Time in therapeutic range

Warfarin anticoagulation for atrial fibrillation in a community-based practice

Derek Gateman MD CCFP **Melissa Elizabeth Trojnar** MD CCFP(FPA) **Gina Agarwal** MBBS PhD CCFP FCFP

Abstract

Objective To evaluate the effectiveness of an outpatient, nurse-administered warfarin anticoagulation protocol for the treatment of atrial fibrillation, and to identify clinical or biographical data that predict poor international normalized ratio control.

Design Retrospective cohort study.

Setting St Paul Family Health Network in Brantford, Ont.

Participants A total of 150 patients with nonvalvular atrial fibrillation.

Main outcome measures Time in therapeutic range (TTR) for each patient and for the clinic overall. The groups of patients above and below a target TTR of 60% were compared by stepwise binomial logistic regression.

Results A time-weighted average TTR for the clinic was determined to be 58.76%, based on 183 452 patient-days taking warfarin. The regression analysis did not find a statistically significant association between TTR and any predictors. A trend indicating a 5-fold increase in the odds of inadequate anticoagulation was observed in current smokers (odds ratio of 4.71; 95% CI 0.97 to 22.93).

Conclusion Compared with data from prospective randomized trials and meta-analysis, the anticoagulation protocol employed at the St Paul Family Health Network produced an average TTR near the lower end of the target threshold. Current smokers might be at greater risk of being below this target.

EDITOR'S KEY POINTS

- The time in therapeutic range (TTR) is a commonly used quality measure for anticoagulation therapy with warfarin. Maximizing TTR has been shown to provide the most benefit for preventing stroke, major hemorrhage, and death.

- This study assessed the effectiveness of a community practice's warfarin-dosing protocol using TTR as a quality measure and identified demographic factors that predicted inadequate anticoagulation in this patient population.

- The mean TTR in the study group was 58.76%, showing that the protocol achieved a TTR in the range in which anticoagulation therapy has been shown to confer a benefit compared with antiplatelet therapy. Compared with other community practices, this mean TTR is at least average, but it is still at the lower end of the target threshold.

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Un RIN dans la fourchette thérapeutique

Utilisation de la warfarine comme traitement de la fibrillation auriculaire dans une clinique communautaire

Derek Gateman MD CCFP Melissa Elizabeth Trojnar MD CCFP(FPA) Gina Agarwal MB BS PhD CCFP FCFP

Résumé

Objectif Évaluer l'efficacité d'un protocole d'anticoagulation administré par des infirmières et qui utilise la warfarine comme traitement de la fibrillation auriculaire (FA); et identifier les facteurs cliniques et individuels qui prédisposent à un mauvais contrôle du RIN.

Type d'étude Une étude de cohorte rétrospective.

Contexte Le *St Paul Family Health Network* à Brantford, en Ontario.

Participants Un total de 150 patients présentant une FA non valvulaire.

Principaux paramètres à l'étude Un RIN dans la fourchette thérapeutique pour chaque patient et pour l'ensemble de la clinique. Les groupes de patients qui avaient des valeurs supérieures ou inférieures au RIN cible de 60% ont été comparés étape par étape à l'aide d'une régression logistique binomiale.

Résultats En se basant sur 183 452 jours-patients traités à la warfarine, on a calculé que le RIN avait une moyenne pondérée dans le temps de 58,76% pour l'ensemble de la clinique. L'analyse de régression n'a pas révélé d'association significative entre le RIN et un autre facteur. On a observé une tendance indiquant que les fumeurs actifs avaient 5 fois plus de chances d'avoir une anticoagulation inadéquate (rapport de cotes 4.71; IC à 95% 0.97 à 22.93).

Conclusion En comparaison avec les données de méta-analyses et d'essais randomisés prospectifs, le protocole d'anticoagulation utilisé au *St Paul Family Health Network* a résulté en un RIN près de la limite inférieure de la valeur cible. Les fumeurs actifs pourraient être plus susceptibles d'avoir une valeur inférieure à cette cible.

POINTS DE REPÈRE DU RÉDACTEUR

- Un rapport international normalisé (RIN) se situant dans la fourchette thérapeutique est une mesure de qualité généralement utilisée lors d'une anticoagulation à l'aide de la warfarine. Il est établi que le fait de garder le RIN le plus longtemps possible dans la zone thérapeutique est ce qu'il y a de plus efficace pour prévenir un accident vasculaire cérébral (AVC), une hémorragie majeure et un décès.

