

Effectiveness and Safety of a 10mg Warfarin Initiation Nomogram in Asian Population

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Abstract: Anticoagulant responses to warfarin vary among patients, based on genetic factors, diet, concomitant medications, and disease state. We evaluated the effectiveness and safety of a 10mg warfarin initiation nomogram in an Asian population. Retrospective cross-sectional audit studies were conducted from March 2009 to March 2010. The use of a 10mg-loading dose to initiate warfarin treatment resulted in 33(84.6%) patients attaining a therapeutic INR within four days (mean time, 2.6 days). There was no significant correlation between age, gender, race, and serum albumin for the time to reach a therapeutic INR. A significant correlation was noted for patient's baseline INR and time to reach a therapeutic INR ($P<0.05$). No significant differences were observed in time to reach a therapeutic INR in patients treated with specific class of concomitant drugs or patients with specific disease states. The overall incidence of over-anticoagulation was 35.9%; however, no bleeding episodes were encountered. In conclusion, the use of a 10mg warfarin nomogram was effective in rapidly achieving a therapeutic INR. However, the nomogram's safety is debatable owing to the high over-anticoagulation rate warfarin-administered patients. Caution is recommended in the initiation of warfarin treatment using the 10mg nomogram.

Keywords: Warfarin, INR, coagulation, anti-coagulation, nomogram.

INTRODUCTION

Thromboembolic diseases are a major cause of morbidity and mortality in many countries (White, 2003). The risk factors for thromboembolic diseases include hematologic disorders, patient-related factors, disease states and surgical factors (Anderson and Spencer, 2003).

Warfarin, a vitamin-K antagonist, is widely prescribed for prophylaxis and the treatment of venous and arterial thromboembolic disorders (Hirsch *et al.*, 2001). The effectiveness and safety of warfarin is dependent on maintaining a prothrombin time within a therapeutic range that is expressed as the international normalized ratio (INR). However, the initiation of warfarin therapy is complicated by its narrow therapeutic index. The anticoagulant response of individuals to warfarin treatment is influenced by various genetic and clinical factors, including disease state, concomitant medications and diet (Ansell *et al.*, 2001). These patient-specific factors necessitate daily INR monitoring during the initiation of warfarin anticoagulation. Despite close monitoring, both supratherapeutic and sub therapeutic INRs are common during initiation of treatment with an increased risk of bleeding during this early period.

Warfarin dosing can be divided into three phases: Initiation, induction, and maintenance. Currently there is no established optimal dosing strategy for initiation of warfarin. Most patients are initiated on a 5 to 10mg/day dose with dose adjustments made based on the observed

INR. This 'trial and error' approach to determine the optimal dose poses a challenge. Effective warfarin dose ranges from 1 to 40mg/day (Ansell *et al.*, 2004). Given the wide variation in warfarin dose and dose response, careful monitoring of the patient is required, especially in the initiation phase.

Recently, the use of specific dosing schemes called nomograms has been suggested to facilitate warfarin dosing. Numerous nomograms have been evaluated and published but each has its limitations (British Society of Haematology, 2011). Most nomograms recommend either a 5 or 10mg/day initiation dose. However, the use of a 10mg warfarin initiation dose may increase the risk of bleeding early in the treatment regimen. The 10mg warfarin nomogram has been used in the Caucasian population. However, to date no studies have evaluated the suitability of this nomogram in multiracial Asian populations. Therefore, the aim of this study was to evaluate the effectiveness and safety of a 10mg warfarin initiation nomogram in an Asian population.

MATERIAL AND METHODS

Study design and setting

This study was a retrospective cross-sectional audit conducted in a tertiary government hospital in Malaysia. The study focused on patients admitted to the medical ward during the period of March 2009 to March 2010. The study was approved by the Medical Research Ethics Committee (MREC) Malaysia and registered with the National Medical Research Registry (NMRR-10-676-6602).

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Study Sample

The patient sample eligibility criteria for inclusion in the study consisted of individuals that were initiated a 10mg warfarin dose and were identified by reviewing pharmacy medication records and medical records. The inclusion criteria were patients ≥ 18 years old who were initiated with warfarin using the nomogram adopted from the British Society of Haematology (table 1). Patients were excluded if there was an interruption in warfarin therapy during admission and treatment, if their baseline INR > 1.4 , they had underlying liver disease or had thrombocytopenia (platelet $< 50 \times 10^9$ cells/ml).

