ECRONICON OPEN ACCESS

EC CLINICAL AND MEDICAL CASE REPORTS

Research Article

International Normalized Ratio Variability around Holidays and Predictors of Poor Time in Therapeutic Range in Patients Treatment with Warfarin

David J Silva[1], Ravi Mandapati[2] and Huyentran N Tran[3]*

[1]*Pharmacist, Department of Pharmacy Services, Yale New Haven Hospital, New Haven, CA, USA*

[2]*Professor of Medicine and Pediatrics, Director, Loma Linda University International Heart Institute, Loma Linda University Medical Center, Loma Linda, CA, USA*

[3]*Associate Professor, Department of Pharmacy Practice, School of Pharmacy, Loma Linda University, Loma Linda, CA, USA*

***Corresponding Author:** Huyentran N Tran, Associate Professor, Department of Pharmacy Practice, School of Pharmacy, Loma Linda University, Loma Linda, CA, USA.

Received: April 18, 2023; **Published:** April 26, 2023

Abstract

Warfarin has long been the standard-of-care anticoagulant in treating and preventing thromboembolic events in a range of conditions, most commonly for atrial fibrillation (AF) [1]. However, Direct Oral Anticoagulant (DOAC) use has risen significantly in recent years, with a shift from 7.4% to 66.8% from 2011 to 2019 among Medicare Part D beneficiaries taking oral anticoagulants. Despite the increasing use of DOACs, warfarin is still often used in patients who may be poor DOAC candidates due to renal or hepatic impairment, extremes of body weight, drug interactions, or for conditions in which DOAC efficacy and safety is sub-optimal or has not been well-established [2].

Keywords: *Warfarin; Atrial Fibrillation (AF); Direct Oral Anticoagulant (DOAC)*

Introduction

The therapeutic effects of warfarin are directly linked to maintaining the International Normalized Range (INR) within a target range (a goal of 2 - 3 for most indications) [3]. It is well established that INR is highly sensitive to many interacting factors including dietary vitamin K intake, alcohol intake, and drug interactions or comorbid conditions affecting warfarin metabolism and clearance. Demographic factors of age, height, weight, sex, race, and ethnicity - in addition to patient-specific genetic determinants of warfarin metabolism and the vitamin K cycle - have also shown influence on warfarin sensitivity.

Commonly used methods of assessing patients' consistency of INR values relative to their target therapeutic range include the traditional method (calculating a proportion of therapeutic INR values), and the Rosendaal method (using linear interpolation between known INR values to estimate a time in therapeutic range [TTR]) [4,5]. Maximizing the amount of time a patient spends within therapeutic range is associated with improved bleeding and thrombotic outcomes [6-8]. When compared to dual antiplatelet therapy (DAPT) in patients with AF, a predicted TTR of at least 58 - 65% was required to provide clinical benefit with warfarin [9]. Although TTR-specific thresholds remain a topic of debate, poor anticoagulation control is generally defined as TTR < 65% across modern guidelines [10-12].

Independent predictors of poor anticoagulation control as defined across a range of populations have included advanced age, female sex, hospitalizations, number of medications, alcohol use, non-alcohol substance use, smoking and various comorbidities including psychiatric conditions and cancer [13-19]. Despite the many known factors influencing INR, we were unable to identify any published literature examining how potential changes in patient-specific behaviors and environmental factors around holiday periods may impact INR variability. Several factors surrounding holiday periods may be clinically significant, including the following: use of travel-associated antibiotics or malaria prophylaxis that could alter vitamin K production by intestinal flora; acute infections such as gastritis that could impair dietary vitamin K absorption; variations in temperature and altitude that have shown impact on coagulability; and changes in diet, alcohol use, or medication adherence [20-23].

Aim of the Study

Our study aimed to assess INR variability during holiday periods, and to identify additional predictors associated with poor INR control.

