Comparison of 10-mg and 5-mg Warfarin Initiation Nomograms Together with Low-Molecular-Weight Heparin for Outpatient Treatment of Acute Venous Thromboembolism

A Randomized, Double-Blind, Controlled Trial

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Background: **The optimal means of achieving therapeutic oral anticoagulation in the outpatient setting has not been determined.**

Objective: **To compare a 10-mg dosing nomogram with a 5-mg nomogram that has been suggested to be sufficient for warfarin initiation.**

Design: **Randomized, controlled clinical trial.**

Setting: **Outpatient venous thromboembolism services of four tertiary care hospitals.**

Patients: **201 of 210 consecutive patients with objectively confirmed diagnoses of acute venous thromboembolism.**

Intervention: **All patients were treated with subcutaneous low-molecular-weight heparin for a minimum of 5 days until a therapeutic international normalized ratio (INR) was achieved. Patients were randomly assigned to initially receive a 10-mg or 5-mg dose of warfarin.**

Measurements: **The primary end point was time in days to therapeutic INR. Secondary end points were the proportion of patients who had achieved a therapeutic INR by day 5, the total number of INR assessments, the number of INR measurements greater than 5.0, incidence of recurrent venous thromboembolism and major bleeding, and survival.**

Results: **210 consecutive patients met the inclusion criteria. Of these, 9 were excluded and 201 were randomly assigned to study groups (104 to the 10-mg group and 97 to the 5-mg group). Demographic characteristics of both groups were similar. Patients in the 10-mg group achieved therapeutic INR 1.4 days earlier than patients in the 5-mg group ($P < 0.001$). Eighty-three percent of patients in the 10-mg group achieved a therapeutic INR by day 5 versus 46% in the 5-mg group ($P < 0.001$). Fewer INR assessments were performed in the 10-mg group than in the 5-mg group (8.1 vs. 9.1; $P = 0.04$). There were no significant differences between the two groups in recurrent events, major bleeding, survival, and number of INR measurements greater than 5.0.**

Conclusion: **The 10-mg warfarin initiation nomogram is superior to the 5-mg nomogram because it allows more rapid achievement of a therapeutic INR.**

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The management of venous thromboembolism has improved substantially in the past 10 years. Conventional therapy consists of unfractionated or low-molecular-weight heparin for 5 to 7 days, together with oral anticoagulation with warfarin given for a minimum of 3 months (1, 2). Low-molecular-weight heparin facilitates outpatient treatment, and warfarin is usually initiated within 24 hours. Clinical trials have demonstrated that low-molecular-weight heparin may be safely discontinued after 5 days once the international normalized ratio (INR) has remained greater than 1.9 for 24 hours (2, 3).

Nurses or pharmacists often coordinate outpatient management of venous thromboembolism with appropriate physician support (4). For outpatient therapy, minimizing the time to a therapeutic INR is advantageous because it potentially decreases the cost and inconvenience of low-molecular-weight heparin therapy. The initiation of warfarin treatment is problematic, however, because of variations in dose response. A dosing nomogram to facilitate safe, timely warfarin initiation to achieve therapeutic INRs would be useful.

We previously developed and tested a nomogram for the initiation of warfarin therapy using a 10-mg loading dose and found that it was superior to standard physician practice because it resulted in shorter time to a therapeutic INR (5). This nomogram, however, required daily INR testing and was therefore not ideal for outpatient management. We subsequently revised the nomogram so that it requires INR assessments only on days 3 and 5 during the first 8 days of therapy. We found that the revised nomogram was successful: Almost 90% of patients had a therapeutic INR by the 5th day of treatment (6). The objective of our current study was to perform a randomized, controlled trial comparing the effectiveness and feasibility of a warfarin nomogram using a 10-mg loading dose with those of a nomogram using a 5-mg loading dose for the management of outpatients with acute venous thromboembolism.

