

Evaluation of Anticoagulation Initiation and Comparison of Low Versus High Initial Warfarin Doses

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Background: In clinical practice, warfarin is often initiated with a 10-mg loading dose in an attempt to reduce the time required to reach a therapeutic international normalized ratio (INR). Recent guidelines recommend starting warfarin at the average maintenance dose of 5 mg on the same day as heparin initiation and overlapping heparin with warfarin for at least four to five days until a therapeutic INR has been obtained on two consecutive days.

Objective: To evaluate the appropriateness of anticoagulation initiation in our facility and to further compare the therapeutic efficacy, clinical outcomes, and safety of low (≤ 5 mg) versus high initial warfarin doses (>5 mg).

Methods: A retrospective chart review was conducted on hospitalized patients initiated on warfarin therapy.

Results: Mean time to reach a therapeutic INR was significantly longer for the low-dose group than for the high-dose group (4.6 days [95% CI: 3.9–5.2] vs. 3.2 days [95% CI: 2.7–3.6], $P=0.0009$). There was no significant difference between groups with respect to recurrence of thromboembolic events, frequency of elevated INRs, held warfarin doses, vi-

tamin K administration, and bleeding events. Approximately 60% of patients at our facility were initiated on warfarin at the recommended 5-mg dose. Over 70% of patients were started on warfarin within 24 hours of heparin initiation, however, only 27% had heparin overlap with warfarin for at least four to five days until two consecutive therapeutic INRs were obtained prior to discharge. Just less than 10% of patients were discharged prior to obtaining a therapeutic INR and almost 40% were discharged before two consecutive therapeutic INRs were obtained.

Conclusion: We found that there was a significant difference in the mean time to reach a therapeutic INR between the low- and high-dose groups. However, we found no significant difference between groups with regard to clinical outcomes such as recurrence of thromboembolic events. Although the majority of patients at our institution were initiated at the recommended dose within 24 hours of heparin initiation, there was a large percentage of patients with inappropriate heparin duration; also, many of the patients were discharged before two therapeutic INRs were obtained.

In clinical practice, warfarin is often initiated with a 10-mg loading dose in an attempt to reduce the time required to reach a therapeutic international normalized ratio (INR). However, initiating warfarin with large loading doses can potentially result in a number of complications. Loading doses of warfarin might increase the risk of elevated protimes and hemorrhage, especially in elderly patients who are often overly sensitive to warfarin.¹ In addition, there is evidence that loading doses of warfarin might increase the risk of a transient hypercoagulable state at the initiation of warfarin therapy.²

Based on these potential problems associated with warfarin loading doses, recent clinical guidelines recommend initiating warfarin therapy at the average daily dose of 5 mg rather than administering loading doses of 7.5 to 10 mg.³ It has also been recommended that physicians consider initiating warfarin at doses of less than 5 mg in certain groups of individuals; for example: the elderly, patients with liver disease or impaired nutrition, patients with cardiac failure, individuals with low body weight, or those with bleeding diathesis.^{1,3} When a rapid anticoagulant effect is desired, heparin is often co-administered with warfarin. In these situations, guidelines recommend starting warfarin on the same day as heparin initiation and overlapping heparin therapy with warfarin for at least four to five days until an INR of 2 or more has been obtained on two consecutive days.⁴

Whether or not these guidelines are being instituted in actual clinical practice, however, is uncertain. Therefore, this study was conducted to evaluate the appropriateness of anticoagulation initiation in our facility and to further compare the therapeutic efficacy, clinical outcomes, and safety of low initial warfarin doses versus regimens with loading doses among hospitalized medical patients.

Methods

A retrospective chart review was conducted on inpatients started on warfarin at the VA Medical Center in Fargo, North Dakota. Study subjects were selected from a computer-generated report of patients discharged from the hospital between September 1998 and April 2001 with the primary diagnosis of atrial fibrillation (A-fib), deep vein thrombosis (DVT), pulmonary embolism (PE), or Q-wave myocardial infarction (MI). Patients were excluded if they had been on warfarin prior to admission or if an interacting drug had been started after initiation of warfarin therapy. Initial and subsequent warfarin dosing was at the discretion of the physician. Patients were assigned to low and high initial warfarin dose groups. The low-dose group consisted of patients who had received an initial warfarin dose of 5 mg or less, and the high-dose group was composed of patients who had received an initial warfarin dose greater than 5 mg.

Baseline and subsequent INRs and hemoglobin levels were recorded for each patient. Heparin duration and length of stay were also determined. The day that warfarin was started in relationship to heparin initiation was also recorded. Other demographic information collected included age, weight, type of heparin therapy (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], or none), and concurrent medications.

