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ORIGINAL ARTICLE

Effect of a simple two-step warfarin dosing algorithm on anticoagulant control as measured by time in therapeutic range: a pilot study

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Summary. *Background:* The efficacy and safety of vitamin K antagonists for the prevention of thromboembolism are dependent on the time for which the International Normalized Ratio (INR) is in the therapeutic range. The objective of our study was to determine the effect of introducing a simple two-step dosing algorithm, as compared with dosing by anticoagulation clinic staffs on the basis of their experience, on time in therapeutic range (TTR) of warfarin therapy. *Methods:* We compared TTRs of all clinic patients before and after the introduction of a simple two-step dosing algorithm at a single anticoagulation clinic in Canada, between 1 August 2006 and 24 December 2008. TTR was calculated using the linear interpolation method of Rosendaal. *Results:* We included 873 patients in the 'before' phase and 1088 patients in the 'after' phase. Introduction of the dosing algorithm significantly increased TTR of patients with a therapeutic INR range of 2–3 from 67.2% to 73.2% ($P < 0.001$), and that of patients with a therapeutic INR range of 2.5–3.5 from 49.8% to 63.8% ($P < 0.001$). *Conclusions:* The introduction of a simple two-step warfarin-dosing algorithm in place of dosing by experienced anticoagulation clinic staff significantly improved mean TTR for patients in a tertiary-care anticoagulation clinic. This inexpensive and widely applicable algorithm has the potential to improve warfarin control.

Keywords: dosing algorithm, time in therapeutic range, warfarin.

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Introduction

Oral vitamin K antagonists (VKAs) are effective for the prevention of thromboembolic complications in patients with atrial fibrillation (AF) or prosthetic heart valves, and for the prevention and treatment of venous thromboembolism, but can cause bleeding. The risks and benefits of VKAs are dependent on the time for which the International Normalized Ratio (INR) is in the therapeutic INR range [1]. Accordingly, time in therapeutic range (TTR) has become a quality measure for VKA management.

The method of VKA dose adjustment appears to be a key determinant of TTR. The 2008 guidelines of the American College of Chest Physicians (ACCP) for the management of patients receiving VKAs recommend one of the following three approaches to optimize TTR: (i) the use of an anticoagulation clinic; (ii) computerized dose adjustment; or (iii) patient self-monitoring [1]. This recommendation is based on the results of observational studies and randomized trials. In a systematic review of 67 studies of anticoagulation management, patients treated at a specialized anticoagulation clinic had significantly higher TTR than those receiving usual care (65.6% vs. 56.7%, $P < 0.0001$), and those who were self-managed had significantly higher TTR than those who were not self-managed (71.5% vs. 63.1%, $P = 0.03$) [2]. In the Automated Program for Oral Anticoagulant Treatment randomized trial, computerized dose adjustment significantly improved TTR as compared with usual care (71.2% vs. 68.2%, $P < 0.001$) [3]. Not all patients, however, have access to an anticoagulation clinic or can afford a home monitoring device, and the acquisition and maintenance costs of computerized methods of dose adjustment are substantial.

Warfarin dosing algorithms are an attractive alternative method for VKA dose adjustment, because they are simple, inexpensive and widely applicable, but maintenance dosing algorithms have undergone only limited evaluation [4,5]. The goal of our study was to assess the effectiveness of a simplified

manual dosing algorithm in patients receiving long-term warfarin therapy who were being managed at a single specialist anticoagulation clinic. This algorithm was developed by the Anticoagulation Clinic of Henry Ford Hospital on the basis of expert clinical experience (S. Kaatz, personal communication) but was never formally validated.

Materials and methods

The study protocol was approved by the Research Ethic Board of McMaster University and Hamilton Health Sciences Corporation, and the study was conducted at the Hamilton General Hospital.

Study design

In the first part of the study, we determined mean TTR at the Hamilton General Hospital anticoagulant clinic in patients whose dose of warfarin was adjusted by anticoagulation clinic staff on the basis of their clinical experience. In the second part of our study, we measured mean TTR at our clinic after the introduction of the warfarin dosing algorithm.

