treatment		1.49±0.40	2.42±0.59
After 2 weeks of treatment		1.77±0.79	2.43±0.50
After 3 weeks of treatment		1.85±0.76	2.39±0.36
After 4 weeks of treatment		1.62±0.48	2.35±0.37
After 8 weeks of treatment		1.77±0.68	2.40±0.34
After 12 weeks of treatment		1.42±0.50	2.42±0.28
ANOVA	f	3.152	13.532
	P-value	0.006*	<0.001*

INR=International Normalized Ratio.
* Significant difference.

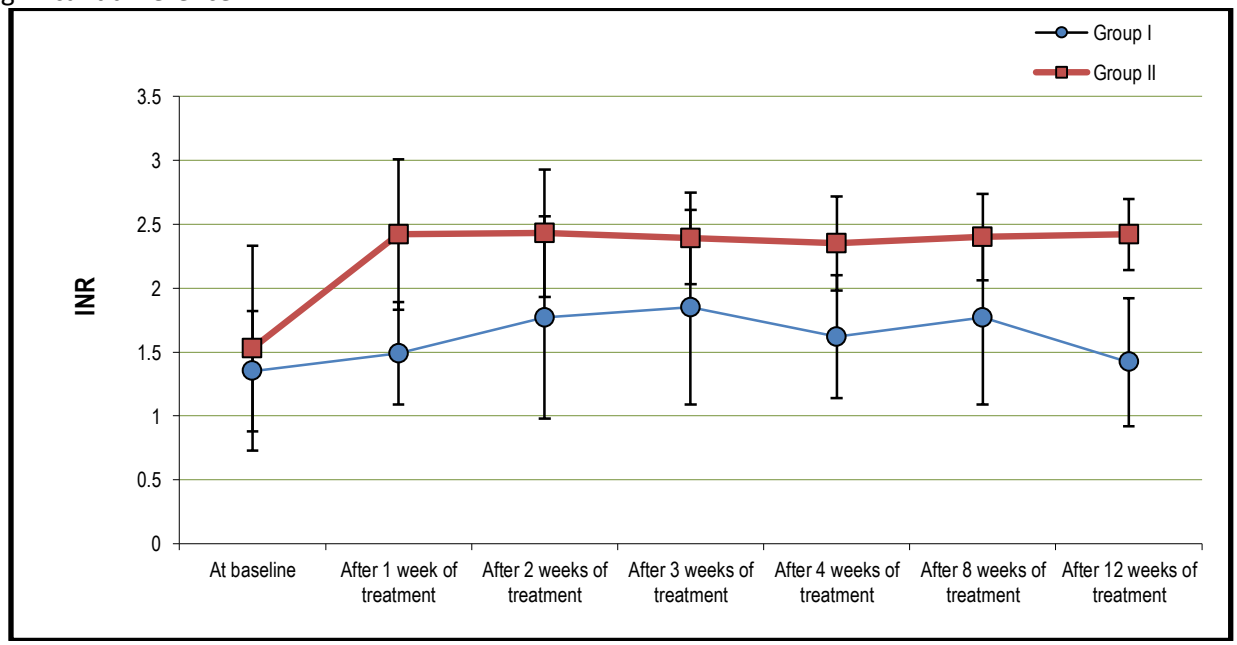

Figure 1: Change in INR level by treatment groups at baseline and after one week, two weeks, three weeks, four weeks, eight weeks and 12 weeks of treatment.
Data presented as mean ±SD.
INR =International normalized ratio.

