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**Abstract**

## Predictors of warfarin-induced bleeding in a South Indian cardiology unit

**Objectives:** Warfarin-induced bleeding results in increased morbidity and mortality and higher cost of healthcare. The objective of the study is to identify the predictors of warfarin-induced bleeding in the Cardiology Unit of a teaching hospital. **Materials and Methods:** A cross-sectional study was carried out for a period of six months in a tertiary care teaching hospital. A total of 235 patients were enrolled in the study, to identify the predictors of warfarin-induced bleeding. Only prescriptions with warfarin were selected for the study. The chi square test was used to find the association between demography and risk factors. **Results:** Out of 235 patients, 61 (25.95%) had developed warfarin-induced bleeding and the majority were in the age group of 41 – 61 years (60.65%), and it was also found to be higher in women (62.29%). The length of stay was > 14 days (65.57%) and the number of drugs prescribed was in the range of 6 – 12 (52.45%). Aspirin (40.98%), Heparin (36.06%), Clopidogrel (22.95%), and Streptokinase (14.75%) were the most common drugs involved, and other comorbid conditions like diabetes (37.70%), hypertension (32.78%), smoking (57.37%), and alcohol (32.78%) were found to be major predictors of warfarin-induced bleeding in this study. The severity of warfarin-induced most of the bleeding reactions were moderate (44.26%) and the most common site of bleeding was gastrointestinal system (34.42%). **Conclusion:** Predictors of warfarin-induced bleeding were found to be female gender, length of stay, number of medications, drugs like aspirin, heparin, and clopidogrel, and other comorbidities like smoking, alcohol, and hypertension.

**Key words:** Anticoagulant, bleeding, cardiology, cross-sectional study

## INTRODUCTION

Warfarin is the most common anticoagulant. In current

use in the medical practice'. Its narrow therapeutic index, changes with concomitant medication use, and acute illnesses are common causes of bleeding. Warfarin-induced bleeding results in increased morbidity, mortality, and higher cost of healthcare.<sup>[1]</sup> There are many factors that are considered to be risk factors for warfarin-induced bleeding complications. Generally they are, elderly patients, multiple comorbidities, polypharmacy, history of hypertension, social habits, insufficient social support, and reduced functional status.<sup>[2,3]</sup> Patients taking Warfarin should be aware of the risks of taking other prescribed or purchased

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medicines, herbal products, and certain foods without first seeking advice. Successful and safe anticoagulation depends on patient education, good compliance, and communication with the patient and with the individuals responsible for their clinical care.<sup>[4]</sup> The scope for occurrence of an adverse event related to warfarin is great because of the biological variation in response to treatment and because of the large number of individuals involved in the patient's care. Monitoring regimens based on patient characteristics, intensity and duration of therapy, along with simple prediction rules, can reduce the risk of warfarin-related bleeding.<sup>[5,6]</sup> The main objective of the study is to identify the predictors of warfarin-induced bleeding in the Cardiology Unit of a teaching hospital.

## MATERIALS AND METHODS

A cross-sectional study was carried out for the period of six months (January to June 2010) in an Indian teaching hospital. Ethical approval was obtained from the Institutional Ethics Committee prior to study initiation. The patients admitted consecutively to a Cardiology Unit were included in the study. Only prescriptions with warfarin were selected for the study. Prescriptions from each patient during his / her hospitalization in the ward during the study period were included. Information such as demographics, complaints on admission, and routine biochemical investigations were obtained from the patients' clinical records. Details necessary for evaluation regarding previous allergies, concomitant medications, comorbidities, and others were collected. All the prescriptions of the study population were screened for predictors of warfarin-induced bleeding. Patients diagnosed with cardiac problems either as a main diagnosis or as additional diagnosis were identified using the International Classification of Diseases —Tenth Edition (ICD-10). Certain demographic characteristics were studied to find out the predictors. The factors studied were: (a) patient characteristics [gender, age (> 18 years), comorbidities and length of stay], (b) drug characteristics [number of drugs] and laboratory investigations. The 'case definition' in the present study were the patients who developed bleeding with warfarin and with warfarin along with other drugs (drug–drug interaction). The severity of bleeding could be classified into mild, moderate, and severe. Mild bleeding could be noted as petechial bleeding, mild blood loss (clinically significant) or bleeding not requiring transfusion; moderate bleeding could be noted as gross blood loss, requiring transfusion; and severe bleeding could be noted as debilitating blood loss, retinal or cerebral, associated with fatality.<sup>[7]</sup>

### Statistical analysis

Frequencies with percentage were used to summarize age, sex, length of stay, number of drugs dispensed,

frequency of bleeding, drugs involved in the bleeding, and comorbidities. The chi square test was used to find the association between age, sex, length of stay, number of drugs dispensed, frequency of bleeding, drugs involved in the bleeding, and comorbidities. A 'p' value of < 0.05 was considered statistically significant. The entire analysis was performed using SPSS v.15.

## RESULTS

A total of 235 prescriptions were analyzed during the six-month study period, in the Cardiology Unit. Of these 235 prescriptions, 61 (25.95%) patients had developed warfarin-induced bleeding. Thirty-seven (60.65%) of them who had developed bleeding were in the age group of 41–61 years, followed by 12 (19.67%) who were > 61 years, and this was found to be higher in women 38 (62.29%) than in men 23 (37.71%). The length of stay for 40 (65.57%) was > 14 days and the number of drugs prescribed were in the range of 7–12 for 32 (52.45%). Aspirin 25 (40.98%), Heparin 22 (36.06%), Clopidogrel 16 (22.95%), and Streptokinase 9 (14.75%) were the most common drugs used, and other comorbid conditions like diabetes 23 (37.70%), hypertension 20 (32.78%), smoking 25 (57.37%), and alcohol 20 (32.78%), which were the identified predictors of warfarin-induced bleeding in this study, are summarized in Table 1.