Patients

All patients managed by our anticoagulation clinic were eligible for inclusion. Patients were excluded if the INR was measured less frequently than once every 3 months, if the nominated therapeutic INR range was inconsistent with the recommendations of the 7th conference of the ACCP [6], if the patients were treated with a VKA other than warfarin, or if the patient was participating in another warfarin dose management study.

Warfarin dose adjustment

Anticoagulation clinic staffs were responsible for all warfarin prescriptions throughout the study period. Before the introduction of the algorithm, warfarin dose adjustments were based on clinical experience. After introduction of the simple two-step algorithm presented in Table 1, anticoagulation clinic staff based warfarin dose prescriptions on the recommendations provided by the algorithm. This algorithm is designed for use in patients already stabilized on warfarin, and takes into account patients' most recent INR result(s) and the previous weekly warfarin dose prescription. The algorithm recommends no dose change when the INR is in the therapeutic range, a 10% adjustment in the weekly dose of warfarin when two consecutive INR results are out of range by no more than 0.5 units below or 1.0 unit above the therapeutic INR range, and a 10%–20% adjustment in the weekly dose of warfarin when the deviation from the therapeutic INR range is more extreme. For very high INRs, warfarin is held and/or vitamin K is administered as appropriate. To identify possible reasons for out of range INRs, patients were asked about missed doses of warfarin, or changes in diet (increase or decrease in vitamin K-rich foods), medications (e.g. antibiotics or amiodarone), or intercurrent illness.

Data collection

A standardized data collection form was used to record the following patient information: age, sex, indication for warfarin therapy, therapeutic INR range, INR result, and recommended weekly dose of warfarin. Data were collected for the period 1 August 2006 to 30 September 2007 ('before' introduction of the algorithm) and 15 July 2008 to 24 December 2008 ('after' introduction of the algorithm). During the intervening period, no data were collected, but clinic staff began using the two-step dosing algorithm.

Data analyses

TTR TTR was calculated using a modification of the Rosendaal linear interpolation method [7]. This method assumes that there is a linear relationship between two consecutive INR results and determines the proportion of time for which the INR is below, within or above the therapeutic range [7]. We excluded the following periods in our calculation of TTR: (i) the interval between two consecutive INR measurements if more than 8 weeks (56 days) separated the two results [8]; and (ii) 1 week before and 3 weeks after temporary warfarin interruption. Only those patients who had at least 90 evaluable days in the 'before' phase or 30 evaluable days in the 'after' phase were eligible for inclusion in the final analyses.

Consistency of dosing with the two-step dosing algorithm We calculated the proportion of warfarin dosing recommendations during the 'before' phase of the study that happened to be consistent with the algorithm, and compared this with the consistency of warfarin dosing prescriptions with the algorithm during the 'after' phase. We defined dosing as being consistent with the algorithm if the prescribed dose was within 5% of the algorithm recommended dose.

Statistical analyses

Statistical analyses were performed with SAS statistical software (version 9.1; SAS Institute Inc., Cary, NC, USA). The significance of any differences in baseline characteristics between the 'before' and 'after' phase study populations were tested with a chi-square test for categorical variables and with an independent *t*-test for continuous variables. To evaluate the differences in baseline characteristics between patients receiving warfarin for different indications, we used analysis of variance (ANOVA). Univariate linear regression analysis was used to explore the relationship between percentage consistency of dosing with the two-step warfarin-dosing algorithm and mean TTR. A two-sided *P*-value of < 0.05 was taken to indicate statistical significance.

