



CODEN [USA]: IAJ PBB

ISSN: 2349-7750

INDO AMERICAN JOURNAL OF PHARMACEUTICAL SCIENCES

<http://doi.org/10.5281/zenodo.2632693>
Available online at: <http://www.iajps.com>

Research Article

FACTORS ASSOCIATED WITH THE USE OF WARFARIN AND THE RISK OF BLEEDING: CROSS-SECTIONAL STUDY

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Article Received: February 2019

Accepted: March 2019

Published: April 2019

Abstract:

Background and Objectives: There are multiple factors associated with the risk of bleeding for patients undergoing warfarin treatment. Therefore, the objective of this study was to investigate the incidence of major and minor bleeding for patients undergoing warfarin treatment. In addition, the study explored the association between various factors and the risk of major and minor bleeding.

Methods: A cross-sectional design was used for patients with atrial fibrillation who were attending the anticoagulation clinic at King Abdul Aziz Medical City, Riyadh, Saudi Arabia. Hospital medical records were used to identify patients taking warfarin. The exclusion criteria were patients taking other anticoagulants, who had end-stage liver disease, or who were on hemodialysis. Data were analyzed according to sociodemographics, comorbidities, abnormal liver function, labile INR, and drug-induced bleeding.

Results: A total of 264 patients were included in this study. The results revealed that female patients experienced major bleeding more frequently than did their male counterparts. Older age patients had more episodes of major or minor bleeding. In addition, hypertension was more prevalent in those who experienced any type of bleeding. The study also revealed that having diabetes decrease the risk of major bleeding.

Conclusion: These study results showed that diabetic and hypertensive patients had improved bleeding outcomes. Health care providers and policy makers need to increase efforts to reduce the burden of the factors associated with bleeding.

Keywords: Major Bleeding- Minor Bleeding- Anticoagulants - Warfarin - Labile INR- Saudi Patients- Coumadin

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Please cite this article in press Abdullah Uthman Althemery et al., *Factors Associated with The Use of Warfarin and The Risk of Bleeding: Cross-Sectional Study.*, Indo Am. J. P. Sci, 2019; 06(04).

INTRODUCTION:

Warfarin is on the World Health Organization's (WHO) list of essential medications [1]. According to an analysis of the worldwide use of anticoagulants, warfarin was the most trending medication between 2004 and 2017 [2]. In a study for the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (AF), one third of a Middle Eastern sample group was treated with Vitamin K agonists, including warfarin [3]. Three large hospitals in the capital of Saudi Arabia have estimated that the majority of AF patients received warfarin treatment, either alone or co-administered with other medication [4].

Evidence has shown that warfarin effectively prevents ischemic stroke in such patients [5]. Other demonstrated properties include the prevention of thrombus recurrence and the limitation of clot extension [6,7]. Moreover, findings have shown that patients with mechanical heart valve prostheses benefit hugely from the reduced risk of major embolisms [8].

Despite the widespread use of warfarin, bleeding is considered to be a common adverse side effect, and all patients using this treatment should monitor themselves closely in case of this side effect [9]. Previous studies have shown variations in incidences of minor and major bleeding, with a higher rate associated with the former [10]. Although definitions of major and minor bleeding vary, the consensus is that major bleeding is defined as bleeding that requires interventions, while minor bleeding is defined as bleeding that requires minimal management [11].

Estimating the risk of bleeding, as a result of sociodemographic and clinical factors, is a major concern internationally [12,13]. Ranges of factors are associated with the risk of bleeding for patients undergoing warfarin treatment [14–16]. The administration of other medications, such as acetylsalicylic acid, adenosine diphosphate receptor antagonists, and nonsteroidal anti-inflammatory drugs, have been shown to induce bleeding [14]. Fang et al. [15] found that older patients were more prone to the risk of bleeding than their younger counterparts, while Kearon et al. [16] concluded that several comorbid conditions, including diabetes, stroke, renal failure, and liver failure, also increase the risk. It was concluded that further studies are needed to estimate the risk of both major and minor bleeding by calculating these factors collectively [17].