Methods

Study sample

This study was approved by the Institutional Review Board of Loma Linda University Medical Center. This study was a retrospective cohort study using data from a pharmacist-managed anticoagulation clinic associated with a tertiary care, academic medical center located in the United States. Adult patients anticoagulated on warfarin and receiving care at the clinic between January 1, 2017 and September 30, 2020 were included (Figure 1). Patients with fewer than two INR values were excluded due to limitations of applying the Rosendaal Method.

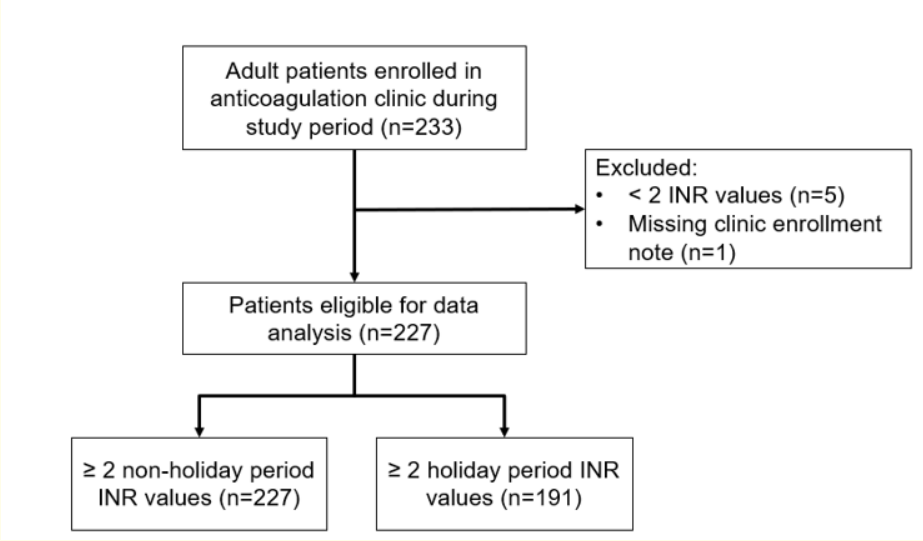

Figure 1: *Patient inclusion diagram.*

A holiday cohort was defined, consisting of patients with at least 2 consecutive INR values recorded during defined holiday periods, and all INR values recorded outside of holiday periods were excluded from their analysis. Conversely, the non-holiday cohort consisted of

patients with at least 2 consecutive INR values recorded during defined non-holiday periods, and all INR values recorded within holiday periods were excluded from their analysis.

Data sources

Retrospective review of electronic health records (EHR) was performed, and clinical and demographic data were extracted including age, sex, ethnicity, race, social history (smoking, alcohol, marijuana, and illicit substance use), zip code, and number of hospitalizations and emergency department (ED) visits within the health system during the study period. Past medical history including psychiatric conditions and individual components of the CCI score were identified via The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, 10th Revision (ICD-10) coding [24]. Median household income was inferred using patient ZIP Code Tabulation Areas and was compared to the national median household income for 2017 [25,26].

Documented INR values and dates of INR within the study period were recorded for all included patients. Values listed during hospitalization periods were excluded, since these patients may experience intentional interruptions in warfarin therapy not reflective of baseline anticoagulation control. If multiple INR values were documented on a given day, the value furthest from goal INR was used for a more conservative estimate of in-range INR.

The index date was defined by the earliest documented clinic pharmacist encounter in the EHR within the study period. The pharmacist clinic note on the index date was used to extract the defined INR goal, the indication for anticoagulation, and the number of concomitant medications as listed during medication reconciliation. Study exit date was defined if patients were listed as transitioning off warfarin in clinic notes, became deceased, or if the end of the study period was reached.

Holiday periods were defined as each of ten U.S. Federal holidays, including three days before and after the holiday date. Holidays included were: New Year's Day, Martin Luther King Jr Day, Washington's Birthday/Presidents' Day, Memorial Day, Independence Day, Labor Day, Columbus Day, Veteran's Day, Thanksgiving Day, and Christmas Day.