Table 1 Two-step warfarin dosing algorithm (maintenance)

Goal of INR 2.0–3.0		Goal of INR 2.5–3.5	
INR	Action	INR	Action
≤ 1.5*	Increase weekly dose by 15%; repeat INR determination in 7–14 days	≤ 1.5*	Increase weekly dose by 20%; repeat INR determination in 7–14 days
1.51–1.99*	If falling or low on two or more occasions, increase weekly dose by 10%; repeat INR determination in 7–14 days	1.51–1.99*	If unexplained, increase weekly dose by 15%; repeat INR determination in 7–14 days
		2.00–2.49*	If falling or low on two or more occasions, increase weekly dose by 10%; repeat INR determination in 7–14 days
2.00–3.00	No change	2.50–3.50	No change
3.01–3.99*	Do not hold warfarin. If rising or high on two or more occasions, decrease weekly dose by 10%; repeat INR determination in 7–14 days	3.51–4.49*	Do not hold warfarin. If rising or high on two or more occasions, decrease weekly dose by 10%; repeat INR determination in 7–14 days
4.00–4.99	Hold for 1 day. Decrease weekly dose by 10%; repeat INR determination in 7–14 days	4.50–4.99	Hold for 1 day. Decrease weekly dose by 10%; repeat INR determination in 7–14 days
5.00–8.99	Hold warfarin. Consider oral vitamin K 2–4 mg† if at increased risk of bleeding. If INR still high 24 h later, consider giving 1–2 mg of additional oral vitamin K† and restart at lower dose (decrease weekly dose by 15%) when INR is therapeutic. Check INR weekly until stable	5.00–8.99	Hold warfarin. Consider oral vitamin K 2–4 mg† if at increased risk of bleeding. If INR still high 24 h later, consider giving 1–2 mg of additional oral vitamin K† and restart at lower dose (decrease weekly dose by 15%) when INR is therapeutic. Check INR weekly until stable
≥ 9.0	Hold warfarin and give oral vitamin K 5.0–10.0 mg.† Monitor more frequently and repeat vitamin K if necessary	≥ 9.0	Hold warfarin and give oral vitamin K 5.0–10.0 mg.† Monitor more frequently and repeat vitamin K if necessary
Serious bleeding regardless of INR	Hold dose and give intravenous vitamin K 10 mg and fresh frozen plasma, recombinant factor VIIa, or prothrombin complex concentrates, depending on the urgency of the situation	Serious bleeding regardless of INR	Hold dose and give intravenous vitamin K 10 mg and fresh frozen plasma, recombinant factor VIIa, or prothrombin complex concentrates, depending on the urgency of the situation

INR, International Normalized Ratio. *Clinical and professional judgement may allow variation in the application of the algorithm. †The preferred method of vitamin K administration in non-emergency situations is orally. Avoid subcutaneous or intramuscular administration.

Results

Figure 1 shows the flow of patient enrollment and data collection; 873 patients were included in the 'before' phase and 1088 patients in the 'after' phase of the study. Five hundred and forty-seven patients participated in both phases.

The number of INRs was 14 867 'before' and 7977 'after' algorithm implementation, and the total numbers of evaluated patient days were 323 879 and 146 858, respectively. AF was the most common indication for warfarin in both phases of the study, accounting for almost half of the patients (Table 2). AF patients were significantly older than patients with other indications for warfarin ($P < 0.001$).

Distribution of INR results

Figure 2 shows that INR results in the 'before' phase of the study were more or less normally distributed around the therapeutic range in patients with a range of 2.0–3.0, but were clustered around the lower end in patients with a therapeutic INR range of 2.5–3.5. In the 'after' phase, there were fewer subtherapeutic INR results ($P < 0.01$), but the proportion of supratherapeutic INR results was not significantly different from that in the 'before' phase.

Change in TTR following implementation of the two-step dosing algorithm

Following implementation of the two-step dosing algorithm, mean TTR increased from 67.2% to 73.2% ($P < 0.001$) in patients with a therapeutic range of 2.0–3.0, and from 49.8% to 63.8% ($P < 0.001$) in patients with a therapeutic range of 2.5–3.5. Mean TTRs were significantly improved in patients with AF, mechanical aortic valve replacement, and mechanical mitral valve replacement (66.7–73.4%, $P < 0.01$; 67.6–75.1%, $P < 0.01$; and 49.8–62.7%, $P < 0.01$, respectively), and there were directionally consistent, albeit non-significant improvements, in TTR in patients with venous thromboembolism (67.6–70.8%, $P = 0.28$) and in those with other indications for warfarin (68.6–70.4%, $P = 0.4$).