The previous literature has evaluated the warfarin treatment for AF patients in Saudi Arabia [18–20], the majority of which focused on exploring the association between adherence and bleeding without focusing on the type of bleeding [18–20]. However, in this study an investigation for the association between patients' sociodemographic and clinical factors with the risk of major and minor bleedings was conducted. Thus, the objective was to explore the frequency of major and minor bleeding for patients undergoing warfarin treatment at a major hospital in the KSA. The second objective was to identify the greatest risk factors for bleeding in Saudi patients. Knowing the significant factors can help health care providers be ready for, and prevent all types of bleeding.

METHODS:

Type of research design

This cross-sectional study was conducted at King Abdulaziz Medical City (KAMC), Riyadh, KSA. The study protocol was approved by the King Abdullah International Medical Research Center Institutional Review Board, with an approval number (RC14/026).

Sample and setting

All AF patients attending the clinic between March and April 2014 who undergo warfarin treatment were invited to the study and referred to a clinical pharmacist for evaluation.

Inclusion and exclusion criteria

The inclusion criteria were patients receiving warfarin treatment for AF (either valvular or nonvalvular) who had at least ten readings for international normalized ratio (INR) and had available laboratory information on the hospital information system. The exclusion criteria were patients taking anticoagulants other than warfarin, who had been diagnosed with end-stage liver disease, who were on hemodialysis, and/or who had been on warfarin therapy for less than four weeks.

Variables and measurements

The independent variables included: age, gender, diabetes, hypertension, congestive heart failure, stroke, abnormal renal function, abnormal liver function, labile INR, and drug-induced bleeding. These factors were adapted using previous publications [12,13,17]. Patients were categorized as having diabetes, hypertension, congestive heart failure, or stroke if this was indicated in their medical records or they were undergoing treatment related to one or more of these conditions. Abnormal renal

function was indicated if the patient was diagnosed with chronic renal disease or if serum creatinine levels were more than 120 $\mu\text{mol/L}$. Abnormal liver function was indicated if the patient was diagnosed with chronic liver disease or if the liver enzyme levels were two times higher than upper normal levels, similar approach was utilized in previous literatures [21]. Labile INR was adapted as more than four of ten readings [22], being taken at least one week apart, falling outside the therapeutic range [23]. Finally, drug-induced bleeding was specified if the patient was taking acetylsalicylic acid, adenosine diphosphate receptor antagonists, or nonsteroidal anti-inflammatory drugs.

The dependent variables included major bleeding and minor bleeding. The former was stated for bleeding events that required an invasive procedure or blood transfusion, or that involved bleeding from a critical site (such as intra-cerebral bleeding). The latter was cited for bleeding events that did not require an invasive procedure or blood transfusion and involved bleeding from a non-critical site such as the gums or nose [24].

Data analysis procedures

A series of descriptive statistical analyses was conducted in which patients were compared with and without incidence of bleeding, either major or minor. Two logistic regression tables were produced to explore the association between different factors and the risk of either type of bleeding. The R Studio-integrated development environment was used to perform statistical analyses such as chi-squared

testing and logistic regression with p -value less than 0.05, which were considered statistically significant

RESULTS:

Features of patients with anticoagulant therapy

Table 1 displays the baseline characteristics for the medical records of patients who visited the anticoagulation clinic and received warfarin treatment. Without controlling for other factors, the characteristics of patients who had major or minor bleeding episodes showed no statistical significance difference from those who had no such incidents.

Examining the frequencies closely, the results show that female patients experienced major bleeding more frequently than did their male counterparts. However, female patients were less susceptible to minor bleeding incidents. Older age was more dominant in those who had major or minor bleeding. In addition, hypertension was more prevalent in those who experienced any type of bleeding; nonetheless, the difference did not attain the statistical significance level.

Patients who had been diagnosed with stroke had fewer events of major or minor bleeding than those who had not. The same pattern was seen in patients with congestive heart failure, while those with abnormal liver or kidney functions did not show any more vulnerability to bleeding episodes than their counterparts. Most patients who were on other anticoagulant medications did not experience either type of bleeding event.

