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Healthcare Effect and Safety of Patients with Persistent Non-Valvular Atrial Fibrillation Using NOAC and Warfarin

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ABSTRACT

Background: For patients with persistent non-valvular atrial fibrillation (NVAF), chronic anticoagulation has traditionally been the mainstay of therapy. Warfarin and other vitamin K antagonists were the sole choices up until recently.

Objective: To evaluate the healthcare effect and safety of patients with persistent with NVAF using Novel oral anticoagulant (NOAC) and those using warfarin group.

Patients and Methods: The study consisted of 124 patients with non-rheumatic atrial fibrillation on their anticoagulation drug. Patients were classified into two main groups according to the drug used as an anticoagulant: Group I: 62 patients with non-valvular atrial fibrillation take warfarin drug 39 men and 21 women ranging in age from 40 to 75 years old. Group II: 62 patients with nonvalvular atrial fibrillation take NOAC drugs, 36 men and 25 women of varying ages 40 to 75 years.

Results: Thrombotic complications: In NOAC group I: there were 5 cases of thrombotic complications per year. In Marivan group II: there were 15 cases of thrombotic complications per year. The net result showed that the incidence rate of occurrence of thrombosis among the marivan group was 25% per year compared to 8.2% in the NOAC group. There was a statistically significant difference between both groups regarding thrombotic complications. The net result showed that the incidence rate of occurrence of thrombosis among the marivan group was 20% per 6 months compared to 8.2% in the Noac group. There was a statistically significant difference between both groups regarding thrombotic complications.

Conclusion: Overall evidence indicates that NOACs can be considered a safe and effective alternative to warfarin in these subgroups of patients.

Keywords: Conventional anticoagulant therapies, Recent anticoagulant therapies, Atrial fibrillation.

INTRODUCTION

The most prevalent persistent arrhythmia in clinical practice is atrial fibrillation (AF), which has a significant excess of cardiovascular morbidity and death [(1)].

For patients with persistent nonvalvular atrial fibrillation (NVAF), chronic anticoagulation has always been the mainstay of therapy, and up until recently, the only accessible alternatives have been warfarin and other vitamin K antagonists [(2)].

Patients with AF and VTE are being treated with new oral anticoagulants more often. Continued safe usage should result from a complete grasp of their pharmacology and practical advice on how to utilize them [(3)].

For fifty years, oral anticoagulant treatment has been mostly based on coumarins or vitamin K antagonists (VKAs). Their efficacy has been demonstrated in carefully planned clinical trials for the primary and secondary prevention of venous thromboembolism, the primary prevention of acute myocardial infarction in high-risk men, the primary prevention of stroke, recurrent infarction, or death in patients with acute myocardial infarction, and the prevention of systemic embolism in patients with prosthetic heart valves or atrial fibrillation [(4)].

The aim of this study was to evaluate the healthcare effect and safety of patients with persistent NVAF using NOAC and patients using warfarin groups.

PATIENTS AND METHODS

The work was carried out during the years 2015 and 2016 in the cardiology department, faculty of medicine, Zagazig University and Civil Aviation Cardiology Clinics.

Patient population:

The study consisted of 124 patients with nonrheumatic atrial fibrillation on their anticoagulation drug. Patients were classified into two main groups according to the drug used as an anticoagulant:

- **Group I**: 62 patients with nonvalvular atrial fibrillation take warfarin drug 39 males and 21 females ranging in age from 40 to 75 years of age.
- **Group II**: 62 patients with nonvalvular atrial fibrillation take NOAC drugs 36 men and 25 women of varying age from 40 to 75 years.

Exclusion criteria:

- Pregnancy.
- Rheumatic heart disease.
- Prosthetic valves.
- High Has-Bled score value.
- Congenital heart disease.

Methods:

All patients studied were subjected to the following:

1. **History taking:** Age, sex, and risk factors such as diabetes, hypertension, in addition to congestive

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heart failure, venous thrombosis, transient ischemic attack, and thromboembolic or hemorrhagic complications.

2. **Clinical examination:** A general and local cardiac clinical examination was performed. Body mass index (BMI) was calculated.
3. **Twelve lead surface electrocardiograms** were used to define the patient's rate, rhythm, and type of atrial fibrillation.
4. **Transthoracic echocardiographic examination:** Measurements were obtained according to the standard of the American Society of Echocardiography.
   - ***a) 2-d guided M-mode was recorded to measure:***
     - Left ventricular (LV) diameter in systole and diastole, fractional shortening (FS), and ejection fraction (EF). The long-axis parasternal view was utilised. Values were carefully measured at or just below the level of the mitral valve leaflet tips, perpendicular to the long axis of the LV. The myocardial wall and cavity interface and the wall and pericardium interface are where the electronic callipers are placed in this respect. According to the American Society of Echocardiography 2015, internal dimensions were determined using 2-d guided M-mode [(5)].
   - ***b) Two-dimensional echocardiography to assess:***
- Organic valvular heart disease.

