

Original Article

Evaluation of time in therapeutic range among patients receiving warfarin therapy: A retrospective cohort study at one private hospital in Thailand

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ABSTRACT

The quality of warfarin therapy is often measured by the percentage of time that a patient spends within target international normalized ratio (INR) range (time in therapeutic range, TTR). It has been found that TTR can strongly predict both bleeding and thromboembolic events. This retrospective cohort study was conducted to evaluate the mean TTR and the predictors of inadequate anticoagulation control among subjects attending the warfarin clinic at one private hospital in Thailand during June 2012 and May 2016. Study subjects consisted of patients who had been taking warfarin for all indications with target INR 2.0-3.0. TTR was calculated through the Rosendaal method which provides the percentage of days when INR values are in desired range. A total of 196 patients (71.9% female, mean age 69.55 years) recruited represented the average TTR value of 60.46%. The stratification of patients according to anticoagulant control levels indicated that the poor control group (TTR < 65%) and the good control group (TTR ≥ 65%) contained 103 patients (52.55%) and 93 patients (47.45%), respectively. The mean TTR value of the poor control group was significantly lower than the good control group (43.64% vs. 79.09%; $P < 0.001$). It was found that comorbid heart failure, history of non-adherence, warfarin-drug interaction and warfarin-food/herb interaction were associated with the status of poor anticoagulant control (adjusted OR were 7.258, 18.232, 2.886 and 5.828, respectively). Recognition of these predictive factors could be beneficial in improving pharmaceutical care activities in order to optimize TTR value among patients receiving warfarin therapy.

1. INTRODUCTION

Warfarin, a vitamin K antagonist (VKA), currently remains the most widely prescribed oral anticoagulant (OAC) despite increasing use of non-VKA or direct OACs (DOACs) apixaban, edoxaban, rivaroxaban and dabigatran¹. The unique pharmacologic properties of warfarin especially the narrow therapeutic index with up to a 20-fold inter-individual variation in therapeutic dose complicate its long-term use^{2,3}. Several factors affecting the pharmacodynamics and pharmacokinetics

of warfarin such as comorbid diseases, food, herb, drug and genetic interactions render treatment more challenging and requiring close monitoring of international normalized ratio (INR) so as to ensure optimal anticoagulation control^{2,4}.

The quality of warfarin therapy is often measured by the percentage of time that a patient spends within the target INR range (time in therapeutic range, TTR)¹. It has been found that TTR can strongly predict both bleeding and thromboembolic events⁵. Maximizing the TTR value will lead to the optimal benefit for preventing stroke, major hemorrhage and death⁶. The most commonly used method to calculate TTR is the Rosendaal linear interpolation method⁷. The value is calculated from the number of days within target range divided by the total number of days in the observation period. The unknown INR data between dates of measurement are interpolated using a linear function to assign an estimated INR value to every day within the monitored period⁶. The good INR control is typically defined as a TTR \geq 65%. However, several studies in patients receiving VKAs demonstrated that this goal is hardly achieved or maintained over time⁷. Multiple factors have been identified as predictors of poor INR control including younger in age, current smokers, new users of warfarin, being treated in community settings, non-adherent to treatment, multiple physical or mental co-morbid disease states, lack of knowledge about warfarin use reason or food-drug interaction, the number of current medications above four as well as cytochrome P450 2C9 (CYP2C9) or vitamin K epoxide reductase (VKORC1) polymorphisms⁶⁻¹⁰.

The Bangkok Christian Hospital is one of the Thailand's leading private hospitals located in the center of Bangkok. A warfarin clinic of this hospital was established in year 2009. All patients receiving warfarin are normally asked to attend the warfarin clinic. Pharmacists working in the clinic are responsible for warfarin therapy monitoring and patient education. The quality of the treatment, using TTR as a surrogate measure, has never been evaluated in this selected setting. Therefore, we conducted this study to analyze the TTR among subjects attending the warfarin clinic and identify the proportion of patients achieving a good TTR

control (TTR \geq 65%). In addition, predictors of inadequate anticoagulant control (TTR < 65%) were also evaluated.

2. MATERIALS AND METHODS

2.1 Study design and ethics

This is a retrospective cohort study conducted in one private hospital of Thailand. The protocol was approved by the ethics committee of the Faculty of Pharmacy at Srinakharinwirot University (approval No. 006/M2560). Permission to perform the study including the processes of collecting patients' information from medical records and hospital databases was obtained from the director of the Bangkok Christian Hospital.

