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A Comparative Study between Conventional and Recent Anticoagulant Therapies in Atrial Fibrillation

Ekhlas Mohamed Hussein, Mohamed Wafaie Morsi Aboleieneen, Mohammed Mostafa Al-Daydamony, Ali Abd El-fatah Morsi Atwa

[1]Department of Cardiology, Faculty of Medicine, Zagazig University, Zagazig, Egypt.

***Corresponding author**: Ali Abd El-fatah Morsi Atwa, **Mobile:** (+20)1007169349, **Email:** ali_atwa@ymail.com

ABSTRACT

Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1-2% of the general population. With an aging population, its prevalence is estimated to increase two-fold in the next 50 years**.** The prevalence of AF increases remarkably with age, being 0.5% at 40-50 years of age and 5-15% at 80 years of age. Men are more often affected than women.

Objective: This study was aimed to evaluate and compare the healthcare effect and safety of nonvalvular atrial fibrillation (NVAF) patients using novel oral anticoagulants (NOACs) with patients using warfarin.

Patients and Methods: This study included a total of 124 patients with non-rheumatic atrial fibrillation on their anticoagulation drug, attending at Department of Cardiology, Zagazig University Hospitals, and Cardiology Clinic, Ministry of Civil Aviation, during the period from 2015 to 2016. Patients were divided into two groups NOACs, group I and warfarin, group II. **Results:** revealed that there was a statistically significant difference between both groups regarding hemorrhagic complications. The rate of occurrence of hemorrhage among the warfarin group was 8.3% per year compared to 3.3% of the NOACs group. Results revealed also that there was a statistically significant difference between both groups regarding thrombotic complications. The rate of thrombosis among the warfarin group was 25% per year compared to 8.2% of the NOACs group.

Conclusion: It could be concluded that the overall evidence indicates that NOACs could be considered a safe and efficacious alternative to warfarin as a treatment option for atrial fibrillation.

INTRODUCTION

The most prevalent persistent heart arrhythmia, atrial fibrillation (AF), affects 1-2 % of the general population. With age, the prevalence of AF dramatically rises, from 0.5% at 40 to 50 years of age to 5 to 15% at 80 years of age. In the next 50 years, its prevalence is predicted to double due to an ageing population [(1)]. Men are impacted more frequently than women [(2)]. Numerous diseases and cardiovascular risk factors are linked to AF, which may result in structural, electrical, or both types of (ion-channel) remodeling [(3)].

One in five strokes is due to the arrhythmia atrial fibrillation, which is linked to a 5-fold increased risk of stroke. Particularly lethal strokes in people with AF are ischemic strokes. Compared to individuals who suffer from stroke or other reasons, those who survive become more impaired and are more likely to experience a recurrence. As a result, stroke caused by AF doubles the chance of death and quadruples the expense of care [(4)].

Vitamin K antagonists (VKAs), such as warfarin used to be the standard of care for stroke prevention in patients with non-valvular AF (NVAF**)** [(5)]. The advent of the non-vitamin K antagonist OACs (NOACs) apixaban, dabigatran, edoxaban, and rivaroxaban has provided a convenient, efficacious, and tolerable alternative to anticoagulation with warfarin. Unsurprisingly, the NOACs are increasingly used in everyday clinical practice [(6)]**.**

Although anticoagulation with warfarin may effectively reduce the risk of cardioembolic stroke in patients with atrial fibrillation (AF), warfarin has a narrow therapeutic window. In the RE-LY trial with carefully selected and monitored patients, the proportion of time in therapeutic range (TTR), defined by the international normalized ratio (INR) of 2 to 3, varied from 44% to 77%, depending on the study or clinical center [(7)].