Table 1: Warfarin nomogram adopted from British Society of Haematology 2011

Days	INR	Warfarin dose (mg)
First	< 1.4	10
Second	< 1.8	10
	1.8	1
	> 1.8	0.5
Third	< 2.0	10
	2.0-2.1	5
	2.2-2.3	4.5
	2.4-2.5	4
	2.6-2.7	3.5
	2.8-2.9	3
	3.0-3.1	2.5
	3.2-3.3	2
	3.4	1.5
	3.5	1
	3.6 to 4.0	0.5
	> 4.0	0
Fourth	< 1.4	> 8
	1.4	8
	1.5	7.5
	1.6-1.7	7
	1.8	6.5
	1.9	6
	2.0-2.1	5.5
	2.2-2.3	5
	2.4-2.6	4.5
	2.7-3.0	4
	3.1-3.5	3.5
	3.6-4.0	3
	4.1-4.5	Miss out next day's dose then give 2mg
	> 4.5	Miss out 2 doses then give 1mg

Data collection

Data collection consisted of a review of medical records by the researcher. The clinical information collected included demographic characteristics, warfarin indication and dosage, target INR range, concurrent diseases and medications, baseline INR, liver function and renal

profile, administration of vitamin K, or fresh frozen plasma, and incidence of bleeding.

STATISTICAL ANALYSIS

Descriptive statistics were used and continuous data was reported as the mean $\pm$ standard deviation. The associations between age, serum albumin, baseline INR, gender, and race were evaluated with the Pearson correlation test and Spearman rank-order correlation. Independent *t*-tests were used to determine significant differences between concomitant drug use and comorbidities. Logistic regression analysis was used to determine predictors of over-anticoagulation. A *p*-value of < 0.05 was considered statistically significant. A Chi-Squared test was used to evaluate effects of concomitant drugs on INR. Statistical analyses were performed with the Statistical Package for Social Science (SPSS version 16.0, Chicago).

RESULTS

Demographics

A total of 175 patients were identified that were on warfarin therapy in the medical wards during the study period. However, only 51 patients were initiated with 10mg warfarin therapy. After screening for inclusion and exclusion criteria, a total of 39 patients met the inclusion criteria and forevaluation in this study. Among the 39 subjects, 17 were male and 22 were female with mean age of 55.6 years. There were 12 (30.8%) patients above 65 years of age. The study subjects were mostly Malay (51.3%). The most prevalent clinical diagnosis for warfarin therapy was atrial fibrillation (76.9%). The demographics of the study population are shown in table 2.

Table 2: Study population demographics

Variable	Value (%)
Age, (mean $\pm$ SD)	55.6 $\pm$ 13.5
Gender, n	
Male	17(43.6)
Female	22(56.4)
Race, n	
Malay	20(51.3)
Indian	7(17.9)
Chinese	8(20.5)
Others	4(10.3)
Indication, n	
Atrial fibrillation	30(76.9)
Deep vein thrombosis	4(10.3)
Pulmonary embolism	2(5.1)
Stroke	1(2.6)
Cardiac thrombus	2(5.1)

Effectiveness of 10mg warfarin nomogram

The therapeutic INR range for the indications of warfarin in this study population was an INR of 2-3, which was in accordance with recommendations (Hirsh *et al.*, 2001). The mean time to reach the therapeutic INR in this study was 2.6 days. The INR distribution pattern indicated the 33 (84.6%) patients attained a therapeutic INR within 4 days of treatment. No correlations were found for time to reach a therapeutic INR and age, serum albumin, gender and race (table 3). However, the patient's baseline INR did correlate with time to reach a therapeutic INR ($p=0.05$), demonstrating that an increase in the baseline INR correlated with a decrease in the time interval to reach a therapeutic INR (table 3).

Table 3: Correlation between variables and time to reach a therapeutic INR

Variable	r	P-value
Age	0.03 ^a	0.428
Serum albumin	0.180 ^a	0.273
Baseline INR	- 0.301 ^a	0.031
Gender	0.181 ^b	0.269
Race	- 0.084 ^b	0.611

^a Pearson Correlation

^b Spearman Rank Correlation

$p < 0.05$ considered significant

Table 4: Effect of concomitant drugs on time to reach a therapeutic INR

Concomitant drugs	Treated (n)	Not treated (n)	P-value ^a
LMWH	34	5	0.391
Antiplatelet	15	24	0.769
Beta Blocker	17	22	0.773
ACEIs	12	27	0.116
Statin	29	10	0.512
Antibiotics	11	28	0.751
Diuretics	12	27	1.000
Carbimazole	4	35	0.639

LMWH=Low molecular weight heparin; ACEI=Angiotensin converting enzyme inhibitors

^a Chi-squared test

$p < 0.05$ considered significant

Concomitant drugs used by the subjects in this study were grouped into drug classes by pharmacological basis of action. Drugs with known interactions with warfarin were included in this analysis. Only one subject used amiodarone and as a result, it was removed from the analysis. There was no significant difference ($P > 0.05$) in the time required to reach a therapeutic INR between patients receiving a specific drug class and patients not receiving the drugs (table 4). Similarly, there was no significant difference ($P > 0.05$) in the time required to reach a therapeutic INR between patients who had

specific underlying diseases compared to patients without the disease (table 5).

