Cardiology and Angiology: An International Journal

9(4): 47-56, 2020; Article no.CA.62662
ISSN: 2347-520X, NLM ID: 101658392

Study of INR Profile in Patients on Vitamin K Antagonists in Tanta University Hospital Egypt

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Authors' contributions

This work was carried out in collaboration among all authors. Author DMAI participated in the following-up of the patients during hospitalization and patients follow up data and prepared the collected clinical data to be ready for statistical analysis and were the major contributor in writing the manuscript. Author MAA participated in the following-up of the patients in OPD and interpretation of data. Authors MMEM and EED analyzed and interpreted the patient data and share in writing the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/CA/2020/v9i430148
Editor(s):
(1) Prof. Stefano Omboni, Italian Institute of Telemedicine, Italy.
Reviewers:
(1) El Khazraji Abdelhak, Morocco.
(2) Marwan M. Merkhan, University of Mosul, Iraq.
Complete Peer review History: http://www.sdiarticle4.com/review-history/62662

Original Research Article

Received 01 September 2020
Accepted 06 November 2020
Published 23 November 2020

ABSTRACT

Background: Oral vitamin K antagonists are highly effective in the prevention and treatment of thromboembolic disease. Optimal use of these agents in clinical practice is challenged by their narrow therapeutic window. We aimed to Study the international normalized ratio values in patients on vitamin K antagonists to find out which patient characteristics that are associated with good INR control.
Methods: From June 2019 till May 2020 we studied 502 patients receiving vitamin K antagonists (VKAs) as an oral anticoagulant treatment for thromboembolic prevention for at least more than 1 month. The cases were classified into two groups according to time to therapeutic range (TTR); group I included 289 patients with TTR < 65 and group II that included 213 patients with TTR ≥ 65. We included patients with atrial fibrillation, prosthetic valve replacement or deep venous thrombosis.
Results: In univariate regression analysis, increasing age, male gender, lower level of education, diabetes mellitus, hypertension, smoking, chronic kidney disease, coronary artery disease and higher CHADS-VASC were revealed as risk factors for poor response (time to therapeutic range (TTR) < 65). With multivariate logistic regression analysis, lower level of education, HTN, smoking,

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CKD and higher CHADS-VASC were revealed as independent risk factors for poor response (TTR < 65).

Conclusion: This study indicated that, poor education, hypertension, smoking, chronic kidney disease, and high CHADS VSAC score were independent predictors of poor time to therapeutic range (TTC) control.

Keywords: Oral anticoagulant; INR; TTR.

ABBREVIATIONS

AF : Atrial Fibrillation
AUC : Area Under
CAD : Coronary Artery Disease
CKD : Chronic Kidney Disease
DM : Diabetes Mellitus
DVT : Deep Vein Thrombosis
HTN : Hypertension
INR : International Normalization Ratio
NOACs : New Oral Anticoagulants
OAT : Oral Anticoagulant Therapy
PE : Pulmonary Embolism
PT : Prothrombin Time
ROC : Receiver Operating Characteristic
TTR : Time to Therapeutic Range
VKA : Vitamin K Antagonist
WHO : World Health Organization

1. INTRODUCTION

Thrombosis is responsible for about 1 in every 4 deaths worldwide, and it is a significant participant to global disease burden and mortality [1,2]. Oral anticoagulant therapy (OAT) have a valuated rule in lowering morbidity and mortality results from thrombosis related conditions. The main treatment target for anticoagulation therapy is to reduce the risk of thromboembolic disease in patients with atrial fibrillation (AF), mechanical heart valves, deep vein thrombosis (DVT) and pulmonary embolism (PE), and concurrently lessening the risk of bleeding as a result of toxicity.

Available oral anticoagulants include the Vitamin K antagonists (VKAs) such as warfarin, and the newer/novel oral anticoagulants (NOACs) such as dabigatran [3,4]. Warfarin is available and low cost in comparison to other anticoagulant so it is the most frequently used oral anticoagulant worldwide, the narrow therapeutic index and the largely variable toxic dose that discriminates warfarin constitute a challenge to its effectual and safe use in clinical practice [5,6].