Among 61 cases, 21 (34.42%) gastrointestinal cases formed the most common site of bleeding followed by 13 (21.31%) skin, 12 (19.67%) genitourinary / hematuria, 11 (18.03%) hematoma of soft tissue, and four (6.55%) cerebral hemorrhage. The severity of warfarin-induced bleeding, classified based on the site, is represented in Table 2.

## DISCUSSION

The present study revealed that the overall incidence of the predictors of warfarin-induced bleeding in the study population was 25.95%, which was low, compared to similar studies.<sup>[8]</sup> Warfarin is metabolized by the Cytochrome P450 2C9 enzyme (CYP2C9). Up to 35% of the patients had inherited a form of the enzyme with reduced activity. When this deficiency was present in a patient, Warfarin cleared more slowly, leading to high blood levels, which then increased the risk of excessive bleeding. Two genetic variants could lead to a reduced activity of CYP2C9. They were CYP2C9\*2 and CYP2C9\*3. As we did not do this genetic test, the patients in my study might not have inherited this form of the enzyme with reduced activity. Therefore, the predictability was 25.95%. A major limitation to this study was that CYP2C9 and VKORC

**Table 1: Predictors of warfarin-induced bleeding**

Patient demographics	Presence of bleeding (N = 61)	Chi square value ( $\chi^2$ )	P value ( $P < 0.05$ )
Age (years)		12.421	0.006
21 – 40	12 (19.67)		
41 – 60	37 (60.65)		
> 60	12 (19.67)		
Gender group		3.304	0.048
Male	23 (37.70)		
Female	38 (62.29)		
Length of stay (days)		10.49	0.001
< 7	5 (8.19)		
8 – 14	16 (26.22)		
> 14	40 (65.57)		
No of drugs taken		48.32	0.000
< 6	6 (9.83)		
7 – 12	32 (52.45)		
> 12	23 (37.70)		
Drugs			
Aspirin	25 (40.98)	10.30	0.001
Heparin	22 (36.06)	7.21	0.014
Clopidogrel	16 (26.22)	7.581	0.031
Streptokinase	9 (14.75)	2.421	0.065
Comorbid conditions			
Diabetes	23 (37.70)	17.12	0.000
Dyslipidemia	20 (32.78)	8.12	0.193
Hypertension	20 (32.78)	13.21	0.003
Smoking	25 (40.98)	21.33	0.000
Alcohol	20 (32.78)	12.43	0.000

Figures given in parenthesis are in percentage

**Table 2: Severity of warfarin-induced bleeding**

Bleeding site	Mild bleeding	Moderate bleeding	Severe bleeding
Gastrointestinal	3 (4.91)	12 (19.67)	8 (13.11)
Skin	11 (18.03)	2 (3.27)	-
Genitourinary/ Hematuria	4 (6.55)	6 (9.83)	2 (3.27)
Hematoma of soft tissue	4 (6.55)	7 (11.47)	2 (3.27)
Cerebral hemorrhage	-	-	4 (6.55)

Figures given in parenthesis are in percentage

had not been done. The small sample size was likely to be the other reason.<sup>[9]</sup> A higher rate of warfarin-induced bleeding was present in women 38 (62.29%) than in men 23 (37.71%). Higher rates of warfarin-induced bleeding (37 (60.65%)) were present in the age group of 41 – 61 years. There is a controversy in the literature on the relationship between age and developing drug-induced adverse drug reactions (ADRs). This corresponds to the other studies, which reported that ADRs were common in elderly people who were on multiple drug regimens.<sup>[10,11]</sup> Risk factors for major or fatal bleeding in patients taking warfarin sodium included, a higher starting international normalized ratio (INR), age 65 years and older, variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs, and long duration of warfarin therapy.<sup>[4]</sup> Other risk factors for a major bleed occurring during warfarin anticoagulation were: Comorbid conditions, atrial fibrillation, and the first 90 days of warfarin therapy. Our findings showed that the patterns of

incidence of the predictors of warfarin-induced bleeding were positively associated with the patient's age, gender, number of drugs prescribed, length of hospital stay, and Aspirin 25 (40.98%), Heparin 22 (36.06%), Clopidogrel 16 (22.95%), and streptokinase 9 (14.75%) were the most common drugs involved, along with other comorbid conditions like diabetes 23 (37.70%), hypertension 20 (32.78%), smoking 25 (57.37%) and alcohol 20 (32.78%). These results were matched with similar studies.<sup>[12,13]</sup> Our findings of the severity of warfarin-induced for most of the bleeding reactions were 27 (44.26%) moderate type, followed by 22 (36.06%) mild, and four (6.55%) severe type of bleeding reactions. The most common site of bleeding observed in the present study was the gastrointestinal system (21 (34.42%)). These results were in accordance with the previous reports available in the literature.<sup>[14]</sup> Regular monitoring of INR should be performed on all the patients. More frequent monitoring, careful dose adjustment, and a shorter duration of therapy may be warranted in patients at high risk for bleeding.

## CONCLUSION

The identified predictors of warfarin-induced bleeding were found to be female gender, length of stay, number of medications, drugs like aspirin, heparin, and clopidogrel, and other comorbidities like smoking, alcohol, diabetes, and hypertension. Monitoring regimens based on patient characteristics, intensity and duration of therapy, along with simple prediction rules, can reduce the risk of warfarin-related bleeding.

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