Safety of the 10mg warfarin nomogram

Of the 33 patients who achieved a therapeutic INR, 19 (48.7%) remained in the therapeutic INR range over the four days of treatment. Fourteen patients (35.9%) were over-anticoagulated with an INR value exceeding 3 (table 6). 6 patients (15.4%) did not achieve the target INR. 4 patients (10.3%) were over-anticoagulated and had an INR above 4. Despite a relatively high incidence of over-anticoagulated patients, none of the patients had bleeding complications or required administration of vitamin K or fresh frozen plasma. However, the warfarin dose was withheld in all 4 patients with an INR above 4. There were no adverse events related to low INR levels. Multivariate analysis found no specific factors that could serve as predictors of over-anticoagulation in this study population (table 7).

Table 5: Effect of co-morbidities on time to reach a therapeutic INR

Comorbidities	Present (n)	Not present (n)	P-value ^a
Diabetes	11	28	0.525
Hypertension	17	22	0.246
Ischemic Heart Disease	8	31	0.478
Heart Failure	6	33	0.231
Infection	5	34	0.391

^a Chi-squared test

$p < 0.05$ considered significant

Table 6: Value of INR achieved on day-4 of warfarin initiation (n=39)

INR	Value n (%)
<2	6 (15.4)
2-3	19 (48.7)
>3	14 (35.9)
Proportion of over-anticoagulation	
INR 3.1-3.5	8 (20.5)
INR 3.6-4	2 (5.1)
INR 4.1-4.9	3 (7.7)
INR > 5	1 (2.6)

Table 7: Multiple logistic regression of variables involved in predicting over-anticoagulation

Variable	e^{β} (odds ratio)	P-value
Age	0.967	0.435
Gender	0.257	0.145
Race ^a	1.0	0.533
Serum albumin	1.035	0.679
Baseline INR	178.6	0.144
Comorbidities	1.186	0.852

^aReference category

DISCUSSION

Warfarin therapy is associated with a high incidence of over-anticoagulation which may cause bleeding, particularly during the initiation phase. The inter and intraindividual variability in response to warfarin makes accurate dose prediction difficult. Because of this variability, there is controversy on the optimal starting dose or 'loading phase' for warfarin. Current dosing guidance is based on a recommendation of a loading dose of 5mg or 10mg. Recently, work has shown that patients given a 10mg loading dose of warfarin were at risk of supratherapeutic levels (Crowther *et al.* 1999). However, patients treated using the 10mg warfarin nomogram achieved targeted INR 1.4 days earlier than those in the 5mg group. The mean number of days to reach a therapeutic INR was 4.2 days in the 10mg group and 5.6 days in the 5mg group, with no significant difference in adverse events related to warfarin therapy (Kovacs *et al.*, 1998). Other studies support this observation, with therapeutic INR levels reached within the first 5 days after a 10mg loading dose (Kovacs *et al.*, 1998; Wells *et al.*, 2009). Since most of these studies were carried out in Caucasians, we investigated the role of a 10mg warfarin loading dose in a local Asian population. We found that the 10mg warfarin nomogram used in this study was effective in attaining a therapeutic INR in 84.6% of evaluable patients by day 4.

The 10mg warfarin dosing nomogram used in this study achieved a therapeutic INR in a majority of the patients within 4 days. The target INR was achieved in a shorter time interval than reported in previous studies (Kovacs *et al.*, 1998). A possible explanation for this result is a difference in the population characteristics of the study subjects in this study compared to the study populations reported in the literature, which primarily represent Caucasians. Interestingly, previous studies have shown that ethnicity has been shown to independently affect warfarin dose requirements and is potentially related to genetic variability (Dang *et al.*, 2005). Malaysia is a multiracial country consisting of three main races: Malay, Chinese and Indian. There are reports suggesting that racial background may influence warfarin dose requirements (Gan *et al.* 2003). Mean warfarin doses required by Indian patients have been found to be significantly higher than doses required for Malay and Chinese (Gan *et al.* 2003). The cause for this difference is unclear, but may be due to allelic variance in CYP2C9, which metabolizes warfarin. The CYP2C9*2 allele was present in Indian patients, and this CYP variant has significantly less warfarin metabolic potential than CYP2C9 (Gan *et al.*, 2004). However, in this study, no difference was observed between the three races and the time to achieve a therapeutic INR, and it is possible that local patients will require a shorter time to achieve a therapeutic INR than previously reported.

