Cardiology and Angiology: An International Journal

10(3): 32-38, 2021; Article no.CA.70437
ISSN: 2347-520X, NLM ID: 101658392

Evaluation of Time in Therapeutic Range of Patients with Non-Valvular Atrial Fibrillation on Oral Anticoagulation with Vitamin K Antagonist in Delta Region

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/CA/2021/v10i330172
Editor(s):
(1) Prof. Francesco Pelliccia, University La Sapienza, Italy.
Reviewers:
(1) José D. Méndez, Diseases.National Medical Center, Mexico.
(2) Alexandr Ceasovschih, Grigore T. Popa University of Medicine and Pharmacy, Romania.
Complete Peer review History: http://www.sdiarticle4.com/review-history/70437

Original Research Article

Received 20 April 2021
Accepted 25 June 2021
Published 26 June 2021

ABSTRACT

Background: Non-valvular atrial fibrillation (AF) is the most common cardiac arrhythmia with a prevalence as high as 1.5±2.0% in the general population. This arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world. The aim of study was to evaluation of the patients in delta region who have non-valvular AF and on oral anticoagulation with Vitamin K antagonist as regard the time they spend within therapeutic range.
Patients and Methods: A total of 100 patients were included in this study for evaluation of the patients in delta region who have non-valvular AF and on oral anticoagulation with Vitamin K antagonist as regard the time they spend within therapeutic range.
Results: Our study showed that only 35% achieved the recommended TTR (percent time in therapeutic range) above 60% from studied risk factors, none showed statistical significance.
Conclusions: The quality of anticoagulant control was lower that reported in European countries with a significant proportion of patients had TTR below 60%.

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Keywords: Non-Valvular atrial fibrillation; oral anticoagulation; Vitamin K antagonist; delta region.

1. INTRODUCTION

Non-valvular atrial fibrillation (AF) is the most common cardiac arrhythmia with a prevalence as high as 1.5±2.0% in the general population. This arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world [1].

As reported in several precedent studies, an increase in age is a risk factor in patients with AF. Thus, as the population is aging, the incidence rate of AF is likely to increase, and hospital utilization rate and the mortality rate are expected to increase as well. In addition, AF is a disease that becomes a risk factor for stroke and systemic embolism [2]. In particular, strokes accompanied by AF showed a higher mortality rate and hospitalization costs than strokes not accompanied by AF [3].

The 2014 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guidelines recommend medicines for preventive treatment according to the risk of a stroke for a patient with AF [4]. According to a systematic literature review of 54 studies reported from 1998 to 2008 [5], less than 70% of patients were treated with an anticoagulant even after they were determined to be in a high-risk group by the CHA_2DS_2 score used to determine the stroke risk level, and 2/3 of the studies reported that less than 60% of the patient group with a history of stroke or transient ischemic attack were treated.

Vitamin K antagonist (VKA), which is considered to be a standard of care among the anticoagulant medicines to prevent strokes in patients with AF, has a very narrow therapeutic range, thus regular monitoring is required to avoid potential adverse events [6].

Guidelines recommend continuous anticoagulation for the majority of AF patients, either by non-vitamin k antagonist oral anticoagulants (NOACs) or Vitamin K antagonists, such as warfarin [7]. Particularly warfarin therapy may be challenging due to a narrow therapeutic range; outside it, patients are exposed to an increased risk of either thromboembolism or hemorrhage. A generally accepted quality measure in warfarin therapy is the time patients spend within the therapeutic range (percent time in therapeutic range; TTR) [8].

The aim of this study was to assess evaluation of the patients in delta region who have non-valvular AF and on oral anticoagulation with Vitamin K antagonist as regard the time they spend within therapeutic range.

2. PATIENTS AND METHODS

Our observational study was conducted on 100 patients who have non-valvular AF and on oral anticoagulation with Vitamin K at the department of cardiology, Tanta university hospitals after approval from Ethical Committee and obtaining informed written consent.

Exclusion criteria were patients had valvular AF (moderate to severe mitral stenosis), prosthetic valve, non-valvular AF on new oral anticoagulants (NOACS) or Patient refusal.

The study patients were divided into two groups according to response, patients with TTR less than 60 were considered as non-responder (group I, n=65). Patients with TTR ≥ 60 were considered as responder (group II, n=35).

All patients in this study were subjected to the following: History taking, clinical examination, twelve-lead electrocardiogram, transthoracic echocardiography and laboratory investigation.

The patient was diagnosed as AF by ECG then echocardiography was done to exclude valvular AF, the patient was assessed for risk of thromboembolism by CHA_2DS_2_VASc score [9] which include congestive heart failure, hypertension, age more than 65 years, diabetes mellitus, stroke, vascular disease, sex (female gender), the patient with CHA_2DS_2_VASc score 1 or more was anticoagulated with warfarin according to ESC guidelines 2016 [10] then the patient received anticoagulation by Vitamin K antagonist (warfarin) then the patient received anticoagulation by Vitamin K antagonist (warfarin) and follow up was by INR every week until patient reach therapeutic level and then INR was followed every month until 6 months then time in therapeutic range was calculated which is the time patients spend within the therapeutic range [11].

