Evaluation of adverse drug reaction in patients warfarin therapy

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ABSTRACT

This research aimed to understand the adverse drug reaction (ADR) in heart disease outpatients who were administered warfarin at a hospital in Bandung city. The research was conducted using a cross-sectional design with an observational approach. Subsequently, data were collected from 74 patients who met the inclusion criteria. The causality assessment was made by the Naranjo Algorithm and the incidence of bleeding was classified based on the Bleedscore™. The result showed that the most common ADR were nausea, dizziness, stomach ache, ecchymosis, petechiae, bleeding in the mouth, melena, etc. Furthermore, the INR value was the most significant factor in the incidence of ADR. It was 6.445 using a value of $P = 0.001$ or a confidence interval of 95%. The most common side effect of warfarin in cardiac outpatients was superficial bleeding, followed by internal bleeding (melena). The INR value is the most significant factor in measuring the incidence of ADR.

Key words: Adverse drug reaction, bleeding, international normalized ratio value, warfarin

INTRODUCTION

Cardiovascular disease is one of the biggest causes of death in the world, killing about 17.9 million people in 2016, which accounted for 31% of all deaths worldwide.[1] Subsequently, the prevalence of heart disease in Indonesia and the province of West Java is 1.5% and 1.6%, respectively, as reported by the Basic Health Research (RISKESDAS), Ministry of Health in 2018.[2] Anticoagulants are a class of drugs used to inhibit the formation and functions of several blood clotting factors to treat cardiovascular diseases. Warfarin is an example of an anticoagulant that inhibits the formation of Vitamin K. Warfarin has a narrow therapeutic index indicated for the prevention and treatment of venous thromboembolism, thromboembolic complications with atrial fibrillation, and pulmonary embolism. The main problem with warfarin use is the high variation in response between individuals, which results in many cases of drug-related problems in the form of adverse drug reactions (ADRs).[3]

ADR have a clinical and economic impact, including a decrease in the quality of life. In various studies, it has been considered a major cause of morbidity and mortality.[4] Anticoagulant drugs like warfarin is a major cause of ADRs, accounting for 60% of those that require hospitalization and 70% of those that occur in hospitals.[5] The study conducted by Budnitz *et al.*[6] also showed that warfarin is the most commonly prescribed drug that causes ADR, leading to emergency department (ED) visits.[6] Consequently, it is the first-order drug with the most cases at ED visits in the US.[7]

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Bleeding is a serious, life-threatening ADR from warfarin use and, patients can see its manifestation in the form of nosebleeds, bleeding in the gastrointestinal tract, melena, or bruises.[8] Bleeding due to warfarin correlates with international normalized ratio (INR) value. A previous study showed that 44% of patients who experienced bleeding had an INR value >3.0, whereas 48% of patients with a thromboembolic event had an INR value of <2.15.[9] In addition, risk factors for ADR, including warfarin-associated bleeding are advanced age, serious comorbidities such as cancer, chronic kidney disease, liver dysfunction, arterial hypertension, stroke, alcohol abuse, and concomitant use of antiplatelet or other drugs.[9]

Since there are no studies in Indonesia that examine the ADR of warfarin, an evaluation of such ADRs is carried out in heart disease patients at a hospital in Bandung city. This study aims to obtain information related to the incidence of ADRs while receiving warfarin therapy and also factors related to prevention and diagnosis of serious reactions so that necessary follow-up can be carried out, such as adjustments to drug use.

METHODS

Study design
This study used a cross-sectional approach, collecting observational data by searching primary data using the Naranjo Algorithm for ADR events, and assessing the causality based on probability scores. Bleeding events were classified based on the *BleedScore*™. Meanwhile, secondary data were obtained in the form of sociodemographic and clinical data from medical records consisting of gender, age, height, weight, indications, doses of warfarin given, duration of therapy, other diseases, other drugs being taken, and the patient's INR value.

Ethical approval
This research study was submitted for permission to The Health Research Ethics Committee, Faculty of Medicine, University of Padjadjaran. This permission has been approved by the Ethics Commission of Padjadjaran University, Bandung, Indonesia (No. 28/UN6. KEP/EC/2021).

Eligibility criteria
Inclusion criteria are all outpatients that treated with oral warfarin at the cardiac polyclinic who came for control in March 2021 at Hasan Sadikin Hospital, patients who had been on warfarin for at least 1 month, and patients with INR laboratory data were eligible for this study. However, the exclusion criteria included unwillingness to be the subject of research and incomplete or untraceable medical records.

Population and sample
The sample in this study was outpatient cardiac polyclinic according to the inclusion criteria. The total population of patients treated with warfarin during the data collection period was 90 patients. The minimum sample required is 73 samples (using the Slovin formula).