Outcomes

The proportion of INR values in range was calculated by dividing the number of in-range INR values by the number of INR assessments. The Rosendaal method used linear interpolation to estimate INR values on unmeasured days to calculate a TTR by diving the estimated number of days within range by the total number of days on therapy; freely available formula templates from INR Pro were used for traditional and TTR calculations [27]. A time-weighted TTR was calculated by dividing the sum of all patients' days within range by the sum of all patients' days on therapy [13]. Individual components of the CCI were tabulated into a total score and stratified as ≥ 3 or < 3. Among the subgroup of patients with AF, CHA2DS2-VASc scores were calculated.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences version 28 (SPSS-27) [28]. Proportion of therapeutic INR was compared between holiday and non-holiday cohorts. Additional statistical analysis was performed to identify risk factors associated with poor INR control (as defined by TTR thresholds). Multivariate logistic regression was performed using a backward, stepwise (Wald) elimination, removing variables with non-significant odds ratios (OR) at each step until a final prediction model was generated**.** An approach of "purposeful selection" was used to determine variables entering the multivariate initial model, using potential risk factors (identified from previous literature) found to be significant during univariate logistic regressions [29].

Results

Total patients assessed numbered 233. Five patients were excluded due to having < 2 INR values recorded. One patient was excluded due to missing a warfarin clinic enrollment note. In total, 227 patients were eligible for data analysis and included in the overall cohort.

For the overall cohort, the proportion of INR values in range was 2589/5363 (48.3%); the time-weighted TTR was 55.7% from 134,618 total observed days; and mean TTR was 52.3% (distribution shown in figure 2). A TTR ≥ 65% was achieved in 73 patients (32.2%), and a TTR ≥ 60% in 90 patients (38.6%).

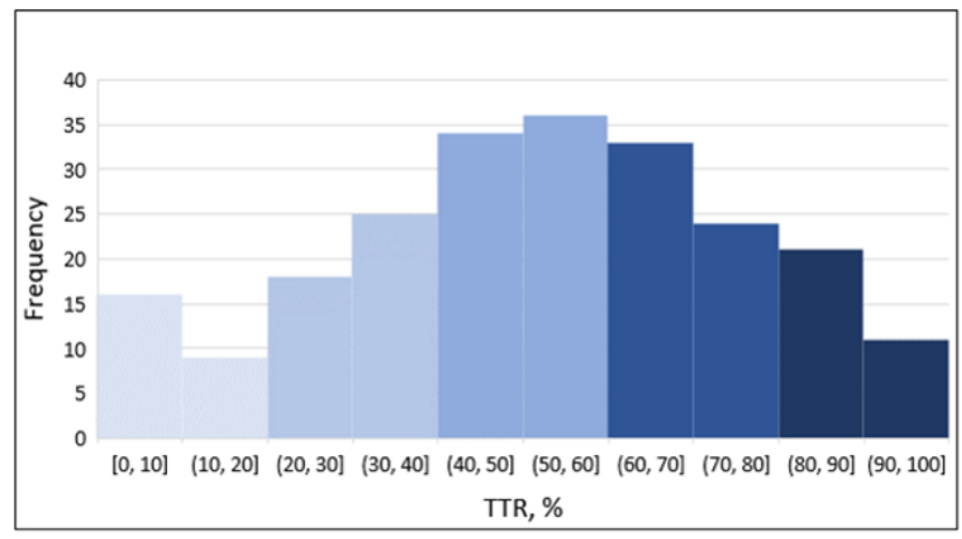

Figure 2: *Mean time in therapeutic range frequency histogram.*

There were significant differences between characteristics of TTR ≥ 65% and TTR < 65% groups, with the TTR ≥ 65% cohort having older age, more stroke indications, more INR goals of 2 - 3, fewer hospitalizations, fewer males, and fewer ED visits (Table 1). Among the TTR ≥ 65% group, the proportion of INR values in range was 1217/2076 (58.6%), mean TTR was 79.5%, and time-weighted TTR was 76.6% from 49,766 total observed days. Among the TTR < 65% group, the proportion of INR values in range was 1343/3217 (41.8%), mean TTR was 39.5%, and time-weighted TTR was 43.4% from 84,852 total observed days.

