Saudi Pharmaceutical Journal (2015) **23**, 642–649

King Saud University

Saudi Pharmaceutical Journal

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Factors influencing warfarin response in hospitalized patients

Mahmoud I. Abdel-Aziz [a], Mostafa A. Sayed Ali [a], Ayman K.M. Hassan [b], Tahani H. Elfaham [c,*]

[a] *Department of Clinical Pharmacy, Faculty of Pharmacy, Assiut University, Assiut, Egypt*
[b] *Department of Cardiovascular Medicine, Assiut University, Assiut, Egypt*
[c] *Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut, Egypt*

Received 23 December 2014; accepted 20 February 2015
Available online 28 February 2015

KEYWORDS

Warfarin;
Anticoagulation therapy;
INR;
Hospitalized patients

Abstract The objective of this study was to investigate the influence of simultaneous factors that potentially keep patients far from achieving target INR range at discharge in hospitalized patients. Prospective cross-sectional observational study conducted at the Cardiology Department and Intensive Care Unit (ICU) of the Assiut University Hospitals. One-hundred and twenty patients were enrolled in the study from July 2013 to January 2014. Outcome measures were discharge INRs, bleeding and thromboembolic episodes. Bivariate analysis and multinomial logistic regression were conducted to determine independent risk factors that can keep patients outside target INR range.

Patients who were newly initiated warfarin on hospital admission were given low initiation dose (2.8 mg ± 0.9). They were more likely to have INR values below 1.5 during hospital stay, 13 (27.7%) patients compared with 9 (12.3%) previously treated patients, respectively (p = .034). We found that the best predictors of achieving below target INR range relative to within target INR range were; shorter hospital stay periods (OR, 0.82 for every day increase [95% CI, 0.72–0.94]), being a male patient (OR, 2.86 [95% CI, 1.05–7.69]), concurrent infection (OR, 0.21 [95% CI, 0.07–0.59]) and new initiation of warfarin therapy on hospital admission (OR, 3.73 [95% CI, 1.28–10.9]).

Gender, new initiation of warfarin therapy on hospital admission, shorter hospital stay periods and concurrent infection can have a significant effect on discharge INRs. Initiation of warfarin without giving loading doses increases the risk of having INRs below 1.5 during hospital stay

* Corresponding author at: Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt. Tel.: +20 1004008481; fax: +20 882332776.
E-mail address: elfahamt@yahoo.com (T.H. Elfaham).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jsps.2015.02.004

and increases the likelihood of a patient to be discharged with INR below target range. Following warfarin dosing nomograms and careful monitoring of the effect of various factors on warfarin response should be greatly considered.

1. Introduction

Warfarin has been utilized as an anticoagulant drug for about 60 years but still causing a variety of adverse effects. Routinely, warfarin is monitored by measuring the International Normalized Ratio (INR). The target INR range for most indications of warfarin therapy is 2–3 or 2.5–3.5 (Keeling et al., 2011; Holbrook et al., 2012). Keeping patients within target INR range is a challenge. A number of worldwide studies have been conducted to examine the response to warfarin therapy in both ambulatory and hospital settings (Doecke et al., 1991; Brigden et al., 1998; Fang et al., 2006; Clark et al., 2014). Response to warfarin therapy is patient specific; however, various factors have been reported to alter warfarin response and target INR such as older age, disease states, warfarin dose and influence of other medications (Doecke et al., 1991; Brigden et al., 1998; Demirkan et al., 2000; Hylek et al., 2001; Froom et al., 2003; Torn et al., 2005; Fang et al., 2006; Clark et al., 2014). Conflicting results have been reported for some of these factors such as age, gender and concurrent disease states (Fihn et al., 1996; Demirkan et al., 2000; Sivrikaya et al., 2013). The presence of these factors can keep patients away from achieving target INR range and may cause unnecessary complications. Consequently, monitoring and watching for these influential factors is essential. The objective of this study was to report on the degree to which various factors can hinder achieving target INR range in a sample of adult Egyptian patients on their discharge from hospital care setting.

2. Methods

2.1. Study design and settings

This prospective cross-sectional observational study was conducted at Cardiology Department and Intensive Care Unit (ICU) of Assiut University Hospitals. The study was approved by the Research Ethics Committee at the Faculty of Medicine of Assiut University.

2.2. Study participants

All patients admitted to the Cardiology Department and ICU of Assiut University Hospitals and received warfarin anticoagulation therapy, from July 2013 till January 2014, were included in the study.

2.3. Data collection

Patients' data regarding warfarin anticoagulation therapy were collected by reviewing patients' medical records, laboratory measurements of INR and when necessary by interviewing health care professionals as well as patients when some data were missing. Actual warfarin usage and INR measuring laboratories were monitored for one month before designing and formulating data collection sheets.

