Evaluation of an initiation protocol of 4 mg of warfarin for atrial fibrillation in the outpatient setting

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Abstract

Objective To describe the efficacy and safety of an initiation algorithm for 4 mg of warfarin in ambulatory patients with atrial fibrillation.

Design Prospectively planned retrospective chart review.

Setting Centre for Family Medicine Family Health Team in Kitchener, Ont.

Participants Ambulatory patients requiring anticoagulation for atrial fibrillation.

Interventions Patients were prescribed 4 mg of warfarin to be taken once daily for 3 days. An international normalized ratio (INR) measured on the morning of the fourth day was used to predict the maintenance dose of warfarin. Subsequent INR measurements were obtained biweekly until patients reached their actual maintenance dose.

Main outcome measures Number of INR values greater than or equal to 4.0 before the warfarin maintenance dose was achieved. Secondary outcome measures included thromboembolic and bleeding events, number of days required to reach therapeutic INR, and correlation between predicted and actual warfarin maintenance dose.

Results Twenty-five patients were included in the study. The average age was 76.0 years (range 56.0 to 89.0), and 17 patients were women. The average $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischemic attack) score was 2.0. Only 1 patient had an INR greater than 4.0 during the study period. The mean time to achieve a therapeutic INR was 11.0 days. The day 4 INR was moderately predictive of the maintenance dose ($r^2 = 0.47$). There were no adverse events that required medical attention during the study period.

Conclusion In this pilot study, an initiation algorithm for 4 mg of warfarin was safe and achieved a therapeutic INR within a reasonable time frame in outpatients with atrial fibrillation.

EDITOR'S KEY POINTS

- In this pilot study, the initiation protocol of 4 mg of warfarin was associated with a low risk of excessive anticoagulation. There were no major bleeding episodes or thromboembolic events.
- A therapeutic international normalized ratio (INR) was achieved in 11.0 days on average, which is consistent with another outpatient protocol, but slightly longer than warfarin induction regimens for inpatients. Eleven days seems acceptable, as rapid achievement of a therapeutic INR is unnecessary for patients with stable, chronic atrial fibrillation.
- The nomogram used in this study was helpful in predicting the maintenance dose of warfarin. The day 4 INR explained nearly half of the variability in the maintenance dose.

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Évaluation d'un protocole d'anticoagulation utilisant une dose initiale de 4 mg de warfarine pour traiter un patient externe souffrant de fibrillation auriculaire

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Résumé

Objectif Vérifier l'efficacité et l'innocuité d'un algorithme basé sur une dose initiale de 4 mg de warfarine chez un patient atteint de fibrillation auriculaire.

Type d'étude Revue de dossiers planifiée à l'avance.

Contexte Le Centre for Family Medicine Family Health Team à Kitchener, Ontario.

Participants Patients ambulatoires nécessitant une anticoagulation pour fibrillation auriculaire.

Interventions On a prescrit aux patients une dose de 4 mg de warfarine par jour pour 3 jours. On s'est servi du rapport normalisé international (RNI) du matin du quatrième jour pour prévoir la dose de maintien de la warfarine. Par la suite, on a mesuré le RNI deux fois par semaine jusqu'à l'obtention de la dose de maintien du patient.

Principaux paramètres à l'étude Nombre de valeurs de RNI supérieures ou égales à 4,0 avant l'atteinte de la dose de maintien. Les paramètres secondaires incluaient les accidents thromboemboliques et hémorragiques, le nombre de jours requis pour atteindre un RNI thérapeutique et la corrélation entre la dose de maintien de la warfarine choisie et celle prédite.

Résultats Les 25 patients qui ont participé à l'étude avaient en moyenne 76 ans (entre 56 et 89) et 17 étaient des femmes. En moyenne, leurs scores $CHADS_2$ (Insuffisance cardiaque, hypertension, âge ≥ 75 ans, diabète et accident vasculaire cérébral ou ischémie cérébrale transitoire) étaient de 2,0. Un seul patient a eu un RNI supérieur à 4,0 durant la période de l'étude. La durée moyenne pour atteindre un RNI thérapeutique était de 11,0 jours. Le RNI du jour 4 était modérément indicatif de la dose de maintien (r2=0,47). Il n'y a eu aucun événement indésirable nécessitant une intervention médicale durant la période de l'étude.