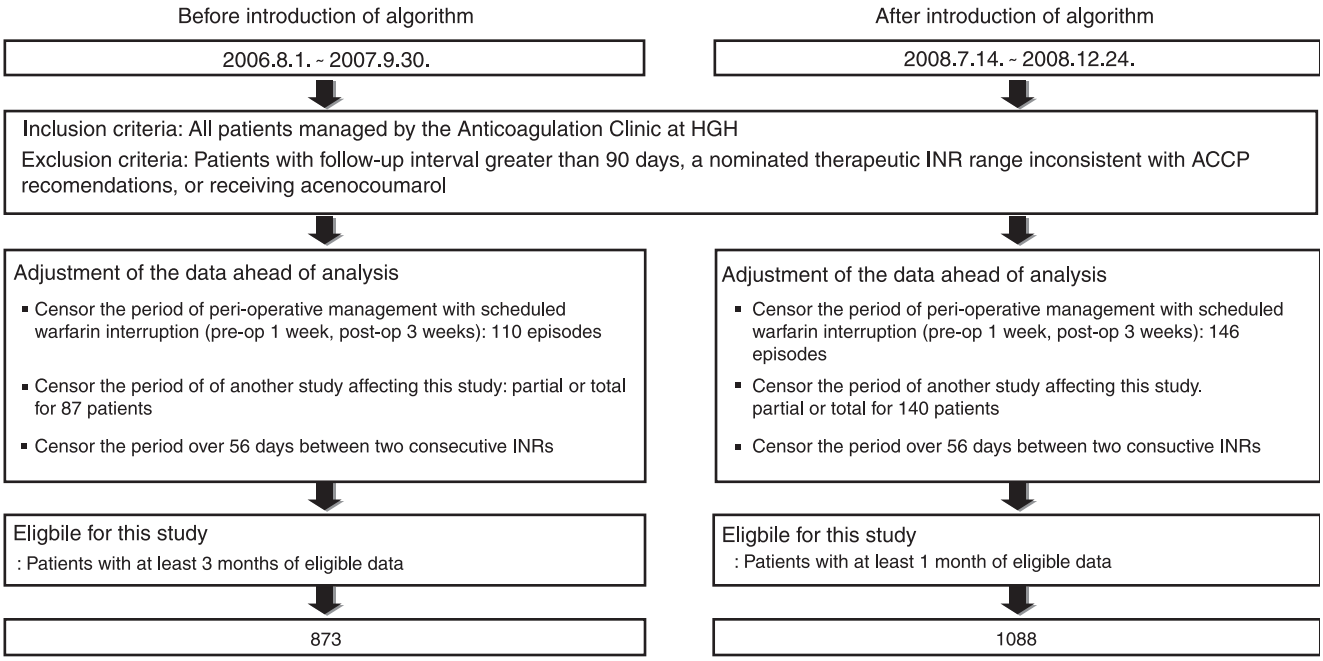


Fig. 1. Study flow chart. ACCP, American College of Chest Physicians; HGH; Hamilton General Hospital; INR, International Normalized Ratio.

Table 2 Patient baseline characteristics

Indication of OAC	Therapeutic INR range	*n* (%)			Male, *n* (%)			Age (years)		
		Before	After	*P*-value	Before	After	*P*-value	Before	After	*P*-value
Atrial fibrillation	2.0–3.0	388 (44.4)	499 (45.8)	0.53	239 (61.6)	295 (59.1)	0.53	74.4	73.4	0.50
AVR (mechanical)	2.0–3.0	217 (24.9)	214 (19.7)	< 0.01	148 (68.2)	161 (75.2)	< 0.01	64.8	63.9	0.42
VTE	2.0–3.0	104 (11.9)	147 (13.5)	0.29	64 (61.5)	69 (46.9)	0.29	65.2	61.8	0.08
Others*	2.0–3.0	46 (5.3)	77 (7.1)	0.10	24 (52.2)	46 (59.7)	0.10	63.4	65.3	0.48
MVR (mechanical)	2.5–3.5	118 (13.5)	127 (11.7)	0.22	47 (39.8)	45 (35.4)	0.22	66.1	65.5	0.69
Total	–	873 (100)	1088 (100)†	–	522 (59.8)	635 (58.4)†	–	69.2	68.5	0.22

AVR, aortic valve replacement; INR, International Normalized Ratio; MVR, mitral valve replacement; OAC, oral anticoagulant; VTE, venous thromboembolism. *Includes patients with peripheral vascular disease, recurrent ischemic stroke without atrial fibrillation, or congestive heart failure. †Includes 24 patients with mechanical AVR and additional risk factor for thromboembolism (atrial fibrillation, myocardial infarction, left atrial enlargement, poor ejection fraction).

