Real-Life International Normalized Ratio Profile in Patients with Non-Valvular Atrial Fibrillation Prescribed Vitamin K Antagonist

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Coagulation status with vitamin K antagonists (VKAs) needs to be monitored carefully to ensure maximal efficacy with minimal complication rates.

Aim. To study the international normalized ratio (INR) values in patients on VKAs in selected area, find out which patient characteristics that is associated with good INR control and calculation of the time in the therapeutic range (TTR) according to the number of INR/Patient.

Material and methods. A total of 200 patients with non-valvular atrial fibrillation prescribed vitamin K antagonist as anticoagulant were evaluated. They were divided into two groups: group I with TTR⩾65% (n=93) and group II with TTR<65% (n=107). Stroke and hemorrhagic risks were calculated by means of the CHA_2DS_2-VASc score and HAS-BLED score, respectively. Presence of comorbid diseases was assessed by the Charlson index. TTR was calculated using Rosendaal method.

Results. Patients in group I (TTR⩾65%) were younger (p<0.001), more often men (p<0.074) with a high level of education (p<0.001), had lower stroke and hemorrhagic risks (mean CHA_2DS_2-VASc score was 1.0 and HAS-BLED score – 0.0), and also had fewer comorbidities (mean Charlson index was 0.0; p<0.001) compared to patients in group II (TTR<65%). The rate of inadequate control with VKAs (TTR<65) was 52%. Multivariate logistic regression analysis was done to see the significant independent predictors for a good INR control i.e. TTR⩾65%. It was found that high level of education compared to lower levels is the only significant independent predictor for obtaining good INR control (odds ratio=133, 95% confidence interval 34.24-514.44, p<0.001)

Conclusion. It was found that high level of education compared to lower levels is the only significant independent predictor for obtaining good INR control.

Keywords: vitamin K antagonists, international normalized ratio, coagulation.

For citation: Farag S.I., Arafa O.S., Hassan A.A.E., Mashhour H.M., Bendary A.M. Real-Life International Normalized Ratio Profile in Patients with Non-Valvular Atrial Fibrillation Prescribed Vitamin K Antagonist. *Rational Pharmacotherapy in Cardiology* 2020;16(4):522-527. DOI:10.20996/1819-6446-2020-08-14

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Received: 08.12.2019
Accepted: 21.01.2020

Introduction

Vitamin K antagonists (VKAs), although no longer the only option, remain the pharmaceutical group more widely employed, due to their relatively low cost and grate experience. Coagulation status with VKAs needs to be monitored carefully to ensure maximal efficacy with minimal complication rates. The international normalized ratio (INR) is used to express the coagulation state, and the maximum efficacy is achieved at rates from 2 to 3. Several formulas have been proposed to assess the quality of anticoagulation. Among those formulas, the time in the therapeutic range (TTR) is the more extended and has proven to be a major determinant of the efficacy and safety of anticoagulation with VKAs [1].

VKAs have a narrow therapeutic range (INR 2-3), and literature analysis reveals poor quality of anticoagulation control [2], but it also shows important differences among countries [1].

In patients with suboptimal anticoagulation control with VKAs, strategies aimed to improve this control must be undertaken, including switching to a non-vitamin K antagonist oral anticoagulant (NOAC), however, this occasional may not be possible due to many factors such as pregnancy and advanced degrees of renal impairment [3].

Therefore, we thought that it may be important and useful if we could evaluate the quality of anticoagulation using VKAs among our patient population.

This study aimed to study the INR values in patients on VKAs in the selected area; find out which patient characteristics that are associated with good INR control.

Material and methods

Study design and patients selection. A single center, cross-sectional observational study was conducted at cardiology department at Benha University Hospital, Egypt during the period from October 2018 to September 2019 after approval from the Ethics Committee. The study enrolled 200 patients with non-valvular atrial fibrillation receiving VKAs as an oral anticoagulant treatment for thromboembolic prevention. An informed written consent was taken from all patients.

Patients were divided into two groups according to TTR:

1) Group I: patients with TTR⩾65%;
2) Group II: patients with TTR<65%.

The study was designed to screen not less than 2000 INR laboratory tests from these patients.

Patients less than 18 years, hospitalized at the moment, or if they are participating in a clinical trial and unwilling or unable to provide written informed consent were excluded.

The collected data were age, gender, risk factors (hypertension, diabetes mellitus, smoking, obesity, dyslipidemia), history (stroke/transient ischemic attack [TIA], coronary artery disease [CAD], chronic kidney disease [CKD], chronic hepatic diseases), education level, left ventricular ejection fraction (LVEF), stroke and hemorrhagic risks (were calculated by means of the CHA_2DS_2-VASc score and HAS-BLED score, respectively). Presence of comorbid diseases was assessed with the Charlson index. TTR was calculated using Rosendaal methods.

Laboratory investigations included complete blood count, blood sugar, serum creatinine, Hb_{A1C}, ALT and AST. Coagulation status was determined by sequential INR values as per the local protocol. The INR test was done once per month to all patients for one year follow up. Every patient had at least 10 values registered in the study.