Table 1: The baseline characteristics for patients who received warfarin treatment

	Major bleeding					Minor bleeding				
	Yes		No		p	Yes		No		p
	n	%	n	%		n	%	n	%	
Gender										
Female	10	3.79	134	50.76	0.51	11	4.17	133	50.38	0.06
Male	6	2.27	114	43.18		18	6.82	102	38.64	
Age										
<65	3	1.14	84	31.82	0.21	10	3.79	77	29.17	0.85
≥65	13	4.92	164	62.12		19	7.20	158	59.85	
Diabetes mellitus										
No	11	4.17	109	41.29	0.05	16	6.06	104	39.39	0.27
Yes	5	1.89	139	52.65		13	4.92	131	49.62	
Hypertension										
No	3	1.14	51	19.32	0.86	3	1.14	51	19.32	0.15
Yes	13	4.92	197	74.62		26	9.85	184	69.70	
Stroke										
No	14	5.30	212	80.30	0.82	23	8.71	203	76.89	0.30
Yes	2	0.76	36	13.64		6	2.27	32	12.12	
Congestive heart failure										
No	14	5.30	203	76.89	0.57	24	9.09	193	73.11	0.93
Yes	2	0.76	45	17.05		5	1.89	42	15.91	
Abnormal renal function										
No	11	4.17	203	76.89		24	9.09	190	71.97	0.80
Yes	5	1.89	45	17.05	0.19	5	1.89	45	17.05	
Abnormal liver function										
No	15	5.68	244	92.42		28	10.61	231	87.50	0.52
Yes	1	0.38	4	1.52	0.19	1	0.38	4	1.52	
Labile INR										
No	7	2.65	129	48.86	0.52	12	4.55	124	46.97	0.25
Yes	9	3.41	119	45.08		17	6.44	111	42.05	
Co-admin of Anticoagulants										
No	12	4.55	155	58.71		17	6.44	150	56.82	0.58
Yes	4	1.52	93	35.23	0.31	12	4.55	85	32.20	

Associations between patients' factors and the risk of bleeding

Two logistic regression models were performed to explore the significant factors associated with both major and minor bleeding (Table 2). No significant association was detected between age, stroke, congestive heart failure, abnormal renal function, abnormal liver function, labile INR, and drugs and the risk of either major or minor bleeding.

For gender, no significant association was found between this variable and major bleeding; a significant association was seen between it and the risk of minor bleeding. The coefficient of the gender variable had a Wald statistic equal to (2, N = 264) =

4.06, $p < .05$. The odd ratio for females was (2.45) with a 95% confidence interval of [1.03, 5.84], which suggests that females were more than twice as likely to experience minor bleeding.

Diabetic patients were significantly associated with the risk of major bleeding. The coefficient of the diabetes variable had a Wald statistic equal to (2, N = 264) = 4.42, $p < .05$. The odd ratio for patients without diabetes was (0.27) with a 95% confidence interval of [0.08, 0.92]. Compared to patients with diabetes, those without were about 75% less likely to suffer major bleeding. No significant association was inferred between the diabetes variable and minor bleeding.

For patients with hypertension, no significant association was discovered between said variable and major bleeding. However, such an association was perceived between it and the risk of minor bleeding. The coefficient of the hypertension variable had a

Wald statistic equal to $(2, N = 264) = 4.06, p < .05$. The odd ratio for hypertension was (4.20) with a 95% confidence interval of [1.04, 16.96], suggesting that warfarin users without hypertension were four times more likely to have a minor bleeding event compared to those with the condition.