- Dans cette étude, on a évalué l'efficacité d'un protocole utilisé pour établir la dose de warfarine dans une clinique communautaire en utilisant le RIN comme mesure de qualité; on a aussi vérifié les facteurs démographiques qui prédisposent à une anticoagulation inadéquate dans cette population de patients.

- Le RIN moyen chez les participants à l'étude était de 58,76%, ce qui indique que le protocole a résulté en une valeur de RIN dans la fourchette considérée avantageuse par rapport à un traitement antiplaquettaire. En comparaison avec d'autres cliniques communautaires, ce RIN moyen est au moins dans la moyenne, mais il est encore à l'extrémité inférieure de la cible seuil.

Cet article a fait l'objet d'une révision par des pairs.
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Atrial fibrillation (AF) is the most common of the sustained supraventricular tachyarrhythmias.[1] It is associated with thromboembolic events, in particular embolic stroke. The annual risk of embolic stroke in patients with AF without anticoagulation is 1.9% to 18.2%.[2] Warfarin anticoagulation in AF prevents thromboembolism, but there are risks related to both insufficient and excessive anticoagulation. Complications of supratherapeutic anticoagulation, including hemorrhagic stroke, major bleeding, and death, are common reasons for hospitalization.[3,4] There is an even greater risk of ischemic stroke associated with subtherapeutic dosing.[5] Anticoagulation management is a recognized challenge in primary care.[6]

Maximizing time within the therapeutic range—ie, an international normalized ratio (INR) between 2 and 3—has been shown to provide the most benefit for preventing stroke, major hemorrhage, and death.[3-5] This time in therapeutic range (TTR) is a commonly used quality measure for anticoagulation therapy with warfarin.[3] Current literature suggests that greater TTR correlates with improved patient outcomes for patients treated with warfarin for AF.[7] There is a lack of consensus with regard to an acceptable target for TTR in practice. Different registries have documented TTRs of 55%,[8] 58%,[3] and 76%,[9] with TTR generally being higher in clinical trials than in community practice.[10] At a minimum TTR threshold of 58% to 65%, warfarin is superior to antiplatelet agents.[11] Thrombosis Canada states that good INR control is "defined arbitrarily as a TTR >60%."[6]

Age, sex, socioeconomic status, smoking status, comorbid medical and psychiatric conditions, alcohol abuse, polypharmacy, and frequent hospitalizations are correlated with TTR.[3,12-15] Screening tools to predict nonadherence to warfarin demonstrate promise in secondary care settings[16]; the strongest associations are with those who are currently smoking, disabled, or cognitively impaired.[17]

Use of TTR algorithms in a primary care setting might be useful, but none of these algorithms has been generated in this setting. We sought to assess the effectiveness of a community practice's current warfarin-dosing protocol, using TTR as a quality measure. In addition, we aimed to identify demographic factors that would predict inadequate anticoagulation in this population.

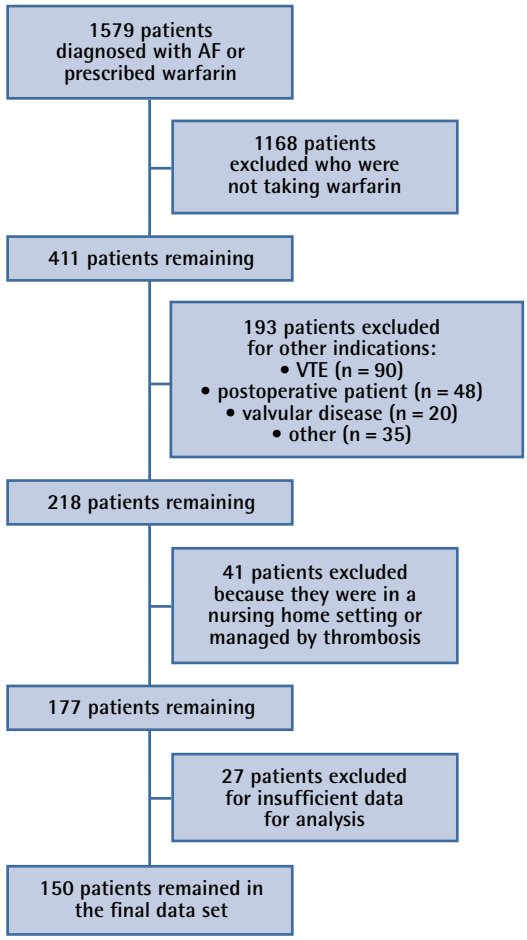
METHODS

This was a descriptive cross-sectional study. The setting was the urban southern Ontario community of Brantford; participants were patients rostered with the St Paul Family Health Network, a family health organization with 9 family physicians. The clinic used a nurse-administered protocol for the adjustment of outpatient warfarin dosing.[18]