Hemorrhage or thrombosis due to over- or under-dosing may have devastating consequences. Poor coagulation control may increase the risk of thromboembolic events, warfarin-related bleeding, and thrombotic events. Also, a recent study shows the importance of identifying the patient with atrial fibrillation with a higher risk of stroke and administering proper anticoagulation. New oral anticoagulants (NOACs), i.e., dabigatran, apixaban, rivaroxaban, and edoxaban, are not inferior to warfarin in preventing ischemic stroke systemic embolism in patients with non-valvular AF [(8)].

For all vascular events, non-hemorrhagic events, and mortality. However, no consensus exists regarding the indication for the use of these agents in patients with AF. The quality of anticoagulation control may depend on genetic factors, notably CYP2C9 and VKORC1 polymorphisms, and on non-genetic patient-related factors, such as gender, race/ethnicity, and paroxysmal vs. permanent AF. Dr. Lip and colleagues recently introduced a validated assessment scheme based on clinical variables to aid in distinguishing patients with AF who are likely to do well on warfarin from those who are likely to have poor anticoagulation control. This appears to provide valuable information relevant to the safety and effectiveness of treatment while avoiding the time and expense of a pharmacogenetics study [(7)].

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In previous decades, chronic anticoagulation has been the standard for patients with chronic nonvalvular atrial fibrillation (NVAF). Warfarin and other vitamin K antagonists were the only available options until recently. The target-specific oral anticoagulants rivaroxaban, dabigatran, and apixaban have been approved by the US Food and Drug Administration (FDA) for the treatment of NVAF. These agents have predictable pharmacokinetic properties, minimal food-drug interactions, and do not require frequent monitoring as compared to warfarin [(4)].

This study was aimed to evaluate and compare the healthcare effect and safety of nonvalvular atrial fibrillation (NVAF) patients using novel oral anticoagulants (NOACs) with patients using warfarin.

PATIENTS AND METHODS

This study included a total of 124 patients with non-rheumatic atrial fibrillation on their anticoagulation drug, attending at Department of Cardiology, Zagazig University Hospitals, and Cardiology Clinic, Ministry of Civil Aviation, during the period from 2015 to 2016.

The included patients with non-valvular atrial fibrillation were divided into two groups; **Group 1 (warfarin)** included 62 patients taking warfarin, 39 males and 21 females aged 40 to 75 years, and **Group 2 (NOAC)** included 62 patients taking NOAC drugs, 36 males and 25 females aged 40 to 75 years.

Exclusion criteria:

Patients with Rheumatic heart disease, congenital heart disease, prosthetic valves, with high HAS-BLED score value and pregnant women were excluded. Patients with other indications for oral anticoagulant therapy or potential contraindications for NOAC or warfarin treatment were excluded.

All patients were subjected to:

- history taking (Age, gender, risk factors, and thromboembolic or hemorrhagic complications).
- Clinical examination through twelve leads surface electrocardiograms
- Biochemical laboratory investigations (kidney, liver, and thyroid function tests, total cholesterol, and international normalized ratio).
- Transthoracic echocardiographic examination:
  - The measurements were obtained according to the standard of the American Society of Echocardiography
  - 2-d guided M-mode was recorded to measure LV systolic and diastolic diameter, fractional shortening (FS), and ejection fraction (EF)

It was performed in a parasternal long-axis view. Values were carefully obtained perpendicular to the LV long axis and measured at or immediately below the level of mitral valve leaflet tips. In this regard, the electronic calipers are positioned on the interface between the myocardial wall and cavity and between the wall and the pericardium. Internal dimensions were obtained by 2-d guided M-mode according to the American Society of Echocardiography 2015 [(9)].