Follow-up:

The patients were regularly followed up in the cardiology clinic, where general and local examinations were performed.

- Assessment of risk factors and symptoms and signs of complications such as thrombotic or hemorrhagic.
- Twelve leads surface electrocardiogram to follow patient rate and rhythm.
- Laboratory monitoring of patients for the traditional group and fundus examination for the new group.
- The use of phone calls to ask for a reason for delaying follow-up time.

Dead cases during follow-up were excluded. Note about them in the introduction.

Ethical approval:

The study was approved by the Ethics Board of Zagazig University.

Statistical analysis

The SPSS application (Statistical Package for Social Science), version 18.0, was used to computerize and statistically analyse the data that had been obtained. Frequencies and relative percentages were used to depict qualitative data. The chi-square test was employed to determine how qualitative factors differed from each other. Quantitative information was presented as mean and SD (Standard deviation). To determine the difference between two quantitative variables, the t-value was computed. The 5% level is set as the significance criterion (p-value). P value less than 0.05 was regarded as significant.

RESULTS

Result of demographic data (table 1)

1- **Age:** In Noac group I: it ranged from 40 to 75 years with a mean of 62±7.7. In Marivan group II: ranged from 40 to 75 years with a mean of 62±7.6. There was a statistically non-significant difference between both groups in age.

2- **BMI:** In Noac group I: it ranged from 26 to 31 kg/ m^2 with a mean of 28.3±2.3. In marivan group II: it ranged from 24 to 30 kg/ m^2 with a mean of 27±2.8. The BMI value was higher in group I than (P value < 0.05).

3- **Gender:** In Noac group I: it was 36 males and 25 females. In marivan group II: it was 39 males and 21 females. There was a statistically nonsignificant difference between both groups in sex.

Results of comorbidities data (table 1)

1- **Congestive heart failure** In Noac group I: it was 19 CHF and 42 Non-ChF. In marivan group II: it was 19 CHF and 41 non-CHF. There was a statistically nonsignificant difference between both groups for congestive heart failure.

2- **Diabetes mellitus:** In Noac group I: it was 22 Diabetic and 39 Non-Diabetic. In marivan group II: it was 21 diabetic and 39 non-Diabetic. There was a statistically nonsignificant difference between both groups with respect to diabetes mellitus.

3- **Hypertension:** In Noac group I: it was 61 hypertensive patients. In marivan group II: it was 60 hypertensive patients. There was a statistically nonsignificant difference between both groups with respect to hypertension.

4- **Transient Ischemic Attack:** In Noac group I: was one patient of 61 patients. In marivan group II: was one patient out of 60 patients. There was a statistically nonsignificant difference between both groups concerning the transient ischemic attack.

5- **Venous thrombosis:** In Noac group I: it was 19 DVT and 42 non-DVT. In marivan group II: it was 16 DVT and 44 Non-DVT. There was a statistically nonsignificant difference between both groups in venous thrombosis.

6- **Stroke** In Noac group I: it was 5 patients with a stroke history and 56 negative stroke histories. In marivan group II: it was 5 patients with a stroke history and 55 negative stroke histories. There was a statistically nonsignificant difference between both groups with respect to stroke.

Table (1): Characteristics of the 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** **Females**	 36 25	 39 21	0.46	0.49
Congestive heart failure **Yes** **No**	 19 42	 19 41	0.004	0.95
Diabetes mellitus **Yes** **No**	 22 39	 21 39	0.01	0.9
Hypertension **Yes**	 61	 60	0.0	0.99
Transient ischemic attack **Yes** **No**	 1 60	 1 59	0.0	0.99
Venous thrombosis **Yes** **No**	 19 42	 16 44	0.29	0.58
Stroke **Yes** **No**	 5 56	 5 55	0.001	0.97

Hemorrhagic complications

In Noac group I: There are 2 cases of hemorrhagic complication per year. In Marivan group II: there are 5 cases of hemorrhagic complications per year.

The net result shows that the rate of occurrence of hemorrhage among the marivan group was 8.3% per year compared to 3.3% in the Noac group.