Inclusion criteria for patients were a diagnosis of nonvalvular AF, anticoagulation therapy using warfarin during the study period, and anticoagulation managed by the clinic's nurse-run protocol. Patients for whom anticoagulation was managed by specialist clinics or who resided in a long-term care facility were excluded (**Figure 1**).

Those patients who had an INR measured between January 1, 2007, and December 31, 2012, were identified and their charts were reviewed individually. Investigators determined if a formal diagnosis of AF had been documented on the chart and if the patient had been prescribed warfarin for anticoagulation for AF during the study period. Clinical and demographic factors were extracted from the electronic medical record including age, sex, median household income inferred from patient address, specific comorbid medical or psychiatric conditions, smoking status, number of concurrent prescribed medications, and number of hospitalizations.

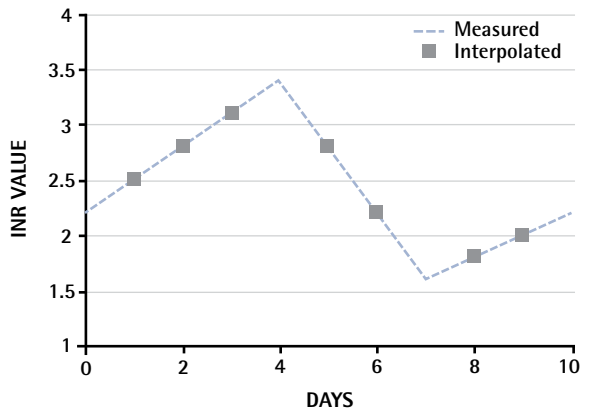
Figure 1. Case recruitment



AF—atrial fibrillation, VTE—venous thromboembolism.

Linear interpolation was used to calculate the TTR for each patient (**Figure 2**).[19] The unknown INR values between dates of observation were interpolated using a linear function so as to apply an estimated INR value to every day within the observation period. The TTR was calculated as the number of days within target range divided by the total number of days in the observation period. Additionally, this method allowed for the combining of ranges of data that had been split by warfarin interruption. Calculations were performed with the assistance of a template produced and made freely available by INR Pro.[20]

Figure 2. Linear interpolation example



INR—international normalized ratio.

After calculating TTR for each patient, outliers with a TTR of less than 5% or a total number of days on anticoagulation less than 30 were identified. These cases were reviewed to ensure the inclusion criteria applied; one patient was excluded in this way on the basis of atrial flutter as the indication for anticoagulation. Some conservative estimates were used to reduce bias. For instance, if more than one INR value was recorded for a single day, then the value furthest from target was kept and the other values were excluded. Patients with 3 or fewer recorded INR values were excluded owing to the limitations of the interpolation technique.

Finally, an aggregate assessment of the clinic's anticoagulation protocol was determined from the total TTR. This was calculated from the sum of all patients' time in therapeutic range divided by the sum of all patients' time in the observation period. Effectively, this ratio was equivalent to a time-weighted average of each patient's TTR value.

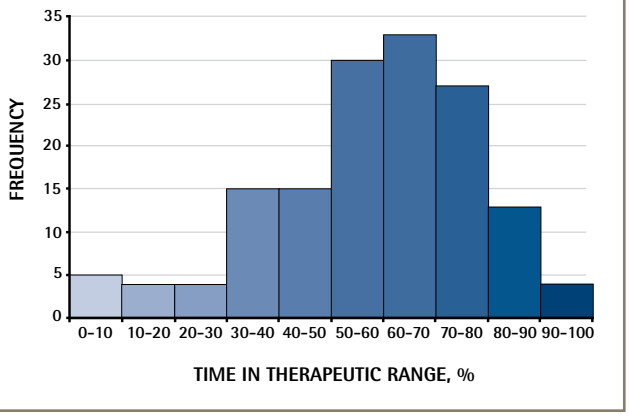
The primary outcome chosen was the total TTR for this office's anticoagulation protocol. The secondary outcome was the identification of predictors of poor INR control.