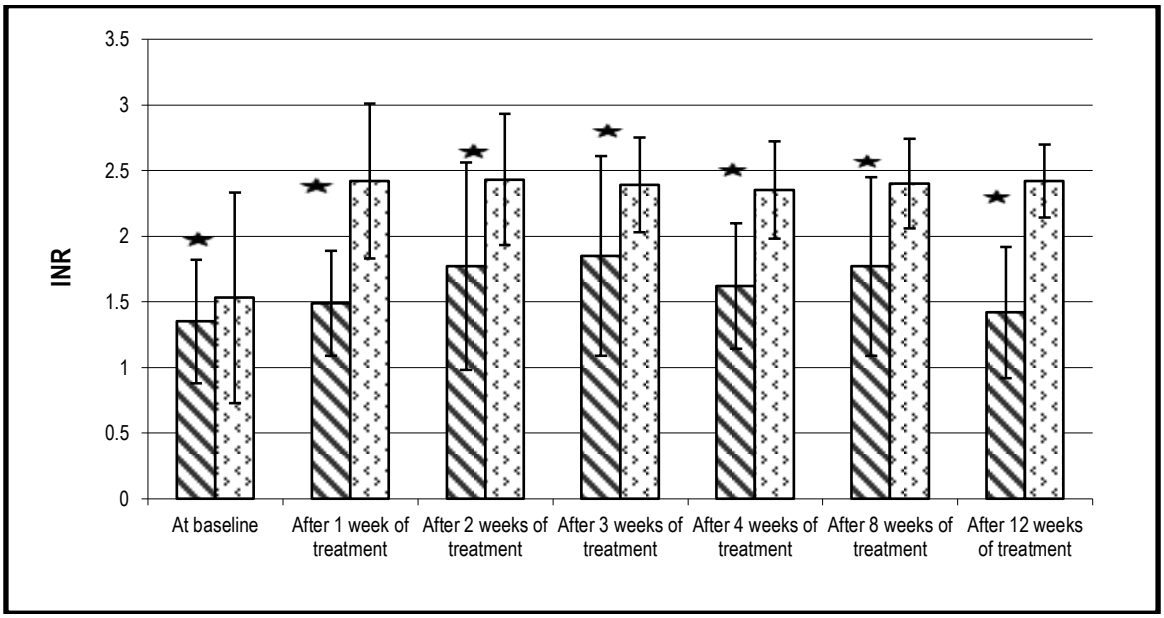

Figure 2: Comparison in INR level by treatment groups at baseline and after one week two weeks, three weeks, four weeks, eight weeks, and 12 weeks of treatment.
Data presented as mean ±SD.
INR = International normalized ratio.

Treatment dosage	Groups				*P-value*
	Group I Warfarin titrated to a target INR (therapeutic range 2-3) N=30		Group II Rivaroxaban 20 mg od N=30		
	No.	%	No.	%	
Stroke	4	13.33	2	6.66	0.386
NCNS systemic embolism	2	6.66	2	6.66	0.999
Myocardial infarction	1	3.33	1	3.33	0.999
Transient ischemic attack	2	6.66	1	3.33	0.552

* Significant difference

DISCUSSION

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia of clinical significance. While AF rarely causes life-threatening hemodynamic compromise, it is an important independent risk factor for cardiogenic embolic stroke and systemic arterial thromboembolism.[16] Most clinicians agree that the risk-benefit ratio of warfarin therapy in low-risk patients with AF is not advantageous. Warfarin therapy proved to be beneficial in higher risk patients with AF. A target INR of 2-3 is traditionally used in this study, as this limits the risk of hemorrhage while providing protection against thrombus formation.[26] The data obtained from this study showed that rivaroxaban may be superior to warfarin for prevention of stroke and transit ischemic attack in patients with nonvalvular AF who were at risk of thromboembolism as only 6.66%of the patients in the rivaroxaban treatment group haddeveloped stroke compared with 13.33% of the patients in the warfarin treatment group.

There was an a non significant double increase in the rate of the transient ischemic attack in the warfarin treatment group compared with the rivaroxaban treatment group (6.66% and 3.33%, respectively).These data are supported by the results obtained from ROCKET AF study where the rate of stroke or systemic embolism was significantly lower in the rivaroxaban group compared with warfarin therapy (1.7% vs 2.2% per year, $P<0.001$)[1] and the same result was also reported by Fang MC, *et al.,*[27]where patients with rheumatic heart disease and AF hadan even higher risk for stroke (17 fold). The risk of NCNS systemic embolism and MI was not different between warfarin and rivaroxaban-treated groups, while Chatterjee *S, et al.,*[28]reported that rivaroxaban showed consistent noninferiority to warfarin in the rates of MI as there was a

relative risk reduction for MI of 18% in the patients treated with rivaroxaban,

Treatment dosage	Groups				*P-value*
	Group I Warfarin (titrated to a target INR therapeutic range 2-3) N=30		Group II Rivaroxaban 20 mg od N=30		
	No.	%	No.	%	
Major and nonmajor clinically relevant	18	60	5	16.66	0.000*
Death due to bleeding	0	0	0	0	--------
Major bleeding events					
Critical organ bleeding¶	2	6.66	0	0	0.143
Intracranial hemorrhage	2	6.66	0	0	0.143
Hemoglobin drop≥2 g/dL	6	20	0	0	0.006*
Transfusion of two or more units of packed red blood cells or whole blood	2	6.66	0	0	0.143
Nonmajor clinically relevant bleeding	8	26.66	5	16.66	0.344

Table 7: Rates of bleeding events.