Statistical analysis
Univariate analysis was employed for descriptive analysis to determine the characteristics of each research variable, such as the number and percentage (*n*, %). Furthermore, bivariate analysis was also used with Chi-square to find variables that can be included in the multivariate model with $P < 0.25$. Finally, multivariate regression (logistics regression) was employed to see the factors related to the incidence of ADR as seen from the odds ratio (OR) with $P < 0.05$.

RESULT AND DISCUSSION

Data collection
Data were collected from 74 patients who had met the inclusion criteria. The data obtained are primary in the form of direct interviews using the Naranjo algorithm of the ADR. Furthermore, each point in every question will be summed and matched with the Naranjo Algorithm Scale, a score of 0 which is *Doubtful* indicates that it is not a side effect; 1–4 implies it is *Possible* to be a side effect; 5–8 means it is *Probably* a side effect of the suspected drug; 9 is *Definite implying that* side effects are certain. In addition to primary data, secondary data obtained from medical records were also taken.

Characteristics of the participants
Sociodemographic and clinical characteristics of the participants and the results of the bivariate analysis (*P* value) using Chi-square can be seen in Table 1. It also shows the results of the multivariate analysis using logistic regression. The average of the respondents' age was 40–64 years and 62% of the patients were women. The most common indications for warfarin treatment are for patients with rheumatic heart disease. Furthermore, the sociodemographic and clinical characteristics of the patients considered as a factor affecting the incidence of ADR was tested using the statistical method of multivariate regression analysis or logistic regression to see the risk of the independent variables or predictors on the incidence of ADR as seen from the OR value. Table 1 shows variables that passed the candidate test to include the multivariate model were drug interaction, comorbidities, INR values, and dose ($P < 0.25$).

Adverse drug reactions and causality Naranjo algorithm
Table 2 shows the incidence of ADR from warfarin in cardiac outpatients at one of Bandung city hospitals. Of the 74 participants, 43 patients (58%) experienced ADR and 31 (42%) did not experience ADR. The most common ADR was superficial bleeding (63%) in the form of ecchymosis or purple/blue blackish bruising that generally appeared on the hands or feet, followed by bleeding when brushing teeth and petechiae or red spots.

Table 1: Sociodemographic and clinical characteristic

Characteristics	n	Incidence of ADR		χ^2 P	Multivariat regression P OR (95% CI)	Final model P OR (95% CI)
		Yes	No			
Gender						
Male	28±6.3	14	14	0.270	-	-
Female	46±5.8	29	17			
Age (years)						
<60	60±8.2	35	25	0.935	-	-
≥60	14±4.1	8	6			
Drug interaction						
Yes	48±3.9	31	17	0.125[a]	0.611	
No	26±2.7	12	14		1.329 (0.444-3.980)	
Comorbidities						
Yes	16±3.5	7	9	0.189[a]	0.064	0.037
No	58±11.2	36	22		0.287 (0.076-1.076)	0.256 (0.071-0.921)
INR value						
Achieved	28±3.2	10	18	0.001[a]	0.003	0.001
Not achieved	46±8.1	33	13		5.740 (1.802-18.282)	6.445 (2.120-19.594)[b]
Dosis (mg)						
≤3	49±9.2	26	23	0.218[a]	0.596	
>3	25±7.3	17	8		1.359 (0.437-4.224)	

[a]Significance results (<0.25) were included in multivariate analysis (logistic regression), [b]The most significance factor of the incidence of ADR. OR: Odds ratio, CI: Confidence interval, INR: International normalized ratio, ADR: Adverse drug reaction

Table 2: The incidence of adverse drug reactions Warfarin and causality of Naranjo

ADR of Warfarin	Incidence (n)	Possible (n)	Probable (n)
Nausea	3±1.2	3	
Stomachache	1±2.4	1	
Headache	1±0.5	1	
Superfisial	27±4.9		
Ecchymosis (bruising/ blue-purple-black spots)	21±5.1	10	11
Petecie (small red or purple spots)	2±1.3	2	
Bleeding after brushing teeth	4±1.7	3	1
Internal			
Epitaxis (nosebleed)	5±1.1		5
Melena	8±2.8	4	4
Bleeding from the genitals	1±1.2	1	
Bleeding in the mouth	6±2.7	1	5
Alarming	0		