Statistical analyses were performed to identify risk factors for poor INR control, as indicated by a lower-than-target TTR. Analyses were conducted using the binomial logistic regression method; a stepwise approach was adopted, starting with 8 patient characteristics that have been previously described as potential risk factors. Variables that were identified as having non-significant odds ratios (ORs) were removed from the model.

RESULTS

The 150 patients included had a total of 183 452 days observed while taking warfarin. Of that, there were a total of 107 794.7 days within therapeutic range. This results in a time-weighted TTR of 58.76%. Using unweighted measures of central tendency, the mean (SD) TTR was 58.05% (20.26%). The skewed distribution of TTR is illustrated in **Figure 3**.

Figure 3. Frequency histogram of time-in-therapeutic-range values



The patients were compared within 2 groups: those with TTR greater than or less than 60%, a predefined target. The characteristics of each group are summarized in **Table 1**. The ORs for these considered characteristics are reported in **Table 2** and plotted in **Figure 4**.

Regression using a full model showed that current smoking status was the most significant variable. In subsequent steps removing the less significant variables, smoking status persisted as the most significant variable. This trend indicated that being a current smoker might have an association with TTR less than 60% (OR=4.71, 95% CI 0.97 to 22.93). However, there were no statistically significant predictors found in the regression.

DISCUSSION

We sought first to assess the effectiveness of the St Paul Family Health Network's protocol. A 2008 study published in *Circulation* found that oral anticoagulation with

Table 1. Characteristics by group

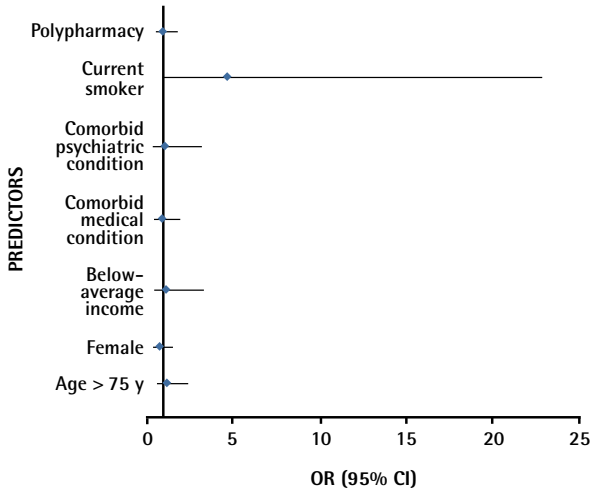
CHARACTERISTIC	BELOW TARGET (N = 73)	ABOVE TARGET (N = 77)	TOTAL (N = 150)
Mean (SD) age, y	73.3 (7.9)	73.6 (7.7)	73.5 (7.8)
Male, n (%)	31 (42)	39 (51)	70 (47)
Median (SD) household income, $	69 954.21 (6553.34)	68447 (6856.50)	69180.50 (6730.70)
Current smoker, n (%)	2 (3)	9 (12)	11 (7)
Comorbid medical condition, n (%)	57 (78)	58 (75)	115 (77)
Comorbid psychiatric condition, n (%)	8 (11)	9 (12)	17 (11)
Mean (SD) no. of hospital discharges	3.01 (4.31)	2.83 (2.74)	2.92 (3.58)
Mean (SD) duration of warfarin treatment within study period, d	1170.65 (796.93)	1272.64 (720.44)	1223.01 (757.79)

Table 2. Predictor of time in therapeutic range

EXPOSURE	OR (95% CI)
Age > 75 y	1.237 (0.635-2.409)
Female	0.770 (0.394-1.501)
Below-average income	1.164 (0.410-3.303)
Comorbid medical condition	0.893 (0.407-1.961)
Comorbid psychiatric condition	1.107 (0.384-3.191)
Current smoker	4.712 (0.968-22.925)
Polypharmacy	0.987 (0.532-1.830)
Frequent hospitalization	1.581 (0.400-6.241)

OR—odds ratio.

Figure 4. Effect of predictors expressed as ORs with 95% CIs



OR—odds ratio.

vitamin K antagonists was beneficial compared with dual antiplatelet therapy in nonvalvular AF only when an average TTR was maintained above 58% to 65%.[11] Centres that could not achieve this target should not pursue anticoagulation over antiplatelet therapy. The mean TTR in our study group was 58.76%, indicating that the protocol achieves a TTR that is within target. Compared with other community practices, the mean TTR from the St Paul Family Health Network is at least average, or perhaps better, but it is still at the lower end of the target threshold.[10,15] This suggests that other Ontario primary care providers could feasibly implement the INR protocol[18] used at St Paul Family Health Network and provide anticoagulation that is equal to most other studied protocols in clinic settings. Equal, however, might not be adequate.