Statistical analysis. All continuous variables were presented as mean±SD or median (range). Discrete variables were presented as values (percentages). Baseline characteristics were compared between patients with adequate (TTR⩾65%) or inadequate (TTR<65%) VKA control. Student's t-test and Mann-Whitney test used to compare mean of two groups of quantitative data of parametric and non-parametric, respectively. Categorical data were compared using the chi-square test. Logistic regression analyses were employed for univariate analyses and for multivariate adjustment. Multivariate models were performed including variables with recognized clinical relevance with VKA control and those with a $p<0.1$ in the univariate analysis. Results were presented as odds ratios (ORs) and 95% confidence intervals (95%CIs). A 2-sided value of $p<0.05$ considered to be significant for all analyses. All statistical analyses were performed using computer program SPSS (Statistical package for social science) version 20 (SPSS Inc., Chicago, IL).

The Rosendaal method uses linear interpolation to assign an INR value to each day between successive observed INR values [4]. Rosendaal method for %INR in range – method which INR specific person-time is calculated by incorporating the frequency of INR measurements and their actual values, and assuming that changes between consecutive INR measurements are linear over time. Poor anticoagulation control is defined as an estimated TTR<65% [5].

Results

A total of 248 patients with non-valvular atrial fibrillation receiving VKAs as an oral anticoagulant treatment for thromboembolic prevention were evaluated. Forty-eight patients were excluded as they did not complete registry of INR controls, the final sample for the analysis of quality of anticoagulation with VKAs consisted of 200 patients.

Participants were divided into two groups according to TTR:

1) Group I: 93 patients (46.5%) with TTR⩾65%;

2) Group II: 107 patients (53.5%) with TTR<65%.

Baseline clinical characteristics of study groups. The mean age for group I was 41.53±14.83 and 52.69±15.82 years for group II with statistically significant difference (p<0.001). 50 patients (53.8%) were male in group I compared to 44 patients (41.1%) in group II with no significance difference (p<0.074). High level of education was more prevalent in group I (p<0.001). Chronic diseases (diabetes mellitus, hypertension, smoking, dyslipidemia, and obesity) were prevalent in group II. History of CAD, stroke/TIA, CKD, and chronic hepatic disease were highly prevalent in group II (table 1).

Laboratory investigation and LVEF of studied groups are illustrated in (table 2).

CHA_2DS_2-VASc score stroke risks assessment: the median of the score was 1.0 with the range between (0.0-3.0) for group I while it was 2.0 with the range between (1.0- 4.0) for group II with statistically significant difference (p<0.001).

HAS-BLED score hemorrhagic risks assessment: the median was 0.0 with the range between (0.0-1.0) for group I while it was 1.0 with the range between (0.0-3.0) for group II, with statistically significant difference (p=0.001).

Charlson comorbidity index: the median was 0.0 with the range between (0.0-2.0) for group I and 3.0 with the range between (1.0-5.0) for group II,

Table 1. Comparison between group I and II according to baseline clinical characteristics

Characteristics	Group I (TTR⩾65%; n=93)	Group II (TTR<65%; n=107)	Statistical test	p
Age, years	41.5 ±14.8	52.7 ±15.8	5.13[a]	<0.001
Male, n (%)	50 (53.8)	44 (41.1)	3.19[b]	0.074
Education level, n (%)				
Low	0	37 (34.6)		
Middle	19 (20.4)	66 (61.7)	125.44[b]	<0.001
High	74 (79.6)	4 (3.7)		
Chronic diseases, n (%)				
Diabetes mellitus	20 (21.5)	50 (46.7)	13.92[c]	<0.001
Hypertension	33 (35.5)	45 (42.1)	0.90[c]	0.34
Smoking	23 (24.7)	32 (29.9)	0.67[c]	0.41
Dyslipidemia	23 (24.7)	35 (32.7)	1.54[c]	0.22
Obesity	25 (26.9)	43 (40.2)	3.93[c]	0.048
History, n (%)				
CAD	24 (25.8)	41 (38.3)	3.55[c]	0.06
Stroke/TIA	9 (9.7)	25 (23.4)	6.61[c]	0.01
CKD	12 (12.9)	34 (31.8)	10.01[c]	0.002
Chronic hepatic disease	15 (16.1)	36 (33.6)	8.04[c]	0.005

Values are mean±standard deviation or number (%)

[a]Student's t-test, [b]chi-square test, [c]Mann-Whitney test

TTR – time in the therapeutic range, CAD – coronary artery disease, TIA – transient ischemic attack, CKD – chronic kidney disease

Table 2. Comparison between group I and II according to lab results and left ventricular ejection fraction