Among a subgroup of patients with AF (n = 113), the mean CHA_2DS_2-VASc score was 4.04; the proportion of INR values in range was 1346/2605 (48.8%); mean TTR was 52.9%. A TTR ≥ 65% was achieved in 33% of patients, and TTR ≥ 60% in 39.3% of patients.

All 227 patients were included in the non-holiday cohort, while 191 of those patients were also included in the holiday cohort; as expected, there was a large degree of patient overlap due to having qualifying INR values in both cohorts, although a patient's INR values are distinct to either group based on time periods. Baseline characteristics are not described here due to the patient overlap between the two cohorts, although there were no significant differences between groups. The proportion of therapeutic INR among the non-holiday cohort was 2169/4549 (49.5%), and among the holiday cohort was 420/814 (47.6%); this difference was not statistically significant (p-value = 0.589). Additionally, within the holiday cohort no significant differences were found when testing mean proportions of therapeutic INR across each of the individual holidays.

Significant univariate regression risk factors chosen to enter the multivariate initial model included: age ≥ 65, number of medications, CCI score ≥ 3, psychiatric conditions, smoking history, number of hospitalizations, number of ED visits, and household income below

Variable	TTR < 65% (n=154)	TTR ≥ 65% (n=73)
Indication, n (%)		
AF	76 (49.4)	37 (50.7)
VTE	61 (40)	23 (31.5)
Mechanical valve	22 (14)	7 (9.6)
Stroke	9 (6)	17 (23.3)*
Other†	27 (17.5)	6 (8.2)
INR goal, n (%)		
2-3	129 (83.8)	69 (94.5)*
2.5-3.5	11 (7.1)	4 (5.5)
Other‡	14 (9.1)	0 (0)
Age (yr), median (IQR)	68 (59, 77)	74 (64, 81)*
Sex (male), n (%)	65 (42)	28 (38)*
Ethnicity - Hispanic, n (%)	33 (21)	17 (23)
Race, n (%)		
White	108 (70.1)	60 (82.2)
Black/African American	19 (12.3)	3 (4.1)
Hispanic/Latin Origin	14 (9.1)	6 (8.2)
Asian	9 (5.8)	3 (4.1)
American Indian/Alaska Native	2 (1.3)	1 (1.4)
Pacific Islander/Native Hawaiian	1 (0.65)	0 (0)
Unknown	1 (0.65)	0 (0)
Medications, median (IQR)	11 (8, 14)	9 (6, 12)
Charlson Comorbidity Index Score, mean (SD)§	4.98 (2.64)	4.67 (2.08)
CCI score ≥ 3, n (%)	124 (80.5)	62 (84.9)
Psychiatric condition	35 (23)	18 (25)
Healthcare encounters, mean (SD)		
Hospitalizations	1.9 (3.1)	0.85 (1.6)*
ED visits	1.0 (1.6)	0.59 (1.2)*
Median household income ($), median (IQR)	65,956 (56,005, 72,739)	66,560 (57,855; 71,245)
Median household income below national level, n (%)	71 (46)	27 (37)
Current alcohol use n (%)	33 (21.4)	9 (12.3)
Current tobacco smoker n (%)	7 (4.5)	1 (1.4)
Current marijuana use n (%)	5 (3.2)	3 (4.1)
Current illicit substance use n (%)	2 (1.3)	0 (0)

Table 1: *Baseline characteristics.*

VTE: Venous Thromboembolism; IQR: Interquartile Range; SD: Standard Deviation.

**Indicates statistically significant difference between groups.*

† Other: LV thrombus, APLS, Factor V Leiden, Protein C Deficiency, PAD, LVAD.

‡ Other: 2.5-3, 1.8-2.5, 2-2.5, 1.8-2.2, 2-3.5.