There are several alternatives that might improve warfarin management. There is some evidence to support increasing the frequency of INR measurement to improve TTR.[21] Unfortunately, more frequent measurements place a strain on laboratory resources; point-of-care INR testing offers not only a convenient alternative, but also can achieve a TTR of 74% when testing weekly.[22] An Edmonton study of pediatric warfarin self-management, although small, has achieved a TTR above 90% with no hemorrhagic or thrombotic events.[23] While nurse-managed algorithms such as the one studied here have been found to have outcomes similar to physician-managed monitoring, recent studies show Web-based algorithms might outperform both, achieving a TTR as high as 76%.[24,25] A New Zealand study showed that a pharmacist-managed algorithm, based on point-of-care testing and directed by an online tool, improved TTR to 78.5%, compared with 61.8% using standard care.[26] In fact, the use of computer-assisted dosing is recommended by the British Committee for Standards in Haematology, which recognizes its superiority to manual dosing.[27] While not yet widely used, point-of-care testing, computer decision tools, and patient self-management tools are promising.

If warfarin management cannot be further optimized, then alternatives should be considered. The 2014 National Institute for Health and Care Excellence guideline for the prevention of stroke in people with AF advises the use of direct oral anticoagulants (DOACs) in favour of warfarin when the TTR is less than 65%.[28] From the data presented here, we note that 61% of patients receiving warfarin anticoagulation managed by the office's protocol

fall short of this target TTR. Prescribers must therefore work to identify the subset of patients with nonvalvular AF who will have poor INR control; some of these might consider a DOAC as first-line therapy.

In our analysis, only currently being a smoker showed a strong trend toward significance as a risk factor, reaching statistical significance during some of the regression process. This suggested that being a current smoker was associated with a 5-fold increase in the odds of receiving inadequate anticoagulation. However, it might be that the study was underpowered to detect the significance of this particular risk factor, owing to the small numbers of smokers overall (n=11). Our study was powered appropriately for all other predictors apart from psychiatric morbidity (n=17).[29] Further study, perhaps with a larger, multicentre population, might support our finding that smoking while taking oral anticoagulation is a risk factor for poor INR control. If so, then the association of smoking cessation interventions and patient INR control should also be evaluated.

Limitations

Retrospective analyses rely on recorded data being complete, accurate, and accurately abstracted. This might not always be the case. Further, our study was conducted in a single family health network, and the results might therefore not be generalizable. This also placed limits on the number of patients studied such that the study might have been underpowered to detect the significance of the most promising risk factor for poor INR control. Additionally, some conservative estimates were used to reduce the risk of bias, and there are limitations to the interpolation technique used, thus TTR could have been overestimated or underestimated in some cases.

Conclusion

Our study finds that a common approach to warfarin anticoagulation management in community practice primary care produced a TTR that is both above average, and yet also inadequate. This should spur primary care providers to explore new tools like Web-based algorithms and to facilitate nurse- or pharmacist-run clinics. If more frequent monitoring improves TTR, then point-of-care testing and patient-self management tools will be necessary. Unfortunately, these are underused and underfunded in practice today. Furthermore, we encourage prescribers to review the use of warfarin for nonvalvular AF and consider increasing the use of DOACs where warfarin cannot be further optimized. Identifying the patients in whom INR control will be poor remains a challenge. Our data show patients who currently smoke might be at greater risk, but a strong predictive tool does not exist. Prescribers must ultimately rely on their clinical acumen.

Dr Gateman is a family physician at the Fischer Family Primary Care Centre in Listowel, Ont, and Assistant Clinical Professor in the Department of Family Medicine at McMaster University in Hamilton, Ont. **Dr Trojnar** is a family physician anesthesiologist at Listowel Memorial Hospital. **Dr Agarwal** is Associate Professor in the Department of Family Medicine and the Department of Clinical Epidemiology and Biostatistics at McMaster University.

Contributors
All authors contributed to the concept and design of the study; data gathering, analysis, and interpretation; and preparing the manuscript for submission.

Competing interests
None declared

Correspondence
Dr Derek Gateman; e-mail **derek.gateman@medportal.ca**

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