2.2 Study subjects and data collection

The study took place during April to May 2017. Data from medical records and databases between 1 June 2012 and 31 May 2016 were retrospectively reviewed since the clinical information of patients attending warfarin clinic was started to systematically document by the hospital pharmacists in year 2012. Study subjects consisted of the patients of the warfarin clinic that were 18 years old or more who had been taking warfarin for all indications with target INR 2.0-3.0. INR values measured during the first 3 months after initiating warfarin (3 months window) were dismissed from the TTR calculation in order to allow the stability of warfarin therapy. Patients who had insufficient data from medical records and databases, had less than 4 recorded INR values for TTR calculation, and were lost to follow-up for at least 1 year were excluded from the assessment. Diagram of subject selection is shown in Figure 1.

Demographic and clinical characteristics of eligible patients extracted from medical records and databases included: sex, age, social history, comorbid disease, number of co-prescribed medication, indication for warfarin therapy and drug related problem (i.e., non-adherence, warfarin-drug interaction, warfarin-food/herb interaction, dosage too low and dosage too high, and event of warfarin-related adverse drug reaction), which were documented by the hospital pharmacist of the warfarin clinic.

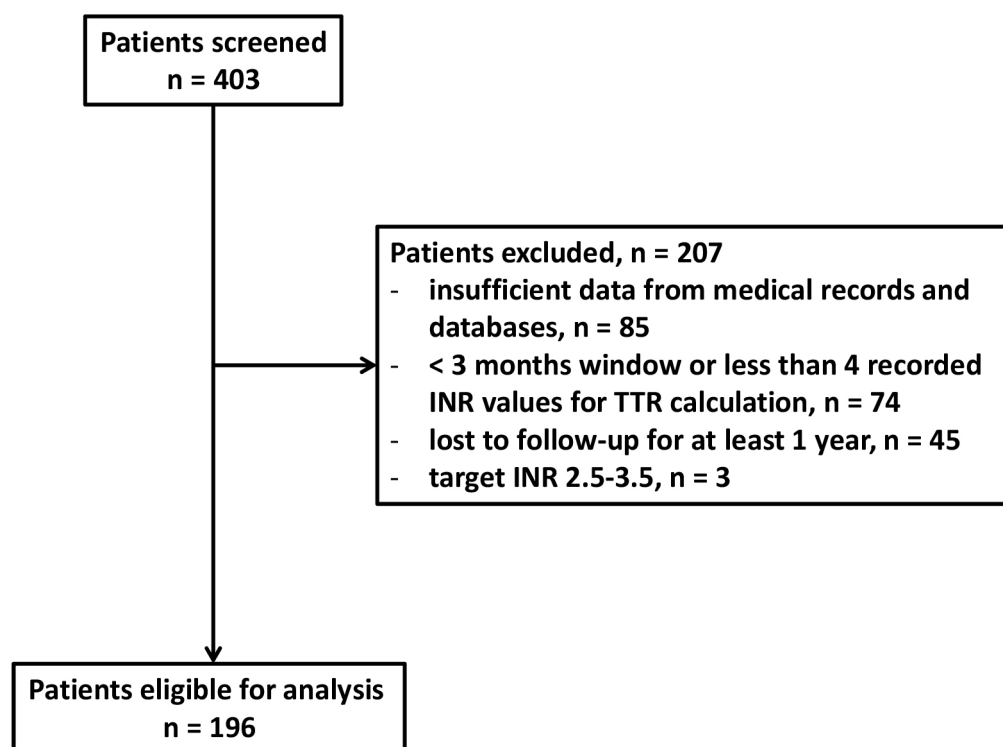


Figure 1. Diagram of study subject selection

TTR was calculated through the Rosendaal method¹¹ which provides the percentage of days when the INR values are in the desired range (2.0-3.0). The value was obtained by TTR calculation documentation 2015 (Healthcare Analytics) program. A poor anticoagulation control was defined as TTR < 65% and good control as TTR \geq 65%.