METHODS

Patients

Consecutive outpatients with a diagnosis of objectively confirmed acute venous thromboembolism (deep venous thrombosis or pulmonary embolism) who presented to the thrombosis clinics of four Canadian academic centers were candidates for study inclusion. Patients were not admitted to the study if they had a baseline INR greater than 1.4, had thrombocytopenia (platelet count $< 50 \times 10^9$ cells/

mL), were younger than 18 years of age, required hospitalization, had received oral anticoagulant therapy within the previous 2 weeks, or were at high risk for major bleeding (as judged by the attending physician).

Design

This study was a randomized, double-blind (physician–patient), controlled trial. Randomization was stratified by study center and presence of active malignant disease. The randomization sequence was computer generated by the trial statistician. The details of the randomization sequence, which were not known to the investigators or to the study coordinator, were contained in sets of sequentially numbered, opaque, sealed envelopes. The outside of each envelope was marked only with the name of the hospital, whether the patient had a malignant condition, and a patient number. Patients were assigned to 5-mg or 10-mg warfarin induction by using previously validated nomograms (**Table 1** and **Figure 1**) (6, 7). The 5-mg nomogram, as published, specifies a dose range on each day after the first day of treatment with no indication of how to choose the dose (7). For the current study, we chose the higher dose whenever a range was indicated. The research ethics boards at each of the participating institutions approved the study, and informed consent was obtained from all participants.

Interventions

Study participants were randomly allocated to warfarin induction with a 10-mg or 5-mg warfarin nomogram (**Table 1** and **Figure 1**) (6, 7). Baseline data collected included demographic characteristics (age, sex), diagnosis, weight, presence of active malignant disease, complete blood count, and INR. International normalized ratios were measured in local licensed clinical laboratories. Treatment was initiated on the first day (day 1) with subcutaneous low-molecular-weight heparin (dalteparin [200 U/kg of body weight] or tinzaparin [175 U/kg]). Low-molecular-weight heparin was continued for a minimum of five daily injections until the INR was therapeutic (>1.9). The initial warfarin dose was determined by using treatment allocation. All warfarin doses were administered in the evening, and blood samples for INR assessments were drawn before 10:00 a.m. Patients in the 10-mg group received 10 mg of warfarin on each of the first 2 days, whereas patients in the 5-mg group were given 5 mg on each of the first 2 days. Subsequent dose adjustments after day 3 were made by using the respective nomograms. International normalized ratios were measured in all patients on the mornings of days 3, 4, and 5. The 10-mg nomogram, unlike the 5-mg nomogram, did not require an INR measurement on day 4 for dosing; however, a measurement was performed for study end point purposes only. If a patient did not have a therapeutic INR by day 5, the INR was measured daily until it was therapeutic. Local attending physicians directed management of warfarin monitoring from day 8 to day 90.

Table 1. **5-mg Warfarin Initiation Nomogram***

Day	INR	Warfarin Dose, *mg*
1		5
2		5
3	<1.5	10
	1.5–1.9	5
	2.0–3.0	2.5
	>3.0	0
4	<1.5	10
	1.5–1.9	7.5
	2.0–3.0	5
	>3.0	0
5	<2.0	10
	2.0–3.0	5
	>3.0	0
6	<1.5	12.5
	1.5–1.9	10
	2.0–3.0	7.5
	>3.0	0

* Adapted from Crowther et al. (7). INR = international normalized ratio.

Context

The optimal methods for achieving therapeutic levels of anticoagulation with warfarin remain uncertain.

Contribution

In this randomized trial of two warfarin dosing nomograms, a 10-mg initiation dose led to a therapeutic international normalized ratio (INR) 1.4 days sooner than a 5-mg initiation dose. The two nomograms had the same rate of adverse events and the same proportion of INR values greater than 5.0.