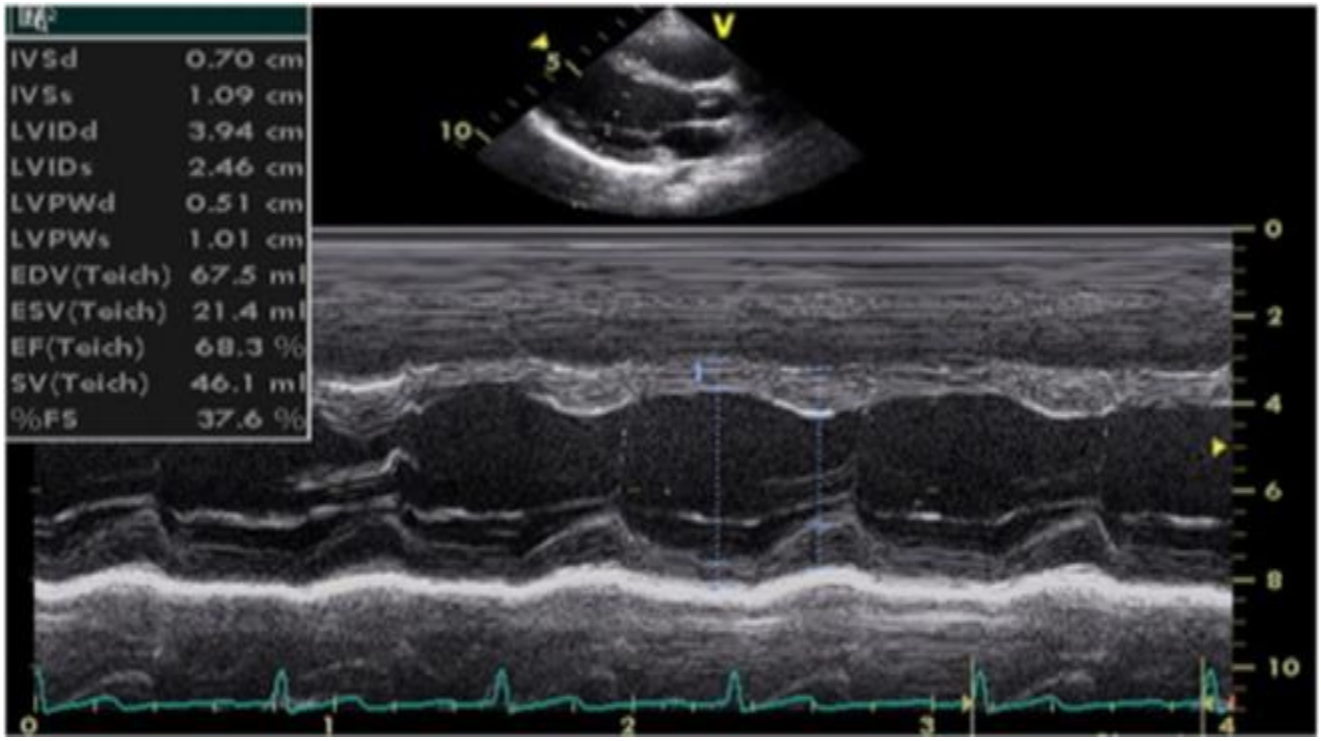

Figure (1): Demonstration of 2-d guided M-mode

- Two-dimensional echocardiography to assess organic valvular heart disease.
- **Follow up :** Patients were regularly followed up at a cardiology clinic where general and local examinations were performed. Dead cases during follow-up were excluded.

Ethical approval:

The study was approved by the Ethics Board of Zagazig University and an informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version **18.0**. Qualitative data were represented as frequencies and relative percentages. Chi-square test was used to calculate the difference between qualitative variables. A p-value of <0.05 indicates significant results. The Kaplan–Meier estimator may be useful to examine recovery rates, the probability of death, and the effectiveness of treatment. It is a statistic, and several estimators are used to approximating its variance.

RESULTS

Demographic characteristics

The included patients were age and gender matched with mean age 62±7.7 in NOAC group and 62±7.6 years in warfarin group with no significant difference. Most patients were males with no statistical significance difference among the two groups.

Regarding comorbidity risk factors of the included subjects, there was no statistically significant difference between both groups (**Table 1**).