The efficacy and safety of therapy with VKAs (e.g. warfarin) depends mainly on careful monitoring and maintenance of the international normalization ratio (INR) within an optimal therapeutic range [7]. The importance of therapeutic monitoring of INR is further confirmed by the fact that warfarin therapy is contraindicated in cases when INR monitoring is not practical. Poor INR monitoring can result in toxicity, bleeding and increased mortality [8].

The recommended target therapeutic range for INR is 2.0–3.0 for most of the disease indications and 2.5–3.5 for those with cardiac valve prosthesis [9,10]. Supra-therapeutic OAT with warfarin, with a resultant effect of high INR, puts patients at hazard of bleeding or warfarin toxicity. On the other hand, sub-therapeutic anticoagulation and a subtherapeutic INR may not protect anticoagulated patients against thromboembolic events. Studies have shown that warfarin is largely under-prescribed; and this has resulted in increased morbidity and mortality among affected patients [9].

Studies have shown that for every bleeding episode caused by warfarin prevents 20 strokes. Thus, it can be concluded that the benefit of suitable use of warfarin outdo the risk of toxicity. The efforts to improve safe warfarin therapy, aside from careful INR monitoring, involves patient education, good record keeping and rational drug prescription [11]. Time in therapeutic range is a recommended measure of outcomes of oral anticoagulation management and a good way of assessment the quality of management of an anticoagulation clinic [12].

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 related, but not limited to financial issues and some biological barriers against the widespread reliance of NOACs such as pregnancy status and advanced degrees of renal impairment. Therefore, we thought that it may important and useful if we could evaluate the quality of anticoagulation using VKAs among our patient population [13].

2. METHODS

The study was conducted at our cardiology department over the period of 12 months in the period from June 2019 till May 2020 on 502 patients receiving vitamin K antagonists (VKAs) as an oral anticoagulant treatment for thromboembolic prevention for at least more than 1 month. The patients were divided into two groups according to time to therapeutic range (TTR); group I included 289 patients with TTR < 65 and group II that included 213 patients with TTR ≥ 65. Inclusion criteria were, patients with atrial fibrillation, prosthetic valve replacement or deep venous thrombosis. Exclusion criteria, included age <18 years, hospitalization at the moment, or if they are participating in another clinical trial. For all subjects, the following were done: complete history were obtained from all cases including: Demographic data (age, sex, residence and educational level), general medical history and associated comorbidities, indication for the use of oral anticoagulants, the dose and duration for use of warfarin.

Laboratory investigations, measurement of INR for 5 follow up visits to calculate the TTR - The INR is derived from prothrombin time (PT) which is calculated as a ratio of the patient's PT to a control PT standardized for the potency of the thromboplastin reagent developed by the World Health Organization (WHO) using the following formula [14]. INR=Patient PT ÷ Control PT.

Technique: Venous blood was directly obtained into a tube with a light blue top (contain anticoagulant -sodium citrate 3.2%), the tube was then inverted a few times, gently and as soon as possible, for proper mixing with the anticoagulant, the total time between sample collection and testing should not exceed 24 hours [15].

Time in Therapeutic Range (TTR); TTR estimates the percentage of time a patient's INR is within the desired treatment range or goal [16]. Each patient's TTR was calculated using the Rosendaal method. The Rosendaal linear interpolation methodology is based on the INRDAY software program (Dr. F.R. Rosendaal, Leiden, The Netherlands) that assumes a linear relationship exists between two INR values and allows the researcher to allocate a specific INR value to each day for each patient [17].

2.1 Statistical Analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD. Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data) while Mann Whitney U test was used for non-normally distributed Data (non-parametric data) and a P value of less than 0.05 was considered to be statistical significance. Univariate and multivariate logistic regression analysis was used to estimate the dependent and independent risk predictor of categorical outcome.

3. RESULTS

This is a cross sectional observational study that included 502 patients receiving vitamin K antagonists (VKAs) as an oral anticoagulant treatment for thromboembolic prevention for at least more than 1 month. The patients were divided into two groups according to time to therapeutic range (TTR); group I that included 289 patients with TTR < 65 and group II that included 213 patients with TTR ≥ 65.

Demographics data was shown in Table 1, the patients mean age in group I was 56.13 ± 14.21 years which was statistically significant higher than patients in group II (45.29 ± 16.04 years) (P< 0.001). there were 134 males (46.4%) and 155 females (53.6%) in group I while there were 78 males (36.6%) and 135 females (63.4%) in group II which was statistically significant difference between the two groups (p=0.029).