Assessment of therapeutic efficacy was based upon the mean time to reach a first therapeutic INR, and the mean time to reach two consecutive therapeutic INRs. The time to reach a therapeutic INR was defined as the number of days required to obtain an INR between 2 and 3 with day one recorded as the day after the first dose of warfarin. In addition, mean length of heparin duration and hospital stay (from time of anticoagulation start until discharge) were recorded. Clinical outcome was measured by recurrence rate of any thromboembolic event within three months following warfarin initiation.

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Comparison of Initial Warfarin Doses

Assessment of safety was based upon occurrence of bleeding episodes during hospital stay (major vs. minor vs. none). A bleed was considered major if it was fatal, life-threatening (intracranial or retroperitoneal), or bleeding with a hemoglobin drop greater than 2 gm/dl requiring medical treatment. All other bleeding events were considered minor. The number of INRs greater than 3, the number of held warfarin doses, and vitamin K administration were also documented.

Finally, we evaluated the appropriateness of anticoagulation initiation based upon the following factors: the percentage of patients started on warfarin at the recommended 5-mg dose, the percentage of patients started on warfarin within 24 hours of heparin initiation, the duration of heparin overlap with warfarin (appropriate, longer than recommended, shorter than recommended, no overlap, or no heparin therapy), the percentage of patients discharged prior to obtaining a therapeutic INR, and the percentage of patients discharged prior to obtaining two consecutive therapeutic INRs.

Statistical analysis was performed on selected data using the SAS 8.0 statistical analysis program. The *t*-test was used to compare numerical variables. The χ^2 and Fisher's exact test were used to evaluate nominal variables. Statistical difference was considered significant if the *P*-value was 0.05 or less.

Results

After review of the computer-generated report, 62 patients fulfilled all study criteria. Thirty-eight patients (61.3%) were in the low-dose group compared with 24 patients (38.7%) in the high-dose group. All patients in the low-dose group received 5 mg as the first dose. The high-dose group had a mean initial dose of 9.4 mg \pm 1.1 mg. The mean three-day cumulative dose in the low-dose group was substantially lower than the three-day mean of the high-dose group (16.5 mg \pm 3.4 mg vs. 25.4 mg \pm 3.9 mg). There was no significant difference between groups in respect to age, weight, or baseline INR.

Forty-one patients (66.1%) were treated for DVT, 16 patients (25.8%) were treated for A-fib, four patients (6.5%) were treated for PE, and one patient (1.6%) was treated for Q-wave MI. Fifty-four patients (87.1%) received UFH, six patients (9.7%) received LMWH, and two patients (3.2%) did not receive any heparin therapy.

Ten patients (26.3%) in the low-dose group were already receiving a medication known to significantly interact with warfarin compared with two patients (8.3%) in the high-dose group. Seven patients (18.4%) in the low-dose group were on a drug known to be a significant inducer of warfarin metabolism compared with one patient (4.2%) in the high-dose group. Two patients (5.2%) in the low-dose group were on a drug known to be a significant inhibitor of warfarin metabolism compared with one patient (4.2%) in the high-dose group. One patient in the low-dose group was on both an inhibitor and an inducer of warfarin metabolism (Table 1).

The mean time to reach a therapeutic INR was significantly longer for the low-dose group than for the high-dose group (4.6 days [95% CI: 3.9 to 5.2] vs. 3.2 days [95% CI: 2.7 to 3.6], *P*=0.0009). The mean time to reach two consecutive therapeutic INRs was longer for the low-dose group, but the difference was not statistically significant (5.2 days [CI: 4.6 to 5.7] vs. 4.3 days [CI: 3.5 to 5.1], *P*=0.07). Four patients (10.5%) in the low-dose group were discharged prior to obtaining a therapeutic INR compared with one patient (4.2%) in the high-dose group. Eleven patients (28.9%) in the low-dose group were discharged prior to obtaining two consecutive therapeutic INRs compared with 12 patients (50%) in the high-dose group.

The percentage of patients obtaining a therapeutic INR within four days of warfarin initiation was significantly higher in the high-dose group than in the low-dose group (91.3% vs. 55.9%, *P*=0.007). However, there was no significant difference between groups in terms of the percentage of patients obtaining two consecutive therapeutic INRs within five days of warfarin initiation (83.3% vs. 63%, *P*=0.28).

There was a trend towards longer duration of heparin therapy in the

Table 1 Patient Demographics

	≤ 5 mg n=38	>5 mg n=24	Total
Age (years, mean \pm SD)	64.2 \pm 11.3	65.3 \pm 13.5	
Weight (kg., mean \pm SD)	92.5 \pm 24.4	93.3 \pm 20.6	
Baseline INR (mean \pm SD)	1.1 \pm 0.1	1.0 \pm 0.1	
Indication (# patients):			
A-fib	7	9	16
DVT	29	12	41
PE	2	2	4
Q-Wave MI	0	1	1
Heparin Type (# patients)			
UFH	32	22	54
LMWH	5	1	6
None	1	1	2
Drug Interaction (# patients):			
Inhibitor	2	1	3
Inducer	7	1	8
None	28	22	50
Both	1	0	1

low-dose group than in the high-dose group (6.2 vs. 5.1 days, *P*=0.07). There was no statistically significant difference in length of hospital stay between the two groups (7.6 vs. 6.9 days, *P*=0.34).