¶Critical organ bleeding include intracranial, spinal, ocular, pericardial, articular, Retroperitoneal, intraparenchymal, intraventricular, and subdural subarachnoid.
* Significant difference.

although the superiority of this agent needs to be validated in high quality randomized head-to-head trials of rivaroxaban against drugs of the same class with a similar mechanism of action and other new oral anticoagulants. Although only three (10%) patients had a previous stroke or TIA in warfarin treatment group and five (26.6%) in the warfarin treatment group had previous stroke or TIA, the number of patients who developed a stroke or TIA treated with warfarin were double those treated with rivaroxaban. On the contrary, these results were not consistent with Graeme J. Hankey, *et al.,*[7]studieswhere among the patients with previous stroke or TIA (2.79%) of rivaroxaban treatment group versus (2.96%)of the warfarin treatment group had developed stroke or TIA after the treatment period. Recently, the ARISTOTLE, RE-LY, and ROCKET AF trials showed that apixaban, dabigatran, and rivaroxaban are associated with a lower rate of stroke or systemic embolism in the overall population of patients with AF.[28] However, in the three subgroup analyses of these trials in patients with previous stroke or TIA, the proportion of patients who reached the endpoint of development of stroke or TIA was not significantly different in either ofrivaroxabanorwarfarin treated groups.

Our study results showed that, compared with warfarin, rivaroxaban had a lower risk of the principal safety endpoint, including major and nonmajor clinically relevant bleeding. Rivaroxaban caused a significantly lower risk of hemoglobin decrease ≥2 g/dl (no cases were reported in the rivaroxaban-treated group versus six cases in the warfarin-treated group, *P*=0.006).Bleeding that required transfusion was frequently reported more in the warfarin-treatedgroupcompared with the rivaroxaban-treated group. Critical organ bleeding and fatal bleeding were non significantly lower in rivaroxaban-treated patients. Intracranial bleeding that proved fatal or involved a critical anatomical site occurred less frequently in the rivaroxaban group, this has been explained by the presence of large amounts of tissue factors in the cerebral vascular beds could modulate vascular hemostatic activity within brain vessels whereby warfarin decreases factor VII activity, but the newer agents do not affect the tissue factor-factor VIIa complex,[29] and this is consistent with Fang MC, *et al.,* results where warfarin reduces 30 days mortality from ischemic stroke as it increases intracranial hemorrhage related mortality.[27] In contrast, the ROCKET AF investigators trial demonstrated that the rate of major and nonmajor clinically relevant bleeding was not different between warfarin and rivaroxaban groups (14.9% vs 14.5% per year, *P*=0.44)[1]. This is consistent with our study results where bleeding from gastrointestinal sites, including upper, lower, and rectal sites, epistaxis and hematuria, which is considered as nonmajor clinically relevant bleeding, occurring nonsignificantly between warfarin group compared with rivaroxaban group (26.66% vs. 16.66% respectively; *P*=0.344), wasreported more frequently as an adverse event in the warfarin group as did bleeding that led to a drop in the hemoglobin level or bleeding that required transfusion. It has been

demonstrated that higher rates of GI bleeding with rivaroxaban relative to warfarin could be due to exacerbation of surface bleeding by the presence of active anticoagulant in the gut. Whereas warfarin has over 99% bioavailability and unabsorbed warfarin is inactive, rivaroxaban is partially excreted in the feces as an active drug.[30]Despite the fact that ROCKET AF Trial of American College of Cardiology showed that rivaroxaban caused a significantly higher risk of hemoglobin decrease ≥2 g/dl and transfusion compared with warfarin. On the other side, critical bleeding and fatal bleeding were significantly lower in rivaroxaban-treated patients and also intracranial hemorrhage was significantly lower in the rivaroxaban group and this is consistent with our study. Minimalbleeding was similar in the rivaroxaban and warfarin groups as epistaxis (6.9% vs. 5.7%; *P*≤0.001) and hematuria (2.7% vs. 2.2%; *P*=0.011) were reported more frequently as an adverse event in the rivaroxaban group.[31]Dr. Patel wrote, "Importantly, rivaroxaban was associated with significantly lower rates of intracranial hemorrhage and fatal bleeding, but a higher incidence of major bleeding from a gastrointestinal site than from/of warfarin".[12] Atrial fibrillation is associated with around two-fold higher risk of death, which is in part due to the strong association between AF and thromboembolic events, according to the data from the Framingham heart study.[32,33]However, in our study there were no reported cases ofdeath in either of thestudied treatment group. Rivaroxaban compared with warfarin led to an overall reduction risk of major and nonmajor clinically relevant bleeding and a lower risk of intracranial hemorrhage and fatal bleeding. We identified, consistently with previous studies, several baseline factors associated with the risk of major bleeding, including age, sex, diastolic blood pressure, prior gastrointestinal bleeding and ASA use, and anemia. Careful assessment of bleeding risk in patients with AF is required to support clinical decision making for stroke prevention therapy. The identified risk factors for bleeding for both oral anticoagulation groups must be taken into consideration during treatment.