2.4. Data analysis

All statistical analyses were performed using IBM SPSS v. 22.

Data are presented as mean (standard deviation), median (interquartile range) or proportions as appropriate. A p-value of less than 0.05 was considered significant for all comparisons and all tests were two-tailed.

Independent sample t-test with bootstrap was used to compare mean difference between two unrelated groups. Non-parametric tests; Mann–Whitney U test and Kruskal Wallis H test were used to find difference in discharge INRs within the different groups.

Pearson and spearman's rank correlations with bootstrap were used to examine associations between groups.

Multinomial logistic regression was used to examine the influence of different factors on the state of discharge INRs (below, above and within target range groups).

3. Results

3.1. Baseline characteristics

Table 1 shows baseline patients' characteristics. A total of 120 patients were admitted to the Cardiology Department and the ICU. Their mean age was 48.35 years. Seventy-one (59.2%) patients were females. The majority of patients 83 (69.2%) were non-educated, and only 9 (7.5%) patients finished university education. One hundred patients (83.3%) were admitted to the Cardiology Department. Warfarin was most commonly prescribed for atrial fibrillation, 66 (55%) patients.

3.2. Warfarin management metrics

Table 2 shows warfarin management metrics for the patients. Seventy-three patients were previously treated with warfarin before hospital admission and 47 (39.2%) patients were newly initiated warfarin on hospital admission. Prescribed dose, admission and discharge INRs were significantly higher for patients previously treated with warfarin.

3.3. Warfarin prescribed dose in different patient groups

Table 3 shows difference in prescribed warfarin doses in different patient groups. Elderly patients ($\geqslant$60 years) and patients with congestive heart failure were given lower mean prescribed doses than other patients. Patients with mechanical valve replacement were given higher mean prescribed dose than

Table 1 Patients' baseline characteristics.

Total number of the patients	120 (100%)
Mean age	48.4 ± 15.5
Sex	
Males	49 (40.8%)
Females	71 (59.2%)
Education	
Non-educated	83 (69.2%)
Primary education	17 (14.2%)
Vocational education	11 (9.2%)
University education	9 (7.5%)
Place of admission	
Cardiology department	100 (83.3%)
Cardiovascular Intensive Care Unit	20 (16.7%)
Indication for warfarin therapy	
Atrial Fibrillation	66 (55%)
Mechanical valve replacement	11 (9.2%)
MVR	5
AVR	1
DVR	5
Cardiomyopathy	13 (10.8%)
Thromboembolism	5 (4.2%)
DVT	3
PE	2
Myocardial infarction	4 (3.3%)
Stroke	1 (0.8%)
Multiple conditions	17 (14.2%)
Other conditions	3 (2.5%)

MVR: mitral valve replacement, AVR: atrial valve replacement, DVR: double valve replacement, DVT: deep venous thrombosis, PE: pulmonary embolism. Other conditions refer to clinical indications rather than reported in the table.

other patients. In patients who were previously treated with warfarin, age was significantly related to current warfarin dose (maintenance dose), $r = -.31$, 95% BCa CI [−.5, −.08], $p = .008$.

3.4. Risk of bleeding from warfarin

Ten patients suffered from bleeding during hospital stay. All bleeding episodes were considered minor or minimal such as epistaxis, hemoptysis, hematemesis and rectal bleeding. Out of the 10 patients, 2 patients were ⩾65 years ($p = .69$), 2 had congestive heart failure ($p = .016$) and 6 had liver disease ($p = .003$).

3.5. State of discharge INRs

Table 4 shows the description of median and interquartile ranges of discharge INR values and analysis of factors potentially affecting them. Newly initiated warfarin patients 27 (22.5%), were more likely to have discharge INR values below target range compared with previously treated patients 24 (20%) ($p = .012$). Also, newly initiated warfarin patients were more likely to have INR values below 1.5 during hospital stay, 13 (27.7%) patients compared with 9 (12.3%) patients respectively ($p = .034$). Of the newly initiated warfarin patients, one patient suffered from new thrombus formation during hospital stay and 6 (5%) patients had INR values ⩾5 during hospital stay compared with 8 (6.7%) previously treated warfarin patients ($p = .76$).

The number of weeks of hospital stay was significantly related to discharge INRs, $r_s = .25$. 95% BCa CI [.05–.42], $p = .008$.

Out of 22 hypertensive patients, 12 (54.6%) were newly initiated warfarin on hospital admission ($p = .1$). Out of the 76 patients who had rheumatic heart disease, 54 (71.1%) patients were previously treated with warfarin ($p = .003$).

