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Real –life International Normalized Ratio (INR) profile ; Egyptian study

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Abstract

Warfarin remains widely used by patients with cardiovascular diseases].Due to high interindividual variability, the anticoagulant activity of warfarin has to be monitored using the international normalized ratio (INR).The most widely recommended approach for evaluating the quality and safety of anticoagulation is to estimate the percentage of time in therapeutic range (TTR). It was a single center, cross-sectional observational study that was conducted at cardiology department at Benha University Hospital. This study was designed to: Study the INR values in patients on VKAs in the selected area., Calculation of the time in the therapeutic range (TTR) when is possible according to the number of INR/Patient., Find out which patient characteristics that are associated with good INR control. Patients were subdivided into two sub groups; sub group I : patients with TTR ≥ 65% , sub group II : patients with TTR < 65% .The study was designed to screen not less than 2000 INR laboratory tests from these patients.

Mean TTR was 60.27%+_24.48% for the Rosendaal method. After multivariate adjustment,variables associated with good anticoagulation control were university studies (OR: 1.99, 95% CI: 1.08-3.64), chronic hepatic disease (OR: 8.15, 95% CI: 1.57-42.24), low comorbidity expressed as Charlson index(OR: 0.87, 95% CI: 0.76-0.99) , no previous cardiac disease (OR: 0.64, 95% CI: 0.41-0.98), lower risk of bleeding assessed as hypertension, abnormal enal/liver function, stroke, bleeding history or predisposition, rlabile international normalized ratio, elderly age, and use of drugs or alcohol { HAS-BLED} (OR: 0.81, 95% CI: 0.69-0.95), and lower heart rate OR: 0.99, 95% CI: 0.98-0.99). Our study shows a rate of inadequate control with AVKs of 54%, and 46% of the patients spent more than half the time outside the therapeutic range. .In our study, having a university degree was associated with adequate anticoagulation control.We believe that higher education helps patients to understand the importance of anticoagulant treatment adherence.

Keywords: Warfarin, International normalized ratio (INR), Time in therapeutic range (TTR), Education and control.

1.Introduction

Warfarin remains widely used by patients with cardiovascular diseases [1].Due to high interindividual variability, the anticoagulant activity of warfarin has to be monitored using the international normalized ratio (INR) to ensure that an adequate yet safe dose is taken [2,3]. The therapeutic and adverse effects of warfarin depend largely on the percentage of time during which the INR is within the therapeutic range [4].The most widely recommended approach for evaluating the quality and safety of anticoagulation is to estimate the percentage of time in therapeutic range (TTR), that is to say the time spent within the therapeutic international normalized ratio limits [5,6]. The estimated time spent in the TTR was assessed by the Rosendaal method Indeed, oral anticoagulation can lead to adverse outcomes (bleeding or thromboembolic events) directly related to INR outside the therapeutic window [7].With this study we sought to assess the prevalence of poor anticoagulant control in patients under VKA treatment in the prevention of stroke. Poor anticoagulation control was defined as an estimated TTR <65%.[8].

2. patients and methods

It was a single center, cross-sectional observational study that was conducted at cardiology department at Benha University Hospital during the period from October 2018 to april 2019. This study was designed to: Study the INR values in patients on VKAs in the selected area., Calculation of the time in the therapeutic range (TTR) when is possible according to the number of INR/Patient., Find out which patient characteristics that are associated with good INR control.

A total of 994 patients receiving vitamin K antagonists (VKAs) as an oral anticoagulant treatment for thromboembolic prevention were evaluated. After the exclusion of 46 patients with incomplete registry of INR controls, the final sample for the analysis of quality of anticoagulation with VKAs consisted of 948 patients. Patients were excluded for age <18 years, hospitalization at the moment, or if they were participating in a clinical trial. Patients unwilling or unable to provide written informed consent were also excluded. Coagulation status was determined by INR values of the 6 months previous to the study entry. The INR values were registered together with other clinical and analytical variables

2.1 Patient's characteristics

Age ,Gender ,Risk factors (hypertension, diabetes mellitus, smoking, obesity, dyslipidemia) History (Stroke/TIA, CAD, CKD,

chronic hepatic disease) ,Indication for VKA (AF, DVT, prosthetic valve), Education level, LVEF, Presence of comorbid diseases was assessed with the (Charlson index),TTR.