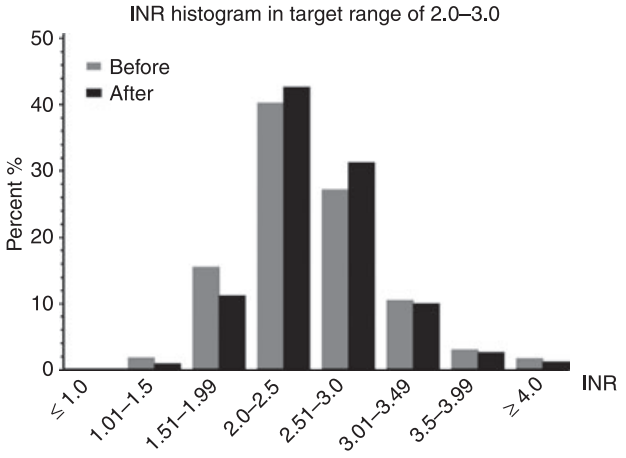
Consistency of dosing with the two-step dosing algorithm

For patients with a therapeutic INR range of 2–3, 71% of warfarin dosing prescriptions during the 'before' phase happened to be consistent with the warfarin dosing algorithm, whereas 'after' its introduction, 90% of warfarin dosing prescriptions were consistent with the algorithm. For patients with a therapeutic range of 2.5–3.5, 56% of warfarin dosing prescriptions during the 'before' phase were consistent with the warfarin dosing algorithm, whereas 'after' its introduction, 81% of warfarin dosing prescriptions were consistent with the algorithm (Table 3). The proportion of subtherapeutic INR results that led to a change in the dose of warfarin increased from 38.5% in the 'before' phase to 56.2% in the 'after' phase for patients with a therapeutic range of 2.0–3.0, and from 23.5% to 43.6% in those with a therapeutic range of 2.5–3.5. The proportion of supratherapeutic INR results that led to a change in the dose of warfarin increased from 33.1% to 54.7% in patients with a therapeutic range of 2.0–3.0, and from 38.5% to 71.6% in those with a therapeutic range of 2.5–3.5. The mean interval between INR tests in the 'before' phase was 26 days, as compared with 24.2 days in the 'after' phase, reflecting a small increase in the frequency of testing following the introduction of the algorithm.

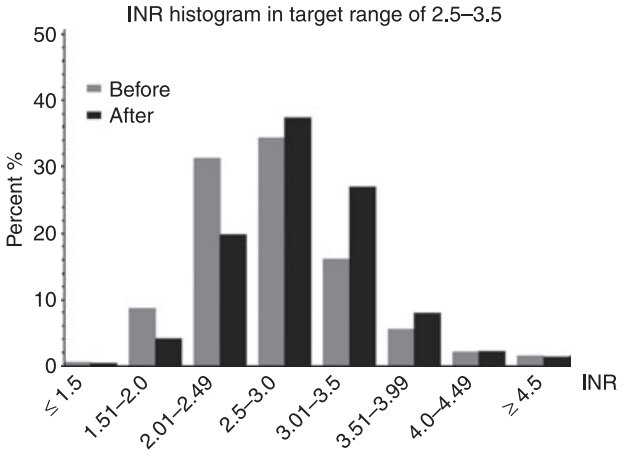
Figure 3 shows scatter plots of TTR vs. consistency of dosing with algorithm recommendations in the 'before' phase of the study: 54% ($r^2 = 0.54$) of the variation in TTR was explained by consistency of dosing with the algorithm when the therapeutic INR range was 2.0–3.0, and 65% ($r^2 = 0.65$) of the variation in TTR was explained by consistency of dosing with the algorithm when the therapeutic range was 2.5–3.5.

