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# Non Vitamin k Antagonist Oral Anticoagulation Assessment in Non Valvular Atrial Fibrillation Using Transcranial Doppler Ultrasonography

Mohamed Ahmed Zaki<sup>1,\*</sup>, Hamouda Abdel Khalek El-Bahnasy<sup>2</sup>

<sup>1</sup>Department of Neurology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

<sup>2</sup>Departement of Cardiology, Damietta Faculty of Medicine, Al-Azhar University, Damietta, Egypt

## Email address:

drmohammedzaki86@gmail.com (Mohamed Ahmed Zaki), ddr.hamouda@yahoo.com (Hamouda Abdel Khalek El-Bahnasy)

\*Corresponding author

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**Abstract:** *Background:* Warfarin with optimized international normalization ratio (INR); is significantly affect the Micro embolic signals (MES), in many studies. Non vitamin k antagonist oral anticoagulants (NOACs) are recently approved for stroke prevention in non valvular AF. In contrast to Warfarin; effect of NOACs on MES is not yet fully researched. *Aim:* To determine the effect of NOACs on MES, in comparison to warfarin in non valvular AF, to reflect the potential embolization risk. *Methods:* The incidence and number of MES was studied in patients with non valvular AF. Two groups in the current study; the first, patients were put on warfarin with INR levels were optimized to (2-3), and considered as a control group. The second; patients were put on NOAC (rivaroxaban, 15 mg /day). Study patients were recruited from cardiology outpatient clinics and departments (Al-Azhar University hospitals; Cairo and New Damietta, Egypt). Patients of the both groups were subjected to MES detection and counting by transcranial Doppler ultrasonography (TCD) monitoring. *Results:* MES did not detected in 22.5% in study groups; no statistically significant differences between study groups. The incidence and number of MES; within the warfarin group; MES were detected in (30 patients, 75%), while within the rivaroxaban group (32 patients, 80%). The average number of MES; in group one were (11.65 ±7.20), and in group two (11.50 ±7.20), with no significant statistical difference also. *Conclusion:* The effect of warfarin and NOAC use is not statistically different and Rivaroxaban is not inferior to warfarin.

**Keywords:** Anticoagulation, NOACs, Cerebral Microembli, Nonvalvular Atrial Fibrillation, Transcranial Doppler Ultrasonography

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## 1. Introduction

Atrial fibrillation is the most common arrhythmia, it was estimated to affect in average 1% of the general population [1]. AF is a crucial risk factor for cardiogenic ischemic stroke, and stroke risk in patients with AF has been estimated as between 1% and 20% annually [2]. Stroke related to AF has the character of; high clinical severity, significantly causing disability, easier to relapse and high mortality rates. The term non valvular AF, refers to AF in the absence of, a mechanical prosthetic heart valve, or moderate to severe mitral stenosis

[1, 2].

Warfarin is used lifelong for cardio embolic stroke prevention; but the narrow therapeutic margin, drug or food interactions with the frequent need to adjust dosing with INR levels optimization, increase its burden, use limitation and pave the way for a new NOACs to develop [1-8].

NOACs are considered and approved by AF guidelines worldwide as the preferred choice of anticoagulation, to prevent stroke in non valvular AF [4]. NOACs; have an improved efficacy and safety ratio without, the need for routine coagulation monitoring. After the indication for oral anticoagulation is established; NOACs are preferred over

vitamin K antagonist (VKA) in all NOAC eligible AF patients, while warfarin is still the best and the only choice in valvular AF [6-10].

Asymptomatic subclinical cerebral micro embolization; has a strong relationship with stroke risk, and MES have been detected in a number of clinical conditions, including AF. Many studies approved; a high relationship between the warfarin anticoagulation levels and MES, in various diseases [11, 12].

Quantification of subclinical a symptomatic emboli signals; may allow more precise estimation of embolic risk and an objective treatment effects assessment, but there are still several less well researched aspects of NOACs use, including the effect on embolic signals detection.

The effect of NOACs, in a symptomatic subclinical MES, in non valvular AF patients, in comparison to warfarin use, will be assessed in the current study, to judge the potential embolic risk.

## 2. Patient and Methods

Between 2022, Jan. and 2023, Jan.; this prospective study, with a symptomatic non valvular AF patients was conducted. Patients were recruited from cardiology outpatient clinics and departments (Al-Azhar University hospitals; Cairo and New Damietta, Egypt). Study patients were divided into two groups; 1<sup>st</sup> group was put on warfarin; with INR levels optimized at (2-3), and was considered as a control group. The 2<sup>nd</sup> one put on NOAC (rivaroxaban 15mg) [6].

### 2.1. Inclusion and Exclusion Criteria

An eighty; non valvular a symptomatic AF patients, with CHADS score 2 or more, were included in this study. Patients with non valvular AF were defined as, any AF patient without prosthetic valve and moderate to severe valvular heart lesion. Patients with; a previous history of stroke, transient ischemic attacks (TIAs), another known embolization source rather than AF, patients with non-optimized INR levels ( $< 2$ ), and closed temporal windows with unobtainable Doppler signals were excluded from study.