§Differences between groups for individual components of CCI score were nonsignificant.

national median. No other factors were found to be significant on univariate testing, including anticoagulation indication, INR goal, and all baseline characteristics previously detailed. Significant predictors of poor INR control (TTR < 65%) identified in the final prediction model included age 65+ (OR = 2.3; 95% CI, 1.18 - 4.52), psychiatric condition (OR = 2.1; 95% CI, 1.01 - 4.45), hospitalizations (OR = 1.24; 95% CI, 1.04 - 1.49), and number of medications (OR = 1.07; 95% CI, 1.01 - 1.14) (Figure 3). When a cutoff of TTR < 60% was used for the same model above, significant factors in the final prediction model included number of hospitalizations (OR = 1.28; 95% CI, 1.09-1.5), number of medications (OR = 1.06; 95% CI, 1.01-1.12), and CCI score ≥ 3 (OR = 2.2; 95% CI, 1.02-4.75).

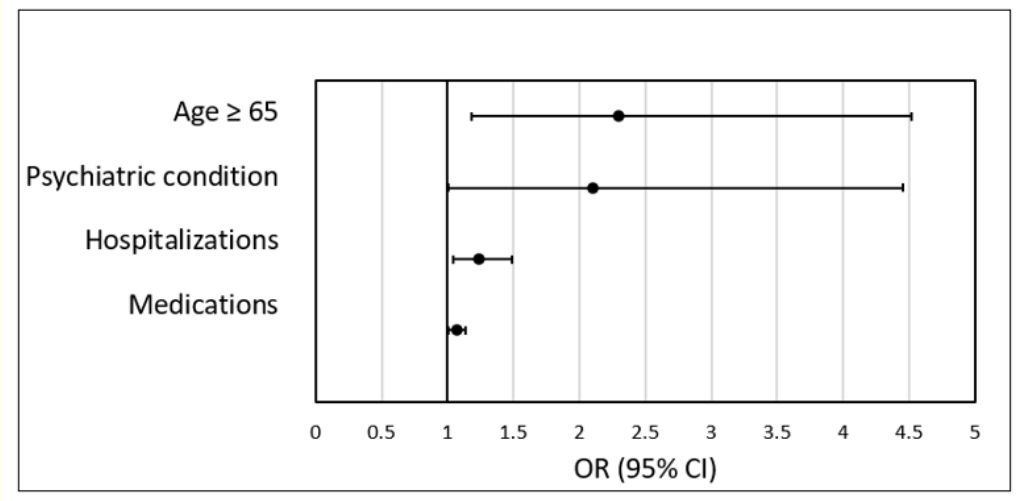

Figure 3: *Significant predictors of time in therapeutic range < 65%.*

Discussion

In this single-center study, there was not found to be significant INR variability during holiday periods relative to non-holiday periods. Contrary to our hypothesis, no signal of holiday periods negatively impacting anticoagulation control was noted.

Average TTR was suboptimal, although consistent with a comparable, lower end of what has been seen in real-world data from similar studies [13,14,18,30]. As observed across sites and study populations, few patients on warfarin will achieve an acceptable TTR, and even fewer an optimal TTR. Approximately one third of our patients had a TTR of at least 65%, the high end of the proposed threshold for netting clinical benefit with use of warfarin over antiplatelets [9]. Additionally, when considering the therapeutic benefit of warfarin relative to DOACs, an ideal, higher goal TTR of > 70% has more recently been proposed [11,12].

Data from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) demonstrated that among patients with an initially high degree of anticoagulation control (TTR ≥ 80%), there may be poor durability in maintaining this degree of TTR beyond the initial treatment phase [31]. However, in contrast to ORBIT-AF, a recent population-based study in Canada did showcase durability of high-quality TTR and advised an emphasis on support for well-managed anticoagulation clinics [32]. Difficulty achieving (and maintaining) adequate TTR on warfarin may support the transition of eligible patients to DOACs.