Table (1): Characteristics of studied groups

	NOAC group	Marevan group	t- value	p-value
	$\overline{X}$ ±SD	$\overline{X}$ ±SD		
Age (years)	62±7.7	62±7.6	0.4	0.6
BMI (kg/m²)	28.3±2.3	27±2.8	2.8	0.01
SEX				
Males	36	39	0.46	0.49
Females	25	21		
Congestive heart failure Yes	19	19	0.004	0.95
No	42	41		
Diabetes mellitus				
yes	22	21	0.01	0.9
No	39	39		
Hypertension				
Yes	61	60	0.0	0.99
Transient ischemic attack				
Yes	1	1	0.0	0.99
No	60	59		
Venous thrombosis				
Yes	19	16	0.29	0.58
No	42	44		
Stroke				
Yes	5	5	0.001	0.97
No	56	55		

- **Biochemical laboratory tests:** All laboratory investigations are depicted in **(Table 2).**
- **Coagulation profile:** In both two groups, INR vary from 1 to 3, however, mean value of INR of Marevan group (2±1) was prolonged than NOAC group (1±0.5) with highly statistically significant difference.
- **Thyroid function test:** There was a statistically non-significant difference between both groups regarding both TSH and T3 (P=0.4).
- **Kidney function tests:** There was a statistically non-significant difference between both groups regarding creatinine (P=0.4).
- **Live function tests:** There was a statistically significant difference between both groups regarding AST with a P value < 0.05.
- **Lipid profile:** There was a statistically significant difference between both groups regarding total cholesterol levels with a P value < 0.05.

Table (2): Blood chemistry findings of both groups

	NOAC group $\overline{X}$ ±SD	Marevan group $\overline{X}$ ±SD	t- value	p-value
Creatinine (mg/dL)	0.8±0.03	0.8±0	0.7	0.4
AST (U/L)	30.3±1.2	30±0	2.3	0.04
TSH (mIU/L)	4.8±0.04	4.8±0.01	0.7	0.4
T3 (nmol/L)	0.84±0.14	0.86±0.15	0.7	0.4
Cholesterol (mg/dL)	204±25	181±16	5.8	0.0
INR	1±0.14	2±0.5	6.9	0.0

During the follow up stage among Marevan group participants, there were no significant differences regarding the laboratory tests with start point and after six months follow up **(Table 3).**

Table (3): Blood chemistry finding at a different time during the follow-up of Marevan group

	Marevan group			
	At start point $\overline{X}$ ±SD	After six month $\overline{X}$ ±SD	Paired t- value	p-value
Creatinine (mg/dL)	0.81±0.05	0.8±0.13	0.6	0.4
AST (U/L)	24.7±5.8	23.8±5.8	1.6	0.11
	At start point $\overline{X}$ ±SD	**After 12 months** $\overline{X}$ ±SD		
Creatinine (mg/dL)	0.81±0.05	0.78±0.17	1.1	0.2
AST (U/L)	24.7±5.7	23.7±5.4	1.4	0.15

The incidence rate of occurrence of complications:

Hemorrhagic complications

The incidence rate of occurrence of hemorrhage among Marevan group is 8.3% per year compared to 3.3% of NOAC group. hazard ratio (HR) is 3.3 with 95% confidence interval (CI) is (0.3 -35). The difference was statistically non-significant (p =0.3)**.** In NOAC group I, there were 2 cases of hemorrhagic complication per year, while among Marevan group II, there were 5 cases of hemorrhagic complications per year. There was a statistically significant difference between both groups regarding hemorrhagic complications **(Table 4, Figure 1).**

Table (4): Incidence rate of occurrence of haemorrhage of both groups

	NOAC group	Marevan group	HR	(95% CI)		p-value
Hemorrhage at year				Lower	0.3	
Yes	2(3.3)	5(8.3)	3.3	Upper	35	0.3
No	59(96.7)	55(91.7)				
Hemorrhage at 1st 6 months				Lower	-	
Yes	0(0)	2(3.3)	-	Upper	-	0.24
No	61(100)	57(96.7)				
Hemorrhage at 2nd 6 months				Lower	0.26	
Yes	2(3.3)	3(5)	1.52	Upper	8.8	0.67
No	59(96.7)	57(95)				