Conclusion Dans cette étude pilote, on a observé qu'un algorithme utilisant une dose initiale de 4 mg de warfarine était sécuritaire et permettait d'atteindre un RNI thérapeutique dans un laps de temps raisonnable chez des patients externes présentant une fibrillation auriculaire.

POINTS DE REPÈRE DU RÉDACTEUR

- Dans cette étude pilote, l'utilisation d'une dose initiale de 4 mg de warfarine était associée à un faible risque d'anticoagulation excessive. Il n'y a pas eu d'épisode de saignement majeur ni d'accident thromboembolique.
- En moyenne, le rapport normalisé international (RNI) thérapeutique a été atteint en 11 jours, ce qui concorde avec un autre protocole pour des patients externes, mais est légèrement plus long que les régimes d'introduction de la warfarine chez des patients hospitalisés. Ces 11 jours semblent acceptables puisqu'il n'est pas nécessaire d'atteindre un RNI thérapeutique plus rapidement chez un patient présentant une fibrillation auriculaire chronique stable.
- Le nomogramme utilisé dans cette étude était utile pour prévoir la dose de maintien de la warfarine. Le RNI du jour 4 expliquait près de la moitié de la variabilité de la dose de maintien.

Cet article a fait l'objet d'une révision par des pairs.
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Improved life expectancy and better management of cardiovascular disease have led to increasing use of oral anticoagulation in the geriatric population.[1] Despite the recent availability of several alternatives, warfarin is still commonly used because of potential safety and cost issues associated with newer anticoagulants.[2-4]

The highest risk of bleeding in an individual taking warfarin appears to be in the first 30 days after starting therapy, which might relate in part to uncertainty surrounding the dose of warfarin required.[5] Several warfarin initiation protocols have been developed in an attempt to reduce the risk of thromboembolic and bleeding complications during the first few weeks of therapy.[6,7] Many of the initiation algorithms use an initial dose of either 10 mg or 5 mg of warfarin.[6,7] The generalizability of these dosing algorithms to patients with atrial fibrillation is limited, as they were studied in younger patients with venous thromboembolic disease; the use of these protocols might be associated with an unacceptable risk of excessive anticoagulant effect in elderly individuals.[8]

The use of an initiation protocol of 4 mg of warfarin in hospitalized geriatric patients with atrial fibrillation was associated with a reasonable time to reach therapeutic range and a low risk of excessive anticoagulant effect.[9] To our knowledge, this protocol has not been studied in an outpatient population. Such a study would be valuable, as warfarin is commonly initiated in ambulatory settings for patients with atrial fibrillation.[10]

The objective of this pilot study is to describe the efficacy and safety of an initiation algorithm for 4 mg of warfarin in ambulatory patients with atrial fibrillation.