Discussion

Patients managed by our anticoagulation clinic with a therapeutic INR range of 2–3 had a mean TTR of 67.2% when clinic



INR	Before	After	*P*-value
< 2.0	17.6	12.6	< 0.01
2.0 ≤ ≤ 3.0	67.2	73.2	< 0.01
> 3.0	15.2	14.2	0.19



INR	Before	After	*P*-value
< 2.5	41.3	25.0	< 0.01
2.5 ≤ ≤ 3.5	49.9	63.8	< 0.01
> 3.5	8.8	11.2	0.12

Fig. 2. International Normalized Ratio (INR) histogram of INR results before and after introduction of the algorithm. INR results in the 'before' algorithm implementation were more or less normally distributed around the therapeutic range in patients with a range of 2.0–3.0, but were clustered around the lower end of the therapeutic INR range in patients with a range of 2.5–3.5. In the 'after' algorithm implementation, there were fewer sub-therapeutic INR results, particularly for patients with a therapeutic range of 2.5–3.5, but the proportion of supratherapeutic INR results was not substantially different.

staff adjusted the dose on the basis of their experience, but this increased to 73.2% after introduction of a simple two-step dosing algorithm. The corresponding improvement in TTR among patients with a therapeutic INR range of 2.5–3.5 was from 49.8% to 63.8%. Overall, TTR for both INR ranges increased from 64.9% to 72.0%, and warfarin dosing consistent with the algorithm increased from 68.7% to 88.9%, in the

Table 3 Comparisons of mean percentage time in therapeutic range (TTR) and percentage consistency of warfarin dose prescriptions with the two-step dosing algorithm recommendations 'before' and 'after' its implementation

	Mean % TTR			% Consistency of dose prescriptions with algorithm recommendations		
Indication of OAC	Before	After	*P*-value*	Before	After	*P*-value*
INR 2.0–3.0						
Atrial fibrillation	66.7	73.4	< 0.01	71.1	90.3	< 0.01
AVR (mechanical)	67.6	75.1	< 0.01	70.1	90.3	< 0.01
VTE	67.6	70.8	0.28	69.9	90.3	< 0.01
Others[*]	68.6	72.4	0.40	73.0	88.9	< 0.01
INR 2.5–3.5						
MVR (mechanical)	49.8	62.7	< 0.01	55.8	81.7	< 0.01
Overall	64.9	72.0[‡]	< 0.01	68.7	88.9[‡]	< 0.01

AVR, aortic valve replacement; INR, International Normalized Ratio; MVR, mitral valve replacement; OAC, oral anticoagulant; VTE, venous thromboembolism. **P*-values were adjusted by age. [†]Includes patients with peripheral vascular disease, recurrent ischemic stroke without atrial fibrillation, or congestive heart failure. [‡]Includes 24 patients with mechanical AVR and additional risk factor for thromboembolism (atrial fibrillation, myocardial infarction, left atrial enlargement, poor ejection fraction).

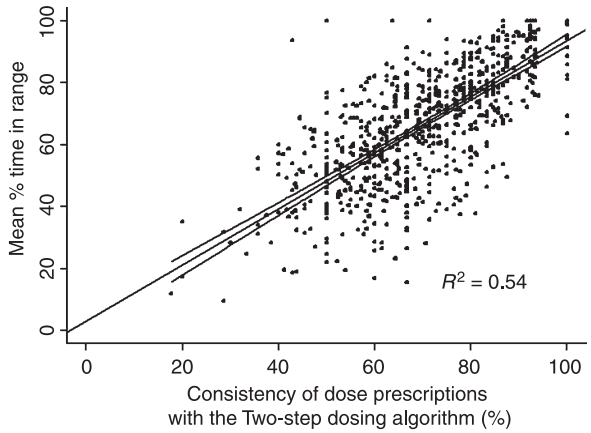


Fig. 3. Scatter plot of individual patient percentage time in therapeutic range (TTR) vs. percentage consistency of warfarin dosing prescriptions with the algorithm recommendation. Before algorithm implementation, 54% (r^2 = 0.54) of the variation in TTR was explained by consistency of dosing with the algorithm dosing recommendation when the therapeutic range was 2.0–3.0, and 65% (r^2 = 0.65) of the variation in TTR was explained by consistency of dosing with the algorithm dosing recommendation when the therapeutic range was 2.5–3.5.