Stepwise comparison using Kruskal–wallis test showed that patients with multiple conditions and mechanical valve replacement had significantly higher median discharge INR compared with other indications of warfarin therapy. Similarly, it showed that patients who were admitted from 2 to ⩽3 weeks and ⩾3 weeks had significantly higher median discharge INR values compared with patients admitted for less than 2 weeks.

Out of 52 (43.3%) patients who had infection; 21 (17.5%) patients suffered from active rheumatic heart disease, 15 (12.5%) patients suffered from chest infection, 13 (10.8%) patients suffered from infective endocarditis and 3 (2.5%) patients suffered from urinary tract infection.

3.6. Multinomial logistic regression of factors that potentially affect discharge INRs

Multinomial logistic regression whereby clinical and other patient characteristics were included in the model (Table 5)

Table 2 Warfarin management metrics.

	Patients previously treated with warfarin $n = 73$ (60.8%)	Patients newly initiated warfarin on hospital admission $n = 47$ (39.2%)	p-Value	BCa 95% CI
	Mean (standard deviation)			
Prescribed dose[c]	4.1 mg (±2.2)	2.8 mg (±0.9)	.001[b]	0.76, 1.86
Discharge dose	4 mg (±2.6)	3.5 mg (±1.2)	.16	−0.18, 1.28
Days of hospital stay	9.2 days (±5)	10 days (±8.3)	.56	−3.77, 1.98
Number of INR measurements	3.4 (±2.8)	3.7 (±4.4)	.64	−2.09, 1.12
Admission INRs	2.7 (±2.2)	1.3 (±0.3)	.001[b]	0.90, 1.92
Discharge INRs	2.9 (±1.9)	2.2 (±1.5)	.02[a]	0.07, 1.34

BCa 95% CI: Bias corrected and accelerated 95% confidence interval.
[a] Significant at $p < .05$.
[b] Significant at $p < .01$, bootstrap for independent samples t-test based on 1000 bootstrap samples..
[c] Prescribed dose means current dose for previously treated warfarin patients and initiation dose for newly initiated warfarin patients.

Table 3 Comparing the mean prescribed warfarin doses between study groups.

Character	Number of patients (%) $N = 120$ (100%)	Mean prescribed dose (SD)	p-Value	BCa 95% CI
Age			.004[a]	−1.55, −0.34
Age ⩾ 60	29 (24.2%)	2.9 (±1.1)		
Age < 60	91 (75.8%)	3.8 (±2.1)		
Mechanical valve replacement[b]			.002[a]	1.23, 3.11
Yes	25 (20.8%)	5.3 (±2.6)		
No	95 (79.2%)	3.2 (±1.4)		
Congestive heart failure			.003[a]	−1.96, −0.61
Yes	70 (58.3%)	3.1 (±1.5)		
No	50 (41.7%)	4.3 (±2.2)		

BCa 95% CI: Bias corrected and accelerated 95% confidence interval.
[a] Significant at $p < .01$, bootstrap for independent samples t-test based on 1000 bootstrap samples.
[b] All patients with mechanical valve replacement including those with multiple conditions.

Table 4 Factors that potentially affect median and interquartile ranges of the discharge INR values.

Character	Number of patients (%) $N = 120$	Median INR (IQR)	p-Value
Sex			.27
Male	49 (40.8%)	1.9 (1.5–2.5)	
Female	71 (59.2%)	2.1 (1.6–3.1)	
Age category			.29
Young	2 (1.7%)	3.4	
Adult	89 (74.2%)	2.1 (1.6–3)	
Elderly	29 (24.2%)	1.8 (1.4–3)	
Education			.12
Non-educated	83 (69.2%)	2.1 (1.5–3.1)	
Primary education	17 (14.2%)	2.2 (1.8–2.8)	
Vocational education	11 (9.2%)	3.3 (1.9–3.7)	
University education	9 (7.5%)	1.6 (1.2–2.1)	
Place of admission			.88
Cardiovascular Department	100 (83.3%)	2.1 (1.6–2.9)	
Cardiovascular ICU	20 (16.7%)	2.2 (1.3–3.1)	
Indication for warfarin therapy			.01[a]
Atrial Fibrillation	66 (55%)	1.9 (1.5–2.7)	
Mechanical valve	11 (9.2%)	2.6 (2.3–3.5)	
Cardiomyopathy	13 (10.8%)	1.7 (1.4–2.2)	
Thromboembolism	5 (4.2%)	1.8 (1.7–8.8)	
MI	4 (3.3%)	1.7 (1.2–2)	
Multiple conditions	17 (14.2%)	3.1 (2.1–4.4)	
Other conditions	3 (2.5%)	2.6	
Number of weeks of hospital stay			.024[a]
< 1 week	45 (37.5%)	1.9 (1.3–2.7)	
1–<2	55 (45.8%)	2.1 (1.6–2.8)	
2–<3	14 (11.7%)	2.4 (1.9–4.1)	
⩾3	6 (5%)	3.8 (2.4–4.4)	
State of warfarin therapy			.001[b]
Previously treated	73 (60.8%)	2.3 (1.8–3.4)	
Newly initiated	47 (39.2%)	1.7 (1.3–2.3)	
Comorbidities			
Hypertension	22 (18.3%)	1.7 (1.2–2.5) vs. 2.1 (1.6–3.1)	.038[a]
Diabetes mellitus	23 (19.2%)	1.7 (1.3–2.9) vs. 2.1 (1.6–3)	.13
Congestive heart failure	70 (58.3%)	1.9 (1.4–2.3) vs. 2.6 (1.7–4)	.006[b]
Rheumatic heart disease	76 (63.3%)	2.3 (1.7–3.2) vs. 1.7 (1.4–2.3)	.006[b]
Non-rheumatic valvular heart disease	10 (8.3%)	1.7 (1.2–2.5) vs. 2.1 (1.6–3)	.14
Ischemic heart disease	20 (16.7%)	1.7 (1.3–2.3) vs. 2.1 (1.6–3.1)	.05
Liver disease	23 (19.2%)	2.1 (1.3–2.6) vs. 2.1 (1.5–3)	.62
Infection	52 (43.3%)	2.38 (1.9–3.6) vs. 1.8 (1.4–2.4)	.004[b]
Other comorbid conditions	43 (35.8%)	2.1 (1.6–3) vs. 2.1 (1.5–2.9)	.79