Patients received rivaroxaban achieved the target INR required to prevent stroke and NCNS systemic embolism after one week of starting the treatment without any requirements related to food, drugs intake, inter patient variability as required to be controlled during treatment with warfarin, while patients received warfarin showed statistically significant difference in INR during treatment period due to many restrictions that cause this inter- and inter- patients variability. Only 55% of the studied patients in the warfarin-treated group achieved the INR therapeutic range, while 35% of patients in each group were on concomitant aspirin. Warfarin may be less preferable in patients who are consistently noncompliant with doses if the target INR goal is rarely achieved. Strong evidence supports the recommended INR target of 2.5 (range 2-3). The American College of Cardiology/American Heart Association/European Society of Cardiology 2006 Guidelines suggestion that a lower target of INR (1.6-2.5) may be considered in patients unable to tolerate standard intensity warfarin therapy is not evidence-based. Narrower target ranges have been suggested in certain situations (e.g., INR 2-2.5 has been recommended in patients requiring warfarin, aspirin, and clopidogrel following percutaneous coronary intervention).[34]Such narrow ranges are not supported by good evidence, making achieving therapeutic INRs more difficult, and usually result in the need for more frequent INR testing. Target INR range 2-3 should be used for most patients with AF which was proven by this study. Target INR can be achieved by rivaroxaban 20mg once daily without requiring a frequent INR testing and this is supported by the statistical nonsignificance between INR results after each treatment period.

In this study, rivaroxaban was not inferior to warfarin for the prevention of stroke or systemic embolism in patients with nonvalvular AF who were at risk of thromboembolism. Patel, *et al.,* noted that patients with previous stroke or TIA had higher rates of stroke and NCNS systemic embolism but lower rates of major bleeding on anticoagulant therapy than those without previous stroke or TIA.[35] After testing for interaction, we also noted that the treatment effects of rivaroxaban and warfarin in patients with previous stroke or TIA were consistent with those in patients without previous stroke or TIA. The more reliable results of the overall trial population can thus be generalized to patients with AF and previous stroke or TIA. Therefore, rivaroxaban is an alternative to warfarin for the prevention of recurrent stroke as well as initial stroke, particularly given the lower rates of intracranial and fatal bleeding with rivaroxaban than with warfarin.T he INR measurement, dose adjustment, and dietary restrictions are not required for patients who receive rivaroxaban. Rivaroxaban offers a significant advantage over warfarin by overcomes its drawbacks including unpredictable pharmacodynamics and pharmacokinetics, multiple food-drug and drug-drug interactions, considerable inter- and intra-individual variability in dose response, and requirement for regular coagulation monitoring. At present, there is a substantial clinical need for an oral anticoagulant to replace vitamin K antagonists for long-term prevention or treatment of patients with venous and arterial thromboembolic events. There is currently a variety of new, promising, oral anticoagulants at various stages of clinical evaluation, with the most advanced being the direct factor-Xa inhibitor rivaroxaban.

CONCLUSION

This study demonstrated that the efficacy of rivaroxaban inferior to that of dose-adjusted warfarin for the prevention of thromboembolic events in subjects with nonvalvular atrial fibrillation as measured by the composite of stroke and NCNS systemic embolism. Our study indicates that rivaroxaban compared with warfarin provides important safety benefits in patients with AF at moderate-to-high risk for stroke or systemic embolism.

Rivaroxaban compared with warfarin led to an overall reduction risk of major and nonmajor clinically relevant bleeding and a lower risk of intracranial hemorrhage and fatal bleeding. Therefore, rivaroxaban seems to be an attractive alternative to warfarin for prevention of stroke or systemic embolism in patients with AF and previous stroke or TIA.

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