'before' and 'after' phases of the study. These results suggest that the introduction of a simple, inexpensive warfarin dosing algorithm in place of dosing based on clinical experience significantly improves mean TTR for warfarin-treated patients.

The greatest improvement in TTR with the use of the algorithm was achieved in patients with a therapeutic INR range of 2.5–3.5 in whom TTR was < 50% prior to the introduction of the algorithm. Poor INR control in patients with a therapeutic INR range of 2.5–3.5 as compared with

those with a therapeutic INR range of 2.0–3.0 might, at least in part, be explained by the greater sensitivity of higher INRs to dietary and drug effects. The relationship between warfarin dose and INR is log-linear, and small changes in drug levels can be expected to cause greater variability in the INR when the therapeutic range is 2.5–3.5 than when it is 2.0–3.0. An additional factor that could explain the poor INR control in patients with a therapeutic range of 2.5–3.5 is concern by prescribers that higher INRs will increase the risk of bleeding. Concern by prescribers about the risk of bleeding with higher INRs could potentially explain why consistency of dosing with the algorithm in the 'after' period was lower for patients in the INR range 2.5–3.5 than for those in the INR range 2.0–3.0. Despite this, our data demonstrate that use of a standardized dosing algorithm in patients with a therapeutic range of 2.5–3.5 substantially increases TTR, especially by decreasing time spent below the therapeutic range.

There is limited evidence regarding the effect of warfarin maintenance dosing algorithms on quality of INR control [4,5]. The beneficial effect of anticoagulation clinics on TTR has been attributed to improved standardization of dosing, but it is unclear what proportion of anticoagulation clinics use an algorithm to guide dosing. Computerized dosing systems employ an algorithm to make dosing recommendations, but the details of these algorithms are not published, to protect commercial interests. Thus, we do not know to what extent dosing algorithms account for the superior INR control observed in anticoagulation clinics and with the use of computerized systems as compared with dosing based on clinical experience, or the characteristics that explain the success of algorithms. To our knowledge, our study is the first to show that the implementation of a simple two-step warfarin dosing algorithm significantly improves INR control in a large-scale anticoagulation clinic. We suspect that the success of the algorithm evaluated in our study can be explained by strict standardization of warfarin dose adjustment and relatively small dose modifications when the INR is out of range.

Our study has several potential limitations. First, our before–after comparison was not randomized, and we cannot exclude the impact of factors other than the algorithm on the improvement in TTR that we observed. However, the correlation that we observed between consistency of warfarin dosing prescriptions and TTR during the 'before' phase of the study supports the importance of the algorithm in determining TTR. Second, there were some differences between the 'before' and 'after' phases of the study in the characteristics of included patients and the duration of data collection. However, adjustment of our analyses for significant differences in patient characteristics did not alter our conclusion and a shorter duration of data collection in the 'after' phase does not introduce bias, but simply reduces statistical power. Finally, our study was not designed to determine whether improvement in TTR translates into an improvement in clinical outcomes. However, the strong, consistent, dose-related (better outcome with higher TTR) and biologically plausible association between TTR and outcomes that has been previously reported suggests that an improvement in TTR is likely to yield an improvement in outcome. This conclusion will be definitively tested in a large cluster randomized trial that is currently in the advanced stages of planning.

Conclusion

We showed in a 'before–after' study that introduction of the simple two-step warfarin dosing algorithm in place of dosing by clinic staff based on experience was associated with a significant improvement in mean TTR for patients in our tertiary-care anticoagulation clinic. As many patients in the general community do not have access to other recommended evidence-based methods of warfarin dosing, we are now conducting a cluster randomized trial to determine whether our simple two-step dosing algorithm can improve TTR in a community setting.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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