Clinical Implications

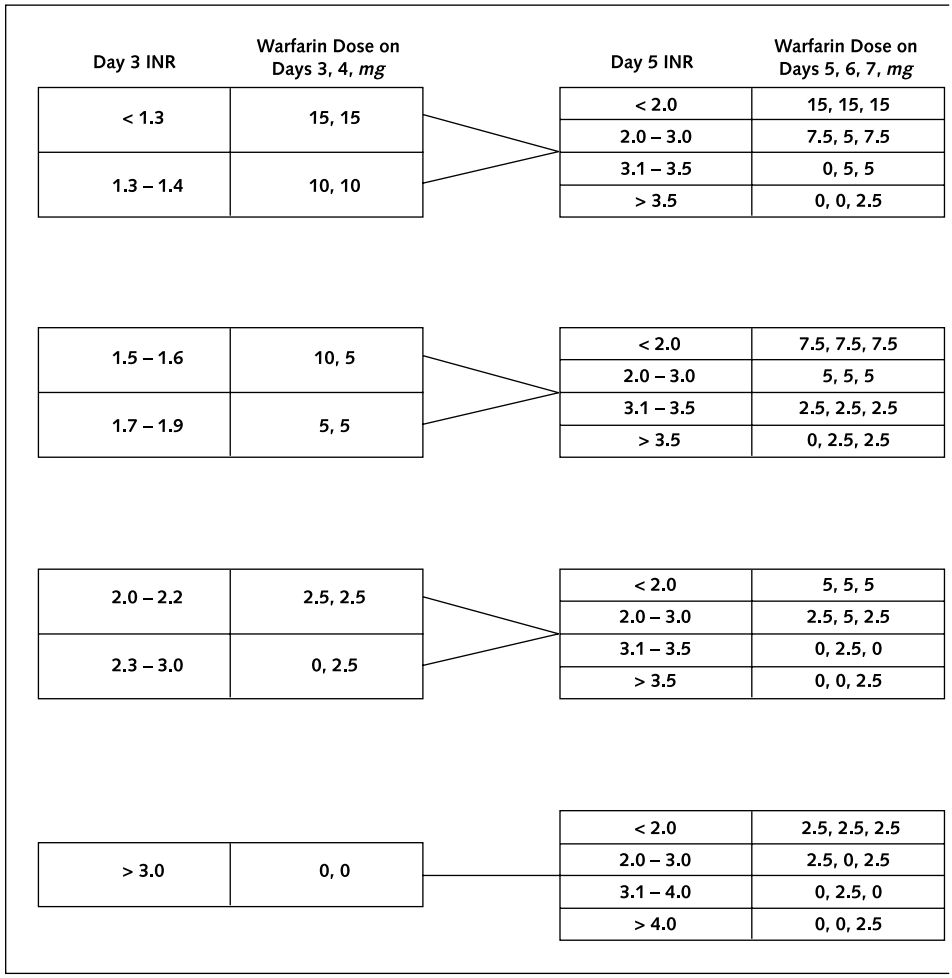
Physicians can more quickly get their patients to a therapeutic INR with warfarin by using a dosing nomogram that starts with a 10-mg dose rather than a 5-mg initiation dose.

–The Editors

End Points

The primary end point of the study was time in days to a therapeutic INR (>1.9). The secondary end points included the proportion of patients whose INRs were within the therapeutic range (2.0 to 3.0) on the 5th day, incidence of recurrent venous thromboembolism within 90 days of diagnosis (as defined by previously published criteria [2, 3]), incidence of major bleeding within 28 days of diagnosis (as defined by previously published criteria [2, 3]), number of INR measurements greater than 5, absolute number of INR assessments in the first 28 days, and 90-day survival. An adjudication committee consisting of three study investigators evaluated all clinical events in a

Figure 1. **10-mg warfarin initiation nomogram.**



All patients receive 10 mg on day 1 and day 2. INR = international normalized ratio.

blinded fashion, and end points were determined by consensus.

Hypothesis

We tested the hypothesis that patients managed with a 10-mg warfarin induction nomogram would achieve therapeutic INRs more rapidly than patients managed with a 5-mg warfarin nomogram. We believed these improvements would occur without increased risk for bleeding.