2.1 Statistical Analysis

The data were analyzed using MedCalc ver. 18.2.1 (MedCalc, Ostend, Belgium). The mean,

standard deviation (SD) and range for parametric numerical data, while Median and Inter-quartile range (IQR) for non-parametric numerical data, whereas numbers and percentages were used to represent non-numerical data. Tests of significance (Mann-Whitney's, Chi square, multiple and logistic regression analysis, and ROC Curve analysis) were used. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable. P-values less than 0.05 (5%) was considered to be statistically significant.

3. RESULTS

There were no statistically significant differences in age, BMI, gender, smoking and risk factors between study groups (Table 1).

There were no statistically significant regarding the CHA_2DS_2-VASc score and type of AF between study groups (Table 2).

There were no statistically significant regarding the echocardiographic parameters (EF%, LA diameter, estimated pulmonary artery pressure, mitral valve state, RWMA, left ventricular hypertrophy, aortic valve state, tricuspid valve state) between the study groups. **(**Error! Reference source not found (Table 3).

4. DISCUSSION

Large variations in TTR occur between individuals, sites, and countries, all of which affect patient outcomes. Hence, we conducted the current study to evaluate time in therapeutic range in patients with non-valvular AF patients on oral anticoagulant Vitamin K antagonist treatment in delta region.

In ROCKET-AF trial, 6983 patients taking warfarin, recruited from 45 countries grouped into 7 regions, the overall TTR mean was 55.2.in East Asia mean TTR was 50.5, in India mean TTR was 35.9, in Eastern Europe mean TTR was 49.7, in Western Europe mean TTR was 63, in South Africa mean TTR was 54.8, in Latin America mean TTR was 55.2 and in North America mean TTR was 64 [12].

In the RE-LY trial, 18 113 patients were recruited from 951 clinical centers in 44 countries; the mean of TTR was 67.2. RE-LY trial also reported mean TTR across some European [Sweden (77%), Italy (77), Greece (56), Belgium (66) Finland and Australia (74%)] and Asian countries [Taiwan (44), china (55), Korea (55), Malaysia (56) and Hong Kong (64)] [13].

Table 1. Patient characteristics in the study groups

		Group I (n=65)	Group II (n=35)	P
Age		64 ± 9	63 ± 10	0.651
BMI		24.9 ± 2.6	24.6 ± 3.6	0.625
Gender	Males	26 (40.0%)	12 (34.3%)	0.574
	Females	39 (60.0%)	23 (65.7%)	
Smoking		14 (21.5%)	9 (25.7%)	0.636
Diabetes Mellitus		19 (29.2%)	11 (31.4%)	0.819
Hypertension		61 (93.8%)	32 (91.4%)	0.651
Ischemic Heart Disease		26 (40.0%)	14 (40.0%)	0.567
Cardiomyopathy		8 (12.3%)	6 (17.1%)	0.506
Family History		25 (38.5%)	16 (45.7%)	0.482

BMI: body mass index

Table 2. CHA_2DS_2-VASc score, and type of AF between study groups

		Group I (n=65)	Group II (n=35)	P
CHA_2DS_2-VASc Score	≤2	25 (38.5%)	18 (51.4%)	0.212
	>2	40 (61.5%)	17 (48.6%)	
Type of AF	Paced	7 (10.8%)	2 (5.7%)	0.605
	Paroxysmal	30 (46.2%)	19 (54.3%)	
	Permanent	28 (43.1%)	14 (40.0%)	

Table 3. Echocardiographic parameters between study groups

Groups	Group I (n=65)	Group II (n=35)		P
EF %	58.4 ± 9.5	58.7 ± 9.3		0.850
LA Diameter	4.4 ± 0.7	4.2 ± 0.7		0.198
Estimated Pulmonary Artery Pressure	26.0 ± 12.0	25.0 ± 11.0		0.738
Mitral Valve	Normal	29 (44.6%)	12 (34.3%)	0.712
	Mild MR	23 (35.4%)	13 (37.1%)	
	Moderate MR	10 (15.4%)	8 (22.9%)	
	Severe MR	3 (4.6%)	2 (5.7%)	
RWMA		20 (30.8%)	15 (42.9%)	0.227
Left Ventricular Hypertrophy		13 (20.0%)	8 (22.9%)	0.738
Aortic Valve	Normal	58 (89.2%)	26 (74.3%)	0.122
	Mild AR	6 (9.2%)	5 (14.3%)	
	Moderate AR	1 (1.5%)	3 (8.6%)	
	Mild AS	0 (0.0%)	1 (2.9%)	
Tricuspid Valve	Normal	28 (43.1%)	16 (45.7%)	0.976
	Mild TR	18 (27.7%)	9 (25.7%)	
	Moderate TR	12 (18.5%)	7 (20.0%)	
	Severe TR	7 (10.8%)	3 (8.6%)	

EF: ejection fraction, LA: left atrium, MR: mitral regurge, AR: aortic regurge, AS: aortic stenosis, TR: tricuspid regurge

In ARISTOTLE trial, 18 201 patients with AF were randomized to apixaban or warfarin and were followed for at least 12 months, the mean TTR was 66 [13].