The percentage of patients with high level of education was statistically significant higher in group II (55.4%) as compared with group I (13.1%) while the percentage of illiterate and patient with middle school level of education were higher in group I (26.3% and 60.6% respectively) as compared with group II (8% and 36.6%).

Group I had statistically significant more diabetic and hypertensive patients (p value was<0.001), also smokers were more in group I than group II (P value was 0.01). The percentage of cases with CKD and CAD in group I was statistically significantly higher as compared with group II (P < 0.001).

Indications for use of OACs in the current study; In group I there were 193 cases (66.8%) with AF which was statistically significant higher as compared with group II (45.1%) (P< 0.001). The percentage of cases who use OACs for prosthetic valve were 18.7% in group I which was statistically significant lower as compared with group II (26.3%) (p=0.039). The percentage of cases who use OACs for thromboembolism were 14.5% in group I which was statistically significant lower as compared with group II (28.6%) (p=0.001), Table 2.

Table 2 showing the duration of use of warfarin; in group I, 25.3% of the cases used warfarin for duration less than 1 year and 74.7% use warfarin for ≥ 1 year while in group II, 38.02% of the cases used warfarin for duration less than 1 year and 66.98% use warfarin for ≥ 1 year. The percentage of cases who used warfarin for more than 1 year was higher in group I as compared to group II with statistically significant difference between the two groups (p=0.019).

The mean CHADS-VASC2 score in group I was 2.63 ± 2.02 with range between 0 and 8 which was statistically significant higher as compared with group II (1.22±1.06) with range between 0 and 3 (P< 0.001), Table 2, Fig. 1. The best cutoff point of CHADS-VASC to predict the good response TTR (≥ 65) was >1.5 with 68.5% sensitivity, 63.4% specificity, 70.8% NPV, 65.3% PPV and total accuracy of 66.8%, (Fig. 2).

Table 3 showing the predictors of bad TTC control; with univariate regression analysis, increasing age, male gender, lower level of education, DM, HTN, smoking, CKD, CAD and higher CHADS-VASC were revealed as risk factors for poor response (TTR < 65). With multivariate logistic regression analysis, lower level of education HTN, smoking, CKD and higher CHADS-VASC were revealed as independent risk factors for poor response (TTR < 65).

4. DISCUSSIONS

Oral vitamin K antagonists are effective in the treatment and prevention of thromboembolic disease. The Vitamin K antagonists (VKAs) have narrow therapeutic window, making their optimal use in clinical practice challenging. Long-term INR control is often summarized using the percentage of time spent in therapeutic range (TTR) [18]. Despite good anticoagulation control for patients on warfarin is important, few studies have investigated patient-level predictors of good TTR [19,20].

Table 1. Baseline clinical, demographic & characteristics of studied 2 groups

Characteristic	Group I, TTR < 65 (N=289)	Group IITTR > 65 (N=213)	T value	P* Value
Age (*years*)*:* Mean± SD	56.13 ± 14.21	45.29 ± 16.04	7.997	<0.001*
Gender, No.% (M/F)	134/155(46.4%/53.6%)	78/135(36.6%/63.4%)	x^2= 4.775	0.029*
Residence				
Rural	126(56.1%)	105(49.3%)	x^2= 2.250	0.134
Urban	127(43.9%)	108(50.7%)		
Level of education				
No/illiterate	76(26.3%)	17(8.0%)	x^2=27.837	<0.001*
Middle school level	175(60.6%)	78(36.6%)		
Higher level of education	38(13.1%)	118(55.4%)		
Medical history and risk factors				
Hypertension	161(55.7%)	61(28.6%)	x^2=36.431	<0.001*
Diabetes Mellitus	136(47.1%)	44(20.7%)	x^2=37.136	<0.001*
Smoking	88(30.4%)	34(20.2%)	x^2=6.696	P=0.010*
CKD	64(22.1%)	5(2.3%)	x2=40.540	< 0.001*
CAD	82(28.4%)	21(9.9%)	x2=25.775	< 0.001*