Sample Size

Using data from our pilot nomogram to estimate standard deviation (1 day), we calculated that 92 patients per group would be required to show a 0.5-day difference in time to a therapeutic INR (90% power; two-sided $\alpha = 0.05$). We considered a 0.5-day difference to be the minimal clinically important difference because it would yield a significant proportion of patients who would not require low-molecular-weight heparin therapy beyond 5 days.

Statistical Analysis

All statistical analyses were performed according to a pre-established analysis plan and by intention to treat. We used SPSS software for all analyses (SPSS, Inc., Chicago, Illinois). Baseline characteristics were described by using descriptive statistics. Mean time to therapeutic INR was compared between the groups by using the unpaired Student *t*-test. Proportions (including the proportion in each group with a therapeutic INR on day 5) were compared by using the unadjusted chi-square test. No interim analyses were conducted. Two-sided significance tests were used throughout, and a *P* value less than 0.05 was considered statistically significant. Multiple linear regression was performed to explore determinants of time to therapeutic INR (after appropriate testing was done to prove the suitability of this analysis). Biologically plausible predictors (age, sex, weight, presence of cancer, and treatment assignment) were included in the original model. Backward stepwise regression was performed, and a *P* value greater than 0.20 was used for variable removal.

RESULTS

Between August 1999 and June 2000, 210 patients were approached for participation in the study. Two pa-

tients were excluded because they had a baseline INR greater than 1.4, 2 were excluded because they required hospitalization, and 5 were excluded because they had received warfarin in the previous 2 weeks. The last patient completed follow-up in September 2000. A total of 201 eligible, consenting patients were enrolled and randomly assigned to treatment (**Table 2**). One hundred four patients were assigned to the 10-mg group, and 97 were assigned to the 5-mg group. The baseline characteristics of both groups were similar, although the 10-mg group included more men. The overall age range was 18 to 98 years, and 32 patients (16%) were older than 75 years of age. All patients were followed for 90 days.

Patients in the 10-mg group achieved a therapeutic INR 1.4 days earlier than patients in the 5-mg group ($P < 0.001$). In addition, many more patients in the 10-mg group than in the 5-mg group achieved a therapeutic INR by day 5 (83% vs. 46%; $P < 0.001$) (**Figure 2**). The 5-mg group also required more INR assessments in the first 28 days (9.1 vs. 8.1; $P = 0.04$). Only two episodes of major bleeding were observed, one in each group, and rates of recurrence of venous thromboembolism did not differ significantly between the two groups ($P = 0.09$). Our conclusions about safety are guarded, however, given the study's limited power for safety assessment. The groups did not differ in the number of INR measurements greater than 6.0 (5 in the 10-mg group and 6 in the 5-mg group) or greater than 5.0 (9 in the 10-mg group and 11 in the 5-mg group) during the first 4 weeks. Of the 20 measurements greater than 5.0, 15 occurred between day 10 and day 28 and only 5 occurred in patients older than 75 years of age.

Although no statistical differences were seen in any of the outcomes among study centers, it is important to note that the study was not powered to detect such differences because the numbers of patients cared for at each center were relatively low. The patients in each group were, however, balanced among centers.

Regression diagnostics confirmed that the data assumptions for linear regression were satisfied. The final linear regression model included treatment assignment ($P < 0.001$), weight ($P < 0.001$), sex ($P = 0.006$), and age ($P = 0.036$) as significant variables influencing time to therapeutic INR. Cancer was eliminated as a significant variable ($P > 0.2$). Among the significant variables, treatment assignment had the lowest P value and was therefore the most significant. Because the 10-mg group included 20% more men than the 5-mg group, an interaction term for sex and group was added to the model; however, it had no significant effects. After adjusting for age, sex, and weight, we found that the adjusted and unadjusted differences in time to therapeutic INR were identical (1.4 days). The overall regression coefficient was 0.357, indicating that more than one third of the variability in the data can be explained by the model.