A study investigated the TTR among 4987 adult Turkish patients. TTR of patients was 49.52. 55.3% had HTN, 23.2% had coronary artery disease, and 24.5% had congestive heart failure, 20.8% were smoker and 38.4% had non-valvular AF [14].

An Iranian study on 470 patients with non-valvular AF with a mean age 58.02 years, 60.2% women and majority of population were above 75 years. 142 cases had ischemic heart disease 142 had HTN and 104 had DM. their mean TTR was 54.9 [15].

A study in Kuwait included 369 patients with non-valvular AF with a mean age 62.89 years, 56% women, 78% had hypertension and 58% had diabetes. TTR by Rosendaal method was 52 [16].

A cross-sectional study in Eastern Switzerland, 332 patients with non-valvular AF and on Vitamin K antagonist treatment were followed for at least 6 months. 202 patient achieved TTR above 65% which represent 61% of patients included in the study, 62% male and mean age was 74 years [17].

In comparison to our study, a retrospective analysis of 377 Portuguese treated with Vitamin K antagonists. The mean age was 71 years, and 59.4% of the patients were male. 26% had DM, 67% had HTN, and 14.9% had ischemic heart disease. Most of the patients had non-valvular AF (72.4%), while valvular AF (19.1%) and venous thromboembolic disease (3.4%) were less common. The average CHA_2DS_2-VASc was 3.58. Mean TTR was 59.3 in non-valvular AF group vs. 64 in valvular AF group [18].

Many reasons may account for the differences in TTR across countries. Granger et al. [19] showed that age, gender, lower income, black race, frequent hospitalizations, associated drugs intake, active cancer, substance abuse, psychiatric disorders, dementia, and chronic liver disease to all be independently associated with lower TTR.

Interestingly, the setting of warfarin management has also been shown to impact on the quality of anticoagulation control.

A large systematic review included 67 studies with a total of 906 patients to evaluate which

study-level factors significantly influenced anticoagulation control. They reported patients from community practices showed significantly worse anticoagulation control than those from anticoagulation clinics [19].

Another meta-analysis to evaluate the efficacy of specialty clinic versus usual care by community physicians on anticoagulation control, Patients in anticoagulation clinics had an average TTR of 63 % compared to 51 % for individuals monitored in community practice [20].

The cut-off for a good response in NICE guidelines was TTR above 65% while it was above 70% in European guidelines [7].

In large Swedish registry, analysis of 40 449 patients showed low risk of complications reported in well managed AF patients [21]. Their cut-off was TTR above 70% which is higher than the cut-off of the current study.

ESC guidelines change the cut-off point of good anticoagulation control with Vitamin K antagonists from 65% to 70% and treatment with Vitamin K antagonist with high TTR (>_70%) could be as effective as novel oral anticoagulants in preventing adverse outcomes [22].

In FANTASIIA registry, DM, PAD, and HAS-BLED score were independently related with poor anticoagulation control [23]. Unlike our results, in which we couldn't prove association between DM and anticoagulation.

Similarly, in cross sectional study done by Farsad et al. [15] on a total of 470 patients, there were no significant differences in TTR between male and females (p = 0.38).

In contrary to our results, Melamed et al. [24] studied TTR in 906 patients diagnosed with AF in the United States who were treated with warfarin for at least 6 months. They concluded that poor control (TTR < 60% in their study) was significantly associated with females.

Caldeira et al. [18] reported that the female gender was the only characteristic that was significantly associated to poor anticoagulation control (TTR < 60%) in the multivariable regression analysis with an odds ratio 1.73 and 95% confidence interval 1.14-2.62 (p = 0.01).

Limitation of this study are a small sample size with single center study and short period of follow-up.

5. CONCLUSIONS

Mean TTR of 44.6 (±29.1) and 65% were non-responder (a TTR less than 60) in Egyptian patients diagnosed with non-valvular AF who were receiving Vitamin K antagonists therapy. We couldn't identity factors that might be related to poor anticoagulant control among included patients.

CONSENT AND ETHICAL APPROVAL

Our observational study was conducted on 100 patients who have non-valvular AF and on oral anticoagulation with Vitamin K at the department of cardiology, Tanta university hospitals after approval from Ethical Committee and obtaining informed written consent.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/70437