p-values were generated using non-parametric tests (Mann–Whitney U and Kruskal Wallis tests) as appropriate.
IQR: interquartile range, ICU: Intensive Care Unit, MI: myocardial infarction.
[a] Significant at $p < .05$.
[b] Significant at $p < .01$.

Table 5 Potential factors affecting state of discharge INR values: multivariate multinomial logistic regression.

Predictor	Beta (SE)	95% CI for odds ratio		
		Lower	Odds ratio	Upper
Below target range vs. within target range				
Intercept	0.69 (1.39)			
Age	0.02 (0.02)	0.99	1.02	1.05
Prescribed warfarin dose	0.18 (0.14)	0.9	1.19	1.58
Days of hospital stay	−0.2 (0.07)[b]	0.72	0.82	0.94
Gender (female vs. male)	−1.06 (0.51)[a]	0.13	0.35	0.95
Congestive heart failure	0.54 (0.55)	0.58	1.72	5.08
Liver disease	0.09 (0.67)	0.3	1.1	4.05
Infection	−1.58 (0.54)[b]	0.07	0.21	0.59
State of warfarin therapy (newly initiated vs. previously treated patients)	1.32 (0.55)[a]	1.28	3.73	10.9
Above target range vs. within target range				
Intercept	−1.66 (1.64)			
Age	0.01 (0.02)	0.96	1.01	1.05
Prescribed warfarin dose	0.08 (0.15)	0.8	1.08	1.46
Days of hospital stay	0.11 (0.06)[a]	1	1.12	1.24
Gender (female vs. male)	−0.31 (0.6)	0.23	0.73	2.39
Congestive heart failure	−0.58 (0.6)	0.17	0.56	1.81
Liver disease	−0.98 (0.83)	0.07	0.37	1.88
Infection	0.19 (0.59)	0.37	1.21	3.89
State of warfarin therapy (newly initiated vs. previously treated patients)	−0.45 (0.74)	0.15	0.64	2.73

Note. Within target range group was used as the reference groups. $R^2 = .351$ (Cox & Snell), .401 (Nagelkerke). Model $\chi^2(16) = 49.37$, $p < .001$.
[a] $p < .05$.
[b] $p < .01$.

showed that the best predictors of achieving below target INR range relative to within target INR range were; shorter hospital stay periods (0.82 times less likely for every day increase, $p = .006$), being a male patient (2.85 times more likely, $p = .039$), infection (0.21 times less likely, $p = .003$) and patients newly initiated warfarin therapy on hospital admission (3.73 times more likely, $p = .016$).

Whereas, the best predictor of achieving above target relative to within target INR values was; longer duration of hospital stay (1.12 times more likely for every day increase, $p = .048$).

4. Discussion

The present study investigated the potential effect of various factors on warfarin response.