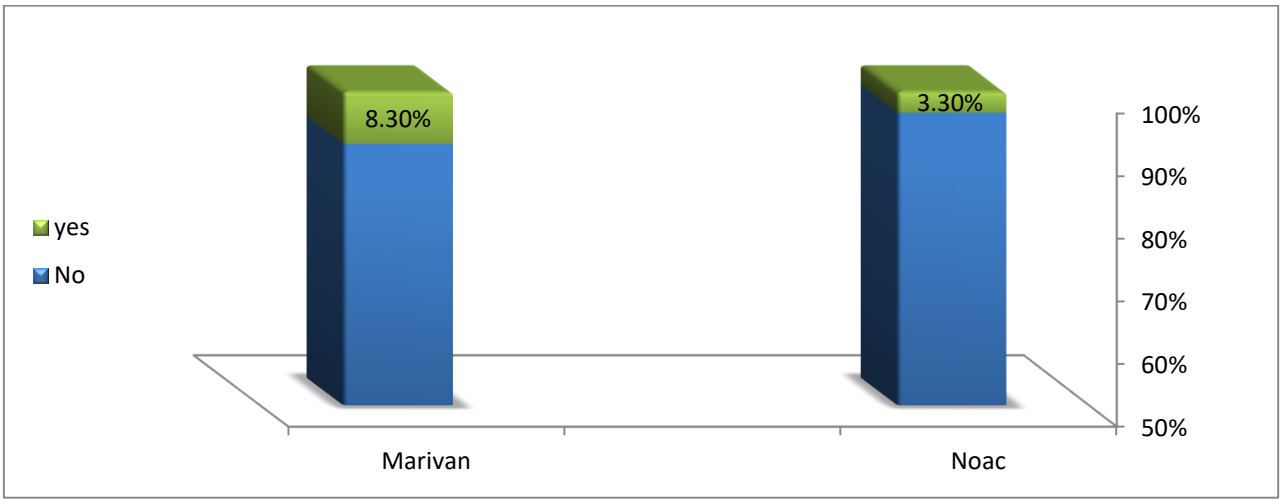

Figure (1): Incidence rate per year of occurrence of hemorrhage of both groups

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Thrombotic complications

In NOAC group I there were 5 cases of thrombotic complications per year, while Marevan group II, there were 15 cases of thrombotic complications per year.The net result showed that the incidence rate of occurrence of thrombosis among Marevan group was 25% per year compared to 8.2% of NOAC group **(Table 5).** There was a statistically significant difference between both groups regarding thrombotic complications (p=0.008).

a) First six months: In NOAC group I, there were 5 cases with thrombotic complications per six months. However, among Marevan group II, there were 12 cases with thrombotic complications per 6 months. The net result showed that the incidence rate of occurrence of thrombosis among Marevan group was 20% per 6 months compared to 8.2% of NOAC group. There was a statistically significant difference between both groups regarding thrombotic complications (p=0.025).

b) Last six months: In NOAC group I there were no cases of thrombotic complications per 6 months. While 3 cases with thrombotic complications per 6 months were reported among Marevan group II. The net result shows that the incidence rate of occurrence of thrombosis among the Marevan group was 5% per 6 months compared to 0% of NOAC group. There was a non statistically significant difference between both groups regarding thrombotic complications (p=0.37) **(Table 5).**

Table (5): Incidence rate of occurrence of thrombosis of both groups

	NOAC group	Marevan group	HR	(95% CI)		p-value
Thrombosis at year				Lower	1.6	
Yes	5(8.2)	15(25)	5.7	Upper	20.6	0.008
No	56(91.8)	45(75)				
Thrombosis at 1st 6 months				Lower	1.2	
Yes	5(8.2)	12(20)	4.4	Upper	15.7	0.025
No	56(91.8)	48(80)				
Thrombosis at 2nd 6 months				Lower		
Yes	0(0)	3(5)	-	Upper	-	0.37
No	61(100)	57(95)			-	