METHODS

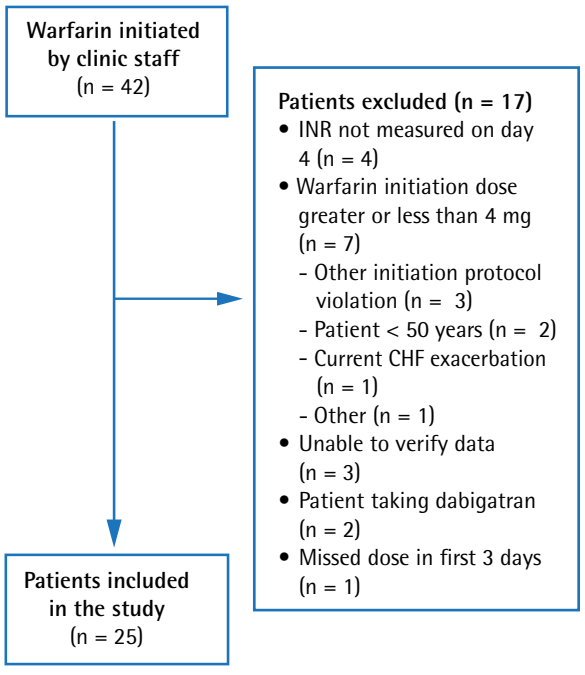
Patients

A retrospective chart review was performed that included patients referred to the anticoagulation clinic at the Centre for Family Medicine Family Health Team in Kitchener, Ont, from February 2006 to May 2012. Participants were limited to those requiring anticoagulation for atrial fibrillation. Only new users of warfarin were included in the study. Patients who were not initiated according to the protocol using 4 mg of warfarin were excluded from the study. Additionally, patients taking dabigatran were excluded, as it has been shown to interfere with international normalized ratio (INR) measurements (**Figure 1**).[11]

Warfarin induction regimen

The regimen for induction of 4 mg of warfarin proposed by Siguret and colleagues was followed.[9] All patients received a 4-mg dose of warfarin at 6:00 PM for 3 days, with the first day of warfarin treatment designated as day 1. An INR measured in the morning on day 4 was used to determine the dose of warfarin (**Table 1**) to be taken until the next scheduled INR test. The predicted weekly maintenance dose was determined by multiplying this dose by 7. Pharmacists who were experienced with anticoagulation dosing adjusted subsequent warfarin doses as necessary based on INR measurements, typically obtained biweekly (more than

Figure 1. Patient selection



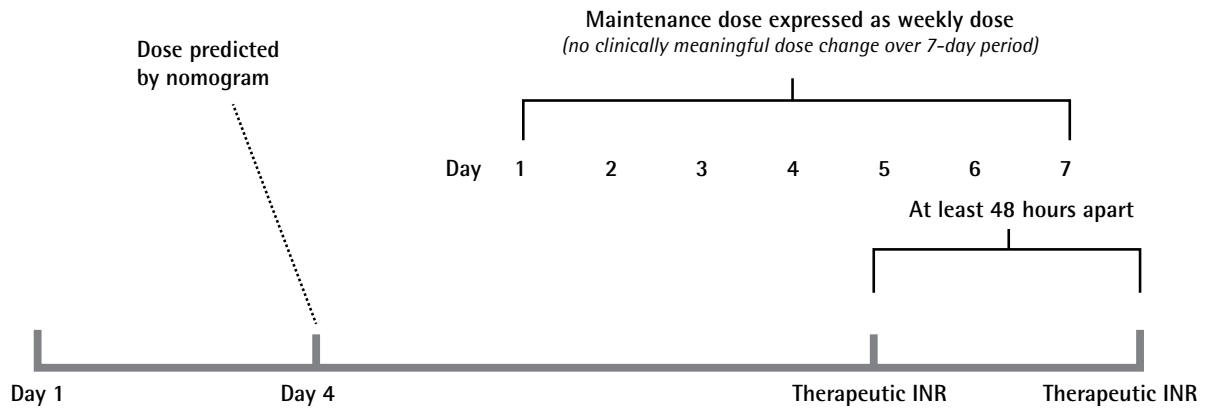
CHF—congestive heart failure, INR—international normalized ratio.

Table 1. Warfarin initiation algorithm

DAY	INR VALUE	WARFARIN DOSE AT 6:00 PM
1	Do not measure	4 mg
2	Do not measure	4 mg
3	Do not measure	4 mg
4	< 1.3	5 mg
	1.3 or 1.4	4 mg
	1.5 or 1.6	3 mg
	1.7 or 1.8	2 mg
	1.9 to 2.4	1 mg
	≥ 2.5	Repeat INR measurement daily. Hold warfarin until INR < 2.5, then administer 1 mg

INR—international normalized ratio.
Data from Siguret et al.[9]

Figure 2. Pictorial representation of definitions



INR—international normalized ratio.