Table 2: Logistic regression models exploring the significant factors associated with both major and minor bleeding

Variable	Major Bleeding Model			Minor Bleeding Model		
	OR	95% CI	p value	OR	95% CI	p value
Gender						
Female	0.55	(0.16-1.91)	0.317	2.45*	(1.03- 5.84)	0.049
Male	Reference			Reference		
Age						
<65	2.02	(0.55-7.49)	0.296	0.90	(0.39- 2.12)	0.851
≥65	Reference			Reference		
Diabetes						
No	0.27*	(0.08-0.92)	0.041	0.52	(0.22- 1.21)	0.170
Yes	Reference			Reference		
Hypertension						
No	1.98	(0.43-9.12)	0.414	4.20*	(1.04- 16.96)	0.048
Yes	Reference			Reference		
Stroke						
No	1.29	(0.26-6.39)	0.813	2.05	(0.72- 5.82)	0.182
Yes	Reference			Reference		
Congestive Heart Failure						
No	0.81	(0.15-4.34)	0.837	1.04	(0.33- 3.26)	0.980
Yes	Reference			Reference		
Abnormal Renal Function						
No	3.39	(0.93-12.28)	0.065	0.77	(0.26- 2.31)	0.644
Yes	Reference			Reference		
Abnormal Liver Function						
No	5.67	(0.46-70.01)	0.184	2.23	(0.19- 26.24)	0.444
Yes	Reference			Reference		
Labile INR						
No	1.56	(0.54-4.55)	0.634	1.81	(0.24- 1.26)	0.871
Yes	Reference			Reference		
Drugs						
No	0.64	(0.19-2.22)	0.524	0.96	(0.80- 4.01)	0.972
Yes	Reference			Reference		

*significance at 0.05 level

DISCUSSION:

In this study, the characteristics and frequency of patients who were using warfarin treatment were explored, as well as their association with minor and major bleeding at a major hospital in the KSA. Various factors were shown to be significantly associated with the risk of both types of bleeding.

In previous studies, various associations were presented between the risk of bleeding among diabetic patients and warfarin treatment [16,25]. The American College of Chest Physicians Evidence-

Based Clinical Practice Guidelines list diabetes as a major risk factor for bleeding with anticoagulant therapy [16]. However, according to the ARISTOTLE trial, warfarin and novel anticoagulants have no significant difference in terms of the risk of bleeding for diabetic patients [25,26]. The results revealed that non-diabetic patients are at increased risk of developing major bleeding. This may be attributed to the fact that Saudi patients with diabetes tend to visit the clinics more frequently and would get more INR screenings compared to those without diabetes [27,28].

Similar to diabetes, having hypertension has been shown to improve the bleeding outcomes for the analyzed group of patients. Conventionally, hypertension has been considered a risk factor for both minor and major bleeding [16]. However, Arima *et al.*[29] found that a decrease in major vascular events and hemorrhage was associated with adequately controlled blood pressure. This may explain why these Saudi hypertensive patients showed fewer incidences of minor bleeding compared to their counterparts.

According to the study analysis, females in Saudi Arabia treated with warfarin were more prone to bleeding than males. This result is in line with the previous literature [16], wherein being female was considered to be a risk factor for developing bleeding. Ebell (2010) concluded that renal failure was required to be included in studies predicting the risk of bleeding for patients using warfarin [17]. Accordingly, the current study included renal impairments patients but could not find any significant association for the risk of either minor or major bleeding. Al-Saikhan *et al.*[30] found that patients' knowledge and attitude were significantly associated with INR control. Similar studies with additional theoretical based variables would help healthcare practitioners to predict bleedings.

This study successfully addressed the association between bleeding and other factors for warfarin users while highlighting the importance of other comorbid conditions when controlling both major and minor bleeding. However, it failed to assess other factors beyond the clinical aspect. Genetic differences have been shown to play a major role in this risk [31]. Future researchers could explore the association between bleeding and patients' reported outcomes, which would provide a different perspective.

CONCLUSION:

The findings of this study showed that diabetic and hypertensive patients had enhanced bleeding results, although such patients were previously reported as being at high risk of bleeding. The study results also revealed that female patients are still vulnerable to both minor and major episodes of bleeding. Health care providers would benefit from these results by addressing the bleeding issues associated with gender. This study will help the researchers assess other factors beyond the clinical aspect or patient-reported outcomes.

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