2.3 Data analysis

All statistical data analyses were performed using SPSS version 21.0 (IBM Corp, 2012). Descriptive statistics were used to describe the demographic and clinical characteristics of the patients. The continuous variables and the categorical variables were presented as mean \pm standard deviation (SD) and percentage (%), respectively. Comparisons of continuous variables between poor control group and good control group were performed by independent t-test or Mann-Whitney U-test. Univariate associations between categorical variables were explored using chi-square test or Fisher's exact test, as appropriate. The significant factors that identified with univariate analyses were entered into the multivariate logistic regression model to determine the predictors of poor anticoagulation control which were reported as adjusted

odds ratio (OR) and 95% confidence interval (CI). For all planned analyses, $p < 0.05$ was considered statistically significant.

3. RESULTS

A total of 196 patients were recruited in the present study. Most of them were female (71.9%) with a mean \pm SD age of 69.55 ± 12.35 years (range 28-93 years). The mean \pm SD TTR for these patients was $60.46 \pm 22.61\%$.

The stratification of patients according to anticoagulant control levels indicated that the poor control group (TTR < 65%) and the good control group (TTR \geq 65%) contained 103 patients (52.55%) and 93 patients (47.45%), respectively. Demographic and clinical characteristics of the two groups are shown in Table 1.

The mean TTR value of the poor control group was significantly lower than the good control group ($43.64 \pm 17.03\%$ vs. $79.09 \pm 9.74\%$; $P < 0.001$). There was no significant difference between the two groups with respect to sex, age, alcohol intake or indication of warfarin therapy. There was statistically significant difference across the two TTR categories (poor control group vs. good control group) in terms of the pro-

portions of patients with history of smoking (37.86% vs. 19.35%; $P = 0.004$), comorbid heart failure (30.10% vs. 13.98%; $P = 0.007$), comorbid thyroid gland disease (22.33% vs. 9.68%; $P = 0.017$) and co-prescribed with more than 4 drugs (95.15% vs. 81.72%; $P = 0.003$). Compared with the good control group, the drug related problems including history of non-adherence (70.87% vs. 12.90%), warfarin-drug interaction (48.54% vs. 22.58%), warfarin-food/herb interaction (64.08% vs. 23.66%) and minor bleeding event (27.18% vs. 5.38%) were reported more

frequently in poor control group (all $P < 0.001$).

Regarding the predictors of poor control, the multivariate logistic regression analysis was conducted to evaluate the independent effects of each significant variables obtained from univariate analysis (Table 2). It was found that comorbid heart failure, history of non-adherence, warfarin-drug interaction and warfarin-food/herb interaction were associated with the status of poor anticoagulant control (adjusted OR were 7.258, 18.232, 2.886 and 5.828, respectively).

Table 1. Demographic and clinical characteristics of the subjects compared between two groups^a.

Characteristics		Poor control group (N = 103) n (%)	Good control group (N = 93) n (%)	P value
TTR (%; mean \pm SD)		43.64 \pm 17.03	79.09 \pm 9.74	< 0.001 ^b
Sex	Male	33 (32.04)	22 (23.66)	0.192
	Female	70 (67.96)	71 (76.34)	
Age (years; mean \pm SD)		68.98 \pm 13.63	70.17 \pm 10.79	0.501
Age (years)	< 65	31 (30.10)	23 (24.73)	0.401
	\geq 65	72 (69.90)	70 (75.27)	
Social history	Smoking	39 (37.86)	18 (19.35)	0.004 ^b
	Alcohol intake	8 (7.77)	11 (11.83)	0.337
Comorbid disease	Dyslipidemia	35 (33.98)	38 (40.86)	0.320
	Diabetes mellitus	50 (48.54)	39 (41.94)	0.353
	Hypertension	64 (62.14)	56 (60.22)	0.783
	Heart failure	31 (30.10)	13 (13.98)	0.007 ^b
	Thyroid gland disease	23 (22.33)	9 (9.68)	0.017 ^b
Number of co-prescribed drug	\leq 4	5 (4.85)	17 (18.28)	0.003 ^b
	> 4	98 (95.15)	76 (81.72)	
Indication of warfarin therapy	Atrial fibrillation	61 (59.22)	58 (62.37)	0.653
	Deep vein thrombosis	15 (14.56)	18 (19.35)	0.371
	Pulmonary embolism	7 (6.80)	5 (5.38)	0.679
	Atherosclerotic disease	12 (11.65)	6 (6.45)	0.208
	Stroke	8 (7.77)	6 (6.45)	0.721
Drug related problem	History of non-adherence	73 (70.87)	12 (12.90)	< 0.001 ^b
	Warfarin-drug interaction	50 (48.54)	21 (22.58)	< 0.001 ^b
	Warfarin-food/herb interaction	66 (64.08)	22 (23.66)	< 0.001 ^b
	Dosage too low	6 (5.83)	5 (5.38)	0.892
	Dosage too high	2 (1.94)	1 (1.08)	1.000
	Minor bleeding event	28 (27.18)	5 (5.38)	< 0.001 ^b
	Major bleeding event	1 (0.97)	1 (1.08)	1.000