In the present study, the sole demographic factor that affected the time to reach a therapeutic INR was the initial baseline INR. It was noted that the initial baseline INR had an inverse correlation with the time to reach a therapeutic INR. Therefore, the higher the baseline INR, the greater the time required to reach the targeted INR. This was a surprising finding, since it was thought that the higher the baseline INR, the quicker therapeutic INR would be reached. The reason for this correlation is unclear, but the findings should be useful for identifying patients that may require closer monitoring.

Concomitant drugs have the potential to influence the pharmacodynamics of warfarin via alterations in clotting factor synthesis or catabolism, or may directly affect hemostasis. Retrospective studies indicate that 54% to 79% of warfarin patients in a variety of clinical settings are prescribed medications that could potentially interact with warfarin and its mechanism of action or metabolism (Snaith *et al.*, 2008). Warfarin drug interactions of clinical importance include the concomitant use of NSAIDs such as aspirin, cephalosporins, statins, heparin, amiodarone, azole antifungals and thyroxine, which are known to potentiate the effect of warfarin. In the present work it was noted that some patients on the study were prescribed drugs having the potential to increase the effect of warfarin. These were aspirin, enoxaparin, fondaparinux, amiodarone, acetylcholine inhibitors, beta blockers, cephalosporins, carbimazole and diuretics. Nonetheless, concomitant use of interacting drugs in this study did not have a significant effect on the time required to reach a therapeutic INR.

Similarly, comorbid disease states can affect anticoagulant responses to warfarin (Whitely *et al.*, 2007). Hepatic dysfunction potentiates the response to warfarin through impaired synthesis of coagulation factors. Hypermetabolic states produced by fever and hyperthyroidism can increase warfarin responsiveness by increasing the catabolism of vitamin K dependent coagulation factors. Congestive heart failure can affect warfarin response due to hepatic congestion, resulting in abnormal liver function and reduced clotting factor synthesis. The presence of hypertension, cerebrovascular disease, renal insufficiency, and malignancy increases response to warfarin bleeding risk (Whitely *et al.*, 2007). The majority of the study population in this present work had co-morbidities including hypertension, diabetes mellitus and congestive heart failure. Despite these observations, no differences were observed in the time to achieve a therapeutic INR between patients with and without comorbidities.

Despite achieving therapeutic INR in a shorter time period than previously reported (Kovacs *et al.*, 1998), only 48.7% of the study subjects remained within the therapeutic INR threshold throughout the initial four days of warfarin treatment. Fourteen patients (35.9%) had INR

values above the therapeutic range (INR > 3) which can increase bleeding risk. This percentage is higher than reported another study (Harrison *et al.* 1997) which had a 20% incidence of over-anticoagulation (INR>3). Haemorrhage or bleeding is the main complication of warfarin therapy. Key factors associated with warfarin-mediated haemorrhagic adverse events include indication for anticoagulation therapy, intensity of anticoagulation, concomitant illness and medications, and whether the patient is new to therapy or on established long term therapy. Previous clinical work has also shown that bleeding rates vary by indication for long term anticoagulation therapy (Connolly *et al.*, 1991; Levine *et al.*, 2001). In patients with mechanical heart valves, major bleeding rates of 1.4% per patient year have been reported. Additionally, annual rates for major bleeding in atrial fibrillation patients were found to be between 0.4% and 2.6% per year (Connolly *et al.*, 1991; Levine *et al.*, 2001). Rates of minor bleeding in these indications have been reported to be as high as 15.4% per year. A meta-analysis showed that bleeding rates were higher in the first three months of warfarin therapy compared with rates of bleeding in patients on established treatment (Linkins *et al.*, 2003). It has been reported that the death rate doubles with each unit of INR increase >2.5 (Oden and Fahlen, 2002).

There are several factors which predispose a patient to over-anticoagulation (Ansell *et al.*, 2001). These are age, race, concomitant drugs, baseline INR, and comorbidities (Beyth *et al.*, 1998). This study failed to identify any significant predictors of over-anticoagulation from the independent demographic variables that were tested. Although no patients in the current study presented with bleeding episodes, the possibility of serious over-anticoagulation should not be excluded due to the short duration of data collection. Since bleeding risk increases with an INR >4, the risk was small in group of patients that were studied. Apart from risk of bleeding, another issue due to over-anticoagulation may be an increase in length of hospital stay until INR levels stabilize in a therapeutic range. This has cost implications for the health care system.