We observed that warfarin initiation dose was not prescribed according to the guidelines. The starting dose of the majority of patients who were newly initiated warfarin in the hospital was 3 mg. Doses lower than 3 mg were initiated in the elderly (> 70 years) and liver disease patients. When initiating warfarin therapy, loading dose is usually given to rapidly elevate INR and reduce the time needed to achieve target INR range. Studies have suggested that warfarin initiation dose between 5 and 10 mg is appropriate and effective (Ageno et al., 2012). Some studies have suggested that 10 mg loading dose is not superior to 5 mg loading dose and that 5 mg dose may avoid the development of potential hypercoagulate state (Harrison et al., 1997; Crowther et al., 1999). However, other studies recommended 10-mg dosing nomogram over 5-mg nomogram because it allowed more rapid achievement of target INR and it was safe (Kovacs et al., 2003; Monkman et al., 2009). Initiation dose ⩽5 mg is appropriate in the elderly, patients with liver disease, impaired nutrition, congestive heart failure and in patients with increased risk of bleeding (Gurwitz et al., 1992; Garcia et al., 2005; Ageno et al., 2012). This may explain why newly initiated warfarin patients were more likely to have discharge INR values below target range than those who previously initiated it. This may also explain why newly initiated warfarin patients were more likely to have INR values below 1.5 during hospital stay. It was reported that values of INR below 1.5 increase the risk of thromboembolism (Rose et al., 2009; Nordstrom et al., 2010).

Elderly patients (⩾60 years) had lower median INR than adult and young patients. Although the results were not statistically significant, our data were inconsistent with published studies. In a USA study conducted on 530 patients, the prothrombin time ratio, when adjusted for dose, was significantly increased in older patients (Gurwitz et al., 1992). Moreover, older age was found in a number of studies to increase the risk of INR ⩾5 and warfarin-associated bleeding (Froom et al., 2003; Torn et al., 2005; Fang et al., 2006). However, age did not appear to be an important determinant of risk for warfarin-associated bleeding except may be for age ⩾80 years (Fihn et al., 1996). Low Median INR and low incidence of bleeding events in our elderly patients are probably due to that elderly patients were given smaller mean prescribed warfarin doses than others. In patients who were previously treated with warfarin, age was significantly related to the maintenance dose. This was consistent with other published studies that older patients require lower maintenance warfarin doses (Redwood et al., 1991; Garcia et al., 2005).

Women had a slightly non-significant higher median discharge INR compared with men. Women were less likely to be discharged with INR values below target range. A retrospective, longitudinal cohort study conducted on 12,006 patients showed that patients with respiratory illness, as well

as women, patients with cancer and those with an elevated baseline INR, are at high risk of anticoagulation and should have additional INR monitoring (Clark et al., 2014). Other studies showed that women required lower maintenance doses of warfarin than men (Absher et al., 2002; Garcia et al., 2005; Whitley et al., 2007). However, a retrospective study was conducted on 403 males and 403 females found that men had significantly higher baseline INR than women in patients without any known liver disease or anticoagulant medication (Sivrikaya et al., 2013). The effect of gender on INR values and warfarin response may require further investigation.

Patients with multiple conditions and mechanical valve replacement (especially MVR and DVR) had the highest median discharge INR compared with others. This is probably due to these patients require higher target INR of 2.5–3.5 compared with others (mainly from 2 to 3). Consequently, they were given larger mean prescribed warfarin doses to achieve higher target INR.

Patients who were admitted for more than two weeks had the highest median INR values. Also, the number of weeks of hospital stay was significantly related to discharge INRs. Our finding showed that longer duration of hospital stay decreased the likelihood of having INR values below target range and increased the likelihood of having INR values above target range. This may suggest that longer hospital stay periods are required to achieve a desired change in the INR values and patients who were discharged with INR values below target range did not stay for adequate time to have their INRs properly adjusted. Moreover, patients who stayed for longer hospital periods had deteriorated health conditions which might affect discharge INRs or that they were kept longer to have their INRs properly adjusted before discharge.

Hypertensive patients had a lower median INR before discharge than other patients. There has been no reported evidence in the literature on the effect of elevated blood pressure on INR or warfarin pharmacodynamics and pharmacokinetics. Also, our subjects did not take any antihypertensive medication that can interact with warfarin. However, the reason for this may be due to the fact that more than half of hypertensive patients were newly initiated warfarin on hospital admission. As mentioned before, newly initiated warfarin patients were more likely to have discharge INR values below target range than those who previously initiated it. In general, the use of warfarin is contraindicated in patients with malignant, severe and uncontrolled hypertension, due to increased risk of intracerebral hemorrhage. Warfarin may be needed to be used cautiously and INR should be monitored more frequently in patients with severe or uncontrolled hypertension (MHRA, 2009).