^a Values are n (%) unless otherwise indicated. ^b Significant difference between 2 groups were found (P value < 0.05).

Table 2. Predictors of poor anticoagulant control (TTR < 65%) in multivariate logistic regression analysis.

Factors	Adjusted OR	95% CI	P value
Smoking	2.179	0.807- 5.881	0.124
Heart failure	7.258	2.321-22.698	0.001 ^a
Thyroid gland disease	2.584	0.847- 7.882	0.095
Number of co-prescribed drug > 4	3.320	0.728-15.141	0.121
History of non-adherence	18.232	7.147-46.509	< 0.001 ^a
Warfarin-drug interaction	2.886	1.159- 7.187	0.023 ^a
Warfarin-food/herb interaction	5.828	2.338-14.523	< 0.001 ^a
Minor bleeding event	3.029	0.801- 11.453	0.102

^aSignificant difference between 2 groups were found (P value < 0.05).

4. DISCUSSION

The quality of anticoagulation control, as measured by TTR, varies widely among hospitals, study sites, physician practices, health care systems and countries^{12,13}. TTR shows a significant relationship with therapeutic benefits and adverse clinical outcomes¹⁴. Several warfarin guidelines including that of The Heart Association of Thailand represent that the good INR control is defined as a TTR \geq 65%^{15,16}. For present study, 196 patients included had an average TTR of 60.46%, indicating that they experienced a poor anticoagulation control. However, this value of which > 60% is not quite far from good control range and is considered as the lower end of the target TTR which can provide the potential advantages in some recommendations^{6,12}. One study in patients with atrial fibrillation suggested setting a minimum target TTR of 60% to 65%. If this goal cannot be achieved, therapy with OAC should be reconsidered because of the limited therapeutic benefit¹². Regarding the stratification of patients according to anticoagulant control levels, the data of our study showed that nearly half of the patients (93; 47.45%) had good INR control with the mean TTR of 79.09%, whereas approximately half (103; 52.55%) had poor control with the mean TTR of 43.64%. Since poor control status links to risk of warfarin therapy, patients in this group should be identified individually. Analysis of the root cause and setting up the protocol to improve TTR needs to be considered in order to optimize benefit and reduce harm in these selected patients.

Data from 102 patients with non-valvular atrial fibrillation of Siriraj Hospital, Thailand showed the average TTR of 58.34% which was very close to that of our study¹⁷. Lower mean TTR (40.2%) was found from the study in 206 outpatients who visit warfarin clinic, Queen Sirikit Heart Center of the Northeast, Thailand¹⁸. The difference of TTR value among our study and study of Queen Sirikit Heart Center may be partly due to the variations in TTR calculation method (Rosendaal method which provides the percentage of days when the INR values are in the desired range vs Traditional method which represents the percentage of in-range INR values to the total number of INR values¹⁹) and the study population especially the most common indication of warfarin therapy (atrial fibrillation vs valve replacement).

Studies from some countries located in Western Asia, South Africa, America, North America and Europe reported the wide range of TTR value (40%-64%) indicating the high variability of TTR in different settings which had the differences in the ethnicity, cultures, dietary habit as well as study protocols or algorithms of OAC management^{6,8,9,20-24}. Compared with our study, the mean TTR found in those studies is perhaps better but generally lower. However, our value is still at the level that needs to be improving for reaching the target of good control.

Our results showed that history of non-adherence, comorbid heart failure, warfarin-drug interaction and warfarin-food/herb interaction were independent predictors of poor anticoagulant control. Non-adherence displayed the strongest factor

associated with 18-fold of getting suboptimal anticoagulation. Substantial numbers of patients with non-adherence in the poor control group significantly affected the quality of anticoagulation control. This is in accord with the results from the study of Kimmel *et al.*, which demonstrated a significant association between underadherence with warfarin regimens and underanticoagulation²⁵. Causes of medication non-adherence among patients in our setting should be further clarified to correct this pivotal warfarin therapy problem.