DISCUSSION

Outpatient treatment of venous thromboembolism has become conventional practice in many medical centers because it decreases cost and improves quality of life (4). However, arranging outpatient treatment is time consuming and human resource intensive because of the need to coordinate low-molecular-weight heparin injections and laboratory testing. The minimum duration of low-molecular-weight heparin therapy is 5 days (1, 2, 3, 8). Therapy beyond that point is not likely to be harmful but increases expense. Warfarin monitoring is particularly problematic in outpatient settings. Therapeutic levels must be ensured efficiently, in a safe and efficacious manner, but the time and cost involved with low-molecular-weight heparin therapy must be reduced.

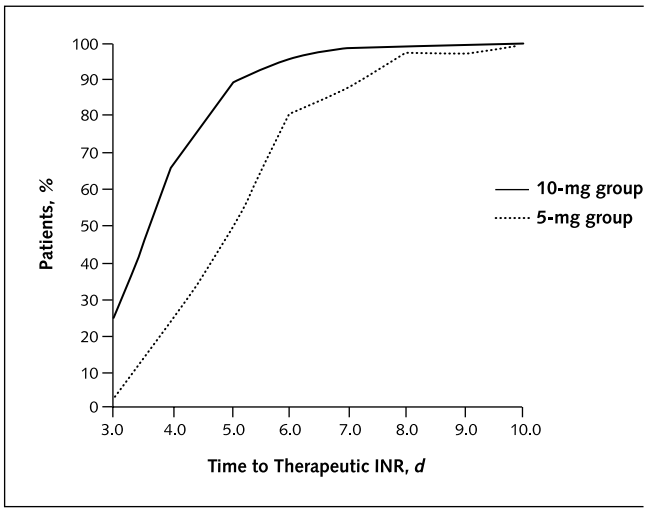
In this study, one of the first of its kind performed exclusively in outpatients, we convincingly demonstrate that a nomogram based on a 10-mg starting dose is more effective than a 5-mg nomogram for outpatient treatment

Table 2. **Comparison of the 10-mg and 5-mg Nomogram Groups***

Variable	10-mg Nomogram Group	5-mg Nomogram Group	*P* Value
Baseline characteristics			
Patients, *n*	104	97	
Mean age ± SD, *y*	55.4 ± 17.4	55.6 ± 17.2	
Men/women, *n/n*	65/39	47/50	
Cancer, *n* (%)	26 (25)	22 (23)	
Mean weight ± SD, *kg*	83.5 ± 18.6	83.4 ± 20.0	
Results			
Mean time to INR >1.9 ± SD, *d*	4.2 ± 1.1	5.6 ± 1.4	<0.001
Patients therapeutic by day 5, *n* (%)	86 (83 [74–89])	45 (46 [36–57])	<0.001
Venous thromboembolism at 90 days, *n* (%)	3 (2.9 [0.6–8.2])	0 (0 [0–3.7])	0.09
Major bleeding episodes at 90 days, *n* (%)	1 (0.96 [0.02–5.2])	1 (1.03 [0.03–5.6])	
Deaths at 90 days, *n*	0	1	
Mean INR tests in the first 4 weeks ± SD, *n*	8.1 ± 2.4	9.1 ± 2.3	0.04
Patients with INR >3.0 in the first 4 weeks, *n*	81	84	>0.2
Patients with INR ≥5.0 in the first 4 weeks, *n*	9	11	>0.2
Patients with INR ≥6.0 in the first 4 weeks, *n*	5	6	>0.2
Total INR >3.0 or <2.0 in the first 4 weeks, *n*	186	207	>0.2

* Values in square brackets are 95% CIs. INR = international normalized ratio.