CONCLUSION

This study demonstrated that the use of a 10mg warfarin loading dose to initiate anticoagulation therapy was effective in achieving A therapeutic International Normalized Ratio (INR) of 2-3 in a majority of the patients within 4 days. However, the relatively high percentage of over-anticoagulation on the fourth day observed in this study population requires further assessment. The local population evaluated was more sensitive to warfarin and required lower doses than previous reports have shown. However, the effectiveness does not outweigh the potential risk of bleeding

associated with the high incidence of over-anticoagulation (35.9%) observed in this study.

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REFERENCES

- Anderson FA and Spencer FA (2003). Risk factors for venous thromboembolism. *Circulation*, **107**: 1-9.
- Ansell J, Hirsh J, Dalen J, Bussy H, Anderson D, Poller L, Jacobson A, Deykin D and Matchar D (2001). Managing oral anticoagulant therapy. *Chest*, **119**: 22S-38S.
- Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A and Hylek E (2004). The pharmacology and management of vitamin K antagonists: The Seventh ACCP Conference on Antithrombotic and Thrombolytic therapy. *Chest*, **126**(3S): 204S.
- Beyth RJ, Quinn LM and Landefeld CS (1998). Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med.*, **105**: 91-99.
- British Society of Haematology (2011). Guidelines on oral anticoagulation with warfarin 4th edition. British Committee for Standards in Haematology.
- Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA and Joyner C (1991). Canadian Atrial Fibrillation Anticoagulation (CAFA) study. *J. Am. Coll. Cardiol.*, **18**: 349-355.
- Crowther M, Ginsberg JB, Kearon C, Harrison L, Johnson J, Massicotte MP and Hirsh J (1999). A randomized trial comparing 5mg and 10mg warfarin loading doses. *Arch. Intern. Med.*, **159**: 46-48.
- Dang MT, Hambleton J and Kayser SR (2005). The influence of ethnicity on warfarin dosage requirement. *Ann. Pharmacother.*, **39**(6): 1008-1112.
- Gan GG, Phipps ME, Ku CS, Teh A and Sangkar V (2004). Genetic polymorphism of the CYP2C9 subfamily of 3 different races in warfarin maintenance dose. *Int. J. Hematol.*, **80**: 295-296.
- Gan GG, Teh A, Goh KY, Chong HT and Pang KW (2003). Racial background is a determinant factor in the maintenance dosage of warfarin. *Int. J. Hematol.*, **78**: 84-86.
- Harrison L, Johnston M, Massicotte MP, Crowther M, Moffatt K and Hirsh J (1997). Comparison of 5mg and 10mg loading doses in initiation of warfarin therapy. *Ann. Intern. Med.*, **126**: 133-136.
- Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J and Deykin D (2001). Oral anticoagulants:

- Mechanism of action, clinical effectiveness and optimal therapeutic range. *Chest*, **119**: 8S-21S.
- Kovacs MJ, Cruickshank M, Wells PS, Kim H, Chin-Yee I, Morrow B, Boyle E and Kovacs J (1998). Randomized assessment of a warfarin nomogram for initial oral anticoagulation after venous thromboembolic disease. *Haemostasis*, **28**: 62-69.
- Levine MN, Raskob G, Landefeld S and Kearon C (2001). Hemorrhagic complications of anticoagulant treatment. *Chest*, **156**: 108S-121S.
- Linkins LA, Choi PT and Douketis JD (2003). Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: A meta-analysis. *Ann. Intern. Med.*, **139**(11): 893-900.
- Oden A and Fahlen M (2002). Oral anticoagulation and risk of death: A medical record linkage study. *BMJ*, **325**: 1073-1075.
- Snaith A, Pugh L, Simpson CR and McLay JS (2008). The potential for interaction between warfarin and coprescribed medication. *Am. J. Cardiovasc. Drugs*, **8**(3): 207-212.
- Wells SP, Le Gal G, Tierney S and Carrier S (2009). Practical application of the 10mg warfarin initiation nomogram. *Blood Coagul. Fibrin.*, **20**: 403-408.
- White RH (2003). The epidemiology of venous thromboembolism. *Circulation*, **107**: 14-18.
- Whitely HP, Fermo JD, Chumney EC and Brzezinski WA (2007). Effect of patient-specific factors on weekly warfarin dose. *Ther. Clin. Risk Manag.*, **3**(3): 499-504.