There was a statistically significant difference between both groups regarding hemorrhagic complications. The risk ratio (HR) is 3.3, with a 95% confidence interval (CI) of (0.3 -35). The difference is statistically insignificant, p =0.3 **(Table 2).**

Table (2): Incidence rate of the occurrence of hemorrhage in both groups

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

Thrombotic complications: (table 3)

In Noac group I: there were 5 cases of thrombotic complications per year. In Marivan group II: there were 15 cases of thrombotic complications per year. The net result shows that the incidence rate of thrombosis occurrence among the marivan group was 25% per year compared to 8.2% in the Noac group (table 3). There was a statistically significant difference between both groups regarding thrombotic complications.

a) First six months:

In Noac group I: There were 5 cases with thrombotic complications per 6 months. In Marivan group II: There were 12 cases with thrombotic complications per 6 months. The net result shows that the incidence rate of thrombosis among the marivan group was 20% per 6 months compared to 8.2% in the Noac group. There was a statistically significant difference between both groups regarding thrombotic complications (Table 3).

b) Last six months:

In Noac group I: There are 0 cases with thrombotic complication per 6 months. In Marivan group II: there were 3 cases with thrombotic complications per 6 months. The net result shows that the incidence rate of thrombosis occurrence among the marivan group was 5% per 6 months compared to 0% of the Noac group. There was a statistically significant difference between the two groups concerning thrombotic complications (Table 3).

Table (3): Incidence rate of the occurrence of thrombosis in both groups

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

DISCUSSION

There was a nonsignificant difference between both groups as demographic, comorbidities, and laboratory data were randomly collected.

Regarding hemorrhagic complications during the follow-up period, the rate of new hemorrhagic complications among the warfarin group was 8.3% per year compared to 3.3% of the NOAC group. This is consistent with the ROCKET trial who found 3.6% of the warfarin group and 3.4% of the NOAC group. Also, the results of the ENGAGE trial, found 3.43% of the warfarin group and 2.75% of the NOAC group had hemorrhagic complications. Inconsistence with our results, the clinical trial called prevention of stroke in higher-risk populations with nonvalvular atrial fibrillation [(6)], in which 3.69% with warfarin and 4.1% in the NOAC group had hemorrhagic complications.

The hemorrhagic complication is likely to result in a temporary cessation of anticoagulant therapy, which raises the question of when it can be reinitiated after the successful resolution of the bleeding event. Optimal timing of resumption should be individualized for the particular circumstances of each patient, particularly the risk of ischemic events versus the risk of recurrent hemorrhage. Our results match with **Steffel *et al.*** [(7)], who showed that NOAC had less hemorrhagic complication than warfarin. We must explain that when, or even if, resumption of oral anticoagulation assumes even greater importance after bleeding event, the trial has suggested that resumption can begin as soon as 10–14 days after a hemorrhagic event if the risk of cardiogenic thromboembolism is high, while other authors have recommended delaying resumption of oral anticoagulation until 10–30 weeks [(8)].

In this study, we found that the effect of NOAC versus warfarin on the efficacy has been consistent between all these subgroups. Regarding safety, in those subgroups where warfarin showed increased rates of bleeding relative to NOACs, this appears to have been driven by increases in bleeding rather than major bleeding. It was worth noting that, compared to NOACs, reduced rates of hemorrhagic events, critical site bleeding, and fatal bleeding. Nonetheless, although bleeding was unlikely to have serious or long-term sequelae, such bleeding may contribute to patients discontinuing treatment with warfarin, which may result in an increased risk of thromboembolic or bleeding events, depending on which, if any, therapy was used to replace warfarin for continuing stroke prophylaxis. The rates of hemorrhagic events were low in patients prescribed NOAC and in patients prescribed warfarin. Therefore, the observation that the rates of hemorrhagic events in warfarin-randomized patients were significantly higher in patients was of particular importance. This finding suggests that NOACs may offer a significantly improved benefit–risk profile for stroke prophylaxis in this part of the world [(6, 9, 10)].

This alignment with the guidelines of the American Heart and Stroke Association for oral antithrombotic agents for the prevention of stroke in nonvalvular AF supports the use of warfarin and NOAC to prevent first and recurrent strokes in patients with nonvalvular AF [(11)].

Guidelines recommend the individualized selection of antithrombotic agents based on risk calculations, cost, tolerability, patient preference, potential drug interactions, and other clinical characteristics, including Time in Therapeutic Range (TTR) if the patient had taken warfarin. When determining the selection of warfarin versus NOACs.

A dilemma was erupted in that the TTR cannot be known at the time of initial treatment. As a result, it was difficult to identify newly diagnosed patients with AF who would do well on warfarin and who also have high values for the time in the therapeutic range. This is desirable because the main benefits of NOAC compared to warfarin may be marginal in those with a therapeutic range times that exceed high. However, the reduction in intracranial bleeding was still evident. In a recent meta-analysis with data from four phase 3 clinical trials of NOAC, NOAC had a favorable risk-benefit profile compared to warfarin that was consistent between various groups of patients [(12)].

CONCLUSION

Overall evidence indicates that NOACs can be considered a safe and effective alternative to warfarin in these subgroups of patients.

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Competing interests: Nil.

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