ADR: Adverse drug reaction

INR values and comorbidities had a significance of <0.05 and were considered factors associated with the incidence of ADR. Furthermore, patients were categorized into two groups, comprising those with acceptable INR values between 2 and 3, and those with unacceptable INR values <2 and >3. Subsequently, about 28 patients had an INR within the target range, while 49 patients were not within the targetted INR range. The *P* value obtained is 0.001, where the INR value influences the incidence of ADR and was the most significant factor in the incidence of ADR on warfarin use. OR INR obtained from the analysis carried out is 6.4, where patients with an unacceptable INR value would experience an ADR 6 times higher than patients with an acceptable INR value. Subsequently, ADR associated with warfarin are directly related to the level of INR level INR. The study by Gulseth *et al*.[9] discovered that the ADR of warfarin with an INR range that did not reach the target (2 and >3) was as high as 44% of patients who experienced bleeding with an INR level >3. Meanwhile, 48% of patients who experienced thromboembolic events had an INR level <2.15.[9] In this study, 23 patients with INR values >3.0 experienced bleeding events seen from the classification of the *Bleedscore*™ Subsequently, as many as 14 patients experienced bleeding when INR values were below 3.0.

Comorbidities are found in patients in the form of hypertension, diabetes mellitus, hyperthyroidism and gout. Their presence in patients was found to be statistically significant to the incidence of ADR with a *P* = 0.037. This is supported by a retrospective cohort study by Zhang *et al*.[10] and a prospective cohort study by Bassi *et al*.,[11] which found that patients with comorbidities were at greater risk of developing ADR.[10,11] The presence of multiple disease conditions simultaneously predisposes the patient to drug-disease interactions that can eventually lead to ADR. A total of 8 patients with hypertension experienced bleeding, and it was found that hypertension is one of the risk factors for ADR and warfarin-related bleeding.[11]

Table 1 shows the *P* value from the bivariate analysis for the candidate test of the multivariate logistic regression analysis

Table 3: Drug interactions of Warfarin

Interaksi	Obat	*n*
Increase the effect of warfarin	Erythromycin	34±7.9
	Lansoprazole	7±2.6
	Simvastatin	3±2.5
	Allopurinol	3±2.1
	Clopidogrel	2±1.6
	Omeprazole	1±1.3
	Acarbose	1±1.2
Decrease the effect of warfarin	Spironolakton	6±3.8

model is 0.935, which indicates that there is no relationship between age and the incidence of ADR. These results are consistent with previous research by Ozturk *et al*.,[12] which found no statistically significant difference between age and the incidence of bleeding due to warfarin-related ADR, as well as a previous study by Sari *et al*.,[13] which found no relationship between age and the incidence of ADR on antiretroviral drug treatment.[13] This is in contrast to the cohort study conducted by Fang *et al*.[14] which showed that elderly patients over 80 years of age had a greater risk of warfarin-related bleeding events[14] as well as the study conducted by Uygungül *et al*.[15] that age is related to the incidence of ADR related to warfarin bleeding, with the elderly being at a higher risk of bleeding events, but this is also in line with the INR value of patients who are unstable and do not reach the target range.[15] According to the literature, age has a significant effect on the development of ADR at extreme ages, particularly in geriatric patients with various disease conditions who are more vulnerable to ADR.[16] In addition, the limited number of elderly patients can also limit the statistical significance because some elderly patients receive treatment at the Geriatric Clinic.

The most widely used drug that poses warfarin-related interactions by increasing its effect is erythromycin, which is used by 46% of the population, while spironolactone, which is used by 8% [Table 3], reduces the effects of warfarin. Drug interactions that occur are not statistically significant to ADR with $P = 0.615$. However, according to the data, 31 out of 48 patients who had a drug interaction experienced an ADR, while 14 out of 26 patients who did not have a drug interaction did not have an ADR. This variable may not have reached statistical significance due to the small sample size.

One of the main factors related to ADR is the dose administered, drug formulation, and pharmacokinetic or pharmacodynamic abnormalities.[17] Furthermore, drug doses were categorized based on the patient's average daily dose, at 3 mg or higher. The results showed no relationship between drug dose and the incidence of ADR ($P > 0.05$). Every drug is given according to the recommended dose by looking at various factors. The dose given between individuals is not the same, and the dose of warfarin is given by looking at the main factor, namely

the INR value of patients who are monitored regularly.[18] Subsequently, another factor that may influence the risk of bleeding is genetic variants. Gene mutation in Vitamin K epoxide reductase complex 1 (VKORC1) and CYP2C9 gene mutations can lead to a higher risk of bleeding in patients taking warfarin.[19,20] In addition to affecting the activity of warfarin, of course, this will have an impact on ADR in the form of bleeding where a study conducted by Reitsma *et al*.[21] showed that the genetic polymorphism of VKORC1 has a high risk of bleeding (OR = 1.7, 95% confidence interval: 1.1–2.5).[21]

CONCLUSION

The most common side effect of warfarin in cardiac outpatients was superficial bleeding, followed by internal bleeding (melena). The INR value is the most significant factor in measuring the incidence of ADR.

Conflicts of interest
There are no conflicts of interest.

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