Factors identified in our model as independent predictors of poor TTR are consistent with previously published literature. Number of medications and number of hospitalizations have been associated with poor TTR, and it is not surprising that both were found to be

significant in our model across both TTR cutoffs [14,16]. Although there is no standard cutoff to define polypharmacy, a threshold of ≥ 5 medications has been referenced [16,30,33,34]. From the Veterans Affairs Study to Improve Anticoagulation (VARIA), 4 or more hospitalizations per year was associated with a 9.4% decrease in TTR [14]. Fewer studies have examined and found significance with socioeconomic factors such as income level and education, or burden of comorbid conditions through Charlson Comorbidity Index (CCI) scores [19,35,36]. A CCI threshold of ≥ 3 has been associated with poor outcomes and is often cited as a marker for severe burden of disease [24,35]. Our study uniquely examined the association of CCI ≥ 3 with poor TTR, of which previous assessments have been limited to a single study which defined "low-quality control of INR" at a much lower threshold of < 25% [35]. In our current study, when a threshold TTR ≥ 60% was used in our multivariate model, CCI ≥ 3 was found to be a significant predictor of poor TTR, but was not significant when using TTR ≥ 65%. This may suggest that higher CCI scores predict very poor degrees of anticoagulation control.

Our study also found an association of psychiatric conditions with poor TTR, as is consistent with previous studies [14,16]. However, no other comorbid conditions were found to be significant in our model, and prior evidence has found variable associations of TTR with non-psychiatric conditions [13-16]. This may emphasize a further need for capturing and stratifying psychiatric and non-psychiatric comorbid conditions as possible risk factors, particularly with scoring systems such as CCI only capturing dementia as one aspect of a range of psychiatric conditions [14,16,26]. Our study found older age (≥ 65) to be associated with poor TTR, although previous literature has shown the impact of age on TTR to be varied and complex, possibly with a biphasic relationship [19,37,38].

Given the imbalances in patient characteristics among our TTR groups, more patients in the TTR ≥ 65% group were anticoagulated for stroke, had an INR goal of 2-3, and had fewer hospitalizations and ED visits. It has been previously noted that patients with a more stable anticoagulation status were more likely to have an INR goal under 3 - including the standard INR goal of 2-3 [39]. This may signal that our more optimally anticoagulated patients were less often experiencing bleeding or thrombotic events related to anticoagulation.

Limitations of the Study

Our single center retrospective study has several key limitations. The method of purposeful selection of variables is not without its own limitations, and our multivariate regression model may not have included additional variables potentially associated with poor TTR. Further, other key factors that have been associated with poor TTR - such as poor patient adherence - were data points unable to be extracted and utilized in our model [40].

Our study extracted data on indication(s) for anticoagulation and defined INR goal at earliest clinic visit note within the study period. This method failed to capture subsequent changes in INR goals - such as the time-variable goals of On-X aortic heart valves - or as indications were phased in or out (e.g. initially anticoagulated for a deep vein thrombosis, but now have had a mechanical mitral valve replacement). Although we excluded INR values during patient hospitalizations, low INR values during planned interruptions in therapy (such as prior to a procedure) may skew data with low values and weigh down aggregate measures. Similarly, new-start warfarin patients being bridged until therapeutic may also skew data with low values.

There are also inherent limitations of each method of therapeutic INR assessment. Unlike TTR, there remains to be seen an accepted, optimal proportion of therapeutic INR values (using the traditional method) as identified through an association with clinically meaningful outcomes. Because it relies on the total number of INR values, the traditional method may also be skewed by patients with more frequent INR testing. With the Rosendaal method, Technical limitations of the Rosendaal Method prevented TTR from being calculated among holiday and non-holiday cohorts due to linear interpolation producing overlap between holiday and non-holiday periods; so, only the traditional method could be used for this between-group comparison. Given the method of linear interpolation, extended time between values may also skew overall TTR. It is difficult to draw meaningful comparisons between proportion of therapeutic INR and TTR.