48 hours apart) following day 4. This was continued until patients reached their actual maintenance doses (**Figure 2**). All INR measurements were completed using a point-of-care electronic device.

Outcome measures

Our primary outcome measure was the number of INR values that were greater than or equal to 4.0 before the warfarin maintenance dose was reached. We chose this as our primary end point because INR values greater than 4.0 have been associated with a substantial risk of major bleeding events.[12] Secondary outcomes included bleeding events that required medical attention, symptomatic thromboembolic events, the number of days required to reach a therapeutic INR (INR greater than 2.0 after at least 5 days of therapy), and the correlation between the nomogram-predicted maintenance dose based on the day 4 INR and the actual warfarin maintenance dose (Pearson correlation, r^2). The warfarin maintenance dose was considered to have been achieved when 2 consecutive therapeutic INRs were obtained at least 48 hours apart in the absence of clinically meaningful warfarin dose changes. The warfarin maintenance dose was expressed as a weekly dose of warfarin (in mg) by adding the daily doses starting 4 days before the first therapeutic INR was obtained (**Figure 2**). A change of at least 10% in the weekly dose was considered a clinically meaningful dose change.

RESULTS

Twenty-five of 42 patients met the inclusion criteria. Reasons for exclusion are described in **Figure 1**. The average age of the patients was 76.0 years. The average $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischemic attack) score was 2.0, and 44.0% of patients reported using acetaminophen regularly. Additional patient demographic characteristics are listed in **Table 2**.

Only 1 patient had an INR of greater than 4.0 during the study period (INR = 4.1). This patient also experienced superficial bleeding on the shins that did not require medical attention. Of note, this patient was also taking prednisone. There were no other INR values greater than 4.0. When considering secondary outcome measures, there were no episodes of bleeding requiring medical attention, nor were there any thromboembolic events. An average of 11.0 days (95% CI 8.3 to 13.6) was needed for patients to reach a therapeutic INR. The average predicted and actual weekly maintenance doses were 26.9 mg (95% CI 22.8 to 31.0) and 31.9 mg (95% CI 26.5 to 37.2), respectively. The predicted and actual doses correlated modestly ($r^2 = 0.47$; **Figure 3**).[9] The difference between predicted and actual daily doses was within 1 mg in 17 patients (68.0%), and the predicted dose was equal to the actual dose in 3 patients (12.0%).

Three patients were found to have deviated from the study protocol either by missing warfarin doses or failing to comply with scheduled INR test dates. A separate analysis of patients who did not deviate from the warfarin dose and test date recommendations did not identify important differences.

DISCUSSION

The objective of our study was to evaluate the use of a simple warfarin initiation protocol for outpatients

Table 2. Patient demographic characteristics: *N* = 25.

CHARACTERISTIC	VALUE
Female sex, n (%)	17 (68.0)
Mean (SD; range) age, y	76.0 (9.4; 56.0 to 89.0)
Mean (SD; range) body weight,* kg	84.0 (26.6; 53.5 to 144.4)
Mean (SD; range) eGFR,† mL/min	59.2 (19.5; 25 to 103)
Comorbidities, n (%)	
• Hypertension	19 (76.0)
• Heart failure	3 (12.0)
• Coronary artery disease	3 (12.0)
• Diabetes	9 (36.0)
• Stroke or TIA	1 (4.0)
• Hypothyroidism	5 (20.0)
• Hyperthyroidism	2 (8.0)
Mean (SD) $CHADS_2$ score	2.0 (0.7)
Warfarin potentiating medications, n (%)	
• Acetaminophen‡	11 (44.0)
• Antibiotics	2 (8.0)
• Proton pump inhibitors	8 (32.0)
• Amiodarone	1 (4.0)
• Selective serotonin reuptake inhibitors	3 (12.0)