2.2 study design

Patients were subdivided into two sub groups sub group I : patients with TTR ≥ 65% , sub group II : patients with TTR < 65% . The study was designed to screen not less than 2000 INR laboratory tests from these patients.

2.3 Statistical analysis

All continuous variables showed normal distribution and are presented as mean ± SD. Discrete variables are presented as values (percentages). Baseline characteristics were compared between patients with adequate (TTR ≥65%) or inadequate (TTR < 65%) VKA control.

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 value < 0.1 in the univariate analysis. Results are presented as odds ratios(ORs) and 95% confidence intervals (95% CIs). A 2- sided P value of <0.05 was considered to be significant for all analyses. All statistical analyses were performed using SPSS version13.0 (SPSS Inc., Chicago, IL).

3.Results and discussion

Mean age of the study population was 73.8 ± 9.4years, and42.5% of the patients were women.

Unadjusted analyses Table (1) revealed higher
control rates for higher education level; absence of cardiovascular risk factors: hypertension (78.52%
TTR ≥65% vs 83.69% TTR < 65%; OR: 0.71, P =0.04), diabetes mellitus (27.25% TTR ≥65% vs 34.37% TTR < 65%; OR: 0.72, P =0.02), less comorbidity expressed as lower mean Charlson index (1.09 TTR ≥65% vs 1.30 TTR < 65%; OR: 0.86, P=0.01), lower thrombotic risk (CHADS2: 2.22TTR ≥65% vs 2.40 TTR < 65%; OR: 0.89, P = 0.02) and hemorrhagic risk(HAS-BLED: 1.90 TTR ≥ 65% vs 2.08 TTR < 65%; OR: 0.85, P = 0.01), and better glycemic control(glycated hemoglobin 6.10 TTR ≥65% vs 6.35 TTR < 65%; OR: 0.86, P = 0.02). Prevalence of poor anticoagulation control was 54% (515 patients with TTR < 65%). Mean TTR was 60.27% ± 24.48% for the Rosendaal method.

Each patient was 90.41± 36.72 days within the therapeutic range out of the 180 days of registry. After multivariate adjustment Table (2), variables associated with good anticoagulation control were university studies (OR: 1.99, 95% CI: 1.08-3.64), chronic hepatic disease (OR: 8.15, 95% CI: 1.57-42.24), low comorbidity expressed as Charlson index(OR: 0.87, 95% CI: 0.76-0.99) , no previous cardiac disease (OR: 0.64, 95% CI: 0.41-0.98), lower risk of bleeding assessed as HAS-BLED (OR: 0.81, 95% CI: 0.69-0.95), and lower heart rate (OR: 0.99, 95% CI: 0.98-0.99).

Our study shows a rate of inadequate control with AVKs of 54%, and 46% of the patients spent more than half the time outside the therapeutic range. The poor control of anticoagulation is of concern. Prognosis of patients under anticoagulant treatment has been proven to differ significantly according to INR control [9,10,11] and some strategies are now available to improve the quality of oral anticoagulation. Those strategies include the use ofcomputer-assisted dosing tools, self-monitoring, improve in patient compliance, use of dedicated anticoagulation clinics, genotype-guided dosing,
and switch to NOACs [9,12,13] .Causes of the low achievement of adequate anticoagulation are multiple, including underuse of strategies designed to improve control, therapeutic inertia, comorbidities, and socioeconomical variables that preclude the use of NOACs.

A large observational study involving 6250 patients from France, Germany, Italy, and the United Kingdom treated with VKAs and with available INR has recently been published. Good VKA control was defined as TTR >70%; the rates of inadequate control found were 52% in France, 56% in Germany, 54% in Italy, and 45% in the United Kingdom [14] .

Whereas an older meta-analysis including studies performed in the United States showed a mean TTR of 57% and 51% of time within range.[9]. A more recent study showed TTR values between 70.3% and 81.4% among Western European countries[15].