Still, observing multiple summary measures of anticoagulation control may allow for a broader view and avoid the limitations of either method viewed alone. Recently, several risk-adjusted TTR scoring systems have been proposed, including SAMEe-TT_2R_2 and PROSPER, for predicting risk of poor anticoagulation control given the presence of patient-specific risk factors [15,17,19]. These systems may represent a more tailored approach to assessing patient risk, and better characterize bleeding and thrombotic risks as associated with TTR.

Conclusion

Focused, interdisciplinary efforts are needed to target high-risk patients treated with warfarin, including those with polypharmacy or frequent hospital encounters. Further, ongoing assessments of patient-specific risk factors (such as psychiatric conditions) are needed to continue the provision of high-yield care. For patients in which it is feasible and indicated, switching from warfarin to a DOAC may be warranted to optimize anticoagulation status and improve patient outcomes. In summary, this appears to be the first study examining INR variability around holiday periods. Additionally, the findings of this study further confirm certain key, previously identified predictors of poor anticoagulation status.

Bibliography

1. Troy A and Anderson TS. "National Trends in Use of and Spending on Oral Anticoagulants Among US Medicare Beneficiaries From 2011 to 2019". *JAMA Health Forum* 2.7 (2021): e211693.
2. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges (2022).
3. Ta Michael Lee M and Klein TE. "Pharmacogenetics of warfarin: challenges and opportunities". *Journal of Human Genetics* 58.6 (2013): 334-338.
4. Rosendaal FR., *et al*. "A method to determine the optimal intensity of oral anticoagulant therapy". *Journal of Thrombosis and Haemostasis* 69.3 (1993): 236-239.
5. Siddiqui S., *et al*. "Variability in the Calculation of Time in Therapeutic Range for the Quality Control Measurement of Warfarin". *Innovations in Cardiac Rhythm Management* 9.12 (2018): 3428-3434.
6. Vestergaard AS., *et al*. "The importance of mean time in therapeutic range for complication rates in warfarin therapy of patients with atrial fibrillation: A systematic review and meta-regression analysis". *PLOS ONE* 12.11 (2017): e0188482.
7. Erkens PMG., *et al*. "Benchmark for Time in Therapeutic Range in Venous Thromboembolism: A Systematic Review and Meta-Analysis". *PLoS ONE* 7.9 (2012): e42269.
8. Haas S., *et al*. "Quality of Vitamin K Antagonist Control and 1-Year Outcomes in Patients with Atrial Fibrillation: A Global Perspective from the GARFIELD-AF Registry". *PloS One* 11.10 (2016): e0164076.
9. Connolly SJ., *et al*. "Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range". *Circulation* 118.20 (2008): 2029-2037.
10. Recommendations | Atrial fibrillation: diagnosis and management | Guidance | NICE (2022).
11. Antithrombotic Therapy for Atrial Fibrillation. *Chest* (2022).

12. Hindricks G., *et al*. "2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC". *European Heart Journal* 42.5 (2021): 373-498.

13. Gateman D., *et al*. "Time in therapeutic range: Warfarin anticoagulation for atrial fibrillation in a community-based practice". *Canadian Family Physician* 63.10 (2017): e425-e431.

14. Rose AJ., *et al*. "Patient characteristics associated with oral anticoagulation control: results of the Veterans AffaiRs Study to Improve Anticoagulation (VARIA)". *Journal of Thrombosis and Haemostasis* 8.10 (2010): 2182-2191.

15. Rose AJ., *et al*. "Risk-Adjusted Percent Time in Therapeutic Range as a Quality Indicator for Outpatient Oral Anticoagulation". *Circulation: Cardiovascular Quality and Outcomes* 4.1 (2011): 22-29.

16. Razouki Z., *et al*. "Pathways to poor anticoagulation control". *Journal of Thrombosis and Haemostasis* 12.5 (2014): 628-634.

17. Apostolakis S., *et al*. "Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT_2R_2 score". *Chest* 144.5 (2013): 1555-1563.