The two groups were similar in respect to recurrence of thromboembolic events. Three patients (7.9%) in the low-dose group compared with two patients (8.3%) in the high-dose group had a documented recurrent thromboembolic event within three months of warfarin initiation (*P*=0.36). All patients had therapeutic INRs at the time that they were admitted for the recurrent events (Table 2).

The frequency of elevated INRs and held doses was similar between the two groups. Five patients (13.2%) in the low-dose group compared with three patients (12.5%) in the high-dose group had an INR greater than 3 within the first five days of warfarin initiation (*P*=0.30). Three patients (7.8%) in the low-dose group compared with two patients (8.3%) in the high-dose group had one or more warfarin doses held during their hospital stays (*P*=0.36). There were no documented bleeding episodes in either the low- or high-dose groups. One patient in the low-dose group received 1 mg oral of vitamin K and had one dose held following an INR of 6.6 on day two of warfarin initiation. A repeat INR on the following day, however, revealed that the INR had returned to a baseline of 1.

Out of the 60 patients who received heparin, 45 (75%) were started on warfarin within 24 hours of heparin initiation. Seventeen patients (27.4%) had heparin therapy overlap with warfarin initiation for at least four to five days along with two consecutive INRs of 2 or greater obtained prior to discharge. A total of 14 patients (22.6%) had four to five days of overlap with only one INR of 2 or greater obtained prior to discharge. Four patients (6.5%) had four to five days of overlap without any therapeutic INRs obtained prior to discharge. Six patients (9.7%) were on heparin for greater than five days after two consecutive INRs of 2 or greater had been obtained. Seventeen patients (27.4%) were on heparin for less than four days with or without an INR of 2 or greater. Two patients (3.2%) received heparin therapy, but heparin was discontinued prior to warfarin initiation. Two patients (3.2%), one with PE and one with A-fib, did not receive any heparin therapy (Table 3). In addition, five out of 62 (8%) patients were discharged prior to obtaining a therapeutic INR, and 23 out of 62 (37%) were discharged prior to obtaining two consecutive therapeutic INRs.

Comparison of Initial Warfarin Doses

Table 2 Comparison of Low vs. High-dose Groups

Outcome Variable	≤5mg n=38	>5mg n=24	
Dose (mg, mean ± SD)	5.0 ± 0	9.4 ± 1.1	
Three-Day Dose (mg, mean ± SD)	16.5 ± 3.4	25.4 ± 3.9	
Time to first INR ≥ 2 (days, mean ± SD)	4.6	3.2	P=0.0009
Time to Two Consecutive INRs ≥ 2 (days, mean ± SD)	5.2	4.3	P=0.07
INR ≥ 2 within four days (%)	55.9	91.3	P=0.007
Two Consecutive INRs ≥ 2.0 within five days (%)	63	83.3	P=0.28
Recurrent Event* (# patients)	3	2	P=0.36
Heparin Duration (days, mean ± SD)	6.2	5.1	P=0.07
Length of Stay (days, mean ± SD)	7.6	6.9	P=0.34
INR > 3 within five days (%)	13.2	12.5	P=0.36
Dose Held (# patients)	3	2	P=0.36
Vitamin K (# patients)	1	0	
Bleeding (# patients)			
Major	0	0	
Minor	0	0	
None	38	24	

*Within three months of warfarin initiation

Discussion

In our study, we evaluated the appropriateness of anticoagulation initiation and compared the safety and efficacy of low versus high initial warfarin doses in hospitalized medical patients. We found that the low-dose group took a significantly longer time to reach a therapeutic INR than the high-dose group. Although not statistically significant, our study showed that there was a trend towards longer time to reach two consecutive INRs in the low-dose group. There was no difference between groups with regard to frequency of recurrent thromboembolic events or length of hospital stay. The frequency of bleeding episodes, the number of INRs greater than 3, the number of held warfarin doses, and vitamin K administration were also similar between the low- and high-dose groups.