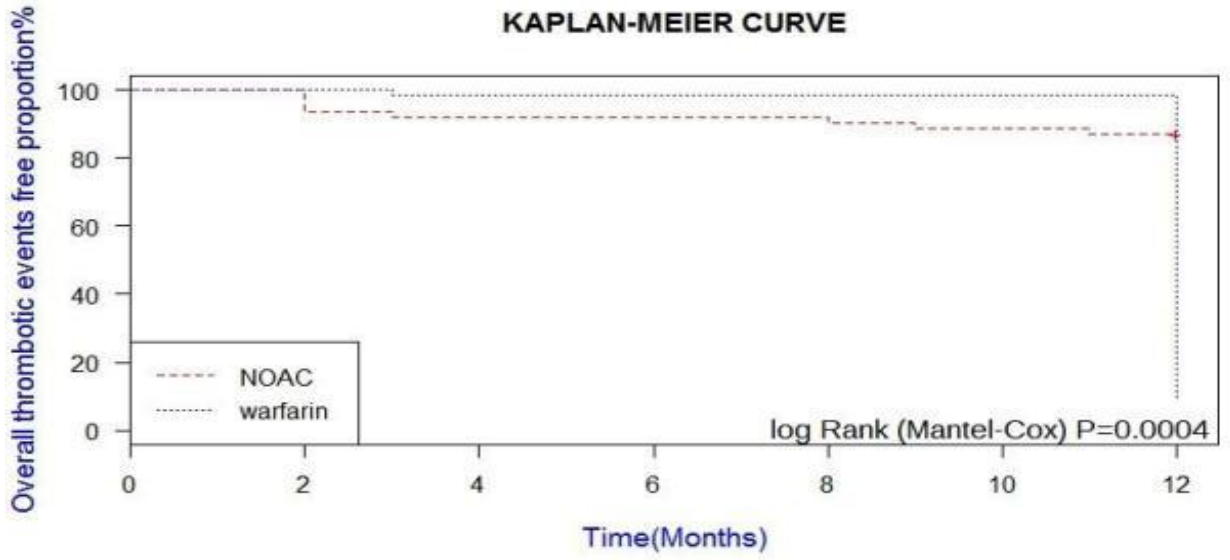

Figure (2): Comparison between both groups for thrombotic events at year of both groups.

Results of the relationship between risk factors and complication data

This table shows that the TIA patients' HR=12.6 95% CI (1.5 – 106) regarding the occurrence of hemorrhage.

Whereas there was an unsignificant difference between patients who have comorbidity and others Without disease regarding the occurrence of hemorrhage p>0.05.

This table shows there was a non-significant difference between patients who have comorbidity and occurrence of thrombosis in the first six months p>0.05 except for the history of venous thrombosis HR= 26 CI (6 -116) p= 0.00 and history of stroke HR= 4 CI (1.4 - 11) p= 0.006.

Hemorrhagic complication:

There was a statistically significant difference in transient ischemic attack regarding hemorrhagic complications with P value = 0.02. There was a statistically unsignificant difference of remaining risk factors regarding hemorrhagic complications with a P value > 0.05

Thrombotic complication:

There was a statistically significant difference between stroke and venous thrombosis regarding thrombotic complications, with a P-value = 0.006 with stroke and a P-value < 0.05 with venous thrombosis. There was a statistically unsignificant difference in remaining risk factors regarding hemorrhagic complications with a P-value > 0.05.

A) First six months.

There was a statistically significant difference between stroke and venous thrombosis regarding thrombotic complications, with a P value = 0.001 with venous thrombosis. There was a statistically unsignificant difference of remaining risk factors regarding hemorrhagic complications with a P value > 0.05.