In our study, the variables associated with adequate VKA adjustment were higher education, expressed as having a university degree; low comorbidity, expressed as low Charlson index; no previous cardiac disease, lower risk of bleeding and chronic hepatic disease.

Classic studies evaluating compliance with anticoagulants revealed that younger age, male sex, or nonwhite race were factors associated with lack of compliance [16]. A more recent study revealed poor compliance with anticoagulants in patients with higher educational level, current employment, and lower scores on mental health or cognitive functioning[17]. This apparent controversy was explained by the decreased trust in physicians among more educated subjects, whereas poor

cognition has been associated with worse treatment adherence also in other areas.[18].

In our study, having a university degree was associated with adequate anticoagulation control.We believe that higher education helps patients to understand the importance of anticoagulant treatment adherence. he association we have found between education and control is not limited to university studies; on the contrary, we can see a progressive increase in the OR for adequate control for progressively higher levels of education Table (1).

The explanation of how chronic liver disease are associated with adequate VKA control is unclear.We speculate that both patients and physicians are more careful when anticoagulating patients with chronic liver disease.

We must acknowledge several study limitations, the main limitation was the relatively small sample size.,The result were obtained from a single medical center, No data exist about which patients had their INR controls performed by general practitioners, cardiologists, hematologists, or anticoagulation clinics, or by self-monitoring, Aspects that could lead to INR variations, such as diets and use of herbal and/or dietary supplements, were not assessed

Table (1) Univariate Comparison of the Population With Effect of Each Variable on the Quality of Anticoagulation

Variable	TTR <65% (n=515)	TTR ≥65% (n=433)	P Value
Age	73.75	74.33	0.34
Female sex	42.33	44.34	0.53
Education			
Cannot write (Ref)	6.99	4.39	
Primary	71.26	68.82	0.14
Secondary	15.34	15.24	0.16
Higher education	2.52	3.70	0.07*
University degree	3.88	7.85	0.00*
HTN	83.69	78.52	0.04*
Hyperlipidemia	53.40	56.58	0.33
DM	34.37	27.25	0.02*
Smoking history			
Nonsmoker (Ref)	61.36	62.82	
Current smoker	5.63	3.00	0.06
Recent former smoker (< 1 year)	2.33	2.08	0.76
Former smoker (< 1 year)	30.68	32.10	0.88
Chronic kidney disease	22.52	19.40	0.24
Chronic hepatic disease	0.58	1.85	0.09
stroke			
Ischemic	9.51	. 10.39	0.70
Hemorrhagic	0.78	0.69	0.88
CAD	20.78	19.63	0.66
CHA2DS2-VASc score, mean	3.87	3.70	0.10
HAS-BLED score, mean	2.08	1.90	0.01*
Charlson index	1.30	1.09	0.01*
LVEF, %, mean	58.09	58.53	
Hg, g/dL, mean	13.69	13.63	
sCr, mg/dL, mean	1.09	1.06	
HbA1c, %, mean	6.35	6.10	

Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; HbA1c, glycated hemoglobin; Hg, hemoglobin; HTN, hypertension; sCr, serum creatinine;
TTR, time in the therapeutic range.

Table (2) Multivariable Analysis, Variables Associated With TTR ≥65%.

Variable	OR	95% CI	P Value
University studies	1.99	1.08-3.64	0.03
Chronic hepatic disease	8.15	1.57-42.24	0.01
Charlson index	0.87	0.76-0.99	0.03
No previous cardiac disease	0.64	0.41-0.98	0.04
HAS-BLED	0.81	0.69-0.95	0.01

Abbreviations: CI, confidence interval; HASBLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly age, and use of drugs or alcohol; INR, international normalized ratio; OR, odds ratio; TTR, time in the therapeutic range.

4. Conclusion

Patients who receive VKAs to prevent stroke for AF spend <50% of the time within therapeutic range. Efforts must be made to improve efficacy and security of chronic anticoagulation.

It was found that high level of education compared to lower levels is the only significant independent predictor for obtaining good INR control (TTR ≥ 65%).

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