Patients with congestive heart failure had a lower median discharge INR and a lower incidence of bleeding events compared with other patients. This was not consistent with published reports and studies which have demonstrated that patients with congestive heart failure have increased response to warfarin therapy and increased risk of bleeding and high INR (Petitti et al., 1989; Doecke et al., 1991; Hylek et al., 2001; Self et al., 2006). The suggested mechanism for increased warfarin response in congestive heart failure patients is probably due to hepatic congestion and dysfunction (Self et al., 2006). The liver is the site for the synthesis of vitamin K clotting factors. Oxygen limitation theory is another suggested mechanism (Le Couteur and McLean, 1998; Hylek et al., 2001). Also, malnutrition is common in congestive heart failure patients (Carr et al., 1989). This may be associated with decreased dietary intake of vitamin K. The decreased discharge INR for congestive heart failure patients in our study was probably due to that they were given lower mean prescribed warfarin doses compared with others.

Patients with liver disease were more likely to experience bleeding episodes during their hospital stay. This was consistent with other published studies where liver disease was associated with increased risk of hemorrhage (Landefeld et al., 1987; Zhang et al., 2006). Liver disease is well documented to affect warfarin response and cause defective hemostasis and prolongation of prothrombin time (Donaldson et al., 1969; Mammen, 1992; Demirkan et al., 2000). As mentioned above, initiation doses of $\leqslant$5 mg are appropriate for patients with liver disease and signs of bleeding should be observed and monitored.

Patients with rheumatic heart disease had a higher median discharge INR compared with other patients. This could be explained by that most rheumatic heart disease patients were diagnosed before admission and were previously treated with warfarin. As mentioned before, previously treated warfarin patients were more likely to have higher discharge INR values compared with newly initiated patients. Many of rheumatic heart disease patients had prosthetic valve replacement (mainly MVR and DVR). Warfarin was given to these patients targeting higher INR values of 2.5–3.5. Thus, rheumatic heart disease patients were given higher mean prescribed doses than others to achieve higher target INR values. Also, some patients with active rheumatic heart disease were given broad spectrum antibiotic amoxicillin/clavulanate. Isolated cases of increased INR were seen in patients taking warfarin concurrently with amoxicillin/clavulanate (Davydov et al., 2003; Johnson et al., 2005).

Patients with infection had a higher median discharge INR compared with other patients. They were less likely to be discharged with INR values below target range. All of these patients received antibiotics and the higher median INR is probably due to potential interaction of antibiotics with warfarin. Patients with infective endocarditis were prescribed amoxicillin/clavulanate for up to 12 g daily. Antibiotics were reported to potentially interact with warfarin (Glasheen et al., 2005; Ghaswalla et al., 2012). Another possible reason is that fever associated with infection increased response of warfarin by increasing catabolism of vitamin K dependent coagulation factors (Hirsh et al., 2003). Also, there is a potential interaction between paracetamol prescribed for fever and warfarin (Hylek et al., 1998; Lopes et al., 2011). A study was conducted on 12,006 patients found that acute upper respiratory tract infection increases the risk of excessive anticoagulation independent of antibiotic use (Clark et al., 2014). Patients with infection should be closely monitored for potential increased response of warfarin and drug interactions.

5. Conclusion

Various factors were found to affect warfarin response. Days of hospital stay significantly predicted whether patients were discharged with INR values below or above target range relative to within target range. Gender, concurrent infection and new initiation of warfarin therapy significantly predicted

whether patients were discharged with INR values below target range relative to within target range. Initiating warfarin therapy without giving loading doses can decrease the risk of bleeding events during hospital stay. However, it increases the incidence of having INR values $\leqslant 1.5$ and consequently increases the risk of new thrombus formation. Also, it increases the odds for the patients to be discharged with INR values below target range or can increase the duration of hospital stay to get the INRs properly adjusted. Following warfarin dosing nomograms and careful monitoring of the effect of various factors on warfarin response should be greatly considered.

6. Limitations

One of the strengths of our study is that we investigated the simultaneous effect of various factors on warfarin response in hospitalized patients. But, we were not encountered with the genetic effect of the subjects. However, previous studies on the pharmacogenomics of warfarin in the Egyptian community were reported which found that genetic factors are important determinant of warfarin dose requirement (Shahin et al., 2011; Bazan et al., 2012).

References

Absher, R.K., Moore, M.E., Parker, M.H., 2002. Patient-specific factors predictive of warfarin dosage requirements. Ann. Pharmacother. 36 (10), 1512–1517.

Ageno, W., Gallus, A.S., Wittkowsky, A., Crowther, M., Hylek, E.M., Palareti, G.American College of Chest, 2012. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis. 9th ed: American College of Chest physicians evidence-based clinical practice guidelines. Chest 141 (Suppl. 2), e44S–e88S.

Bazan, N.S., Sabry, N.A., Rizk, A., Mokhtar, S., Badary, O., 2012. Validation of pharmacogenetic algorithms and warfarin dosing table in Egyptian patients. Int J Clin Pharm 34 (6), 837–844.