*T= independent samples t-test; x^2= Chi-square test *: statistically significant (p< 0.05); MI= myocardial infarction; BMI=body mass index; M/F=male/female; P value <0.05 considered significant*

Table 2. Indications, duration for use of OACs and CHADS-VASC2 score in 2 groups

Characteristic	Group I (TTR < 65 (N=289)	Group II (TTR > 65 N=213	X^2	P* Value
AF	193(66.8%)	96(45.1%)	46.328	<0.001*
Prosthetic valve	54 (18.7%)	56 (26.3%)	3.876	<0.001*
Thromboembolism	42 (14.5%)	61(28.6%)	8.523	<0.001*
Duration of use of warfarin				
< 1 year	73(25.1%)	81(38.02%)	5.328	0.019*
≥ 1 year	216 (74.7%)	132(66.98%)		
CHADS-VASC2 score	2.63 ± 2.02 (0-8)	1.22± 1.06 (0-3)	z=9.331	<0.001*

*AF= atrial fibrillation X^2= Chi-square test *: statistically significant (p< 0.05)*

Table 3. Univariate and multivariate analysis of predictors of TTR < 65

Variables	Univariate analysis	B (OR)	Multivariate analysis 95% CI	P value
Age	< 0.001*	1.019	0.995 – 1.044	0.119
Gender	0.029*	1.287	731 – 2.236	0.389
Residence	0.134			
Education level	< 0.001*	0.438	0.239 – 0.827	0.001*
Diabetes mellitus	< 0.001*	1.293	0.731 – 2.288	0.377
Hypertension	< 0.001*	0.473	254 – 0.913	0.026*
Smoking	0.010*	3.186	1.628 – 6.165	0.001*
CKD	< 0.001*	4.507	1.556 – 13.06	0.006*
CAD	< 0.001*	0.910	0.469 – 1.766	0.781
CHADS-VASC	< 0.001*	0.523	0.396-0.691	<0.001*

*CKD= Chronic kidney disease; CAD=Coronary artery disease; CI: confidence interval *: statistically significant (p< 0.05) B: regression coefficient*

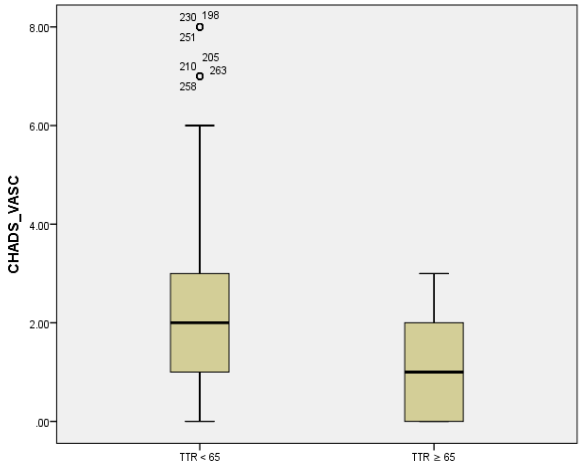

Fig. 1. CHADS-VASC2 score in the cases in the two study subgroups

This study was done at our cardiology department aiming to study the INR values in patients on VKAs, finding the predictors of poor INR control in such cases. In our study, we have shown that common clinical and demographic factors can impact the quality of oral anticoagulation, making it practical to discriminate patients who are less likely to keep within the target INR range.

We included a total of 502 cases starting on oral vitamin K antagonists. They were divided into two groups according to time to therapeutic range (TTR); group I that included 289 patients with TTR < 65 and group II that included 213 patients with TTR ≥ 65.

The main findings of the current study was that, poor education, hypertension, smoking, chronic

kidney disease, and high CHADS-VSAC score were independent predictors of poor TTC control.

In study that was conducted by Farsad et al, to asses TTC control, of the sample patients, 37.3% were in the good control category (TTR > 70%), 24.6% were in the intermediate category (50% >TTR < 70%), and 38.1% were in the poor control category (TTR < 50%) [21]. Another study reported that the mean TTR was 49.1%, and only 31% of patients achieved TTR >60%, and 17% had TTR >70%, [22] this is much lower than percent reported in our study. Dlott et al. reported that the mean time in the therapeutic range was 53.7% overall and improved with time on treatment, increasing from 47.6% for patients with <6 months of testing to 57.5% for those with ≥6 months of testing [23].