Recently, two randomized clinical trials were conducted to evaluate the safety and efficacy of warfarin initiation regimens. The first of these two trials, conducted in 1997, compared 5- versus 10-mg doses in the initiation of warfarin therapy. Patients who received a 10-mg loading dose achieved a therapeutic INR more rapidly than those in the 5-mg group (44% vs 8% after 36 hours; $P=0.005$). However, the study found that the 5-mg group was at least as effective as the 10-mg group in producing a therapeutic INR by day four to five.⁵

Another randomized trial was conducted in 1999 that also compared initial warfarin doses of 5 versus 10 mg. The authors again concluded that the use of 5-mg initiation regimens is just as effective as 10-mg loading doses in obtaining a therapeutic INR by day four to five; there was also a trend toward less overanticoagulation in the 5-mg group.⁶

In contrast to our study, these two studies were randomized clinical trials that utilized dosing nomograms and algorithms for subsequent warfarin dosing. In our retrospective trial, initial and subsequent warfarin dosing was at the discretion of the prescribing physician. As in our study, the first trial found that patients who received a 10-mg loading dose achieved an INR greater than 2 more rapidly than patients who received an initial dose of 5 mg.⁵

Both of the previous trials found that the 5-mg group was at least as effective as the 10-mg group in obtaining a therapeutic INR by day four to five. Although we found a significant difference between groups in mean time to reach a therapeutic INR, the mean time for our low-dose group to obtain either one therapeutic INR or two consecutive therapeutic

Table 3 Evaluation of Heparin Therapy

Duration of Heparin Overlap	# Patients	(%)
Four to five days:		
With 2 INRs ≥ 2.0	17	27.4
With 1 INR ≥ 2.0	14	22.6
No INRs ≥ 2.0	4	6.5
> 5 days after 2 INRs ≥ 2.0	6	9.7
< 4 days with or without INR ≥ 2.0	17	27.4
No Overlap	2	3.2
No Heparin	2	3.2
Totals:	62	100

INRs was similar to the four- to five-day range observed in these trials (4.6 and 5.2 days, respectively).^{5,6}

Another retrospective study was recently conducted to further evaluate warfarin initiation regimens, mainly in elderly surgical patients. The investigators found no significant difference between low- versus high-dose groups in mean time to first therapeutic INR (3.4 days vs. 3 days; $P=0.38$). The low-dose group had fewer bleeds and fewer doses held, but the results were not significant. There was also no difference in vitamin K administration found between the two groups.⁷

Despite the small sample size of our study, we found that the low-dose group took a significantly longer time to reach a therapeutic INR than the high-dose group. Although there was no significant difference between groups, there was a trend towards a longer mean time to reach two consecutive therapeutic INRs in the low-dose group in our study. The lack of statistical significance might be attributed to the fact that there was a large percentage of patients in the high-dose group (50%) compared with the low-dose group (28.9%) who were discharged before two consecutive therapeutic INRs were obtained.

The frequency of a recurrent thromboembolic event was similar between the two groups. All five patients who were admitted with a recurrent thromboembolic event had received heparin therapy along with warfarin initiation. One patient was discharged prior to obtaining two consecutive therapeutic INRs. All other patients had obtained at least two

Comparison of Initial Warfarin Doses

consecutive therapeutic INRs before discharge. None of the previous studies evaluated for clinical outcomes such as recurrence of thromboembolic events. In addition, our study found no significant difference between low- and high-dose groups in frequency of elevated INRs, held warfarin doses, vitamin K administration, and bleeding events.

The conclusions that can be drawn from this study are limited by the fact that we evaluated retrospective chart data. The lack of randomization might have resulted in differences between the two groups that could account for our findings independent of the warfarin dose itself. For example, there was a greater percentage of patients in the low-dose group (18.4%) than in the high-dose group (4.2%) who were on a drug known to induce warfarin metabolism. In addition, the small sample size limited the power of the study to detect differences between the two groups.

In our study, we also evaluated the appropriateness of anticoagulation initiation at our facility. Approximately 60% of patients at our facility were initiated on warfarin at the recommended dose of 5 mg. Over 70% of the patients at our facility were started on warfarin within 24 hours of heparin initiation; however, only 27% had heparin overlap with warfarin for at least four to five days until two consecutive therapeutic INRs were obtained prior to discharge. Just less than 10% of patients were discharged prior to obtaining a therapeutic INR and almost 40% were discharged before two consecutive therapeutic INRs were obtained.

In conclusion, we found that there was a significant difference in the mean time to reach a therapeutic INR between the low- and high-dose groups. However, we found no significant difference between groups with regard to clinical outcomes such as recurrence of thromboembolic events. Despite a longer mean time to reach a therapeutic INR, the low-dose group was able to reach a therapeutic INR by day four to five of warfarin initiation, if not sooner. We recommend that larger prospective studies be conducted to further examine the differences in clinical outcomes between patients started on low and high initial warfarin doses in actual clinical practice. Although the majority of patients at our institution were initiated at the recommended dose, a large percentage of patients had inappropriate heparin duration and a large percentage of patients were discharged before two therapeutic INRs were obtained.

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