Characteristics	Group I (TTR⩾65%; n=93)	Group II (TTR<65%; n=107)	Mann-Whitney test	p
LVEF, %	60.0 (54.0-64.0)	55.0 (46.0-61.0)	3.89	<0.001
Hb, g/dl	11.64 (10.64-12.75)	11.6 (10.78-12.94)	0.29	0.77
Hb_{A1C}, %	4.79 (4.21-5.21)	4.9 (4.31-6.9)	2.45	0.014
Serum creatinine, mg/dl	1.08 (0.87-1.2)	1.1 (0.9-1.64)	2.34	0.019

Values are median (interquartile range)

TTR – time in the therapeutic range, LVEF – left ventricular ejection fraction, HB – hemoglobin

with statistically significant difference (p<0.001). *TTR%*: the median of TTR% was 68.0 % with the range between (67.0-70.0) for group I while in group II was 52.0% with the range between (48.0-57.0) with statistically significant difference (p<0.001).

Multivariate logistic regression analysis was done to see the significant independent predictors for a good INR control i.e. TTR⩾65%.

It was found that high level of education compared to lower levels is the only significant independent predictor for obtaining good INR control (OR=133, 95%CI 34.24-514.44, p<0.001) (table 3).

Discussion

In our study, patients in group I were younger, more often men with a high level of education, had lower stroke and hemorrhagic risks, and had fewer comorbidities compared to patients in group II. However, when adjusting to all these previously mentioned factors in a multivariate logistic regression model, it was found that high level of education compared to lower levels is the only significant independent predictor for obtaining good INR control (OR=133, 95%CI 34.24-514.44, p<0.001). The observed very high OR for high educational level together with the very wide CI is due to the small sample size of the study. This small sample size has led also to the unexpected results that many other predictors (e.g. thromboembolic and bleeding indices) felt short of showing a significant association with good INR control. In our study, the rate of inadequate control with VKAs (TTR<65) is 52%. These results agree with the result obtained by Vicente et al. [6] who studied the relation between good INR control and high education and found that the rate of inadequate control with VKAs (TTR<65) was 54%.

Table 3. Multivariate logistic regression analysis for prediction of good international normalized ratio control

Characteristics	OR (95%CI)	p
Age, years	1.01 (0.95-1.08)	0.772
Female gender	0.63 (0.13-2.98)	0.56
Chronic kidney disease	3.60 (0.12-107.77)	0.46
Chronic hepatic disease	1.1 (0.1-11.83)	0.937
High education	132.72 (34.24-514.44)	<0.001
CHA_2DS_2-VASc score	1.73 (0.55-5.46)	0.354
HAS-BLED score	0.74 (0.21-2.68)	0.652
Charlson index	0.71 (0.25-1.98)	0.507

INR – international normalized ratio, OR – odds ratio, CI – confidence interval

A large observational study involving 6250 patients from France, Germany, Italy, and the United Kingdom treated with VKAs showed that the rates of inadequate control were 52% in France, 56% in Germany, 54% in Italy, and 45% in the United Kingdom [7]. This implies that our rates agree with the international rates of poor anticoagulation. In contrast, a more recent study showed TTR values between 70.3% and 81.4% among Western European countries [8], as this study is representative only of physicians with a cardiological background.

Our results were in accordance with the result obtained by X. Li et al. [9] in which investigators showed that TTR was strongly related to both the patients' anticoagulation knowledge level and the patients' educational level.

The current study results are also similar to the results obtained by E.O.Y.L. Tang et al. [10] who found that knowledge was a determinant of anticoagulation control, and more attention should be given to the education of elderly and illiterate patients among population of Hong Kong.

In contrast to our findings, a study by A.B. Platt et al. [11] revealed poor compliance with anticoagulants in patients with higher educational level. This apparent controversy was explained by the decreased trust in physicians among more educated subjects. Another controversial study conducted in the US by W.L. Baker et al. [12] reported that there was no significant relationship between patient warfarin knowledge and INR control.

In our study, there was a statistically significant difference between studied groups as regard CKD and Charlson index ($p=0.002$ and $p<0.001$, respectively). These results agree with the results obtained by R. Agnes et al. [13].

The current study showed a statistically significant difference between studied groups as regard age ($p<0.001$) being younger in group I (TTR$\geqslant$65%) which is discordant with the results obtained by Skeppholm and Friberg [14] who showed that younger patients spent more time out of therapeutic range than older patients.

Conclusion

In our center, more than one half of patients with a clinical indication for oral anticoagulation (53%) were poorly controlled (TTR<65%). This is in line with most (but not all) international figures. It was found that high level of education compared to lower levels is the only significant independent predictor for obtaining good INR control (TTR$\geqslant$65%). So, much effort is needed to educate the patients about good control of INR and how to adjust dose of warfarin.

Study limitation

The main limitation was a relatively small sample size. The results were obtained from a single medical center. The follow-up duration was limited. Aspects that could lead to INR variations, such as diets and use of herbal and/or dietary supplements, were not assessed. Larger studies with longer follow up period are required for more valid results.

Disclosures. All authors have not disclosed potential conflicts of interest regarding the content of this paper.

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