Brigden, M.L., Kay, C., Le, A., Graydon, C., McLeod, B., 1998. Audit of the frequency and clinical response to excessive oral anticoagulation in an out-patient population. Am. J. Hematol. 59 (1), 22–27.

Carr, J.G., Stevenson, L.W., Walden, J.A., Heber, D., 1989. Prevalence and hemodynamic correlates of malnutrition in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am. J. Cardiol. 63 (11), 709–713.

Clark, N.P., Delate, T., Riggs, C.S., Witt, D.M., Hylek, E.M., Garcia, D.A., Ageno, W., Dentali, F., Crowther, M.A., 2014. Warfarin interactions with antibiotics in the ambulatory care setting. JAMA Intern. Med. 174 (3), 409–416.

Crowther, M.A., Ginsberg, J.B., Kearon, C., Harrison, L., Johnson, J., Massicotte, M.P., Hirsh, J., 1999. A randomized trial comparing 5-mg and 10-mg warfarin loading doses. Arch. Intern. Med. 159 (1), 46–48.

Davydov, L., Yermolnik, M., Cuni, L.J., 2003. Warfarin and amoxicillin/clavulanate drug interaction. Ann. Pharmacother. 37 (3), 367–370.

Demirkan, K., Stephens, M.A., Newman, K.P., Self, T.H., 2000. Response to warfarin and other oral anticoagulants: effects of disease states. South Med. J. 93 (5), 448–454, quiz 455.

Doecke, C.J., Cosh, D.G., Gallus, A.S., 1991. Standardised initial warfarin treatment: evaluation of initial treatment response and maintenance dose prediction by randomised trial, and risk factors for an excessive warfarin response. Aust. NZ J. Med. 21 (3), 319–324.

Donaldson, G.W., Davies, S.H., Darg, A., Richmond, J., 1969. Coagulation factors in chronic liver disease. J. Clin. Pathol. 22 (2), 199–204.

Fang, M.C., Go, A.S., Hylek, E.M., Chang, Y., Henault, L.E., Jensvold, N.G., Singer, D.E., 2006. Age and the risk of warfarin-associated hemorrhage: the anticoagulation and risk factors in atrial fibrillation study. J. Am. Geriatr. Soc. 54 (8), 1231–1236.

Fihn, S.D., Callahan, C.M., Martin, D.C., McDonell, M.B., Henikoff, J.G., White, R.H., 1996. The risk for and severity of bleeding complications in elderly patients treated with warfarin. The National Consortium of Anticoagulation Clinics. Ann. Intern. Med. 124 (11), 970–979.

Froom, P., Miron, E., Barak, M., 2003. Oral anticoagulants in the elderly. Br. J. Haematol. 120 (3), 526–528.

Garcia, D., Regan, S., Crowther, M., Hughes, R.A., Hylek, E.M., 2005. Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. Chest 127 (6), 2049–2056.

Ghaswalla, P.K., Harpe, S.E., Tassone, D., Slattum, P.W., 2012. Warfarin–antibiotic interactions in older adults of an outpatient anticoagulation clinic. Am. J. Geriatr. Pharmacother. 10 (6), 352–360.

Glasheen, J.J., Fugit, R.V., Prochazka, A.V., 2005. The risk of overanticoagulation with antibiotic use in outpatients on stable warfarin regimens. J. Gen. Intern. Med. 20 (7), 653–656.

Gurwitz, J.H., Avorn, J., Ross-Degnan, D., Choodnovskiy, I., Ansell, J., 1992. Aging and the anticoagulant response to warfarin therapy. Ann. Intern. Med. 116 (11), 901–904.

Harrison, L., Johnston, M., Massicotte, M.P., Crowther, M., Moffat, K., Hirsh, J., 1997. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. Ann. Intern. Med. 126 (2), 133–136.

Hirsh, J., Fuster, V., Ansell, J., Halperin, J.L., 2003. American heart association/American college of cardiology foundation guide to warfarin therapy. Circulation 107 (12), 1692–1711.

Holbrook, A., Schulman, S., Witt, D.M., Vandvik, P.O., Fish, J., Kovacs, M.J., Svensson, P.J., Veenstra, D.L., Crowther, M., Guyatt, G.H.American College of Chest, 2012. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis. 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 141 (Suppl. 2), e152S–e184S.

Hylek, E.M., Heiman, H., Skates, S.J., Sheehan, M.A., Singer, D.E., 1998. Acetaminophen and other risk factors for excessive warfarin anticoagulation. JAMA 279 (9), 657–662.

Hylek, E.M., Regan, S., Go, A.S., Hughes, R.A., Singer, D.E., Skates, S.J., 2001. Clinical predictors of prolonged delay in return of the international normalized ratio to within the therapeutic range after excessive anticoagulation with warfarin. Ann. Intern. Med. 135 (6), 393–400.