In the current study, age was significantly younger in cases with TTR > 65 (45.29 vs. 56.13 years in the group with TTR<65, p<0.001). Old age was a significant risk factor for poor INR control on univariate analysis, but was non-significant on multivariate analysis, (Table 3). Multiple previous studies have disagreed with our findings. Apostolakis et al. reported that age older than 50 years was a significant positive predictor of good TTR. On the contrary, age < 50 years was a significant predictor of poor TTR (p<0.001) [24]. Authors attributed that finding by the fact that younger patients experienced worse TTR, perhaps as a result of compliance parameters associated with the more active lifestyle of young patients.

In study done by Dlott et al, patients in the 55 to 64 year age group had higher TTR (2.4%; 95% CI, 1.9–2.9) and those in the 35 to 44year age group had lower TTR (−3.8%; 95% CI, −5.1 to −2.5) [23]. Nevertheless, Parsad and his associates did not see any tendency towards poor control in old age cases [21].

Our study, showing a significant difference between the two groups regarding gender (P=0.029). Females represented 53.6 and 63.4% of cases in both groups respectively. Male gender was a significant risk factor for poor TTR on univariate analysis (p=0.029). However, that significance faded on multivariate analysis (P= 0.389). Study done by Witt DM, has also denied any significant effect of gender on TTC control on multivariate analysis [20]. These results agreed with our findings.

On the contrary, a previous study has reported that male gender was a significant predictor for good control (OR: 1.15; 95% CI: 1.04– 1.28) [25]. Other studies had confirmed that finding [24,26]. Dlott and his associates reported that women had lower TTR than men (−1.3%; 95% CI, −1.5 to −1.0) [23].

In our study there was no significant difference between the two groups regarding residence areas (p=0.134). Residence did not constitute a significant risk factor for poor INR control. Similarly, Fang et al, showed that geographical region did not significantly predict warfarin use [27].

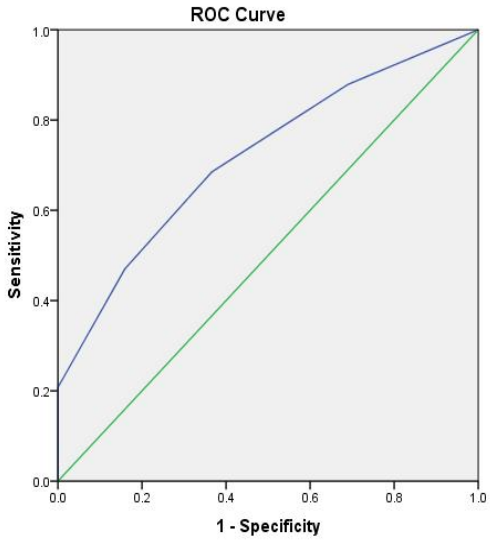

Fig. 2. Analysis of diagnostic criteria of CHADS -VASC in prediction of TTR (≥ 65)

In the current study, the level of education was significantly different between the study groups. High education level was present in 55.4 and 13.1% of cases in good and poor controlled groups respectively (p<0.001). Poor educational level was strongly associated with poor INR control. This result was similar to findings reported by Parsad et al., who reported that there was no significant difference between the studied patients regarding the level of education (p = 0.43) [21].

Although there is a scarcity of studies assessing the influence of educational level on INR outcomes, our findings could be explained by, low education level may have a significant negative impact on patient healthy habits including drug compliance, this agree with Taibanguay N and his associates [28].

In the current study, diabetes mellitus was a significant risk factor for poor INR control on univariate analysis. It was present in 47.1% and 20.7% of cases in both groups respectively. Boulanger et al. have reported that the presence of diabetes is a significant risk factor of poor INR control (OR: 0.86: 95% CI: 0.76–0.97) [25]. Nelson and his associates have confirmed that association (OR 1.21, 95% CI 1.03–1.42) [26]. Both of the previous studies agreed with our findings.

Regarding hypertension in the current study, it was more prevalent in the poorly controlled group (55.7 vs. 28.6% of cases in the other group p< 0.001) and was a significant risk factor for poor INR control. It was previously reported that AF patients with a history with comorbidities such as hypertension had over 20% higher risk of poor TTR outcome (ORs between 1.21 and 1.25) [29]. This comes in line with our findings.