Patients were subjected to; complete history taking, full clinical examination, twelve- leads electrocardiogram (ECG) to asses cardiac rhythm for the AF presence documentation, echocardiography, carotid duplex, liver and kidney function tests, INR level, and MES detection, counting by TCD.

Echocardiographic evaluation had been completed, while the patient was in the left lateral decubitus position. We used the Philips iE 33 Xmatrex machine (Philips, Philips IE 33 Ultrasound, Bothell, Washington, USA), ultrasound device, and a 4S-RS (3.5-Mhz) probe. Two cardiologists carried out the investigations. They were experts in the field and were blinded to categorization of patients. Images were recorded from the parasternal and apical positions by the two dimensional, M-mode, and Doppler echocardiography methods. All examinations were done in agreement with American Society of Echocardiography guidelines for the

assessment of left-ventricular structures, systolic function, diastolic function, and calculation of significant values [13, 14].

TCD monitoring; for 60 minutes, to detect MES, using TCD8 software, in multi dop X<sup>4</sup> device was done in both middle cerebral arteries (MCA), simultaneously, at depth between 45 – 55 mm, through the temporal windows [15].

MES; were known after the exclusion of the false signals, using the criteria (short lasting, intensity increase  $> 3$ db, unidirectional, producing whistle, chirping or clicking sound) [15].

### 2.2. Ethical Issues

The study protocol; was approved by the institutional ethical and research committee of Damietta faculty of Medicine. Full explanation, information about the study procedures and aim with complete consenting were obtained from every patient. Ethical code of research conduct of Helsinki declaration was conducted all through the study.

### 2.3. Statistical Analysis of Data

The collected data; were arranged, tabulated, and statistically analyzed using statistical package for social science, version 16 (SPSS Inc., Chicago, Illinois, USA). Numerical data; were presented as mean  $\pm$  SD, whereas categorical data; were presented as frequency and percent. Comparison between groups; was done by independent samples t test. Comparison between groups of categorical variables; was done by X<sup>2</sup> test or Mann- Whitney test when appropriate P value less than 0.05 were considered significant for interpretation of results.

## 3. Results

Eighty patients; diagnosed as non valvular AF, were included in current study, after exclusion of four patients due to failure to obtain the ultrasound signals through the temporal window.

All of the included patients were a symptomatic, and the other causes of embolization, were excluded by ECG, echocardiography and carotid duplex.

As regard to the general characteristics; there were no significant differences between the both groups including; age, sex, hypertension, diabetes, obesity, echocardiographic parameters (table 1, figure 2).

MES; not detected in (10 patients, 25%) in group I, while in group II (8 patients, 20%), with no significant difference in both groups (Figure 1). In the rest of patients; in both groups, MES were detected as, (30 patients, 75%) in group I and (32 patients, 80%) in group II, without also any significant difference ( $P=0.7$ ), (table 2, figure 1, 2).

The embolic load (number of MES); in group I was (11.65  $\pm$ 7.20), and in group II (11.50  $\pm$ 7.20), with no significant difference between the two groups ( $P=0.92$ ), (table 2, figure 2).

**Table 1.** General characteristics of study groups.

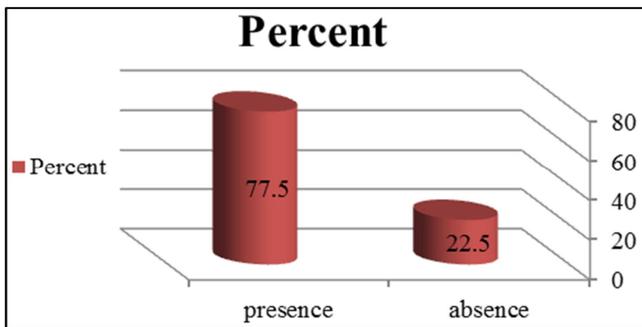
Variables	Group (I): Patients on warfarin N=40	Group (2): Patients on rivaroxaban N=40	P value
Age	36.35±10.40	36.45±10.93	0.9
Male sex	16 (40%)	14 (35%)	0.8
HTN	11 (27.5%)	13 (32.5%)	0.8
DM	3 (7.5%)	3 (7.5%)	1.0
Obesity	11 (27.5%)	11 (27.5%)	0.8
Left atrium Dimension	3.27±0.38	3.27±0.38	1.0
Ejection fraction	58.50±6.97	59.40±7.69	0.58

No significant statistical differences between the both groups, regarding the general characteristics.

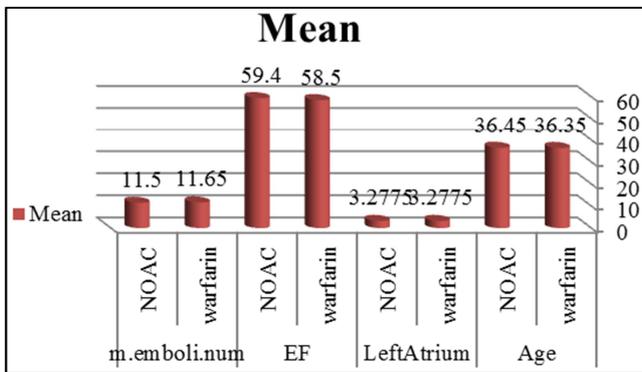
**Table 2.** MES in study groups.