Johnson, M.C., Wood, M., Vaughn, V., Cowan, L., Sharkey, A.M., 2005. Interaction of antibiotics and warfarin in pediatric cardiology patients. Pediatr. Cardiol. 26 (5), 589–592.

Keeling, D., Baglin, T., Tait, C., Watson, H., Perry, D., Baglin, C., Kitchen, S., Makris, M.British Committee for Standards, 2011. Guidelines on oral anticoagulation with warfarin – fourth edition. Br. J. Haematol. 154 (3), 311–324.

Kovacs, M.J., Rodger, M., Anderson, D.R., Morrow, B., Kells, G., Kovacs, J., Boyle, E., Wells, P.S., 2003. 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. Ann. Intern. Med. 138 (9), 714–719.

Landefeld, C.S., Cook, E.F., Flatley, M., Weisberg, M., Goldman, L., 1987. Identification and preliminary validation of predictors of major bleeding in hospitalized patients starting anticoagulant therapy. Am. J. Med. 82 (4), 703–713.

Le Couteur, D.G., McLean, A.J., 1998. The aging liver. Drug clearance and an oxygen diffusion barrier hypothesis. Clin. Pharmacokinet. 34 (5), 359–373.

Lopes, R.D., Horowitz, J.D., Garcia, D.A., Crowther, M.A., Hylek, E.M., 2011. Warfarin and acetaminophen interaction: a summary of the evidence and biologic plausibility. Blood. 118 (24), 6269–6273.

Mammen, E.F., 1992. Coagulation abnormalities in liver disease. Hematol. Oncol. Clin. North Am. 6 (6), 1247–1257.

MHRA, M.a.H.p.R.A., 2009. Warfarin: Changes to Safety Information. <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON065505>, (retrieved 12.06.14).

Monkman, K., Lazo-Langner, A., Kovacs, M.J., 2009. A 10 mg warfarin initiation nomogram is safe and effective in outpatients starting oral anticoagulant therapy for venous thromboembolism. Thromb. Res. 124 (3), 275–280.

Nordstrom, B.L., Kachroo, S., Nutescu, E., Schein, J., Fisher, A., Bookhart, B., Mody, S.H., 2010. Risk of venous thromboembolism after total knee or hip replacement in patients with low INR values. CHEST J. 138 (4_Meeting Abstracts), 400A–400A.

Petitti, D.B., Strom, B.L., Melmon, K.L., 1989. Prothrombin time ratio and other factors associated with bleeding in patients treated with warfarin. J. Clin. Epidemiol. 42 (8), 759–764.

Redwood, M., Taylor, C., Bain, B.J., Matthews, J.H., 1991. The association of age with dosage requirement for warfarin. Age Ageing 20 (3), 217–220.

Rose, A.J., Ozonoff, A., Grant, R.W., Henault, L.E., Hylek, E.M., 2009. Epidemiology of subtherapeutic anticoagulation in the United States. Circul.: Cardiovasc. Quality Outcomes 2 (6), 591–597.

Self, T.H., Reaves, A.B., Oliphant, C.S., Sands, C., 2006. Does heart failure exacerbation increase response to warfarin? a critical review of the literature. Curr. Med. Res. Opin. 22 (11), 2089–2094.

Shahin, M.H., Khalifa, S.I., Gong, Y., Hammad, L.N., Sallam, M.T., El Shafey, M., Ali, S.S., Mohamed, M.E., Langaee, T., Johnson, J.A., 2011. Genetic and nongenetic factors associated with warfarin dose requirements in Egyptian patients. Pharmacogenet. Genomics 21 (3), 130–135.

Sivrikaya, A., Baran, H., Abusoglu, S., Ozturk, B., Vatansev, H., Ali, U., 2013. Effect of gender and age on the prothrombin time (PT), activated partial thromboplastin time (aPTT) levels and international normalized ratio (INR). Int. J. Mevlana Med. Sci. 1 (2), 27–30.

Torn, M., Bollen, W.L., van der Meer, F.J., van der Wall, E.E., Rosendaal, F.R., 2005. Risks of oral anticoagulant therapy with increasing age. Arch. Intern. Med. 165 (13), 1527–1532.

Whitley, H.P., Fermo, J.D., Chumney, E.C., Brzezinski, W.A., 2007. Effect of patient-specific factors on weekly warfarin dose. Ther. Clin. Risk Manage. 3 (3), 499–504.

Zhang, K., Young, C., Berger, J., 2006. Administrative claims analysis of the relationship between warfarin use and risk of hemorrhage including drug–drug and drug-disease interactions. J. Manage. Care Pharm. 12 (8), 640–648.