Nevertheless, we disagree with the results of previous two studies. Nelson et al. reported that hypertension was a significant predictor for good INR control (OR 0.73, 95% CI 0.64–0.83) [26]. The positive effect of hypertension mentioned in these studies could be due to antihypertensive medications like calcium channel blockers, which was reported to improve INR control in cases receiving oral anticoagulants [24].

Our study revealed that chronic kidney disease was more prevalent in the poorly controlled group (22.1 vs. 2.3% of cases in the other group (p<0.001). On multivariate analysis, it was an independent risk factor for poor TTP (p=0.006). Previous study had confirmed the relations between chronic kidney disease and poor INR control [24]. Björck et al. reported that renal disease was associated with an increased risk for poor TTR of 47% [29]. Furthermore, Efird et al. reported that increased creatinine levels were associated with poor TTP control [30].

In the current study, the presence of coronary artery disease was significantly more prevalent in the poorly controlled group (28.4 vs. 9.9% of cases in the other group (p < 0.001). However, it was not independent risk factor on multivariate analysis (p=0.781). Another study has reported that the presence of more than 2 comorbidities (including coronary artery disease, peripheral vascular disease, previous stroke, pulmonary disease, and renal disease) was a significant negative predictor of poor TTR (p < 0.001) [24].

In our study, smoking was an independent risk factor for poor TTR (P=0.001). Smokers represented 28.4 and 9.9% of cases in both groups respectively (P=0.01). Likewise, Macedo et al. reported that smoking was a significant risk factor for poor TTP control in in both AF and VTE cases [19]. Interestingly, the effect of smoking appears to diminish after patients give up smoking. Studies suggest that smoking may interact with warfarin by altering in its metabolism, but the clinical evidence of this interaction remains inconclusive [31,32]. Based on our findings, smoking cessation advice should be imposed before starting of warfarin therapy.

Regarding the indication of anticoagulant therapy in the current study, it was significantly different between the two groups (p<0.05), (Table 2). Similarly, Witt et al. reported significant difference between the two groups regarding the prevalence of atrial fibrillation and valvular disorders (p<0.001). Nevertheless, the incidence of VTE did not differ significantly between the two groups (p = 0.856) [20].

In the current study, there was a significant difference between the two groups regarding the duration of anticoagulant therapy (p=0.019). Longer durations were observed in the poorly controlled group. This could be explained by the fact that as medication intake becomes longer, there is more chance for drug non adherence, or taking other medications that may interact with it due to the development of other diseases. Conversely, Witt et al. study showed no significant impact of anticoagulant duration on TTR (p = 0.743) [20].

CHADS-VASC score showed significantly higher values in cases with low TTR (3.63 vs 1.22 in the other group ($p<0.001$) Table 2, Fig. 1. That score was an independent risk factor for poor INR control. Another study has reported that high CHADS2 and CHA2DS2VASc scores were associated with poor TTR [22]. Schein et al., also reported that high CHADS2 score was associated with decreased TTR [33].

We furtherly assessed the role of CHADS-VASC score to predict poor coagulation control. Using a cut-off value of 1.5, that score had sensitivity and specificity of 68.5 and 63.4% respectively to predict good TTR control, with an accuracy of 66.8%. (Fig. 2) Our results showed that there are strong association between CHADS-VASC score and TTR control. As TTR becomes poorly controlled, it is expected to have more risk of complications.

This study has several limitations. The included patients were exclusively treated in academic or teaching hospitals, which limits the generalizability of our findings. Also, other variables including the number and type of associated medications should have been recorded. Therefore, more studies should be conducted in the future to cover these perspectives.

5. CONCLUSION

Based on the result of this study, it was evident that poor education, hypertension, smoking, chronic kidney disease, and high CHADS VSAC score were independent predictors of poor TTC control.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICS APPROVAL

This study was approved by the local ethics committee of faculty of medicine Tanta university, Egypt. Written informed consent was obtained from all patients in this study ref No; 32955/02/19.

AVAILABILITY OF DATA AND MARTIAL

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

ACKNOWLEDGEMENTS

We would like to thank our colleagues, nurses, and technicians in our cardiology department for helping in collecting data and completion of our study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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