Heart failure was the next independent predictor of poor TTR control discovered in our study (OR = 7.258, 95% CI 2.321-22.698). This finding is fairly consistent with the result from another study in patients with atrial fibrillation conducted in Israel (OR = 1.41; 95% CI 1.05-1.88)²². However, the threshold of poor control defined in that study (TTR < 60%) was different from ours. Negative impact of comorbid heart failure including the interactions between warfarin and multiple drugs used as well as the poor medication adherence in heart failure patients were explained as the potential mechanisms^{22,26}. Additionally, having heart failure could impact OAC effectiveness through various factors such as vascular abnormalities, impaired blood flow and biological variation in coagulation system²⁷. On the contrary, one study in Tehran, Iran did not recognize this outcome. Analysis in patients with non-valvular atrial fibrillation receiving treatment with warfarin showed no significant difference between the TTR categories (good control TTR: > 70%, intermediate control TTR: 50%-70%, and poor control TTR: < 50%) and the history of comorbid heart failure⁸.

It is well known that drug interactions are a leading cause of fluctuating INR value. Several types of drugs, foods, herbs and dietary supplements have been reported to interact with warfarin which can lead to the events of adverse outcomes in patients²⁸. Regarding this issue, we identified warfarin-drug interaction and warfarin-food/herb interaction as significant predictors of poor TTR control with odds ratio of 2.886 and 5.828, respectively. Kilic *et al.*, conducted the study to evaluate the factors affecting adequate anticoagulation control (TTR > 70%) in patients treated with warfarin for any reason. The results indicated that know to food-drug interaction with warfarin was independent predictor of adequate

INR control (OR = 1.583, 95% CI 1.350-1.857)¹⁰. Although our study did not investigate the knowledge of food interaction with warfarin, it might be extrapolated that events of warfarin-food interactions was partly related to lack of knowledge of the patients. On the other hand, the study of Yomsrikhen *et al.*, in Warinchamrab hospital, Thailand did not recognize these predictors. Their results represented that factor related to poor anticoagulation control (TTR < 60%) was polypharmacy but not drug interactions²⁹. For our study, more than 4 co-prescribed drugs was significantly associated with poor TTR control ($p = 0.003$) but this factor was not found to be an independent predictor of poor TTR control (OR = 3.320; 95% CI 0.728-15.141) in multivariate logistic regression analysis.

According to our results, it could be implied that non-adherence, comorbid heart failure and drug interactions were the important contributors to uncontrolled TTR in warfarin-treated patients of the Bangkok Christian Hospital. The ongoing process of assessing and encouraging medication adherence needs to be done throughout the treatment period. Providing the special attention with patients who have comorbid diseases especially heart failure which can lead to clinical significance warfarin-disease interaction is recommended. Screening of potential drug, food or herb interactions with warfarin should be conducted strictly. Improvements in patient counseling and education may help in prevention of these drug therapy problems.

This study has some limitations. Firstly, it was the retrospective design relied on the recorded information in patients' file which the completeness and accuracy might be limited. Therefore, we could not clarify some problems in definite detailed such as the cause of non-adherence or type of drugs or herbs that interact with warfarin. Secondly, classification of TTR categories with threshold value of 65% was different from some other studies, and then the direct comparison of study results between two studies might be misinterpreted. Next, the study was performed in single private hospital which might limit the generalizability of the findings to other settings.

5. CONCLUSIONS

The result of the present study demonstrated mean TTR value of 60.46% among 196 patients

taking warfarin with target INR 2.0-3.0. Almost half of them (93 patients; 47.45%) had good INR control, whereas a little more than half (103 patients; 52.55%) had suboptimal control. Quality of warfarin management was negatively affected by history of non-adherence, comorbid heart failure and drug interactions. These predictive factors obtained from our analysis could be beneficial in improving pharmaceutical care activities in order to optimize TTR value. Further study is needed to evaluate the effects of anticoagulation control on therapeutic and adverse outcomes in patients receiving warfarin therapy.

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Conflict of interest (If any)

Neither of the authors has any potential conflict of interest to disclose.

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Ethical approval

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