18. Farsad BF., *et al*. "Evaluation of Time in Therapeutic Range (TTR) in Patients with Non-Valvular Atrial Fibrillation Receiving Treatment with Warfarin in Tehran, Iran: A Cross-Sectional Study". *Journal of Clinical and Diagnostic Research* 10.9 (2016): FC04-FC06.

19. Lin KJ., *et al*. "Prediction Score for Anticoagulation Control Quality Among Older Adults". *Journal of the American Heart Association* 6.10 (2017): e006814.

20. Penning-van Beest FJA., *et al*. "Risk of major bleeding during concomitant use of antibiotic drugs and coumarin anticoagulants". *Journal of Thrombosis and Haemostasis* 6.2 (2008): 284-290.

21. Salobir B., *et al*. "Intensity of Long-Term Treatment with Warfarin Is Influenced by Seasonal Variations". *Pathophysiology of Haemostasis and Thrombosis* 32.4 (2002): 151-154.

22. Van Patot MCT., *et al*. "Risk of impaired coagulation in warfarin patients ascending to altitude (>2400 m)". *High Altitude Medicine and Biology* 7.1 (2006): 39-46.

23. Ringwald J., *et al*. "Travel and Oral Anticoagulation". *Journal of Travel Medicine* 16.4 (2009): 276-283.

24. Charlson ME., *et al*. "A new method of classifying prognostic comorbidity in longitudinal studies: development and validation". *Journal of Chronic Diseases* 40.5 (1987): 373-383.

25. ACS Profile Report: 2015-2019 / Missouri Census Data Center (2022).

26. Bureau UC. 2010-2014 ACS 5-year Estimates Census (2022).

27. Using the Rosendaal method for calculating Therapeutic Time in Range (TTR) (2022).

28. IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.: IBM Corp (2016).

29. Bursac Z., *et al*. "Purposeful selection of variables in logistic regression". *Source Code for Biology and Medicine* 3.1 (2008): 17.

30. Mannucci PM., *et al*. "Multimorbidity and polypharmacy in the elderly: lessons from REPOSI". *Internal and Emergency Medicine* 9.7 (2014): 723-734.

31. Pokorney SD., *et al*. "Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry". *American Heart Journal* 170.1 (2015): 141-148.

32. McAlister FA., *et al*. "Time in therapeutic range and stability over time for warfarin users in clinical practice: a retrospective cohort study using linked routinely collected health data in Alberta, Canada". *BMJ Open* 8.1 (2018): e016980.

33. Proietti M., *et al*. "Polypharmacy and major adverse events in atrial fibrillation: observations from the AFFIRM trial". *Clinical Research in Cardiology European Society of Cardiology* 105.5 (2016): 412-420.

34. Guidelines for medical treatment and its safety in the elderly (2022).

35. Rouaud A., *et al*. "Comorbidities against Quality Control of VKA Therapy in Non-Valvular Atrial Fibrillation: A French National Cross-Sectional Study". *PLoS ONE* 10.3 (2015): e0119043.

36. Dlott JS., *et al*. "National assessment of warfarin anticoagulation therapy for stroke prevention in atrial fibrillation". *Circulation* 129.13 (2014): 1407-1414.

37. Abohelaika S., *et al*. "Impact of age on long-term anticoagulation and how gender and monitoring setting affect it: implications for decision making and patient management". *British Journal of Clinical Pharmacology* 82.4 (2016): 1076-1083.

38. Marcatto LR., *et al*. "Age is associated with time in therapeutic range for warfarin therapy in patients with atrial fibrillation". *Oncotarget* 7.34 (2016): 54194-54199.

39. Witt DM., *et al*. "Outcomes and predictors of very stable INR control during chronic anticoagulation therapy". *Blood* 114.5 (2009): 952-956.

40. Sevilla-Cazes J., *et al*. "Association Between Patient-Reported Medication Adherence and Anticoagulation Control". *The American Journal of Medicine* 130.9 (2017): 1092-1098.

Volume 6 Issue 5 May 2023