B) Last six months:

There was a statistically significant difference between stroke and transient ischemic attack regarding thrombotic complications with a P value = 0.01 with stroke and a P value = 0.006 with a transient ischemic attack. There was a statistically unsignificant difference of remaining risk factors regarding hemorrhagic complications with a P value > 0.05.

Table (6): Incidence rate and hazard ratio of hemorrhage per year regarding risk factors

Variables	Hemorrhage					
	With disease %	Without disease %	HR	With disease vs. without (95% CI) lower	upper	P
Congestive heart failure (38)	10.5	3.6	4	.41	40.5	0.232
Diabetes (43)	7	5	1	.08	12.5	0.997
Stroke (10)	20	4.5	5	1	26	0.05
TIA (2)	50	5	12.6	1.5	106	0.02
Venous (35)	8.5	4.6	1.3	.11	16.2	0.825
Cholestrole (40)	5	6.2	1.3	.12	16	0.835
SEX	Male (5.3)	Female (6.5)	1.45	.27	8.2	0.64
Age/year	≤70(5.9)	>70(0)	-	-	-	0.98

Table (7): Incidence rate and hazard ratio of thrombosis at year regarding risk factors

Variables	Thrombosis at year					
	With disease %	Without disease %	HR	With disease vs. without (95% CI)		P
Congestive heart failure (38)	21	14.4	1.4	0.6	3.6	0.3
Diabetes (43)	7	21.8	0.3	0.09	1.05	0.06
Stroke (10)	50	13.5	4	1.4	11	0.006
TIA (2)	50	16	3	0.4	22	0.27
Venous (35)	51	2.3	26	6	116	0.00
Cholesterol (40)	15	17.2	0.9	.28	3.3	0.951
SEX	Male (21)	Female (8.6)	.33	.090	1.2	0.09
Age	=<70(15.6)	>70(5.2)	0.2	0.03	2.1	0.9

DISCUSSION

This study showed that, regarding thrombotic complication, the incidence rate of occurrence of thrombosis among the warfarin group was 20% per 6 months compared to 8.2% of NOACs group. There was a statistically significant difference between both groups regarding thrombotic complications, comparing with the last six months, which showed that the incidence rate of occurrence of thrombosis among the warfarin group is 5% per 6 months compared to 0% of NOACs group which denoted that there was a statistically significant difference of both groups regarding thrombotic complications. The difference between two period results may belong to a dose of a drug used as may be the use of loading dose in the side of NOACs prevent the high incidence in first six months thrombotic complication. Warfarin also has a high incidence of thrombotic complication in the first six months which may be due to weak target INR in this period in comparison to the last six months or may be due to warfarin taking a long time to reach the target INR and also the possibility of bleeding and need to stop and replace with other agents as prophylactic anticoagulation.

This agreed with the result of **Schulman** [10] who stated that NOACs were superior in initial prophylactic anticoagulation instead of warfarin and seem to show that, while all NOACs may provide improvements in quality-adjusted life-years vs. warfarin, this was associated with increased cost. Furthermore, apixaban appears to be more cost-effective.

Canestaro *et al.* [11] reported that the treatment effect of NOACs vs. warfarin was consistent for patients with or without prior stroke, transient ischemia attaches, venous thrombosis, diabetes, and those with or without HF. These factors needed to be considered when selecting the optimal therapy for individual patients, but not at the cost of offsetting important reductions in other adverse clinical outcomes. Thus, the overall evidence indicates that NOACs can be considered a safe and efficacious alternative to warfarin in these patient subgroups.

This study showed that a significant difference in value for hemorrhagic complications in transient ischemic attach. This did not match the fact that there was no significant difference between them. This may be due to the abuse of antiplatelet therapy after the prophylactic anticoagulation role for patients, making them more liable to hemorrhagic complications. There was a significant difference in seek of NOACs group against warfarin group.