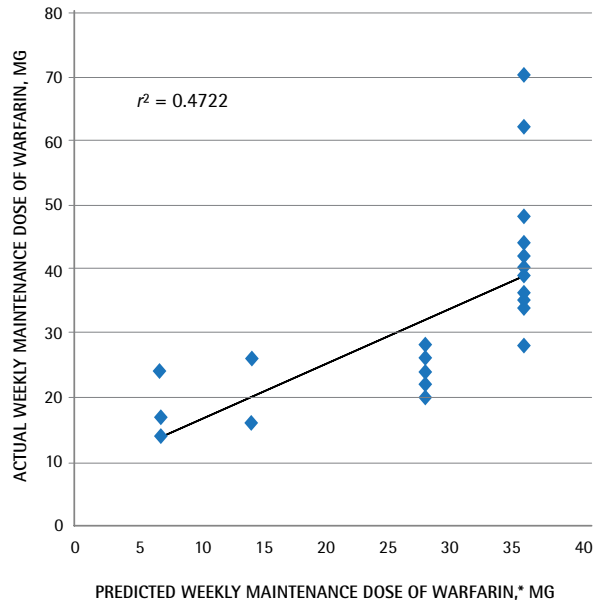
$CHADS_2$—congestive heart failure, hypertension, age ≥ 75 y, diabetes mellitus, and stroke or TIA; eGFR—estimated glomerular filtration rate; TIA—transient ischemic attack.
*Data missing for 4 patients.
†The eGFR for 1 patient was recorded as > 120 mL/min and was not incorporated into the mean.
‡For 1 patient it was unclear whether he or she was taking acetaminophen.

with atrial fibrillation. There were 3 main findings. First, the nomogram used was associated with a low risk of excessive anticoagulation. There were no major bleeding episodes or thromboembolic events. Only 1 patient had an INR greater than 4.0, with concurrent prednisone use as a possible contributor.

Second, a therapeutic INR was achieved in 11.0 days on average, which is consistent with another outpatient protocol, but slightly longer than warfarin induction regimens for inpatients.[6-8] Eleven days seems acceptable, as rapid achievement of a therapeutic INR is unnecessary for patients with stable, chronic atrial fibrillation,[13] and evidence suggests that the risk of bleeding is highest in the first 30 days of warfarin therapy.[5]

Finally, the nomogram was helpful in predicting the maintenance dose of warfarin. The day 4 INR alone explained nearly half of the variability in the maintenance dose. This is rather impressive considering that a different algorithm using a variety of clinical and pharmacogenetic factors was able to explain only 43% of the variability in warfarin dosing among patients.[14]

Figure 3. Correlation between the predicted weekly maintenance dose of warfarin and the actual weekly maintenance dose



*Predicted weekly maintenance dose based on the nomogram for 4 mg of warfarin from Siguret et al.[9]

Limitations

There are important limitations to this study. First, despite the low incidence of bleeding and thromboembolic events in the study population, our sample of 25 patients was not large enough to adequately assess these end points. Second, while we found that the day 4 INR could account for 47.2% of the variability in warfarin dose requirements, the derivation and validation study by Siguret and colleagues using the same nomogram reported that the day 4 INR accounted for 84%.[9] This might relate to differences in the patients studied (patients in our study were younger), the setting (warfarin dose administration was supervised and INRs were measured more frequently in the hospital setting), or a combination of these factors. Nonetheless, our study is more reflective of the challenges experienced in an ambulatory practice.

Conclusion

This pilot study demonstrates the utility of a simple warfarin initiation protocol for ambulatory patients with atrial fibrillation. Future studies will aim to enrol more patients in hopes of demonstrating a reduction in bleeding and thromboembolic complications using this algorithm.

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Contributors

All authors made substantial contributions to the design of the study, and to the analysis and interpretation of the data. **Dr Srinivasan Sridhar** and **Dr Leung** drafted the article. **Ms Seymour** and **Dr Nagge** revised the manuscript for important intellectual content. **Dr Nagge** was responsible for the study concept.

Competing interests

None declared

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