Variables	Group (I): Patients on Warfarin, N=40	Group (2): Patients on Rivaroxaban, N=40	P value
Micro emboli absence	10 (25%)	8 (20%)	0.7
Micro emboli presence	30 (75%)	32 (80%)	0.7
Number of micro emboli	11.65±7.20	11.50±7.20	0.92

No significant statistical differences between the both groups, regarding the MES detection and number.



**Figure 1.** MES detection percentage in all subjects in both groups.



**Figure 2.** Independent T test Description between Group I (on warfarin) versus group II (on NOAC).

Shows no significant statistical differences in both groups regarding; number of emboli detection, age, left atrium dimensions, and ejection fraction

### 4. Discussion

MES are commonly detected in various conditions; with a potential cause of cardio embolization, MES were detected in; myocardial infarction, heart valve diseases, prosthetic heart valves, heart failure, right to left shunting, during heart surgical procedures, orthopedic surgical procedures, carotid artery stenosis, AF, with the agreement to the current study, as MES were detected in both study groups (75-80%) [11-18].

MES are a subclinical, a symptomatic; many studies have approved their importance and strong correlation with ischemic cerebral events. Anzola et al.; in a study of MES clinical correlation with cerebral embolism in AF and prosthetic valve; and stated that, embolus detection monitoring seems a promising tool in the assessment of the individual stroke risk in patients with cardiac embolic sources [19].

Christian V, et al.; recommended in their study to reduce MES burden during catheter for AF, and so sequentially reduce thromboembolic burden [20]. And Rodrigo B., et al. stated that; MES demonstrated a significant correlation with ischemic events and could be predictor for the early recurrence of stroke in the long term regarding, risk stratification, recurrence, severity and mortality [21]. After that; many studies researched the therapeutic value of MES, in relation to the anticoagulation with warfarin, and stated; a strong relationship with warfarin use, especially when INR level optimized to the recommended levels. Larbig R, et al.; concluded that; increased INR values correlate with decreased MES during pulmonary vein isolation (PVI) in AF [22]. and in many studies with the relation of INR levels and MES incidence and number (load), with various diseases rather than AF; like, prosthetic heart valve anticoagulation, and eventually stated their significant effect in MES [23, 24].

Since the advent of NOACs; as new drugs with the same therapeutic effect and less adverse reactions, comparison between vitamin K antagonist anticoagulation (VKA), and NOACs still until nowadays occurs, mostly respecting and dealing with the direct clinical thromboembolic events aspects, and many aspects need to be researched. According to some; apixaban with Aspirin resulted in a significant reduction in cerebral MES in Rabbits, derived from carotid arterial thrombosis [25]. While in some studies; comparing the use of uninterrupted anticoagulation with VKA or NOACs noticed that, a significant but comparable number of the patients in both groups still experience the evidence of silent cerebral micro embolic event (SCE) [26]. So the issue is still debated; at 2018, authors stated that, in spite of NOACs, is associated with higher ischemic stroke risk together with lower risk of hemorrhage than warfarin use, but

patients on warfarin are more strongly anticoagulated [27]. And other studies stated that; NOACs anticoagulants have been proven to be safer and equally effective compared with warfarin in stroke prevention for patients with non-valvular AF [28]. Rivaroxaban (xalerto) 20 mg /day was non inferior than warfarin (with targeted INR 2 – 3) [29]. Moreover in some; NOACs are superior to warfarin for the prevention of stroke and systemic embolism in patients with AF and significant reduction in intra cerebral hemorrhage and mortality [10].

In a study of the clinical relevance of MES detection in non valvular AF patients were anticoagulated with rivaroxaban, dabigatran and warfarin; and concluded that, screening for MES can give us an idea for the stroke risk, as there are no differences between the three drugs used [29]. In the current study; with the comparison to the previous studies, rivaroxaban 15 mg /day in comparison to warfarin (with target INR 2 – 3), regarding the MES incidence and number, there was no significant difference and rivaroxaban is non-inferior to warfarin.

## 5. Conclusion

A symptomatic subclinical cerebral micro embolizations; were detected in non valvular AF patients, without statistical difference between the use of warfarin and NOACs. Rivaroxaban is non-inferior to warfarin use as anticoagulation in non valvular AF regarding the effect on MES detection and load, and so thromboembolic risk reduction.

## 6. Future Recommendations

Another study with a more longer time and larger patients scale; concerning with MES (load) number and clinical thromboembolic event, to put a cut point of MES number, at which the patient will be under the highest embolic risk, to judge their use as a follow up monitoring test.

## Author Contributions

Zaki MA. Data collection, critical review and manuscript revision.

EL-Bahnasy HA. Data collection, critical review and manuscript revision.

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