This agreed with **Canestaro *et al.*** [11] who had demonstrated consistent benefits vs. warfarin across a range of patient subgroups at increased risk of major bleeding, including those most likely to be encountered in clinical practice.

This study showed that, there was a statically significant difference in value for thrombotic complications in patients with a risk factor of venous thrombosis, stroke, and transient ischemic attack, which matched the result of stroke and transient ischemic attack. Our results showed that stroke was a risk factor for thrombotic complications: Statistically, there is a significant difference in the previous stroke regarding thrombotic complications with P value=0.006 with stroke, venous thrombosis as a risk factor to thrombotic complication: Statistically, there was a significant difference of venous thrombosis regard thrombotic complications with P value<0.05 with venous thrombosis, transient ischemic attack as a risk factor to thrombotic complication also with diabetic patients beside a female patient with a weak difference need more research [12].

This study showed that, there was a statistically significant difference in transient ischemic attack regarding thrombotic complications with P value=0.006 with the transient ischemic attack, hemorrhagic complications results show that the rate of occurrence of hemorrhage among warfarin group is 8.3% per year compared to 3.3% of NOACs group which denote statistically significant difference of both groups regard hemorrhagic complications in seek of NOACs and thrombotic complications results show that the rate of occurrence of thrombosis among warfarin group is 25% per year compared to 8.2% of NOACs group which denote There was a statistically significant difference of both groups regard thrombotic complications in seek of NOACs, so final result shows more prevention from thrombotic complication and also a hemorrhagic complication in the side of NOACs.

Tsai *et al.* [13] who aimed to compare the clinical outcomes of warfarin use and NOAC use in patients with AF with a history of ICH using a nationwide cohort with AF. A nationwide cohort study from January 1, 2012, to December 31, 2016, was performed using data from the Taiwan National Health Insurance Research Database. The dates of analysis were July 1 to September 1, 2019. The study population comprised patients with AF with a history of ICH and a CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, prior stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease], age 65-74 years, sex category [female]) of at least 1 for men or at least 2 for women who had received warfarin or NOACs. The clinical outcomes were examined using Cox proportional hazards regression analyses among the study population before and after propensity score matching. Exposures Oral anticoagulation with warfarin or NOACs. The study cohort included 4540 patients (mean [SD] age, 76.0 [10.5] years; 2653 men [58.4%]), with 1047 patients receiving warfarin (mean [SD] age, 75.1 [11.4] years; 571 men [54.5%]) and 3493 patients receiving NOACs (mean [SD] age, 76.3 [10.2] years; 2082 men [59.6%]). Compared with warfarin use, NOAC use was associated with statistically significantly lower risk of all-cause mortality (adjusted hazard ratio [aHR], 0.517; 95% CI, 0.457-0.585), ICH (aHR, 0.556; 95% CI, 0.389-0.796), and major bleeding (aHR, 0.645; 95% CI, 0.525-0.793), whereas the rate of ischemic stroke was similar in the 2 groups (aHR, 0.879; 95% CI, 0.678-1.141). These results were generally consistent after propensity score matching among 973 patients in each group.

CONCLUSION

It could be concluded that the overall evidence indicates that NOACs could be considered a safe and efficacious alternative to warfarin as a treatment option for atrial fibrillation.

The current study showed that the treatment effect of NOACs vs. warfarin concerning efficacy has been consistent across all subgroups. Concerning safety, warfarin showed increased rates of bleeding relative to NOACs, which appear to reduce hemorrhagic events, critical-site bleeding, and fatal bleeding, depending on which, if any, therapy is used to replace warfarin for continuing stroke prophylaxis. Rates of hemorrhagic events are low in patients prescribed NOACs.

This finding suggests that NOACs may offer a significantly improved benefit–risk profile for stroke prophylaxis. Specifically, the treatment effect of NOACs vs. warfarin was consistent for patients with non-rheumatic atrial fibrillation.

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