Figure 2. **Time to therapeutic international normalized ratio (*INR*) in each study group.**



of acute venous thromboembolism. Patients who received a 10-mg starting dose achieved a therapeutic INR (>1.9) more rapidly, were more likely to have a therapeutic INR by day 5 of low-molecular-weight heparin therapy, and required less INR testing. Treatment assignment was the most significant predictor of time to therapeutic INR even when we controlled for other significant variables (sex, age, or weight).

Crowther and colleagues suggested that a 5-mg loading dose of warfarin is as efficient as a 10-mg loading dose for achieving a therapeutic INR by the 5th day of therapy (7, 9). However, they examined a large, heterogeneous inpatient sample and their results may therefore not be relevant to outpatient treatment. Moreover, Crowther and colleagues did not report clinical end points of recurrent venous thromboembolism or bleeding, and their nomogram requires daily INR assessment, which is not ideal for outpatient management. Despite these concerns, however, use of their 5-mg nomogram is increasing (10). We could not reproduce their results when we used their nomogram in our own patients, which was an impetus for our current study.

In another study (11), Crowther and colleagues randomly compared their 5-mg and 10-mg nomograms in 53 patients. They found that 66% of patients in the 5-mg group and 24% in the 10-mg group achieved the primary end point, which was an INR of 2.0 to 3.0. These findings differ from our current results; we found that our two study groups did not differ in achievement of INRs greater than 3.0 but that more patients in the 10-mg group achieved therapeutic INRs by day 5 (**Table 2**).

The superiority of our 10-mg nomogram has several potential explanations. First, our study sample consisted only of patients with a diagnosis of acute venous thromboembolism. Second, we included only outpatients; we have shown elsewhere that inpatients are more sensitive to warfarin and therefore may not need a higher loading dose (5). Third, our nomogram was designed to identify patients who, based on the day 3 INR, required a higher dose of warfarin to achieve a therapeutic INR by day 5. These patients received a day 3 dose of 15 mg, which is higher than that used by Crowther and colleagues (7, 9). Fourth, Crowther and colleagues' 10-mg nomogram is different from the 10-mg nomogram we developed and used in this study.

Our 10-mg nomogram was designed for outpatient management of venous thromboembolism. It is particularly advantageous for this patient population because it does not require daily INR testing. If a patient has a therapeutic INR on day 5, then he will need only two INR assessments in the first 7 days of warfarin therapy besides the baseline assessment. In addition, by allowing more patients to achieve a therapeutic INR by day 5, our 10-mg nomogram can potentially reduce the cost and inconvenience of low-molecular-weight heparin treatment by decreasing the proportion of patients requiring more than 5 days of therapy.

Because our study was underpowered for clinical end points, no safe conclusions can be drawn from the lack of statistical difference between the two nomograms in major bleeding, survival, or recurrent venous thromboembolism. Moreover, on the basis of the exclusion criteria, our study sample was not at high risk for bleeding, although no patients were excluded from the study because of high bleeding risk. It is important to emphasize that our nomogram is not designed for inpatients, who are more sensitive to warfarin because of poor dietary status and concomitant use of broad-spectrum antibiotics that decrease vitamin K absorption from enteric flora. Patients with a baseline INR greater than 1.4 were excluded from our study; therefore, this nomogram should not be used for them.

Since the 10-mg nomogram was designed for rapid initiation of warfarin, practitioners may choose lower-dose initiation when warfarin is started for primary prophylaxis (for example, in patients with atrial fibrillation). Our study included patients of all ages. Patients older than 75 years of age did not have a disproportionate number of INR measurements greater than 5.0, so the 10-mg nomogram should be safe for them. Although there is a concern about more rapid depletion of protein C levels with a 10-mg loading dose (9), patients should be protected from adverse consequences if they receive appropriate anticoagulation with low-molecular-weight heparin, as was provided in our study.

In summary, we found that a 10-mg warfarin initiation nomogram was superior to a 5-mg nomogram because it allowed more outpatients to achieve a therapeutic INR in a shorter period of time. The 10-mg nomogram lends itself well to outpatient management of acute venous thromboembolism, and we recommend its use in this clinical setting.

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